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Cardiovascular Complications of COVID-19

Acute and Long-Term Impacts

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Series Editor

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Maciej Banach
Editor

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Springer

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As it is probably my 40th book as an editor, coeditor, or author, thus it is the highest time to express my great thanks to my amazing family—Ewelina, Zuzanna, Bartlomiej, Kamil, Filip, Paulina, as well as to my wonderful Parents. Without you it would not be possible to be in a place I am now, and without you it would not be possible to still think that, in fact, I have not started yet!

Taking this opportunity I would also like to kindly thank all the experts worldwide that enabled to know the structure and mechanism of action of SARS-CoV-2; those that have worked so hard on vaccines, and new versions of them based on the new coronavirus variants; those that have tried to educate about the pandemic, importance of suitable prevention and therapy, and vaccinations; and those that have had to face with all fake news, anti-vaccinations movements, and sometimes even with governments, which still do not understand what the word prevention really means.

Foreword

As of November 2022, nearly 3 years after the SARS-CoV-2 virus was first identified, more than seven million people are reported to have died from COVID-19. Modeled estimates from the Institute for Health Metrics and Evaluation (IHME) place the actual death toll closer to 18 million, while nearly six billion people have been infected. Massive disruptions to civilization, commerce, and progress persist around the globe.

The grave threat to health posed by COVID-19 remains. Health care workers—whom we owe an unparalleled debt of gratitude for their heroic efforts to battle an unfamiliar and unrelenting killer—must continue to marshal their energy and resources, their medical and scientific expertise and ingenuity, to determine how to best minimize suffering and save lives in patients with COVID-19.

Understanding of SARS-CoV-2 dynamics and COVID-19 epidemiology has advanced rapidly yet characterizing the disease's clinical features and pathophysiological mechanisms remains an evolving science. Contrary to initial perceptions that COVID-19 primarily affected the respiratory system, we now know it to be a multi-organ disease that can induce a variety of symptoms, often including cardiovascular complications. This link between COVID-19 and cardiovascular disease (CVD) is multidirectional; a considerable percentage of infected patients develop cardiovascular complications that can worsen their prognosis, and patients with pre-existing cardiovascular conditions are more likely to have poor outcomes. Moreover, initial estimates suggest that the COVID-19 pandemic has directly and indirectly impacted the global burden of CVD—as measured by diagnosis, care delivery, morbidity, and mortality rates—although these effects appear to be highly variable.

The following volume, *Cardiovascular Complications of COVID-19,* represents the first comprehensive effort to distill and communicate current knowledge about the emerging connections between COVID-19 and CVD. Written by renowned cardiologists and leading researchers, the book summarizes information about COVID-19—viral biology, disease epidemiology, and clinical features—providing context for a series of chapters that synthesize the current state of knowledge on the pathophysiology, prognostic impact, and treatment of cardiovascular complications observed in acute-phase COVID-19, including myocardial injury, heart failure,

atherosclerotic events, myocardial infarction, heart arrhythmias and coagulation dysregulation potentially leading to thrombosis, and stroke, among others. In particular, the effects of the cytokine storm and intense inflammation that are key features of COVID are discussed.

The book also highlights the cardiovascular complications of long COVID, synthesizes evidence about the potential role of commonly used CVD drugs (including statins and, more controversially, ACE inhibitors) in preventing or treating COVID-19, and discusses how pandemic restrictions have changed health care delivery through the adoption of e-services and digital tools.

By providing clear and relevant information regarding the clinical implications and potential therapeutic options for COVID-19 patients with cardiac complications, *Cardiovascular Complications of COVID-19*—a dispatch from the battle front in the continued struggle to overcome the disease—will serve as an invaluable resource for doctors, nurses, and other health care providers. It is a welcome and essential resource in our joint fight against COVID-19 and its complications.

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Preface

The coronavirus disease 2019 (COVID-2019) pandemic has been the largest challenge that physicians, nurses, and healthcare providers need to face in the last decade. Since December 2019 we have observed almost 600 million infection cases and almost 6.4 million deaths. It is important to strongly emphasize that the COVID-19 pandemic will stay with us forever similarly to other infections we usually deal with, such as influenza, parainfluenza, and adenovirus infections. New variants will be also discovered, as it is now with Omicron BA.4 and BA.5, and the most recent BA. 2.75 variant called Centaurus. COVID-19 is not the only pandemic we need to face now; we can observe more and more patients, who were not suitably diagnosed, monitored, and treated during the pandemic (fear of the hospitalization, limited availability to medical services), and due to this fact, we can now observe huge health debt, with which we will fight for at least several years. Finally, even 80% of recovered patients might have different symptoms, which are defined as long-COVID syndrome. Cardiovascular complications are one of the most common, and based on our studies even every third patient after SARS-CoV-2 recovery (irrespective of whether the course was symptomatic or not, and of the health status during infection—from healthy patients to those with concomitant diseases) may have different cardiovascular complications—from new-onset diabetes, new-onset hypertension, impairment of the left ventricle function to myocarditis, to lung thrombosis, heart failure, or acute coronary syndrome. Within those even every fourth (27.5%) may have serious cardiovascular complications, which are life-threatening and require immediate hospitalization. Thus, it is the highest time to focus on prevention to effectively avoid all those complications, and to reduce COVID-19-related health debt.

Based on the above, the aim of this book, entitled *Cardiovascular Complications of COVID-19: Acute and Long-Term Impacts*, was to provide the most current knowledge to physicians, nurses, medical and public health experts, and healthcare providers on how to predict, prevent (based on the well-established risk factors), and optimally treat cardiovascular complications both during the acute face of COVID-19 and during long-COVID. You may find here the most recent epidemiological data, information on the risk factors, how to manage these patients using

approved diagnostic methods and therapies, what is the role of vaccines in the prevention of early and long-term complications, and how to effectively reduce the risk of long-COVID symptoms. You may find here the results of the most important RCTs, cohort studies, registries as well as the recommendations of national and international societies on the management of cardiovascular complications in patients with COVID-19 and long-COVID. *Have a nice reading!*

Łódź, Poland Maciej Banach

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Abbreviations

+ssRNA	Positive-sense single-stranded RNA
ACE2	Angiotensin-converting enzyme 2
ADE	Antibody-dependent enhancement
AKT	Protein kinase B
APC	Antigen-presenting cells
APN	Aminopeptidase N
ARDS	Acute respiratory distress syndrome
CBP	Convalescent blood products
CEACAM1	Carcino embryonic antigen-related cell adhesion molecule 1
CFDA	China food and drug administration
CFR	Case fatality ratio
COVID-19	The Coronavirus disease-2019
CRISPR	Clustered regularly interspaced short palindromic repeats
CT	Computerized tomography
DIC	Disseminated intravascular coagulation
DMV	Double-membrane vesicles
DPP4	Dipeptidyl peptidase 4
DRF	Damage response framework
dsRNA	Double-stranded RNA
ERGIC	Endoplasmic reticulum golgi intermediate compartment
FDA	Food and drug administration
HCoV-229E	Human coronavirus 229E
HCoV-HKU1	Human coronavirus HKU1
HCoV-NL63	Human coronavirus NL63
HCoV-OC43	Human coronavirus OC43
HLA	Human leukocyte antigen
IBV	Infectious bronchitis virus
ICTV	International committee on taxonomy of viruses
IFN-γ	Interferon-gamma
IL	Interleukin
JAK	Janus kinase

kb	Kilobases
mAb	monoclonal antibodies
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MHC	Major histocompatibility complex
MODS	Multiple organ dysfunction syndromes
MOF	Multiple organ failure
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear Factor κ-light-chain-enhancer of activated B cells
nsps	Nonstructural proteins
ORF	Open Reading Frame
PdCoV	Porcine delta coronavirus
RAS	Renin-angiotensin system
RBD	Receptor-binding domain
RBM	Receptor-binding motif
RER	Rough endoplasmic reticulum\
RTC	Replicase-transcriptase complex
RT-qPCR	Real-time quantitative polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARSCoV-2	Severe acute respiratory syndrome coronavirus-2
ssRNA	Single-stranded RNA
STAT3	Signal transducer and activator of transcription 3
TLRs	Toll-like receptors
TMPRSS2	Transmembrane protease serine 2
TNF-α	Tumor Necrosis Factor-alpha
WHO	World Health Organization

Introduction

In Wuhan, China, a positive-strand RNA virus (SARS-CoV-2) was first detected in December 2019. It rapidly spread and affected populations worldwide, and case fatality rates range from 2% to 3%. SARS-CoV-2 genome comprises ssRNA (single-stranded RNA) which is approximately ~30 kb in size [1]. Both nonstructural proteins (nsps) and structural proteins are encoded by the genome. Structural proteins include the nucleocapsid proteins (N), spike glycoproteins (S1 and S2), envelope proteins (E), and membrane proteins (M), which are all located near the 3′ end of the strand [2]. Cytokine storms are often caused by uncontrolled inflammatory responses and result in high mortality. IFN-γ, IL-1, IL-6, TNF-α, and IL-18 are crucial cytokines that are released through nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 3 (STAT3), Toll-like receptors (TLRs), Janus kinase (JAK), protein kinase B (AKT),

mammalian target of rapamycin (mTOR) signaling pathways during cytokine storms [3]. In brief, infected epithelial cells with the SARS-CoV-2 express angiotensin-converting enzyme 2 (ACE2), which induces activation of immune cells resulting in acute respiratory distress syndrome (ARDS) [4]. Beyond vaccination, there is no fully efficient agent or method recommended for pre- and post-exposure with SARS-CoV-2; however, several medications are used. For instance, Remdesivir as an anti-viral drug is prescribed for coronavirus disease 2019 (COVID-19) patients with respiratory symptoms, which causes faster recovery [5]. Hydroxychloroquine is used to prevent viral replication in severe acute respiratory syndrome (SARS), as used in the Middle East respiratory syndrome (MERS) patients years ago. Lopinavir/Ritonavir are recommended as anti-viral agents in viral infections such as HIV; corticosteroids such as dexamethasone and methylprednisolone [6] are used to reduce the mortality rates of patients and decreases the inflammatory reactions and the macrophage activation syndrome. Tocilizumab is used in patients with ARDS and reduces the elevated levels of IL-6 [7]. Aside from chemical agents, herbal medicines such as curcumin and quercetin are used to treat COVID-19 by suppressing the inflammatory signaling pathways and cytokines [8].

Method of Search

From PubMed, Google Scholar, Scopus, and Cochrane library, we collected data on published clinical and animal studies between 2000 and April 2021 in English. Also, search terms included “SARS CoV-2” or “COVID-19” and “Biology” or “Variants” or “Structure” or “Origins” or “Inflammatory response.”

The SARS-CoV-2 Biology

Coronaviruses are classified as a subgroup of RNA viruses with the ability to cause diseases in mammalian and avian species. They compose a positive-sense single-stranded RNA (+ssRNA) genome ranging from 26.4 to 31.7 kb in size. The genome has a 5′ methylated cap and a 3′ polyadenylated tail [9]. Coronaviruses contain the largest genome among the RNA viruses, making them capable of plastic gene adaptation and modification [10]. This family causes numerous viral infections while more lethal variants give rise to SARS, MERS, and COVID-19 [11]. Molecular biology revealed that the disease caused by the coronaviruses family is a consequence of virus genome transcription and replication and delayed or disturbed immune responses [12, 13]. Subsequently, upregulation of the inflammatory pathways and the immune cells invasion in different tissues provokes a malfunctioning cycle of the host immune response [14–16]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronaviruses responsible for the ongoing COVID-19 pandemic. It is the seventh identified coronavirus capable of causing illness in

humans after human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV) [17]. The genome sequence of SARS-CoV-2 is 79% similar to SARS-CoV and 50% to MERS-CoV [18]. The bat coronavirus (RaTG13), spotted in *Rhinolophus affinis* from Yunnan province, China, shares 96.2% full-length genome sequence and 90% open reading frames in the genome with SARS-CoV-2 [19, 20]. However, recent reports are still speculating about the virus reservoir. It remains elusive how the virus was transmitted to humans and which animals acted as an intermediate reservoir [21, 22]. As Fig. 1.1 exerts [23], the virus morphology is simple. The coronavirus virion consists of the RNA genome, helical nucleocapsid, and viral membrane containing S1, S2, M, and E [24]. All coronaviruses have a similar structure. The first two-thirds of coronaviruses genomes are open reading frame (ORF) (contain ORF1a and 1b), which encode the 16 nsps [9]. The later reading frames encode S1 and S2, E, M, and N [25]. The differences between the coronaviruses are owed to the number and function of accessory proteins. The reading frames between the nonstructural and structural proteins encode the accessory proteins. The distinguishing point of these viruses is the spike that controls the virus activities and virulence and the diverse accessory proteins that combat against the host immune system [26, 27]. The differences between the functional domains of the spike protein genome of SARS-CoV and

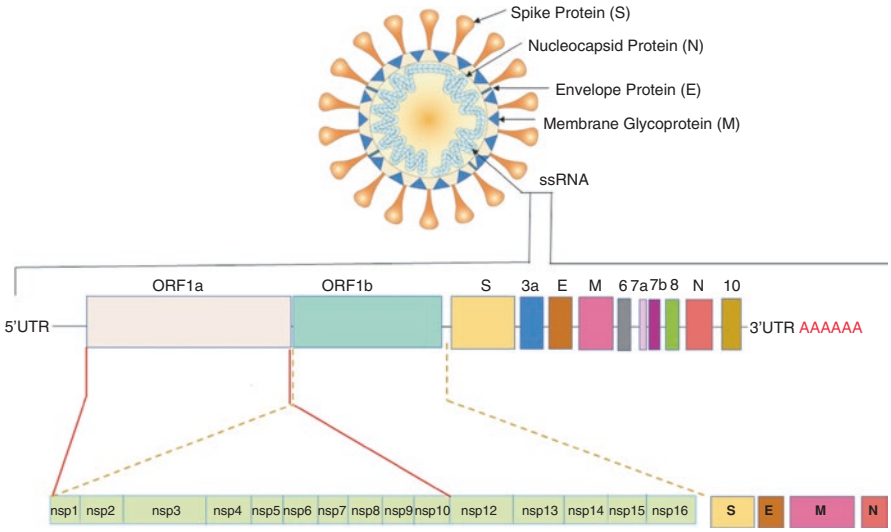

Fig. 1.1 The SARS-CoV-2 morphology and genome sequence. Schematic representation of the coronavirus virion entailing RNA genome, nucleocapsid (N), membrane (M), envelope (E), and the spike (S) proteins on the surface of the virus. The RNA genome has a 5′ cap and 3′ poly (A) tail. The replicas contain open reading frames (ORFs) 1a and 1b encoding 16 nonstructural proteins (nsp1-nsp16). The remaining ORFs encode the structural protein (S, E, M, and N) and accessory proteins [23]

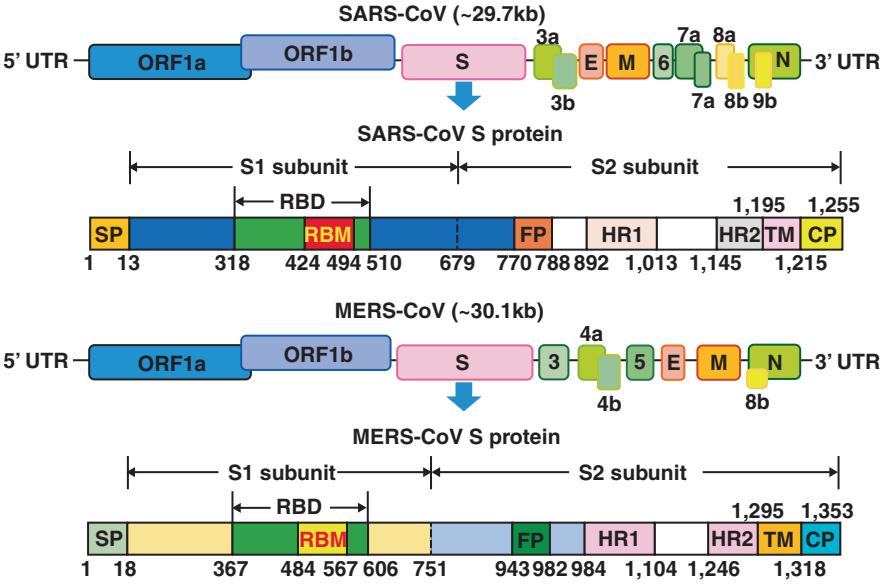

Fig. 1.2 The genome sequence of SARS-CoV and MERS-CoV, differences between the spike protein of each genome. The S protein consists of two functional subunits (S1 and S2). The S1 subunit comprises a receptor-binding domain (RBD), and the RBD comprises a receptor-binding motif (RBM). The S2 subunit includes heptad repeat regions (HR1 and HR2), fusion peptide (FP), transmembrane domain (TM), and fusion peptides (FP)

MERS-CoV have been demonstrated in Fig. 1.2 [28]. There are two subunits of spike protein, S1 and S2. The S1 subunit has a receptor-binding domain (RBD) that binds the receptor-binding motif (RBM) to the host surface. Moreover, the S2 subunit mediates the receptor attachment and the host membrane fusion [23, 29]. The primary host receptor for SARS-CoV and SARS-CoV-2 is the ACE2, while for MERS-CoV is dipeptidyl peptidase 4 (DPP4) [30–33]. Afterwards, in an outbreak of SARS-CoV in 2000, scientists started to search for other human viruses that can cause severe illnesses. In 2010, the MERS-CoV appeared, and the existing research platform from SARS-CoV empowered the scientists to develop a DNA-based vaccine against MERS-CoV infection in March 2020 [34]. When SARS-CoV-2 appeared in 2020 and caused the pandemic, the previous vaccine design methods were reproducible, and the RNA-based COVID-19 vaccine was presented in 2021 [35, 36].

The SARS-CoV-2 Origins

Coronaviruses can typically be categorized into four different genera: alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacuronavirus. Alpha coronaviruses include HCoV-229E and HCoV-NL63 [37]. Beta viruses contain HCoV-OC43, MERS-CoV, SARS-CoV-2, HCoV-HKU1, and SARS-CoV. Likewise, gamma

coronaviruses are comprised of the avian infectious bronchitis virus (IBV) [38]. Delta coronaviruses categories are concluded swine delta coronavirus (PdCoV). Coronavirus is one of the newly emerging viruses that led to many deaths. Its evolution is high-speed, and the virus mutates in different ways and creates various strains [39]. Understanding the virus's evolutionary patterns will help discover more effective treatments and vaccines. The members of the coronaviridae family have been studied in different species of fish, birds, camels, and bats [40]. The most common viruses that infect mammals are alpha and beta coronaviruses, while gamma and delta coronaviruses infect birds. Understanding the evolution or mutation pattern that the virus may have in the future may be helped by evolutionary history [41].

HCoV-229E

Initially, this coronavirus strain was called B814. Another infection with an unidentified respiratory virus led to the formation of a strain cell culture that initiated the infection. This strain eventually became a prototype for HCoV-229E [42]. Under the electron microscope, the B814 and the HCoV-229E strain are very analogous to the avian coronavirus, IBV. HCoV-229E contains ether and is composed of 89 nm particles and has single-stranded RNA, coated as genetic material, and after 6 days causes cytopathic effects. The main methods of the HCoV-229E transmission were droplet respiration and foaming [43, 44].

HCoV-OC43

HCoV-229E was discovered after virus samples from common cold patients were taken, and no antibodies were detected toward this virus, proving there was no B814 mutation equivalent to the HCoV-229E [45]. The OC43 strain was spread and eventually formed the HCoV-OC43 species. The HCoV-OC43 species is an enveloped ssRNA virus in the same way as the HCoV-229E species. HCoV-OC43 is the reason for one-third of the common colds. It is an RNA virus with a 31.5 kb size. The HCoV-229E is also involved in one-third of those cases [46].

SARS-CoV

Despite discovering the role of HCoV-229E and HCoV-OC43, these species were initially thought to be the only two types of human coronaviruses. However, a new strain of coronavirus was distinguished in 2002, the SARS-CoV [21] reported in China that is transferred from palm civets to humans. SARS-CoV was found in 2003 in horseshoe bats. It was found to be an enveloping ssRNA virus. The virus has about 14 ORFs with about 30 kb RNA [47].

HCoV-NL63

An immunocompromised infant with respiratory symptoms in The Netherlands was found to have HCoV-NL63 in 2004 [48]. Studies have elucidated that HCoV-NL63 is isolated from the ancestors of HCoV-229E. Also, HCoV-NL63 possesses an ssRNA genome encased and polyadenylated with 27,553 nucleotides. The virus is more prevalent in winter and milder weather [49].

HCoV-HKU1

HCoV-HKU1 was primarily detected in Hong Kong in January 2005 that is related to the Group II prototype of HCoV-OC43. The positive samples of HCoV-HKU1 were often established in temperate countries like Italy and the USA during winter and spring [50]. The virus is a + ssRNA virus with 29,926 nucleotides. RT-PCR performs rapid diagnosis of HKU1 infections with the assistance of specific monoclonal antibodies (mAb) related to HKU1 [51].

MERS-CoV

MERS-CoV was derived from the sputum of a 60-year-old man hospitalized due to renal failure and severe acute pneumonia in 2012. Subsequent serological evidence confirmed the presence of MERS-CoV in camels in the Middle East, North Africa, and East Africa, indicating camels as a reservoir of MERS-CoV [52]. MERS-CoV has a +ssRNA genome of 30.1 kb. The MERS-CoV replicates in virus-induced bilayer vesicles lacking host pattern recognition receptors, preventing its dsRNA host from being detected [53].

SARS-CoV-2

There have been several cases of pneumonia with an unknown cause reported in Wuhan in December 2019. The virus has been renamed Wuhan coronavirus, but the ICTV (International Committee for the Classification of Viruses) named it SARS-CoV-2 and COVID-19 [35]. SARS-CoV-2 shows more minor mutations because of its corrective function. About 13 mutation sites were detected in the SARS-CoV-2 regions of ORF-1ab, −3a, −8, N, and S, including 8782 in ORF1a and 28,144 in ORF8 with mutation rates of 29.47% and 30.53%, respectively [54]. Genetic analysis of a population of 103 genomes associated with SARS-CoV-2 showed that SARS-CoV-2 advanced into two major forms, L and S, which are well characterized via two members of single nucleotide polymorphisms (SNPs) [55]. Cuttings of the spike protein are located at the S1 and S2 junction, as two significant subunits,

which determine the extent of viral infection and the range of host species. The difference in mortality rates is related to viral mutations and evolutionary ability [21].

The SARS-CoV-2 Structure

Coronaviruses are large—average diameter of 80–120 nm and average molecular mass of 40,000 kDa—roughly spherical and relatively pleiomorphic with distinctive surface spikes projections [56]. Their RNA is in the center of the virus and is protected by the nucleocapsid, membrane protein, and lipid bilayer envelope [57, 58]. The viral capsid possesses a lipid bilayer and four types of structural proteins, namely, S, M, E, and N proteins—an approximate molar ratio of S:E:M is 20:1:300 (Fig. 1.1). The S protein is essential to form an interaction with the host cell. In addition to the S protein, the viral surface also encompasses hemagglutinin-esterase dimer (HE), which is not necessary for replication but is vital for the virus entry [59, 60]. The E protein is the minor structural protein and differs diversely among the coronaviruses [61]. Among the primary structural proteins, M is responsible for shaping the envelope [62]. The N protein is tied to the RNA and empowers the virus to take over the host cells [63, 64]. The genome of coronaviruses includes various ORFs. The gene order in all members is 5′-leader-UTR-replicase (ORF1ab)-S-E-M-N-3′UTR-poly (A) tail [65]. Their genome seems to have a bias against cytosine (C) and guanine (G) nucleotides with the highest composition of uracil (U) and adenosine (A) [66]. In addition to these components, 16 nsps (nsp1 to nsp16) differ between the genera of coronaviruses [9]. These nsps perform vital roles in assembling the replication/transcription complex (RTC), RNA polymerization, RNA proofreading, mRNA capping, allosteric activation, and repression of the host immune system [67, 68].

The coronaviruses spike (S) protein anchors to the ACE2 receptors for viral entrance, expressed on numerous cell surfaces. The transmembrane protease serine 2 (TMPRSS2) and lysosomal proteases also play significant roles in the SARS-CoV-2 entry [69]. Following the cytoplasm entry, the virus induces spatial alteration in the endosome, uncoating the viral nucleocapsid (N). Finally, the viral genome is ultimately released within the cytoplasm, and the RTC initiates [70]. Moreover, the SARS-CoV-2 sustains the largest genome with 30,000 bases in the RNA sequence length. A unique feature of SARSCoV2 is its capacity to cleave the spike protein at its polybasic site through furin-mediated cleavage, which increases its virulence. Moreover, it was proposed that the furin-cleavage region at the SARS-CoV-2 spike protein was needed to enable the virus to infect humans as well as animals [21].

SARS-CoV-2 Variants

Coronaviruses belong to the sub-family of *Orthocoronavirinae* in the family *Coronaviridae*, order *Nidovirales*, and realm *Riboviria* [71, 72]. As mentioned, the coronaviruses are sorted into four genera: deltacoronavirus, gammacoronavirus,

Table 1.1 The SARS-CoV-2 variants of concern

Variants of SARS-CoV-2	Linage	First outbreak	First sample detection	Notable mutations
Alpha	B.1.1.7	United Kingdom	September 2020	N501Y, P681H
Beta	B.1.351	South Africa	May 2020	K417N, E484K, N501Y
Gamma	P.1 (B.1.1.28.1)	Brazil	November 2020	K417T, E484K, N501Y
Delta	B.1.617.2	India	October 2020	L452R, T478K, P681R
Omicron	B.1.1.529	South Africa (Botswana)	November 2021	P681H, N440K, N501Y, S477N

betacoronavirus, and alphacoronavirus. However, the number of species increases and many coronaviruses are unspecified [71, 73]. The betacoronavirus and alphacoronavirus uniquely infect mammalian species, while deltacoronavirus and gammacoronavirus infect both mammalian and avian species. The coronavirus infection mostly leads to respiratory, gastrointestinal, and neurologic disorders [74, 75]. Several variants of SARS-CoV-2 are of interest and concern. Generally, a variant is called a variant of interest when it displays evidence of mutation, which is expected to circulate broadly. The Mu and Lambda variants are currently the World Health Organization (WHO) variants of interest. When a variant of interest is more transmissible and detrimental, it becomes a variant of concern. The recently acknowledged variants of concern are presented in Table 1.1 [76, 77].

Conclusion

In December 2019, the outbreak of SARS-CoV-2 spread in Wuhan, China. This virus causes various diseases, from the common cold to ARDS [78, 79]. The prevalence of ARDS also increases with the rise of inflammatory cytokines. The activation of the ACE2 and TMPRSS2 receptors are the main mechanisms of the cytokine storm [80, 81]. High levels of inflammatory cytokines and chemokines in COVID-19 patients are accounted for more elevated levels of IL-6, IL-1β, IL-10, TNF-α, and IFN-γ through the activation of the various signaling pathways such as NF-κB, STAT3, JAK, AKT, and mTOR pathways [82, 83]. Different variants of coronavirus are determined and classified into Alpha coronaviruses (HCoV-229E and HCoV-NL63), Beta viruses (HCoV-OC43), SARS-CoV, HCoV-HKU1, MERS-CoV, and SARS-CoV-2, Gamma coronaviruses (avian IBV), and Delta coronaviruses (PdCoV) [84, 85]. Nevertheless, several types of coronavirus would be distinguished after mutation in humans because of adapting coronaviruses to their human hosts. Genetic evolution in coronaviruses results in mutant versions of coronaviruses that may differ from their ancestral strains in various ways. During this

pandemic, several variants of SARS-CoV-2 have been described. Recently, different therapeutic approaches have been examined to elucidate precise treatment protocols. Therefore, various medications such as Lopinavir/Ritonavir, Hydroxychloroquine, Tocilizumab, Remdesivir, corticosteroids, as well as methylprednisolone, and dexamethasone resulted in a reduction of symptoms and improved outcomes. Furthermore, some herbal medicines such as quercetin, resveratrol, curcumin, have been tried in the treatment of COVID-19 because of their anti-inflammatory characteristics [86]. Currently, multiple vaccines are developed and distributed worldwide, such as Oxford-AstraZeneca, Pfizer- BioNTech, CoronaVac, and COVID Shield, which support people worldwide and decrease the rate and prevention of getting infected with COVID-19; however, even after injection coronavirus vaccines, with different mechanisms of action, it is possible to be infected with new variant of coronavirus due to mutation in different regions of the virus, particularly structural protein areas.

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Chapter 2
COVID-19 Epidemiology and Differences in Incidence and Mortality Between Countries

Melvin Larker and Seth S. Martin

The virus named SARS-CoV-2 which causes the clinical syndrome named Coronavirus Disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019. At the start of the pandemic, experts at Johns Hopkins University created the Johns Hopkins Coronavirus Resource Center Dashboard [Johns Hopkins COVID Dashboard] (COVID-19 Dashboard by the Center for Systems Science and Engineering) (see Fig. 2.1). This resource is continuously updated with COVID-19 data, and managed by many of the field's experts [1, 2]. Data are obtained from reputable sources and aggregated into an easy-to-use interface. Sources include the World Health Organization, European Centre for Disease Prevention and Control, multiple state-level governments in the USA, among others.

Publicly shared on January 22, 2020, the interactive web-based dashboard provides real-time updates on the COVID-19 pandemic, including the total number of cases, the total number of deaths, and the total amount of recoveries in all of the affected countries [1, 2]. The Johns Hopkins COVID Dashboard is equipped with features such as the ability to narrow one's focus on a specific region, and the ability to track vaccination data. The dashboard also allows one to follow the trends of the pandemic and allows the ability to see the waves in which the pandemic presented, and the severity of each wave in comparison with the others (see Fig. 2.2) [3]. Leveraging this dashboard and published studies, the present chapter examines the epidemiology of COVID-19.

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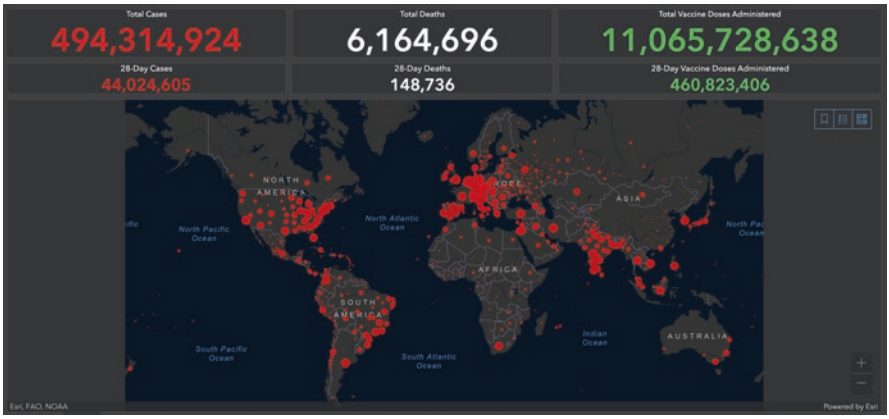

Fig. 2.1 COVID-19 Dashboard as of April 6, 2022 by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

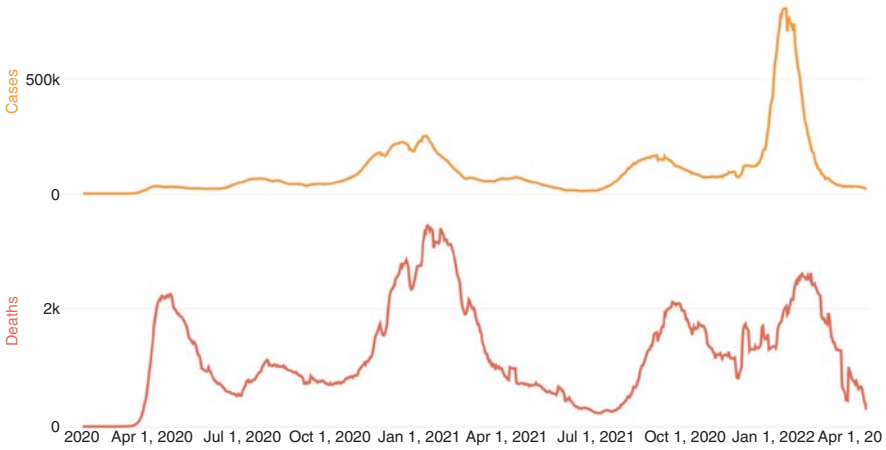

Fig. 2.2 Timeline of COVID-19 cases and deaths in the USA, January 2020 to April 2022

Origins

During the first 50 days of the epidemic, the novel coronavirus killed more than 1800 individuals and infected over 70,000 individuals [4]. The outbreak may have been initiated from the Hunan seafood market in Wuhan city of China, which sold animals such as bats, frogs, snakes, birds, marmots, and rabbits [4, 5]. The Hunan Seafood Market in Wuhan, China, was designated as "ground zero" for the start of the pandemic, and closed doors in January 2020 (see image for timeline). On January 11, 2020, the first COVID-19-related death was reported in China. Due to the infectious nature of COVID-19, the spread was rapid, and on January 23, 2020, other cases appeared in Japan, South Korea, and Thailand [6].

Asian Countries

In addition to Japan, South Korea, Thailand, South Asia soon began to experience an influx of COVID-19 cases. Just a few months into the pandemic, in March 2020, Asian countries had over 170,000 active cases. Of those cases, China had most cases (around 81,000), followed by Iran which had about 41,000 cases [7–9].

The reported case-fatality rate in China at the beginning of the pandemic was about 5.6%, however, other surrounding countries reported a higher average case-fatality rate of 15.2% [10]. As of February 2022, China has experienced a total of 120,110 COVID-19 cases and 4849 deaths, according to data obtained by the Johns Hopkins COVID Center. In contrast, India, which has been one of the Asian countries that has been greatly impacted by the pandemic, has recorded a total of more than 41 million cases and nearly 500,000 deaths as of February 2022.

While the pandemic began in China, many surrounding Asian countries began to experience increasingly more COVID-19 cases [11]. During the earlier months of the pandemic, in March–April 2020, Vietnam had relatively good control over the spread of COVID-19 and affected cases were younger in age. This was credited to policies containing the spread [12]. However, as the second wave of the virus made its way across countries, Vietnam began to experience more cases, and the older population was impacted more. The trend in Vietnam began to mirror many other countries in which the elderly suffered more morbidity and mortality related to COVID-19. This seemed to be influenced by comorbidities such as diabetes, cardiovascular disease, and kidney disease [12]. As of February 2022, Vietnam has a total of more than 2.2 million cases and about 37,000 deaths, with a case-fatality rate of 1.7%.

COVID-19 in the United States of America

The USA has been one of the leading nations plagued by the COVID-19 pandemic. As of February 2022, the USA has experienced more than 75 million recorded cases and nearly 900,000 deaths due to COVID-19. The first COVID-19 case was confirmed in the USA on January 19, 2020, in the state of Washington. After the first case was identified, several actions were taken to help identify and subsequently slow the spread of COVID-19 through the USA [13].

Like most countries described, the COVID-19 pandemic proceeded in multiple waves, with periods of high spikes in cases and deaths. During the initial wave in the USA, the majority of the deaths were in elderly individuals 85 years of age and older—they made up about 30% of the deaths from May to August 2020 [14]. During the early pandemic, higher percentages of underrepresented minorities were being disproportionately impacted by COVID-19. However, as the pandemic progressed, more White Americans were being hospitalized from COVID-19 [15].

The epidemiological trend in the USA reflects policies and guidelines that were enacted at a state level. Separated by regions, states in the Northeast, South, West,

and Midwest all experienced significant COVID-19 related death. However, southern states and western states experienced an increase in COVID-19-related deaths by the middle of 2020, whereas midwestern and northeastern states experienced a decrease in COVID-19-related deaths by that time [14]. Due to isolation efforts, and quarantining, nursing home-related deaths also decreased in the USA by August 2020.

Canada

The impact of the pandemic on Canada was delayed. In January 2020, they had relatively few cases and the length of the first wave was relatively short. Nonetheless, they were heavily impacted by the second and third waves of the pandemic. During the latter waves, like many other countries, their healthcare system demand was at capacity – ICUs were at capacity [16]. According to Johns Hopkins COVID database, there has been a total of 3,081,616 confirmed cases of COVID, and 34,207 deaths in Canada as of February 2022.

The control of the early pandemic was credited to the effective COVID-19 shutdown [17].

For the majority of the pandemic, individuals 29 years of age and younger accounted for most cases, which has been associated with a low mortality rate. The elderly population in Canada made up the majority of the COVID-19 related deaths.

Canada was not unique in which populations were impacted more heavily by the pandemic. Significant impact was seen in lower socioeconomic areas, where individuals may be less likely to be able to quarantine because of financial strains. In addition, individuals with substance use disorders, and incarcerated individuals were impacted. Medical comorbidities were associated with mortality; individuals with cardiovascular disease, lung disease, among others represented 73.5% of the patients who required intensive care in the setting of COVID-19 infection [18, 19].

Mexico

Low- and middle-income countries faced unique challenges when dealing with the COVID-19 pandemic. These included problems with testing, contact tracing, and putting systems into place to effectively control the spread. In this setting, strong spikes in COVID-19-related mortality and morbidity were observed in Mexico [20].

The average age of impacted individuals is 36 years of age. By the end of 2020, Mexico had a case-fatality rate of 26.10 per 10,000 population. In line with sex differences in COVID trends, males had a case-fatality rate of 33.9%, and females had a case-fatality rate of 18.5%. At the end of 2020, COVID-19 had caused 38.6% of all deaths in Mexico. Studies show that individuals in Mexico who have two or more comorbidities are at increased risk of mortality [21].

In February 2022, according to Johns Hopkins COVID Center, Mexico has nearly 4.9 million confirmed cases and 306,920 deaths. Mexico has the second-highest case-fatality rate of 6.2%, only behind Peru.

Peru

It is reported that by May 2020, South America had more than 600,000 cases and 30,600 deaths. South America began to see soring COVID-19-related deaths because of factors such as high poverty rates, poor water supply, and suboptimal healthcare systems, thus a scarcity of medical supplies [22]. The first case of COVID-19 was reported on March 6, 2020. Like many countries during the early phases of the pandemic, Peru implemented strict social distancing measures. These measures were supported by the CDC and have been shown to slow the spread of COVID-19. Soon after the first reported case, Peru reacted almost immediately by closing schools and banning travel from Europe and Asia. Subsequently, they declared a national emergency on March 16, 2020, and set a nighttime curfew on March 18, 2020 [22].

Unfortunately for Peru, despite the strict social distancing measures, they have been severely impacted by the COVID-19 pandemic. They have the highest case-fatality rate (6.3%) when compared to all countries. According to Johns Hopkins COVID Center, they have a total of 3,286,151 confirmed COVID-19 cases, and 206,220 deaths related to COVID-19.

In Peru, the demographics of those heavily impacted by COVID-19 mirror to a large extent the trend in China and the USA. Mortality from COVID-19 in Peru most frequently occurred in individuals over the age of 65. It is estimated that this age group accounts for about 80% of the COVID-19-related deaths. Persons with medical conditions such as heart disease and lung disease are more common in this age group and experience higher mortality [22–24]. At younger ages, men were most likely to die from COVID-19-related deaths, however, as age increased, women were more likely to die [22]. When compared to other countries, such as China, men held the higher mortality rate, regardless of age [22]. COVID-19 has a predilection for heavily populated areas, and this was demonstrated in Peru, as the majority of the cases were in Lima, the capital of Peru.

Brazil

The first COVID-19 case touched down in Brazil on February 26, 2020. About a week later, Brazil's Intensive Care Units were reaching capacity, and mortality rates were soaring above other nations [20]. It was stated in the media that Brazil had sparse resources including pharmacological drugs and mechanic ventilators. According to JHH COVID Center, at the beginning of 2022, Brazil has a total of 25,820,745 confirmed cases of COVID-19 and 629,301 COVID-19-related deaths.

A study in Brazil showed that 55.5% of COVID-19-related hospitalizations were men and more than 39.5% of the hospitalizations were individuals over the age of 60. There are also race-related differences, like many other countries, in Brazil. The majority of the people who were infected with COVID-19 by August 2020 were Black people, about 40.6%, followed by White people at 29.8% [25]. Considering COVID-19-related hospitalizations, 62.5% lasted about 7 days, whereas 23.2% lasted more than 14 days.

The COVID-19-related case-fatality rate in Brazil was impacted by comorbidities as it was in many other countries. Male sex, older age, and heart disease were related to higher mortality rates, but this differed in comparison to European countries and the USA where obesity, respiratory disease, and diabetes were related to high COVID mortality. Data suggest that racial and socioeconomic factors weighed more heavily in Brazil than other factors [25–28].

Colombia

According to the Johns Hopkins COVID Center, the current mortality rate as of February 2022 is 2.3%, making Colombia among the countries with the highest mortality rate. The first COVID-19-related death was reported in April 2020. Most of the statistical data as it relates to Colombia is obtained from Barranquilla, Colombia, which is one of the most populous cities in Colombia, with a population of 1.3 million. Based on a study from Barranquilla, by May 2021, the country had already experienced three waves of the pandemic, with an overall case-fatality rate of 389.4 deaths/100,000 population [29].

In Colombia, nearly 62% of the COVID-19-related deaths occurred in individuals over the age of 65. In addition, the majority of deaths occurred in men. In Colombia, about 48% of their COVID-19-related deaths were in individuals with a comorbid disease, hypertension being the most prevalent, among others such as diabetes, lung disease, and heart disease [29]. As of February 2022, Colombia has experienced a total of 5,966,706 cases of COVID-19 and 135,757 deaths.

Europe

The first case of COVID-19 was reported in France on January 24, 2020. The first death occurred on February 15, 2020. Europe has been a major epicenter of the pandemic since early 2020. Many scholars were baffled at Europe being an epicenter of the pandemic because of the affordability and access to healthcare many of the countries have mastered.

It is reported that France, Italy, San Marino, Andorra, Malta, Spain, and Austria have been ranked in the top ten as having the best healthcare systems in the world [25]. Nonetheless, the United Kingdom, Russia, France, Italy, Spain, and

Germany, accounted for 61% of COVID-19 cases and 65.6% of COVID-19-related deaths in Europe [26, 30]. Even more so, countries such as Italy, which has one of the richest economies in Europe still experienced shortages in healthcare resources [30].

The United Kingdom, while already dealing with a shortage of nurses and doctors, was hit by COVID-19 cases early in the pandemic. [30] As of early 2022, they have a case-fatality rate of 0.9%; 17,923,805 total cases, and 158,856 COVID-19-related deaths. France, a country with great access to healthcare has a case-fatality rate of 0.6%; 20,887,052 total cases, and 133,501 COVID-19-related deaths.

Russia

Russia is the European country with the most COVID-19 cases and COVID-19-related deaths [26, 30]. According to the Johns Hopkins COVID Center, Russia currently has a case-fatality rate of 2.6%. Furthermore, as of early 2022, Russia has a total of 12,612,259 confirmed COVID-19 cases, and 328,664 COVID-19-related deaths.

Given the number of cases and the public health concern, Russia took unique measures to enforce its social distancing and quarantine guidelines. They used facial recognition cameras to enforce the quarantine. In addition, a patient who was suspected of COVID-19 infections was required to wear electronic bracelets to ensure they were self-isolating [30]. Despite those measures, Russia steadily experienced a climb in cases. Studies suggest that it was Russia's delayed response to the pandemic, and travel policies, that influenced the case load [31].

Ukraine

The first case of COVID-19 was detected in Ukraine on March 3, 2020, in an individual who had recently traveled from Italy. Despite Ukraine implementing quarantine measures on March 12, 2020, the country still saw increasing cases of COVID-19. This was attributed to inadequate measures in identifying active cases and Ukraine citizens returning from travel; therefore stricter measures were implemented, including mandatory mask policies and closure of academic facilities [32, 33].

The pandemic in Ukraine has been complicated by active conflict between Russia and Ukraine. Active surveillance, social distancing, and adequate treatment are imperative during any pandemic, and the COVID-19 pandemic is no different. However, active conflict can divert from these efforts. Studies suggest that the healthcare systems in the occupied territories of Ukraine are not equipped to handle the pandemic, which caused a worsening in cases, despite overall prompt actions taken by Ukraine as a whole [32, 34, 35].

Italy

On January 30, 2020, the first case of COVID-19 appeared in Italy in Chinese tourists who tested positive for COVID-19 while in Rome. Following that case, things remained quiescent until February 20, 2020, when an outbreak began in Lombardy, a region of Italy [36]. At the beginning of the pandemic, Italy was recognized as a hotspot. After China, Italy was reported to have the second-largest case-fatality rate [37].

Italy delayed imposing strict restrictions and did not impose a nationwide lockdown until March 2020. Before March 2020, there had been social distancing measures in certain areas, such as Lombardy, but it was not nationwide. Following the soaring cases throughout Italy, beginning with the first locally contracted case in February 2020, nationwide policies were enacted. Some of the measures mirrored those of other countries, such as canceling all large meetings, shows, and sporting events. Unfortunately, by the end of March 2020, the coronavirus spread to all of Italy's regions [38].

Studies in April 2020 showed that most of the COVID-19 cases were in men, and the average age of those affected was 62 years old. Similar observations were made with respect to China and the USA. A study of 6085 Italians who experienced a COVID-19-related death was examined for the risk of underlying comorbidities, and it showed that individuals with heart disease, lung disease, among others, did experience higher mortality [38, 39].

As of February 2022, according to the Johns Hopkins COVID Dashboard, Italy has a total of 11,663,338 confirmed COVID-19 cases and a total of 149,097 COVID-19-related deaths.

Poland

COVID-19 made its appearance in Poland on March 4, 2020. About 2 months after the first case, Poland was seeing an increasing number of infections and deaths. Like many countries, the demographic most affected were women over the age of 75 years old [40]. As of early 2022, Poland has 5,223,507 COVD-19 cases and a case-fatality rate of 1.9%.

During the height of the pandemic, Poland had an in-hospital death rate of 11.5%, which was substantially lower than other countries [41]. It appears that this is related to, as has occurred in other countries, some degree of underreporting. During the third wave of COVID-19, there were about 46,200 deaths, of which 34,700 deaths were reported [42].

South Africa

South Africa is one of the nations with the highest COVID-case-fatality rate. According to the Johns Hopkins COVID Dashboard, South Africa has a COVID-case-fatality of 2.6%, only behind Peru and Mexico. South Africa has been disproportionally impacted by the COVID-19 pandemic. South Africa accounts for 4.4% of the African population, but it accounted for 36.7% of the COVID-19 cases, and 42.3% of the COVID-19-related deaths [43]. As of early 2022, South has 3,725,177 confirmed cases.

African countries, among other middle to low-income countries, have unique challenges as it comes to the COVID-19 pandemic. They lack the resources needed to adequately contain the spread or disseminate information about prevention. They also lack adequate resources needed to treat patients who contract the infectious virus [44].

There are little data on the African countries outside of the Johns Hopkins COVID Dashboard. Nonetheless, African countries have collectively experienced a low COVID-case-fatality rate, outside of South Africa. A study reported, during the earlier phases of the pandemic, African countries such as Egypt, Morocco, Algeria, Ghana, and Nigeria had a high daily cumulative index, meaning the listed countries experienced high COVID-19 daily rates from day 1 of the first case reported to May 18, 2020 [45].

Antarctica

Initially, Antarctica was the only continent that did not experience any COVID-19 cases. This is likely due to the very low human population in Antarctica. Even though Antarctica does not have a consistent population, the continent has placed measures surrounding tourism to prevent spread to the continent [46]. However, COVID-19 eventually reached Antarctica.

Summary The COVID-19 pandemic began in late 2019/early 2020. As of April 2022, there have been more than 490,000,000 cases and 6,000,000 deaths around the globe. COVID-19 impacted nations across the globe and presented in at least three different waves, requiring coordination of care, testing, social distancing, and other measures. Resources and responses have varied by country/region/sovereignty, [47–49] with differences in case numbers and fatality rates. The differences in statistics across countries may in part relate to differences in reporting of COVID-19 cases, with major potential for underreporting related to asymptomatic cases and the lack of testing. Throughout the COVID-19 pandemic, Johns Hopkins has remained committed to providing up-to-date data and trends regarding COVID. Since the release of the COVID-19 vaccination, Johns Hopkins COVID Dashboard provides statistics as to how many people are vaccinated, as well [47–49].

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Chapter 3
Clinical Symptoms and Course of COVID-19

Miłosz Parczewski, Bogusz Aksak-Wąs, and Daniel Chober

SARS-CoV-2 Transmission

The key for the SARS-CoV-2 infection are human-to-human transmissions, however, the virus may also infect and replicate and array of animal hosts, including companion animals, household pets, and farm animals (e.g., minks). Animal replication may play a role as potential reservoir hosts for the virus and associated with possibility of the new variant emergence [1]. First reports on the COVID-19 incubation period defined a medium of 5.5 days with the range between 3 and 14 days. This timeline has been shortened with the emergence of the novel, highly transmissible, and infectious variants. For example, median asymptomatic period for the Omicron variant is three days [2]. Transmission is possible from both asymptomatic and symptomatic hosts. Early stages of the infection are associated with the highest virus transmissibility (the highest viral expression in the upper respiratory tract). Usually the peak of infectivity is 2 days before and 1 day after the symptom onset. However, for the Omicron variant the peak of virus shedding might be delayed to 3–6 days following the initial symptoms. Infectivity of the virus wanes after 7–10 days, except in patients with immunodeficiency where infectivity exceeding 4-week period have been reported [3]. It should be emphasized that viral RNA may be detectable by molecular methods even weeks after infection and **is not a marker of patient infectivity.**

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Virus Replication

In general infection symptoms are dependent on both viral replication and cellular tropism as well as host responses. It is widely known that the S protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), which is well established as a key entry receptor for most host cells [4]. ACE2 is highly expressed on alveolar epithelial cells, intestinal enterocytes or vascular endothelium but also in the array of other tissues including kidneys (tubular and glomerular cells), adipose tissue, heart (myocytes, pericytes and epicardium), nervous system (neurons and glial cells) as well as male and female reproductive system (mostly Leydig and Sertoli cells), skin (epidermis), thyroid gland, thrombocytes, macrophages or even the pancreatic Langerhans islets. This ACE-expression based cellular tropism determines clinical course of the disease [4].

In general two pathways are used by the virus to enter the host cells. The first, early pathway, is the cell surface pathway dependent on the host serine protease (TMPRSS) activation allowing for the S protein to interact with the receptor. Alternative (late) pathway for SARS-CoV-2 entry into host cells is the endosomal-lysosomal endocytic pathway with internalization into endosomes and cathepsin-mediated cleavage triggered by low pH. Pathway use is dependent on the TMPRSS expression: in tissues with the high expression the early pathway is preferentially used, while if the protease is absent, late pathway is utilized. Efficacy of the viral entry is further facilitated by the human Furin, with its cleavage site within the spike protein strengthening the tropism for the airway epithelial cells. After cleavage, viral membranes fuse with the endosomal membrane which facilitates nucleocapsid entry into the cytoplasm [5]. In the cytoplasm the virus releases RNA which is transcribed by the viral RdRP polymerase followed by translation into viral proteins, including structural membrane (M), spike (S), and E. Viral particles are then assembled, packaged, and released by exocytosis. Viral replication results in a negative regulation of ACE2, which in turn leads to the degradation of angiotensin II, production of angiotensins 1–7 and activates the mas oncogene receptor, associated with the negative regulation of angiotensin II, mediated by the type 1 angiotensin II receptor (AT1R) [6, 7]. Activation of AT1R is one of the mechanisms ultimately leading to the acute lung damage. The mechanism of action of the SARS-CoV-2 virus in this context is highly similar to that seen in SARS-CoV [5] (Fig. 3.1).

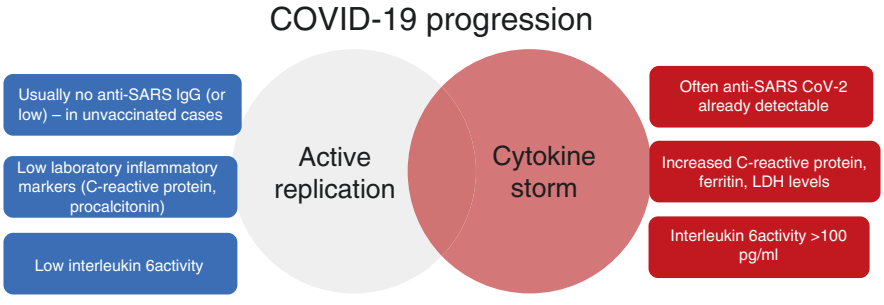

Fig. 3.1 Association between active replication and cytokine storm phase of the SARS CoV-2

Immunological Responses and Cytokine Storm (CS)

Infection with SARS-CoV-2 results in the secretion of large amounts of inflammatory cytokines and chemokines. High levels of IL-2 (interleukin), IL-7, IL-10, G-CSF (granulocyte colony-stimulating factor), TNF (tumor necrosis factor), CXCL10 (CXC-chemokine ligand 10), MCP1 (monocyte chemoattractant protein-1), and MIP1α (macrophage inflammatory protein 1 alpha) in serum were observed in patients with severe COVID-19 resulting in the hyperactivity of the host immune system [5]. Interstitial mononuclear lymphocyte-dominated inflammatory infiltrates in the lungs and severe lymphopenia with hyperactive T cells in the peripheral blood were all found in patients with COVID-19. At the cellular level, in patients with severe COVID-19, release of pro-inflammatory cytokines leads to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte anomalies [8].

COVID-19-associated cytokine storm (CS) is a unique form of a hyperinflammatory response which has been characterized in association with the SARS CoV-2 infection [5]. Cytokine storm, caused by the excessive secretion of cytokines, leads to a severe systemic inflammatory response [9]. In general, the onset of a cytokine storm resembles systemic inflammatory response syndrome (SIRS) with imbalance between pro-inflammatory and anti-inflammatory responses. By definition, the inflammatory response is designed to protect the host from damaging stimuli and is a mechanism necessary for recovery. However, an overactive inflammatory response, as in a cytokine storm syndrome, may cause widespread tissue damage and is directly linked to mortality [10]. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12 are produced *inter alia* by an array of immune cells such as B lymphocytes, T lymphocytes, macrophages, dendritic cells or monocytes [11] as a result of the increased expression and activation of TLR7 and TLR8 in lung tissue [12]. IL-6 is an activator of the JAK/STAT3 pathway during inflammation. Studies from 2020 showed that the IL-6-JAK-STAT3 pathway is strongly associated with the severity of COVID-19 symptoms. Cytokine storm is a characteristic of macrophage activation syndrome (MAS), but in SARS-CoV-2 infection, macrophage parameters differ between those found in classical MAS [2]. In COVID-19 patients, an increased activity of the monocyte activation markers sCD14 and sCD163 were observed [13] while monocytes strongly expressed the ACE2 receptor [14] and induced IL-6 expression, thus contributing to an increase in the severity of the cytokine storm.

Cytokine storm in COVID-19 patients is also associated with massive mononuclear cell infiltration in organs, thrombosis, and tissue hypoxia and leads to alveolar structural damage and lung ventilation dysfunction by damaging the lung capillary mucosa and by promoting alveolar edema [15, 16]. CS is largely responsible for multiple organ dysfunction syndrome (MODS) of which ARDS and/or SIRS are major components. Usually CS evolves in the later stages of infection, more than 5–7 days from the initial symptoms. As IL-6 and IL-1 are significant activators of CS and the inflammatory cascade, of these IL-6 levels have become a laboratory marker of CS [17].

The presence of comorbidities have significant impact on the disease course with the following comorbidities significantly increasing the severity of symptoms: hypertension, diabetes, cerebrovascular disease, cardiovascular diseases, respiratory disease, malignancy, chronic kidney disease, and chronic liver diseases. This is further elaborated in the Chapter 4.

Virus Variants and Associated Evolution in the Clinical Course

Evolution of the SARS-CoV-2 variants especially within the spike region is leading to increase of transmissibility and more effective evading the immune system. Evolution of SARS-CoV-2 has been monitored and assessed by WHO and other worldwide institutions since January 2020. Due to the increasing threat to global public health, new variants have been classified into groups, among which the most important from the current global public health perspective are Variants of Concern (VOCs) [18]. Variants of concern associate with the distinct phenotypic characteristics related to the disease severity, transmissibility, risk of reinfection, diagnostics, and vaccine performance. Well established VOCs, associated with pandemic waves include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) with BA subvariants. For example, Delta variant associated with the increased risk of severe infection requiring in-hospital treatment was less commonly associated with the loss of taste and smell if compared to the original Wuhan strains and augmented the probability of the fungal superinfections including mucormycosis. Number of critical care admissions was also significantly higher for the Alpha and Delta VoC compared to the infections in the early pandemics [19]. On the other hand, Omicron variant, despite increased transmissibility, associated with higher rate of asymptomatic infections [20].

In general, infection with the Omicron variant is expected to be milder than infection with earlier circulating variants, especially Delta, but some patients still develop severe disease requiring hospitalization and causing death [18]. Reports from South Africa show a reduction in the need for hospitalization by 29% among people infected with the Omicron variant, while the British reports show a reduction in the risk of any hospitalization and multi-day hospitalization by 20–25% and 40–45%, respectively, among unvaccinated people who did not have an infection before. SARS-CoV-2. People infected with the Omicron variant show symptoms similar to those caused by the previous variants, but their presence and severity are influenced not only by age, comorbidities, but also by a previous SARS-CoV-2 infection and vaccination [18].

Clinical Stages of COVID-19 [21]

Mild and Asymptomatic Stage

The clinical manifestations range from asymptomatic to life-threatening infection. Depending on the cohort, frequency of asymptomatic, mildly symptomatic or cases with short-term transient symptoms is between 25% and 50%. This data are supported by various metanalyses concluding that at least one-third of observed infections were asymptomatic. Serological cohort studies indicated that even >50% of cases might have been unaware of previous contact with the virus. The first data from China shown that most of the patients present with mild to moderate symptoms of the disease, and therefore, may be treated in an ambulatory setting. In asymptomatic or mildly symptomatic patients dyspnea is not usually present and blood oxygen saturation remains normal (SpO2) ≥95% in ambient air.

Symptomatic Stage

In this stage, patients have clinical and radiological signs of mild to moderate interstitial pneumonia with $SpO_2 < 94\%$ in ambient air. Some patients still develop fever, fatigue, and other extrapulmonary symptoms, as well as a dry cough and shortness of breath. In the UK, infections with the Omicron variant were associated with fewer lower respiratory symptoms compared to earlier variants. The most common reported symptoms in this group of hospitalized patients were: fever, cough, fatigue, sputum production, and shortness of breath.

Severe Disease

Severe disease with respiratory failure (dyspnea, respiratory rate greater than 30/min, $SpO_2 < 90\%$ in ambient air, and/or inflammatory lesions in the lungs covering more than 50% of lung fields within 24–48 h of symptom onset) and cytokine storm syndrome may develop in more than 15% of patients. Neurological symptoms affecting both the central and peripheral nervous systems are common among patients with severe infection. There have been reports of acute cerebrovascular disease (ischemic stroke, intracerebral hemorrhage, deep vein thrombosis), encephalitis, Guillain-Barre syndrome, visual disturbances, dizziness, disturbance of consciousness, ataxia, and convulsions. In addition, patients are at risk of psychiatric complications such as mood or psychotic disorders, anxiety, and insomnia. Currently, it is believed that cardiac involvement is more frequent than initially thought, and it also affects asymptomatic patients with mild and moderate COVID-19.

Acute Respiratory Distress Syndrome/Critical Stage

This stage is associated with critical condition that develops in approximately 5% of patients with respiratory failure, septic shock, and/or multiple organ dysfunction. In addition to acute kidney damage, the liver may experience cholecystitis, pancreatitis, intestinal obstruction, or mesenteric ischemia [22]. Cardiac arrhythmias, acute coronary syndrome, heart failure, myocarditis, and hemodynamic instability occur in more than 20% of patients admitted to the intensive care unit [23]. The risk of venous thromboembolism (VTE), including pulmonary embolism, in critically ill patients with COVID-19 was assessed as high at the start of the pandemic. The incidence of this complication among ICU patients was 31%. More recent studies have shown that the overall risk of VTE in patients with COVID-19, regardless of the severity of the disease, is lower (<1%), although it remains higher than in the general population [23]. Coexisting bacterial or fungal infections concern about 8% of patients and constitute one of the main causes of death, in addition to progression to acute respiratory distress syndrome (ARDS) and multiorgan failure. The most frequently isolated microorganisms are: Streptococcus pneumoniae, Klebsiella pneumoniae, Hemophilus influenzae, and Aspergillus fumigatus. Mucormycosis, first described in India, more often affects diabetic patients treated with glucocorticosteroids, tocilizumab, and undergoing mechanical ventilation [23].

Clinical Symptoms of COVID-19

General Symptoms in the Early, Asymptomatic and Mild Infection

Clinical symptoms evolved in time, which, as stated above, associated with the predominating COVID-19 variant in each pandemic wave. In the early studies the most common symptoms were cough, dyspnea, hyposmia, sputum production, and fever. With novel variants of concern symptoms evolved to predominant headaches, sinusitis or sore throat. For example, the most commonly reported symptoms of infection with the Omicron variant are cough, runny nose, sneezing, headache, fatigue, sore throat, and fever [2]. It should be also emphasized that other mild symptoms, namely shortness of breath, disseminated muscular aches, conjunctivitis, nausea, vomiting, abdominal pain, diarrhea well described in the previous pandemic waves remain to be commonly observed. However, the smell and taste abnormalities (anosmia and ageusia) are currently less common. There are also age-related differences in the symptom characteristics. For example, in pediatric cohorts the most common symptoms were fever, cough, nasal symptoms, diarrhea, and nausea/vomiting. On the other hand, elderly may present with confusion or delirium-like conditions, hypothermia, and body temperature decrease prior to respiratory symptoms [24].

Respiratory Manifestations

As the SARS-CoV-2 virus enters lungs cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which are abundantly expressed on the pneumocytes. This mechanism is well-studied with airway epithelial cells, including human alveolar type II cells being the major target for SARS-CoV-2 [4]. Other involved cellular compartments include vascular endothelium, as well as macrophages and monocytes. Viral tropism to the respiratory tract has evolved with the evolution of VoC, as described above. However, following fever, respiratory manifestations are the most prominent in patients affected by the symptomatic disease. Respiratory symptoms range from cough, dyspnea, increased sputum production, to interstitial pneumonia with acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure [25]. Severity of symptoms is resulting from the imbalance between epithelial cell involvement leading to their apoptosis, immune activation associated thrombosis, and neovascularization.

Early stage damage was associated with the microthrombi at the level of the microcirculation, alveolar type II cell hyperplasia, enlargement of interstitial capillaries, thickening of pulmonary venules, and no hyaline changes. On the other hand, in the late stages pneumonia associated with ARDS microangiopathy is present with angiogenesis, endothelial injury, and hyaline membrane formation and fibrin deposits associated with diffuse alveolar damage. Progression to ARDS is associated with altered pulmonary perfusion, hyperinflammation consistent with the cytokine storm features, and hypercoagulability. Furthermore, microcoagulopathy may progress to involvement of the larger vasculature, capillary congestion, and development of pulmonary thrombosis. Over time parenchymal consolidations evolve. Monocular cell and macrophage infiltrations are present in the interstitial space. As the pneumonia progresses, both bacterial and fungal superinfections may exacerbate the patient condition.

Pneumonia evolves in approx. 20% of COVID-19 cases with the most commonly observed bilateral interstitial lung infiltrates, often diffuse associated and associates with dyspnea, cough, and fatigue on presentation. COVID-19 pneumonia is combination of the three factors: inflammation, endothelial damage, and excessive clotting. Typically, pneumonia is observed after 5–7 days of the symptom onset, however, earlier and rapid evolution of this complication was also noted. Early pneumonia is affecting peripheral parts of the lung tissue and is most likely associated with direct cytotoxic effect of virus replication in the alveolar cells, while in the later disease stages it is related to the imbalance in the immunological responses and cytokine release. Cytokine storm syndrome is one of the factors related with late COVID-19 pneumonia and ARDS [15, 17]. The severity of hypoxemia, especially in the early pneumonia is often more severe if compared to the amount of the pulmonary tissue with inflammatory changes, which may associate with the alteration of pulmonary perfusion and imbalance in the ventilation/perfusion ratio [26].

ARDS is a severe complication, and it can also occur in the course of infections with other pathogens (bacteria, virus, fungus) with tropism for the respiratory tract,

or during sepsis, trauma, or aspiration. In ARDS caused by SARS-Cov-2, renin-angiotensin system imbalance plays a crucial role. It is difficult to estimate how many patients will develop serious complications like ARDS or respiratory failure since available data is inconsistent and should account for the variant variability. Early studies shown that ~33–50% of hospitalized cases develop ARDS, however, this percentage is largely dependent on the age and comorbidities. ARDS is undoubtedly a leading cause of COVID-19 associated mortality. Typically, oxygenation defect with PaO_2/FiO_2 ratio < 300 mmHg and increased dead space ventilation is observed. It is commonly concluded that the outcome of ARDS in the course of COVID-19 is commonly less favorable compared to other etiologies [26].

Radiologic imagining either chest X-ray or computed tomography are now widely implemented for the diagnosis of the COVID-19 pneumonia. Typically, bilateral, multifocal ground glass opacities are observed, most commonly located in the peripheral, posterior or basal parts of the lung [27]. Other described radiologic features include thin reticulation, peribronchovascular thickening, and dilatation. Unilateral changes were observed, especially in the early pneumonia before dissemination of lesions. Usually nodules, excavations or lymph tissue enlargement are not observed. Infrequently (<10%) consolidations or "inverse hello sign" as in organizing pneumonia is present. Obviously, if COVID-19 is overlapping the previous pulmonary disease with abnormalities in the lung tissue, radiological picture is less specific. Over time ground glass opacity may be evolving either to areas with crazy paving, where ground glass areas and intralobular reticulations superimpose, or consolidation areas (usually linear). In majority of cases maximum lung involvement is observed approximately 10 days from the onset of the disease symptoms with subsequent resolution. In mild disease complete resolution of lesions is expected, while more severe cases are associated with the prolonged radiological abnormalities, usually beyond 1–2 months. Fibrotic complications may evolve, however, exact proportion and risk are not entirely understood. Based on the percentage of the lung tissue involvement, the French Society of Thoracic Imaging (SIT) recommends grading lung involvement as absent or minimal (< 10%), moderate (10–25%), extensive (25–50%), severe (50–75%) or critical (>75%) [28].

Extra-Respiratory Manifestations

The presence of ACE2 receptors in extrapulmonary tissues and a tropism of SARS-CoV-2 to these receptors may lead to direct tissue and endothelial damage, dysregulation of local immune responses which commonly lead to a wide array of extra-respiratory disease manifestations. Main extra-respiratory manifestations among patients with COVID-19, included, but are not limited to cardiac, gastrointestinal, hepatic, renal, neurological, olfactory, gustatory, ocular, cutaneous, and hematological symptoms [29].

Hematologic Abnormalities

Lymphopenia may be associated with a severe disease course. The development of severe form of lymphopenia, a progressive decrease in lymphocytes, has been correlated with poor disease prognosis [30]. Lymphopenia may be induced by direct infection of SARS-CoV-2 T cells via the ACE2 receptor expressed on their surface and causing their lysis and/or by increased numbers of regulatory T cells (Treg). In COVID-19 patients, damage to lymphocytes, CD4+T cells and especially CD8+T cells has been observed, involving a reduction in the number of lymphocytes in the peripheral blood and subsequent apoptosis [31]. Lymphocyte apoptosis may be associated with hypercytokinemia that may cause disruption of lymphocyte-producing organs and with a depletion phenotype [32]. Differences in lymphocyte subsets are observed in COVID-19 both in mild to moderate and severe cases, with decrease in the lymphocyte CD4 and CD8 levels.

Lymphopenia and increased neutrophil counts correlated with an increased risk of developing ARDS in COVID-19 patients and an overall more severe disease course. Differences in neutrophil-lymphocyte ratio (NLR) in severe and non-severe patients are significant, with increased NLR in patients with severe COVID-19. A steady increase in neutrophil count, like a steady decrease in lymphocyte count, correlated with a poor prognosis among cases with COVID-19 [33].

Additionally, commonly observed hematologic abnormality include thrombocytopenia, either directly induced by the cytotoxic megakaryocyte effect of the virus or resulting from consumption during microthrombi formation. In majority of cases thrombocytopenia is sell limiting, however it has also been associated with decreased survival.

Prothrombotic Events

Another serious manifestations associated with COVID-19 are thromboembolic episodes, which may include both venous and arterial thromboembolic complications. Thromboembolic disorders remain one of the key and serious complications in COVID-19, due to interactions between inflammation, immunity, and coagulation system, especially during the cytokine storm, resulting in alveolitis, endotheliitis, complement activation, recruitment of immune cells, as well as immunothrombosis. SARS-CoV-2 is also associated with hypercoagulation resulting from the array of disfunctions, including inhibition of the plasminogen and complement activation, platelet disfunction, hyperimmune response or production of antiphospholipid, and antiplatelet antibodies [34]. Thrombosis may be initiated in the pulmonary vasculature, commonly resulting in the microangiopathy. Endothelial damage and subsequent coagulopathy are causative factors of the progression to severe manifestation including disseminated intravascular coagulation and multiple organ failures.

Initial studies found that thrombotic events occurred in 7.7% of patients, despite thromboprophylaxis [35]. Further data reported the incidence of the thromboembolic events to exceed 30%, especially among patients requiring mechanical ventilation. The most common presentation is the venous thrombosis, with key manifestation being pulmonary embolism (PE). Meta-analyses indicate a two-fold increased risk of death in COVID-19 patients who developed a venous thrombotic event. A plethora of studies and analyses have already confirmed a correlation between COVID-19 and the risk of thrombosis disclosing prothrombotic activity of this viral infection. For example, a large meta-analysis reported that pulmonary embolism (PE) and deep vein thrombosis (DVT) were observed in 16.5% and 14.8% of COVID-19 patients, respectively, while in more than half of the patients with PE no DVT was observed [36]. Extremely important complication is disseminated intravascular coagulation (DIC), observed in 4.3%–6.2% of COVID-19 patients, characterized by 26.2 times higher incidence of death. Thrombotic complications associated with increased D-dimer levels reported in significant proportion of patients. Increase in D-dimer levels correlated with the risk of death. Activation of an array of coagulation factors is also commonly observed, and includes increase in plasminogen activator inhibitor 1, factor VIII or von Willebrand factor levels. Fibrinogen levels may also increase and associate with disease progression. Hemostatic abnormalities related to COVID-19 may range from mild to moderate (usually with only 2–3 fold D-dimer increase), medium (D-dimer levels up to six-fold upper normal range, thrombocytopenia, mild prolongation of prothrombin time), and severe with venous thromboembolism, multiorgan failure, and features of organ ischemia. Further details on the thromboembolic events and pulmonary embolism are covered in dedicated book Chap. 12.

Cardiovascular Involvement

Cardiovascular complications of both acute SARS CoV-2 infection and post-COVID-19 may include myocardial injury, acute coronary syndrome, acute vascular injuries, myocarditis, heart failure, cardiomyopathy, arrythmias, as well as cardiovascular complications. All these are covered in details in the dedicated book Chaps. 6 and 7.

Neurological and Neuropsychiatric Manifestations

Neurological and psychiatric symptoms have been described as one of the key clinical features impacting COVID-19 [37, 38]. These are not only associated with the neurological complications following intensive care unit care but may also be linked to the viral and immunologic effects of the infection per se. Involvement of the central nervous system related to the possible expression of viral proteins and its

inflammatory and proapoptotic properties resulting in local inflammation and delayed synaptic signaling has been observed. Furthermore, the involvement of both astrocytes and neurons is associated to the ACE-2 expression on these cells which may relate to the neuropsychiatric symptoms, however, cytokine release and coagulation abnormalities may also significantly contribute.

COVID-19 neurological and neuropsychiatric manifestations are diverse [39], which may range from mild-to-moderate symptoms such as headache and dizziness (more commonly observed with Omicron variant), psychomotor deceleration, memory impairment (including "brain fog," associated with mild to moderate disease), anosmia, ataxia, speech disorders, neuralgia and to medium and severe complications such as neuropathic pain, muscular paresis and paralysis, epileptic seizures, and coma. Cognitive impairments, including personality changes, aggressive behavior, confusion have been observed, exacerbate with age and associate with hypoxia, and kidney disfunction. Features of encephalopathy associated with increased mortality. Inflammatory disorders include mainly encephalitis (demyelinating and limbic), encephalomyelitis, but not meningitis (no inflammatory changes in the cerebrospinal fluid). Peripheral nervous system disorders, though not common may include acute polyneuropathies Guillain–Barré syndrome and Miller–Fisher syndrome) and neuralgias, myalgias, polyneuritis, as well as myopathies [40]. Generalized weakness and fatigue are often observed for prolonged periods of time regardless the severity of the COVID-19. As mentioned before depending on the viral variant and cellular tropism divergent frequencies and severity of the smell and taste disorders have been reported, ranging from the partial to complete loss of smell and taste (infrequently long-term). The exact pathomechanism and reason for the variant related frequency differences remains unclear.

Moreover, from a clinical perspective, vascular disorders (cerebral ischemia, thromboembolic events of the cerebral vasculature, and cerebral bleeding) are one of the most common neurological manifestation of the disease – see relevant Chap. 8.

Psychiatric complications of the disease also remain common and are usually secondary to the disease itself. Wide array of psychiatric disfunctions and disturbances were observed, from depressive and mood disorders, insomnia, and anxiety. Features of post-traumatic stress disorders were also common, resulting both from infection itself, but also from the in-hospital experiences of closure, experience of dyspnea, or personal observations of the exacerbating condition of the fellow intreated patients. Psychotic disorders including suicidal tendencies were also reported [41].

Kidney Involvement

Effectively, ACE2 is expressed in the kidney stronger than in the lungs, however, acute kidney injury with the eGFR decrease (increase in serum creatinine levels), hematuria, and proteinuria has been reported with variable frequencies. Kidney

injury was more frequent in elderly, associated with previous kidney disease, hypertension or diabetes. Exacerbation of the chronic kidney injury is moderate to severe COVID-19 cases is common [42].

The virus may enter the kidney by invading podocytes subsequently involving the ACE2 in the proximal tubule [43]. Interestingly, SARS-CoV-2 infection both prevents ACE2 from attaching to the receptor and alternates ACE2 expression within the proximal tubular cells, especially in the areas of acute tubular injury. Accumulation of the AGII protein, not converted to AG1–7, promotes inflammation by increasing cytokine release and allows macrophage and monocyte infiltration. Kidney injury associated with COVID-19 is either indirect and associates with the multiorgan failure or directly induced by the cytotoxic effect of SARS-CoV-2 in the kidneys. The primary findings in renal biopsies were acute tubular injury and epithelial necrosis, but SARS-CoV-2 infection may exacerbate preexisting kidney conditions, such as lupus nephritis or membranous glomerulopathy. Pathophysiology of COVID-19-related acute kidney injury is related to hemodynamic and immunologic effects of the infection, with elevated CRP and Il-6, D-dimer, and fibrinogen being key laboratory markers associated with such injury. The pathological changes in kidney during COVID-19-associated AKI include tubulointerstitial, glomerular, and vascular damage. The kidney picture presents with diffuse proximal tubule injury with loss of the brush border and necrosis accompanied by vacuolar degeneration and tubulointerstitial fibrosis. In the interstitial compartment, inflammatory cell forms infiltrate, and edema can be seen. In the case of severe kidney injury, the basement membrane is the only barrier between the filtrate and the peritubular interstitium. Because of the increased endothelial permeability, glomerular filtrate leaks from the tubular lumen into the interstitium. In the glomeruli the diffuse and focal segmental fibrin thrombus in the glomerular capillary loops and endothelial injury were observed. In the case of collapsing glomerulopathy, glomerular epithelial damage occurs together with loss of podocytes integrity. Glomerular capillaries are segmental or globally collapsed and sclerotic, with hyperplasia and hypertrophy of the glomerular epithelium. Some cases present with diffuse erythrocyte stagnation in the glomerular capillary or glomerular loop occlusion by erythrocytes over peritubular capillaries [44]. On the vascular level, the picture of COVID-19 associated kidney injury demonstrates vasoconstriction of intrarenal vessels, increased vascular permeability, and microthrombi formation. Vascular endothelium damage occurs, which can be observed as swelling of endothelial cells. The leukocyte–endothelium interactions are enhanced, leading to leukocyte migration into the interstitium.

Gastrointestinal and Hepatic Involvement

COVID-19 gastrointestinal symptoms are commonly underreported and range from mild and transient nausea, abdominal discomfort and pain, loss of appetite but also diarrhea. ACE-2 expression in the gut, including enterocytes and the array of

epithelial cells, including gastric duodenal and rectal ones is extensive and associated with wide array of gastrointestinal functions, namely regulating intestinal amino acid homeostasis, modulating the intestinal microbiome, and influencing the expression of antimicrobial peptides [45]. This results in the high prevalence of intestinal abnormalities during SARS CoV-2 infection resulting both from immunologic imbalance and direct viral cytotoxic effect. In total approx. 20% of patients may report gastrointestinal symptoms of the disease. Patients with COVID-19 may present with decreased levels of probiotic bacteria, such as Lactobacillus and Bifidobacterium, in the gut. Fecal genomes SARS-CoV-2 patients are characterized by the abundance of opportunistic pathogens (*Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*), which may affect the immune system both locally and systemically [46].

Further to gastrointestinal symptoms, abnormality of the liver function tests reflective of the liver injury, was commonly observed among patients with COVID-19. The most common is laboratory abnormality observed in this context is alanine aminotransferase activity increase, followed by elevations in a aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase and hypoalbuminemia. ACE-2 receptors in the liver are mainly expressed on cholangiocytes (bile duct cells), minimally expressed on hepatocytes and absent on Kupffer cells [47]. The mechanism of liver damage may be directly associated with the viral infection of liver cells or is secondary to coexisting conditions such as the use of potentially hepatotoxic drugs, systemic inflammatory response, disseminated intravascular coagulation (DIC), respiratory distress syndrome-induced hypoxia, and multiple organ dysfunction [48]. Preexisting liver disease including non-alcoholic fatty liver, strongly associate with liver injury during COVID-19.

Skin Associated COVID-19 Symptoms

An increasing number of reports describe the cutaneous manifestations of COVID-19 that often precede common respiratory symptoms. Skin lesions may vary from benign maculopapular rash to tissue necrosis [49, 50]. Skin lesions in the course of COVID-19 infection vary based on the virus variant and geographic location, ranging from 0.2% in China to 7.25% in India and 20.4% in Italy. Morphology of symptoms also varied geographically—symptoms of pseudo-frostbite (pseudo-chilblains) were most common in Europe and North America, while very rare in Asian countries [51, 52].

Skin lesions may be divided into five categories, based on the frequency and severity [53]:

1. Pseudo-chilblains lesions most often present as erythematous or purple papules on acral surfaces. Some reports also include vesicles or papules on the erythematous basis. The picture of these changes corresponds to frostbite, but is not accompanied by previous exposure to cold or other damaging factors. The

occurrence of these skin lesions was more often observed in young people, and was associated with late COVID-19 with high survival rate of >98%.
2. Urticarial lesions, most often with transient papules, most common among middle-aged women. In majority of cases lesions disappeared within 24 h.
3. Erythematous and maculopapular rash, mainly involving the trunk, accompanied by itching. These changes affect women slightly more than men.
4. Vesicular lesions, most often affecting the trunk but with variable morphology. Most often, these are vesicular lesions resembling chickenpox and other manifestations of VZV (Varicella-Zoster Virus) infection. These changes most often appear in patients at the onset of the infection.
5. Vascular occlusive lesions, lesions often resembling livedo reticularis (irregular purple reticular lesions, most often in concentric, circular forms), reticular purpura, and acral ischemia (ischemic lesions on distant parts of the body—mainly fingers and toes). Vascular occlusive lesions are the rarest but have the lowest survival rates >78%.

Some patients may have other skin lesions such as: non-necrotic or necrotic purpura, petechiae, cutaneous mottling, eruptive cherry angioma, violaceous macules, aphthous ulcers, purpuric exanthema or telogen effluvium. Those changes may occur in less than 5% of patients [54].

In children there were noted some cases of Kawasaki-like changes connected to COVID-19 infections.

COVID-19 in Children

SARS-CoV-2 infection in children is usually asymptomatic or has mild symptoms. Life-threatening disease and death from COVID-19 are rare. Only 0.1–1.5% of all COVID-19 cases in children require in-hospital treatment and 0.00–0.02% of all child COVID-19 cases resulted in death [55]. The severe course of the disease is associated with comorbidities. The main risk factors include the coexisting chronic respiratory diseases, neurological diseases, congenital genetic defects, cardiovascular diseases (especially heart defects), metabolic disorders (especially diabetes and obesity with a body mass index [BMI] above the 95th percentile for age) and conditions associated with immunosuppression [56].

The symptoms of infection in children and adults are similar, but differ in terms of frequency. Asymptomatic infections in children with documented SARS-CoV-2 infection fluctuate between 15% and 42%. The most common symptoms of COVID-19 are fever, cough, often productive, and sore throat [56]. Dyspnea in the course of pneumonia is closely related to the development of severe or critical symptoms of the disease, in particular, acute respiratory distress syndrome. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea may occur in up to 25% of cases, and lead to reduction in fluid and solid intake [57]. Less common and atypical symptoms among children include chest pain, loss of taste or smell,

changes in the skin (such as discolored areas on the feet and hands), abdominal pain, chills, muscle aches and pain, fatigue, headache, and nasal congestion. In infants and newborns, feeding difficulties are a frequent additional symptom. Symptoms and signs are almost never isolated in children with COVID-19.

Multisystem inflammatory syndrome is a rare but serious complication of COVID-19 in children. This disease is known in Europe as pediatric inflammatory multisystem syndrome (PIMS) and in America as multisystem inflammatory syndrome in children (MIS-C). Patients diagnosed with MIS-C had persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous changes, and in severe cases, hypotension and shock [58]. Some patients may develop symptoms related to myocarditis, cardiac dysfunction, and acute kidney damage.

Long COVID-19

Following COVID-19 infection and array of symptoms may be observed, ranging from psychiatric, neurological, general, cardiac to vascular. Issue is extensively discussed in the relevant Chaps. 22–24 of the book.

Conclusions

As described above, SARS CoV-2 and resulting COVID-19 is associated with the wide array of clinical symptoms, including virtually all vital tissues—basically any tissue where the ACE-2 is expressed. Symptoms result from the direct cytotoxic effect of the virus and immune response associated cytokine storm, as well as vascular involvement and drug induced complications. Furthermore, frequency and pattern of the observed symptoms vary and evolve over time begin largely dependent on the virus variant and its molecular variability but also on the vaccination history. It is expected, that over time pattern, severity and sequence of symptoms may change, as virus will evolve further.

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Chapter 4
Risk Factors of Developing COVID-19 and its Severe Course

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COVID-19 and Related Cardiovascular Risk Factors

Since the beginning of the pandemic several studies have aimed to identify determinants of a higher risk of developing COVID-19 and its severe course [1–3] among a large spectrum of demographic factors and medical conditions. Noteworthy, the utmost attention has been given to risk factors and markers of cardiovascular (CV) disease. Indeed, a high prevalence of clinical conditions associated with increased risk of CV disease has progressively emerged among COVID-19 patients, suggesting their putative association with the risk of developing COVID-19 [4, 5]. In addition, a high incidence of life-threatening CV complications (e.g., myocardial injury, arrhythmias, acute coronary syndrome, and venous thromboembolism) during the clinical course of COVID-19 has risen from early reports [6, 7], suggesting a potential pathophysiological role of CV disease-related comorbidities in precipitating the evolution of SARS-CoV-2 infection towards its most severe forms as well as a possible preventive/therapeutic activity against COVID-19 linked to drugs targeting CV disease risk [8, 9].

Regarding a possible increased susceptibility to SARS-CoV-2 infection in subjects exposed to different risk factors and markers of CV disease, there is no convincing evidence. Instead, it has emerged compelling evidence showing that different CV disease-related clinical factors are associated with an increased risk of COVID-19 severity and mortality [5, 10, 11]. Also, it has been reported that the risk of worse COVID-19 prognosis increases sharply with the increasing number of concomitant demographic and medical conditions associated with increased risk of CV disease [4, 11].

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Among non-modifiable CV risk factors, old age and male sex have been extensively identified as determinants of a higher risk of severe COVID-19 and COVID-19-related death. Instead, among modifiable CV disease-related conditions, smoking, diabetes, obesity, hypertension, dyslipidemia, and chronic kidney disease (CKD) have shown a variable association with COVID-19 outcomes. Indeed, while the impact of smoking on the clinical course of COVID-19 has been inconsistently described, the existence of an independent association between either hypertension, obesity, dyslipidemia, or diabetes, on the one hand, and COVID-19 prognosis, on the other hand, seems reliable.

From a pathophysiological perspective, mechanisms underlying the independent association between the exposure to these factors and adverse outcomes of COVID-19, are only partially understood and remain mainly speculative. Noteworthy, a bidirectional relationship between hyperglycemia, CKD, and alterations of lipid metabolism, on the one hand, and severe COVID-19, on the other hand, appears plausible. Indeed, these conditions not only seem to negatively impact on COVID-19 clinical evolution towards increasing severity, but they also seem to be exacerbated by uncontrolled infection, thereby potentially fueling a vicious circle leading to worse COVID-19 outcomes.

Beyond clinical conditions, also different laboratory and instrumental surrogate markers of increased CV disease risk have been extensively evaluated as possible determinants of COVID-19-prognosis.

This chapter will discuss the available evidence on the relationship between different markers and risk factors of CV disease (i.e., age, sex, smoking, diabetes, obesity, hypertension, dyslipidemia, CKD, and some laboratory and instrumental parameters) and either the risk of getting COVID-19 or COVID-19 prognosis. Also, it will summarize current knowledge on the possible pathophysiological mechanisms explaining this relationship and the potential preventive/therapeutic role against COVID-19 of strategies aimed at controlling CV disease risk.

Age

Several epidemiological studies have shown an age-dependent susceptibility to severe COVID-19, with younger individuals manifesting more likely mild-moderate disease and older individuals being more susceptible to severe disease [12–14]. In a large meta-analysis of 31.864 COVID-19 cases from thirteen European countries, as of April 2020, patients <40–50 years old were a small fraction of the most severe COVID-19 cases [5.4% of intensive care unit (ICU) admissions], whereas those ≥60–70 years were the largest fraction (41.8% of ICU admissions) [15]. Consistently, more recent studies have shown higher severity and worse clinical features of COVID-19 with increasing age [16]. In addition, higher mortality rates have been extensively reported in older age groups as compared to younger ones, with some studies having shown exponential patterns of age-dependent COVID-19-related death for the ages >50 years [17–19].

Overall, the reason of the higher proportion of severe cases and fatal outcomes of COVID-19 in older age groups seems attributable both to the aging process itself, leading to a progressive reduction of lung performance and dysregulation of immune function, and to the increasing prevalence of frailty (i.e., a state of increased vulnerability due to cumulative decline in multiple physiological systems) and concomitant medical conditions, that may contribute to impair the functional reserve of the elderly against infections.

Regarding a possible direct impact of older age on COVID-19 clinical course, there is evidence showing that the aging process is associated with significant structural and functional changes in the respiratory system. Indeed, previous studies have reported a significant decline of respiratory muscle strength, alterations in the alveolar–capillary interface and decreased ventilatory responses to hypoxemia in elderly patients as compared to younger individual, which may contribute to explain the higher risk of worse respiratory symptoms and ICU admission in elderly patients with COVID-19 [20]. Moreover, both innate and adaptative immune response against SARS-CoV-2 may be impaired in older age groups [21]. Specifically, there is evidence showing that the expression of angiotensin-converting enzyme 2 (ACE2), the recognition receptor of SARS-CoV-2, decreases in multiple organs, including lungs, with aging. This may imply a heightened systemic pro-inflammatory response in advanced age groups during COVID-19, which may ultimately lead to more severe disease phenotypes. Indeed, ACE2 converts angiotensin II (Ang II, an inflammatory mediator) to angiotensin 1–7 (Ang 1–7, an anti-inflammatory mediator) and the ACE2-Ang 1–7 anti-inflammatory pathway has been previously reported to be protective against severe acute respiratory distress syndrome (ARDS) [21]. Moreover, aging is associated with a higher prevalence of T-cell immunity dysregulation (e.g., reduced cytokine production and/or cytotoxicity ability of T cells), potentially leading to a reduced SARS-CoV-2 clearance during the acute stages of infection [21]. Also, with aging process B cells display a diminished potential to undergo somatic hypermutation and to generate robust neutralizing antibody titers, which may compromise the resolution of SARS-CoV-2 infection [21].

In line with the hypothesis that the impact of age on COVID-19 outcomes may be also attributable to concurrent frailty and comorbidities, in a large population study (410.199 United Kingdom Biobank participants aged 49–86 years), two frailty and comorbidity measures, namely the Hospital Frailty Risk Score (HFRS) and the Charlson Comorbidity Index (CCI), were reported to significantly improve the predictive ability of demographic variables (i.e., age and sex) towards COVID-19 mortality [22]. However, in the same study, analyses stratified by age showed a weaker association between HFRS and COVID-19 mortality among older-old individuals ($\geq$75 years) as compared to younger-old (<65 years), suggesting that the predictive ability of frailty towards COVID-19 prognosis in the elderly may be greater at younger ages [22].

Overall, there is no convincing evidence on a possible greater susceptibility of older people to get SARS-CoV-2 infection. It has been suggested that very elderly patients (over 80 years old) living in long-stay residential care homes may be at increased risk of resulting positive to SARS-CoV-2 [23]. However, this may be

likely due to possible difficulties in providing patients adequate information and personal protective equipment as well as in employing adequate measures of isolation in this care setting [23]. The biological substrate of a higher predisposition of the elderly to contract SARS-CoV-2 infection needs to be demonstrated.

As to whether some specific therapies should be reserved for the treatment of SARS-CoV-2 infection in the elderly remains elusive. In this regard, some studies are ongoing to evaluate the efficacy and safety of the so-called senolytic drugs, that is anti-aging agents with the potential ability to attenuate age-dependent dysregulation of inflammatory and immune response, as possible adjunctive treatments against COVID-19 [24]. However, currently there is not clear evidence supporting the utility of differentiating the cornerstone of COVID-19 therapy between the older and younger age groups.

Sex

Despite some inconsistency, since early epidemiological reports sex-disaggregated data on SARS-CoV-2 infection have shown approximately equal cases between men and women worldwide [25–27]. However, male sex has progressively emerged as a determinant of increased COVID-19 severity and mortality [27, 28]. Thus, as of 10 February 2022, the COVID-19 Sex-Disaggregated Data Tracker shows that for every ten female hospitalizations, ten ICU admissions, and ten deaths due to COVID-19 there are 12 male hospitalizations, 17 male ICU admissions, and 13 male deaths due to COVID-19, respectively [29].

The mechanisms underlying such differences in clinical manifestations and outcomes of COVID-19 between males and females are not completely elucidated; however, different plausible hypotheses have been posed, considering both sex-related (biological) and gender-related (sociocultural) factors [30, 31].

Regarding the possibility that sex-related factors may explain the gap in COVID-19 prognosis between males and females, there is evidence showing that both hormonal and genetic differences between sexes may play a crucial role in the pathophysiology of COVID-19, by regulating crucial steps of SARS-CoV-2 cell cycle as well as the host innate and adaptive immune response against infection [30, 31]. Particularly, estrogens have been shown to upregulate the expression of ACE2, which may have a role in contrasting the inflammatory response and protecting against ARDS [32]. Also, higher estrogen levels have been associated with a reduced release of pro-inflammatory cytokines, an increased CD4+ and CD8+ T cell activation as well as an enhanced B cell function, which may be crucial to limit organ damage and to improve immune response against SARS-CoV-2 infection [32]. By contrast, testosterone may display an immunosuppressive activity, which may impair the resolution of SARS-CoV-2 infection [33]. Furthermore, several genes encoding for immune mediators are on the X chromosome and have a biallelic expression in females; this may contribute to explain more robust immune responses against SARS-CoV-2 in females as compared to males [32]. Finally, higher

estrogens levels may limit COVID-19-related multi-organ dysfunction by increasing nitric oxide (NO) production and contrasting endothelial dysfunction, which has emerged as a possible pathophysiological step of COVID-19 evolution towards its most severe forms [32, 34, 35].

The hypothesis that gender-related factors may contribute to explain disparities in COVID-19 outcomes between males and females is highly plausible, as well. Thus, for instance, some unhealthy social behaviors with a higher prevalence in males versus females (e.g., smoking and delayed access to health care services) may contribute to interpret the gap between males and females in the prevalence of COVID-19 adverse outcomes [36–38]. In addition, the same social unhealthy behaviors may cluster with some non-communicable comorbidities (e.g., uncontrolled CV risk factors) which may contribute to make men more vulnerable to COVID-19 [36–38].

Interestingly, preliminary evidence shows that an imbalance between male and female sex may also characterize the long-term persistence of symptoms following the initial acute stage of COVID-19, that is the so-called "long COVID-19". Thus, for instance, in a large prospective observational study enrolling 4.182 patients with previous COVID-19, the incidence of long COVID-19 was significantly higher in women than in men (14.9% versus 9.5%) [39]. In this case, the reasons of sexual dimorphism remain substantially unclear and need further clarification. The higher female prevalence of a pre-existing asthma condition, which has been reported to be associated with an increased risk of long COVID-19, could be one of the possible explanations. However, it cannot be excluded that also gender-related factors may be implicated [39].

As to whether there may be disparities between sexes also in the efficacy and safety of preventive and therapeutic treatments against COVID-19, is uncertain. Overall, based on previous reports showing sex-related differences in pharmacokinetics of different drugs and risk of adverse drug reactions, it is safe to speculate that there may be inequalities between males and females in the effects of different drugs against COVID-19 [32]. However, the paucity of sex-disaggregated data from clinical trials on the efficacy and safety of these treatments creates a major lack of knowledge on this topic. Currently, some piece of information is available showing a possible sex imbalance in the pharmacological effects of remdesivir, which has been associated with a slightly higher recovery rate in females than males, and nanoparticle-based vaccines against COVID-19, which seem to display a slightly better efficacy in males than in females [32]. Nonetheless, a better understanding of possible sex-specific differences in pharmacological treatment and prevention of COVID-19 is warranted.

Smoking

The impact of smoking habit on the risk of SARS-CoV-2 infection is controversial. Preliminary reports have reported a lower prevalence of smoking status among COVID-19 patients as compared to the general population, suggesting a lower

susceptibility to SARS-CoV-2 infection among smokers as compared to non-smokers [40]. This piece of evidence has initially led to hypothesize a sort of "smoking paradox" according to which a protection against SARS-CoV-2 infection would derive from nicotine or other chemicals inhaled with smoking [40]. However, the implausibility of a possible protective effect of smoking against becoming infected with SARS-CoV-2 has been pointed out by different lines of evidence: (1) the proven association between smoking and a higher vulnerability to infections in general; (2) the possible methodological flaws of epidemiological studies showing an inverse relationship between smoking and SARS-CoV-2 infection (e.g., underrepresentation of smokers due to incompleteness of data collection or misclassification bias); and (3) the absence of evidence on a pathophysiological link between smoking and lower risk of SARS-CoV-2 infection [41].

Overall, despite some inconsistency most of available literature data show a significant association between smoking habit and worse COVID-19 prognosis. Indeed, although some preliminary reports have not reported any significant association between smoking and the risk of COVID-19 progressing towards severe disease [42], several observational studies and meta-analyses of observational studies have recently described an increased risk of adverse outcomes of COVID-19 in either current smokers or ever smokers (with history of smoking or current smoking) as compared to non-smokers [43–47]. In addition, further supporting the close link between smoking and worse COVID-19 prognosis, a large-scale Mendelian randomization study on the United Kingdom Biobank cohort (421.469 eligible participants, 1.649 confirmed infections, 968 COVID-19-related hospitalizations and 444 COVID-19-related deaths), showed that both genetically predicted propensity to initiate smoking and genetically predicted smoking heaviness (number of cigarettes smoked per day) were significantly associated with higher risk of COVID-19-related hospitalization and COVID-19-related death [48]. In line with this evidence, suggesting a direct and detrimental impact of smoking on COVID-19 prognosis, several biological mechanisms may explain the higher smokers' susceptibility to severe clinical manifestations of SARS-CoV-2 infection [40]. First, chronic smoking may induce mechanical and structural changes in the respiratory tract, which may significantly alter pulmonary function and lead to a higher need of ventilatory support in smokers with COVID-19 [40]. Second, different toxic constituents of inhaled smoking may activate a chronic pro-inflammatory status at the airway level, which may exacerbate the release of inflammatory mediators upon SARS-CoV-2 infection and facilitate COVID-19 clinical evolution towards more severe forms [40]. Third, nicotin and other smoking products may induce immunosuppressive effects, potentially impairing SARS-CoV-2 clearance [40].

Noteworthy, there is also evidence showing that concomitant clinical variables may interact with the association between smoking and COVID-19. Thus, for instance, in different studies age has been demonstrated to significantly influence the effect of smoking on COVID-19 severity, with younger smokers having resulted more vulnerable than older smokers [43, 49].

Currently, as to whether the impact on COVID-19 prognosis may diverge between tobacco smoking and e-cigarette smoking remains elusive. According to

some preclinical data, it is likely that the susceptibility to the most severe manifestations of COVID-19 may not differ between them. Indeed, both tobacco cigarette and e-cigarette smoking are known to expose individuals to nicotine and other harmful chemicals which may promote different biological processes resulting in increased lung inflammation and injury [50]. Also, there is evidence suggesting that e-cigarette smokers may experience COVID-19-related symptoms with higher frequency than age- and sex-matched controls [51]. However, studies specifically addressing the impact of e-cigarette smoking on COVID-19 outcomes are not available.

According to previous reports suggesting a possible protective effect of nicotine uptake with smoking towards SARS-CoV-2 infection, the nicotinic acetylcholine receptor (nAChR) has been proposed as a possible pharmacological target against COVID-19. However, the role of the nicotin-nAChR axis activation in the prevention and treatment of COVID-19 is currently not supported by available studies.

Diabetes

Diabetes has emerged as one of the commonest comorbidities in patients with SARS-CoV-2 infection [52, 53]. However, there is no compelling evidence showing a significant association between diabetes and risk of COVID-19 [52, 53]. Instead, a significant and independent association has been described between diabetes and the risk of severe COVID-19 [53, 54]. In addition, several studies have shown a 2- to three-fold higher risk of COVID-19-related death in patients with diabetes [54, 55]. Noteworthy, although preliminary studies reporting a significant impact of diabetes on COVID-19 prognosis either enrolled patients with type 2 diabetes or did not specify the type of diabetes, more recent evidence shows an increased risk of adverse outcomes of COVID-19 (i.e., COVID-19-related mortality, ICU admission and hospitalization) also in patients with type 1 diabetes [56].

Interestingly, different studies suggest that in the context of diabetes, which is a complex and heterogeneous disease, different phenotypes (e.g., controlled versus uncontrolled diabetes, associated versus not associated with other CV risk factors and related comorbidities) may variably impact on COVID-19 prognosis. In this regard, higher glucose and Hb1Ac levels before hospitalization have been associated with worse in-hospital outcomes of COVID-19 [57–59]. In addition, it has been reported that individuals with a more severe course of diabetes (as depicted by chronic insulin use and concomitance of different comorbidities, including CV disease, CKD, and chronic obstructive pulmonary disease), have a poorer prognosis of COVID-19 compared with individuals with a milder course of disease [56].

Overall, different pathophysiological mechanisms may explain the independent association between diabetes and severe COVID-19 (Fig. 4.1). First, patients with diabetes are in a chronic inflammatory state with elevated pro-inflammatory cytokine levels; this condition may contribute to a higher risk of COVID-19 progression towards severe disease by exacerbating the inflammatory response, on the one hand, and by decreasing T cell and B cell-mediated adaptative immunity, on the other hand

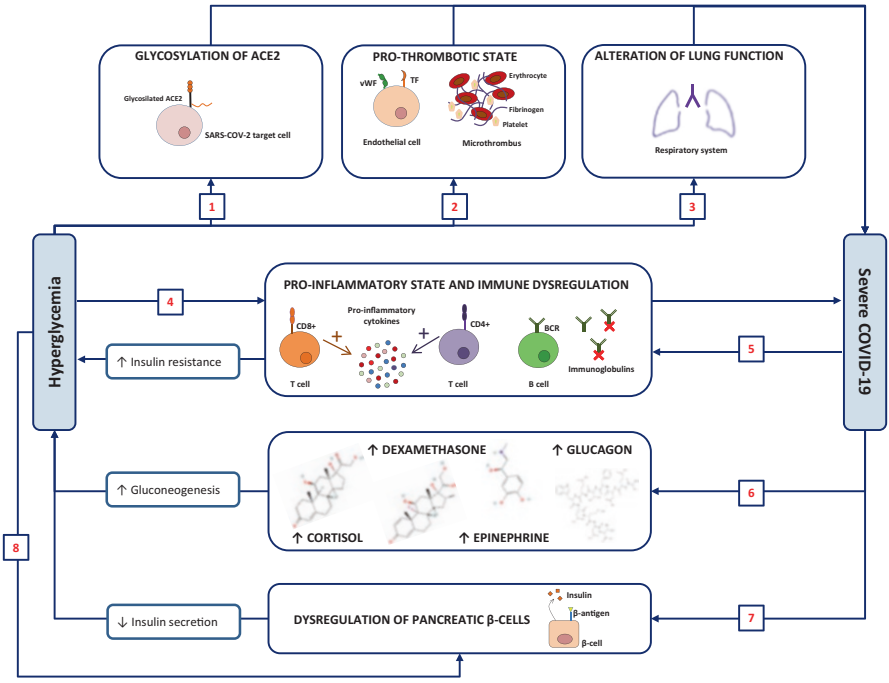

Fig. 4.1 Potential pathophysiological mechanisms explaining the bidirectional association between hyperglycemia and severe COVID-19. Hyperglycemia may promote COVID-19 severity by inducing glycosylation of ACE2 (1), a prothrombotic state (2), alterations of lung function (3), and a pro-inflammatory state associated with immune dysregulation (4). In turn, severe COVID-19 may promote hyperglycemia by inducing increased insulin resistance through worsening pro-inflammatory state and immune dysregulation (5), increasing gluconeogenesis through a higher release of glucagon, epinephrin and cortisol, as well as through dexamethasone therapy (6), and reducing insulin secretion through the dysregulation of pancreatic β-cell function (7). Hyperglycemia may further worsen dysregulation of pancreatic β-cell function (8). *ACE2* angiotensin-converting enzyme 2, *BCR* B cell receptor, *TF* tissue factor, vWF Von Willebrand factor

[52]. Second, poor glycemic control may increase the expression of glycosylated ACE2 on SARS-CoV-2 target cells, whose activation may contribute to dysregulate immune response against the infection [52]. Third, diabetes may be associated with a hypercoagulable state leading to an increased risk of thromboembolic events, which can add to a higher risk of death in the case of COVID-19 [52]. Fourth, chronic uncontrolled hyperglycemia may progressively induce structural changes to the lungs possibly affecting pulmonary function [52]; accordingly, diabetic patients with COVID-19 may be at higher risk of severe respiratory manifestations.

Interestingly, compelling evidence shows that diabetic patients with severe COVID-19 may manifest a worsening of pre-infection glycemic control [60]. As a hypothetical explanation of this finding, it may be hypothesized a bidirectional link between diabetes and severe COVID-19, in which dysregulated glucose metabolism may impact on COVID-19 prognosis, but also severe COVID-19 may unfavorably

impact on glycemic control. According to this hypothesis, both hyperinflammation associated with severe COVID-19 and steroid therapy, which is the cornerstone of medical therapy in patients with severe COVID-19, might increase peripheral insulin resistance, thereby inducing hyperglycemia [60]. In addition, stress hyperglycemia, a clinical feature of acute diseases due to the massive release of hormones stimulating gluconeogenesis (i.e., cortisol, epinephrine, and glucagon), might play a role in increasing serum glucose levels in patients with severe COVID-19 [60]. Furthermore, there is evidence pointing to the possibility of SARS-CoV-2 infecting pancreatic β-cells, thereby having a direct effect on glucose dysregulation by impairing insulin secretion [60]. Overall, hyperglycemia resulting from all the aforementioned mechanisms might lead to glucose-mediated toxicity of β-cells, thereby further decreasing insulin secretion and triggering a vicious circle with a detrimental impact on COVID-19 prognosis in patients with diabetes (Fig. 4.1) [60].

Noteworthy, some antidiabetic drugs have been investigated for their impact on the clinical course of COVID-19. Some studies have shown better outcomes in COVID-19 patients with diabetes taking metformin as compared to those not taking with metformin, likely due to the anti-inflammatory and immunomodulatory effects of this drug [52, 61]. However, metformin is not a preferable choice among antidiabetic drugs in acute infections, due to a possible higher risk of acidosis. According to available studies, the relationship between insulin and prognosis of COVID-19 is controversial [52, 61]. Particularly, several observational studies have shown that insulin therapy is associated with a higher risk of poor prognosis of COVID-19 [61, 62]. However, it is currently unclear as to whether these findings may be explained by the fact that insulin is a surrogate marker of more severe diabetes, rather than a relevant player in the worsening of COVID-19 clinical manifestations [61]. Therefore, further research is required to clarify the clinical impact of insulin in the context of COVID-19.

Although several studies have discussed the potential benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors in COVID-19 patients with diabetes, there is no evidence showing an impact of these drugs on COVID-19 outcomes [61]. Noteworthy, there is preclinical evidence suggesting possible beneficial effects of dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in patients with COVID-19 and diabetes, due to their possible anti-inflammatory role [61]. However, available clinical studies do not consistently show protective effects of DPP4 inhibitors towards worse prognosis in this clinical setting. Also, there is insufficient evidence to support the clinical impact of GLP-1RAs in the treatment of diabetes in the context of COVID-19 [61].

Obesity

Different studies have investigated the existence of a possible association between obesity and the risk of SARS-CoV-2 infection, showing contrasting results [63, 64]. By contrast, consistent evidence shows that obesity is an independent risk factor for

COVID-19 severity [63–66]. Also, despite some reports having shown lower mortality rates in obese as compared to non-obese individuals, suggesting a possible protective effect of obesity towards COVID-19-related death (the so-called obesity survival paradox) [67], most of available observational studies and meta-analyses of observational studies have described increased mortality rates due to COVID-19 in obese patients, independently of multiple confounders [65, 68]. Noteworthy, a linear relationship has been quite consistently described between increasing BMI and the risk of COVID-19 adverse outcomes [69, 70]. Instead, the impact of fat distribution on COVID-19 prognosis remains uncertain [71, 72]. Also, it is uncertain how other clinical variables may interact with the association between excessive fat accumulation and COVID-19 prognosis. Thus, for instance, while in some studies younger age has been reported to strengthen the association between adiposity and COVID-19 adverse outcomes, in other studies the association has been found to be stronger in older age groups [69, 73].

Overall, the reason why obese COVID-19 patients are more likely to meet unfavorable disease outcomes as compared to patients with normal BMI may be plausibly explained by different pathophysiological mechanisms directly linked with excessive fat accumulation. First, an excess of intraabdominal adipose tissue may reduce diaphragmatic excursions during breathing, thereby possibly leading to a reduced effectiveness of respiratory gas exchanges and a quicker progression to hypoxia in obese patients with COVID-19 [74]. Second, obesity may be associated with a chronic proinflammatory state which may be amplified by acute inflammation arising out of SARS-COV-2 infection; accordingly, more severe disease phenotypes are likely in obese patients with COVID-19 [75]. Third, obesity may be associated with insulin and leptin resistance which in turn may be implicated in the impairment of the immune response against SARS-CoV-2 infection [76]. Fourth, the expression of ACE2 receptor may be upregulated in the adipose tissue; accordingly, SARS-CoV-2-infected adipocytes may be a potential viral reservoir and excessive adiposity would make it easier for the virus to replicate and spread, thereby promoting severe disease [72]. Fifth, obesity is characterized by a hypercoagulable state; accordingly, the risk of thromboembolic events, which have been described as potential COVID-19 clinical complications, may be amplified in obese patients with COVID-19 [67].

Interestingly, there is evidence showing that weight loss may favorably impact on COVID-19 prognosis. Indeed, in a large cohort study of 11.809 patients with obesity, previous weight loss through bariatric surgery was associated with a 49% lower risk of hospitalization, a 63% lower risk of need for supplemental oxygen, and a 60% lower risk of severe disease after contracting COVID-19 [77]. However, further studies are warranted to confirm these results and to explore whether also non-surgical weight loss prior to SARS-CoV-2 infection may reduce the susceptibility to severe COVID-19.

Hypertension

Available evidence consistently shows that hypertension is a highly prevalent comorbidity in patients with COVID-19 [78–80]. However, the association between hypertension and the risk of SARS-CoV-2 infection remains uncertain. Instead, there is compelling evidence showing that hypertension is an independent risk factor for poor COVID-19 prognosis [81, 82].

Potential explanations of the independent association between hypertension and COVID-19 prognosis may rely on different biological mechanisms. First, hypertension-mediated end-organ damage and severe COVID-19 clinical manifestations seem to share common pathophysiological pathways which may converge into impaired microcirculatory function in different vascular beds. Particularly, because of a repetitive mechanical stress on the arterial wall, hypertension may activate a pro-inflammatory and pro-oxidative milieu, which in turn may induce endothelial dysfunction and subsequent organ damage [83]. On the other hand, severe COVID-19 is associated with a sharply increase of pro-inflammatory cytokines, which may induce microvascular dysfunction in multiple organs [83]. Therefore, COVID-19 and hypertension may act as a detrimental duet potential facilitating multi-organ failure, a typical feature of severe COVID-19 [83]. Second, the availability of ACE2 may be reduced in hypertensive patients, which could imply a higher risk of severe COVID-19 in presence of hypertension. Indeed, when ACE2 activity is compromised, increased Ang II levels may activate Angiotensin Type-1 Receptor (AT1R) and may induce vasoconstriction and inflammation, potentially facilitating microcirculatory dysfunction and multi-organ failure [83]. Third, uncontrolled inflammation and impaired adaptive immune response are common features of both severe clinical manifestations of COVID-19 and hypertension-related end-organ damage. Thus, hypertension and COVID-19 may act as a double blow facilitating multi-organ failure by exacerbating inflammation and immune responses [83].

A possible variable impact of different hypertension-related parameters [e.g., blood pressure (BP) resistance to treatments, BP variability, and BP control) on the risk of COVID-19 adverse outcomes has been explored in some studies. However, available evidence is inconclusive. In a large retrospective study enrolling 1.897 COVID-19 patients, detection of resistant hypertension at hospital admission (i.e., BP $\geq$ 130/80 mmHg despite the use of three antihypertensive drugs or by target BP with $\geq$4 antihypertensive drugs) was independently associated with a two-fold increased risk of in-hospital mortality due to COVID-19 [84]. However, as no confirmatory evidence is available from prospective studies considering BP values before hospitalization, caution is needed in assuming a direct detrimental impact of resistant hypertension on COVID-19 outcomes. In a large retrospective study enrolling 803 hypertensive patients with COVID-19, BP variability (i.e., standard deviation of the daily mean systolic BP/diastolic BP during hospitalization) was

independently associated with the risk of ICU admission and in-hospital death [85]. However, BP monitoring during the hospital stay may be influenced by uncontrolled confounders and may not reflect faithfully BP values before hospitalization. Therefore, also the results of this study do not allow to drive definitive conclusions. A large cohort study (4.277 COVID-19 patients) showed a lower risk of death in patients with stage 1 uncontrolled blood pressure (140/90–159/99 mmHg in the most recent BP reading before infection) as compared to patients with well-controlled BP (<130/80 mmHg in the most recent BP reading before infection), paradoxically suggesting a possible protective effect of uncontrolled hypertension towards COVID-19 prognosis [86]. This could be explained by assuming that BP control, which is prevalent in hypertension of longer duration, may be a surrogate marker of higher atherosclerotic burden and target organ damage. However, since confirmatory studies are not available, as to whether uncontrolled hypertension may be associated or not with poor COVID-19 prognosis needs to be further explored.

Regarding the potential impact of antihypertensive drugs on COVID-19 prognosis, the safety of angiotensin receptor blockers (ARBs) and ACE inhibitors (ACEIs) in COVID-19 patients has been widely debated in the initial phases of the pandemic [87]. Indeed, the hypothesis that these drugs could increase the expression of ACE2, thereby potentially facilitating SARS-CoV-2 infection and aggravating disease severity, had raised significant concerns. However, current evidence does not support this notion. Particularly, it has not been demonstrated that either ARBs or ACEIs can increase ACE2 levels in lung epithelial cells [87]. Moreover, it has been shown that ACE2 expression plays a protective role against ARDS [88]. Also, it has been observed that the use of ARBs or ACEIs does not increase the severity of COVID-19 in patients with hypertension and may also have beneficial effects towards COVID-19 prognosis [89]. Specifically, a large meta-analysis of 53 studies (39 cohort studies and 14 case-control studies) including a total of 2.100.587 participants showed that both COVID-19 severity and COVID-19-related mortality were reduced significantly by ACEIs/ARBs [89]. Noteworthy, similar results were also reported for other antihypertensive drugs including calcium chanel blockers, β-blockers, or diuretics [89]. Therefore, discontinuation of antihypertensive drugs in COVID-19 patients has no rational.

Dyslipidemia

Currently, there is no convincing evidence showing any association between dyslipidemia and risk of SARS-CoV-2 infection. Instead, a large body of evidence has progressively accumulated on the relationship between dysregulation of lipid metabolism and COVID-19 outcomes [90–93]. Overall, available studies suggest, on the one hand, that pre-existing alterations of lipid metabolism may impact on COVID-19 prognosis and, on the other hand, that COVID-19 may induce a complex derangement of lipid metabolism, which in turn may influence the disease prognosis.

Regarding the impact of dyslipidemia on COVID-19 clinical evolution, observational studies and meta-analysis of observational studies have described a

significant association between pre-existing alterations of lipid metabolism and the risk of severe COVID-19 [90–92]. Also, a recent meta-analysis (28 studies involving 12.995 COVID-19 patients, including 26 cohort studies and 2 case-control studies) has shown that the history of dyslipidemia is associated not only with an increased COVID-19 severity but also with an increased COVID-19 mortality [93]. Interestingly, some studies have suggested the possibility that different dyslipidemia phenotypes may variably impact on the clinical evolution of COVID-19. Thus, for instance, either low HDL cholesterol or high triglyceride levels, clinical features of atherogenic dyslipidemia, have been reported to display a direct association with COVID-19 severity [94, 95].

Although it remains unclear as to whether the association between dyslipidemia and COVID-19 prognosis may be independent of multiple confounders, different pathophysiological mechanisms may potentially explain the higher risk of COVID-19 progression towards more severe phenotypes in patients with pre-existing pro-atherogenic alterations of lipid metabolism (Fig. 4.2). First, in the

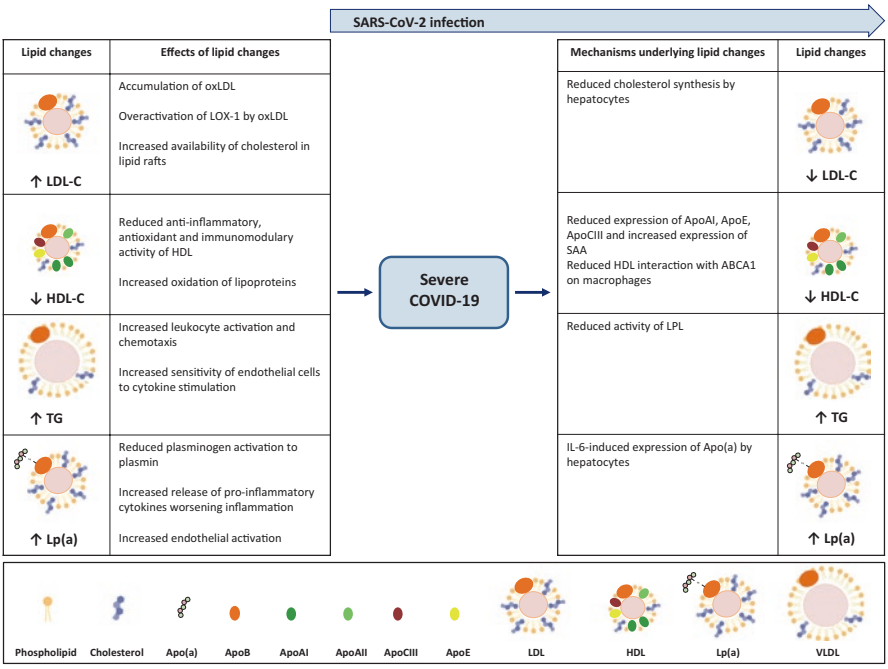

Fig. 4.2 Suggested links between lipid metabolism and severe COVID-19. Pre-existing lipid metabolism alterations [i.e., reduced HDL cholesterol levels and increased LDL cholesterol, lipoprotein (a) and triglyceride levels] may promote COVID-19 severity through different mechanisms. In turn, severe COVID-19 may induce some alterations of lipid metabolism [i.e., reduced LDL cholesterol and HDL cholesterol levels and increased triglyceride and lipoprotein (a) levels] through different mechanisms. *ABCA1* ATP binding cassette subfamily A member 1, *Apo* apolipoprotein, *HDL* high-density lipoprotein, *HDL-C* HDL cholesterol, *LDL* low-density lipoprotein, *LDL-C* LDL cholesterol, *LOX-1* lectin-like oxLDL receptor-1, *Lp(a)* lipoprotein(a), *LPL* lipoprotein lipase, *oxLDL* oxidized LDL, *TG* triglycerides, *VLDL* very low-density lipoprotein

presence of high LDL cholesterol levels an increased oxidative stress related to inflammation may lead to an accelerated formation of oxidized LDL (oxLDL). Noteworthy, these lipoproteins may display the ability to activate and damage the endothelium inducing endothelial dysfunction, which is a crucial pathophysiological moment in the progression of SARS-CoV-2 infection towards its most severe forms [96]. In addition, high LDL cholesterol levels may be associated with a higher cholesterol bioavailability in cellular membranes, which in turn may facilitate virus entry into host cells. Indeed, cholesterol-rich lipid rafts on host cells, which are functional membrane microdomains, act as crucial platforms for SARS-CoV-2 interaction with ACE-2 facilitating virus entry [97]. Second, reduced HDL cholesterol levels may be paralleled by impaired HDL-mediated anti-inflammatory and immunomodulatory activity and, consequently, by uncontrolled inflammatory response during SARS-CoV-2 infection [98]. Third, hypertriglyceridemia could promote inflammation through leukocyte activation (increased expression of CD11b and CD66b by neutrophils and monocytes) and chemotaxis and increased sensitivity to cytokine stimulation of endothelial cells [95].

Regarding the impact of COVID-19 on lipid metabolism, evolutive alterations of lipid metabolism parameters during COVID-19 have been extensively described. Particularly, total cholesterol, LDL-C, and HDL-C levels have been quite consistently reported to decrease in the acute phase of the infection [99, 100], while a slightly increase of triglyceride levels has been described in most of available studies [100, 101]. Although the pathophysiological pathways leading to changes in lipid parameters during COVID-19 are not completely understood, inflammation seems to be implicated both by altering liver function and by reducing reverse cholesterol transport. Indeed, SREBP-2-induced cholesterol biosynthesis has been shown to be suppressed by inflammation-induced upregulation of Sestrin-1 and proprotein convertase subtilisin kexin type 9 (PCSK9) in SARS-CoV-2 infection [102]. In addition, inflammation has been described to reduce hepatic expression of apolipoprotein AI (ApoAI), apolipoprotein E (ApoE), and apolipoprotein C-III (ApoCIII), thereby leading to significant changes in HDL composition [96]. Indeed, reduced levels of ApoAI may reduce the interaction of HDL with ATP binding cassette subfamily A member 1 (ABCA1) on macrophages and increase the activity of enzymes involved in HDL remodeling/catabolism, thereby resulting in decreased HDL cholesterol levels [96]. Concomitantly, low concentrations of ApoE and ApoCIII on HDL may dysregulate the activity of lipoprotein lipase (LPL), which in turn may lead to the accumulation of VLDL and triglycerides [96]. Overall, the clinical implications related to the dysregulation of lipid metabolism occurring in COVID-19 patients are highly debated. Several epidemiological studies have shown a strict association between lower HDL cholesterol levels in the acute phase of infection and worse prognosis in patients with COVID-19 [103, 104] suggesting a possible detrimental impact of low HDL cholesterol on the pathophysiology of COVID-19. Likewise, several observational studies have described a higher risk of COVID-19 severity and mortality in patients with lower LDL cholesterol levels during the acute phase of SARS-CoV-2 infection, suggesting a possible protective impact of higher LDL cholesterol against COVID-19 [105]. However, extreme caution is required in

interpreting this latter point. Indeed, it is uncertain as to whether LDL cholesterol decrease may be a bystander or a player in the pathophysiology of COVID-19.

Interestingly, there is preliminary evidence showing a close link between higher Lp(a) levels and higher COVID-19 severity. In a prospective observational study in 50 hospitalized COVID-19 patients, Lp(a) was found to be significantly associated with the disease severity both at admission and during the hospital stay [106]. In addition, in different observational studies increased Lp(a) levels have been reported to be associated with a higher incidence of different CV complications in COVID-19 patients, including ischemic heart disease and venous thromboembolism [107, 108]. Overall, based on these findings and on the fact that Lp(a) levels are mainly genetically-determined and scarcely affected by concomitant medical conditions, a possible pathogenic role of Lp(a) towards severe COVID-19 could be considered. From a biological perspective, the plausibility of Lp(a) involvement in the evolution of COVID-19 towards its most severe clinical manifestations may be sustained by the well-known pro-inflammatory and pro-thrombotic properties of this lipoprotein [109, 110]. However, further studies elucidating the role of high Lp(a) levels in the pathophysiology of COVID-19 would be essential to support this speculation.

The potential ability of lipid-lowering drugs to impact on COVID-19 outcomes has been widely investigated. To date, different observational studies and meta-analyses of observational studies have shown that statin therapy continuation has a favorable impact on the prognosis of COVID-19 [111, 112]. Speculatively, statins may exert a protective role against COVID-19 by acting at multiple levels, including inhibition of SARS-CoV-2 entry and replication, inhibition of the inflammatory response, attenuation of endothelial dysfunction, and regulation of haemostasis [8]. Beyond statins, other lipid-lowering drugs, including omega-3 fatty acids and fibrates, have been investigated for their impact on COVID-19 outcomes. However, their effects on COVID-19 prognosis currently remain uncertain [113, 114].

Chronic Kidney Disease

Regarding the association between CKD and risk of SARS-CoV-2 infection, literature data are scarce and inconclusive. Instead, despite some inconsistency, numerous observational studies and meta-analyses of observational studies have shown the existence of a significant association between CKD and worse COVID-19 outcomes [115–117]. Noteworthy, a graded association has been extensively described between kidney dysfunction and the risk of both COVID-19 severity and COVID-19 mortality, with the highest risk occurring in patients with kidney failure receiving replacement therapy and those with previous kidney transplant [118–120]. Overall, different explanations of the observed association between CKD and the evolution of COVID-19 towards its most severe forms, may be formulated. First, CKD patients may exhibit functional defects in innate and adaptive immunity [117], which may make them more susceptible to severe COVID-19. Second, the upcoming of concurrent bacterial infections, including bacterial pneumonia and septic

shock, which is highly frequent among hospitalized CKD patients, may complicate the natural course of COVID-19 in these patients [117]. Third, COVID-19 patients with CKD may be less likely to receive recommended therapies for in-hospital care of COVID-19. Indeed, some drugs need dose adjustment in presence of CKD or are contraindicated if estimated glomerular filtration rate (eGFR) is <30 ml/min/1.73 m^2 (e.g., low molecular weight heparins and remdesivir). Also, some therapies can be inappropriately denied to CKD patients due to concerns on their safety or futility [119].

Nonetheless, a bidirectional relationship between CKD and COVID-19, in which not only CKD may impact on the risk of severe COVID-19 but also severe COVID-19 may impact on the risk of CKD, should be considered. Indeed, there are preliminary reports showing an increased risk of CKD after severe COVID-19 resolution. Thus, for instance, a United States study on electronic health records from the Veterans Health Administration assessing post-acute COVID-19 sequelae reported a higher risk of CKD among patients with previous COVID-19, especially among those recovered from severe COVID-19 [121]. As a possible pathophysiological explanation of this finding, it is likely that SARS-CoV-2 infection may induce kidney damage in its acute phase, which in turn may lead to a progressive impairment of kidney function over time. Supporting this hypothesis, some studies have shown that SARS-CoV-2 displays renal tropism [122]. Also, acute tubular injury has been described in kidney autopsy samples of deceased COVID-19 patients [123]. However, additional studies comparing kidney biospecimens of COVID-19 patients between hospitalization and recovery would be crucial to gain further insight on the biological mechanisms linking SARS-CoV-2 infection and new-onset impairment of kidney function.

Additional Markers of Increased CV Disease Risk in COVID-19

The association between several laboratory and instrumental parameters and clinical outcomes of COVID-19 has been an area of intense research globally [124–126]. In this regard, a large body of evidence is available on the significant relationship between different surrogate markers of increased CV disease risk and worse COVID-19 prognosis. Thus, for instance, D-dimer, a well-known parameter of thrombo-inflammation with the ability to discriminate the risk of venous thromboembolism, has been reported as a reliable determinant of ICU admission and in-hospital mortality in COVID-19 patients [127, 128]. Similarly, C-reactive protein, a non-specific acute phase reactant and significant predictor of increased risk of CV disease, has been found to be a significant predictor of COVID-19 prognosis [129]. Moreover, the neutrophil-to-lymphocyte ratio, a marker of inflammation and a possible surrogate marker of preclinical vascular damage in patients at increased CV disease risk [130, 131], has emerged as a frequent statistically significant laboratory parameters in predicting COVID-19 adverse outcomes [124, 132]. Also, in line with

evidence showing the crucial pathophysiological involvement of endothelium in SARS-CoV-2 infection, different measures of endothelial injury and dysfunction [e.g., circulating endothelial cells, soluble intercellular adhesion molecule-1 (sICAM-1), von Willebrand factor antigen (vWF), and brachial artery flow-mediated dilation], which are well-known markers of CV disease, have also shown a significant predictive value towards COVID-19 severity and clinical outcomes [34]. Consistently, a large spectrum of additional biomarkers and clinical measures of increased CV disease may be relevant parameters for the prognostic stratification of COVID-19.

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Chapter 5
Prognosis in COVID-19 Patients: Statistics, Risk Factors

Bozena Sosnowska, Agata Bielecka-Dabrowa, and Maciej Banach

Introduction

In April 2022, the number of death due to COVID-19 is almost 6 million (despite it is predicted that it may be even 13–16 million excess deaths due to COVID-19) and fatality rate is 2%. Fatality rate of COVID-19 continues to change as the pandemic progress [1]. The disease course of COVID-19 varies greatly from asymptomatic infection to severe condition resulting in death [2]. The prognosis of most patients is good but approximately 20% of all COVID-19 patients develop severe or life-threatening complications [3]. The average time from SARS-CoV-2 exposure to symptom onset is 5 days [4–6]. According to data from China, an estimated 10–15% of mild cases progress to severe, and 15–20% of severe cases go on to become critical [3].

Identification of prognostic factors is important for reducing morbidity and mortality caused by the disease [2]. Due to limited antiviral treatment options for COVID-19, the severity of disease is closely related to the prognosis [7]. There is a significant difference between severe and non-severe patients with COVID-19 in

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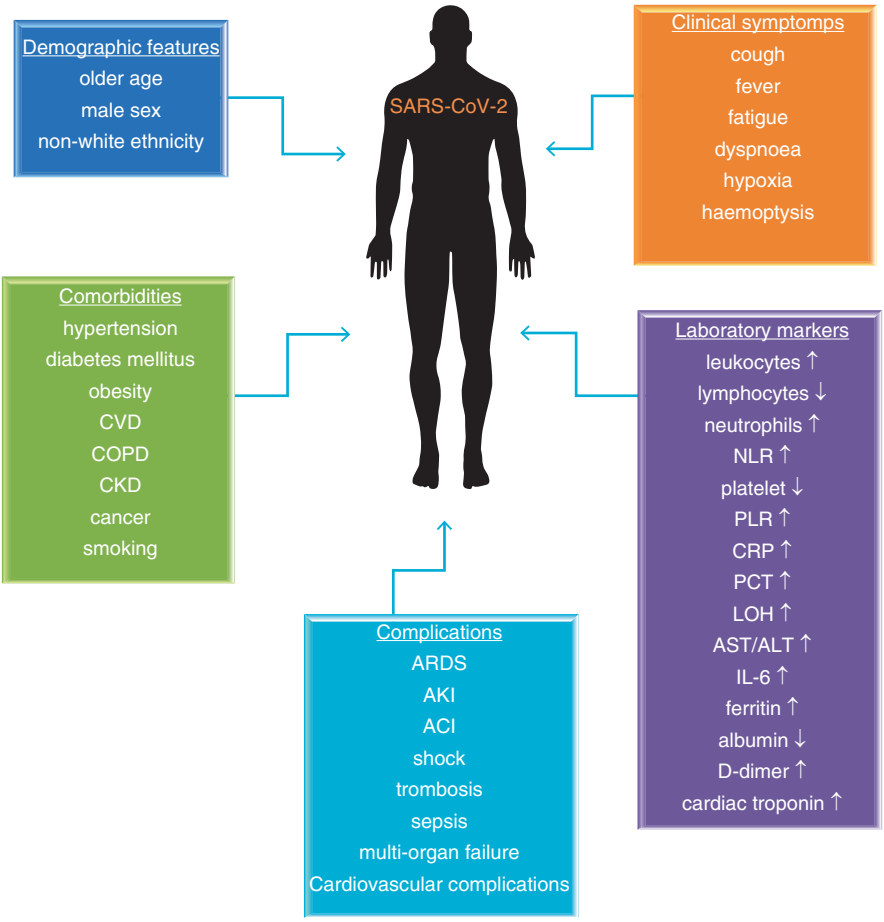

Fig. 5.1 Risk factors associated with the prognosis in COVID-19 patients. *CVD* cardiovascular disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *ARDS* acute respiratory distress syndrome, *AKI* acute kidney injury, *ACI* acute cardiac injury, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *CRP* C-reactive protein, *PCT* procalcitonin, *LDH* lactate dehydrogenase, *AST* Aminotransferase, *ALT* alanine aminotransferase, *IL-6* Interleukin 6

terms of demographic features, clinical symptoms, comorbidities, laboratory parameters, complications, and outcomes [8–10]. The most important factors influencing the prognosis of patients with COVID-19 are discussed below and summarized in Fig. 5.1.

Demographic Features

Age and Sex

COVID-19 causes infection in all age groups, although severe disease is more common in older adults [9]. Older age (>65) is closely associated with the worse prognosis of COVID-19 [7, 11]. The median age of hospitalized patients varies between 49 and 70 years and from 66 to 77 for fatal cases [12–18]. COVID-19 associated hospitalization by age is shown in Fig. 5.2.

It was found that older age is significantly associated with the disease severity and endpoints including death, admission to intensive care unit (ICU), acute respiratory distress syndrome (ARDS), invasive ventilation, and cardiac abnormality [7, 19]. Increased age in patients with COVID-19 is the strongest predictor of death [20]. Elderly patients were more than twice as likely to have severe or critical illness when compared with middle-aged patients [21].

Moreover, it was indicated that ARDS, multiple organ failure, and death are more often in older subjects with pre-existing diseases including diabetes, hypertension, and cardiovascular disease. Reason for poor prognosis for elderly patients is probably associated with a higher frequency of comorbidities or/and age-related immune dysfunction resulting from low-grade chronic inflammation [8].

At advanced age, there is an increased risk of death for both sexes, but at all ages above 30 years males have a significantly higher risk of death than females [22]. The Global Health 50/50 research initiative, which presents an overview of sex-disaggregated data from countries worldwide, indicated that despite similar numbers of COVID-19 cases in men and women there is an increased case fatality rate in men [23]. Some studies indicated that up to 90% of severe cases were men [24].

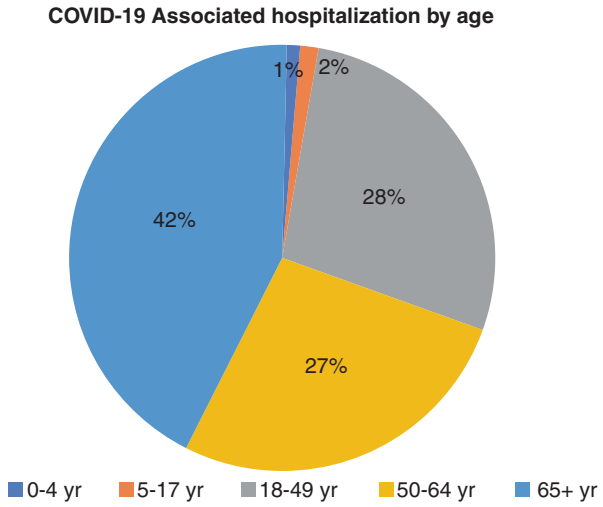

Fig. 5.2 COVID-19 associated hospitalization by age, preliminary data as of 02 APR 2022 (COVID-NET). (Based on the data from [64])

Large-scale meta-analysis of more than 3 million global cases showed that male patients have almost three times the odds of requiring intensive care unit admission and higher odds of death compared to females [25]. ICU mortality in female COVID-19 patients was lower than in male patients (27% vs. 39% respectively), independent of age, disease severity, smoking, obesity, comorbidities, anti-infection/inflammatory therapy, and country [26]. Males had higher risk of reaching severe disease and adverse prognostic endpoints including death, ARDS, admission to ICU, invasive ventilation, and cardiac abnormality [19].

The cause of worse prognosis and death in males compared to females is probably associated with the protection of the X chromosome and sex hormones, which play an essential role in innate and acquired immunity [27, 28]. The greater predisposition of men to become infected with COVID-19 may result from differences in the levels of cell receptors (angiotensin converting enzyme) and molecules that assist the entry of SARS-CoV-2 through the fusion of the virus with the cell membrane (transmembrane serine protease 2) [29].

Ethnicity

Ethnic and race differences among COVID-19 patients' hospitalizations and mortality have been widely reported. African-Caribbean (Black), Latin, and South Asian origin experience grater hospitalization and mortality from COVID-19 than white individuals [30, 31]. Single-site studies revealed that Black people were 1.7 to 2. times more likely to be hospitalized due to COVID-19 than White or other racial and ethnic minority groups [32, 33].

Meta-analysis of 45 articles indicated that race may be associated with COVID-19 outcomes because of the increased occurrence of comorbidities in racial and ethnic minority groups but did not confirmed ethnicity as an independent poor prognostic factor for COVID-19 [34]. However, this study did not analyze the role of socioeconomic determinants, which disproportionately affect racial and ethnic minority populations [35].

Ethnicities other than White were associated with higher COVID-19-related mortality in type 1 and type 2 diabetes [36]. It was found that comorbidities and socioeconomic status only partly contributed to greater admission risk of COVID-19 in Black and mixed ethnicity [37]. Asian patients had a higher risk of experiencing greater COVID-19 cardiorespiratory disease severity than non-Hispanic White patients [38]. Retrospective cohort study of more than one million of individuals, representing diverse racial and ethnic minority groups indicated that an increase incidence of severe COVID-19 among Black/African American and Hispanic individuals is due to higher infection rates, not increased susceptibility to the severe course of disease [39]. The authors concluded that the differences associated with COVID-19 among patients of different races are most likely due to social, not biological, factors [39].

Clinical Symptoms

COVID-19 infection is now recognized as a multisystem disease, causing a wide range of clinical manifestations [40]. Approximately 80% of all SARS-CoV-2 infected patients are asymptomatic or develop symptoms characteristic of mild or moderate pneumonia [41]. Approximately 15% of COVID-19 patients develop severe condition with viral pneumonia with the need of hospitalization. Only about 5% of cases develop critical illness, presenting acute respiratory distress syndrome, all types of shock or multiple organ failure, and require mechanical ventilation or admission to ICU; approximately 2% of cases are fatal [3, 42].

The most common clinical symptoms are fever, cough, dyspnea, fatigue, malaise, and sputum production [8, 43, 44]. Meta-analysis of 45 studies with 4203 patients indicated that the most common clinical symptoms are fever, cough, and dyspnea (80.5%, 58.3%, and 23.8%, respectively) [45]. Early recognition of severe infection may allow early medical intervention and improve outcomes in patients with COVID-19 [7].

Another meta-analysis of 20 studies and in 3326 patients with COVID-19 indicated that some initial symptoms including abdominal pain, dyspnea, hemoptysis, anorexia, diarrhea, fatigue, expectoration, fever, and cough occurred more frequently in severe COVID-19 patients than in mild COVID-19 patients [46]. Recent study indicated that clinical symptoms associated with critical illness were dyspnea, hypoxia, and hemoptysis [47]. Meta-analysis of 26 studies involving 7274 COVID-19 patients indicated that non-survivors in compering to survivors were more likely to present with dyspnea (66% vs. 34%), hemoptysis (4% vs. 3%), chest tightness (46% vs. 30%), expectoration (42% vs. 32%), and fatigue (50% vs. 44%). Moreover, dyspnea, hemoptysis, expectoration, chest tightness, fatigue, and sputum production were found to be significant risk factors of mortality [10, 48].

Patients with dyspnea were six times more likely to have an ICU admission and were more likely to die compared to those without dyspnea [43] what might relate to the fact that dyspnea is more common in COVID-19 patients with ≥2 comorbidities than in those with one comorbidity [49]. Dyspnea and hypoxemia may be developed in severe ill patients within 1 week after onset of the disease and may quickly progress to acute respiratory distress syndrome or end-organ failure [14].

Hypoxemia is an independent prognostic factor for the severe course of COVID-19 [50] and is associated with in-hospital mortality [51]. The study of Huang et al. indicated that 32% of COVID-19 patients showed varying degrees of hypoxemia [12]. The most serious manifestation is worsening arterial hypoxemia, eventually leading to acute respiratory distress syndrome promptly needing mechanical ventilation [3, 49]. Patients with fever had a higher risk of the worse course of COVID-19, mechanical ventilation, and mortality than those without fever [52–54]. Fever greater than 38.5 °C on admission was positively correlated with the severity and mortality of COVID-19 [55].

It was reported that the duration of fever was associated with the prognosis. The time from admission to a normal temperature was 7 days for patients with severe

disease and 2 days for patients with mild disease [56]. Although respiratory manifestations are the most common, studies have reported that gastrointestinal symptoms including diarrhea, nausea/vomiting, and abdominal pain, are also frequent in patients with COVID-19, with a prevalence of up to 30% [57, 58]. It was indicated that gastrointestinal symptoms were strongly associated with severe COVID-19 disease and might be associated with the prognosis with COVID-19 [59–61]. Meta-analysis of 35 studies, including 6686 patients found that gastrointestinal symptoms were a significant risk factor for disease severity [61]. However, last meta-analysis including 53 studies and 55,245 COVID-19 patients found that gastrointestinal symptoms were not associated with higher mortality so the prognostic value of these symptoms in COVID-19 requires further investigation [62]. The prognostic value of gastrointestinal symptoms in COVID-19 might not be as significant as other factors such as age, concomitant diseases, and respiratory manifestations.

Comorbidities and the Course of COVID-19

The presence of comorbidities influences the prognosis and prolongs the recovery time. Individuals with underlying chronic disease have greater risk for severe course of COVID-19 and death [63]. Underlying comorbidities in COVID-19 patients were shown in Fig. 5.3 [64]. The most prevalent affecting the course of the COVID-19 disease and prognosis are hypertension, cardiovascular disease (CVD), diabetes mellitus, and respiratory diseases [8–10, 45, 65]. Recent systemic review including ten studies and 3912 participants indicated hypertension as the most common disease linked with the severe COVID-19 (59.3%), followed by obesity (48.7%),

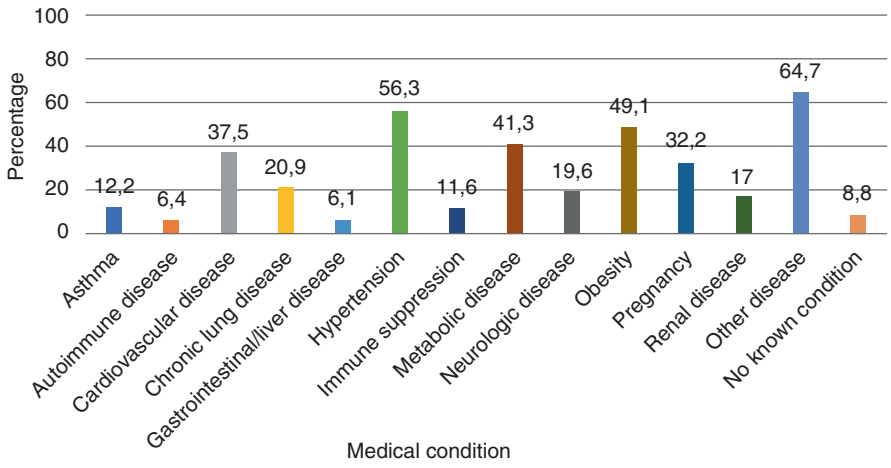

Fig. 5.3 Underlying comorbidities in COVID-19 patients (COVID-NET). Hospitalization data (March 2020–July 2021). (Based on the data from [64])

chronic lung disease (19.8%), metabolic disease (43.6%), and CVD (35.6%) [66]. Study by Hatmi et al. suggested that among comorbidities in COVID-19 patients the most powerful prognostic factors for mortality rate were pre-existing CVD, diabetes mellitus, respiratory disease, and hypertension. Whereas the most important prognostic factors for severity of COVID-19 were CVD and hypertension [3, 65, 67].

COVID-19 itself also may induced cardiovascular complications such as myocardial injury, myocarditis, arrhythmias, acute coronary syndrome, and venous thromboembolism [66–71]. It was indicated that even small amounts of myocardial injury were associated with an increased risk of patient mortality [68]. Meta-analysis of 17 studies with a total of 5815 patients revealed that the most common cardiovascular complications in COVID-19 patients were heart failure, myocardial injury, cardiac arrhythmia, and acute coronary syndrome [69].

Evaluation of the early development of persistent myocardial injury is a useful prognostic tool in patients with severe COVID-19 [72]. Cardiovascular risk factors such as hypertension, diabetes mellitus, and obesity were associated with ICU admission and poor prognosis [66]. Interestingly that lipid disorders are not associated with the severe course of the disease, in opposite in patients in acute phase reduced cholesterol level is observed.

Hypertension

Hypertension is thought to be an independent risk factor for severe COVID-19 and a strong predictor of poor prognosis including ARDS, ICU admission and mortality [73, 74]. Hypertension is found to be the most common comorbidity in COVID-19 patient. Individual studies have shown that the prevalence of hypertension in fatal cases is from 39% to 65% [16–18, 75]. A systematic review indicated that COVID-19 patients with hypertension were two times more likely to require ICU admission and 1.7 times more likely to have more severe disease [74]. In a retrospective study of 803 COVID-19 patients with hypertension, high mean systolic blood pressure, and high variability of systolic / diastolic blood pressure during hospitalization were independently associated with mortality, ICU admission, and heart failure [76]. The prognosis for patients with hypertension is markedly worse when SARS-Cov-2 infection was complicated by myocardial injury and in the presence of CVD [77].

Diabetes Mellitus

Diabetes as a common underlying disease in COVID-19 patients is associated with worse prognosis [12, 78–88]. Diabetes in hospitalized patients with COVID-19 was reported in 3–25% of non-critical [80, 81] and in 15–31% of critical cases [7, 80, 81]. COVID-19 patients with diabetes mellitus have high risk of severe disease, ARDS, shock, multi-organ failure, death, and ICU admissions [80–83]. Recent

meta-analysis with 344,431 COVID-19 patients indicated that the proportion of patients with diabetes was dramatically higher in the severe or non-survival group then in controls. Patients with diabetes had a 3.55-fold higher risk of progression of COVID-19 and 3.83-fold higher risk of mortality compared with those without diabetes [10]. Newly diagnosed diabetes was associated with higher mortality than known diabetes in hospitalized COVID-19 patients [84, 85]. Well-controlled diabetes correlated with a reduced risk of detrimental complications and all-cause mortality in subjects with COVID-19 and pre-existing diabetes [88].

Obesity

Obesity may also be a prognostic factor for severity of COVID-19 and fatal outcomes [89–91]. A meta-analysis of 208 studies and total of more than three million participants from over 32 countries revealed that overweight increased the risk of COVID-19-related hospitalizations but not death while obesity and extreme obesity increase the risk of both hospitalizations and death [92]. In the recent meta-analysis of ten observational studies with 10,233 COVID-19 patients the prevalence of obesity in persons with poor outcomes was 34% [93]. Patients with body mass index (BMI) >35 kg/m^2 need seven times more often the use of mechanical ventilation compared [94]. Moreover, BMI >40 kg/m^2 was found as an independent risk factor associated with mortality, more prominent in patients younger than 50 years [95].

Chronic Obstructive Pulmonary Disease (COPD)

Nationwide population study with 4610 patients indicated that COPD patients had higher risk of ICU care and mechanical ventilation than patients without COPD and the risk for all-cause mortality was approximately two times higher in patients with COPD than in those without [96]. The prevalence of COPD among COVID-19 patients ranges from 0 to 10% worldwide, but most reports are from China [49, 97, 98]. In Europe, the prevalence of COPD is 5.6–11% [99–102]. Progression to severe course of COVID-19 in COPD patients has ranged from 20 to 50% [49, 103, 104]. Mortality with COVID-19 and COPD is also lower compering to other major comorbidities (CVD, diabetes); whereas risk severity seems to be comparable (3–4 folds) [105, 106].

Chronic Kidney Disease

Chronic kidney disease (CKD) is one of the factors that significantly impact COVID-19 patients' prognosis, and influence on the disease severity [106, 107]. Prevalence of CKD in patients with COVID-19 ranged from 0.4 to 49% [108]. Data

on mortality in patients with COVID-19 and CKD are limited and varying from 16% to 53% [109, 110]. Recent review indicated that patients with CKD are more likely to have worse outcomes from COVID-19 compared to individuals without CKD [108]. More advanced CKD relates to higher risk of COVID-19 severity, hospitalization, and mortality [108].

Cancer

The prevalence of cancer among COVID-19 patients range from 0.29% to 2.6% [106, 111–113] and, mortality is estimated from 5% to 8.3% [106, 111] and research results regarding the prognostic significance of cancers in COVID 19 patients are inconclusive. Some studies have found comparable mortality rates between patients with cancer and those without cancer after adjusting for age and comorbidities [114, 115]. Recent large electronic health record based on US study reported higher rates of death among patients with COVID-19 and cancer compared to those without (14.9% vs. 5.26%) [112]. Studies regarding influence of cancer treatment for outcomes in COVID-19 patients are inconsistent [111, 116–118].

Recently published large cohort study indicated that patients with recent cancer treatment and COVID-19 had a significantly higher risk of adverse outcomes, and subjects with no recent chemotherapy and chemoimmunotherapy had similar risk of mortality and ICU stay and a lower risk of mechanical ventilation and hospitalization compared with COVID-19 patients without cancer [119]. It was also found that patients with metastatic solid tumors and hematologic malignant neoplasms had worse outcomes compared with patients with nonmetastatic solid tumors [119].

Special Conditions and Populations of Patients and the COVID-19 Course

Smoking

Smoking history is a high-risk factor for severe course and mortality among patients hospitalized for COVID-19 [65, 120]. Recent meta-analysis of 47 studies with a total of 32,849 hospitalized COVID-19 patients indicated that current smokers have an increased risk of admitting to hospital with severe COVID-19 and are approximately twice as likely to develop severe or critical COVID-19 as former or never-smokers [121]. Authors suspected that smokers are exposed to higher SARS-CoV-2 loads due to elevated expression of angiotensin converting enzyme 2 (ACE2), which may provide a mechanistic explanation for the higher risk of severe disease and mortality in smoking patients with COVID-19 [121, 122].

Mendelian randomization analyses of 281,105 White British subjects showed that genetically predicted propensity to initiate smoking was associated with 45% higher risks of SARS-CoV-2 infection (OR 1.45, 95% CI: 1.10 to 1.91) and 60% higher risk of hospitalization (OR 1.60, 95% CI: 1.13 to 2.27). Genetically predicted increase in number of cigarettes smoked per day was associated with higher risks of infection, hospitalization, and death [120].

Pregnancy

Physiological changes in the immune and respiratory systems during pregnancy may make pregnant women more susceptible to COVID-19 infection. Especially the first trimester of pregnancy may be the period most susceptible to SARS-CoV-2 infection due to early ACE2 expression associated with placental immaturity [123, 124]. Pregnant women with SARS-CoV-2 infection are at increased risk of ICU admission, mechanical ventilation, and death compared with both pregnant women without COVID-19 and nonpregnant individuals with COVID-19 [125–128]. Retrospective cohort study with 14,104 patients indicated that a composite outcome of maternal death or serious morbidity associated with hypertension in pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2 occurred significantly more common in women with COVID-19 compared with individuals without COVID-19 [129].

Children

Children can be infected as easily as adults but are more often asymptomatic and have milder course of disease due to their immature immune systems [130]. A small percentage (<7%) of children admitted to the hospital for COVID-19 develop severe disease requiring mechanical ventilation [131]. The risks factors for the infection of SARS-CoV-2 and the severity of disease are children age and comorbidities [131]. Young infants and older adolescents had higher risk of developing severe disease [131, 132]. Additionally, older children may develop multisystem inflammatory syndrome (MIS-C) with severe disease [133]. This multisystem inflammatory syndrome in children is uncommon (2 in 100,000 persons aged <21 years) [134].

Selected Laboratory Parameters Values and the COVID-19 Course

Leukocyte Counts

Elevated leukocyte count ($\geq 9.5 \times 10^9$/L) is associated with course of COVID-19 disease [14, 49]. Leukocytosis was observed in 28.1% to 68.1% of patients, depending on the severity of the disease and comorbidities [135–138]. Patients with severe and

fatal COVID-19 had significantly increased leukocyte count compared to non-severe disease and survivors [49, 139, 140]. Leukocyte counts were found to be a prognostic marker in diagnosis of progression to serious or severe disease in COVID-19 patients [141]. A meta-analysis of 45 studies identified that elevated leukocyte predicted ICU admission and mortality [45]. Another meta-analysis on 21 studies including 3377 patients indicated that patients with severe disease had a mild increased in leukocyte level (WMD: 0.41×10^9/L), while patients who died had higher level of this parameter (WMD: 4.15×10^9/L) [139]. Meat-analysis of 13 studies with 3027 participants indicated that white blood cells (WBC) $< 4 \times 10^9$/L predicted better clinical status in COVID-19 patients [9]. Myari et al. assessed that WBC belong to one of the most efficient indicators of critical disease [142]. Current evidence suggests that although leukocyte counts can be used as a predictor factor for severe COVID-19 condition, however, other factors should be also taken into account [143].

Lymphocyte Counts

Decreased level of lymphocytes is one of the typical characteristics of SARS-CoV-2 infection, which is associated with poor outcomes [144]. Lymphopenia was observed in up to 96.1% of severe COVID-19 patients, and its degrees correlate with the intensity of proinflammatory cytokine storm, disease severity, and outcome [7, 145–147]. A meta-analysis of 28 studies involving 6449 COVID-19 patients demonstrated that lymphopenia (<1500 lymphocytes/μL) had nearly threefold higher risk of poor outcomes compared with better outcomes [148]. Study on peripheral lymphocyte subset alteration in COVID-19 indicated that severe ill patients had lower total lymphocytes CD4+ T cells, CD8+ T cells, and B cells in compering to patients with mild illness. CD8+ T cells were found to be a potential predictor of COVID-19 severity [149].

Decrease of T-lymphocyte subsets was associated with in-hospital death and severe course of COVID-19. Lower counts of T lymphocyte subsets; lymphocyte (<500/μL), CD3 +T-cell (<200/μL), CD4+ T-cell (<100/μL), CD8+ T-cell (<100/μL), and B-cell (<50/μL) were linked to higher risk of in-hospital death. The alarming values that can predict in-hospital death of lymphocyte, CD3+ T-cell, CD4+ T-cell, CD8+ T-cell, and B-cell were 559/μL, 235/μL, 104/μL, 85/μL, and 82/μL, respectively [150].

Neutrophil Counts

Neutrophil count was found to be a prognostic marker in diagnosis of progression to severe and critical disease in COVID-19 patients [141, 142]. Meta-analysis of 34 studies and 344,431 participants revealed that increased neutrophil count is significantly higher in the severe group than in the non-severe [10]. Neutrophilia was found to be associated with both ARDS development and progression to death [54].

A meta-analysis of 6320 patients found that neutrophil counts identified severe patients with 100% sensitivity and 81% specificity at a cut-off value of $>3.74 \times 10^9$/L [141]. It was found that neutrophil-to-lymphocyte ratio (NLR) is one of the powerful prognostic factors of an early identification of severe COVID-19 [152]. Increase in NLR is commonly observed in COVID-19 patients and is associated with poor clinical outcomes [146, 153].

A scoping review of 529 studies involving 165,020 patients from 28 different countries investigating the correlation between initial laboratory values with mortality and disease severity in COVID-19 indicated that among many reported laboratory values, NLR was the most frequent statistically significant laboratory parameter in predicting disease severity [154].

Study of Liu et al. reported that NLR could be an independent predictor of mortality and the risk of in-hospital mortality was higher by 8% for each unit increase in NLR. This risk was independent of other risk factors of death such as older age, comorbidities, and high level of D-dimer [140, 152]. The cut-off value of NLR (7.4) allowed predicting mortality with high accuracy [155]. Another study revealed that high NLR (≥10) and D-dimer (≥2.0 μg/mL), especially when combined, are strong predictors of death risk for patients with severe COVID-19 [156]. NLR is not only important to stratify the severity of the disease, but also to predict mortality in severe cases [156].

Platelet Counts

Low platelet counts were commonly observed in SARS-CoV-2 infections, it can be detected in almost half of the COVID-19 patients and in almost 95% of those critically ill [10, 157]. Thrombocytopenia usually occurs more than 10 days after the onset of symptoms [150]. The meta-analysis of Zong et al. revealed the association between thrombocytopenia and three-fold enhanced risk of a composite outcome of ICU admission, progression to ARDS, and mortality [158]. Several other studies confirmed that low platelets counts may be predictive markers of the severity of COVID-19 [159, 160]. It was found that platelet count is an independent risk factor of mortality among COVID-19 patients, where a 50×10^9/L increase is associated with 40% decreased mortality [148, 161]. Some authors suggested the value of 150×10^9/L as a cut-off level for platelet count to predict poor prognosis [151]. Among the most common hematologic parameters with evidenced prognostic value in diagnosis of progression to serious or severe disease in COVID-19 patients belongs also platelet-to-lymphocyte ratio (PLR) [162, 163]. Systematic review reported that an elevated PLR is associated with severe illness in COVID-19 patients compering to those with mild disease however cut-off levels for this parameter differ significantly in studies [162, 164–166]. Recent systemic review and meta-analysis revealed that elevated level of PLR on admission in COVID-19 patients is associated with higher morbidity and mortality but further studies regarding the cut-off value of PLR are needed [167].

C-Reactive Protein (CRP)

C-reactive protein after lymphopenia is the most frequently described prognostic biomarker in COVID-19 [148, 168–170]. Meta-analysis of 20 studies including 4843 COVID-19 patients, indicated that elevated CRP (>10 mg/L) is associated with nearly fourfold higher risk of poor outcomes [148]. Another study found that median concentration of CRP was nearly ten-fold higher in critically ill patients compering to mildly ill patients [171]. A study of 1834 COVID-19 patients from Italy and the United Kingdom showed that CRP levels ≥40.0 mg/L were associated with 31.9% mortality, whereas mortality in patients with CRP levels <40.0 mg/L was 15% [172]. High levels of CRP are prognostic markers of disease progression and a risk factor for mortality of severe COVID-19 patients and are indicators of a developing cytokine storm [168–175].

Procalcitonin (PCT)

Procalcitonin is a promising prognostic biomarker of COVID-19 progression [176]. Patients with increased procalcitonin levels are at high risk of progression to critical illness [9]. Increased PCT values are associated with a nearly five-fold higher risk of severe COVID-19 and may have been a marker of bacterial coinfection, thereby resulting in complications of COVID-19 and hence a higher rate of ICU admission in these patients [171, 177]. Single study of Hu et al. indicated that serial PCT measurements may be helpful in predicting the prognosis [178]. The cut-off value of 0.16 ng/mL for PCT predicted mortality with high accuracy [155].

Lactate Dehydrogenase (LDH)

Meta-analysis of 18 studies with 5394 patients showed that elevated LDH values are associated with approximately fivefold more risk of poor outcomes in COVID 19 patients [148]. Similarly study of Henry et al. indicated that elevated LDH levels were associated with six-fold increase odds of severe disease and a 16-fold increase in odds of mortality in COVID-19 patients [139]. A meta-analysis of 45 studies identified that elevated LDH predicted mortality and was the only laboratory parameter which predicted both ARDS and ICU admission [45]. Another meta-analysis of 10,399 patients from 21 studies indicated that the association between LDH elevation and poor prognosis was not affected by age, gender, hypertension, or diabetes [179]. The value of 280 U/L is suggested as a cut-off level for LDH to predict poor prognosis [151]. Moreover, LDH levels >400 U/L on admission to the hospital were independently associated with the severity of the disease, so measuring the LDH value at the beginning of the infection may be a biomarker of severe and critical course of COVID-19 [180].

Interleukin 6 (IL-6)

Interleukin 6 may be increased in COVID-19 patients, and it was indicated as an important marker of disease severity and predictor of mortality [181], and its expression time is longer than other cytokines (TNF and IL-1) [182]. Increased IL-6 was recorded in 87% of severe cases [50]. When identifying patients at high risk for severe COVID-19, a cut-off value for IL-6 greater than 55 pg/mL was indicated. Critically ill patients have significantly higher IL-6 levels compared with moderate and severe patients. IL-6 > 80 pg/mL predicts respiratory failure and need for mechanical ventilation [175] and value of ≥100 pg/mL was associated with mortality in COVID-19 [183, 184]. The concentration of IL-6 > 24 pg/mL at initial assessment predicted the development of hypoxemia requiring hospitalization [185]. The currently accepted theory is that overexpression of IL-6 has a crucial role in the induction and propagation of cytokine storm leading to lung injury and ARDS [186–189].

D-Dimer

D-dimer levels are associated with COVID-19 severity and in-hospital mortality [190]. Elevated D-dimer levels are common in patients with COVID-19, suggest extensive thrombin generation and fibrinolysis and are revealed almost three-fold higher risk of poor outcomes [148, 191, 192]. Meta-analysis of six studies indicated that COVID-19 patients with elevated D-dimers have worse clinical outcomes including all-cause mortality, ICU admission, and acute respiratory distress syndrome [193]. D-dimer level that could predict worse prognosis in COIVD-19 patients varies in literatures between >1 mg/L and >2.14 mg/L [7, 194]. It was proposed that a level of >2.0 mg/L on admission could predict death [194, 195]. COVID-19 patients with high D-dimer levels have longer hospitalizations in ICU and lengths of hospital stay [7]. Monitoring the dynamic changes of D-dimer is a useful marker in predicting the prognosis of COVID-19 patients, and peak D-dimer levels were strongly associated with mortality [196].

Ferritin

Elevated levels of serum ferritin were associated with the development of severe outcomes and mortality in COVID-19. Serum ferritin was proposed as one of the markers for potential progression to critical illness [139]. A single study of 141 patients with COVID-19 indicated that elevated ferritin (>500 μg/L) was observed in all severe patients on admission, and the mild patients had a normal mean serum ferritin level; moreover, severe patients and patients who needed admission to the

ICU had higher ferritin levels than the mild patients (2.6 times and 5.8 times, respectively) [197]. It was showed that each 0.1 mg/L increase of ferritin was associated with 3% shortened ICU survival time [198]. Serum ferritin levels were reported to be significantly increased in non-survivors vs. survivors (WMD: 760.2 ng/mL) and as compared to severe vs. non-severe disease (WMD: 408.3 ng/mL) and were suggested as a parameter to be used for monitoring prognosis in COVID-19 patients over the course of hospitalization [193]. Non-survivors showed ferritin levels on admission around 1400 ng/mL, which is between 3 and 4 times higher than that observed in survivors [199]. Meta-analyses revealed that high ferritin levels were associated with severe COVID-19 mortality and development of ARDS as well as with thrombotic complications [200, 201].

Albumin

Albumin levels were found to be a predictive biomarker for outcomes in COVID-19 patients [202–204]. Decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients [151]. Low serum albumin concentrations in critical illness have been associated with poor outcomes. Hypoalbuminemia (<3.5 g/dL) is present in 74% of patients with severe COVID-19 [205]. It was found that hypoalbuminemia was an independent predictor for mortality in COVID-19 patients [206, 207]. Similarly, a multicenter retrospective cohort study of 1555 COVID-19 patients indicated that low serum albumin levels on admission were associated with a higher risk of all-cause mortality within 30 days of hospitalization. Albumin levels below 2.5 g/dL were associated with an almost 60% higher <30 days in-hospital all-cause mortality [208]. Patients with higher albumin levels on admission had a 72% decreased risk of developing venous thromboembolism for every 1 g/dL increase of albumin. Moreover, higher albumin levels on admission were associated with a lower risk of developing ARDS, admission to the ICU and fewer total adverse events [209].

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT)

Meta-analysis of 18 studies with 6,383 patients reported that elevated AST (>40 IU/L) values are associated with nearly threefold higher risk of poor outcomes in COVID-19 patients [148]. Similarly, elevated ALT (>40 IU/L) were associated with twofold increased likelihood of poor outcomes [148]. Patients with abnormal liver enzyme tests at the time of admission had a higher rate of transfer to the ICU (20% vs. 8%), need for mechanical ventilation (14% vs. 6%), acute kidney injury (22% vs. 13%), and mortality (21% vs. 11%) compared to patients with normal

results [210]. In contrary, Huang et al. did not find any difference in AST and ALT values between severe and no severe cases [12]. Similarly, studies of Aloiso et al. did not confirm prognostic values of ALT in COVID-19 patients [202, 211]. Thus, the role of liver enzymes as prognostic biomarkers is debatable and probably have minimal clinical significance [212].

Cardiac Troponin

Troponin is one of the biomarkers of cardiac injury. In the study of Shi et al. elevation of cardiac troponin I (cTnI) > 28 pg/mL was an independent risk factor for COVID-19 severity and mortality [213]. Elevated troponin levels were rare in COVID-19 patients with a mild course (1–20%), common in severe patients (46–100%), and frequent in the critically ill and fatal outcomes [213–215]. Patients with underlying CVD and increased troponin levels had the higher mortality almost 70% compared to patients with only one of these two risk factors [82].

Elevated levels of cTnI remain an independent predictor of death compering to other elevated acute phase proteins and inflammatory markers in patients with CVD [68]. In the study of Peiró et al. cardiac troponin I was a significantly better predictor for 30-day all-cause death compared to other inflammatory biomarkers such as CRP, D-dimer, and lactate dehydrogenase, and the level as low as 21 ng/L was able to provide excellent prediction capacity [216].

Complications

Complications (early, not associated with the long COVID) are another risk factors associated with death among critically ill patients. Common complication in COVID-19 patients include acute respiratory distress syndrome, acute kidney injury (AKI), acute cardiac injury (ACI), thrombosis, gastrointestinal complications, neurologic complications, sepsis, shock, multi-organ failure, and secondary infections [47, 217, 218]. Experiencing adverse complications has a high risk of COVID-19 mortality. Study of Yang et al. indicated that 67%, 29%, 29%, and 23% of hospitalized COVID-19 patients, experienced adverse complications such as ARDS, AKI, liver dysfunction, and ACI, respectively. Of patients developing ARDS, AKI, ACI, and liver dysfunction adverse complications, 74%, 80%, 75%, and 60% of them died, respectively [15].

Meta-analysis of 12 studies with a total of 3064 COVID-19 patients indicated that the most common complications were acute respiratory distress syndrome (30.93%) followed by acute liver injury (22.8%), shock (10.9%), acute kidney injury (7%), and acute cardiac injury (6.4%). Older populations were a high-risk group of developing adverse complications. It was revealed that as the mean age increased by 1 year, the ARDS, AKI, ACI, and shock increased by a factor of 2.9

[219]. Development of ARDS and progression from ARDS to death is associated with risk factors such as older age, neutrophilia, organ, and coagulation dysfunction [220]. Cardiovascular complications in COVID-19 patients may include myocardial injury, heart failure, arrhythmias, acute coronary syndrome, and venous thromboembolism [66, 221, 222]. Meta-analysis of 3044 confirmed COVID-19 cases from 12 studies indicated that the most common cardiovascular complications were myocardial injury (21.2%) and arrhythmia (15.3%), then heart failure (14.4%) and acute coronary syndrome (1.0%). Myocardial injury and heart failure were more frequent in non-survivors, regardless of a history of CVD [221]. Cardiac complications, which are becoming more prevalent with the progress in the study of COVID-19, influence the development and prognosis of disease.

Reinfection

It was thought that individuals who recovered from COVID-19 generate a robust immune response and develop protective immunity; however, since August 2020, numerous cases with reinfection have been documented [223–225]. Positive COVID-19 antibodies after infection can provide protection against reinfection in most studied patients [226]. Cases of reinfection in patients are relatively rare [227], however, in the time of omicron there were many new cases of reinfection.

A systematic review indicated 17 cases of individuals infected with different genetic strains of SARS-CoV-2 confirmed by PCR. The results indicated that reinfection with different strains is possible, and the second episode of the infection might be more severe in nearly 20% of patients and result in serious complications in elderly and immunocompromised [86]. At present it is unclear how long serum antibodies and virus-specific T cells persist after infection, how common reinfection with SARS-CoV-2 can be and whether it occur in individuals with detectable immune memory [228, 229].

Conclusions and Take-Home Message

Prognosis in COVID-19 patients is closely related to the severity of disease. Between patients with severe and none-severe course of the disease significant difference exists in terms of demographic features, clinical symptoms, comorbidities, laboratory parameters, and complications. Laboratory biomarkers are fast and easy to obtain and preferred modality to monitor and predict prognosis of disease. Continuous controlling of laboratory parameters is essential to identify those patients who may progress to severe status and allow timely preventative efforts and optimization of high-risk patients. Knowledge on COVID-19 prognostic factors is constantly changing (however, hypertension, obesity, diabetes, COPD, seems to be the ones that occur the most often in the available analyses); new biomarkers are

analyzing which could be useful in COVID-19 prognosis [230–236]. Available data also suggest that the optimalization of the underlaying conditions and risk factors may significantly decrease the risk of severe COVID-19 course [230–236]. The creation of a machine learning system to fully analyze the profile of a patient with COVID 19, both in terms of demography, comorbidities, previous infections, and the concentration of laboratory biomarkers, may be an option for early detection of patients at risk of severe COVID-19 requiring hospitalization.

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Part II
Cardiovascular Complications of the Acute Phase of COVID-19

Chapter 6
Myocardial Injury in COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, Treatment)

Stefania Lucia Magda, Roxana Cristina Rimbas, and Dragos Vinereanu

Introduction

Coronavirus disease 2019 (COVID-19) was considered initially a respiratory illness. Respiratory failure is the major cause of morbidity and mortality in COVID-19 patients, with the disease spectrum ranging from asymptomatic subclinical infection to severe pneumonia, progressing to acute respiratory distress syndrome [1, 2]. However, involvement of multiple organs, especially the cardiovascular system, has been extensively reported in the acute phase of infection, and concern is growing that survivors may develop long-term sequelae, particularly after intensive care unit (ICU) admission [3].

Approximately 2 years after its emergence, SARS-CoV-2 is considered a viral pathogen affecting also the vasculature, and potentially resulting in ***myocardial injury*** [3]. This can occur either by direct viral-mediated cytopathic effects or by activation of immune mechanisms, resulting in inflammatory cell infiltration [4].

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Definition of COVID-19 Induced Myocardial Injury

Many reports indicate that myocardial injury is frequent among patients with COVID-19, and is related to poor prognosis [1, 2]. Following recommendations from the Task Force for the Universal Definition of Myocardial Infarction and from the European Society of Cardiology Guidance for the Diagnosis and Management of Cardiovascular Disease during the COVID-19 pandemic, the term ***myocardial injury*** applies to any patient in whom at least one cardiac troponin (cTn) concentration is above the 99th percentile upper reference limit [5].

After careful clinical evaluation, COVID-19 patients with increased cTn, indicative of myocardial injury, should be classified as follows [6]:

1. **Acute non-ischemic myocardial injury**: It applies to patients with dynamic rising and/or falling cTn levels, without clinical evidence of myocardial ischemia;
2. **Chronic myocardial injury**: It applies to patients with chronic, stable (<20% change) cTn increases, and can be frequently encountered in patients with COVID-19 of older age and with high prevalence of chronic cardiovascular diseases;
3. **Acute myocardial infarction (MI)**: It applies to patients with the universal definition of myocardial infarction; risk for type 2 MI is higher in severe forms of COVID-19, because of the respiratory failure with hypoxia and hemodynamic disturbances [6]. Type 2 MIs are common in critically ill patients, especially when previous history of ischemic heart disease is present.

All recent data suggest that acute non-ischemic myocardial injury is the predominant cause for cTn increases in patients with COVID-19 [6, 7]. It can be generated by acute heart failure, myocarditis, stress cardiomyopathy, direct severe acute SARS-CoV-2 injury, critical illness, and pulmonary embolism [6]. Despite emerging reports of myocarditis in patients with COVID-19, cTn increases should not always be considered myocarditis-induced. Clinical context, pre-test probability, and careful evaluation of signs and/or symptoms should inform about the cause of cTn increases [1, 2, 6].

Epidemiology

Initial evidences pointed to myocardial injury as a COVID-19-related complication with an incidence ranging from 7% to 36% [8–12]. In a systematic review from 2020, including 374 patients, cTn levels were significantly higher in those with severe COVID-19 infection compared to those with non-severe disease (OR 25.6; 95% CI 6.8 to 44.5) [13]. Incidence of myocardial injury is reported up to 59% in COVID-19 patients who died [14, 15].

Myocardial injury is predictive of adverse outcomes in COVID-19 patients. Metkus et al. [16] reported a greater than twofold risk of mortality in critical ill patients with myocardial injury. By using nationwide registers in Denmark, Modin

et al. [17] suggested that COVID-19 might be associated with an increased risk of ischemic cardiovascular events. Incidence of acute myocardial infarction 14 days after a positive test for COVID-19 was approximately five times higher by comparison with the 180 days prior to the COVID-19 diagnosis [17].

Patients with myocardial injury are older and have more cardiovascular comorbidities, in particular history of hypertension and ischemic heart disease, than those without cardiac injury [9, 18]. A large meta-analysis, involving 77.317 patients, reported that pre-existing cardiovascular comorbidities or risk factors were significant predictors of cardiovascular complications in COVID-19 patients, in addition to age and gender [19]. Another meta-analysis by Figliozzi et al. concluded that a history of cardiovascular disease triples the risk of severe COVID-19, defined as death, severe infection, hospitalization in an intensive care unit (ICU), and/or use of mechanical ventilation [20]. Case fatality was highest in older groups. Thus, highest mortality occurred in patients aged >80 years, in whom this was six times higher than in younger patients [20].

Prevalence of cardiac dysfunction might be present in 70% of patients with COVID-19 within the first ICU admission, identified by multimodal cardiac assessment, not only by cTn level [21, 22]. A multicenter CMR study by Kotecha et al. showed that myocardial injury during acute COVID-19 infection, requiring hospital admission, is associated with a CMR abnormality in 54% of patients [23]. Moreover, in young athletes recovering from COVID-19, CMR abnormalities consistent with myocarditis have been reported at a higher prevalence than expected, in approximately 1–3% of the athletes [24–28].

Pathogenesis of Myocardial Injury in COVID-19 Patients

Pathogenesis of myocardial injury in patients affected by COVID-19 is not completely understood (Fig. 6.1). In the past, coronaviruses have not been commonly associated with significant myocardial damage. Coronaviruses have the capacity to bind to the metallopeptidase Angiotensin Converting Enzyme-2 (ACE-2), as shown in a study by Li et al., done over a decade ago [29]. Hamming et al. explored the expression pattern of ACE-2 and noted that this is present in several territories, such as lung alveolar epithelial cells, small intestine epithelial cells, arterial and venous endothelial cells, and smooth muscle cells [30]. The variety of ACE-2 tissue expression might explain the correlation between SARS-CoV-2 and extrapulmonary manifestations [29, 30].

Patients with myocardial injury have higher values of **acute inflammatory markers** and leucocytes. These markers are linearly correlated with troponin levels, suggesting that myocardial injury may be closely related in its pathogenesis with sustained inflammatory response determined by COVID-19. Release of inflammatory cytokines during SARS-CoV2 infection can lead to mismatch of oxygen demand, destabilization of coronary plaque, microthrombogenesis, and apoptosis or necrosis of myocardial cells [18, 31–33]. All these mechanisms are not unique to

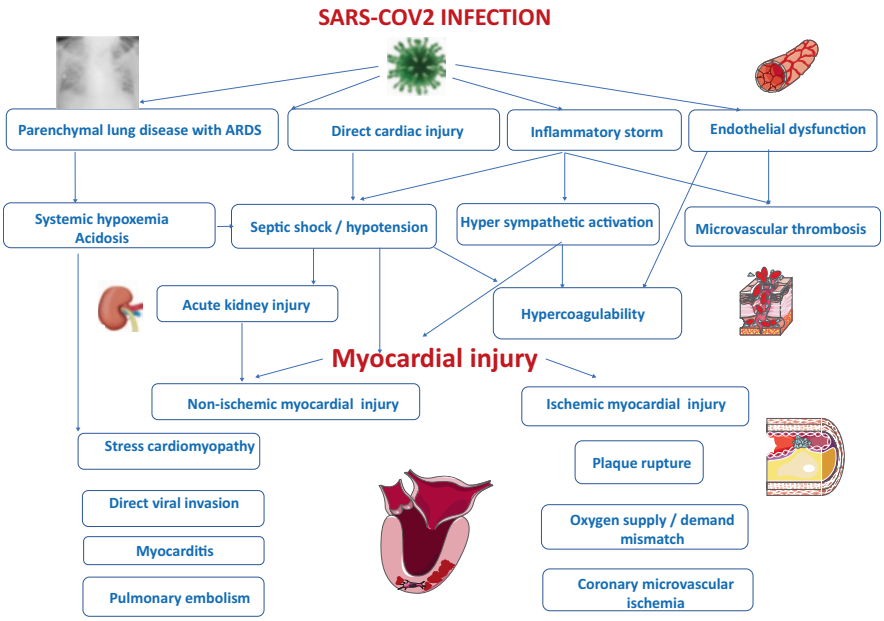

Fig. 6.1 Potential mechanisms involved in myocardial injury in SARS-COV-2 infection

COVID-19, as many severe infections can generate a similar pattern. Nevertheless, there are conflicting reports on the myocardial histology of patients with COVID-19 with evidence of myocardial injury [30–33].

Troponin elevation in the setting of COVID-19 might be explained by different causes [31, 33], as follows:

1. non-ischemic myocardial injury (more commonly) related to different possible mechanisms (e.g., severe hypoxia, sepsis, systemic inflammation, pulmonary thromboembolism, cytokine storm, stress cardiomyopathy);
2. ischemic myocardial injury with different potential mechanisms (e.g., plaque rupture, coronary spasm, microthrombi, or direct endothelial or vascular injury); or,
3. typical viral lymphocytic myocarditis.

It has been noted that patients with a history of cardiovascular disease are more susceptible to cardiac injury during COVID-19 [1, 2]. Different mechanisms have been proposed to explain the increased vulnerability of patients with underlying CVD for severe forms of COVID-19 [7, 33–35]:

1. ineffective adaptation of the cardiovascular system to the increased demand of a severe viral illness;
2. decreased systemic oxygenation during pneumonia;
3. immune dysregulation—T cell and immune signaling dysfunction, recognized as an important factor in the pathogenesis of vascular disease;

4. potential direct viral myocardial injury with local infection within the myocardium, with non-clinical overt inflammation.

The immunologic profile in COVID-19 was addressed in several studies. Laing et al., in an exhaustive immunologic analysis, identified a core peripheral blood immune signature across hospitalized patients with COVID-19. The signature included discrete changes in B and myelomonocytic cell composition, profoundly altered T cell phenotypes, selective cytokine/chemokine upregulation and SARS-CoV-2-specific antibodies [36].

While some investigators have proposed direct virus invasion, as the most likely mechanism for cardiac alterations in COVID-19, others focus more on host inflammatory cell responses. Emerging data indicate that a maladaptive host immune response fueled by excessive activation of innate immune pathways along with pro-inflammatory cytokine surge, dysregulated thrombo-inflammation, thrombotic microangiopathy, and endothelial dysfunction may play a role in the pathogenesis of cardiac injury related to COVID-19 [25, 26].

Although SARS-CoV-2 can enter the cardiomyocyte through an ACE2-mediated pathway and SARS-CoV-2 copies have been detected in the heart tissue [20, 27, 28], cardiac histopathology studies have reported the absence of diffuse lymphocytic myocarditis traditionally seen in viral myocarditis or confluent myocyte necrosis expected in fulminant myocarditis [28–32]. Hearts of patients who died from COVID-19 contain more CD68+ cells, with diffuse distribution, compared with other myocarditis hearts, indicating that cells of the monocyte/macrophage spectrum, rather than lymphocytes, may be dominant in this setting [25].

Other studies revealed that interstitial cells in the myocardium, pericytes, and macrophages, contain SARS-COV-2 RNA by in situ hybridization, and that pericytes infected by SARS-CoV-2 may play a role in capillary endothelial cell or microvascular dysfunction and individual cell necrosis [20, 31–33]. It is important to note that macrophages can mediate both local and systemic responses to viral infection and are also capable of fixing complement, and thus could cause the direct death of nearby myocytes through the activation of apoptotic attack complexes [25, 31]. Consequently, COVID-19 may induce a form of myocarditis that is different from the typical lymphocytic myocarditis generated by other viral infections, being associated with diffusely infiltrative cells of the monocytes/macrophage spectrum [25, 31, 32].

There is also evidence that infection of the secretory cell population in the bronchial branches is influenced not only by ACE2 expression, but also by the proteases TMPRSS2 and Furin, as potential cofactors [7, 36, 37]. However, the role of these proteases in binding, uptaking of SARS-Cov-2 and its replication in the heart cells is not known.

Another emerging mechanism of cTn elevation in patients with COVID-19 is represented by arterial and venous thromboembolism, affecting a large proportion of patients in ICU (16–49%), causing deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, and systemic arterial embolism [38–41].

Autopsy series of patients with COVID-19 have reported endothelial cell infection in several organs, including the heart vessels, with no sign of lymphocytic

myocarditis. Endothelial cell infection could be another possible mechanism of myocardial lesion and troponin elevation [37, 42].

Although myocardial cells are a potential target of SARS-CoV-2, myocarditis has been reported in a limited series of cases, where 7% of deaths were attributed to myocardial damage with circulatory failure, without a certitude diagnosis of myocarditis [43]. Endomyocardial biopsies examined on electron microscopy revealed viral particles contained in macrophages, but not in cardiomyocytes or other specific cardiac cell types [42].

The immunological and inflammatory mechanisms leading to cardiac damage in COVID-19 are numerous and rely mainly on cytokine and interferon inflammatory responses, myocardial interstitial fibrotic response, and T1 and T2 helper cell response [44, 45]. In COVID-19 studies an imbalance between both Th1 and Th2 activity was shown, leading to the inflammatory surge [46].

A recent autopsy study demonstrated, by in situ hybridization (ISH) and immunohistochemistry (IHC) techniques, the presence of an inflammatory infiltrate around epicardial vessels, extending into the outer layers of the vessel wall, outwards into the pericardial adipose tissue and in some cases following the vessels into the myocardium [46]. The inflammatory cells in this infiltrate were predominantly lymphoid in nature, particularly CD4-positive (IHC), with scanty CD8-positive T-cells and CD20-positive B cells. Involvement of nerves was also seen in some cases. In cases where COVID-19 symptoms persisted for more than 14 days, the inflammatory infiltrate was less prominent, and the coronary vessels showed hypertrophy with focal dilatation, or tortuosity of vessels [46]. A fine perivascular fibrosis was also noted around vessels of varying diameters, including capillary vessels. The pericardial adipose tissue was found to be involved in the inflammation in all cases, irrespective of duration of symptoms.

SARS-CoV-2 penetrates into various cells, including the cardiac myocytes, and generates an immediate innate cytokine response, which causes the initial myocardial damage early in the course of the infection, further aggravated by arrival of the T-lymphocytes [46]. ISH and immunofluorescence assays showed that viral signals are present also within the cardiac myocytes. IHC discovered the virus within the vessel lumen and wall, as well as in the close area of the perivascular space, together with activated lymphocytes and cytokine activity [46]. The cytokine and inflammatory cell activity within the vessel lumen could lead to injury of the endothelial border. In all autopsy cases, platelet and fibrin thrombi in myocardial vessels and the myocardial microvasculature were found, persisting even in cases with a prolonged disease [46].

The presence of NP protein signals within the lumen of the vessel also suggests persistence of the virus in circulating monocytes, as another stimulus for the microembolic events. Pathogenic cytokines such as IL-6 [46–49] and IL-1β [9, 49–51], with known profibrotic role, were detected at autopsy in the myocardium of COVID-19 patients, initiating fibrosis, later completed by the expression of collagen I and III [9, 49, 51, 52].

All the above presented data suggest that profibrotic cytokines and mediators released during the myocarditis phase, in susceptible individuals, activate fibroblasts and stimulate fibroblast differentiation, leading to subsequent cardiac

remodeling [46]. Moreover, persistent epicardial adipose tissue inflammation, detected in a majority of cases, is responsible for the secretion of endocrine and paracrine substances and may further aggravate vascular injury [46–49, 51, 52].

Biomarkers Assessment of Myocardial Injury

Several biomarkers (C-reactive protein [CRP], serum amyloid A, Il-6, lactate dehydrogenase [LDH], neutrophil-to-lymphocyte ratio, D-dimers, cardiac troponin, NT-pro BNP, renal biomarkers, lymphocytes and platelet count) are very useful in monitoring the evolution of COVID-19 patients with myocardial injury [53].

Cardiac Troponin

Tissues that express ACE2, including cardiovascular cells and lung tissue, are prone to SARS-CoV-2 infection. As discussed in the previous sections, during COVID-19, myocardial injury occurs mainly through several non-ischemic processes, such as: (1) hypoxia; (2) sepsis; (3) systemic inflammation; (4) pulmonary thromboembolism (through prothrombotic endothelial dysfunction and coagulation activation, triggered by direct viral action and inflammation); (5) cardiac adrenergic hyperstimulation induced by the cytokine storm; and (6) myocarditis [7, 54].

Ischemic elevation of cTn can also be found in COVID 19, mediated by endothelial dysfunction and vascular inflammation, plaque rupture, coronary spasm, microthrombi or direct vascular injury [55]. Meanwhile, cTn values might be increased by concomitant renal failure, which is relatively frequent in severe COVID-19 [7].

Myocardial and Systemic Inflammation

Acute phase and inflammatory markers (such as CRP, serum amyloid A, Il-6, LDH, neutrophil-to-lymphocyte ratio, D-dimers, and procalcitonin) are higher in patients with high troponin levels than in those with mildly elevated troponin. Increases in CRP and D-dimers have strong association with mortality [12].

Other Biomarkers

Myoglobin, creatin kinase isoenzyme MB (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP) are linked to the severity and fatality of COVID-19 [56, 57].

Nevertheless, it is important to keep in mind that levels of all these biomarkers are influenced by factors such as hypoxia or renal function and, therefore, diagnosis of myocardial injury should be a complex one, including clinical factors and several paraclinical parameters, as follows in the next section.

Paraclinical Assessment of Myocardial Injury

ECG

At first evaluation, patients with myocardial injury have frequently ST-segment elevation or depression. Also, some have conduction disturbances and low-voltage criteria. A normal ECG should not exclude myocardial injury and studies have shown that approximately one third of patients with normal ECG at first evaluation develop subsequently changes [14].

Cardiac Ultrasound

Patients with myocardial injury have usually normal ejection fraction. Nevertheless, compared to COVID-19 patients without myocardial injury, those with myocardial injury have more echocardiographic abnormalities, such as higher heart chamber volumes and left ventricular wall thickness, global left ventricular (LV) and/or right ventricular (RV) dysfunction, regional LV wall motion abnormalities, diastolic dysfunction, and pericardial effusion [14].

Most reports do not describe major cardiac ultrasound abnormalities, even in patients with high probability of myocardial injury. Therefore, studies using ultrasound methods, able to discern subtle, subclinical changes, such as speckle tracking echocardiography, with complementary quantification of myocardial work, are very useful in this setting. Even in patients with normal ejection fraction, the presence of lower LV global longitudinal strain and lower myocardial work indexes were correlated to the persistence of symptoms, such as dyspnea, long time after the recovery from the acute disease [58].

A small study from Germany evaluated prospectively patients with myocardial injury hospitalized for COVID-19 by cardiac ultrasound, CMR, and endomyocardial biopsy. Standard echocardiography revealed normal or mildly reduced LVEF, but speckle tracking showed moderately to severely reduced LV global longitudinal strain. CMR showed either myocardial tissue injury or myocardial oedema. Endomyocardial biopsy was performed in a small number of patients and revealed high macrophage numbers, myocardial fibrosis and, in one case, lymphocytic myocarditis. Interestingly, LV global longitudinal strain was significantly improved at follow-up (median follow-up time of 52 days). This study highlights the fact that multimodality imaging, combining speckle tracking

echocardiography with CMR, might be useful in revealing cardiac changes in patients with myocardial injury [59].

Coronary Angiography

Coronary angiography is performed in COVID-19 patients, mainly due to angina symptoms, with or without either ECG or echocardiographic changes. Giustino et al. performed coronarography in 11 out of 305 patients with myocardial injury, defined accordingly to cardiac troponin levels. A total of 8 out of 11 patients had confirmed acute coronary syndromes with significant lesions of the epicardial coronary arteries, whereas the other three patients had normal coronary arteries [14].

Computed Tomography Angiography (CTA)

Computed tomography angiography (CTA) can be considered as an alternative to coronary angiography for the assessment of ongoing chest pain, especially in patients at low risk for acute coronary syndromes (it was used in studies on young, healthy athletes with ongoing/recovering COVID-19) [60]. Coronary CTA may sometimes reveal non-coronary cardiac and vascular changes, such as pericarditis or pulmonary embolism.

Cardiac MRI

Cardiac MRI is the non-invasive gold standard for the assessment of myocardial injury, as recommended by current position statements [22, 61, 62]. MRI T2-weighed sequences can diagnose myocardial oedema and are essential for the evaluation of suspected myocardial inflammation. MRI studies in COVID-19 have shown that myocardial oedema is frequently present in older patients (up to 60%) [21], but can occur also in healthy young athletes (up to 15%) [24, 28, 63]. Two studies including hospitalized patients with documented acute myocardial injury, evaluated through cardiac MRI (cine images, T1 and T2 mapping, late gadolinium enhancement) 2 months after recovery, showed that more than 50% of patients had cardiac abnormalities, with inflammatory and/or ischemic patterns and in a few cases with ongoing myocardial inflammation [21, 62].

Kotecha et al. showed that myocardial injury during COVID-19 requiring hospital admission is associated with CMR abnormalities in approximately half of patients [23]. Three different patterns of myocardial injury were described: non-ischemic, myocarditis-pattern injury (27%); ischemic (infarction and/or inducible ischemia) heart disease related (22%); and non-ischemic, non-specific scar (5%).

Dual pathology, with ischemic and non-ischemic features was observed in 6% of patients. Neither admission nor peak cTn levels were predictive of the diagnosis of myocarditis. No CMR differences regarding evidence of myocarditis, between patients requiring intensive care and those who did not, were noticed. Biventricular function was preserved in patients with myocarditis and was similar to those without myocarditis. Of patients with myocarditis-pattern injury, 1/3 had findings consistent with active myocarditis while 2/3 had healed myocarditis. Diffuse oedema or fibrosis was not detected [23]. This study highlights not only the importance of CMR for the correct diagnosis of myocardial injury in COVID-19, but also its contribution in detecting potential mechanisms [23].

Follow-Up and Treatment

For severe and critically ill patients, treatment should focus on respiratory support with continuous evaluation and management of organ failure. Clinical exam and cardiac ultrasound can diagnose early signs of heart failure. Troponin should be measured at admission and every few days or based on clinical course, in order to identify patients with acute myocardial injury and, consequently, with worse prognosis. Extensive cardiac ultrasound and other imaging methods are indicated only in selected patients, in order to provide supplementary information.

Patients with cardiovascular risk factors or history are at high risk of developing an acute coronary syndrome (ACS) during COVID-19. Acute coronary syndromes in COVID-19 should be managed based on current guidelines, individualized according to characteristics of patients [64, 65].

Systemic anticoagulation should be given in hospitalized patients, as suggested by current protocols, due to high prevalence of hypercoagulability in COVID-19 patients [66]. Several antiviral (remdesivir), anti-inflammatory (dexamethasone), and immunomodulatory (tocilizumab, baricitinib) therapies are currently used in hospitalized patients [67], but their efficacy in patients with organ dysfunction is not confirmed. Special attention should be dedicated to anti COVID-19 drugs interactions with cardiac medication.

Use of ACE inhibitors and angiotensin receptor blockers in patients with COVID-19 is still under some debate, since both medications upregulate the ACE-2 receptors used by the SARS-CoV-2 virus for penetrating into human cells. So far, there is no data to confirm that using these medications increase the risk of COVID-19 infection or aggravate its course. A systematic review by Pranata et al. [68] showed that administration of a RAS inhibitor was not associated with increased mortality or severity of COVID-19 and that, in fact, RAS inhibitors are associated with lower mortality. Several leading cardiology societies recommend continuing RAS inhibitors in patients with COVID-19, unless there are no other contraindications [69].

Treatment protocol for COVID-19 patients with myocardial injury should focus on general and symptomatic treatment, antivirals, respiratory failure treatment, circulatory support, antibacterial for secondary infections, cytokine storm treatment, and corticoids in severe patients [56].

Table 6.1 Strategies for diagnosis and treatment of acute myocardial injury in COVID-19

Diagnosis	Treatment
Complete clinical examination	Patients with confirmed acute myocardial injury should pe continuously monitored
Bed-side hand-held ultrasound	Patients with ACS should be treated according to current guidelines
Initial measurement of hs-troponin with consequent longitudinal monitoring	In patients with myocardial injury without ACS, treatment of COVID-19 should be done according to the clinical course of the disease and current protocols
Initial and longitudinal monitoring of ECG	Systemic anticoagulation should be considered in hospitalized patients
Initial measurement and consequent longitudinal monitoring of inflammation markers	ACEI/ARB should be continued or initiated if needed
Standard and speckle tracking echocardiography, cardiac MRI, cardiac angio-CT, coronary angiography if needed and with clinical benefit	In critically ill patients a multidisciplinary team should decide on strategies for escalation of care (such as mechanical circulatory support)
Right and left heart catheterization in highly selected cases	

hs-troponin high sensitivity troponin, *ACS* acute coronary syndromes, *ECG* electrocardiogram, *MRI* magnetic resonance imaging, *ACEI* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers

In 2020, the American College of Cardiology issued the recommendation that patients with COVID-19 and coronary artery disease should be actively given statins, ACE inhibitors, beta-blockers and aspirin [70]. Table 6.1 summarizes proposed strategies for diagnosis and treatment of acute myocardial injury in COVID-19 patients.

Prognosis

Patients with acute myocardial injury are older, with more cardiovascular disease, and more likely to require intensive care in the course of the disease [9, 18, 71]. Several studies suggest that myocardial injury seems to be a risk factor for severe evolution and for higher mortality in COVID-19. Yang et al. showed that myocardial injury was associated with disease severity at hospital admission, and that high levels of D-dimers, troponin I, and CRP were associated to higher probability of death [72]. Calvo Fernandez et al. highlighted that myocardial injury reflected by two biomarkers (NT-proBNP and hs-troponin) are related to COVID-19 severity, expressed as need for mechanical ventilation or death [73].

Patients with cardiovascular risk factors or previously documented coronary artery disease are at high risk of developing acute coronary syndromes during COVID-19, due to severe increase in myocardial oxygen demand and circulating

cytokines, leading to atherosclerotic plaque rupture instability and rupture. Patients with heart failure are exposed to decompensation during severe infections [74]. Shi et al. assessed a cohort of hospitalized COVID-19 patients, and showed that patients with myocardial injury had a significantly higher in-hospital mortality compared to those without myocardial injury, and that higher hs-troponin increases were linked to higher mortality rates [50]. Similarly, Guo et al. reported higher mortality rates in COVID-19 patients with myocardial injury (expressed as increase in troponin T), the highest mortality rates being observed in patients with underlying cardiovascular disease. This study also underlined the connection between myocardial injury, ventricular dysfunction, and inflammation (reflected by troponin T, NT proBNP and CRP values), and their synchronized influence on mortality [8].

Patients with myocardial injury and COVID-19 have more severe inflammation and high levels of cTn, but also of other biomarkers reflecting myocardial stress, such as creatin kinase, myoglobin, and NT-proBNP [74]. Elevated cTn was also associated with a higher risk for other in-hospital adverse events, such as acute kidney injury and low oxygen saturation [6, 7].

Data from literature regarding the prognostic value of cTn increases in COVID-19 patients have important practical implications, indicating cTn as an additional guiding tool for key clinical decisions in critically ill patients, such as identifying subjects who would benefit from prompt intubation and thus avoiding the delay that often causes the irreversible worsening of clinical outcomes [8, 50, 75].

Conclusions

There are ten key points on myocardial injury in COVID-19 patients, as follows:

1. The term “myocardial injury” applies to any patient in whom at least one cardiac troponin concentration is above the 99th percentile upper reference limit;
2. Incidence of myocardial injury in COVID-19 is higher when using high sensitivity troponin assays and in patients with severe illness;
3. Main mechanism of myocardial injury in COVID-19 is immune dysregulation—T cell and immune signaling dysfunction;
4. Currently, there is no reliable proof of direct infection and replication of SARS-CoV-2 in the heart cells;
5. Acute phase and inflammatory markers (D-dimers, C-reactive protein, lactate dehydrogenase, and procalcitonin) are higher in patients with high troponin levels, and strongly correlated with mortality;
6. Careful evaluation is essential for COVID-19 patients with troponin increases suggesting myocardial injury, in order to classify them correctly as chronic myocardial injury, acute non-ischemic myocardial injury, or acute myocardial infarction;
7. Myocardial injury is independently associated with increased risk of in-hospital mortality;

8. Use of serial cTn measurements, along with other inflammatory and thrombotic markers, as well as complementary imaging methods (such as cardiac ultrasound and CMR) among patients presenting to the hospital with SARS-CoV-2 infection may facilitate COVID-19 stage classification, patient triage, and risk stratification;
9. A treatment protocol for COVID-19 patients with myocardial injury should focus on general and symptomatic treatment, antivirals, respiratory failure treatment, circulatory support, antibacterial for secondary infections, cytokine storm treatment, and corticoid treatment in severe patients;
10. Troponin monitoring in COVID 19 is a very useful guiding tool for key clinical decisions in critically ill patients.

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Chapter 7
Acute Coronary Syndrome: Destabilization of Atherosclerotic Plaque in COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, and Treatment)

Stanisław Surma, Joanna Lewek, and Maciej Banach

Only constant, daily learning and internal discipline is the duty of the medic, otherwise it may be harmful to the patient

Professor Franciszek Kokot, a great Polish doctor and scientist

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was first identified in December 2019 in Wuhan, China. This coronavirus belongs to the family of zoonotic viruses, and its genetic material is single-stranded ribonucleic acid (RNA). SARS-CoV-2 causes the disease named COVID-19 (Coronavirus Disease 2019) in accordance with the recommendations of the World Health Organization (WHO), which is an acute infectious disease of the respiratory system. The disease was declared a global pandemic by the WHO on March 11, 2020 [1]. COVID-19 has

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become the most important public health issue worldwide due to its rapid spread, morbidity, and mortality. COVID-19 has a mortality of around 1.4% and a transmission rate of around 2.5–3.0 (the number of newly infected people per previously infected person). Between infected hosts, COVID-19 is primarily transmitted through contact with droplets that contain viral particles with a mean incubation of about 5 days. Droplets are any medium in which a human can release the virus, such as coughs, sneezes, and mucous. They generally cannot travel more than 2 m from their origin [2]. According to WHO SARS-CoV-2 infection has been confirmed in over 420 million people worldwide, while nearly six million people have died in the course of COVID-19.

COVID-19: Short Clinical Characteristics Through the Prism of Cardiology

COVID-19 is a multiorgan disease with a wide spectrum of clinical symptoms, causing permanent, long-term consequences following acute SARS-CoV-2 infection. The first phase covers the onset of the disease and is characterized by mild to moderate flu-like symptoms. In this phase, it is possible to infect other people and the presence of the virus in the respiratory tract can already be detected using the reverse transcription polymerase chain reaction (RT-PCR) method. Some patients recover fully and in some of them develops the second stage of the disease [3]. The dominant symptoms in the second phase of the disease are associated with the development of pneumonia (associated with hypoxemia and dyspnea). In this phase of the disease, lung opacity on chest X-ray or ground glass opacities on computed tomography can be detected [4–6]. Subsequently, the patient's condition may improve or worsen along with the need for intubation and artificial ventilation, which is already characteristic of the third phase of COVID-19. Patients in this phase suffer from severe, generalized inflammation and symptoms of sepsis. These patients require hospitalization in the intensive care unit. High mortality is observed in patients in the third phase of the disease [8]. The severity of the course, the type of clinical symptoms, and the mortality in the course of COVID-19 depend on age (greater severity at the age of over 65) and comorbidities (mainly diabetes, cardiovascular diseases, including hypertension, chronic lung diseases, and chronic kidney diseases) [7].

Thus, the typical clinical spectrum of COVID-19 includes fever, cough, myalgia, dyspnea, with frequent progression to pneumonia, which in one-third of the cases eventually leads to acute respiratory distress syndrome (ARDS), of which another third warrant critical care. A meta-analysis of 423,117 patients showed that the mortality rate among hospitalized COVID-19 patients was 17.62% (95% CI: 14.26–21.57%) [9].

It should be noted that the target of SARS-CoV-2 is primarily the respiratory system, but a significant proportion of COVID-19 patients develop cardiovascular complications, which is associated with a worse prognosis. A meta-analysis of 3044

COVID-19 patients showed that the most common cardiovascular complications were myocardial injury (21.2%, 95% CI 12.3–30.0%) and arrhythmia (15.3%, 95% CI 8.4–22.3%), followed by heart failure (14.4%, 95% CI 5.7–23.1%) and acute coronary syndrome (ACS) (1.0%, 95% CI 0.5–1.5%) [10]. Another meta-analysis of 4157 COVID-19 patients showed that incidence rate of arrhythmia, myocardial injury, and heart failure was 10.11%, 17.85%, and 22.34%, respectively. The pooled incidence rates of cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), and creatine kinase (CK) elevations were also reported at 15.16%, 10.92%, and 12.99%, respectively [11]. Thus, cardiac complications are relatively common in COVID-19 patients. It should be noted, however, that apart from the direct influence of COVID-19 on the cardiovascular system, factors related to pandemic and lockdown also play an important role, such as: discontinuation of cardioprotective drugs, deferring interventional procedures, outpatients visit interruption, decrease and delayed hospital presentation for ACS and heart failure, increase of complicated ACS [12]. This is confirmed by the observation that myocardial injury (among all COVID-19 patients) ranges from 17% to 66%, while de novo myocardial damage affects 7–11% of patients [13]. All this makes the influence of SARS-CoV-2 and COVID-19 infection on cardiovascular risk and cardiological complications very complex and not fully understood. Overall, the clinical course of COVID-19 ranges from asymptomatic myocardial injury to more serious complications such as type 1 myocardial infarction, arterial or venous thromboembolism, or myocarditis [14, 15]. The impact of COVID-19 on future cardiovascular risk is also extremely important. At the present state of knowledge, it is probably necessary to distinguish at least three fields of interest for cardiologists regarding SARS-CoV-2 infection (Table 7.1). In addition, acute cardiovascular complications secondary to COVID-19 is summarized in Fig. 7.1.

Thus, as given in Table 7.1, the risk of an acute coronary event applies to both the acute phase of COVID-19 and the long time after recovery. From a clinical point of view, it is also important that the severity of the course of COVID-19 does not correlate with a higher risk of long-term complications. In a multicenter cohort study by Davis et al., including 3762 COVID-19 patients from 56 countries, 66 long-term complications of COVID-19 were identified. The study found that patients with moderate COVID-19 were at the highest risk of long-term complications. Paradoxically, patients with a very severe course of COVID-19 were characterized by a low risk of long-term complications in a 7-month follow-up. Moreover, in this study it was found that the risk of cardiological symptoms such as fainting, pain/burning in chest, tachycardia during the 7-month follow-up remained at a similar level (peakless symptoms), while symptoms such as bradycardia, palpitations or visibly inflamed/bulging veins most often occurred 2 months after recovery [29].

In summary, SARS-CoV-2 infection can cause numerous complications of the cardiovascular system, both in the acute phase and after recovery. It is worth mentioning that in order to emphasize the high clinical significance of COVID-19 cardiological complications in the literature, the term COVID-AMI is used, including, inter alia, induced by this disease: myocardial infarction (MI), acute viral myocarditis, and stress cardiomyopathy. COVID-AMI has been defined as the elevation of

Table 7.1 Summary of the possible cardiovascular complications of COVID-19. Based on [16–27]

Disease stage	Time of occurrence/ duration of the complication	Potential cardiac complications	Additional information
Acute COVID phase	1–4 weeks	• Myocardial injury (17%) • Acute coronary syndrome • Heart failure • Arrhythmias (23%) • Thromboembolic events (≥31%) • Myocarditis • Arterial thrombotic events • Venous thromboembolism • Takotsubo syndrome • Pericardial effusion/ pericarditis • Pulmonary embolism • Cardiogenic shock • Acute pulmonary heart Common cardiovascular symptoms: • Chest pain • Arrhythmia • Elevated levels of LDH and D-dimer, thrombin, vWF Cardiac imaging techniques main findings in COVID-19 patients with cardiac involvement: • Echocardiography: RV dilatation and reduced EF; increased PASP; LV diastolic dysfunction; wall motion abnormalities; impaired LVGLS • CMR: LGE; myocardial edema; impaired LVEF; increased LV volume; pericardial effusion	The exact incidence is difficult to estimate. In most cases, SARS-CoV-2 infection contributes to the progression of an already existing cardiovascular disease. More frequently, they are merely a derivative of a typical clinical sequence: infection → pneumonia → respiratory failure → cardiorespiratory failure and multiple organ failure. When this group of patients is excluded, the "cardiac manifestations" of COVID-19 affect merely 1–2% of patients, or maybe even less

Table 7.1 (continued)

Disease stage		Time of occurrence/ duration of the complication	Potential cardiac complications	Additional information
Prolonged COVID	Post-COVID syndromes	4–12 weeks after recovery	• Chest pain • Palpitations • Myocarditis • Postural orthostatic tachycardia syndrome • Abnormal heart rhythm • Pericarditis • Dyspnea • Thromboembolism • Vasculitis • Multisystem inflammatory syndrome in children (IMS) • Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS) • Hypertension	That type of syndromes seems particularly interesting to pediatricians because it is in the population of children where multiple organ failure is most frequently described
	Long/ chronic-COVID syndromes	>12 weeks after recovery	• Chest pain (5–21%) • Cerebrovascular disorders (stroke, TIA) • Resting heart rate increase • Palpitations (10%) • Arrhythmias (AF, sinus tachycardia, sinus bradycardia, VA, atrial flutter) • Inflammatory heart disease (myocarditis [2–3%], pericarditis) • Ischemic heart disease (ACD, MI, ischemic cardiomyopathy, angina) • Other cardiac disorders (HF, non-ischemic cardiomyopathy, cardiac arrest, cardiogenic shock) • Thrombotic disorders (pulmonary embolism, deep vein thrombosis, superficial vein thrombosis) • Hypertension • Diabetes Laboratory findings: Increases: D'dimer, NT-proBNP, CRP, serum ferritin, procalcitonin, IL-6	We have the least knowledge about long-COVID syndromes

LDH lactate dehydrogenase, *vWF* von Willebrand factor, *RV* right ventricle, *EF* ejection fraction, *PASP* pulmonary artery systolic pressure, *LV* left ventricle, *LVGLS* left ventricle global longitudinal strain, *CMR* cardiac magnetic resonance, *LGE* late gadolinium enhancement, *LVEF* left ventricle ejection fraction, *TIA* transient ischemic attack, *AF* atrial fibrillation, *ACD* acute coronary disease, *HF* heart failure, *NT-proBNP* NT-proB-type natriuretic peptide, *CRP* C-reactive protein, *IL-6* interleukin 6

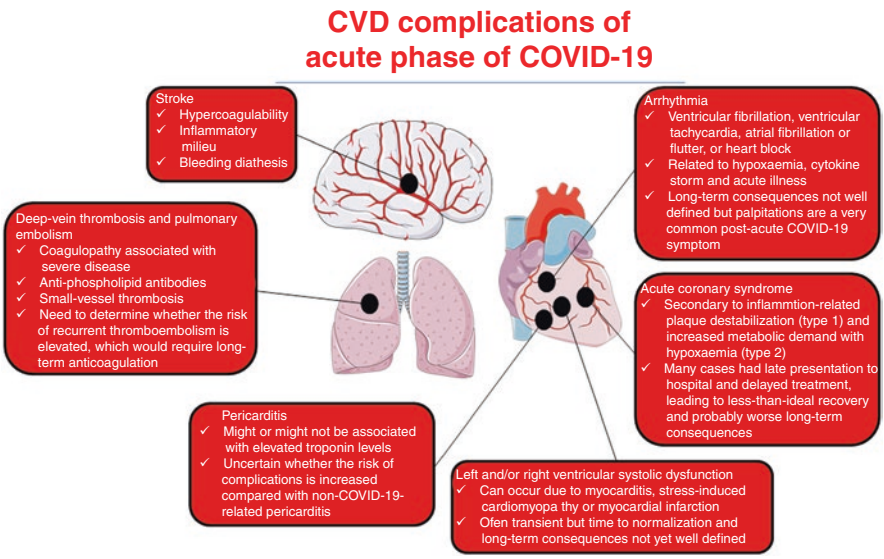

Fig. 7.1 Acute cardiovascular complications secondary to COVID-19. Based on [28]. The figure was prepared using Servier Medical Art

high sensitivity cardiac troponin (hs-cTn) above the 99th percentile of its upper limit of normal or evidence of new electrocardiographic (ECG) or echocardiographic abnormalities [30].

Epidemiology and Risk of ACS During SARS-CoV-2 Infection

The COVID-19 pandemic has brought unprecedented changes to our world and healthcare system. Atherosclerotic changes appear from childhood [31]. A number of risk factors, such as hyperlipidemia, hyperhomocysteinemia, arterial hypertension, hyperuricemia, smoking, metabolic syndrome, hypertriglyceridemia, and diabetes, accelerate the intensification of atherosclerotic lesions, leading to the progression of atherosclerotic disease cardiovascular disease (ASCVD), such as coronary artery disease (CAD), which in consequence leads to ACS [32]. It is worth mentioning that different viral infections also increase, threefold to tenfold, risk of ACS [19]. ASCVD represents the number one cause of morbidity and mortality worldwide [33, 34]. Therefore, from a clinical point of view, the interaction between the COVID-19 pandemic and the ASCVD pandemic is important. It is indicated that COVID-19 is a new factor increasing the risk of CAD progression and, consequently, the occurrence of ACS [14, 35]. The issues and clinical problems associated with ACS in patients with COVID-19 and the impact of the pandemic on care for these patients are summarized in Fig. 7.2.

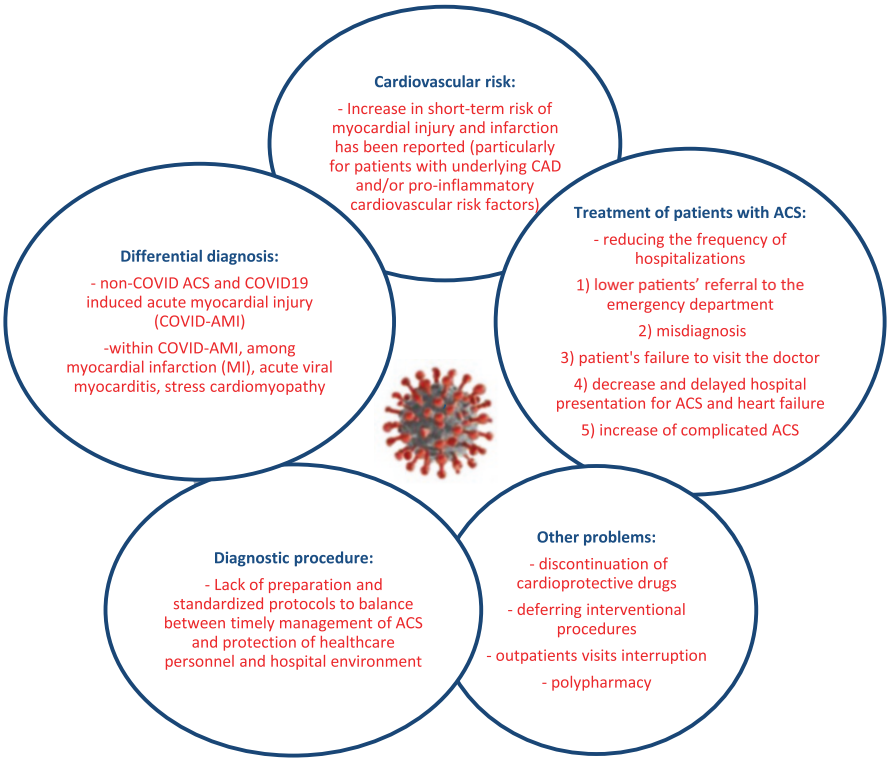

Fig. 7.2 Clinical problems related to SARS-CoV-2 infection and the COVID-19 pandemic for ACS and their care. *CAD* coronary artery disease, *ACS* acute coronary syndrome

The relationship between CAD and COVID-19 appears to be two-way. On the one hand, patients with CAD have a significantly higher risk of severe COVID-19 (HR = 1.48; 95% CI: 1.14–1.93)/(OR = 3.42; 95% CI: 2.83–4.13) [36, 37]. On the other hand, COVID-19 increases the risk of ACS in 1-year follow-up (HR = 1.72; 95% CI: 1.56–1.90) [22]. The results of epidemiological studies indicate that venous thromboembolism (VTE) is a much more common complication in patients with COVID-19 compared to arterial thromboembolism (ATE). A recent meta-analysis examining 102 studies found that overall incidence of COVID-related VTE was 14.7% (95% CI, 12.1–17.6), rising to 23.2% in critically ill patients (95% CI, 17.5–29.6) [38]. Overall incidence of ATE in COVID-19 patients were 3.9% (95% CI: 2.0–6.5) [38]. The prevalence and risk of ACS in patients with COVID-19 is summarized in Table 7.2 [10, 22, 38–49].

Thus, the prevalence of ACS among COVID-19 patients is not high, around 2%. Of course, whether this percentage is high depends on the current state of the COVID-19 pandemic. For example, currently, on average, 13,500 COVID-19 patients are hospitalized in Poland. Among this group, about 270 people are likely to experience ACS during hospitalization or in short-time after recovery. It should

Table 7.2 Summary of selected studies assessing the incidence and risk of ACS in patients with COVID-19

Author; year; bibliography	Sample size; origin; type of study	Follow-up	Key findings	Clinical conclusions
Modin D. et al., 2020 [39]	5119 Danish [OS]	14 days	Incidence risk of MI: 5,9; 95% CI: 1.9–18.2, $p = 0.002$ Prevalence: 0.3%	COVID-19 may increase the risk of ischemic cardiovascular events
Cantador E. et al., 2020 [40]	1419 Spain [OS]	During hospitalization	0.2% COVID-19 patients developed an ACS during hospitalization	The incidence of ACS in hospitalized COVID-19 patients is not high
Fauvel C. et al., 2020 [41]	1240 France [OS]	During hospitalization	0.5% COVID-19 patients developed an ACS during hospitalization	The incidence of ACS in hospitalized COVID-19 patients is not high
Bilaloglu S. et al., 2020 [42]	3334 USA [OS]	During hospitalization	Among ICU patients 18.6% had arterial event vs. in non-ICU patients 8.4% arterial. A significant increase in the risk of an arterial event was observed among: men, patients with existing CAD and patients with a D'dimer concentration >500 ng/ml	COVID-19 may increase the risk of ACS in selected groups of patients
Dweck M. et al., 2020 [43]	1216 Multicenter [OS]	During hospitalization	ACS de novo occurred in 3% of COVID-19 patients	The incidence of ACS in hospitalized COVID-19 patients is not high
Matsushita K. et al., 2021 [44]	280 France [OS]	During hospitalization	Higher incidence of type 2 MI (29% vs. 4%, $p = 0.0497$), and higher level of D'dimer ($p = 0.02$)	Type 2 MI is more common in COVID-19 patients
Katsoularis I. et al., 2021 [45]	86,742 Sweden [OS]	28 days	Incidence risk ratio of MI after COVID-19 diagnosis: • First week: 8·44; 95% CI: 5·45–13·08, $p = 0.0014$ • Second week: 2·56; 95% CI: 1·31–5·01, $p = 0.0067$ • 3–4 weeks: 1·62; 95% CI: 0·85–3·09, $p = 0.16$ Prevalence: 0.2%	COVID-19 is a risk factor for acute myocardial infarction

Table 7.2 (continued)

Author; year; bibliography	Sample size; origin; type of study	Follow-up	Key findings	Clinical conclusions
Alquézar-Arbé A. et al., 2022 [46]	74,814 Spain [OS]	During diagnostics period	Incidence of ACS in COVID-19 patients was 1.48% (95% CI: 1.21–1.78%) The patients with the highest risk of ACS were: CAD, fever and chest pain	Overall incidence of ACS in patients with COVID-19 attending the emergency department was low
Xie Y. et al., 2022 [22]	153,760 USA [OS]	12 months	Hazard ratio and 12-month burdens (per 1000 persons) of incident post-acute COVID-19: • Ischemic heart disease (overall): 1.66; 95% CI: 1.52–1.80; burden: 7.28; 95% CI: 5.80–8.88 • ACS: 1.72; 95% CI: 1.56–1.90; burden 5.35; 95% CI: 4.13–6.70) • MI: 1.63; 95% CI: 1.51–1.75; burden 2.91; 95% CI: 2.38–3.49) • Angina: 1.52; 95% CI: 1.42–1.64; burden 2.50; 95% CI: 2.00–3.03	The risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial
Kunutsor SK. And Laukkanen JA. 2020 [47]	2 studies [MA]	–	Incidence of ACS in COVID-19 patients was 6.2% (95% CI: 1.8–12.3)	ACS is not a very common complication in patients with COVID-19
Tan BK. et al., 2021 [38]	16 studies [ma]	–	ACS in 1.1% (95% CI: 0.2–3.0) hospitalized patients. Subgroup analysis: • In ICU patients: 5.1%; 95% CI: 2.8–8.1 • Non-ICU patients: 2.8%; 95% CI: 0.5–6.7	The incidence of ACS in hospitalized COVID-19 patients is not high and depends on the severity of the disease
Zhao Y-H. et al., 2021 [10]	4 studies [MA]	–	Incidence of ACS in COVID-19 patients was 1.0% (95% CI: 0.5–1.5%)	The incidence of ACS in hospitalized COVID-19 patients is not high

(continued)

Table 7.2 (continued)

Author; year; bibliography	Sample size; origin; type of study	Follow-up	Key findings	Clinical conclusions
Jafari-Oori M. et al., 2022 [48]	6 studies [MA]	–	Incidence of ACS in COVID-19 patients was 1.3%	The incidence of ACS in hospitalized COVID-19 patients is not high
Pellicori P. et al., 2021 [49]	16 studies [SR]	–	Mean incidence of 1.7% for ACS (range 0–3.6%) in COVID-19 patients	The incidence of ACS in hospitalized COVID-19 patients is not high

OS observational study, *MA* meta-analysis, *SR* systematic review, *MI* myocardial infarction, *ACS* acute coronary syndrome, *ICU* intensive care unit, *CAD* coronary artery disease

be remembered that, as shown by Lewek et al., the presence of diabetes, elevated level of CRP and troponin, heart rate variability parameters, and worsening of left ventricular ejection fraction increases the risk of severity of cardiovascular complications following COVID-19 infection [50]. Moreover, it should be noted that the study results indicate that the risk and 1-year burden of ACS in survivors of acute COVID-19 are substantial. Therefore, it is very important to long period of time clinical observe COVID-19 survivors.

When mentioning the long-term impact of SARS-CoV-2 infection on the risk of ACS, the impact of the COVID-19 pandemic on the frequency of hospitalization of patients with ACS should also be emphasized. In addition to millions of infected patients, non-COVID-19 care is also severely undermined due to change in human behavior and resource availability. Treatment of medically emergent conditions like ACS are particularly vulnerable and worldwide there were reports of reduction in ACS admissions with worsened in-hospital outcome. A meta-analysis of 40 studies by Helal et al. showed a 28.1% reduction in the rate of admission with ACS during the COVID-19 pandemic period compared with the same period in 2019 [51]. Another meta-analysis by Sofi et al. covering 111,557 STEMI cases from 57 countries showed a reduction in the incidence rate-ratio of hospitalization in patients with ST-elevation myocardial infarction (STEMI) by 20% (IRR = 0.80; 05% CI: 0.76–0.84, $p < 0.05$) during COVID-19 pandemic period [52]. The observed reduction in the frequency of hospitalization of patients with ACS is caused by several factors, such as: reduced availability of medical services for patients without COVID-19 and patients' fear of SARS-CoV-2 infection in the hospital (negative psychological response, emotional distress, distrust/avoidance behaviors, and reluctance to activate pre-hospital networks.). In fact, healthcare avoidance and treatment delay were apparent and may further translate into poorer medium- or long-term cardiovascular outcome such as higher incidence of heart failure (HF) [53]. A

meta-analysis by Chew et al. including 19,140 and 68,662 STEMI patients underwent primary PCI during and before the pandemic showed that door to balloon time increased (WMD: 8.10 minutes; 95% CI: 3.90–12.30, $p = 0.0002$). Moreover, was showed that in-hospital mortality was higher during the pandemic (OR = 1.27; 95% CI: 1.09–1.49), especially in low- middle-income countries [54]. Rashid et al. found that the incidence of COVID-19 in hospitalized ACS patients was associated with lower rates of guideline-recommended treatment (they were less likely to receive an invasive coronary angiography, PCI, and dual antiplatelet medication) and significant mortality hazard (OR = 3.27; 95% CI: 2.41–4.42 and 30-day mortality OR = 6.53; 95% CI: 5.1–8.36) [55]. Similar results were obtained by Kite et al. in a study involving 144 patients with STEMI and 121 with NSTEMI, who were compared with the cohort of patients with ACS before the COVID-19 (control group, CG) pandemic period. It was shown that symptom-to-admission times were significantly prolonged (COVID-STEMI vs. CG: 339.0 min vs. 173.0 min; $p < 0.001$; COVID NSTEMI vs. CG: 417.0 min vs. 295.0 min; $p = 0.012$). Mortality in COVID-STEMI patients was significantly higher than in CG subjects in both subgroups (COVID-STEMI: 22.9% vs. 5.7%; $p < 0.001$; COVID-NSTEMI: 6.6% vs. 1.2%; $p < 0.001$), which remained following multivariate propensity analysis adjusting for comorbidities (COVID-STEMI subgroup OR = 3.33; 95% CI: 2.04–5.42). Cardiogenic shock occurred in 20.1% of COVID-STEMI patients vs. 8.7% of CG subjects ($p < 0.001$) [56]. In the study by De Luca et al., including 16,674 patients with STEMI, significant reduction in primary percutaneous coronary intervention (PPCI) as compared with 2019 was demonstrated (incidence RR = 0.843; 95% CI: 0.825–0.861, $p < 0.0001$). Moreover, the pandemic was associated with a significant increase in door-to-balloon time [40 min (95% CI: 25–70) min vs. 40 min (95% CI: 25–64) min, $p = 0.01$] and total ischemia time [225 min (95% CI: 135–410) vs. 196 min (95% CI: 120–355) min, $p < 0.001$], which may have contributed to the higher in-hospital [(6.5% vs. 5.3%, $p < 0.001$) and 30-day (8% vs. 6.5%, $p = 0.001$)] mortality observed during the pandemic [57]. It is also worth mentioning the results of the study by Fardman et al., covering 1466 MI patients. It has been shown that during the COVID-19 pandemic: time from symptom onset to reperfusion was extended from 180 min (IQR: 122–292) in 2018 to 290 min (IQR: 161–1080, $p < 0.001$) in 2020; hospitalization during was independently associated with an increased risk of the combined endpoint (malignant arrhythmia, congestive heart failure, in-hospital mortality, cardiogenic shock, mechanical complications, electrical complications, re-infarction, stroke, and pericarditis) in the multivariable regression model (OR 1.65, 95% CI 1.03–2.68, $p = 0.04$). Moreover, the rate of mechanical complications was four times higher during the COVID-19 era (95% CI: 1.42–14.8, $p = 0.02$) [58]. Alhejily showed that the COVID-19 pandemic was associated with a deterioration in the prognosis of ACS patients by: higher number of deaths ($p = 0.01$), need for urgent coronary artery bypass graft ($p = 0.001$) and higher risk of stroke ($p = 0.01$). It was found that mortality among ACS patients was related to a delay in presentation from the time of onset of symptoms [59]. Importantly, De Rosa et al. showed an increase in STEMI fatality rate (RR = 3.3; 95% CI: 1.7–6.6; $p < 0.001$) and complications (RR = 1.8; 95% CI: 1.1–2.8; $p = 0.009$) during the

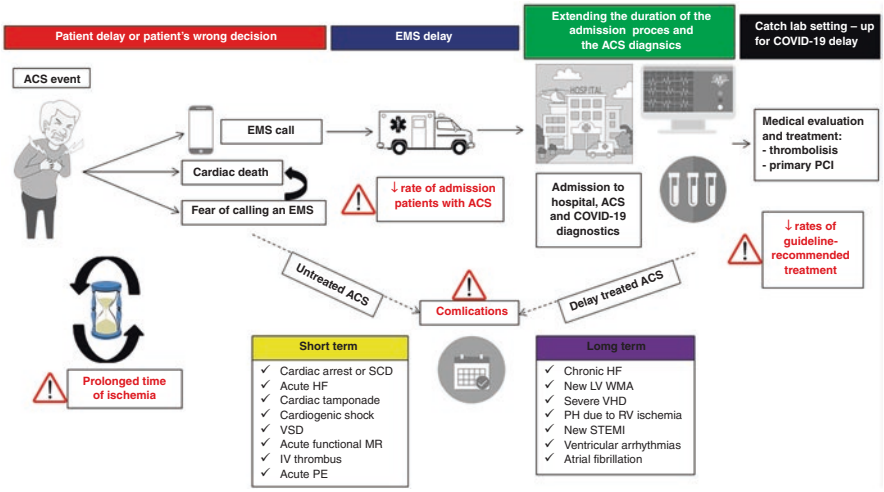

Fig. 7.3 Summary summarizes the impact of the COVID-19 pandemic on the diagnostic and therapeutic process of ACS. Based on information from [30, 51, 61]. *ACS* acute coronary syndrome, *EMS* emergency medical services, *PCI* percutaneous coronary intervention, *SCD* sudden cardiac death, *HF* heart failure, *VSD* ventricular septum defect, *MR* mitral regurgitation, *IV* intraventricular, *PE* pulmonary embolism, *LV* left ventricular, *WMA* wall motion abnormalities, *VHD* valvular heart disease, *PH* pulmonary hypertension, *RV* right ventricular, *STEMI* ST elevation myocardial infarction

pandemic, compared to 2019 [60]. Figure 7.3 summarizes the impact of the COVID-19 pandemic on the diagnostic and therapeutic process of ACS.

Thus, the COVID-19 pandemic has worsened the diagnosis and treatment of ACS (almost half of patients with ACS not reaching the hospital and not receiving timely treatment), which could have serious consequences for the health care system in the future.

ACS During SARS-CoV-2 Infection and Prognosis

As already mentioned, the presence of CAD worsens the prognosis of COVID-19 patients [36, 37]. The situation is similar with the ACS. In a study by Saad et al., involving 76,434 patients, it was shown that among patients with out-of-hospital STEMI and COVID-19 vs. out-of-hospital STEMI without COVID-19, the rates of in-hospital mortality were 15.2% vs. 11.2% (absolute difference = 4.1%; 95% CI: 1.1–7.0, $p = 0.007$). Among patients with in-hospital STEMI and COVID-19 vs. in-hospital STEMI without COVID-19, the rates of in-hospital mortality were 78.5% vs. 46.1% (absolute difference = 32.4%; 95% CI: 29.0–35.9, $p < 0.001$) [62]. In a study by Cammann et al., including 121 patients with ACS, it was shown that the coexistence of COVID-19 was more often associated with the risk of death

(p = 0.004) [63]. A meta-analysis of five observational studies, conducted by Thakker et al., including 2266 patients, showed a higher in-hospital risk of mortality in the STEMI and SARS-CoV-2 patients (OR = 5.24; 95% CI: 3.63–7.56) [64]. A meta-analysis of nine studies by Abdelghany et al., including 6664 patients, showed that the coexistence of COVID-19 with ACS was associated with a higher risk of death from any cause (RR = 4.58; 95% CI: 3.23–6.50, $p < 0.001$) and from cardiovascular cause (RR = 3.83; 95% CI: 1.32–11.12, $p = 0.01$) [65]. A study by Çınar et al. including 721 patients with ACS showed, for the first time, that 1-year mortality rates were higher in the ACS participants with COVID-19 than in the ACS participants without COVID-19 (21.3% vs. 6.5%, respectively). An ACS along with COVID-19 was the only independent predictor of 1-year mortality (HR = 2.902; 95% CI: 1.211–6.824, $p = 0.018$). According to the Kaplan–Meier survival curves, patients with ACS and COVID-19 had a lower chance of survival in the short-term and 1-year periods [66].

In the study by Alquézar-Arbé et al., which showed that the need for hospitalization and admission to intensive care and in-hospital mortality were higher in cases COVID-19 with ACS than in COVID-19 without ACS (OR = 6.36; 95% CI: 1.84–22.1, OR = 4.63, 95% CI: 1.88–11.4, and OR = 2.46, 95% CI: 1.15–5.25, respectively) [46]. A meta-analysis of 3044 COVID-19 cases by Zhao et al. showed a higher incidence of cardiac injury in non-survivors (RR = 6.91; 95% CI: 3.19–14.95, $p = 0.009$) [10]. In turn, the meta-analysis by Jafari-Oori et al. found that incidence of AMI was associated with increased risk of mortality (RR = 2.57; 95% CI: 1.99–3.15, $p < 0.001$) [48]. Moreover, in a study by Lu et al., covering 10,696 hospitalized COVID-19 patients, showed that in-hospital mortality odds ratio of acute cardiac injury [serum cTn concentration above the 99th percentile upper reference limit (0.014 ng/ml) any time during hospitalization] patients was 4.45 (95% CI: 3.92–5.05, $p < 0.001$) compared to non-acute cardiac injury patients [67]. It should be mentioned that, as demonstrated by Xie et al., the risk and 1-year burden of ACS in survivors of acute COVID-19 are substantial, which is objectively related to a deterioration in the quality of life and prognosis of these patients [22].

Thus, the occurrence of COVID-19 in a patient with ACS and the occurrence of ACS (in short and long time after recovery) in a patient with COVID-19 significantly worsen the prognosis. It should also be emphasized that the deterioration in the level of diagnosis and treatment of ACS caused by the COVID-19 pandemic also worsens the prognosis of patients with ACS (who have not necessarily developed COVID-19).

Pathogenesis of ACS Induced by SARS-CoV-2 Infection

The pathogenesis of ACS in a patient with COVID-19 is complex and may be considered through direct mechanisms (damage to vascular endothelial cells [EC]) and indirect mechanisms (cytokine storm) [68, 69].

There are different potential etiologies of COVID-ACS due to plaque rupture or thrombosis (type I MI and MI with non-obstructive coronary arteries—MINOCA) or to supply demand mismatch (type II MI) [68]. Each one is the result of a direct or indirect effect of severe viral infection, as explained in Figs. 7.4 and 7.5. The most recognized mechanisms include cytokine-mediated systemic inflammatory response, pro-thrombotic activation of the coagulation cascade, endothelial dysfunction, and hypoxic injury due to oxygen supply/demand imbalance [68–73].

SARS-CoV-2 coronavirus initially infects upper airway epithelial cells followed by bronchial ciliary epithelial cells and type II pneumocytes, where it binds to the surface receptor, angiotensin converting enzyme 2 (ACE2). For SARS-CoV-2 endocytosis, it is necessary to cut off its spines made of the S protein. This reaction is catalyzed by serine protease 2 (transmembrane protease serine 2; TMPRSS2) [74]. It should be mentioned that the increased expression of ACE2 may explain the course of COVID-19 in diabetic patients—ACE2 is also known to be overexpressed in these patients [70]. ACE2, the most important entry receptor of SARS-CoV-2, is a homologue of ACE and is a key anti-inflammatory component of the renin aldosterone angiotensin system (RAAS), an important regulator of blood pressure as well as renal, vascular, and myocardial function and physiology. ACE2 is an anti-inflammatory regulator by converting Ang II into Ang (1–7) and Ang (1–9). ACE2 after SARS-CoV-2 binding is internalized and degraded. Hence ACE2 activity on the cell surface is reduced leading to increase the concentration of angiotensin 2 and decrease the concentration of angiotensin (1–7). Disturbed angiotensin metabolism, changes in ratio between angiotensins with distinct biological activities leading to domination of atherogenic angiotensin 2 can increase the damage to vascular endothelium [75]. Moreover, SARS-CoV-2 limits ACE2 expression is indicated to promote cleavage ACE2 by the specialized proteinase A disintegrin and metalloproteinase

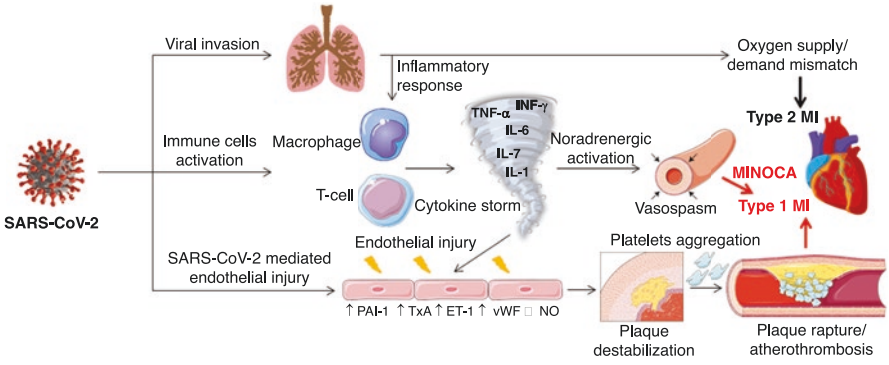

Fig. 7.4 Pathophysiology of ACS in SARS-CoV-2 infection. Based on information from [30, 68–72]. *IFN-γ* interferon γ, *TNF-α* tumor necrosis factor α, *IL-1* interleukin 1, *IL-6* interleukin 6, *IL-7* interleukin 7, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *PAI-1* plasminogen activator inhibitor-1, *TxA* thromboxane A, *ET-1* endotheline 1, *vWF* von Willebrand factor, *NO* nitric oxide, *MI* myocardial infarction, *MINOCA* myocardial infarction with non-obstructive coronary arteries. The figure was prepared using Servier Medical Art

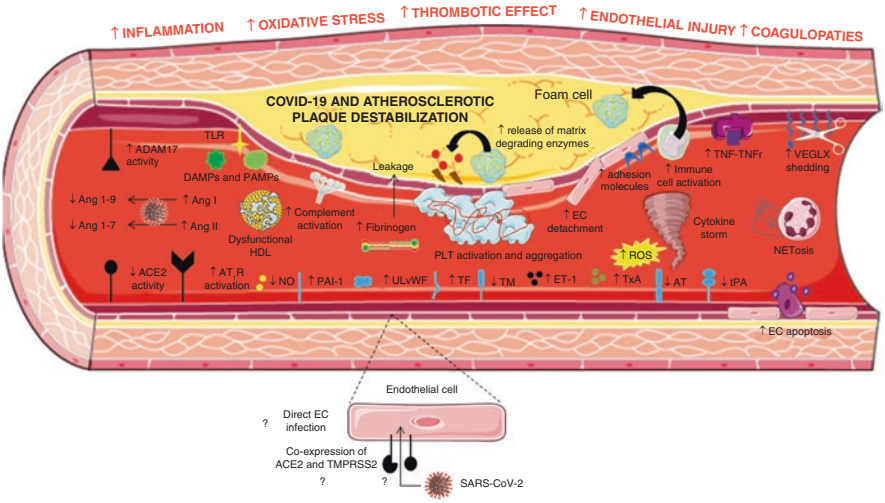

Fig. 7.5 Pathogenesis of atherosclerotic plaque destabilization in COVID-19 patients. Based on information from [30, 68–73]. *ADAM17* a disintegrin and metalloproteinase 17, *TLR* toll-like receptor, *DAMPs* damage-associated molecular patterns, *PAMPs* pathogen-associated molecular patterns, *Ang* angiotensin, *ACE2* angiotensin converting enzyme 2, *AT1R* angiotensin 1 receptor, *HDL* high-density lipoprotein, *NO* nitric oxide, *PAI-1* plasminogen activator inhibitor-1, *ULvWF* ultralarge von Willebrand factor multimers, *TF* tissue factor, *TM* thrombomodulin, *ET-1* endothelin 1, *TxA* thromboxane, *EC* endothelial cell, *TMPRSS2* transmembrane protease serine 2, *AT* antithrombin, *tPA* tissue plasminogen activator, *TNF* tumor necrosis factor, *TNFr* tumor necrosis factor receptor, *VEGLX* vascular endothelial glycocalyx, *NETosis* neutrophil extracellular traps, *PLT* platelet, *ROS* reactive oxygen species, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2. The figure was prepared using Servier Medical Art

17 (ADAM17) and shedding from the cell surface, leading to a reduction in ACE2's protective role on ECs and other organs [73]. Angiotensin II, through the AT_1R receptor, is characterized by: vasoconstriction, anti-natriuretic, pro-inflammatory, pro-oxidative, and pro-thrombotic effects, which promotes the progression of atherosclerosis [73, 75]. Angiotensin II perturbs endothelial functions in multiple ways, including by monocyte recruitment, formation of ROS (Nox2, regulated by angiotensin-II contributes to oxidative stress in the endothelium via production of reactive oxidant species), activation of pro-inflammatory pathways including through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) regulation, as well as promoting plasminogen activator inhibitor-1 (PAI-1) production in ECs [73]. Reactive oxygen species significantly reduce the production of vasorelaxant nitric oxide [76]. The destabilization of atherosclerotic plaque in COVID-19 patients may be caused by the high concentration of pro-inflammatory cytokines and pro-atherogenic, such as: IL-1β, IL-6, IL-8, IL-18, TNF-α (create a so-called cytokine storm), E-selectin, P-selectin, and soluble form of vascular cell adhesion protein 1 (sVCAM-1) [68, 70]. Immune cell activation and increasing the level of adhesive molecules increases the penetration of monocytes under the vascular endothelium into atherosclerotic plaque. There, foam cells are formed, which by

producing matrix-degrading enzymes (MMPs) increase the instability of the atherosclerotic plaque [77].

Coagulopathies are another factor contributing to the destabilization of atherosclerotic plaque. SARS-CoV-2 infection is associated with the onset of coagulopathy. In fact, D-dimer levels are enhanced in acute COVID-19 cases [78]. Cytokine storm leading to increased production of tissue factor (TF), ultralarge von Willebrand factor multimers (ULvWF), thromboxane, plasminogen activator inhibitor-1 (PAI-1), and endothelin 1 (ET-1). The activation of the coagulation cascade, resulting in a hypercoagulability status characterized by increased production of thrombin [68]. Procoagulant state of COVID-19 patients is the imbalance of von Willebrand factor (vWF) and ADAMTS13 (cleaves ULvWF), as evidenced by increased vWF antigen levels and decreased ADAMTS13 activity in hospitalized COVID-19 patients' plasma [79]. In addition, neutrophils and monocytes are strongly contributing to the development of ARDS and thrombosis by inducing hyperinflammation. Neutrophil extracellular traps (NETs), which are extracellular decondensed chromatin structures mixed with antimicrobial proteins and released in response to infections, are also associated with thrombosis and endothelial injury. Biomarkers of NET formation were increased in the blood of patients with severe COVID-19 and related to thrombotic events as, for example, high levels of neutrophil platelet aggregations were detected [80]. In the course of COVID-19, platelets are also activated. Increased transcription of S100A8/A9 in platelets of COVID-19 patients and circulating levels of its protein productMRP8/14, a known pro-inflammatory heterodimer secreted by activated platelets and neutrophils, was also found to correlate with COVID-19 severity [81]. Moreover, activated ECs lower activity of thrombomodulin and tissue plasminogen activator, favoring thrombus accumulation [73]. Increased fibrinogen concentration may also contribute to the progression of atherosclerotic lesions [82].

Atherosclerotic endothelial dysfunction and SARS-CoV-2-triggered acute inflammatory responses may accelerate atherosclerotic lesion growth and plaque rupture [68]. This notion is supported by reports from cases of acute myocardial infarction with spontaneous dissection of coronary arteries in patients affected by severe manifestations of COVID-19 [83]. In addition, it seems that lesion composition does impact on the risk for CVD-associated complications in COVID-19 since higher calcification was correlated with a higher risk of severe COVID-19 [84]. An important role in the pathogenesis of atherosclerosis progression in the course of SARS-CoV-2 infection is also played by the disruption of high-density lipoprotein (HDL) function [85].

The significant influence of genetic predisposition in the pathogenesis of atherosclerosis progression in COVID-19 patients is also indicated. To shed more light on the impact of atherosclerosis for COVID-19 Das and Podder retrieved data of differentially expressed genes for both, atherosclerosis, and COVID-19, from publicly available microarray and RNAseq datasets and performed a protein–protein interaction network analysis. Further functional enrichment revealed inflammatory response genes to be more abundant, particularly MyD88 was identified as a crucial linker of atherosclerosis and COVID-19 [86].

In the course of COVID-19, the vascular endothelium is damaged. Sustained endothelial activation and inflammation may lead to endothelial injury during COVID-19 disease course [73]. It has been shown that in patients with COVID-19 there is an increase in the level of biomarkers of endothelial damage, such as thrombomodulin [68]. Moreover, increased circulating glycocalyx degradation products including syndecan-1, chondroitin sulfate, and hyaluronic acid were found in COVID-19 patients and were associated with disease severity [87]. Additionally, increased activity of glycocalyx modifying enzymes such as heparinase and hyaluronidase were measured [87]. Increased numbers of circulating ECs, which putatively detached from the vessel wall due to pathological insults, were found to correlate with COVID-19 severity [88]. Interestingly, elevated circulating EC frequency persisted in recovered convalescent patients suggesting long-term effects of SARS-CoV-2 infection on vascular function [89]. EC detachment and apoptosis lead to exposure of pro-thrombotic mediators such as basement membrane proteins, and abluminally deposited vWF [90]. It is also worth noting that activation of the complement system has been observed in patients with COVID-19. Activation of the complement system can also injury EC, especially if those are already dysfunctional and do not sufficiently express protective, membrane-bound complement regulators [70, 91]. Additionally, EC injury is compounded by toll-like receptor (TLR) activation by viral RNA recognition, with resulting increased reactive oxidative species (ROS) production [73].

The co-expression of ACE2 and TMPRSS2 in vascular ECs is controversial, therefore it cannot be clearly stated whether SARS-CoV-2 can directly infect these cells. Accumulating evidence now suggests that damage of the vascular system is rather mediated by an augmented inflammatory response [70].

The severe hypoxic state, combined with other mechanisms observed in COVID-19, such as sepsis, tachyarrhythmias, anemia, hypotension, and shock, can induce a myocardial damage due to the mismatch between oxygen supply and demand in the absence of atherothrombotic lesions, findings consistent with the diagnosis of type 2 MI [92, 93]. Compared with type 1 MI, patients with type 2 MI show distinct clinical features and poorer prognosis, largely related to the higher prevalence of coexisting systemic diseases [68].

MI with non-obstructive coronary arteries (MINOCA) has been reported in patients with COVID-19 [68]. Several mechanisms have been proposed for these cases, including plaque erosion, microthrombi, or coronary vasospasm [68, 93]. The pathophysiology seems to be multifactorial and encompasses inflammatory activation, oxidative stress, and endothelial dysfunction in the context of COVID-19-related coronary syndrome [68, 94].

In conclusion, the pathogenesis of ACS in the course of COVID-19 is multifactorial and is mainly related to the indirect action of SARS-CoV-2. Considering that patients with a severe course of COVID-19 often suffer from CAD-related diseases (diabetes, hypercholesterolemia, obesity, and hypertension), it should be emphasized that SARS-CoV-2 infection may be a trigger of destabilization of the existing atherosclerotic plaque (Fig. 7.6) [95]. ACS in patients with COVID-19 may also be unrelated to the destabilization of atherosclerotic plaque—MI type 2 and MINOCA.

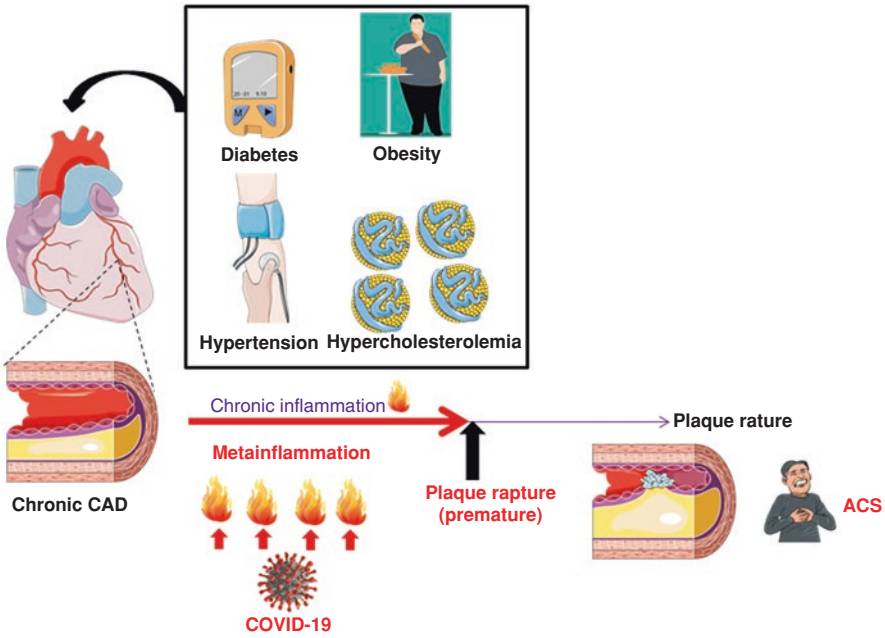

Fig. 7.6 The link between COVID-19 cytokine storm and ACS. Based on information from [95]. *CAD* coronary artery disease, *COVID-19* coronavirus disease 2019, *ACS* acute coronary syndrome. The figure was prepared using Servier Medical Art

Diagnostics and Treatment Aspects

From a clinical point of view, the diagnosis of COVID-19 induced ACS is extremely important. It should be emphasized that troponin elevation in patients with COVID-19 infection seems to be lower than in most cases of ACS or acute myocarditis, European Association of Percutaneous Cardiovascular Interventions (EAPCI) suggests considering marked elevation (e.g., >5 times the upper normal limit) in a patient who is not critically ill to suspect COVID-AMI [96]. Differential diagnosis is very important. Differential diagnosis is very important. In a study by Fanaroff et al. was shown that among patients with suspected ACS presenting to emergency departments, the initial history, physical examination, and electrocardiogram alone did not confirm or exclude the diagnosis of ACS [97]. In patients with COVID-19, it should be considered that similar symptoms (ACS-like presentations in COVID-19 infection) may occur in the course of microvascular thrombosis, pericarditis, myocarditis, cytokine-mediated myocardial injury, pulmonary embolism, stress-induced cardiomyopathy [98]. As regards patients hospitalized for COVID-19 with suspected ACS, European Association of Cardiovascular Imaging (EACVI) recommends evaluating the pre-test probability (PTP) based on symptoms, ECG signs, age, sex, previous history, and cardiovascular risk factors, to use coronary CT angiography for intermediate PTP, and to reserve ICA only for cases with very high PTP or STEMI, high-risk NSTEMI or crescendo angina [99]. The proposed algorithm for the differential diagnosis and management of patients with COVID-19 and suspected ACS is shown in Fig. 7.7.

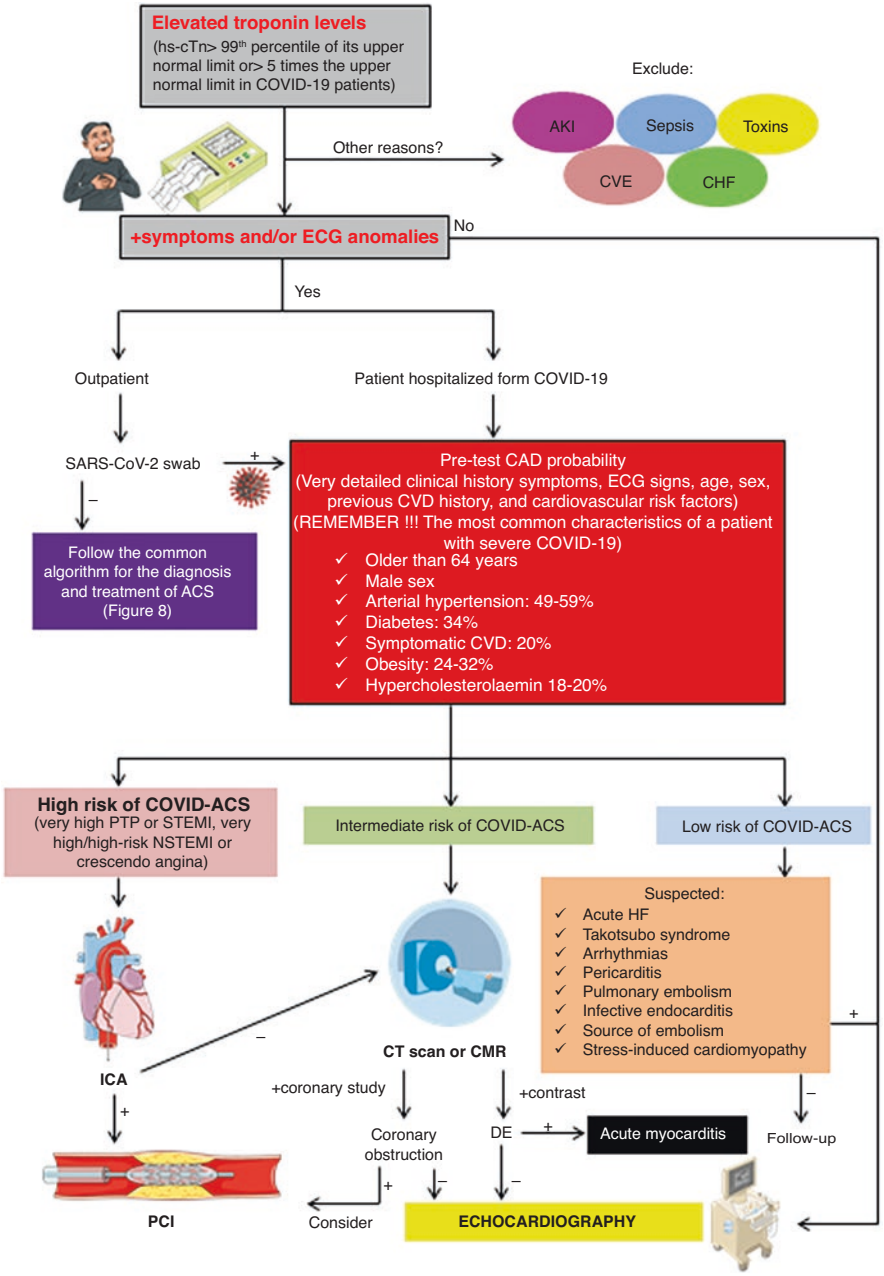

Fig. 7.7 Algorithm for the diagnosis of COVID-induced acute coronary syndrome optimizing the available imaging techniques. Based on information from [30, 70]. *AKI* acute kidney injury, *CVE* cerebrovascular event, *CHF* congestive heart failure, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *ECG* electrocardiography, *CVD* cardiovascular disease, *ACS* acute coronary syndrome, *PTP* pre-test CAD probability, *CAD* coronary artery disease, *ICA* invasive coronary angiography, *PCI* percutaneous coronary intervention, *CMR* cardiac magnetic resonance, *CT* cardiac tomography, *DE* delayed enhancement. The figure was prepared using Servier Medical Art

It should be emphasized that: (1) ICA should be performed only in patients with suspected type 1 MI [96] and who are expected to derive meaningful changes in outcome from invasive management; therefore, patients with high level of comorbidities, poor quality of life, and frailty should be early assigned to medical therapy, since additional investigations are futile; and (2) the use of echocardiography, which has always been regarded as a "gatekeeper" for differential diagnosis of cardiovascular disease, should be reconsidered in this emergency period. Transthoracic echocardiography should not be routinely performed if patients are asymptomatic and stable, but it remains the first line approach in patients with high suspicion of COVID-AMI, to address diagnosis [100].

STEMI: ESC Guidance for the Diagnosis and Management of Cardiovascular Disease During the COVID-19 Pandemic [101]

The COVID-19 pandemic should not compromise timely reperfusion of ST-segment elevation MI (STEMI) patients. In line with current guidelines, reperfusion therapy remains indicated in patients with symptoms of ischemia of <12 h duration and persistent ST-segment elevation in at least two contiguous electrocardiogram (ECG) leads. To that purpose, and in the absence of previous SARS-CoV-2 testing, all STEMI patients should be managed as if they are COVID-19 positive [101]. The main principles of STEMI management in the COVID-19 pandemic are the following (Fig. 7.8):

1. The maximum delay from STEMI diagnosis to the reperfusion of 120 min should remain the goal for reperfusion therapy under the following considerations.
   (a) Primary percutaneous coronary intervention (PCI) remains the reperfusion therapy of choice, if feasible within this time frame and performed in facilities approved for the treatment of COVID-19 patients in a safe manner for healthcare providers and other patients.
   (b) Primary PCI pathways may be delayed during the pandemic (up to 60 min in some networks experience) due to delays in the delivery of care and the implementation of protective measures.
   (c) If the target time cannot be met and it is not contraindicated, fibrinolysis should be performed in accordance with ESC guidelines recommendations [102].
2. As SARS-CoV-2 test results are not immediately available in STEMI patients, any STEMI patient should be considered potentially infected.
3. All STEMI patients should undergo testing for SARS-CoV-2 as soon as possible (fast COVID-19 testes enabling the results even in several to dozen minutes are recommended) following first medical contact irrespective of reperfusion strat-

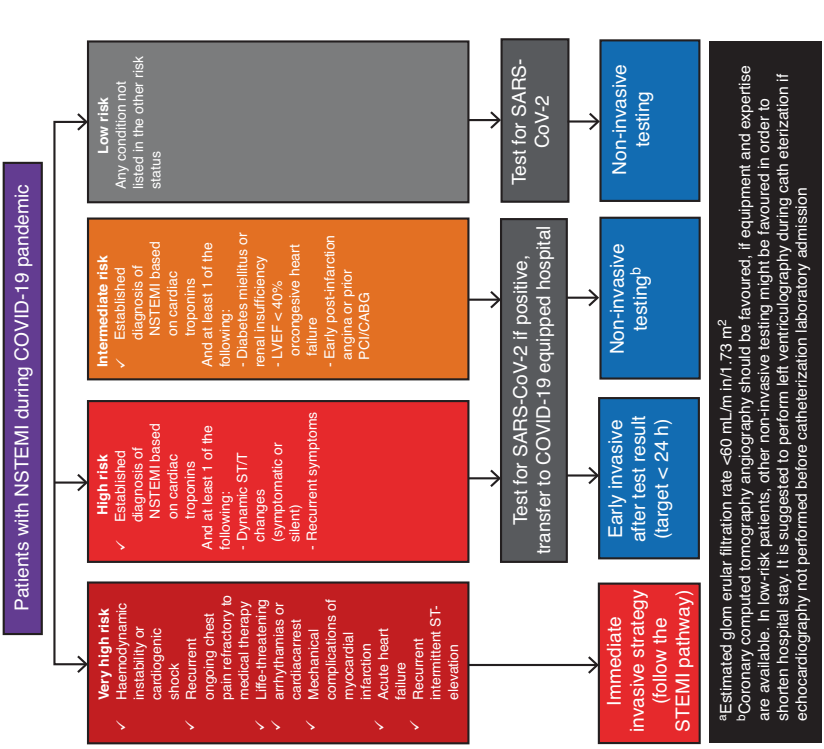

Fig. 7.8 Management of patients with STEMI or NSTEMI during COVID-19 pandemic—ESC 2021 guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic [101]. *COVID-19* coronavirus disease 2019, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation MI – myocardial infarction, *CABG* coronary artery bypass graft, *LVEF* left ventricular ejection fraction, *NSTEMI* non-ST-segment-elevation MI, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

egy, at the latest upon admission to the ICU post primary PCI. Until the result of the test is known, all precautionary measures should be taken to avoid potential infection of other patients and HCP.
4. Consider immediate complete revascularization if indicated and appropriate to avoid staged procedures and reduce hospital stay.
5. All physicians involved in the management of patients with STEMI should be familiar with indications, contraindications, and dosage of fibrinolysis and adhere to established administration protocols [102].

Left ventriculography should be considered during catheterization if echocardiography has not been performed before catheterization laboratory admission or is not feasible soon after the procedure. The treatment of the non-culprit lesions should be manager according to patients' clinical stability as well as angiographic features of those lesions. In the presence of persistent symptomatic evidence of ischemia, subocclusive stenosis, and/or angiographically unstable non-culprit lesions, PCI during the same hospitalization should be considered. Treatment of other lesions should be delayed, planning a new hospitalization after the peak of the outbreak [101].

NSTEMI: ESC Guidance for the Diagnosis and Management of Cardiovascular Disease During the COVID-19 Pandemic [101]

The management of patients with non-ST-segment elevation ACS should be guided by the risk stratification and intensity of involvement in the epidemics. In geographic territories with significant pandemic involvement, testing for SARS-CoV-2 should be performed as soon as possible following first medical contact, irrespective of treatment strategy, to allow healthcare providers to implement adequate protective measures and management pathways. Patients should be categorized into four risk groups (i.e., very high risk, high risk, intermediate risk, and low risk) and managed accordingly (Fig. 7.8).

For patients at high risk, medical strategy aims at stabilization while planning an early (<24 h) invasive strategy. The time of the invasive strategy may, however, be longer than 24 h according to the timing of testing results.

Patients at intermediate risk should be carefully evaluated taking into consideration alternative diagnoses to type I MI, such as type II MI, myocarditis, or myocardial injury due to respiratory distress or multiorgan failure or Takotsubo syndrome. In the event any of the differential diagnoses seem plausible, a non-invasive strategy should be considered, and coronary computed tomography angiography (CCTA) should be favored, if equipment and expertise are available.

When there is a positive SARS-CoV-2 test, patients should be transferred for invasive management to a COVID-19 hospital equipped to manage COVID-19-positive patients. At times of high demand on the infrastructure and reduced availability of catheterization laboratories or operators, non-invasive conservative

management might be considered with early discharge from the hospital and planned clinical follow-up.

Patients with troponin rise and no acute clinical signs of instability (ECG changes, recurrence of pain) might be managed with a primarily conservative approach. Non-invasive imaging using CCTA may speed up the risk stratification and avoid an invasive approach allowing for early discharge.

ACS Prevention

As indicated by the recommendations of ESC, in patients with chronic CAD, diagnosis and therapy should be carried out depending on the current clinical state. Remote clinical follow-up should be warranted to reassure patients and capture possible changes in clinical status that might require hospital admission in selected high-risk profile patients. Moreover, patients with chronic CAD should not withdraw aspirin for secondary prevention [101].

Statin therapy improves the prognosis of COVID-19 patients and reduces the risk of ACS due to the ability to stabilize atherosclerotic plaque [85, 103]. It has been shown that patients with COVID-19 who took statins had a lower risk of severe disease (with the significant reduction of the intubation and ICU admission risk) and a lower risk of death [85, 104, 105]. It is recommended to reduce the statin dose/discontinue statin therapy in patients with COVID-19 and features of rhabdomyolysis [101]—drug-to-drug interactions should be always taken into account in these patients [106]. The control of lipid disorders is also an important factor in the prevention of ACS and the severe course of COVID-19. Recommendations for the treatment of lipid disorders in people with COVID-19 of the Polish Lipid Association (PoLA) are presented in Table 7.3 [107]. Based on this, the authors strongly recommend that in individuals with COVID-19, optimum statin therapy should be

Table 7.3 Recommendations on treatment of lipid disorders in patients with COVID-19 [107]

Recommendations	Class	Level
In individuals with COVID-19, treatment of elevated LDL cholesterol concentration should be optimized as soon as possible, especially in those at high or very high cardiovascular risk, in whom the highest recommended statin doses should be used	IIa	C
Initiation or intensification of therapy and its monitoring is also possible by means of teleconsultations	I	C
Adequate control of cardiovascular risk factors, including in particular achievement of therapeutic goals for LDL cholesterol, becomes particularly important during the pandemic due to the need to reduce the risk of cardiovascular events and mortality in patients with COVID-19, in the circumstances of limited availability of healthcare resources	I	C
In individuals with COVID-19, optimum statin therapy should be continued, also during hospitalization, as this may be associated with improved prognosis	IIa	B

COVID-19 coronavirus disease 2019, *LDL* low density lipoprotein

continued, also during hospitalization, as this may be associated with improved prognosis (IIaB) [107].

In the case of antihypertensive treatment, it is recommended to continue the current therapy [101]. The latest meta-analysis by Lee et al., including 86 clinical studies, showed that angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) appear safe in the context of SARS-CoV-2 infection and should not be discontinued [108].

Glycemic control is also an important factor in the prevention of ACS. Risovic et al. have shown that poorer glycemic control before COVID -19 is associated with higher inflammation parameters, worse outcomes, and required modification of their treatment during hospitalization [109]. The meta-analysis by Kan et al., including 18 clinical trials, showed that oral antidiabetic drugs are safe in patients with COVID-19 [110].

In summary, good control of risk factors for CAD progression is the basis of COVID-ACS prevention. It should also be remembered to control non-classical risk factors for ACS, such as periodontal diseases, which are very common in the population and constitute a risk factor for the more severe course of COVID-19 [111] and other inflammatory diseases that aggravate the progression of atherosclerotic lesions [112].

Conclusions

COVID-19 has become a very serious problem in world medicine, and we might predict that will be with us forever. CVD increases the risk of a severe course of COVID-19. On the other hand, various cardiac complications, including ACS, are observed in the course of COVID-19. An increased risk of CVD, including ACS, is also observed in COVID-19 survivors in the course of the so-called Long-COVID. In the general population of COVID-19 patients, the incidence of de novo ACS has been shown to be around 2%. The impact of the COVID-19 pandemic on the diagnosis and treatment of ACS is also significant. During the pandemic, there was a significant reduction in hospitalizations for ACS, which may increase the incidence of heart failure and other cardiological complications, including CVD deaths. On the other hand, the time of pandemic is also characterized by an increased incidence of complications and higher mortality among hospitalized ACS patients. The occurrence of ACS in the course of COVID-19 worsens the prognosis of patients.

The pathogenesis of ACS in the course of COVID-19 includes mainly indirect mechanisms, such as: cytokine storm, dysregulation of the RAA system, coagulopathies, activation of the complement system, vascular endothelial dysfunction, etc. COVID-19 is a trigger of destabilization pre-existing atherosclerotic plaque.

In the management of patients with ACS and COVID-19, the recommendations of the European Society of Cardiology should be used. The mainstay of ACS prevention is good control of risk factors for the progression of atherosclerosis,

including optimal CVD therapy, without discontinuation of the treatment during hospitalization due to COVID-19.

Due to the dynamic progress of knowledge, the authors point to the need to follow current scientific reports.

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Chapter 8
Acute Vascular Injury in COVID-19

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Introduction

The pulmonary manifestations of coronavirus disease 2019 (COVID-19) are perhaps the most devastating, however, the clinical implications of extra-pulmonary involvement are increasingly recognized. Vascular injury and dysfunction have emerged as critical players in the pathophysiology of COVID-19. Involvement of the vascular system is a well-recognized sequelae of a number of infectious processes, the robust thrombo-inflammatory response to COVID-19 is unique in a number of respects. Thrombotic complications predominate in the venous system, culminating in venous thromboembolism; however, a substantial number of potentially life-threatening ischemic complications have been reported in almost every vascular territory. Early recognition and effective treatment are essential in mitigating the long-term consequences of these events.

In this chapter, we outline the pathophysiology of vascular involvement, followed by a detailed description of the spectrum of vascular disease in COVID-19

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including vaccine related complications. Finally, we delve into management of these complications in terms of both treatment and prophylaxis.

Pathophysiology

The florid procoagulant state and resulting thromboembolic complications in COVID-19 arise from a combination of hyperinflammation (immune-thrombosis), endothelial cell (EC) dysfunction, and dysregulation of the renin-angiotensin-aldosterone (RAAS) pathway (Fig. 8.1) [1, 2].

Inflammatory responses during acute infection result in successful viral clearance in the majority of individuals. Failure to adequately suppress viral replication results in a number of complications including diffuse alveolar damage (DAD) [3]. Simultaneously, resident ECs undergo necroptosis due to a combination of direct viral infection and collateral damage from exuberant host inflammatory responses [4]. This results in the activation and release of several procoagulant molecules including tissue factor and von Willebrand factor [1]. Recruitment of neutrophils potentiates EC damage and thrombotic risk by generating neutrophil extracellular traps (NETosis) as well as cytotoxic reactive oxygen species [5]. Dysregulation of the complement system further contributes to thrombogenic endotheliopathy [6]. Deposition of C5b-9 (membrane attack complex) is enhanced by NETs which

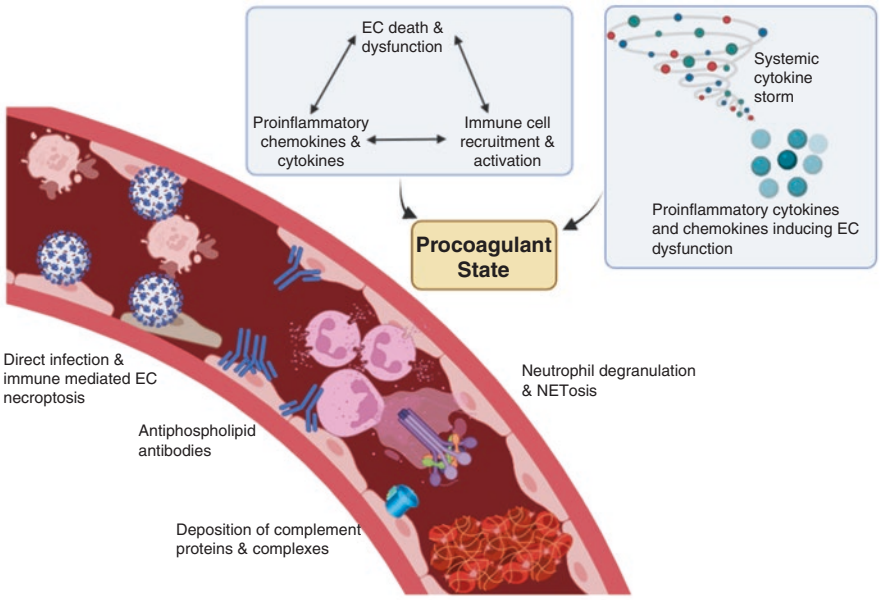

Fig. 8.1 Pathophysiologic mechanisms of acute vascular injury in COVID-19

provide a scaffold, further perpetuating endothelial injury [7]. Thus, in addition to DAD, diffuse thrombosis, microhemorrhage, and vessel wall edema all appear to contribute in varying degrees to the respiratory failure seen in severe COVID-19 [1]. The resulting hypoxia further amplifies this hypercoagulable milieu by promoting the release of tissue factor and PAI-1, inhibiting anticoagulant pathways, and stimulating a systemic inflammatory response. This self-perpetuating cycle results in elevated levels of soluble P-selectin and thrombomodulin - markers of EC activation associated with increased disease severity [8].

Presence of antiphospholipid autoantibodies in the vessel wall has been reported in COVID-19, indicating a role of antibody-mediated vasculitis [9]. These antibodies stimulate NETosis, potentially amplifying a vicious cycle of complement, platelet, and EC activation [10]. These events ultimately establish a feedforward loop of inflammation and endothelial injury, resulting in systemic endotheliitis, capillary leakage, and aberrant activation of the coagulation cascade [11].

During homeostasis, ECs secrete nitric oxide (NO) which favorably modulates vascular tone while suppressing the production of cytokines, chemokines, and adhesion molecules as well as leukocyte activation [12]. COVID-19 related EC dysfunction leads to NO deficiency, and loss of the aforementioned vasculo-protective effects [13].

The RAAS system, in particular angiotensin-II, helps maintain vascular homeostasis via a multitude of downstream effects on vasoconstrictor, inflammatory and fibrotic pathways [14, 15]. Angiotensin converting enzyme 2 (ACE-2) curbs these deleterious activities by cleaving angiotensin-II to angiotensin 1–7, a peptide known to possess anti-inflammatory, antioxidant, and anti-fibrotic properties [16]. However, COVID-19 viral entry triggers the proteolytic cleavage and shedding of ACE-2 from the surface of host cells, limiting its protective effects [16]. This also results in elevated plasma angiotensin-II levels which have been found to correlate with disease severity [17].

Clinical Presentation

In this section, we review the wide spectrum of micro and macrovascular angiopathy in COVID-19 (Table 8.1), followed by a brief overview of vaccine-induced immune thrombotic thrombocytopenia.

Respiratory

Venous thromboembolism (VTE) in the form of deep vein thrombosis (DVT) and pulmonary embolism (PE) are serious complications in hospitalized patients with COVID-19. Early in the pandemic, VTE was reported in up to a third of critically ill

Table 8.1 Spectrum of vascular injury in COVID-19

Organ system	Macrovascular	Microvascular	Comments
Respiratory	Deep vein thrombosis—pulmonary embolism	• Pulmonary microthrombi • Septal endotheliitis	Most common complication
Cardiovascular	Acute coronary syndrome Coronary emboli/spasm/dissection Acute limb ischemia	• Kawasaki-like disease • Coronary vasculitis • Coronary microthrombi • Coronary microangiopathy	Correlates with disease severity
Central nervous system	Ischemic stroke	• Microvascular inflammation • Anticardiolipin antibodies	More severe neurological deficits Younger age Greater re-occlusion following endovascular interventions
Gastrointestinal	Mesenteric ischemia		Poor prognosis—40% mortality Atypical distribution—spares watershed areas
Renal	Acute kidney injury Frequent clotting of dialysis circuits	• Lymphocytic endotheliitis • Microangiopathy	Severity correlates with extent of proteinuria
Dermatological	Vasculitis	• Pauci-inflammatory thrombogenic vasculopathy • Microvascular thrombi	Vasculitis possibly heralds acute limb ischemia. Limited data
Systemic Vasculitis		• Kawasaki-like syndrome	Predominantly pediatric phenomenon Type 3 hypersensitivity

patients. Since then, a steady decline is observed, with current rates resembling those encountered in any acutely ill non-COVID-19 hospitalization [18, 19].

A growing body of histopathological evidence indicates that in addition to the well-described parenchymal alveolar damage, endothelial dysfunction contributes substantially to severe respiratory distress in COVID-19 [20]. Early postmortem studies report the presence of pulmonary microthrombi as well as a degree of endothelial dysfunction, far greater than that observed with other viral pneumonias [21, 22]. A relative predominance of microvascular angiopathic changes over the more typical features of acute respiratory distress syndrome such as hyaline membranes and type II pneumocyte hyperplasia has been reported in severe cases [7]. This is associated with extensive deposits of complement fractions C5b-C9, and C4d along with inflammation of septal capillaries and luminal fibrin deposition [22–25].

Cardiovascular

Cardiovascular involvement spans a wide spectrum from myocardial infarction and pulmonary embolism to acute myocardial injury, myocarditis, heart failure, and arrhythmias [26].

At a macrovascular level, acute coronary syndrome (ACS) may occur on the backdrop of underlying coronary disease, via mechanisms analogous to those encountered in a non-COVID setting, namely atherothrombosis. On the other hand, de novo ACS in the setting of severe infection is often related to the ongoing hyper-inflammatory state with resultant immune vasculitis compounded by hypercoagulability [27, 28]. Coronary spasm, embolism, dissection as well as disease of the coronary microcirculation can all result in ACS in these patients.

Acute myocardial injury, defined by an elevation in cardiac biomarkers above the 99th percentile of the upper reference limit, is encountered in about 20% of hospitalized COVID-19 patients and 20–40% of critically ill patients [29–31]. This is likely a result of supply-demand mismatch in the setting of sepsis and hypoxic respiratory failure. Microvascular angiopathy with immune-mediated myocardial injury in the setting of a systemic hyperimmune state and cytokine release further contributes [32]. Autopsy data indicates varying degrees of vascular fibrosis, but with conflicting data regarding microvascular involvement. Most autopsy series have not found clear signs of coronary microangiopathy such as inflammation, thrombosis, or evidence of viral particles in ECs [24, 25, 33]. A more recent study, however, reports the presence of non-occlusive fibrin microthrombi in the coronary microvasculature [34]. The clinical significance of these findings remains uncertain at this time.

Acute limb ischemia (ALI) is reported in between 3% and 15% of hospitalized patients, with a predominance of lower extremity involvement [35, 36]. Obesity, advanced age, and the presence of traditional cardiovascular risk factors are all associated with higher rates of ALI. Of note, up to 20% of cases occur in younger patients with no significant comorbidities as well as in patients with relatively mild infections. More recently, ALI has been reported after SARS-CoV-2 vaccinations, which is described in further detail in the subsequent sections.

The aforementioned cardiovascular complications are not specific to COVID-19 and have been reported with a number of viral infections and septic states. However, COVID-19 is associated with a disproportionately dysregulated immune response with robust endothelial damage leading to significantly higher event rates [29, 37].

Central Nervous System

Neurological manifestations of COVID-19 range from delirium, seizures, and encephalitis to headache, anosmia or hypogeusia in milder cases [38, 39].

Ischemic stroke (IS) in itself appears to be relatively infrequent, reported in 0.4–2.7% of patients, with rates increasing in proportion to disease severity [40, 41]. IS is observed at slightly younger ages and may be associated with greater rates of early re-occlusion following mechanical thrombectomy as compared to non-COVID-19 patients, possibly indicating an underlying hypercoagulable state [42, 43]. COVID-19 related IS also appears to be more severe and debilitating than that encountered in non-COVID-19 patients (National Institute of Health Stroke Scale, NIHSS 19 vs 8) [44]. Limited data indicates the potential contribution of anticardiolipin antibodies to IS in these patients [40].

In one autopsy series, multifocal microvascular injury was seen in the brain and olfactory bulbs of 9 out of 13 patients [45]. Focal or diffuse perivascular CD8+ lymphocytic infiltrates, as well as microscopic thrombotic and hemorrhagic infarcts have been reported indicating a component of microvascular inflammation in all parts of the brain and meninges [45, 46]. Both ECs and myocytes in the brain express the ACE2 receptor, which potentially facilitates viral invasion of the central nervous system [47].

Gastrointestinal

Expression of ACE-2 in enterocytes, smooth muscle cells, and ECs of the gastric and intestinal walls contribute to gastrointestinal involvement in COVID-19 [47]. Isolation of the virus in stool samples further supports the role of direct viral invasion [48]. Rectal shedding of the virus can persist up to 47 days after resolution of symptoms, contributing to prolonged fecal-oral transmission [48, 49]. Diffuse endothelial inflammation in submucosal vessels with areas of mesenteric ischemia, and lymphocytic infiltrates in the bowel wall further contribute to gastrointestinal involvement [13, 49].

Gastrointestinal symptoms such as diarrhea, nausea, vomiting, and loss of appetite are reported in 15% of patients with COVID-19 [48]. In contrast to hepatobiliary dysfunction, the presence of gastrointestinal involvement is not associated with a worse prognosis [48]. In fact, in a small series of 247 patients, the presence of gastrointestinal symptoms was associated with a trend towards lower rates of intensive care unit admission and decreased short-term mortality [50].

Perhaps the most devastating gastrointestinal complication is mesenteric ischemia which has been reported in up to 4% of critically ill patients [51]. Prognosis is very poor with mortality reported to be as high as 40% in these patients [52]. Inability to report symptoms in intubated patients often delays diagnosis, hence mandating strict vigilance for nonspecific findings such as rising lactate, worsening acidosis, and feeding intolerance. The terminal ileum is most commonly involved and interestingly watershed areas are only rarely ischemic in these patients [53]. The reason for this pattern of involvement remains unclear.

Renal

Acute kidney injury (AKI) is reported in 36.6% of hospitalized patients, with 14.3% of them requiring renal replacement therapy [54]. While mild proteinuria could reflect tubular injury, frank albuminuria is believed to result from either direct podocyte damage or endothelial dysfunction [37, 55]**.** AKI increases with disease severity and is independently associated with increased mortality in COVID-19 [54, 56–58]. Endothelial dysfunction can be a result of both direct viral entry and the systemic cytokine storm [32]. In the kidneys, ACE-2 is not expressed in the mesangium or glomerular endothelium, but rather predominates in podocytes and epithelial cells of the proximal tubules [47, 59, 60]. Other histopathological findings include, viral inclusion particles in ECs, complement deposition and lymphocytic endotheliitis, highlighting the role of microangiopathy and endothelial dysfunction to kidney dysfunction [13]. Furthermore, the systemic procoagulant milieu results in frequent clotting of renal replacement therapy circuits [61].

Dermatological

Dermatologic manifestations of COVID-19 include acro-cutaneous lesions, maculopapular erythematous rashes, petechiae and, less frequently, chickenpox-like lesions, and urticaria [62, 63].

Potential mechanisms include vasculitis, microvascular thrombi, and cytokine storm [55, 63]. Experts suggest that vasculitis could indicate underlying hypercoagulability and potentially herald future limb ischemia, though current data is insufficient to conclusively support this hypothesis [64]. Histopathological changes include pauci-inflammatory thrombogenic vasculopathy with deposition of C5b-9 and C4d complement fractions [7].

Systemic Vasculitis

Histopathological studies report evidence of direct viral infection of ECs with diffuse endothelial inflammation and apoptosis as well as mononuclear infiltrates of the vascular intima suggestive of COVID-19 related vasculitis [13]. Increasing rates of a Kawasaki-like disease, a systemic vasculitis primarily involving the coronary arteries have been reported in seropositive children [65]. However, the limited sample size of this series limits further generalizations at this time. This possible COVID-19 related vasculitis is postulated to be a type III hypersensitivity reaction given the extensive immune complex deposition in the vascular wall [66].

Vaccine-Related Complications

Rarely, COVID-19 vaccines are reported to induce vascular dysfunction resulting in a syndrome termed, vaccine-induced immune thrombotic thrombocytopenia (VITT) [67]. This is believed to result from generation of antibodies against platelet-factor 4 (PF4), with subsequent activation of platelets, monocytes, neutrophils, and ECs to stimulate the coagulation cascade [68]. It is hypothesized that vaccine components such as the adenoviral hexon protein, form complexes with PF4, exposing neoantigens and stimulating autoantibody production [68].

VITT is typically observed between 5 and 30 days after vaccination, often accompanied by flu-like symptoms [67]. It has been reported with both Astra-Zeneca and Janssen vaccines [68]. The lack of VITT with other adenoviral vaccines raises the question of potential differences in vaccine constituents and/or reporting. A study from Norway identified 5 cases among 130,000 individuals who received the Astra-Zeneca vaccine (1 in 26,000), while a recent 2022 surveillance study reported much lower rates of 1 in 263,000 [69, 70]. Preliminary reports suggest a female predominance, although this has not been conclusively demonstrated [67]. Patients with VITT generally present with thrombocytopenia and concomitant arterial and venous thrombosis [70]. Cerebral venous thrombosis accounts for the majority of thrombotic events, while pulmonary embolisms, ischemic stroke, acute limb ischemia, and myocardial infarctions have also been reported. Interestingly, patients may develop multiple thrombi, often at atypical sites including the splanchnic, adrenal, and ophthalmic veins. The specific mechanism underlying this unusual distribution remains unclear. VITT may also result in disseminated intravascular coagulation, with patients exhibiting highly elevated D-dimer and decreased fibrinogen levels [70]. While thrombosis predominates, serious bleeding has also been observed particularly in individuals with cerebral venous thrombosis [70].

Treatment

Management of most thromboembolic complications associated with COVID-19 is in large part similar to that of non-COVID-19 patients. In the following section, we review the management of the most commonly encountered complications, focusing on aspects unique to COVID-19 (Table 8.2).

Anticoagulation

Prophylactic anticoagulation (AC) is routine practice in the management of hospitalized patients with COVID-19 [71]. The role of therapeutic AC in critically ill patients, however, has been much more controversial. Early reports of frequent

Table 8.2 Overview of management of vascular injury in COVID-19

Complication	Medical management	Interventions	Comments
Anticoagulation	Prophylactic AC for all patients. No role for empiric treatment dose AC regardless of disease severity		
Acute coronary syndrome	Parenteral anticoagulation Antiplatelet therapy Beta-blocker agents ACEI/ARB *Medical therapy should be directed by current guidelines regardless of COVID status*	PCI/CABG Fibrinolysis is not recommended unless access to PPE or a revascularization capable center are limitations	Favor culprit vessel only PCI Catheterization laboratory: Terminal clean, avoid intubation and aerosolization Monitoring in telemetry bed is acceptable in hemodynamically stable patients to optimize ICU/CCU bed availability
Ischemic stroke	Antiplatelet therapy Statins	Pharmacological Thrombolysis Mechanical thrombectomy	Critical risk-benefit analysis prior to thrombolysis Tele-stroke is validated to assess NIHSS High risk of re-occlusion following endovascular interventions PT, OT, and speech therapy should be offered regardless or COVID status
DVT/PE	Therapeutic AC with Inpatient LMWH (less personnel exposure) or UFH Apixaban or rivaroxaban in the outpatient setting if no drug interactions	Thrombolysis Mechanical thrombectomy	Frequent reassessments of hemodynamic stability are needed despite greater personnel exposure PERT teams are critical to management
Acute limb ischemia	Therapeutic AC with Inpatient LMWH (less personnel exposure) or UFH	Thrombectomy, embolectomy, thrombo-suction, angioplasty fasciotomy, direct catheter thrombolysis or bypass	Critical risk-benefit analysis prior to thrombolysis or any intervention

AC anticoagulation, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CABG* coronary artery bypass graft, *CCU* cardiac care unit, *DVT* deep venous thrombosis, *ICU* intensive care unit, *LMWH* low molecular weight heparin, *NIHSS* National Institutes of Health Stroke Scale, *OT* occupational therapy, *PCI* percutaneous coronary intervention, *PE* pulmonary embolism, *PERT* pulmonary embolism response team, *PPE* personal protective equipment, *PT* physical therapy, *UFH* unfractionated heparin

acute thromboembolic events including limb ischemia, ischemic strokes, and myocardial events prompted the widespread, empiric use of therapeutic dose AC in critically ill patients. This area has been the subject of extensive study and the current consensus of most societal guidelines is that *empiric* intermediate or full-dose

therapeutic AC has no role in regular practice regardless of disease severity [72–76]. Regarding the choice of anticoagulant in this setting, no significant difference has been found between agents, with selection driven by concomitant bleeding risk, renal function and potential drug interactions.

Acute Coronary Syndrome

The medical management of myocardial infarction in patients with COVID-19 is not significantly different from that of non-COVID-19 patients [77–79]. Primary percutaneous coronary intervention (PCI) remains the preferred form of reperfusion regardless of COVID-19 status [80]. Fibrinolytic therapy with tenecteplase may be considered if personal protective equipment (PPE) is limited [81]. However, the use of fibrinolysis is controversial in countries such as the USA in which PCI is the standard of care for myocardial infarction [81]. Patients who receive fibrinolysis still need transfer to a PCI-capable center, since up to half of these patients will require a rescue PCI [79, 82]. Furthermore, bleeding complications as well as occurrence of alveolar hemorrhage after fibrinolysis, could paradoxically result in greater resource utilization in these patients [83, 84].

Professional societies recommend revascularization with PCI in both ST-segment elevation and non-ST segment elevation myocardial infarction, with the addition of a terminal clean of the catheterization room following the procedure and the use of powered air purifying systems, where available [77, 80]. It is important to differentiate true acute coronary syndrome from myocardial injury which is frequently encountered in these patients and not an indication for urgent revascularization [77]. Similarly, elective procedures for stable coronary artery disease, stable peripheral artery disease, and non-urgent structural interventions should be deferred until protection of personnel can be assured [77].

Additional recommendations to protect staff include performing intervention only on the culprit vessel and avoiding endotracheal intubation in the catheterization laboratory itself (intubating prior to arrival to the catheterization laboratory where possible) [78–80]. Furthermore, to optimize intensive care resources, patients who are hemodynamically stable after an acute coronary syndrome can be monitored in an intermediate care telemetry unit, rather than occupying a bed in the intensive care unit [79, 82].

Ischemic Stroke

Medical therapy of ischemic stroke is similar to that of non-COVID-19 patients [85, 86]. Additional consideration of the extent of multisystem organ dysfunction and overall prognosis is critical before employing thrombolysis in these patients. Hepatic or renal compromise, thrombocytopenia and derangements of the

coagulation profile which are frequently encountered in these patients all have a substantial impact on the risk-benefit profile of thrombolysis. Regarding the optimal choice of agent, no comparison studies exist at this time to indicate preference of one agent over another.

With regard mechanical thrombectomy, outcomes appear to be similar to those reported prior to the pandemic [87]. Despite this, however, a 61% reduction in the number of endovascular thrombectomies is reported since the onset of the pandemic [88]. Mechanical thrombectomy should be reserved for patients who clearly meet criteria for thrombectomy according to the current guidelines, and in whom it can be performed in a timely manner and with protected personnel [86]. Neuroangiographic suites should undergo terminal cleaning, and members should always wear full PPE [86, 89].

Following initial treatment, rehabilitation planning and assessments by physical, occupational, and speech therapy is integral to further care regardless of COVID-19 status [89]. Finally, telemedicine has emerged as an integral tool to monitor patients after an IS [90]. Tele-stroke is a particularly important area that permits accurate assessment of the National Institutes of Health Stroke Scale (NIHSS), thus minimizing delays in diagnosis and initiation of appropriate therapies.

Venous Thromboembolism, DVT, and PE

The management of VTE poses a few unique challenges in patients with COVID-19. Firstly, the management of two similarly presenting, but vastly different etiologies of respiratory failure in the same patient is often challenging. Secondly, the need to protect personnel and avoid unnecessary exposures has led to frequent empiric treatment of possible PE in patients with COVID-19 before imaging confirmation [91].

Given the aforementioned challenges, pulmonary embolism response teams (PERT) are critical to ensure timely diagnostic and therapeutic decision-making [91]. Patients with COVID-19 and VTE should immediately be started on parenteral anticoagulation [74, 91]. Low molecular weight heparin (LMWH) is often preferred as it minimizes personnel exposure due to lower dosing frequency, reduces the risk of heparin induced thrombocytopenia as well as heparin resistance [74]. Although some oral anticoagulants (apixaban and rivaroxaban) were initially considered acceptable for initial therapy, the potential for rapid clinical deterioration and the risk of drug interactions make parenteral therapy the treatment of choice in the acute setting. On the other hand, in the outpatient setting and in low risk patients, oral anticoagulants are entirely appropriate [74].

Hypotension or signs of imminent hemodynamic compromise (worsening gas exchange, progressive right ventricular dysfunction on echocardiography, increasing levels of cardiac biomarkers) should prompt thrombolysis, either with systemic delivery or catheter-directed thrombolysis [74]. Frequent reassessments are therefore necessary despite the additional personnel exposure. It should be emphasized

that thrombolysis is recommended when there is an objective diagnosis of pulmonary embolism, and not just based on clinical suspicion, given a theoretical higher risk of alveolar hemorrhage in COVID-19 [74, 92]. Thrombolysis has been associated with a significant, though transient clinical benefit in oxygenation and hemodynamics [93, 94]. Between thrombolysis and thrombectomy, there is currently insufficient data to favor one intervention over another in patients with COVID-19, and the decision should be made by the PERT team on a case by case basis [91].

Acute Limb Ischemia

Parenteral anticoagulation should be initiated at the earliest clinical suspicion of acute limb ischemia [95, 96]. Thereafter, the choice of intervention is decided on a case by case basis, taking into consideration personnel exposure, bleeding risk, and the patient's hemodynamic stability to undergo an invasive procedure [95, 97, 98]. In addition, it is essential to be cognizant of the patient's overall prognosis, as thrombosis may be a terminal manifestation of illness, referred to as "agonal thrombosis" [97, 99]. In this regard, intervention in a terminally ill patient might paradoxically result in more harm than good. It is also hypothesized that endovascular interventions in COVID-19 might result in poorer outcomes based on pre-pandemic evidence that hypercoagulable states portend poorer outcomes post-revascularization [100].

Options for intervention include thrombectomy or embolectomy, endovascular thrombo-suction, angioplasty fasciotomy, direct catheter thrombolysis or bypass, with no definite superiority of any particular approach established [97, 98, 101]. In a systematic review of 34 studies, 199 patients with acute limb ischemia were analyzed among whom 41.8% were medically managed while 58.2% underwent interventional therapy [97]. In this study, medical treatment was associated with significantly higher mortality, as compared to any intervention (OR 4.04, 95% CI 1.1–15.2, p 0.045), though amputation rates were equivalent between groups.

Prophylaxis

Three well recognized pathways have been described via which the vascular system is impacted by COVID-19. Each of these serve as potential targets of intervention.

Anticoagulation

Emerging evidence indicates that the risk of thromboembolic events associated with COVID-19 extends into the post-hospital discharge period, well after resolution of the acute clinical syndrome. Similar trends have been reported following

hospitalization for other acute medical illnesses, with up to 57% of VTE events occurring after discharge [102].

Though data is limited, the Food and Drug Administration has approved prophylactic treatment with Rivaroxaban 10 mg daily for 31–39 days after discharge in high-risk patients (IMPROVE VTE risk score ≥4 or a score 2–3 with a plasma D-dimer >2 times the upper limit of normal) [71]. Furthermore, the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (SSC-ISTH) recommends either LMWH or a direct oral anticoagulant for at least 2 weeks and up to 6 weeks post-hospital discharge in patients with VTE risk factors who are at low bleeding risk [75].

Anti-Inflammatory Therapies

Given the central role of a hyperinflammatory response in the pathogenesis of coagulopathy in COVID-19, interventions targeting the immune system have been found to be highly effective at minimizing disease severity. While there is sparse clinical data investigating the direct effect of these interventions at limiting vascular injury, the observed improvement of outcomes with anti-inflammatory therapies is likely at least in some part due to the alleviation of immuno-thrombosis. Specifically, inhibition of the complement system may be highly effective at limiting thromboembolic events and EC dysfunction [6]. C5 blockade via the monoclonal antibody (eculizumab) prevents the formation of the membrane attack complex (MAC) while still allowing upstream complement proteins to exert beneficial antiviral effects. Clinical trials are currently underway to test the efficacy of eculizumab during COVID-19 and associated coagulopathy [6, 103].

Statins

Statins are integral in the management of numerous cardiovascular diseases and have even demonstrated benefit in certain infectious conditions such as tuberculosis and HIV [104]. Studies report mortality benefit in varied clinical scenarios including bacteremia, viral pneumonia as well as elderly patients with community acquired pneumonia [105–107]. These benefits are attributed to their anti-inflammatory and immunomodulatory effects via mTOR and NF-κB modulation [108]. With regard to COVID-19, data has been rather conflicting with the largest retrospective study on the topic by Ayeh et al. ($n = 4447$) as well as a meta-analysis of nine observational studies indicating no benefit in mortality or risk of severe disease [108, 109]. On the contrary, the authors reported an association between statin use and prolonged hospitalization and need for invasive mechanical ventilation. In summary, based on currently available evidence routine empiric statin use does not carry a clinical benefit and may in fact be associated with some harm, especially when also considering the added risk of hepatotoxicity with statin therapy.

RAAS Inhibition

The RAAS system and in particular ACE2 receptors are integrally involved in the pathophysiology of COVID-19, raising interest in the therapeutic potential of RAAS modulation. Early preclinical studies raised concerns that RAAS inhibition (RAASi) could result in upregulation of ACE2 receptors, thereby augmenting viral entry [110]. More recent data however has allayed such concerns and in fact highlight the potential utility of RAASi in mitigating endothelial dysfunction in states of systemic stress [111–113]. At present, the consensus of most professional societies is to continue pre-existing RAASi in patients who develop COVID-19 [114]. Data is insufficient to support the de novo initiation of these agents in COVID-19.

Conclusion

Increasingly, the vascular system is recognized as a major target of COVID-19 that plays a critical role in dictating clinical outcomes. The particularly robust systemic immune response encountered with this virus, compounded by a multitude of effects on the complement and RAAS systems result in numerous thromboembolic complications. Better understanding these mechanisms lays the foundation to devise targeted therapies to minimize the morbidity and mortality of these complications. COVID-19 raises unique challenges in delivering optimal medical therapy and a concerted, multidisciplinary approach is essential to optimizing patient outcomes.

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Chapter 9
Heart Failure and Acute Circulatory Failure in COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, Treatment)

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Epidemiology

The first infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is dated on December 12, 2019 in Wuhan, China [1]. Since this date the coronavirus disease 2019 (COVID-19) has spread globally and challenged both the economic and the medical sector. While it is primarily affecting the lung, COVID-19 also has effects on the cardiovascular system. Cardiac involvement, detected by increases in serum troponin, has been reported in up to 20% of patients [2], and it has been described to be associated with severe clinical course including higher mortality rates [3], developing acute respiratory distress syndrome [4, 5], and other organ complications [6].

Cardiac involvement may include different scenarios including myocardial infarction, myocarditis, as well as heart failure (HF). Current data suggest that there was a substantial reduction in HF admissions during the COVID-19 pandemic by up to 66% [7]. Simultaneously, patients who were hospitalized showed more severe symptoms like dyspnea or peripheral edema and the mortality rates were elevated compared to the pre-pandemic area [7, 8]. On the other side, pre-existing HF has been found to be an independent risk factor of a severe clinical course during a SARS-CoV-2 infection [9]. HF prevalence varied between 4% and 21% in hospitalized COVID-19 patients and increased up to 43% in patients who needed an intensive care unit (ICU) stay [10, 11]. Beside its prognostic value for a severe

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COVID-19 course, new data have shown that HF itself can be the result of a COVID-19 infection with prevalence values varying between 3% and 25% [12, 13].

Influence on Prognosis

COVID-19 caused by SARS-CoV-2 has rapidly spread worldwide to date, causing more than 6,100,000 deaths as of April fourth, 2022, according to the World Health Organization [14]. The mortality rate for patients hospitalized with COVID-19 is already about three-fold higher than that of patients hospitalized with seasonal influenza [15]. Particularly, patients with pre-existing cardiovascular disease generally have worse prognosis, with mortality rates of 10% or more reported [16].

HF patients are placed at particularly high risk of morbidity and mortality from this viral infection, because of their impaired immunity, general weakness, and poor hemodynamic capacity to respond to serious infections [17]. In general, the case fatality rate for septic patients without cardiovascular impairment is around 20%, but it rises to 70–90% when complicated by HF [18]. HF patients also produce more inflammatory cytokines by monocytes than healthy individuals, while producing fewer anti-inflammatory cytokines [19]. Severe COVID-19 infection causes an extensive systemic inflammatory response that requires enhanced cardiac performance and high cardiac output, while the aforementioned pathologies make it even more difficult for HF patients to overcome their critical condition.

Pre-existing HF

It has been reported that the prevalence of pre-existing HF in COVID-19 patients ranges from 4% in some areas of China to up to 21% in older European populations [2, 20], and many studies have been published on the prognostic impact of a history of HF in patients hospitalized with COVID-19 [21–23]. Pre-existing HF was not only significantly associated with the need of hospitalization for COVID-19, but also with the incidence of severe COVID-19 infections, ICU admissions, and ventilator use [24]. Furthermore, patients with pre-existing HF were associated with a close to two-fold increased mortality rate compared to COVID-19 patients without prior HF history [25].

New Onset of HF

Some reports have been published indicating on the prevalence and prognosis of new-onset HF as a manifestation of a COVID-19 infection in patients with previously healthy subjects. A retrospective report from Wuhan, China, has indicated that

HF was the fourth most common outcome of the diseases in COVID-19 patients [13]. In COVID-19 patients with no history of HF, new onset of HF was observed in one-quarter of those admitted to the hospital and in one-third of those admitted to the ICU [13, 25]. Another retrospective study evaluating 131 patients who have died of COVID-19 found that 49% of all-cause deaths in patients without a history of cardiovascular disease were attributable to HF [26].

Therefore, both pre-existing and new-onset HF have consistently been shown to be strong prognostic factors in COVID-19 patients.

Cardiogenic Shock

Cardiogenic shock is a rare, but life-threating late complication in patients with COVID-19, and several case reports have shown patients to go into cardiogenic shock. Tavazzi et al. reported the case of an elderly patient with influenza-like symptoms who rapidly went into cardiogenic shock, demonstrating myocardial localization of SARS-CoV-2 [27]. Yu et al. reported that 3 of 226 patients (1.3%) admitted to the ICU with severe COVID-19 had developed cardiogenic shock [28]. A study by Ángel et al. from Spain reported that 3 of 4 patients with COVID-19 who developed cardiogenic shock had died, with a mortality rate as high as 75%. Notably, these patients had no cardiovascular risk factors or significant co-morbidities [29]. An appropriate management and treatment of these patients requires a careful understanding of hemodynamic and diagnostic significances.

Pathogenesis

COVID-19 is a respiratory disease caused by SARS-CoV-2, a novel enveloped RNA beta coronavirus [30]. Although the primary target of SARS-CoV-2 is the respiratory system, the cardiovascular system may also be affected via various pathways. In fact, the incidence of acute myocardial injury, defined as a marked elevation of cardiac biomarkers, is found in 17–20% of all COVID-19 patients [2, 13]. Regardless of its mechanism, the myocardial injury can potentially lead to acute HF.

The mechanism of myocardial injury in patients with COVID-19 is likely to be multifactorial. Various pathologies have been considered including direct injury by myocardial invasion of SARS-CoV-2 via angiotensin converting enzyme 2 (ACE2) receptors, systemic inflammation, an imbalance in myocardial demand and supply, hypoxic injury, endothelial dysfunction, coagulation abnormalities, and many more [31–34]. Among these pathologies, direct viral injury to cardiomyocytes and systemic inflammation with cytokine storms appear to be particularly involved in myocardial injury. The following provides an overview of putative mechanisms by which COVID-19 may cause myocardial injury and HF (Fig. 9.1).

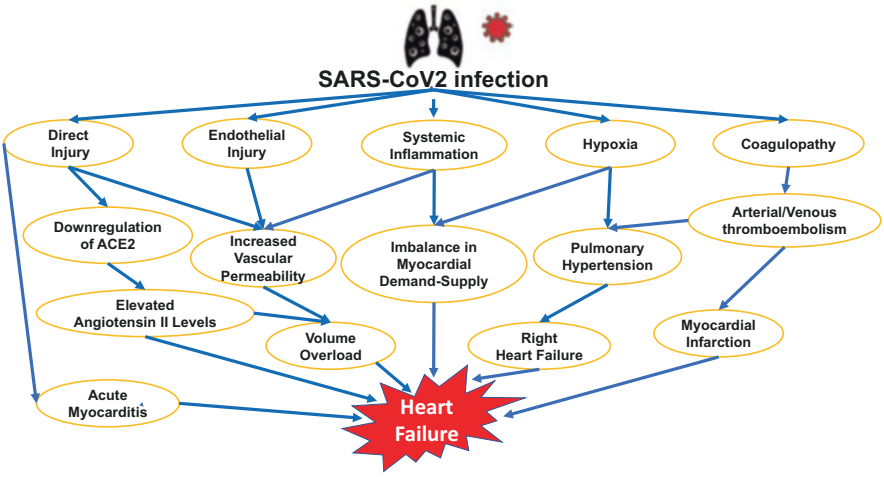

Fig. 9.1 Pathogenesis of Heart Failure in COVID-19 Patients. ACE2, angiotensin converting enzyme 2; COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Direct Injury

SARS-CoV-2 enters human cells by binding to ACE2, a type I membrane protein which is largely located in the lungs and small intestine, as a receptor for cell entry [35]. ACE2 has beneficial effects on the cardiovascular system by regulating blood pressure, resisting atherosclerosis, and improving cardiac function via neurodegeneration regulation [36, 37], and this receptor has also been reported to be present in cardiac tissue and vascular endothelial cells [38].

Murine models infected with severe acute respiratory syndrome coronavirus (SARS-CoV), which belongs to the same family as SARS-CoV-2 with a very similar in structure and pathogenicity [39, 40], demonstrated that ACE2-dependent myocardial infection triggered a significant down-regulation in ACE2 expression, resulting in myocarditis, pulmonary oedema, and acute respiratory failure [41]. The presence of SARS-CoV in the myocardium of deceased patients was also reported to be associated with a significant decrease in ACE2 protein expression [41]. Besides, SARS-CoV infection and the spike protein of SARS-CoV not only down-regulated ACE2 expression but also increased angiotensin II levels [42]. These finding generate that ACE2 might also play a pivotal role in myocardial injury caused by SARS-CoV-2 infection.

Systemic Inflammation

Acute systemic inflammatory response and cytokine storm cause multiple organs injury, leading to multiorgan failure [43]. Many studies have shown that patients with severe COVID-19 have high levels of inflammatory cytokines in the circulatory system [10, 44]. Cytokines and chemokines from SARS-CoV-2 can also cause tubular and endothelial dysfunction and promote systemic vascular permeability, resultant in hemodynamic disturbance from changes in vascular fluid volume, leading to acute HF decompensation [45, 46]. Furthermore, increased cardiometabolic demand enhanced by severe systemic inflammation can lead to an imbalance between myocardial oxygen demand and supply, resulting either in new-onset HF or acute exacerbation of pre-existing HF [47].

Hypoxic Injury

Hypoxia is a common and lethal clinical manifestation in patients with severe COVID-19 [4, 48, 49]. SARS-CoV-2 infection-induced hypoxia can cause pulmonary vasoconstriction and pulmonary hypertension, leading to right-sided and global HF [50, 51]. Furthermore, hypoxic injury induced by respiratory failure can lead to secondary myocardial injury, possibly exacerbating cardiac function [52]. Therefore, hypoxia can be closely involved in myocardial injury in COVID-19 patients.

Endothelial Dysfunction-Induced Coagulation Disorders

As mentioned above, ACE2 receptor is expressed in the vascular endothelium [38], and endothelial dysfunction and inflammatory response with activation of the complement and thrombin system occur when SARS-CoV-2 invades these epithelial membranes [34, 53, 54]. Platelet-leukocyte aggregates occur alongside the vascular endothelium injured by SARS-CoV-2, leading to the development of coagulopathy with elevated D-dimers and fibrin degradation products, and eventual development of microthrombuses [54]. In early reports from China, Guan et al. reported that about 60% of patients with severe COVID-19 had elevated D-dimer levels (>0.5 mg/L) [48]. Ning et al. from China also reported that the non-survivors with COVID-19 revealed significantly higher fibrin degradation products and D-dimer

levels than survivors, and 71.4% of non-survivors met the clinical criteria for disseminated intravascular coagulation during their hospital stay [55]. Endothelial injury may also cause increased vascular permeability and decreased levels of nitric oxide production from capillaries [45, 56]. The vascular endothelial dysfunction and coagulation abnormalities developed by SARS-CoV-2 may contribute to the development of multiple cardiovascular manifestations like myocardial infarction and HF, as well as impaired function of multiple organ systems in COVID-19 patients.

Treatment

Chronic Heart Failure Treatment

The treatment of chronic heart failure should follow the recommendation of current guidelines and depends on the underlying phenotype [57]. In all cases, the underlying pathology should be addressed, if possible (e.g., optimizing myocardial oxygen supply by myocardial revascularization in patients with coronary heart disease). In patients with reduced ejection fraction a combined administration of ACE inhibitors, betablockers, mineralocorticoid receptor antagonist, and sodium-glucose cotransporter inhibitors are generally recommended by the European Society of Cardiology (Class I A). For optimal dose adjustment blood pressure and laboratory monitoring is important. In patient, who remain symptomatic, the ACE inhibitor may be replaced by sacubitril/valsartan. While the aforementioned drugs are proven to prolong survival rates, additional drugs like diuretics, ferric carboxymaltose, or digoxin can be prescribed for symptom relief.

Besides pharmacological treatment, implantable devices such as implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT), may be considered. An ICD is indicated in patients, who survived a sudden cardiac death as a secondary prevention, or in patients with a left ventricular ejection fraction (LVEF) $\leq$35% despite optimal medical treatment for at least 3 month (primary prevention). In patients with prolonged QRS complex, cardiac resynchronization therapy may improve symptoms and reduce morbidity and mortality. The highest evidence for CRT is described in patients with left bundle brunch block (LBBB) and a QRS duration $\geq$150 ms. However, also in non-LBBB electrocardiogram patterns and prolonged QRS duration, a CRT may be helpful for symptom relief and survival rates. In patients with mildly reduced ejection fraction (LVEF 40–49%) the pharmacological treatment is equivalent. However, the evidence of proof is lower. The lowest evidence exists for patients with HF and a normal ejection fraction, termed HF with preserved ejection fraction. In the latter scenario fluid overload should be avoided by diuretics, but there are no pharmacological treatments with proven benefits for survival other than the use of empagliflozin 10 mg daily so far.

Acute Heart Failure Treatment

In the scenario of acute HF, patients commonly complain different symptoms, which may be addressed simultaneously. Hypoxemia, defined as SpO2 < 90%, should be treated primarily by oxygen supply. In cases of oxygen supply alone not being sufficient to increase SpO2 or persistent dyspnea and respiratory frequencies above 25/min non-invasive ventilation is recommended by the ESC guidelines. Finally, if the aforementioned strategies did not result in a sufficient oxygenation, invasive ventilation may be indicated. Fluid overload should be addressed by intravenous diuretics. Due to their rapid onset of action, loop diuretics are commonly used. Inotropes and/or vasopressors are commonly necessary to maintain a sufficient cardiac output and blood pressure.

In patients in whom pharmacological treatment does not result in a satisfactory stabilization, mechanical support may be provided. Different systems are commercially available including ECLS. A final assessment whether these systems offer higher survival rates is still pending. Therefore, they cannot be generally recommended and their use remains a case-by-case decision.

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Chapter 10
Cardiomyopathy in COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, Treatment)

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The pathophysiology of SARS-CoV-2 is characterized by overproduction of inflammatory cytokines leading to systemic inflammation and multiple organ dysfunction syndrome, acutely affecting the cardiovascular system [1]. The mechanisms of cardiovascular injury caused by SARS-CoV-2 infection have not been fully elucidated, but it is speculated that SARS-CoV-2 affects the cardiovascular system through multiple mechanisms, including direct injury, downregulation of angiotensin-converting enzyme 2 (ACE2), immune injury, hypoxia injury, and psychological injury. Cardiac injury with troponin increase, significantly related to inflammation biomarkers, illustrate a relevant correlation between myocardial injury and inflammatory hyperactivity triggered by viral infection [2]. The SARS-CoV-2 infection occurs through the coupling of S-protein located on the surface of the virus with ACE2, which acts as a receptor for the virus. ACE2 is mostly present in the lungs and seems to be the main gateway for the virus. It is also present in the heart, which can lead to complications [2]. Cardiovascular implications result in a worse prognosis COVID-19 patients,

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emphasizing the importance of precocious detection and implementation of optimal therapeutic strategies. Patients with previously established comorbidities such as cardiovascular diseases are at a particularly high risk of morbidity and mortality from this viral infection. Cardiac injury in patients infected with the novel Coronavirus seems to be associated with higher morbimortality [3]. Moreover, several studies showed that COVID-19 can aggravate pre-existing cardiovascular disease and cause new cardiovascular injuries [3]. It is important to identify cardiac-related manifestations in patients with COVID-19.

The clinical manifestations of cardiac involvement could range from an absolute lack of symptoms in the presence of increased troponin levels, with or without ECG or imaging abnormalities, to arrhythmia and sudden cardiac death, pulmonary embolism, acute coronary syndromes, myocarditis, acute heart failure, and cardiogenic shock [4].

Heart Failure, Cardiomyopathies and COVID-19

The link between COVID-19 and heart failure (HF) is intricate. During the pandemic period the reduction of HF hospitalizations is observed due to patient fear and lack of free hospital possibly leading to an increase in HF mortality. The history of HF is a risk factor for a more severe clinical course of COVID-19 [5] and on the other hand HF can be a consequence of COVID-19-related myocardial damage—Fig. 10.1. HF patients were more prone to develop myocardial injury [4, 5].

In a prospective cohort study, among 5279 people with laboratory confirmed SARS-CoV-2 infection, more than a half were admitted to hospital, of whom 1904

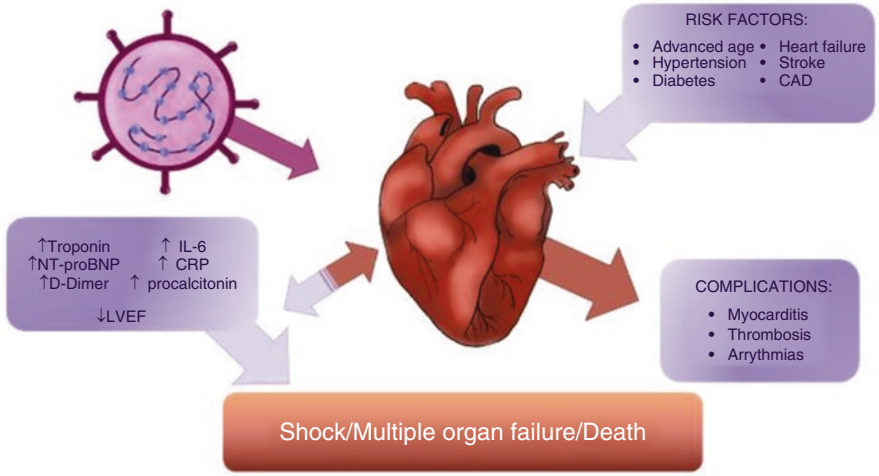

Fig. 10.1 The influence of SARS-CoV-2 on myocardial injury

(69.5%) were discharged alive [5]. In this analysis the strongest risks for critical illness besides age were associated with heart failure (1.9, 1.4 to 2.5), BMI >40 (1.5, 1.0 to 2.2), and male sex (1.5, 1.3 to 1.8) [5]. A clinical study of 99 cases with confirmed COVID-19 from Wuhan showed that 11 (11%) patients had died of which two patients had no previous history of chronic heart disease but developed heart failure and eventually died of a sudden cardiac arrest [6]. Additionally, Chen et al. [7] reported that cardiac complications were observed more frequently in 113 deceased patients with COVID-19, including acute cardiac injury (72/94; 77%) and heart failure (41/83; 49%). New onset of HF was observed in as much as a quarter of hospitalized COVID-19 patients; and in as much as one-third of those admitted to the intensive care unit (ICU) [8], despite not having a history of HF. It was reported that in HF patients, monocytes seem to produce more TNF-α and less IL-10 than healthy subjects [9]. Heart failure in patients with COVID-19 occurs as a result of different myocardial aggression mechanisms such as direct myocardial injury by viral action, indirect and direct inflammatory damage, oxygen supply–demand imbalance, and increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques resulting in acute myocardial dysfunction [10].

In COVID-19 patients presenting acute HF, left ventricle (LV) systolic function is not usually compromised; on the contrary, impairment of right ventricular (RV) systolic function and LV diastolic function can be found [11]. Out of 100 patients hospitalized for COVID-19, 32% were reported to have normal echocardiography, whereas 39% presented RV dilatation and dysfunction and 16% LV diastolic dysfunction, whereas reduced LV ejection fraction (EF) was reported only in <10% [12]. Similar results are described in a large international cohort study [4]. Accordingly, LV diastolic impairment with elevated LV filling pressures (E/e′ ratio) could be observed in a quarter of patients admitted for COVID-19.

Consistently, patients hospitalized with COVID-19 showed high likelihood of presence of HF with preserved ejection fraction (HFpEF) as compared with patients without COVID-19 according to the score of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), and HFpEF was found associated with cardiac structural and functional alterations and myocardial injury [13].

The persistent myocardial damage and fibrosis in the subacute and chronic phases after recovery suggest that COVID-19 may be an independent risk factor for the development of HF [14]. The early identification of patients with cardiac abnormalities is of pivotal importance as they may benefit from cardioprotective therapy and need different follow-up strategies. Heart failure is common and may be encountered de novo as part of the clinical course of COVID-19 or in those with pre-existing cardiac disease. It is thus imperative to understand the diverse interactions between this disease state and the virus to optimize the management of these patients.

In the study of Omidi et al. the authors aimed to describe the creation of systematic search in databases up to August 2020, for all relevant studies about COVID-19 and cardiomyopathies. A total of 29 articles with a total number of 1460 patients were included. Diabetes, hyperlipidemia, hypertension, ischemic heart disease, and

obesity were the most recorded comorbidities among patients with COVID-19 and cardiomyopathy. In the laboratory test, 21.47% of patients had increased levels of troponin. In addition, all of the patients had elevated D-dimer levels. Echocardiographic measurements showed mild, moderate, and severe left ventricular dysfunction present in 17.13%, 11.87%, and 10% of patients, respectively. In conclusion, cardiomyopathies were common disorders in patients with COVID-19 [15].

Stress-Induced Cardiomyopathy and COVID-19

Takotsubo syndrome (TTS) is a type of severe reversible cardiac disability. It is also known as stress-induced cardiomyopathy, broken heart syndrome or stunned myocardium [16, 17]. Leading symptom of TTS is pain localized in the chest with or without dyspnea [16] Characteristic feature of takotsubo syndrome is transient dysfunction of left ventricle (akinesia, dyskinesia or hypokinesia) and it is demonstrated as apical ballooned, midventricular, basal or focal abnormalities in contraction of myocardium. Usually the region of the wall motion abnormalities extends beyond the territory supplied by a single coronary artery [18].

Features that indicate Takotsubo syndrome are visible in electrocardiography. We can observe ST segment elevation/depression, T wave inversion or prolonged QTc [18]. Biochemical markers can be elevated. There is an increased level of troponin, creatine kinase, and brain natriuretic peptide [18]. Similar features can be present in the acute coronary artery, however, in TTS usually there are no presenting abnormalities within coronary arteries [18].

The pathogenesis of TTS is not well understood, there are many theories trying to explain the formation of this cardiomyopathy. Takotsubo syndrome may be caused by physical or emotional stress. There are speculation that increased the level of catecholamine (adrenaline, noradrenaline, and dopamine) might have an impact on the development of Takotsubo cardiomyopathy. High dose of epinephrine can cause switching Gs protein to Gi protein in B2-AR receptors. The result is a decreased level of cAMP inside the cell and it may lead to negative inotropic effect on contraction of myocardium [19]. Another theory is that superphysiological level of catecholamine might lead to increased expression of G protein coupled receptor kinase 2 (GRK2) and B-arrestin2. Those molecules cause desensitization of B1-AR and that can trigger decreased contraction of left ventricle. Both of those theories can explain the apical ballooned since there is a higher presentation of those receptors in the apical region. Also neurological disorders may cause this syndrome. For instance, transient ischemic attack/stroke, seizures or pheochromocytoma could be a trigger [18]. TTS without COVID-19 more often affects postmenopausal women. It might be due to the possible decreased estrogen level. Animal models show that estrogen can protect cardiomyocyte by a downregulation of adrenoreceptors, hypothalamo-sympathoadrenal axis, and a rise in the amount of atrial natriuretic peptide which decreases the load of ventricles.

Previous research showed that infection of SARS-CoV2 can contribute to injury of myocardium and may be associated with higher prevalence of TTS. Infection of SARS-CoV2 can be related with a higher plasma level of catecholamine. Excretion of those hormones is caused by infection and it is a prevention of decompensation. Moreover, patients with severe infection may get intravenous infusion of adrenaline or noradrenaline. Superphysiological level of catecholamine is one of the potential triggers of development of takotsubo syndrome. Catecholamine increases the myocardium's oxygen demand and induces contraction of a vessels [16]. During infection of SARS-CoV2 there is an increased secretion of IL-6, TNF-alfa, and other proinflammatory cytokines (cytokine storm) and it may be connected with higher level of catecholamine [16]. Another elevated biomarker in TTS is N-terminal pro-brain-type natriuretic peptide (NT-proBNP) which is secreted in a larger amount due to the increased ventricular wall stress. The TTS level of a NT-proBNP is correlated with the stage of disfunction of left ventricle [16]. Severe COVID-19 may activate hypothalamic-pituitary-adrenal axis which leads to increased level of ACTH and cortisol. Correlation between hypercortisolism and TTS is not well established. Cortisol may also increase secretion of catecholamine. TTS was noticed in a patient who presented higher level of cortisol [16]. Another theory why COVID-19 may be related with takotsubo syndrome is increased mental stress during quarantine or self-isolation. People who have quarantined have a greater risk of depression, stress, insomnia or anxiety [16].

In the study by Kamal Sharma et al. the correlation between COVID-19 and prevalence of TTS was assessed. TTS in COVID-19 equally concern males (45%) and females (55%) unlike TTS without COVID-19 (males—10.2%, females—89.8%). It may be due to the fact that males suffer more frequently from the infection of SARS-CoV2. There was a significant increase of morbidity in TTS during COVID-19 and these patients have longer hospitalization than in the pre-pandemic era (8 days vs. 4–5 days) [20].

A lot of patients with TTS apart from increase of proinflammatory cytokines had elevated C-reactive protein (CRP), and excessive number of D-dimer what suggested potential relation with decreased function of left ventricle level of D-dimer was also related with the severity of COVID-19 [20]. TTS patients with TTS and COVID-19 presented wall motion abnormalities of both ventricles, changes within ST segment and T wave. There were also present diffused PR intervals and prolonged QTc [20–22].

Sars-cov2 infection may be associated with an increased risk of thromboembolic complications. Study performed by Zhou et al. reported that treatment with heparin reduced 28-day mortality. Administration of anticoagulants should be consider in high-risk COVID-19 patients with TTS (older-aged group, reduced left ventricle effective fraction (LVEF)) [20].

In the study of Kamal Sharma et al. majority of TTS patients were discharged from hospital (74.1%) successfully, but part of them (10/23) developed one or more complication such as cardiogenic shock, atrial fibrillation, heart failure, supraventricular tachycardia, or biventricular heart failure [20]. Patients who developed cardiogenic shock had higher mortality rate 33.3% (2/6 mortality). Triggering factors

had an impact on course of TTS in COVID-19 patients. Patients with COVID-19 and TTS had a higher mortality rate (14.8%) than patients with COVID-19 with pre-existing disease of cardiovascular system without TTS (5.8%) [20].

All high-risk patients with COVID-19 should be diagnosed for TTS. Early detection of TTS may reduce mortality and complication of cardiovascular system. Adequate treatment should be considered with antiplatelet medication, statin, and beta-blockers if its required [20].

There are attempts to treat TTS with neurohormonal drugs. The treatment usually consists of beta-blockers or renin-angiotensin system inhibitors. But there is not any reliable evidence that using of beta-blockers would be effective in preventing the reoccurrence of TTS. Systemic reviews and research papers show that there is no correlation between recurrence of TTS and therapy with beta-blockers. Moreover 30% of 1750 patients in the International Takotsubo Registry study were treated with beta-blockers when they developed TTS. There are no evidence that beta-blockers decrease mortality within 1 year of using this drugs upon discharge after TTS admission. In retrospective analysis, which included 2672 patients, 423 of them where treated with beta-blockers within 2 days of diagnosis of TTS and there was no noticeable change in 30-day in hospital mortality [23].

Information about using renin-angiotensin system inhibitors are inconclusive. The International Takotsubo Registry study reported that there is a correlation between using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and improvement in survival at 1 year. Subsequent Mayo Clinic study of 265 patients with TTS reported that after receiving an angiotensin-converting enzyme inhibitor at discharge, there was no improvement in the 1-year survival [23]. Clinical benefits of using beta-blocker have not been demonstrated, but treatment with ACE-1 could have an impact on ventricular remodeling and improve survival in 1 year [24]. Case-control study of 6000 patients did not found any connection between using ACE-1 and COVID-19. Therefore current protocols recommended continuing treatment with ACE-1 in patients infected by COVID-19 if they did not have other contraindications [24].

Dilated Cardiomyopathy and COVID-19

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilation that is associated with systolic dysfunction. It is postulated that persistent immune activation upon viral infection increases the risk of developing dilated cardiomyopathy in COVID-19 patients [25]. Genetic inheritance arises in 30–48% of patients, and inflammatory disorders such as myocarditis or toxic effects from medications, alcohol, or illicit drugs also result in dilated cardiomyopathy. Viral infection is a known secondary cause of DCM [25].

There are several described case reports presenting de novo dilated cardiomyopathy in children with COVID 19 [26, 27] with significant reduction of ejection fractions and episodes decompensated heart failure.

In patients whose blood troponin levels are elevated after SARS-CoV-2 infection, long-term careful monitoring of cardiac function is necessary after recovery. Furthermore, studies should address whether conditions such as dilated cardiomyopathy would develop following COVID-19 even when patients are asymptomatic.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder and is characterized by cardiac hypertrophy, left ventricular outflow obstruction in the majority of cases, and diastolic dysfunction [28].

In the study of Arabadijan et al. the clinical course and outcomes of COVID-19 in patients with HCM were analyzed [28]. The hospital admission rate was high at 20%. The case fatality rate in this sample was similar to the general population. Both individuals who died had multiple co-morbid conditions associated with higher morbidity and mortality. Among hospitalized patients, the distribution of non-obstructive and obstructive HCM patients mirrors the distribution in unselected HCM cohorts [29]. There were no significant differences in demographics, HCM characteristics, or COVID-19 risk factors between the hospitalized and not hospitalized group. Prior reports have noted that there is ACE2 receptor upregulation in HCM tissue specimens [30].

Another study examined cardiac samples from individuals with dilated cardiomyopathy, hypertrophic cardiomyopathy, and healthy controls, which also supported upregulation of ACE2 in HCM tissue, but did not observe a difference in ACE2 expression between HCM patients taking ACE inhibitor medicines and those who did not [31]. However, the clinical impact of this upregulation in HCM is unclear. Data presented above suggest that HCM in itself does not carry a higher risk of COVID-19 disease severity and complications. Established risk factors for severe COVID-19, such as age and obesity may be more prominent in this patients population.

Restrictive Cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy in COVID-19

The number of data regarding restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are scarce. RCM is characterized by diastolic dysfunction of a non-dilated ventricle. Multiple types of restrictive cardiomyopathies exist and vary in their pathogenesis, clinical presentation, diagnostic evaluation, treatment, and prognosis. Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury [32].

In the study of Yildirim et al. the authors described a case of a 7-year-old female suffering from RCM infected with COVID-19 whose inotropic support and CPAP needed [32].

ARVC is characterized by progressive fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia and sudden death in young individuals and athletes. It primarily affects the right ventricle, and it may also involve the left ventricle [33]. The presentation of disease is highly variable. COVID-19 may trigger malignant ventricular arrhythmias and unmask a clinically silent cardiomyopathy. In the study of Mukhopadhyay et al. the authors showed a case of a 57-year-old man admitted to hospital with ventricular tachycardia (VT) [33]. Patient had a history of two VT episodes requiring direct current cardioversion in the last 3 h followed by another episode in the emergency department that was cardioverted. There was no past history of cardiac illness. Systemic inflammatory markers and cardiac troponin T were progressively increased over the next 4 weeks paralleled by an increase in ventricular premature contraction burden and thereafter started decreasing and returned to baseline by sixth week when the patient became COVID-19 negative by PCR. Subsequently, a single-chamber automated implantable cardioverter-defibrillator implantation was done following which there was a transient increase in these biomarkers that subsided spontaneously. The patient was asymptomatic during 6 weeks of follow-up. The case highlights a life-threatening presentation of COVID-19 and indicates a probable link between inflammation and arrhythmogenicity.

Cardiomyopathies and COVID-19 Vaccines

There were reported some cases of stress cardiomyopathy after COVID-19 vaccines. In the study of Ho et al. there were two cases of stress cardiomyopathy associated with the Pfizer-BioNTech vaccine [34, 35]. Both patients were managed medically. On balance, the benefit of COVID-19 vaccination even in young male populations exceeds the risk of cardiac adverse events.

Considering that the outcomes of myocarditis and pericarditis post-vaccination are good, vaccine uptake in this population should be encouraged in view of the current data. In contrast to the COVID-19 vaccine, adverse reactions to other vaccines are well-known but not as widely publicized. Taken together with the risk benefit ratio of COVID-19 vaccination being highly in favor of vaccination, vaccine hesitancy to the COVID-19 vaccine needs to be addressed actively to encourage higher uptake in the general population [36, 37].

Summary

The COVID-19 pandemic has caused a large number of deaths confirmed cases worldwide, posing a serious threat to public health. Cardiovascular disease is a common comorbidity in patients with COVID-19 and such patients are at higher risk of severe disease and mortality. Acute myocardial injury, defined as an elevation in cardiac troponins, is common in hospitalized patients with COVID-19. Myocardial injury during COVID-19 can be explained by three potential mechanisms: myocardial dysfunction from the direct viral effect on cardiomyocytes—ACE2 mediated direct damage; cardiac injury indirectly due to an excessive immune inflammatory response like cytokine storm; and hypoxia, oxidative stress due to acute respiratory damage resulting in myocardial necrosis from increased myocardial oxygen demand [38].

Cardiomyopathies are one of complications of COVID-19. The most common is TTS. It may be triggered by physical causes, such as increased level of catecholamine and cytokine storm, presented during a SARS-CoV2 infection or emotional triggers related with quarantine or self-isolation. Development of TTS during COVID-19 is also connected with higher mortality rate, especially when patients develop cardiogenic shock. All high-risk patients should be consider to be treated with anticoagulants [20]. Early detection of TTS may reduce mortality and complication of cardiovascular system.

It is important to stratify holistic risk in COVID -19 patients by taking all other comorbidities such as diabetes, neurological disorders, disabilities or pulmonary diseases into consideration. It is worth to analyze the electrocardiogram and measure the levels of biomarkers, such as NT-proBNP, troponins, myoglobin, D-dimers, C-reactive protein, interleukin-2, interleukin-6, and ferritin, to evaluate the high-risk patients presenting with acute COVID-19, and help in early detection of patients in need of hospitalization.

Different pharmacological and non-pharmacological treatments have been studied and applied for COVID-19. The most common non-pharmacological management were nasal oxygen and intubation. Corticosteroids, hydroxychloroquine, azithromycin, antiviral drugs, and β-Blockers were the most common pharmacological treatments. Due to the wide range of disease symptoms and complications, further studies related to each organ involvement are required to cure the disease better and prevent the complications [39].

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Chapter 11
Arrhythmias in COVID-19

Maria Mitkowska, Jakub Langa, and Przemysław Mitkowski

Arrhythmias are quite common in general population, even in subjects with structurally normal hearts. In these latter in general they are rather benign condition. Depending on severity of heart disorder the same arrhythmia could be either benign or potentially severe or even life-threatening condition. In the pathogenesis three factors play important factors: arrhythmia substrate, trigger, and modifiers. Any comorbidity both chronic and acute can influence arrhythmic substrate to make the arrhythmia more severe in terms of quality (i.e., from non-sustained to sustained, from asymptomatic to symptomatic) and quantity (i.e., higher heart rate, more frequent). Each acute condition, including inflammation, can precipitate new-onset arrhythmia or aggravate known arrhythmia. Moreover some drugs which are used to treat infection may modify substrate (i.e., QTc interval prolongation).

Furthermore in first few month of COVID-19 pandemic significant drop in cardiac implantable electronic device (CIED) implantation was seen. In Catalonia region average number of device implantation in 2017–2019 and January and February 2020 was 250 per month (195 pacemakers—PM, 55 cardioverter-defibrillator—ICD) and decline to 207 (161 PM 46 ICD) in March, and to 131 (108 PM, 23 ICD) in April, which could influence the rate of sudden cardiac death episodes [1]. Very similar data were reported from Italian centers where significant drop in number of CIED procedures was noticed during lockdown between March tenth and May fourth in 2020 in comparison to corresponding period in 2019. The authors find decrease in PM implantation by 30.2%, ICD by 48.3%, CRT 48.4%, and CRT replacement by 88.8%, whereas slight increase in PM replacement by 4.5% and ICD by 4.0% [2].

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Epidemiology

Comparison of reasons of acute admissions into cardiology departments, during pandemic and in corresponding 1-month period before, showed 32% reduction in number of cases [3]. It corresponded with reduced number of admissions because of acute coronary syndromes (32%), heart failure (35%), arrhythmia (34%) and with 50% increase due to pulmonary embolism. There were no differences in arrhythmia rates, as a percentage of all cardiac admissions, between 2020 and 2019. In details, the number of patients admitted acutely to cardiac departments because of atrial or ventricular arrhythmia, bradycardia, and atrioventricular block dropped by 31%, 30%, and 50%, respectively.

During pandemic burden of ventricular arrhythmia which needed therapy with implantable cardioverter-defibrillator was lower when compared to pre-pandemic period (IRR 0.68, CI 0.58–0.79, $p < 0.001$) and lower in high incidence of COVID-19 cases in the US states when compared to low incidence, which was parallel to social isolation [4].

Various ECG changes are quite common among patients hospitalized because of SARS-CoV-2 infection (Table 11.1) [5]. None ECG changes were observed in 38.6% of patients, one abnormality was present in 29.7% individuals, two in 19.3%, three in 7.8%, four in 2.9%, five in 1.3% and 6 in 0.3% patients. There were no patients with 7 or 8 lesions.

The rate of various cardiac arrhythmias are summarized in Table 11.2 [6].

The incidence of arrhythmia in patients with COVID-19 pneumonia who were hospitalized, was 16.7%, and was more frequent in those who were transferred to intensive care unit in comparison to those who were not (44.4 vs 6.9%, $p < 0.001$) [7]. Arrhythmia was the reason for referral to cardiological consultation in 43 of 180 patients (23.9%), who required evaluation because of cardio-vascular conditions with the high rate atrial fibrillation as the most frequent (17.7%) [8]. Among 138 patients hospitalized in Wuhan in early pandemic, arrhythmia was present in 16.7% of patients. Arrhythmia was second underlaying reason of moving patients to intensive care unit (44.4%) [9].

Life-threatening ventricular arrhythmias are known complications of viral myocarditis. In COVID-19 patients they may be precipitated by a combination of

Table 11.1 ECG changes in patient hospitalized due to SARS-CoV-2 infection [5]

ECG changes	Incidence (%)
T-wave abnormalities	31.7
QTc interval prolongation	30.1
Arrhythmias	16.3
Axis deviation	11.1
Bundle branch block, fascicular block	9.2
ST-segment changes	7.8
Atrioventricular block	3.9
Pathological Q-wave	2.0

Table 11.2 Incidence of arrhythmia in COVID-19 patients [6]

Type of arrhythmia	Incidence (%)
Sinus tachycardia	40–55
Sinus bradycardia	5–25
Atrial fibrillation/atrial flutter	2–12
Supraventricular tachycardia	0,6–6
Premature ventricular complexes	0–28
Non-sustained ventricular tachycardia	0–15
Sustained VT/VF/TdP	0–1.4
Atrioventricular blocks	0–1.4
Postural orthostatic tachycardia syndrome	4–22
Inappropriate sinus tachycardia	3–4

treatment of QT interval prolonging drugs, metabolic abnormalities and myocarditis [10]. Ventricular tachycardia or fibrillation is reported in 4.8% of SARS-CoV-2 patients [11]. In other study ventricular arrhythmia was present in 3.5% of patients [12].

In general, Australian COVID-19 hospitalized population, a new-onset atrial fibrillation was confirmed in 3.6% of patients and was significantly lower in comparison to Italian and American data (12.1 and 9.6%, respectively) [13–15]. In Turkish population hospitalized with SARS-CoV-2 incidence of AF was 11.4%. This arrhythmia was more likely diagnosed in elderly population with numerous comorbidities, abnormal chest X-rays, increased plasma levels of D-dimer, troponin, urea, and decreased albumins [16]. Comparison of CIED detection of atrial fibrillation within 100 days during COVID-19 pandemic with the same duration period before pandemic showed overall increase of AF episodes incidence rate ratio by 33%, episodes over 1 h by 65% and over 6 h by 54% [17]. Among older population (≥60 years) hospitalized due to COVID-19 infection the prevalence of atrial fibrillation was 21.8% [18]. In patients admitted to intensive care unit (ICU) arrhythmia was present in 37% and in vast majority of cases it was atrial fibrillation or flutter (91%) [12]. New-onset arrhythmia was diagnosed in 68% of cases.

Liberal treatment with hydroxychloroquine has raised concerns about QTc interval prolongation. In the study of *Fteiha* et al. QTc prolongation (60 ms in comparison to value before treatment and/or QTc over 500 ms) was observed in 16% out of 90 patients enrolled. In univariate analysis factors such as age over 65 years, presence of severe or critical illness, congestive heart failure, hypokalemia, CRP elevation, and furosemide intake were associated with QTc prolongation, whereas adjusted analysis showed that only hypokalemia (OR 5.0, CI 1.3–20.0) and furosemide intake (OR 3.7, CI 1.01–13.7) were independent factors increasing likelihood of QTc prolongation [19]. In the other study among 279 COVID-19 patients, QTc prolongation was observed in 69 (24.7%) [20]. End-stage renal disease on hemodialysis (OR 7.7), new-onset bundle branch block (OR 5.2), and treatment with QTc interval prolonging drugs (hydroxychloroquine—OR 2.49, azithromycin—2.87 or both—OR 4.14) were conditions directly associated with QTc prolongation whereas

ACEi (OR 0.24) therapy was inversely related. Fortunately QTc prolongation did not influenced neither increased mortality (21% vs. 13%), nor likelihood of ventricular arrhythmia although any arrhythmia was more frequently observed in subjects with prolong QTc interval (26% vs. 11%, $p < 0.001$). Also in the study done in the Netherlands QTc prolongation over 500 ms or difference of 60 ms were found in 27% of patients treated with chloroquine with average increase of this interval by 32.6 ms [21]. A heart rate over 90 bpm, kidney disfunction, QTc interval below 450 ms were the risk factors for QTc interval prolongation. Different findings were published by Sogut et al. who did not find any patient treated with hydroxychloroquine who presented with QTc prolongation over 60 ms or QTc duration over 500 ms [22]. Even hydroxychloroquine with antiviral treatment regimen (lopinavir/ritonavir or darunavir/ritonavir), although caused ECG changes - mainly repolarization disorders (13.0%)–they did not influence outcome [23]. Likelihood of ECG abnormalities was higher in patients with age over 70 years, with chronic cardiovascular disease, arterial hypertension, chronic kidney disease, initial potential drug interactions, and higher residual (day 3) darunavir concentration. Although combination treatment with hydroxychloroquine and azithromycin was associated with more pronounced prolongation of QTc interval than hydroxychloroquine alone or baseline it allowed to complete 5-days treatment and did not cause malignant ventricular arrhythmia nor cause death secondary to it [24].

The bradycardia incidence could be even 6.9 times more frequently observed in remdesivir recipients in comparison to control (21% vs. 3%, $p = 0.001$), especially in those with body temperature <37.2 C at admission [25, 26].

Moreover in post-acute phase of COVID-19 at sixth month 9% of patients reported palpitations [27].

Influence on Prognosis

The number of ECG lesions listed above (Table 11.1) correlated with in-hospital mortality (Table 11.3) [5]. Abnormal ECG was associated with 1.478 times increase of in-hospital mortality.

Among 1401 patients admitted to the hospital in Italian centers with confirmed diagnosis of COVID-19 in-hospital death was noticed in 30.1% cases. History of ventricular tachycardia, atrial fibrillation, and supraventricular tachycardia did not influence fatal outcome, although atrial fibrillation on admission worsen prognosis [8, 28].

Table 11.3 Mortality rates according to number of ECG changes [5]

No. of ECG lesions	0	1	2	3	4	5	6
Mortality [%]	2.5	5.5	13.6	25.0	44.4	75.0	100.0

COVID-19 new-onset atrial fibrillation is related to 14.26 times higher incidence of thromboembolic event but not death [29]. In the other study AF incidence during COVID-19 hospitalization was related to 2.426 increase of in-hospital mortality. These patients needed much more treatment in intensive care unit (55% vs. 31%) and invasive mechanical ventilation (35% vs. 15%) [16]. In the other study the arrhythmia also increased risk of death rate (37% vs. 28%, $p = 0.015$). Persistence of oral anticoagulation during hospitalization reduced in-hospital death (OR = 0.05, CI 0.01–0.24) [18]. Among patients admitted to ICU, the diagnosis of arrhythmia (mainly AF/AFl) increased 60-days mortality (63% vs. 39%) and was related to 2.01 fold increase in 90-days mortality [11, 30]. Both ventricular tachycardia/fibrillation and atrial fibrillation worsened prognosis in COVID-19 patients [31].

Symptomatic bradycardia in course of COVID-19 infection which required pacing support, had poor outcome with in-hospital and 3-month death rate 57% and 71%, respectively [32].

Even triple antimicrobial therapy with hydroxychloroquine, oseltamivir, and azithromycin or levofloxacin although caused prolongation of QTc interval and QT dispersion it was not related to occurrence of severe arrhythmia [33]. As mentioned above drugs which prolong QTc interval did not influenced prognosis, however, QTc prolongation (≥470 ms) itself increased risk of death (33.3% vs. 8.7%) and severe course (47.1% vs. 20.6%) of infection [34].

Pathogenesis

The pathogenesis of cardiac injury, which may facilitate arrhythmia onset, includes direct heart muscle cell damage and indirect damage caused by cytokine storm [35]. In the pathogenesis of arrhythmia and heart failure during COVID-19 direct involvement of heart or other organs by infection, secondary infection, thrombosis, and abnormal immune response are considered to cause various hemodynamic and homeostatic impairment are considered (Fig. 11.1) [31, 36, 37]. Besides direct viral involvement majority of cardiac complications are seen within inflammatory phase of the disease, when increased plasma levels of IL-6, C-reactive protein, lactic dehydrogenase, d-dimer, ferritin troponins, natriuretic peptides, and transaminase are observed [38].

Several factors facilitate onset of atrial fibrillation in acute COVID-19 disease: fever, hypoxia, and adrenergic drive.

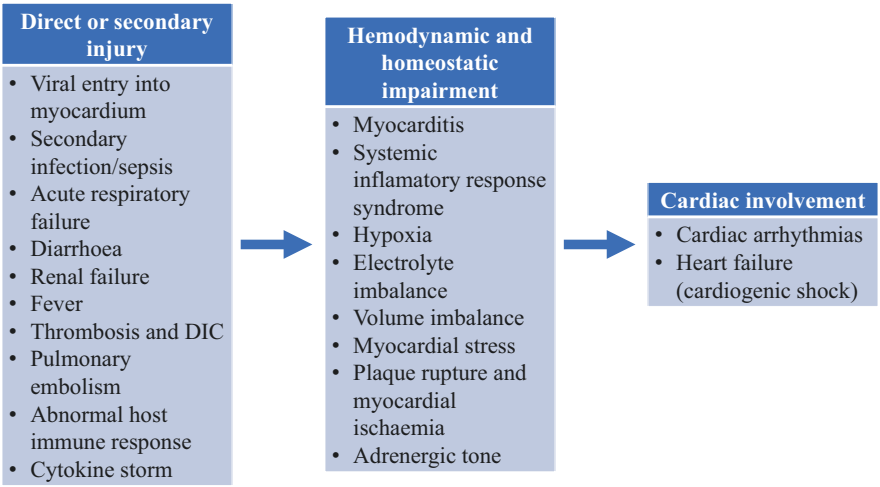

Fig. 11.1 Pathomechanism of arrhythmia and heart failure development in COVID-19 patients [36, 37]

Treatment

In general arrhythmia treatment does not differ between COVID-19 positive patients and general population taking into consideration severity of comorbidities and underlaying cardiac disorders. Landiolol seemed to be effective in rate control in patients with atrial fibrillation, heart rate over 120 bpm and SARS-CoV-2 infection admitted to intensive care unit. Landiolol infusion was started at 0.2 μg/kg/min and progressively increased to achieved 20% reduction in heart rate (HR) [39]. Overall HR reduction was 23% (150 vs. 115 bpm, $p < 0.001$) without significant differences in systolic and diastolic blood pressure.

Protease inhibitor (i.e., lopinavir/ritonavir) treatment may augment the effect of amiodarone, lidocaine, and quinidine so these antiarrhythmic drug should be used with caution. Co-administration of protease inhibitors and flecainide or propafenone (class IC drugs) is not recommended [37].

Acute treatment of *torsade-des-pointes* should include electrolyte correction, overdrive pacing, and isoprenaline infusion [40].

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Chapter 12
Thromboembolic Events in COVID-19

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Abbreviations

ASA	Acetylsalicylic acid
ATE	Arterial thromboembolism
COVID-19	Coronavirus disease 2019
CTPA	CT pulmonary angiography
DVT	Deep venous thrombosis
HFU	Unfractionated heparin
ICU	Intensive care unit
LMWH	Low-molecular-weight heparin
PE	Pulmonary embolism
VTE	Venous thromboembolism
VUS	Venous ultrasound

Patients with coronavirus disease 2019 (COVID-19) are exposed to an increased risk for thromboembolic complications. Thromboembolic events that frequently occur in COVID-19 are most often located in the lungs and are more common in severe COVID-19; thromboembolic events are also associated with significantly higher mortality rates in patients with severe COVID-19 [1–3]. Macroscopic thrombus formation or in situ thrombosis in the branches of pulmonary arteries are found in 60% of deceased COVID-19 patients [4]. Apart from significant generalized pulmonary tissue oedema, autopsy examinations reveal massive inflammatory

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infiltration of leukocytes within endothelial cells (mainly neutrophils) and microthrombosis in pulmonary capillaries, including alveolar septal capillaries [5]. Thrombotic events can also affect medium-sized vessels, leading to pulmonary infarction [5]. The pathogenesis of thromboembolism in COVID-19 is not fully understood, but it is known to involve hypoxemia, excessive inflammatory response, endothelial cell damage, impaired blood flow, and platelet activation. Thromboembolism is common in hospitalized patients, especially in critically ill patients. The prevention and optimal treatment of thromboembolic episodes is still a matter of debate and research. This chapter discusses the main aspects of epidemiology and risk factors, pathophysiological mechanisms, diagnosis, and management of thromboembolic events in COVID-19 patients.

Epidemiology

Thromboembolism in patients with COVID-19 most often manifests as venous thromboembolism (VTE), such as pulmonary embolism (PE) and/or deep vein thrombosis (DVT), and less often by arterial thromboembolism (ATE). An increased risk of blood clots in COVID-19 patients is well documented. An increased incidence of thromboembolic events in COVID-19 patients was first reported as early as at the beginning of the COVID-19 outbreak.

Klok et al. reported that 31% of 184 patients in intensive care unit (ICU) with proven pneumonia secondary to COVID-19 who received usual-care thromboprophylaxis experienced thromboembolic events, including VTE confirmed by computed tomography pulmonary angiography (CTPA) and/or ultrasonography of the lower extremity veins (VUS) (27% of patients), and arterial thromboembolism (3.7% of patients) [2]. In another single center observational study by Lodigiani et al. on a group of 388 patients with COVID-19 infection, including 17% of ICU patients, as many as 21% of ICU patients had VTE despite thromboprophylaxis, and half of the VTE cases were diagnosed within the first 24 h of hospitalization. Overall, VTE occurred in 4.4%, ischemic stroke in 2.2%, myocardial infarction in 1.1% of these patients [6]. In an observational study by Middeldorp et al. of 199 COVID-19 patients, including 38% of ICU patients, 47% of ICU patients developed VTE despite standard thromboprophylaxis, of which 16% within the first 7 days of admission [3].

The frequency of VTE in patients with COVID-19 varies considerably. In 15 observational studies carried out worldwide, the frequency of VTE was 0.9–69% (6.7–69% in ICU patients and 0.9–6.5% in non-ICU patients) [7]. The incidence of VTE was significantly higher than that of ATE (2.7–3.8%) [7]. PE in ICU patients occurred in 16.7% to 35% of critically ill COVID-19 patients, DVT—in 0.5% to 69% of ICU patients, and in 0% to 46.1% of non-ICU patients [7]. The difference in the incidence rates of VTE, PE, and DVT can be attributed to the various diagnostic strategies and algorithms used across hospital departments. In another meta-analysis by Porfidia et al. based on observational studies of 3487 patients hospitalized for

COVID-19 in 30 sites, the risk of VTE was estimated at 26%. PE with or without DVT was diagnosed in 12% of patients, and DVT alone in 14% of patients. In sites that used a standard diagnostic algorithm to confirm VTE, PE was diagnosed in 13% of patients and DVT in 6% of patients. As for sites that used a diagnostic algorithm other than the standard one, PE was diagnosed in 11%, and DVT in 24% of patients [8]. There was also a large difference in the incidence of VTE between hospitalized ICU and non-ICU patients. VTE was diagnosed in 24%, PE in 19%, and DVT alone in 7% of patients receiving ICU care. The incidence of PE was much lower among hospitalized non-ICU patients—9% for VTE in total, 4% for PE, and 7% for DVT [8]. In another meta-analysis of 48 studies by Jimenez et al., the total incidence of VTE was estimated at 17.3% of hospitalized COVID-19 patients, of which two-thirds had DVT and one-third had PE [9]. Distal DVT, catheter-related thrombosis associated with the use of a central venous catheter, or subsegmental PE were diagnosed in a significant proportion of these patients, which may be associated with a local inflammatory response to COVID-19 [9].

These observations are consistent with the data collected in a multicenter observational study by Japanese investigators on a group of 1236 COVID-19 patients—VTE was diagnosed in 22.2% of these patients. The overall incidence rates of VTE varied depending on the severity of COVID-19: 40% with severe COVID-19 (patients who required mechanical ventilation), 11.8% with moderate COVID-19 (patients who required oxygen therapy), and 0% with mild COVID-19 (patients who did not require oxygen therapy) [10].

Pathogenesis

The pathogenesis of thromboembolic complications in patients with COVID-19 is complex and multifactorial [11]. The frequency of VTE in COVID-19 is higher than in other viral diseases, such as infections with H1N1 influenza or SARS-CoV-1, which suggests the involvement of other pathogenetic mechanisms of VTE, although the different research methods used can make such comparison difficult [11–13].. VTE is also much more prevalent in COVID-19 than in acute respiratory distress syndrome (ARDS), which indicates that other additional mechanisms can contribute to the increased risk of VTE, in addition to severe and acute respiratory insufficiency and immobilization [14]. In post-mortem studies of patients who died of acute respiratory failure in the course of COVID-19 infection, diffuse alveolar damage with hyaline membrane formation and atypical type II pneumocyte hyperplasia were predominant in histopathological examinations. Most lung autopsies (33/38) reported platelet–fibrin thrombi in the small pulmonary vasculature [15].

Blood clots in small pulmonary vessels may result from in situ immune-mediated thrombosis and/or classic VTE, or both [11]. Coagulopathy typical of COVID-19 includes mild thrombocytopenia, slightly prolonged prothrombin time, and elevation of fibrinogen and D-dimer [11, 16]. These abnormalities are not specific for COVID-19 as they also occur in sepsis-induced coagulopathy (SIC) and in

disseminated intravascular coagulation (DIC) [17]. The activity of von Willebrand factor (vWf) is typically increased. There is also an increase in inflammatory markers: ferritin, C-reactive protein, procalcitonin, and leukocytosis. Lymphopenia and neutrophilia have been reported [11]. Typically, the levels of antithrombin, protein C/S, and alpha-antiplasmin-endogenous anticoagulants in COVID-19 infection are normal, which distinguishes COVID-19-associated coagulopathy from DIC [18]. Damage to the vascular endothelium induced by the virus and the resulting endothelial dysfunction is an important feature in the pathogenesis of COVID-19-associated thromboembolism. A healthy endothelium provides immune and barrier functions and is also responsible for regulating vascular tone. Activation of endothelial cells and reduction of endothelium-dependent vasodilation promote the development of inflammation and thrombosis [11]. Also, the synthesis of nitric oxide and prostacyclin was found to be impaired in patients with COVID-19 [19]. The vascular tone is also mediated by the local renin angiotensin aldosterone system (RAAS). ACE2 enzyme produces Ang-(1–7) from angiotensin II (AngII), which prevents the accumulation of Angiotensin II to protect the body against excessive vasoconstriction. The SARS-CoV-2 virus suppresses the ACE2 receptor by internalization and inhibits its activity, which causes secondary accumulation of AngII and excessive vasoconstriction mediated by AngII, and the activation of TF and PAI-1 expression on platelets, which promotes intravascular coagulation and pulmonary tissue damage, and can contribute to thromboembolic events [11, 20]. The ACE2/AngII imbalance may be associated with an increased risk of severe COVID-19 and thromboembolic events among patients with diabetes, heart failure, and arterial hypertension [11]. It is not entirely clear whether ACE2 is present in endothelial cells, however, it was confirmed to be present in pericytes (undifferentiated mesenchymal stem cells that encompass blood vessels and surround endothelial cells) [21]..

COVID-19 infection can be accompanied by increased coagulation and fibrinolysis impairment. As a result of endothelial cell damage and dysfunction, collagen and the tissue factor present in the subendothelial layer become exposed, an exogenous coagulation process is activated, fibrinogen is converted to fibrin, and a platelet plug is formed. The tissue factor expression is also mediated by pro-inflammatory cytokines on macrophages and platelets [11]. The endogenous system is activated on contact between coagulation factor XII (Hageman's contact factor) and kallikreins, collagen, and kininogens (plasma proteins). This results in the formation of active factor XII and a cascade reaction that leads to the development of clinically important clots. Endothelial cell activation markers such as von Willebrand factor, factor VIII, and P-selectin are elevated in COVID-19 infection. Their presence in patients with COVID-19 is associated with a worse prognosis [18]. Fibrinolysis is impaired in COVID-19 patients. The levels of plasminogen activator inhibitor PAI-1 increase, ultimately leading to impaired fibrin degradation [18].

Blood platelets clearly play an important role in blood clot formation in COVID-19 infection. Unlike DIC, platelet levels are normal or only slightly decreased. However, platelets can be hyper-activated [22]. Elevated levels and activity of the von Willebrand factor were observed in patients with COVID-19, which

promotes the formation of primary platelet plug and stimulates the activation and aggregation of blood platelets [18]. Hypoxia has been reported in moderate to severe COVID-19 infections [11]. Endothelial cell become dysfunctional in response to hypoxia, and hypoxia-induced transcription factors (HIF) are expressed in endothelial cells and immune cells. HIFs promote thrombosis by stimulating the release of PAI-1, pro-inflammatory cytokines TNFα, IL-2, and by reducing thrombomodulin expression [23]. The activation of HIFs can trigger an excessive immune response [11].

COVID-19 infection is associated with impaired regulation of the immune system, which promotes blood clots. Uncontrolled excessive release of pro-inflammatory cytokines has been reported in severe COVID-19. This process, referred to as a "cytokine storm," is believed to be one of the key mechanisms leading to the critical deterioration in COVID-19 and an increased risk of thromboembolic events [24–26]. During COVID-19 infection, the concentration of cytokines and chemokines such as IL-2, IL-6, TNFα, INFν increases, which exacerbates inflammatory and pro-thrombotic reactions [11, 26]. Patients with COVID-19 experience excessive complement activation, mainly associated with the deposition of C5b-9 complex in the lung tissue, which promotes microthrombosis [27].

Higher levels of WBC count are observed in COVID-19 infection. Pulmonary post-mortem findings revealed massive leukocyte infiltration patterns in the lung tissue [5]. Leukocytes promote the growth of thromboembolic lesions. Neutrophils are hyperactivated in patients with COVID-19, which leads to excessive expulsion of neutrophil extracellular traps (NETs). These are not effectively eliminated from the body. The role of NETs is to catch pathogens such as viruses and bacteria, but they can damage the body's own tissues when in excess. This is because proteases in NETs, including neutrophilic elastase, can facilitate viral entry into cells by modifying surface proteins in the viral envelope. In addition, they promote the formation of blood clots and the activation of the complement system [11, 28].

Genetic risk factors can also predispose to VTE. In addition to the known classic types of thrombophilia, such as protein C or S deficiency, antithrombin deficiency, mutation of the prothrombin gene or factor V Leiden, blood groups ABO may also be predisposed to severe COVID-19 and thromboembolic complications [11]. Patients with blood group A were shown to have a higher risk of severe COVID-19, and the blood group O may have a lower risk of severe COVID-19 illness. This is believed to be associated with the fact that individuals with blood group O have significantly lower expression (c. 25%) of vWF, which is necessary platelet activation [29]. In addition, anti-A antibodies can inhibit the interaction of SARS-Cov-2 with the ACE2 receptor [30]. There are also other known risk factors for VTE in COVID-19 patients, such as older age, immobilization, comorbid cancer, heart failure, chronic respiratory failure, obesity, hormone therapy, etc., which increase the risk of VTE [31]. A meta-analysis by Cui et al. identified male gender, obesity, mechanical ventilation, significant lung parenchymal injury, admission to ICU, and elevated D-dimers and white blood cells at two time points, on admission and before CTPA, as the risk factors for PE in patients with COVID-19 [32].

The Diagnosis of VTE in COVID-19

Diagnostic testing for VTE in patients with COVID-19 may be difficult, but is recommended in international guidelines; the diagnostic approach is similar in patients with COVID-19 and in non-COVID-19 individuals. VTE in COVID-19 patients should be suspected in the case of: a rapid increase in hypoxemia, increasing oxygen requirements disproportionate to changes in lung parenchyma, sudden drops in blood pressure unexplained by other reasons, or the worsening of tachycardia.

CTPA remains the key diagnostic examination for VTE in COVID-19 patients (Fig. 12.1). Venous compression test of the lower extremities should be performed when symptoms of deep vein thrombosis in the legs are present. VUS can be a valuable diagnostic examination especially where VTE is suspected and imaging tests may be difficult, in unstable patients, in patients requiring high-flow nasal cannula oxygenation, CPAP or intubation. In this case, the diagnosis of venous thrombosis validates the presence of VTE and drives the initiation of anticoagulant treatment, but a negative result does not exclude VTE [33]. Right ventricle dysfunction and signs of right ventricle pressure overload are common in patients with moderate to severe COVID-19-related ARDS. A transthoracic echocardiogram (TTE) is not a routine diagnostic test for VTE, but is used for risk stratification in pulmonary

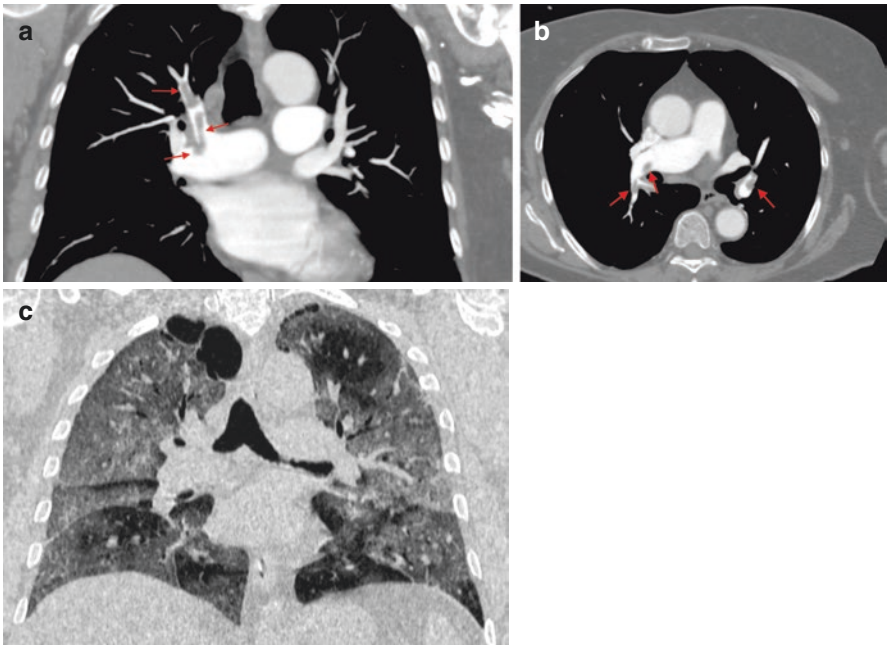

Fig. 12.1 Acute pulmonary embolism in patients with COVID-19 pneumonia. Emboli present in right upper lobe artery (**a**) and intermediate and left lower lobe artery (**b**) at CT pulmonary angiography. Bilateral lung involvement and ground-glass opacities at high-resolution CT lung scan (**c**)

embolism. In some clinical situations, the signs of severe right ventricular dysfunction in an unstable patient or the presence of thrombi in the right heart cavities may warrant anticoagulation or even thrombolytic therapy [34].

D-dimer serves as a valuable marker of activation of the coagulation and fibrinolysis systems [35]. D-dimer is a two-peptide fragment formed from the enzymatic breakdown of cross-linked fibrin. D-dimer is a highly sensitive, yet not very specific marker in the diagnosis of VTE. D-dimer levels are elevated in most patients with SARS-CoV-2 infection [36]. Already in the early stages of the COVID-19 outbreak in Wuhan, almost half of the patients hospitalized for COVID-19 were reported to have elevated levels of D-dimers >500ug/l. Elevations in D-dimers were found in 43% of patients with milder COVID-19 and in 60% of those with severe COVID-19 disease [37]. D-dimer increases in the first day after the infection, and the D-dimer value has been reported to be a valuable predictive and prognostic marker as far as the risk of severe COVID-19 is concerned [38–40]. D-dimer value can be used as a screening test for VTE [41]. COVID-19 patients with VTE events exhibit higher D-dimer levels than COVID-19 patients without VTE [41]. No optimal cut-off point for D-dimer has been established for diagnosing VTE. Mouhat et al. concludes that D-dimer of 2590 μg/L is predictive of pulmonary embolism in patients with COVID-19 with 83% sensitivity and 84% specificity [42]. Three cut-off points for D-dimer and associated risk of VTE were identified in a study of 1739 patients hospitalized for COVID-19. D-dimer <1000 μg/L was associated with a low risk of VTE, D-dimer of 1000–7500 μg/L with an intermediate risk of VTE, and D-dimer >7500 μg/L with a high risk of VTE in patients with COVID-19 [43]. Kwee et al. analyzed 71 studies of patients with COVID-19 with known D-dimer values who also underwent CTPA and proposed a D-dimer value of at least 1000 μg/L as the cut-off point above which CTPA should be carried out to confirm or rule out VTE [44].

Treatment

The management of confirmed new cases of VTE in patients with COVID-19 does not differ from the generally accepted standards of care in VTE [33, 45]. Hospitalized COVID-19 patients with coexisting VTE may benefit more from low-molecular-weight heparin (LMWH) or unfractionated heparin (HFU) than from other anticoagulants due to the lower risk of interactions with antiviral drugs and easier options to reverse the anticoagulant effect in the event of an overdose. Moreover, patients on LMWH do not require additional coagulation monitoring, which means healthcare professionals caring for infected patients are exposed to a lower risk of contracting COVID-19 [33]. Apart from individual case studies, there are no comprehensive studies that examine the thrombolytic therapy for VTE in patients infected with COVID-19, but it should be assumed that the patient management is essentially consistent with the generally accepted standards of care in VTE [33, 45]. Single cases of successful interventional treatment or cardiac surgery in patients with coexisting PE and COVID-19 have also been reported [46, 47].

The duration of anticoagulation treatment following an episode of VTE associated with COVID-19 infection remains controversial. Anticoagulation should last 3 months in moderate to severe COVID-19 infection as a strong reversible risk factor for thromboembolic complications. In VTE associated with mild COVID-19, this risk factor is rather weak and chronic anticoagulation should be continued for a longer period, with regular assessment of the benefit-risk ratio. Long duration of the symptoms of exercise dyspnea, weakness, and fatigue are arguments in favor of extended anticoagulation therapy in COVID-19-associated VTE as these symptoms may indicate persisting lesions in the lung parenchyma or vessels and an increased risk of developing chronic thromboembolic pulmonary disease.

Patients receiving anticoagulants at diagnosis of COVID-19 should continue their treatment and the form of treatment should not be modified, to the extent possible. Except for critically ill patients or patients with artificial heart valves, DOACs are the optimal form of chronic anticoagulation because of the predictable intensity of blood thinning and less frequent treatment monitoring.

Thromboprophylaxis in Patients with COVID-19

Thromboprophylaxis reduces the risk of VTE in hospitalized patients with pneumonia, heart failure, cancer, and in immobilized patients [40]. Antithrombotic prophylaxis should be initiated on admission in all COVID-19 patients, unless it is contraindicated. The doses of antithrombotic prophylaxis have not been yet agreed. In observational studies of patients with COVID-19, a standard dose of low-molecular-weight heparin prophylaxis in all COVID-19 patients was associated with a 21–31% risk of symptomatic VTE [2, 48]. Novel oral anticoagulants or the additional use of acetylsalicylic acid in the context of the pathogenesis of VTE in COVID-19 have also caught the attention of researchers. The differences in international guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 reflect these uncertainties. However, all guidelines highlight the importance of individual decision making according to the assessment of VTE risk factors profile and bleeding risk [33, 49–51] The guidelines of the American Society of Hematology recommend primary antithrombotic prevention at a standard low dose, while the International Society of Thrombosis and Hemostasis recommends higher (intermediate) prophylactic doses for patients at the highest risk (critically ill ICU patients) [51].. Based on recent studies, it has been suggested that therapeutic doses should be considered in hospitalized patients with significantly elevated D-dimers [52, 53]. When the contraindications to pharmacologic thromboprophylaxis exist, mechanical methods should be considered, most preferably graduated compression stockings or intermittent pneumatic pressure.

In a meta-analysis by Jimenez et al. covering 48 studies describing the epidemiology of VTE in hospitalized COVID-19 patients, no significant differences were found in the incidence of VTE depending on the dose of low-molecular-weight heparin used in hospitalized COVID-19 patients [9]. The combined total bleeding

rate was 7.3% [9]. It was the highest in patients on intermediate or high dose LMWH (21.4%), and was significantly higher than in patients receiving standard primary thromboprophylaxis (5%), or in patients who did not receive any prophylaxis (4%) [9]. Major bleeding events occurred in 3.9% of patients [9].

In a multicenter prospective study (The HEP-COVID Randomized Clinical Trial), 557 critically ill patients with severe COVID-19 were randomized. Indications for treatment with therapeutic doses of LMWH were defined as D-dimer levels at least four times the upper limit of normal and a sepsis-induced coagulopathy score (SIC) of 4 or higher. The patients were randomized into two groups—standard thromboprophylaxis or extended LMWH or HFU thromboprophylaxis. The second group received therapeutic-dose LMWH. The therapeutic-dose LMWH was found to reduce the risk of the composite outcome of VTE, ATE, and all-cause mortality in patients hospitalized for COVID-19, but no benefit accrued to patients receiving ICU care [52].

The RAPID study assessed the effectiveness of therapeutic heparin (LMWH or UFH) compared with prophylactic heparin among moderately ill hospitalized patients with COVID-19. The study enrolled 465 hospitalized COVID-19 patients with increased D-dimer levels within 5 days of hospital admission and oxygen saturation ≤93% on room air or D-dimer ≥2 times ULN with normal saturation. Moderately ill patients were defined as patients hospitalized but not requiring mechanical ventilation on admission (non-ICU on admission) [54]. The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or admission to an intensive care unit, assessed up to 28 days of observation. The primary outcome was not achieved in patients assigned to therapeutic heparin, but a reduced mortality rate and low risk of bleeding were observed [54]. Major bleeding occurred in 0.9% of patients assigned to therapeutic heparin and in 1.9% of patients assigned to prophylactic heparin [54].

In a joint open-label randomized trial, REMAP-CAP, ACTIV-4a, and ATTACC investigators assessed whether moderately ill patients hospitalized for COVID-19, i.e., those requiring non-ICU hospitalization, could benefit from additional therapeutic-dose anticoagulation [53]. The study enrolled 2219 patients hospitalized for COVID-19 who were noncritically ill and did not require organ support in an intensive care unit on admission [53]. The patients were randomized to receive either therapeutic-dose anticoagulation or usual-care pharmacologic thromboprophylaxis. The primary outcome was combined in-hospital death and the number of days free of cardiovascular and/or respiratory organ support up to day 21 observation. Of the 1093 patients in the therapeutic-dose anticoagulation group, 94.7% received a LMWH, most commonly enoxaparin. Among the 855 patients in the thromboprophylaxis group, 71.7% received a low dose of a thromboprophylactic drug and 26.5% received an intermediate dose. In the therapeutic-dose anticoagulation group, 82.2% of patients survived until hospital discharge without receipt of organ support during the first 21 days of observation, as compared with 76.4% of patients in the usual-care thromboprophylaxis group. Therapeutic-dose anticoagulation with heparin decreased ICU care and organ support (oxygen delivered by high-flow nasal cannula, NIV/CPAP, mechanical ventilation, or the use of

vasopressors or inotropes) in patients stable at enrollment and these benefits were most pronounced in patients with high levels of D-dimer (≥2 times the upper limit of the normal range [ULN]) [53].

REMAP-CAP, ACTIV-4, and ATTACC investigators also assessed whether the use of therapeutic-dose LMWH in patients requiring ICU could bring additional benefits. A total of 1098 patients were enrolled, 534 assigned to therapeutic-dose anticoagulation and 564 assigned to usual-care thromboprophylaxis. The primary outcome—a composite of organ support-free days and in-hospital death rates evaluated on an appropriate scale, and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge—was not obtained in the therapeutic-dose anticoagulation group [55]. ICU patients did not benefit from more intensive therapeutic-dose anticoagulation, which involves a higher risk of major bleeding. Major bleeding occurred in 3.8% of the patients assigned to therapeutic-dose anticoagulation and in 2.3% of those assigned to usual-care pharmacologic thromboprophylaxis [55].

Another prospective multicenter study with the acronym ACTION assessed the benefits of therapeutic-dose anticoagulation with the use of novel oral anticoagulants compared with prophylactic-dose anticoagulation [45]. Patients receiving therapeutic-dose anticoagulants received rivaroxaban 20 mg or 15 mg 1× daily if diagnosed with renal failure of GFR 30–40 ml/kg/min or concomitantly using azithromycin. If the patient was unstable at baseline, LMWH 1 mg/kg 2× daily or therapeutic dose of HFU was administered. Patients assigned to anticoagulants at prophylactic dose received LMWH or HFU. Patients with confirmed diagnosis of COVID-19 admitted to hospital were enrolled. Inclusion criteria also included D-dimer above the upper limit of normal [45]. Both stable non-ICU and unstable ICU patients were enrolled in the study, although the majority of study subjects were stable noncritically ill patients (elevated D-dimer). A hierarchical composite endpoint was composed of death, duration of hospitalization, and number of days with oxygen therapy at the end of 30 days. 615 patients were enrolled, randomized to therapeutic versus prophylactic anticoagulation in equal proportions. It was demonstrated that the therapeutic-dose anticoagulation did not improve prognosis and was related to an increased risk of major bleeding. Major bleeding was observed in 8% of patients receiving therapeutic-dose anticoagulation and in 2% of patients assigned to prophylactic-dose anticoagulation [45].

A retrospective observational study by Chow et al. enrolled 412 patients hospitalized for COVID-19, of whom 98 (23.7%) received additional acetylsalicylic acid (ASA) during the first 24 hours of hospitalization or within 7 days before admission. It was found that the use of ASA was associated with a lower frequency of ICU admission, mechanical ventilation, and in-hospital death [56]. There were no differences in terms of major bleeding or thrombosis between ASA users and non-users [56]. Another prospective randomized trial REMAP-CAP investigated standard therapy with or without 150 mg of ASA in hospitalized patients with COVID-19 [57]. The primary outcome was 28-day mortality. Almost all patients in the study group received thromboprophylaxis. 34% of patients were receiving thromboprophylaxis with extended-dose LMWH, 60% of patients were administered standard

dose LMWH, and 7% of patients were not receiving any thromboprophylaxis. A total of 7351 patients were randomly allocated to usual care plus ASA and 7541 were randomly allocated to usual care alone. The mortality rate was similar in both groups, 17% among patients in the ASA group vs. 17% of patients in the usual care group. No additional benefits, reduced mortality or lower risk of progressing to invasive mechanical ventilation were found in the group receiving usual care plus ASA. However, ASA was associated with a reduced duration of hospitalization of the patients who survived [57].

In patients with mild COVID-19 who do not require hospitalization, the general recommendations to reduce the risk of VTE should be kept in mind: drinking 1.5–2.0 l of water per day, and avoiding immobilization, tight clothing, and alcohol consumption. Routine thromboprophylaxis is not recommended in these patients [50, 58]. It can be considered individually in patients at high risk of VTE from other causes with a low risk of bleeding [50].

Selected patients with an increased risk of VTE hospitalized for COVID-19 may benefit from primary post-discharge thromboprophylaxis extended to 35 days after discharge. This approach is based on the results of the MICHELLE study [59]. The MICHELLE study enrolled patients hospitalized for COVID-19 with an increased risk of VTE, assessed using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) scale and D-dimer values [59]. These were patients at an increased risk of VTE (IMPROVE score of ≥4) or IMPROVE score of 2–3 and D-dimer >500 ng/mL at discharge [59]. The IMPROVE score predicts the risk of VTE within 3 months of follow-up, taking into account the following risk factors: age >60 years, history of VTE, known thrombophilia, lower limb paresis, immobilization >7 days before or during hospitalization, hospitalization at ICU, and active neoplastic disease [60, 61]. Patients were randomized to receive, at hospital discharge, 10 mg rivaroxaban or no anticoagulation for 35 days [59]. All patients received standard doses of thromboprophylaxis during hospitalization. The primary outcome, defined as a composite of symptomatic or fatal VTE, asymptomatic VTE (PE detected by CTPA or DVT detected by VUS), symptomatic ATE, and cardiovascular death at day 35 of observation occurred in 5 (5%) patients assigned to rivaroxaban and 15 (9%) of 159 patients assigned to no anticoagulation (relative risk 0.33, 95% CI 0.12–0.90; $p = 0.0293$). There were no major bleeding events in the thromboprophylaxis group [59].

Influence on Prognosis

Coexisting VTE and COVID-19 increase mortality in COVID-19 patients [2, 28, 41, 62].

Elevated D-dimer values were shown to be associated with an increased risk of death in COVID-19 patients, both with and without coexisting VTE [63]. Older age, high sequential organ failure assessment (SOFA) score, and D-dimer greater than 1000 μg/L early after admission are associated with a worse prognosis in COVID-19

patients, as reported already in the early days of the COVID-19 outbreak in Wuhan [38]. A follow-up study of 343 COVID-19 patients from Wuhan found that D-dimer ≥2000 μg/L predicted the risk of in-hospital death with a sensitivity of 92% and a specificity of 83% [39]. In another pooled analysis of 6 studies enrolling 1355 hospitalized COVID-19 patients, a D-dimer value of 3590 μg/L was argued to provide good discrimination of the risk of in-hospital death [64]. A large meta-analysis by Li et al. failed to identify a single optimal D-dimer cut-off point useful in estimating the prognosis of patients with COVID-19. Hoverer, it has been unequivocally demonstrated that D-dimer is a reliable prognostic biomarker in COVID-19, and that both 500 μg/L, 1000 μg/L, and 2000 μg/L cut-off points can be used in various populations to identify patients with an increased risk of in-hospital death [40].

Conclusions

Hospitalized COVID-19 patients are at an increased risk of thromboembolic complications. D-dimer elevation is often observed in patients with COVID-19 infection. D-dimer is considered a prognostic marker in these patients, but its specificity is lower when diagnosing venous thromboembolism. Thromboprophylaxis is recommended in all patients hospitalized for COVID-19, unless contraindications exist. Thromboembolic complications in hospitalized COVID-19 patients are associated with a poorer prognosis.

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Chapter 13
Stroke in COVID-19

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Introduction

A practical and updated definition defines stroke as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause [1]. Stroke is a heterogeneous disease with mainly two subtypes, ischemic stroke (IS) and hemorrhagic stroke (HS). Cerebral venous/sinus thrombosis (SVT) although not a classical stroke subtype is included in the analysis of cerebrovascular diseases in the COVID-19 positive population.

The definition of ischemic stroke (IS) is based on underlying brain infarction [1]. The etiology of ischemic stroke is usually classified according to Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification. TOAST denotes five subtypes of ischemic stroke: large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology. The last subtype is diagnosed if either two or more subtypes are identified or if no etiology can be identified or due to incomplete evaluation [2]. The term cryptogenic stroke is used when no definite cause can be identified. The incidence of different etiologic subtypes of ischemic stroke are as follows—large artery

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occlusions, small vessel occlusions both 25%, cardioembolic 20%, cryptogenic 25%. About 5% of IS comprise unusual causes [3]. According to imaging data strokes may be either non-lacunar or lacunar according to their size. Lacunar infarction is diagnosed when a lesion with a diameter of less than 1.5 cm is demonstrated on imaging [2]. Lacunar strokes are caused by underlying small vessels disease [4]. Large vessel occlusion (LVO) is diagnosed on vascular imaging if there is an occlusion either in proximal anterior circulation (in two-thirds of cases) or in vertebral or basilar arteries [5]. The LVO etiology is either atherothrombotic (13%), cardioembolic (33%), other known (5%) or unknown etiology (49%) [6, 7].

Intravenous thrombolysis (IVT) for IS has been introduced after a successful clinical trial (NINDS trial) [8]. Without advanced imaging, this treatment is available only up to 4.5 h after onset of IS [9]. This time frame is extended if multimodal imaging demonstrates salvageable brain tissue [10]. IVT is not fully effective in LVO as after IVT 60–80% of patients still die within 90 days after stroke onset or do not regain functional independence [11]. Therefore, more recently endovascular procedure for mechanical extraction of thrombi is introduced [11] with a time frame of 6 h after onset [12]. With advanced imaging, endovascular treatment can be used within a 6–24 h time window in patients meeting the eligibility criteria of randomized trials [13].

Brief episodes (less than 24 h) of neurological dysfunction without permanent neurological dysfunction resulting from focal cerebral ischemia are called transient ischemic attacks (TIA). Currently, TIA can be diagnosed if there is no evidence of acute infarction on brain imaging [14].

Spontaneous, non-traumatic intracerebral hemorrhage (ICH) is usually caused by rupture of small penetrating arteries secondary to hypertensive changes or other vascular abnormalities [15]. ICH accounts for approximately 10–20% of all strokes [16]. ICH may be primary intraparenchymal hemorrhage (IPH) or intraventricular hemorrhage (IVH) [17]. In older adults, hypertension is the most common underlying cause of ICH [18–20]. Subarachnoid hemorrhage (SAH) is typically associated with rupture of intracranial aneurysms [17]. Aneurysmal subarachnoid hemorrhage injects blood into the subarachnoid space in almost all cases, however, hemorrhage into the ventricles and brain itself is also common [21]. SAH accounts for about 5% of all HS [21].

Cerebral venous/sinus thrombosis (CVT) refers to the formation of blood clots in large dural venous conduits (venous sinuses) and the occlusion of veins on the surface of the cortex. Progressive venous thrombosis can lead to venous infarctions, raised intracranial pressure, and hemorrhagic complications [22, 23]. CVT accounts for about 0.5% of strokes [23].

The stroke-related neurologic deficit is evaluated quantitatively by using a composite measure that incorporates the assessment of the level of consciousness, orientation, neurologic signs—eye movements, the integrity of visual fields, facial movements, arm and leg muscle strength, sensation, coordination, language, speech, and neglect. Higher scores indicate more severe stroke [24]. The modified version of the scale (NIHSS) is used in clinical practice and trials [25, 26]. Stroke subtypes are depicted on Fig. 13.1 [27].

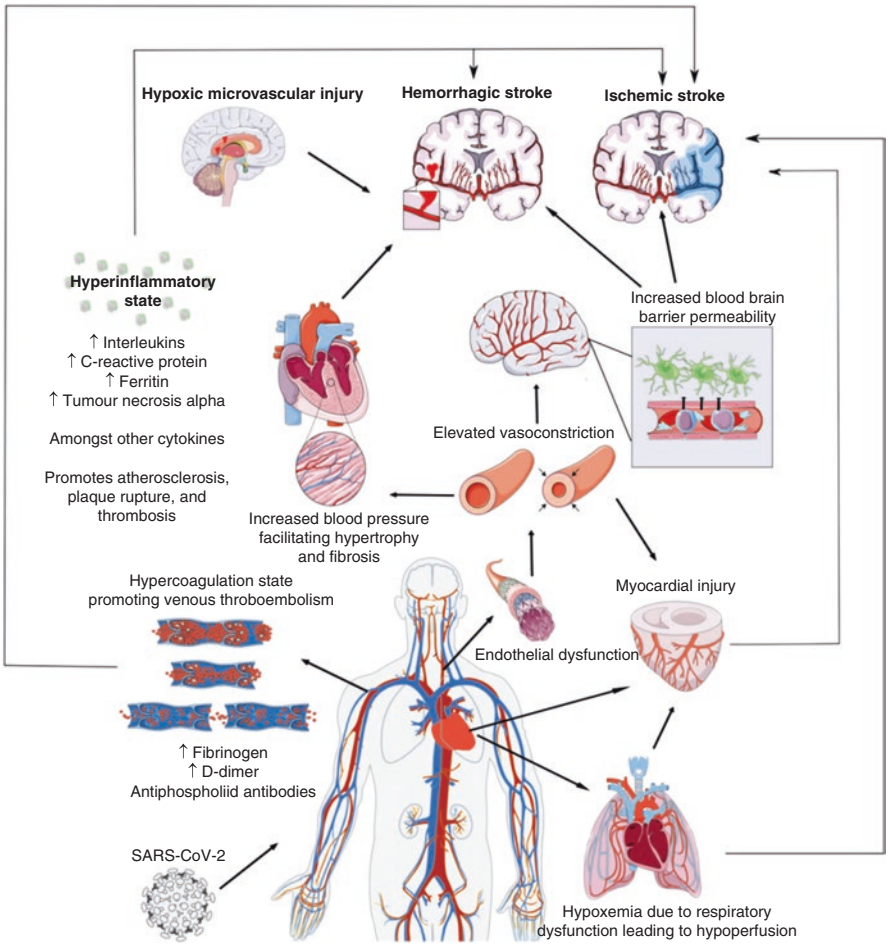

Fig. 13.1 Overview on the possible stroke mechanisms in COVID-19 patients. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. After Nannoni et al. [27]

Ischemic Stroke (IS) and Transient Ischemic Attack (TIA) in COVID-19 Pandemic

Epidemiology of IS and TIA During COVID-19 Pandemic

A meta-analysis concluded that the most common subtype of all stroke in COVID-19 positive patients in 87% of cases is ischemic (IS) [27]. TIA is described in 0.1% of cases [27]. One meta-analysis demonstrated that COVID-19 increases the risk of IS by 1.4. This is not confirmed by data from a large case series where IS (1.3%) among COVID-19 positive patients was not increased compared to COVID-19

negative patients (1.0%) [28, 29]. In some hospital-based series and registry-based data IS has been diagnosed in 0.7–0.9% of hospitalized patients [30–32]. A higher proportion of COVID-19 positive patients with IS (1.3–2.5%) has been reported in large hospital series [29, 31, 33–36].

The influence of pandemic lockdown did not influence significantly the admission of IS in some centers [37–39]. However, the analyses from German academic hospitals and Italian case series showed a significant decline 39% and 85% during the pandemic for IS and TIA admissions [40–43]. Interestingly, the number of IS admissions remained unchanged during the pandemic in another German case series and in a study from the USA comparing admissions for IS with pre-pandemic period [40, 41]. According to a single case series, the admissions for TIA significantly decreased (51%) [42] but data from Japan indicated no change in the proportion of patients with minor strokes/TIA [43]. Also, a trend towards fewer referrals from the ambulance services was noted [43]. An analysis based on hospital series demonstrated that patients' refusal for hospitalization for stroke or MI was increased from 8% in pre-pandemic time to 18% during the pandemic time [40]. Also, delays in admission were noted in some series. The onset-to-door (ODT) time was prolonged during the pandemic [43, 44], although, the alert times for emergency services remained unchanged [40].

The in-hospital care pathways were not significantly influenced by the pandemic. The number of patients admitted to the stroke unit was unchanged during the pandemic compared to pre-pandemic in general [45], although in some centers stroke units were transformed to COVID-19 intensive care units [44]. The door-to-needle times (DTN) and door to groin times (DTG) remained relatively unchanged during the pandemic [44, 46] and even improved in some hospitals [47].

The decreased admission rates were mirrored by a significant decrease in recanalization procedures—by 61% in some centers [37]. In other German, Dutch, Italian, and Japanese series the number of intravenous thrombolysis (IVT) remained the same [37, 41, 44, 46, 48–51] as in the UK case series where the per cent of IVT did not change compared to the pre-pandemic period [45]. A slight drop in IVT was noticed in an Italian multicenter study [42]. Reduced number of IVT procedures were related possibly to delays in patients' admission times after stroke onset [44]. In some centers decrease of admission of strokes of large vessel occlusions (LVO) was noted and the number of endovascular thrombectomies (EVT) dropped significantly (by 62%) [41]. In other hospitals, the numbers of EVT did not change [38, 39, 44, 48, 49, 51–53] [45]. or even increased [38, 46]. However, taking into account historical trends in continuously increasing EVT there was still a relative drop in EVT procedures [46]. The increased number of hospitalization refusals did not translate into higher mortality of IS during the pandemic [40].

Description of IS in COVID-19 Positive Patients

According to the available literature, all patients had the diagnosis of COVID-19within 1 month (up to 33 days) before the onset of IS. Therefore, drawing definite conclusions if COVID-19 plays role in IS pathogenesis and how COVID-19 influences the course and outcome of IS are difficult. In a recent meta-analysis most patients had been admitted due to COVID-19 and IS developed in the course of their disease [27]. This was confirmed by hospital-based series where 90% of IS were diagnosed 14 days after the onset of COVID-19 [35]. In some series COVID-19 was diagnosed before stroke only in few (6%) patients [54]. In large dataset series 9% of COVID-19 positive patients COVID-19 was diagnosed simultaneously with stroke [28] and 20–53% were asymptomatic on admission [29, 55].

The variations in described cohorts explain significant differences in IS in COVID-19 positive patients regarding IS etiologies, clinical features, comorbidities, treatments, and outcomes. A valuable insight comes from the Swiss Registry Study where the physicians in charge evaluated the causal relationship between COVID-19 and IS. COVID-19 was decided to be the principal cause of IS in 24%, the contributing or triggering factor in 36% and COVID-19 was not considered as a contributing factor in 40% of patients [56].

The age range of patients with IS and COVID-19 is broad. The mean age of COVID-19 positive patients with IS was 62 years in the systematic review [57]. In some series COVID-19 positive IS patients are even younger [31, 34]. Among COVID-19 positive IS patients 32% have been younger than 60 years or 36% younger than 55 years in a multicenter study [29, 58]. The age of COVID-19 positive patients with IS was higher compared to COVID-19 positive patients without IS [28, 35]. However, in many case series the mean age between COVID-19 positive and negative patients with IS was similar [28, 43, 54, 56, 59–61].

The proportion of male patients has been various (43–72%) in different studies of COVID-19 positive IS stroke patients [31, 32, 57, 58, 62]. Also, no difference in sex ratios between COVID-19 negative and positive patients has been found in many single case series [35, 54, 61]. Ethnicity seems not to influence the incidence of stroke in COVID-19 positive patients [32].

Clinical, Etiological, and Imaging Features of COVID-19 Positive IS Patients

According to a metanalyses IS in COVID-19 positive patients is severe (median NIHSS 15–16) [27, 57]. A large multinational study showed that 30% of patients have more severe strokes (NIHSS 16 or more) [58]. No differences in stroke severity between COVID-19 positive and negative patients were reported by some authors [33, 54, 56, 61]. However, some case series reported more severe IS in COVID-19 positive patients compared to COVID-19 negative patients [46, 63]. In

one large case series COVID-19 positive patients with IS were significantly more severe than in the contemporary stroke controls [31]. The severity of stroke was the same in different age groups in large series [29].

The etiology of IS is usually classified according to the TOAST criteria [2]. The most common type of stroke in COVID-19 positive patients was cryptogenic (CS) in 45–66% of patients with IS in a meta-analysis [27]. This is confirmed by many case series as well [29, 31, 55, 58–60, 62]. However, in some series the prevalence of CS was lower by 18% [57]. In some series CS stroke had the same prevalence about 34–36% as historical controls and COVID-19 negative patients [54]. Contrary to metanalysis data, decreased number of CS was independently associated with COVID-19 in the Swiss Registry study [56].

Cardioembolism (CE) was the etiologic factor for stroke in 22% of COVID-19 positive patients in the metanalysis and case series [27, 31]. Also, in other series with some exceptions [57, 62] CE was slightly more frequent but in the range of the data from metanalysis [29, 55, 58, 60]. Cardioembolic strokes were largely in the same range for COVID-19 negative and positive patients [54, 59]. Large artery atherosclerosis (LAA) was described in 11% of COVID-19 positive patients in a metanalysis [27] but often reported in a very diverse range [29, 31, 57–60] but less commonly in COVID-19 positive patients (3%) compared to COVID-19 negative patients (15%) [56]. In other series COVID-19 positive and COVID-19 negative patients had a similar frequency of LAA [31, 54]. Small artery occlusion (SAO) has been uncommon (0–3%) in COVID-19 positive patients [27, 31]. SAO has also been uncommon in other series with slightly increased prevalence compared to the meta-analysis data [29–31, 58]. In the hospital-based series there was no difference in IS etiology between COVID-19 positive and negative patients [40, 60, 61].

Large vessel occlusions (LVO) on imaging were found in 80% of cases in the meta-analysis [27]. The proportion of LVO has been of similar range [31, 34, 54, 56, 58, 62] more [31, 64] or less common [54] in COVID-19 positive patients compared to COVID-19 negative patients. In one case series, LVO was more frequent in patients <50 years (69%), compared to other age groups [34]. Simultaneous involvement of different vascular territories was reported in 43% of cases [27]. Frequent involvement of multiple vascular territories is described also in case series [30, 34, 61, 65, 66]. The multivessel occlusions on imaging were more frequent in COVID-19 positive patients (27–50%) compared to (9–13%) patients who were COVID-19 negative [56, 65]. One COVID-19 positive case with occlusion of three vessels is described in the literature [67]. There were fewer lacunar strokes on imaging in COVID-19 positive IS population 8% compared to 18% in COVID-19 negative IS cohort [59].

COVID-19 positive patients with IS have a very high prevalence of comorbidities, described in 71–90% of all patients [33, 35, 55, 57, 62]. They have more IS cardiovascular risk factors compared to COVID-19 positive patients without IS found in a large case series [28] but not in other series where the cardiovascular risk profile was the same for COVID-19 positive patients without IS [35]. Generally, in the case series COVID-19 positive and negative stroke patients had a similar burden of cardiovascular risk factors and treatment at stroke onset [28, 54, 56, 60].

Management of COVID-19 Positive Patients with IS

Only 32% of COVID-19 positive patients with IS compared to 56% of COVID-19 negative IS patients were admitted to the stroke unit [54]. There was no significant difference for onset to hospital arrival times between COVID-19 positive and negative patients [54]. Door-to-needle (DTN) times were the same for COVID-19 positive and negative patients [46, 63] but slightly longer 35 vs. 25 min in other case series, respectively [54]. IVT was performed in 19% of patients with IS and COVID-19. The frequency of IVT varies in different case series [27, 29, 31, 34, 54, 56–59]. In some series the proportion of COVID-19 positive IS patients who received IVT was lower probably due to their late arrival [55, 60]. A recent study demonstrated that IVT is equally effective for COVID-19 positive and negative patients with IS according to their thrombus characteristics [68]. Feasibility, efficacy, and safety of IVT were evaluated in two multicenter studies [50, 63]. Hemorrhagic transformation occurred in 16–17% of cases but only in 4–7% were accompanied by symptomatic intracerebral hemorrhage (sICH) that significantly increased disability after IVT [50, 63]. No differences in occurrence of sICH or outcomes in COVID-19 positive patients were observed compared to COVID-19 negative patients [63].

DTG times were the same for COVID-19 negative and COVID-19 positive or suspected positive patients [46, 54]. EVT was carried out in 26% of patients included in the metanalysis and similar data was reported in the case series [27, 29, 34, 57]. In some case series EVT was performed in smaller number of patients [30, 55]. Generally, the number of revascularization treatments were same in COVID-19 positive and negative patients [28, 40, 50, 54, 56, 59].

Outcome of COVID-19 Positive Patients with IS

COVID-19 positive patients with IS compared to COVID-19 positive patients without IS developed significantly more frequently multiorgan failure (renal, hepatic, and respiratory failure). The risk of pneumonia, pulmonary embolism, deep venous thrombosis, cardiac arrest was the same IS patients with and without COVID-19 had a similar risk of complications in the course of IS [28]. Admission to the ICU was more frequent in COVID-19 positive patients with IS compared to COVID-19 negative patients with IS [54]. Predictors for worse outcomes among both COVID-19 positive and negative patients were higher NIHSS and hyperglycemia at stroke onset [59]. In addition, higher D-dimer levels and lower lymphocyte count were the predictors of worse outcome in COVID-19 positive patients [59]. Hemorrhagic transformation of IS was reported in 8–15% of patients [63, 66] and in some studies it was more common in COVID-19 positive compared to COVID-19 negative patients [69]. In other series hemorrhagic transformation and stroke recurrence was not different among COVID-19 positive and negative patients [56, 63].

COVID-19 positive patients with IS compared to those without IS were significantly less likely to be discharged home (38% vs. 71%) [28] and COVID-19 positive patients with IS were less likely to be discharged home compared to those who were COVID-19 negative [28, 32, 56]. In other studies disability at discharge was not different for COVID-19 positive and negative patients [63].

At 3 months COVID-19 positive patients had significantly worse outcomes compared to COVID-19 negative patients with IS [54, 56]; however, the difference was not confirmed in another case series [59].

COVID-19 positive patients with IS had higher risk of in-hospital mortality compared to contemporary controls with IS (64% vs. 6%) [31, 55, 65, 66]. Also, COVID-19 positive patients with IS had significantly higher in-hospital mortality compared to COVID-19 positive patients without IS (19% vs. 6%) [28]. However, when comparing IS patients who were COVID-19 positive and negative and managed within the same center or according to adjusted data from case series, there was an only mild increase or no difference in in-hospital mortality [28, 32, 56, 63]. Mortality of patients with LVO on imaging and COVID-19 was statistically significantly increased compared to patients with LVO without COVID-19 [54]. COVID-19 was the strongest independent risk factor for in-hospital stroke fatality [66]. COVID-19, age ≥70 years, atrial fibrillation, and any intracranial hemorrhage, including hemorrhagic transformation, were independent risk factors for mortality [66].

Mortality in 3 months was twice higher in COVID-19 positive patients compared to COVID-19 negative patients but that was statistically not significant in one study [56] but significant in other case series [54, 59]. Also, after adjusting by age, NIHSS at onset, admission to the ICU and prior history of diabetes COVID-19 was not an independent factor influencing functional outcome in 3 months [54] but in multivariable analysis, COVID-19 was independently associated with mortality in 3 months [54].

Pathogenesis

The pathogenesis of IS is multifactorial in COVID-19 positive patients. In addition to classical risk factors, COVID-19 causes coagulopathies secondary to immune activation [31, 70, 71], hyperinflammation, including inflammatory cytokine storm [61, 64, 72]. Also, microvascular involvement due to endothelial dysfunction is implicated in IS and COVID-19 [61]. It has been suggested that instead of general CS diagnosis, in the context of severe systemic COVID-19 illness with coagulopathy (increased D-dimer burden) CS with COVID-19 could be diagnosed [70]. Cardioembolic strokes were not more frequent in COVID-19 positive patients with IS, which confirms literature data demonstrating that cardiac arrhythmias are not more frequent in COVID-19 positive patients with severe COVID-19 [61, 73].

Conclusions

Most COVID-19 positive patients with IS have a high burden of risk factors for IS. In many case series clinical, etiological and radiological features of COVID-19 positive patients with IS are not different from COVID-19 negative patients. Indeed, it appears that only in about in quarter of patients COVID-19 is causally related to IS [56]. Much more frequently COVID-19 was a predisposing factor for IS as most patients were already at risk for IS [28]. Case series are mixing generally different IS groups (severe vs. mild or asymptomatic COVID-19 patients) and therefore it is difficult to draw definite conclusions on specific features of IS in COVID-19 positive patients. Although, it is emerging from large case series that LVO on imaging is more common in COVID-19 positive patients than in COVID-19 negative patients but that was not confirmed in series where COVID-19 positive and negative patients were treated within the same center. Also, there was no difference in recanalization procedure numbers or outcomes between COVID-19 positive and negative patients. Although it appears that short-term outcome of COVID-19 positive and negative patients with IS is not significantly different but 3 month outcome is significantly worse for COVID-19 positive patients. Frequent non-neurological complications in the course of the disease further are related to the worse outcomes of these patients [28, 71].

Hemorrhagic Stroke (HS) in COVID-19 Pandemic

Epidemiology of HS During COVID-19 Pandemic

The prevalence of hemorrhagic stroke (HS) during the COVID-19 pandemic is reported to be somewhat increased [42, 74, 75]. A meta-analysis and other retrospective hospital-based cohort studies demonstrated that although numerically the admissions for HS decreased during the pandemic, there was a statistically significant increase in the proportion of hospital admissions for HS compared to all strokes [69, 76–78]. According to the data from one center in the USA, even 40% of all strokes were hemorrhagic during a short time period [79]. However, some hospital-based series have reported a decreased number of HS [41, 42, 80] or no change [45, 51, 77].

HS occurred in 18% [69] to 21% all strokes in COVID-19 positive patients [58]. Data indicate that all types of intracranial hemorrhages are represented in COVID-19 positive patients: intracerebral hemorrhage (ICH) including intraparenchymal hemorrhage (IPH), intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH), and multicompartment hemorrhage (MCH) [58, 75, 81–83]. The prevalence of different types of hemorrhages varies significantly depending on the described cohort. In a large series and metanalyses, IPH is the most common in 63–67% of cases, followed by other types of ICH [27, 58, 81]. Multicompartment hemorrhages

(frequently IPH and SAH combined) are reported in the range of 8% (two and three patients) [58, 69] to 20% (seven patients) [82, 84, 85] from all HS. A similar prevalence (14 cases, 9.5%) was reported in another metanalysis [81]. In a small series of seven patients simultaneously occurring MCH was diagnosed [82].

Intracerebral Hemorrhage (ICH)

The recent meta-analysis based on 97 eligible studies concluded that the overall prevalence of ICH in COVID-19 positive hospitalized patients is between 0.1% and 3.3% [82]. However, the rate was 6.8% for COVID-19 positive patients over 80 years of age [86]. Data from another meta-analysis demonstrate the prevalence of 0.7% [81] and reports from larger databases analysis show similar 0.2–0.3% prevalence rates for ICH in COVID-19 positive and negative patients [83, 87].

Clinical Features of ICH in COVID-19 Positive Patients

A meta-analysis found that the mean age of COVID-19 positive patients with ICH was similar to that without COVID-19 (62 vs. 65) but higher than that for COVID-19 positive patients without ICH [88]. The age at onset was 31–78 years [81] and the mean age was 69 years [89]. Only 16% of patients were less than 50 years old [81] and the mean age of the patients was between 50 and 60 years in some series [83, 84]. In the hospital series, COVID-19 positive patients with ICH were more frequently younger than 75 years (median age 60) which was similar to that for ICH patients without COVID-19 and historical controls [90, 91]. Patients without traditional cardiovascular risk factors for ICH were younger [58, 84].

Patients are predominantly male (58–79%) [81–83, 90, 91] and only 21–33% are female [81, 88, 89, 92]. Hispanic ethnicity is an independent risk factor for ICH [88].

The hematoma volume is larger [88] compared to that of historical controls [90] and also for COVID-19 positive patients without cardiovascular risk factors [58] in some series. ICH is more severe according to the NIHSS scores (15 in ICH COVID-19 positive patients versus 9 in COVID-19 negative controls) [91]. The severity of ICH was even higher for patients who developed ICH at the hospital compared to historical controls [90]. ICH may present as the first symptom and COVID-19 is diagnosed during admission or ICH can develop during the course of COVID-19 [82, 90]. Data indicate that the majority of ICH-s develop during the pre-existing COVID-19: from 54% [91] to 71% [81] and up to 100% of cases in some series [90]. Asymptomatic COVID-19 positive patients presenting with ICH are less common (4 patients, 12.1%) [92]. The interval between the onset of respiratory symptoms and the diagnosis of ICH has ranged from 2 to 25 days [81]. The mean time between hospitalization because of COVID-19 and the diagnosis of ICH was 17 days in the hospital-a based cohort [92].

Comorbidities of COVID-19 Positive Patients with ICH

Alcohol abuse and atrial fibrillation have emerged as independent risk factors for COVID-19 positive patients with ICH [88]. The majority of case series describe ICH COVID-19 positive patients with many pre-existing cardiovascular risk factors for stroke, like hypertension, diabetes mellitus (DM), hyperlipidemia coronary artery disease (CAD), obesity, congestive heart failure (CHF), obstructive sleep apnea (OSA), and systemic lupus erythematosus (SLE) [81]. Patients with ICH and COVID-19 had higher burden of cardiovascular risk factors than the patients with COVID-19 without ICH [79, 88, 89, 93]. In one series, 81% of ICH patients had at least one comorbidity [79]. In another study, 28% of COVID-19 positive patients with ICH did not have any cardiovascular risk factors or comorbidities [58]. This observation is corroborated by data from a series of patients who were hospitalized for COVID-19 and then developed ICH. In this study, hypertension was less common among COVID-19 positive ICH patients compared to historical controls (42% vs. 80%, respectively) [90].

Management of COVID-19 Positive Patients with ICH

Depending on COVID-19 severity many patients receive anticoagulation. The rate and doses for individual patients differ reflecting the severity of COVID-19 [89, 90, 92]. Anticoagulation has been started either at home or at the hospital in 73% of ICH patients compared to 32% of COVID-19 patients without ICH [89]. In the hospital series, anticoagulation was started prior to ICH in 90% [92] to 94% [90] of patients. The most common indication for therapeutic anticoagulation has been elevated D-dimer levels, extracorporeal membrane oxygenation (ECMO) and arterial or venous thrombosis [81, 89, 90, 92]. The dose of anticoagulation has not been associated with the risk of ICH. In a cohort study of ICH patients, 59% of patients with ICH were on a subtherapeutic dose, 29% were consistently in therapeutic range, and 12% in therapeutic range but subtherapeutic prior to diagnosis [90]. In another series, 67% of patients were on therapeutic and 9% on a prophylactic dose of anticoagulation [92]. There were no significant differences in hematoma size or ICH location between patients who were or were not on therapeutic anticoagulation before ICH [89]. As expected, anticoagulation was associated with a fivefold increase in the risk of ICH in a metanalysis [89] and higher risk for ICH was confirmed in the hospital-based case series as well [90, 92].

Course and Outcome of HS in COVID-19 Positive Patients

The number of patients admitted for ICH and diagnosed with asymptomatic COVID-19 is low and their course and outcome depend on ICH severity [82]. COVID-19 positive patients with ICH compared to COVID-19 positive patients without ICH have higher risk of being admitted to the intensive care unit (ICU), respiratory failure requiring mechanical ventilation, requiring vasopressor support, and a higher rate for multiorgan failure during hospitalization [82, 89]. COVID-19 positive patients with ICH had longer ICU stay (17 days vs. 6 days) compared to ICH without COVID-19 [91]. In hospital-based series, 84% of COVID-19 positive patients who developed ICH required mechanical ventilation [90] which is an additional risk factor for ICH [89]. A single center study of 33 patients compared the prevalence of ICH on ECMO in COVID-19 positive and negative patients. They demonstrated that ICH developed in 35% of COVID-19 positive and in 17% of COVID-19 negative patients [94]. The center strictly followed neuromonitoring protocol that included routine examination of signs indicating neurological dysfunction and brain CT scan during or early after ECMO at the center [94].

In the US-based study mortality rate of 40–49% was reported among patients with ICH who were COVID-19 positive [81, 88]. The reported mortality rates were significantly higher compared to the mortality rate of 7–19% observed in patients without COVID-19 [82, 88, 89, 91]. The influence of the severity of COVID-19 on the outcome is confirmed in another study where patients were hospitalized for COVID-19 infection and the clinical course was complicated by ICH. This cohort had a very high mortality rate of 90% compared to contemporary controls (4%) and historical controls (10%) without COVID-19 [90]. Simultaneous MCH was associated with a poor prognosis and a high mortality rate of 71% [82]. Also, in one study 33 COVID-19 positive ICH patients demonstrated ultra-early hematoma growth [95]. Patients who developed COVID-19 before ICH had a significantly higher mortality rate of 58% compared to 48% in patients diagnosed with COVID-19 on admission or later at the hospital [93].

Pathogenesis

The proposed mechanisms of ICH and COVID-19 are related directly to the viral invasion or systemic response. The factors directly related to the virus are direct endothelial injury. Systemic factors like inflammatory cytokine production, coagulation disorder and complement-mediated microvascular thrombosis, platelet dysfunction are playing role in ICH pathogenesis [83, 89]. However, taking into account the low prevalence of ICH among COVID-19 positive patients the exact mechanism for ICH and factors influencing outcome—coagulopathy, multiorgan failure or both factors combined remains unclear [64].

Conclusion

Reviewed literature demonstrates that ICH is a rare but devastating complication of COVID-19, especially when the course of COVID-19 infection is complicated by ICH. ICH significantly worsens the course of COVID-19 and COVID-19 worsens the course of ICH. Many patients with ICH have cardiovascular risk factors for ICH, however, an independent factor that increased ICH risk emerged anticoagulation preceding ICH. Coagulopathy has been present in 74% of patients in hospital series [90], and higher coagulation markers indicate more severe course of COVID-19 [91]. Therefore, anticoagulation was part of treatment in most patients with ICH due to COVID-19 severity before ICH developed. No clear relationship between the dose of anticoagulation and the incidence of ICH is established. According to the present literature data it is reasonable to caution the use of anticoagulants taking into account risk-benefit ratio [89]. Specifically, solid data is still missing whether isolated severely elevated D-dimer levels without suspected or known thrombosis is always an indication for anticoagulation [92], although empiric anticoagulation has been shown to lower 28-day mortality in COVID-19 positive patients with severely elevated D-dimer levels [96]. Also, the disease severity contributes to the incidence of ICH, especially if patients need mechanical ventilation and ECMO that both increase the risk for ICH.

Subarachnoid Hemorrhage (SAH) in COVID-19 Pandemic

Epidemiology During COVID-19 Pandemic

A meta-analysis including 85,645 COVID-19 positive patients concluded that the prevalence of SAH among COVID-19 positive patients was lower (0.1%) compared to that in COVID-19 negative patients (0.2%) [87]. The frequency of SAH cases among COVID-19 positive patients with HS was 15–25% [58, 97]. Only 7% of patients from 27 intracerebral/subarachnoid hemorrhage patients had SAH in a multinational hospital-based COVID-19 patients cohort [30].

Due to the significant impact of quick admission after symptom onset to treatment outcomes in SAH access to medical care during the pandemic has been analyzed in many studies. A large multinational multicenter study evaluating admission of SAH patients 3 months before the pandemic and 3 months during the pandemic demonstrated a relative decline of all SAH by 23% and of aneurysmal SAH by 25%. A relative decline of aneurysmal SAH by 15% was reported by another study as well [98]. Also, a significant drop for aneurysmal SAH during first months of the pandemic was demonstrated in France [99] but according to data from other centers the number of admitted patients for SAH remained unchanged [75]. The authors proposed that one of the reasons for the decline in admissions was the hesitation of the patients for seeking medical help [99].

A significant increase of delay from SAH symptom onset to the admission of respectively 2.7 vs. 0.75 days was noted in China when comparing the data between 2020 and 2019 [99]. Time delays have been documented for both COVID-19 positive and negative patients [100]. Barriers in accessing medical services were also reported in an Italian study, where patients were admitted 1.06 days compared to 0.63 days after symptom onset during the pandemic compared to pre-pandemic time [101]. It is postulated that maybe some patients are not seeking medical care at all [102] and some unexplained deaths at home during the pandemic may be due to undiagnosed ruptured aneurysms [97].

Some studies have shown a general decrease of all aneurysmal SAH treatments, either endovascular or surgical during the pandemic [98]. However, the decrease was not demonstrated in other studies [100, 101]. Delays in encountering medical system have translated into worse neurological presentation on admission for all SAH patients. Poor neurological presentation was recorded in 58% of all SAH patients during the pandemic compared to 21% of that a year earlier. Also, the rates of vasospasm have been higher (6 patients vs. 1) in 2020 compared to 2019 [102]. The percentage of patients with poor outcome for all SAH patients has been higher during the pandemic (54%) compared to pre-pandemic (40%) period, although no significant differences were seen in the type of treatment (endovascular, surgical, or no treatment) between the two periods [100].

Clinical Features of COVID-19 Positive SAH Patients

The literature on COVID-19 positive patients with SAH is very limited and mostly derives from three large descriptive studies and one smaller case series including less than 150 COVID-19 positive patients with SAH [58, 82, 87, 103]. In large series there was no difference in age (respectively 60 and 62 years) or sex in COVID-19 positive and negative patients with SAH [87]. Due to limited data on SAH in COVID-19 patients, the descriptive data of SAH characteristics from case series should be interpreted with care. COVID-19 positive patients with SAH but without aneurysm rupture comprised 42% (14 cases) to 70% (16 cases) of all SAH cases in the meta-analysis and in the multinational study [58, 82]. Only 6% of patients with aneurysmal SAH were COVID-19 positive in one study [100]. In other series aneurysmal SAH patients who were asymptomatic for COVID-19 comprised 40% (four patients), moderate or severe COVID-19 symptoms were present in another 60% [104]. Higher frequency of small aneurysms and dissecting pseudoaneurysms have been described in a small series [104], descriptions of saccular and blister aneurysms are also reported [82, 104].

Course and Outcome of COVID-19 Positive Patients with SAH

An independent risk factor for SAH in COVID-19 positive cohort is hypertension [87]. Interestingly, none of the COVID-19 positive patients (87) received endovascular or surgical procedures for SAH compared to 14/376 patients with SAH who were COVID-19 negative [87]. This is in line with the data from a multinational study where 70% of SAH was non-aneurysmal [58]. In COVID-19 positive aneurysmal SAH patients 9/10 did have endovascular treatment, one died before treatments [104]. Complications such as pneumonia, pulmonary embolism, urinary tract infection, acute kidney injury, hepatic failure, cardiac arrest, acute myocardial infarction, septic shock, and respiratory failure were more frequent in COVID-19 positive than in COVID-19 negative patients with SAH [87]. Also, the in-hospital mortality among COVID-19 positive patients with SAH was significantly higher (31% vs. 12%) compared to COVID-19 negative SAH patients [87]. In aggregated series, 5/10 of symptomatic patients and all asymptomatic COVID-19 patients died, two of them because of complications [82].

Pathogenesis

It is possible that non-aneurysmal SAH is related to inflammatory activity in COVID-19, possibly leading to other mechanisms of SAH than ruptured aneurysms. A potential mechanism for non-aneurysmal SAH may be vasculitis involving the medium- and small-sized arteries in the brain diagnosed by neuroimaging of vessel walls in COVID-19 positive patients (Keller et al., 2020) or according to stroke imaging patterns [103, 105] with CSF findings [106]. Furthermore, autopsy-confirmed endotheliitis affecting small vessels are in line with proposed vasculitis as one of the underlying pathologies in SAH and COVID-19 [107].

Conclusion

According to reviewed data, non-aneurysmal SAH occurs in 42–80% of SAH patients which is higher than expected. Although the prevalence of SAH among COVID-19 positive patients is low it seems that there is an increased number of non-aneurysmal SAH compared to the COVID-19 negative population. The outcome of COVID-19 positive patients is significantly worse than in patients who are COVID-19 negative and have SAH.

Cerebral Venous Thrombosis (CVT) in COVID-19 Positive Patients

Epidemiology of CVT During COVID-19 Pandemic

The general number of reported CVT cases in COVID-19 positive patients is low. A meta-analysis found that 2% (25 patients) of COVID-19 positive patients develop CVT [27]. A recent meta-analyses included 56 adult patients (including 13 patients from one larger series) [108, 109] and another 14 adult patients [110]. In addition, 18 adult patients were described in larger case series [58]. Therefore, the number of patients described with CVT and COVID-19 appears to be around 100.

The prevalence of CVT varies significantly from 0.001 in a population-based study (four patients) [111] to 0.02–1% in-hospital series, pooled data demonstrated that 8% of hospitalized patients were diagnosed with CVT. CVT has comprised 4% of all cerebrovascular events [30, 108].

It is plausible that similarly to other strokes there has been a drop in CVT admissions [112], although the small numbers of CVT cases in general [22] and even smaller number of patients with CVT with COVID-19 [58, 108, 110] prevents drawing definite conclusions. Also, mild to moderate headache as a most common presenting symptom of CVT may have been overlooked in the context of the COVID-19 pandemic [64, 113].

Clinical Features of CVT in COVID-19 Positive Patients

The mean age of patients was 49–54 years [58, 108]. In some case series, the mean age has been higher—63 years [114]. In larger case series comparing COVID-19 positive patients with CVT with a cohort of CVT patients from the same centers treated previously, the mean age of COVID-19 positive patients was, respectively, 51 years compared to 37 years [109]. In a meta-analysis, 18% of patients with CVT were younger than 50 years [108] compared to 78% of patients younger than 55 in a large multinational case series [58]. A small case series of very young patients in the age range of 23–43 years have also been described [110, 115–117]. Click or tap here to enter text.

Female patients comprised of 50–60% [58, 108] but in some smaller series the female preponderance was even higher 88% [115] In others series 70% of reported cases were male [115, 116].

Only a few patients included in the meta-analyses and case series had asymptomatic COVID-19 infection, 95% of them had respiratory symptoms [108–111]. This is in contrast with data from a multicenter and single center series where 45–81% were asymptomatic for COVID-19 [115, 116]. In most reported patients COVID-19

was mild to moderate in severity [108]. In 35% of patients in a multicenter study [115] compared 90% of patients in the meta-analysis CVT was diagnosed after established diagnoses of COVID-19 [108]. CVT was diagnosed on the same day of respiratory symptom onset to 47 days after the COVID-19 onset [108, 114], 90% diagnosed with CVT within 1–8 weeks after respiratory symptoms [108].

Only one patient presented with isolated headache, all others had clinical features of encephalopathy (60%) and the majority presented with focal signs depending on the location of CVT [108]. Seizures were reported in 28% of patients in the meta-analysis [108] but were significantly more frequent (65%) in some case series [114]. In some case series CVT clinical features indicated milder course with headache being the most common symptom in half to all patients [114–116]. Focal signs have been present in 25% of patients and encephalopathy was rare only in 13–31% of patients [110, 114].

The involvement of multiple venous vessels has been 28–67% of patients [58, 108, 109]. The lateral sinus was most frequently (65–75%) affected [108–110, 114], together with superior sinus in 50–65% [109, 110, 114]. In some series there was no predilection of the location of thrombosis [58]. Hemorrhagic lesions were detected in 25–42% of patients [108, 114]. In an analysis of non-COVID-19 CVT patients hemorrhage was present in 39% patients on admission which is comparable to that of COVID-19 positive patients' series [118].

Risk factors for CVT in general population are the factors that cause systemic venous thrombosis: genetic causes, oncological diseases including hematological malignancies, polycythemia vera, transient risk factors like taking oral contraceptives, pregnancy, postpartum period, dehydration, infections, certain medications (hormonal therapy including glucocorticoids), mechanical risk factors like cranial trauma [22, 119]. In the meta-analysis and case series of COVID-19 positive CVT patients, 16% (9/56) to 63% (5/8) of adult patients had the acknowledged risk factors present [108–110, 114, 120].

Course and Outcome of CVT in COVID-19 Positive Patients

Only in 28% (9/35) of patients' full recovery has been reported [109] The prognosis was significantly better in other multinational multicenter series where 75% of patients were discharged home [115]. In-hospital mortality was high (40–46%) for COVID-19 positive CVT patients [108, 110]. In the large case series the COVID-19 positive patients' mortality rate (23%) was only slightly higher compared to the controls (5%) from the same sites [109]. The prognosis was worse for patients with hemorrhagic complications with mortality rate of 60% [108]. A drastic case series of three young patients in the age range of 23–41, without significant risk factors who died with CVT, has been described [117].

Pathogenesis

Several factors have been implicated in COVID-19 CVT. Namely, vascular endothelial dysfunction, hyperviscosity, impaired microcirculation and hypercoagulable, prothrombotic state [121]. Especially, coagulopathy seems to be an additional risk factor for increased CVT. Extremely high D-dimer levels were demonstrated in some case series indicating widespread systemic prothrombotic consequences of COVID-19 infection and worse prognosis although the mechanisms of COVID-19 and CVT are not fully understood [109, 112, 114, 122].

Conclusion

Presented data should be interpreted with caution taking into account the relatively small number of reported COVID-19 positive patients with CVT (around 100 cases) and the differences in described patients' cohorts. Compared to the influenza virus COVID-19 increases the risk for thromboembolic events generally [122]. According to a data analysis COVID-19 is related to higher risk of CVT in older population with less known risk factors for CVT. Clinical features described in COVID-19 positive patients are broadly similar to historical controls (including frequent multiple vessels involvement) [118, 119, 123]. Overall prognostic factors for worse prognosis are the same as for COVID-19 negative patients with CVT (i.e., hemorrhagic complications) [119]. The overall impression is that CVT in COVID-19 positive patients carries a more serious prognosis. The reported high mortality rates seem to be higher than 3–8% in historical patients [22, 118].

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Chapter 14
Pulmonary Embolism After COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, Treatment)

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Introduction

The COVID-19 pandemic since its onset has been responsible for high morbidity and mortality. Coagulation disorders, characterized by an increase in D-dimer and fibrinogen levels, are believed to be the cause of severe complications with an increased risk of thrombosis and of life-threatening pulmonary embolism (PE).

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Epidemiology

Incidence, Risk Factors

Since the start of the COVID-19 epidemic, studies have reported a high risk of pulmonary embolism (PE) in infected patients [1, 2]. Coagulation disorders (increased D-dimer and fibrinogen levels) and the resulting increased thrombotic risk have been reported. Accumulating evidence for systematic reviews and meta-analyses have provided information on the epidemiology, incidence, and mortality related to pulmonary embolism in people with COVID-19.

A first study found a pooled incidence rate for venous thromboembolic events of 28% (95% CI 21–36%) [3]. A large meta-analysis reported an overall pulmonary embolism rate was 13% (95% CI: 11–16%), in ICU, 19% (95% CI:14–25%) and post-mortem diagnosis, 22% (95% CI:16–28%) [4]**.**

A prospective multicentre study has evaluated the pulmonary embolism prevalence in patients admitted for COVID-19, at the time of admission. The prevalence of PE at the time of admission was estimated at 14.2% (95%CI 7.5–20.8) [5].

Another study reported an incidence of PE and mortality rates were 15.3% (95%: 9.8–21.9) and 45.1% (95%: 22.0–69.4), respectively [6]. A large meta-analysis study including severe COVID-19 cases, found risk of mortality between PE and non-PE groups very similar (OR = 1.31, 95% CI 0.82 to 2.08, $p = 0.25$; I2 = 58%) [7].

Risk factors for PE in COVID-19 patients seem to differ from the traditional risk factors for venous thromboembolism (VTE). Indeed a meta-analysis (MA) found traditional risk factors for thrombosis (cancer, history of VTE, obesity) were not associated with VTE [8]. However, the level of evidence for VTE risk factors was highest for D-dimer and CRP levels, procalcitonin, IL-6, and severity markers (mechanical ventilation, inotrope or duration neuromuscular block).

A retrospective study found D-dimer ≥3000 ng/mL, white blood count (WBC) ≥12.0 G/L, and ferritin ≥480 μg/L were independently associated with the VTE diagnosis. The presence of the double criterion D-dimer ≥3000 ng/mL and WBC ≥12.0 G/L was significantly associated with VTE (OR 21.4 [4.0–397.9], $P = 0.004$). Basile M et al. study confirms high D-dimer levels as risk factor for VTE [9].

A recent cohort of 2832 adult patients hospitalized with COVID-19 observed 1.3% post discharge venous thromboembolic events (pulmonary embolism, deep vein thrombosis, and portal vein thrombosis) [10]**.** Factors associated with venous thromboembolism after discharge were a history of venous thromboembolism, D-dimer level greater than 3 μg/mL and predischarge C-reactive protein level greater than 10 mg/dL.

Pathogenesis

The coagulation disorders observed in COVID-19 and which cause thromboses and thromboembolic phenomena have not been fully elucidated. Several mechanisms have been described, however, knowledge of the interaction between the different mechanism identified remains to be established (Fig. 14.1).

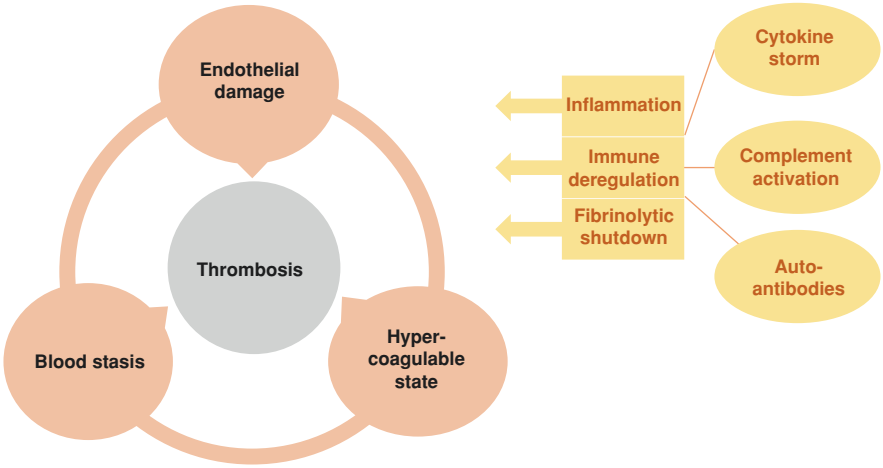

Fig. 14.1 pathophysiology of the increased risk of thrombosis

As in any serious disease, the three factors described by Wirchow [11] which contribute to the thromboembolic risk are present in COVID-19: endothelial damage, state of hypercoagulability, and blood stasis [12]. However, the involvement of inflammation and immune system in hypercoagulability seems to be particularly significant.

SARS-Cov-2 infection of endothelial cells via ACE2 (angiotensin-2 converting enzyme) surface receptors, disrupts the secretion of tPA (tissue plasminogen activator) which has the function of preventing platelet binding and/or initiation of coagulation cascade.

Additionally, endothelial dysfunction leads to excretion of Weibel–Palade body contents with massive release of von-Willebrand factor (vWF), angiopoietin-2, P-selectin, interleukin-8 (among other mediators) which triggers and stimulates the immune response, induces procoagulant and pro-inflammatory reactions, and predisposes to thrombus formation (thromboinflammation) [13].

Recent study demonstrated in hospitalized COVID-19 patients that endothelial disease and platelet activation are features present in people with severe infection Goshua et al. [14]. They observed elevations of vWF, soluble P-selectin, and soluble CD40 ligand in hospitalized patients compared to controls, providing evidence for the existence of endothelial disease and platelet activation in COVID-19 coagulopathy.

Data from studies in severe patients support the existence of a link between inflammation and the procoagulant state [13, 14]. In fact, endothelial damage contributes to hypercoagulability by stimulating the production of clotting factors. Endotheliopathy causes an aberrant inflammatory response with an influx of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, and TNF which participate in the cytokine storm and help activate the system of the complement. Interleukin 6 plays a fundamental role in the activation of the extrinsic coagulation pathway. The endotheliopathy also activates the monocytes and the macrophages which produce the tissue factor which will trigger the extrinsic coagulation cascades [12, 15].

SARS-CoV-2 also activates the complement system directly via classical or lectin pathway or indirectly due to endothelial lesion and thromboinflammation [16].

The concomitant action of all these phenomena leads to vascular lesions, to loss of antithrombogenic properties and to formation of blood clots.

In addition, data from hospitalized patients with COVID-19 in whom antiphospholipid antibodies (anticardiolipin and anti-β2-glycoprotein I) were detected also show that these could play a role in thrombosis [17, 18]. However, the frequency and role of antiphospholipid antibodies in the pathogenesis of COVID-19-associated thrombosis has not yet been elucidated.

Inhibition of endogenous fibrinolysis levels is also an important factor in the genesis of thrombotic phenomena. Fibrinolytic shutdown (endogenous inhibition of the fibrinolytic system) has been described in severe COVID-19 patients by thromboelastography (TEG) and rotational thromboelastometry (ROTEM). In addition, elevation of plasminogen activator inhibitor 1 (PAI-1), an important factor in the regulation of the fibrinolytic system, has been observed in critically ill patients [19, 20].

Thromboembolic Event Prevention and Management in COVID-19 Pneumonia Patients

In March 2020, during the outbreak of COVID-19 pandemic and its association with severe acute respiratory syndrome (SARS), many complications and organ damage were also observed including the occurrence of macro- and micro-vascular complications.

Even in first disease reports from China, severe clinical state was shown to be associated with a hypercoagulability state [21] and macro/micro-thrombosis observations in post-mortem studies [22]. Since then, several pathways merging platelet hyper-reactivity, complement mediated coagulopathy or endothelial dysfunction were described to be involved [23]. The mechanism seeming to differ from the common disseminated intravascular coagulation description in other type of illnesses [24].

Thromboembolic risk increases in case of overweight, long hospital stay, elevated biological inflammation or severe COVID. Physician should carefully assess each patient risk of developing thromboembolism complication to decide the introduction or not of a prophylactic anticoagulation in comparison to the bleeding risk involved by the use of such therapy.

A recent meta-analysis of 10,367 COVID-19 patients reports a high incidence of pulmonary embolism (PE) (21%) (95% confidence interval [95%CI]: 18–24%; $P < 0.001$) in infected by COVID-19 patients compared with non infected individuals, and an even higher cumulative incidence of PE (26%) in intensive care units (ICU) patients (95%CI: 22–31%; $P < 0.001$), whereas the incidence was lower

(17%) in non ICU patients (95%CI: 14–20%; $P < 0.001$) expected as these patients are less severe. The occurrence of PE was associated with the need of an admission in ICU department.

Prophylactic Anticoagulation in Severe Hospitalized Patients

At the early stage of the pandemic during the first wave, d-dimers elevation was rapidly evoked as a risk factor for severity and mortality [25] and through those preliminary results, some authors recommended at first light of March 2020, the initiation of a thrombophylactic anticoagulation using low molecular weight heparin (LMWH) among the most severe patients with high elevation of d-dimers in order to reduce mortality [26]**.** From then, according to the frequent observation of pulmonary embolism (PE) and deep venous thrombosis (DVT) at this time, many teams started to prescribe intermediate or full dose of parenteral anticoagulation but to this day, the optimal strategy for preventive anticoagulation has not well been defined. Still, clinical practice is defined by more than 30 national and international guidelines mainly following results from observational studies [27]**.** Preventive anticoagulation using prophylactic dosage of Enoxaparin or preventive dosage of Apixaban in COVID-19 was rapidly associated with a better survival [28, 29].

On the other hand, the use of a therapeutic oral direct anticoagulation was not shown to be more effective than preventive parenteral anticoagulation but with an increased risk of bleeding [30]**.**

In the REMAP -CAP, ACTIV-4, and ATTAC trials [31], among critically-ill patients, the use of a therapeutic-dose or intermediate-dose anticoagulation rather than the prophylactic dosage of heparin did not permit to show a greater probability of survival and the study was prematurely stopped for futility. The authors evoked the hypothesis of an impossibility via anticoagulation to slow down the cascade of inflammation in most severe patients explaining the absence of benefice at this stage. This increase in anticoagulation dosage may even lead to 176 more bleeding events for 1000 patients but with a potential biased estimation [32]**.**

Prophylactic Anticoagulation in Mild to Moderate Patients

Most of guidelines actually recommend prophylactic-dose anticoagulation for mild to moderate hospitalized COVID-19 patients without PE or DVT rather the use of therapeutic or intermediate dose given the higher risk of bleeding [33]**,** low rate of PE occurrence and low evidence of survival improvement. The ATTACC, ACTIV-4a, and REMAP-CAP [34] investigators observed that a therapeutic-dose heparin or low-molecular-weight heparin increased the probability of survival until discharge

with a reduced need for organ support compared to routine care. In contrast, *Ortega-Paz* et al. [35] who performed a metanalysis of seven randomized clinical trials including more than 5000 patients, showed that an intermediate-dose anticoagulation was not associated with a reduction of all-cause death (17.8% vs. 18.6%; Risk Ratio [RR] 0.96, 95% Confidence Interval [CI] 0.78–1.18) but with an increase in major bleeding (2.4% vs. 1.4%; RR 1.73, 95%CI 1.15–2.60) compared to the usual prophylactic dosage . There is certainly a possibility for higher doses of anticoagulation among patients with mechanical valve prosthesis, high risk of stroke with atrial fibrillation or repeated clotting of vascular access or circulatory assistance.

There is no high evidence for the use of a specific type of anticoagulation which choice is generally guided by availability, local resources or patient clinical characteristics such as acute kidney failure. Given the relative low strength of evidence, individual assessment remains paramount for each patient. Showing that the subject is still of interest in 2021, more than 50 ongoing RCTs were numbered [36] related to an antithrombotic therapy in hospitalized non-severe patients with COVID-19, but most of them in open-label.

Prophylactic Treatment in Outpatient

Despite important clinical interest due to the large majority of individuals being treated in an outpatient setting, there is a clear lack of evidence concerning the use of anticoagulation or antiplatelets drugs in this COVID-19 patient category without proof of on-going thromboembolic venous event. A dozen of RCT are on-going to assess efficiency of various drugs such as Enoxaparin (ETHIC and OVID trials), DOAC (PREVENT-HD) or Aspirin.

Use of Sulodexide in the SulES-COVID trial [37] among outpatients was associated with a relative reduction of hospital admission or oxygen need but without reduction of mortality because of a high rate of lost to follow-up.

The ACTIV-4B Randomized Clinical Trial in 1:1:1:1 [38] did not show efficacity of Aspirin or Apixaban (2.5 mg or 5 mg twice a day) versus placebo to prevent TE occurrence. To note, the study was stopped shortly after its initiation because of a lower rate of event than expected (<2% in every group) and need to be analysed with caution because of the low statistical power. Given the current lack of strong data, systematic use of prophylactic anticoagulation or anti-platelet agents could not be recommended at this point in the general population unless other indication for therapy. Concerning hospitalized children suffering from COVID-19, actual guidance from the NIH recommend to follow the same strategy as for children without COVID-19 [39] (Fig. 14.2).

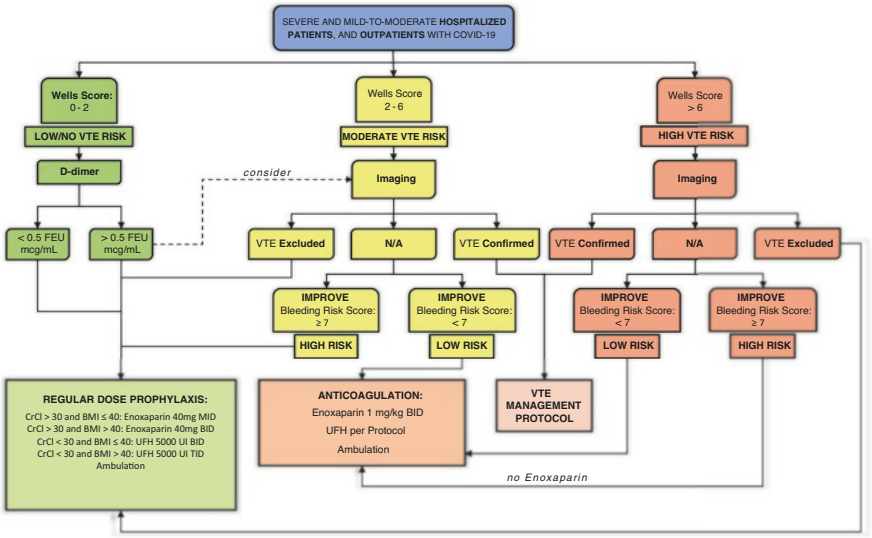

Fig. 14.2 Management of antithrombotic strategy in COVID-19 patients

Anticoagulation After Discharge from COVID-19 Hospitalization

Currently, several scientific societies [40–42] do not routinely recommend the implementation of preventive anticoagulation for COVID-19 patients at discharge from hospital. Individual risk (thromboembolic/bleeding) must carefully be evaluated before considering such treatment after discharge from hospital. Nevertheless, ISTH guidance recommends prophylaxis in all patients who were hospitalized with COVID-19 and meet high-risk VTE criteria such advanced age, ICU admission, active cancer, prior VTE history, thrombophilia, severe immobility or elevated D-dimer.

A Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥ 4 [43] may be a tool to select patients eligible.

The use of Rivaroxaban 10 mg for 31–39 days after discharge among very high-risk patients was approved by the Food Drug Administration (Fig. 14.3).

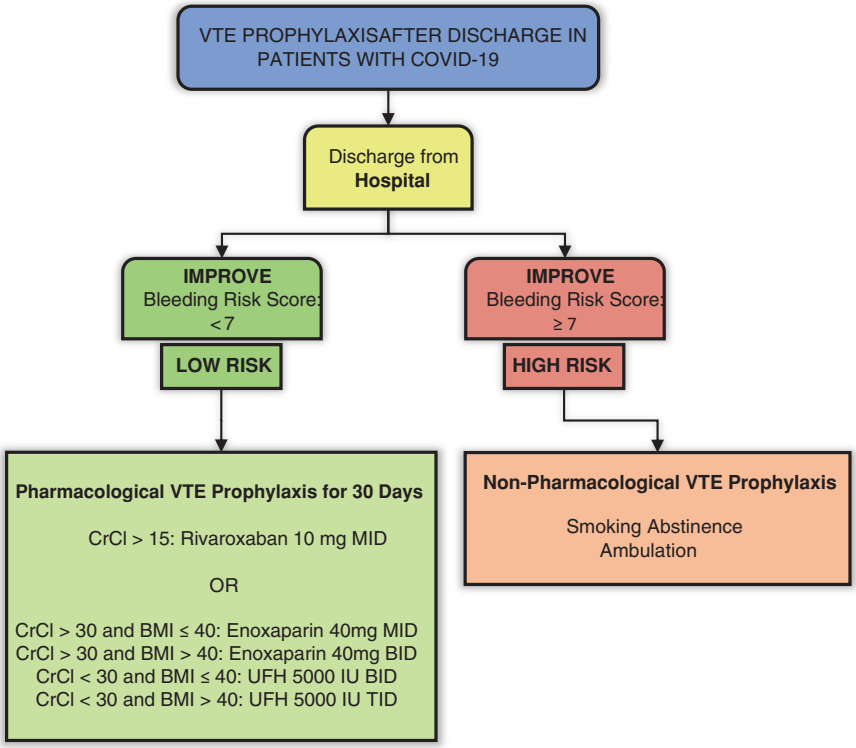

Fig. 14.3 Prophylactic antithrombotic strategy after discharge

Therapeutic Anticoagulation of Incident Thromboembolism Event

In the case scenario of high suspicion of thromboembolic event there is no divergence about the need for therapeutic-dose anticoagulant. Unfractionated heparin (UFH) or LWMH can be prescribed with preference for UFH in case of critically ill patients. NOAC is preferred rather than VKA in absence of contraindication after hospital discharge [41].

Duration of treatment is recommended to be similar to common guidance concerning established pulmonary embolism. The ISTH [44] makes a 3-month anticoagulant recommendation for provoked thromboembolic event in context of COVID-19 pneumonia.

Therapeutic anticoagulant is one of the tools to partially counteract the dramatical coagulopathy with underlying inflammatory storm.

Medium- and Long-Term Prognosis After a Venous Thrombotic Event

A large national Sweden database has evaluated the relative risk in infected patients. Authors analysed the occurrence of deep vein thrombosis (DVT), PE, and major bleeding under treatment in COVID-19 individuals during a control period (before and long after COVID-19 diagnosis) and compared it to the rates in different time intervals after covid-19 diagnosis (days 1–7, 8–14, 15–30, 31–60, 61–90, and 91–180).

Rates of DVT, PE, and bleeding events also were evaluated from day 1 to day 30 post-COVID-19 diagnosis and compared to the events in the control group, composed by peers non-infected by COVID-19.

They reported an increased risk after COVID-19 infection for DVT until day 90, for PE until day 180, and until day 60 for bleeding, obviously depending on the dose and anticoagulant duration, as well as on the global frailty and comorbidities of the patients.

After statistical adjustments for potential biases, the relative risk for DVT was 5, multiplicated by 33 for PE, and a RR of 1.9 for bleeding at day 30.

The higher was the severity of the infection by COVID-19, the higher was the prevalence of thrombotic events (DVT and PE).

COVID-19 therefore is an independent risk factor for DVT, PE, and bleeding, with a persistent risk after the initial infection until 3–6 months for venous thrombotic events, and mainly during the first 60 days for bleeding (related to anticoagulation treatments). Another major study reports PE does not increase the mortality of COVID-19 patients, even if the total mortality was higher in COVID-19 compared with non-COVID-19 patients with PE, probably reflecting a major global frailty of these infected patients.

Perspectives: Ongoing trials aim to better determine the optimal strategy in terms of detection, antithrombotic prophylaxy in high-risk patients, and the preferred curative treatment in terms of choice of drugs, dosage(s), and duration.

Conclusion

COVID-19 infection is associated with an increased risk of deep venous thrombosis and pulmonary embolism. The prevalence is higher in severe clinical forms and ICU patients, even with a prophylactic coagulation. Ongoing research is investigated the optimal risk assessment of thrombotic events and the best personalized preventive antithrombotic therapy.

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Chapter 15
Interaction of Anti-COVID-19 Drugs with Cardiovascular Therapy

Leskovar Dunja, Pećin Ivan, and Reiner Željko

In recent years, the world has been facing a major pandemic of the COVID-19 caused by virus called SARS-CoV-2, an infection of which at the beginning we did not know much about. Guidelines have been constantly changing with the development of new vaccines and antiviral drugs. In an emergency of trying to prevent a cytokine storm and an unfavorable outcome of the infection, the interaction with concomitant therapy was often not considered. Due to the different outcomes of patients treated with the same therapy, the possible interaction of drugs gradually began to be widely considered.

Cardiovascular drugs are the most widely used drugs in the world for secondary and primary prevention as well as treatment of cardiovascular diseases (CVD). In addition to targeted effects on blood pressure, heart rate, levels of blood cholesterol, etc., cardiovascular drugs have other secondary, immunomodulatory, and pleiotropic effects that may interfere with other drugs, especially antiviral drugs. In this chapter, we have summarized the most important interactions between some most widely used cardiovascular drug groups and COVID-19 therapy, their benefits and potential adverse effects.

Our focus is based on antiviral and immunomodulatory therapy (corticosteroids, IL-6 and JAK inhibitors, monoclonal antibodies) used in the treatment of COVID-19.

Statins

Statins are drugs that reduce cholesterol levels by inhibiting 3-hydroxy-3methylgultaryl-coenzyme A (HMG-CoA) reductase in the liver cells and are some of the most prescribed drugs worldwide today. They have numerous pleiotropic effects

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including positive effect on the function of vascular endothelium, stabilization of atherosclerotic plaque, anti-inflammatory and anti-proliferative effects. They reduce tissue factor (TF) expression, synthesis of thrombin and platelet activation. Therefore, they have a strong anticoagulant effect [1]. Statins have also immunomodulating role on differentiation, proliferation, and secretion of immune cells (macrophages, lymphocytes T) and a strong anti-inflammatory effect reducing serum C-reactive protein (CRP), tumor necrosis factor α (TNF-α), as well as interleukins 1 and 6 (IL-1, IL-6) [2]. In addition to these effects, it is not surprising that the role of statins became important in COVID-19 which is characterized by cytokine storm and prothrombogenic effect. Studies have shown a significant reduction in the mortality of patients with COVID-19 who were on statin therapy [3–5]. The first indication that statins might have also a direct beneficial effect on SARS-CoV-2 viruses by inhibiting SARS-CoV-2 main protease was published already at the beginning of the 2020 [6].

Statins are mostly metabolized in the liver by CYP3A4, but also to a lesser extent by CYP2C9, CYP2C8, and CYP2D6. The most common adverse effects include muscle pain, and very rarely in severe cases rhabdomyolysis, and even more rarely acute liver and kidney injury [7]. Therefore, statins are contraindicated in the severe form of COVID-19 which is unfortunately often seen in this pandemic. Even in moderate COVID-19 disease, sometimes severe liver lesions often occur in which cases statins should be discontinued despite their beneficial effects.

During therapy with antiviral agents, such as remdesivir (inhibitor of RNA-dependent RNA polymerase), the dose of statins needs to be adjusted with frequently monitoring of hepatic and renal function. Remdesivir is an inhibitor of CYP3A4 enzyme and therefore it might increase the toxicity of drugs such as statins that are metabolized by this enzyme [8]. Based on clinical studies, it is recommended to reduce the dosage of rosuvastatin and atorvastatin on the lowest possible and often monitor liver enzymes and creatine kinase levels. Lovastatin and simvastatin should be avoided when using remdesivir, and the dosage of atorvastatin or rosuvastatin should not exceed 20 mg/day.

Tocilizumab, a humanized monoclonal antibody that inhibits interleukin 6 receptor α, is indicated in the severe form of COVID-19 (worsening of the clinical condition, progression of hypoxemia, hypercytokinemia). Many studies have shown that the use of tocilizumab adversely affects the lipid profile, i.e. it increases the concentration of total cholesterol, LDL-cholesterol, and triglycerides which further increases cardiovascular risk and the chance thromboembolic events in COVID-19 [9]. Also, studies have shown that concomitant statin therapy reduces the shift in lipid profile during tocilizumab therapy without the risk of major adverse events [10]. Nevertheless, it is important to emphasize that regular monitoring of liver enzymes is necessary, and if ten-fold increase in liver transaminases occurs, tocilizumab is contraindicated.

Corticosteroids (dexamethasone, prednisone, prednisolone, and methylprednisolone) are the basic therapy in preventing cytokine storm during COVID-19. They have strong anti-inflammatory and immunomodulatory effects and act synergistically with statins.

Nevertheless, corticosteroids are inducers of CYP3A4 enzymes. Therefore, the potential toxicity of statins should be monitored.

According to some studies, statin therapy is not contraindicated with the use of monoclonal antibodies such as casirivimab/imdevimab combination or monotherapy with regdanvimab and sotrovimab.

β-Blockers

The cardioprotective effect of β-blockers in COVID-19 is well known. Numerous studies have shown a beneficial effect on sympathetic and cytokine storms that endanger patients mostly [11]. The main beneficial effects include reduction of sympathetic stimulation, pro-inflammatory cytokines, cardiac arrhythmia and cardiac injury. Non-selective β-blockers appear to be more effective due to inhibition of excessive immune response via β2-adrenoreceptors expressed in the airways. On the other hand, selective β-blockers have less adverse effects including bronchospasm and peripheral vasoconstriction. The metabolism of β-blockers depends on the pathway of elimination. Lipophilic β-blockers are completely metabolized by liver, especially by CYP2D6 enzymes. Therefore, slow metabolizers can result in adverse events. Hydrophilic β-blockers (atenolol, bisoprolol, nadolol, and sotalol) are eliminated by kidneys, dependent on glomerular filtration. In acute kidney injury the dosage of the drug should be reduced because of an increased risk of adverse effects.

According to current guidelines and available literature, the use of tocilizumab with beta-blockers during COVID-19 infection is not contraindicated and no interactions have been described. Nevertheless, there are studies on rheumatoid arthritis that indicate a reduced chance of remission with concomitant use of tocilizumab and β-blockers. The proposed mechanism is via β1adrenergic-receptor which inhibit the migration of innate immune cells [12]. In these studies, patients predominantly used selective β-blockers, so further studies are needed to confirm these hypotheses and potential interactions between tocilizumab and β-blockers.

Remdesivir is extensively metabolized by CYP2C8, CYP2D6, and CYP3A4. Therefore, greater caution is required when co-administered with β-lockers [13]. Metoprolol, carvedilol, and bisoprolol are metabolized by CYP2D6 which is highly polymorphic causing different phenotypes of metabolizer. Studies show that 20% of European and 40% of Asian patients have functional polymorphism of CYP2D6 resulting in decreased function and β-blockers intolerance (hypotension, bradycardia, and bronchospasm) [14]. Therefore, dose reduction or discontinuation of therapy should be considered in patients with these adverse events. Despite this, large multicenter studies have not found an association between severe bradycardia and concomitant use of remdesivir and beta-blockers in hospitalized patients with COVID-19 [15]. On the other side, there is a potentially harmful interaction between atazanavir and β-blockers (propranolol, atenolol) due to an additive PR interval prolongation resulting in irregular heart rhythm. Therefore, concomitant use of these two drugs is contraindicated [16].

The synergistic beneficial effect of corticosteroids and β-blockers against cytokine storm is well known, but caution should be advised with prolonged usage of corticosteroids since worsening of arterial hypertension may occur. This effect is described when using prednisone with propranolol since corticosteroids are involved in regulating balance of water and sodium in the body. Nevertheless, β-blocker therapy should not be discontinued because of its strong cardioprotective effect.

Antihypertensive Drugs

Arterial hypertension is one of the most common chronic diseases in the world. The consequences of this disease greatly reduce the quality of life and contribute to an increase in cardiovascular and overall mortality. This is especially important in the era of COVID-19 since studies have shown an association between greater need for ventilatory support in patients with severe COVID-19 infection with arterial hypertension as co-morbidity [17]. According to current guidelines, the first line drugs for arterial hypertension are inhibitors of renin-angiotensin system (RAS): angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) [18]. Clinical studies in the beginning of COVID-19 pandemic indicated an association between SARS-CoV-2 virus and angiotensin-converting enzyme 2 (ACE2), expressed on the surface of alveolar cells in the lungs, suggesting a crucial role of the enzyme for entrance and replication of virus in the cells. This was based upon evidence that ACE2 might be potential cellular receptor for coronavirus spike protein (S-protein). Several in vitro studies have shown an increase in ACE2 levels when using ACEi or ARB. Therefore, there was a great concern about the use of these antihypertensive drugs in COVID-19 patients [19]. Fortunately, a significant number of clinical studies during COVID-19 pandemic excluded the possibility that renin-angiotensin system (RAS)-blocking drugs might increase the level of ACE2 expression in humans [20]. On the contrary, a beneficial therapeutic effect of inhibiting the RAS cascade, a target of ACE2, in patients with COVID-19 and CVD has been suggested [21].

Nevertheless, the discovery of new drugs against COVID-19 has opened up the possibility of drug–drug interaction which potentially could endanger patient's health. This is especially important for the antihypertensive drugs since antihypertensives from several groups are often taken at the same time (fixed combination of RAS-blockers and calcium channel blockers or diuretics).

Clinical studies show that corticosteroids (especially dexamethasone) interact with all groups of antihypertensive drugs, reducing their antihypertensive effect due to their effect on water and sodium balance. Since corticosteroids are the first line treatment for the severe COVID-19, blood pressure needs to be measured more frequently to prevent hypertensive crises. In hypertensive crises during COVID-19 the use of strong vasodilators (e.g., nitroprusside) is recommended.

Although most antihypertensives do not show interactions with antiviral drugs, some interactions have been described. Combining calcium channel blocker

(amlodipine) with antiviral drug atazanavir could prolong PR interval resulting in arrhythmia and cardiotoxicity.

Caution should also be exercised when using nirmatrelvir/ritonavir with amlodipine since these drugs enhance plasma amlodipine concentration resulting with hypotension [22]. So far, the interaction between remdesivir and antihypertensive drugs is not described. Therefore, remdesivir can be used in patients with severe arterial hypertension.

Most monoclonal antibodies against COVID-19 infection do not interact with antihypertensive drugs and therefore their use is safe. These are casirivimab/imdevimab, etesevimab/bamlanivimab, and sotrovimab approved by Food and Drug Administration (FDA). Tocilizumab, on the other hand, interferes with amlodipine by affecting the drug-metabolizing enzymes like CYP3A4 whose substrate is amlodipine [23].

With the development of new drugs targeting the SARS-CoV-2 virus, possible interactions with concomitant therapy, especially cardiovascular drugs, need to be considered. Cardiovascular drugs should be able to be administered in full dose even in the severe forms of COVID-19 because the disease itself increases cardiovascular risk. Therefore, the development of new anti-COVID19 drugs that do not interact with concomitant therapy would be a step further in the fight against this pandemic.

Natural Drugs

It must be mentioned that some natural products might be effective against SARS-CoV-2 since it is known that some dietary supplements, including black seeds, garlic, ginger, cranberry, orange, omega-3 and -6 polyunsaturated fatty acids, vitamins (e.g., A, B vitamins, C, D, E), and minerals (e.g., Cu, Fe, Mg, Mn, Na, Se, and Zn) have antiviral effects. Therefore, they might be used as adjuvant therapy together with antiviral medicines in the management of COVID-19 disease, particularly in patients with CVD, but more clinical studies are needed to prove beneficial effect [24, 25]. Since they were not thoroughly studied in combination with anti-COVID-19 drugs, not much is known about possible interactions between them.

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Part III
Influence of the Treatment of Cardiovascular Diseases on the Course of COVID-19

Chapter 16
Beyond the Vaccines-Bioactive Lipids in COVID-19

Undurti N. Das

Introduction

The current pandemic of COVID-19 caused by SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2), an enveloped virus, enters the cells using its spike proteins (see Fig. 16.1 for the structure of the virus) that can latch on to angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2). Even though effective vaccines have been developed against SARS-CoV-2, the emergence of several mutant strains of the virus rendered these vaccines less effective (see Figs. 16.2 and 16.3 for the life cycle of SARS-CoV-2 virus and the function of various vaccines and monoclonal antibodies used to inactivate it). This suggests that non-conventional methods of inactivating the virus are needed to stem the pandemic not only at present but also in the future. At this juncture, it is pertinent to note that certain polyunsaturated fatty acids (PUFAs) have the unique ability to inactivate many enveloped viruses that could be exploited to prevent and manage not only COVID-19 but several other similar infections.

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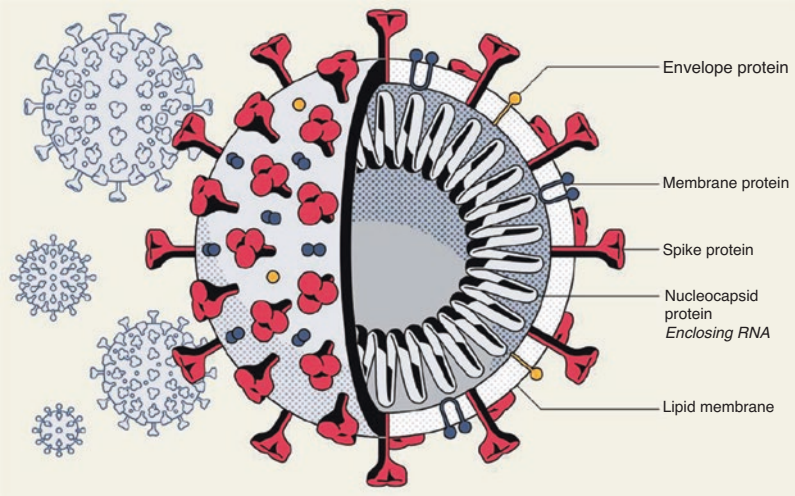

Fig. 16.1 Structure of SARS-CoV-2 that causes COVID-19

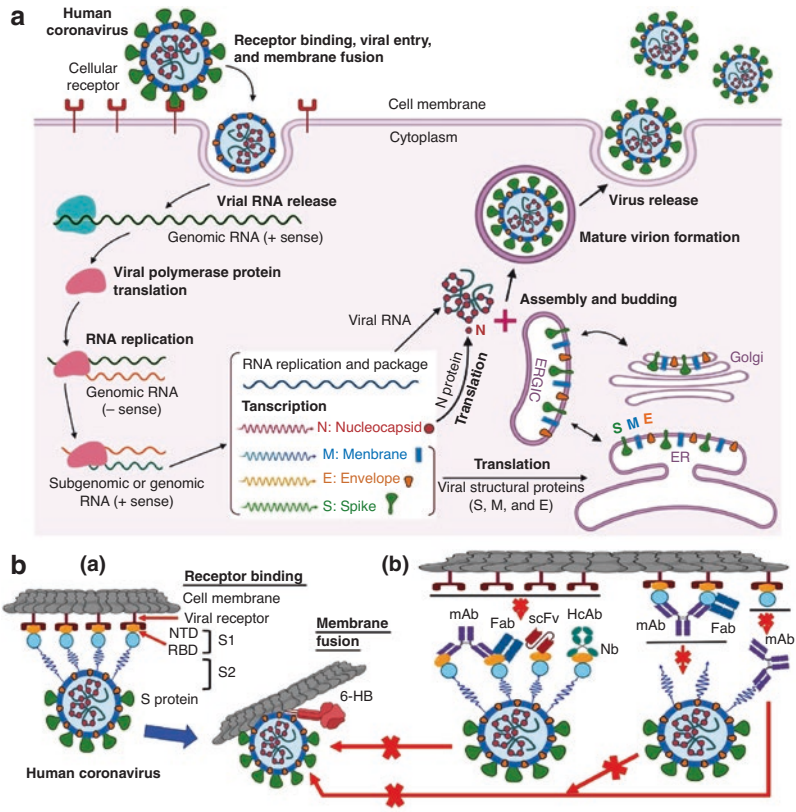

Fig. 16.2 Scheme showing the lifecycle of SARS-CoV-2 and the function of various monoclonal antibodies as to how they neutralize the virus

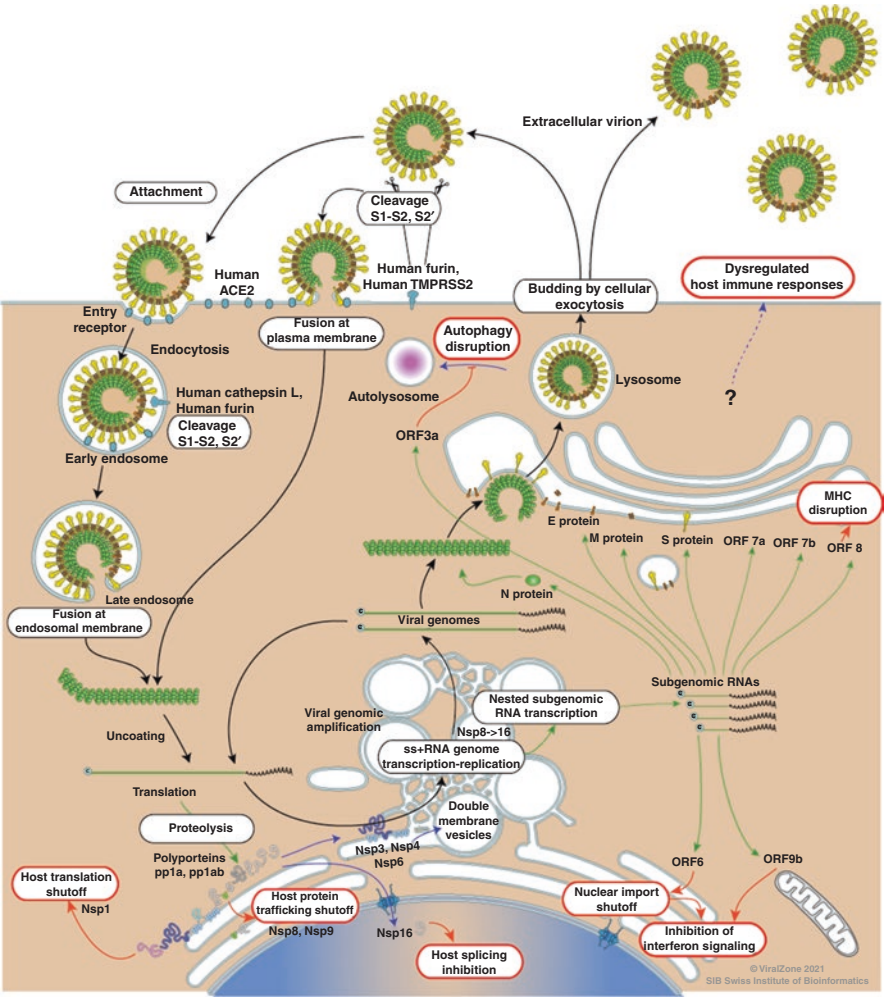

Fig. 16.3 Scheme showing the mechanism(s) by which SARS-CoV-2 infects the cells and survives

Bioactive Lipids LA and AA Can Inactivate SARS-CoV-2

Several studies suggest that (a) arachidonic acid (AA) and linoleic acid (LA) can inactivate several microbes including SARS-CoV-2 [1–13]; (b) polyunsaturated fatty acids (PUFAs) and their metabolites inhibit inappropriate synthesis and secretion of pro-inflammatory interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and HMGB1 (high mobility group box-1) [14–19] that are believed to have a role in cytokine storm seen in those with serious COVID-19 as characterized by cardiovascular dysfunction and ARDS (acute respiratory distress syndrome); (c) PUFAs and their metabolites including prostaglandins, lipoxins, resolvins, protectins, and

maresins facilitate and regulate M1 and M2 macrophages generation that are needed for inducing timely and appropriate inflammation and its subsequent resolution in an orderly fashion to reestablish homeostasis [14, 20–31]; (d) PUFAs and their metabolites mediate and regulate the actions of interferons (IFNs) that are needed for protection against viral infections [14, 32–38]; (e) AA forms precursors to pro-inflammatory prostaglandin E2 (PGE2) and potent anti-inflammatory lipoxin A4 (LXA4) that are needed to induce inflammation and its resolution, respectively, and mitigate cytokine storm and enhance tissue regeneration; and finally (f) co-morbid conditions that are known to enhance mortality due to COVID-19 such as type 2 diabetes mellitus, hypertension, and cardiovascular diseases (especially ischemic heart disease) are associated with low plasma and tissue concentrations of AA and LXA4 [11]. Based on these observations, it is reasonable to suggest that administration of LA and AA and co-factors associated with their metabolism are likely to be of significant benefit in the prevention and management of COVID-19 (see Fig. 16.4 for the metabolism of essential fatty acids, EFAs).

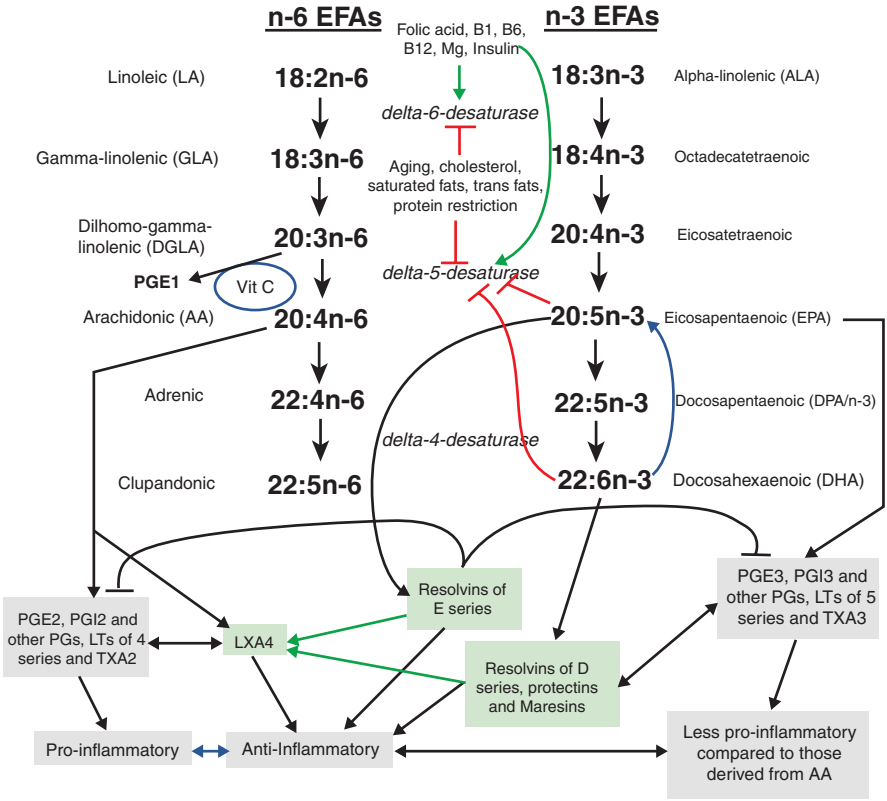

Fig. 16.4 Metabolism of essential fatty acids

Investigations revealed that unsaturated fatty acids linoleic acid (LA, 18:2 n-6), gamma-linolenic acid (GLA, 18:3 n-6), dihomo-GLA (DGLA, 20:3 n-6), arachidonic acid (AA, 20:4 n-6), alpha-linolenic acid (ALA, 18:3 n-3), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3) have the unique ability to inactivate gram-positive and gram-negative bacteria, fungi, and enveloped viruses including but not limited to influenza, hepatitis B virus (HBV), and hepatitis C virus (HCV) [1–13]. Further studies revealed that fatty acids disrupt microbial cell membrane integrity, interfere with microbial metabolic processes including respiratory activity, and uncouple their oxidative phosphorylation because of which microbes become inactive and unable to proliferate and infect tissues. In this context, It is noteworthy that alveolar macrophages, leukocytes, T and B cells, NK cells, and other immunocytes release AA and other unsaturated fatty acids to inactivate microbes that may include SARS-CoV-2 and other similar viruses. It is likely that release of unsaturated fatty acids may form an important aspect of human innate immune response [39–49]. These results imply that release of adequate amounts of unsaturated fatty acids, especially LA and AA, may inactivate SARS-CoV-2 and prevent or suppress COVID-19 [9, 10, 12, 13] for which supplementation or administration of these fatty acids may be necessary.

Toelzer et al. [12] showed that the receptor binding domains (RBDs) of SARS-CoV-2 virus tightly bind LA (and possibly other fatty acids especially AA) in three composite binding pockets that are present in the highly pathogenic SARS-CoV and MERS-CoV. The binding of LA stabilizes a locked S conformation resulting in reduced ACE2 interaction. Furthermore, LA supplementation in combination with remdesivir suppressed SARS-CoV-2 replication, suggesting that intervention strategies could be developed using these fatty acids (see Figs. 16.5 and 16.6). SARS-CoV-2 infected cells release high amounts of AA that, in turn, can inactivate the virus. These results imply that in conditions of AA deficiency (subjects with obesity, hypertension, diabetes mellitus, and coronary heart disease are deficient in AA) the inactivation of SARS-CoV-2 is defective and this renders the cells more susceptible to infection by SARS-CoV-2 and other similar viruses ([13], see Figs. 16.5, 16.6, and 16.7).

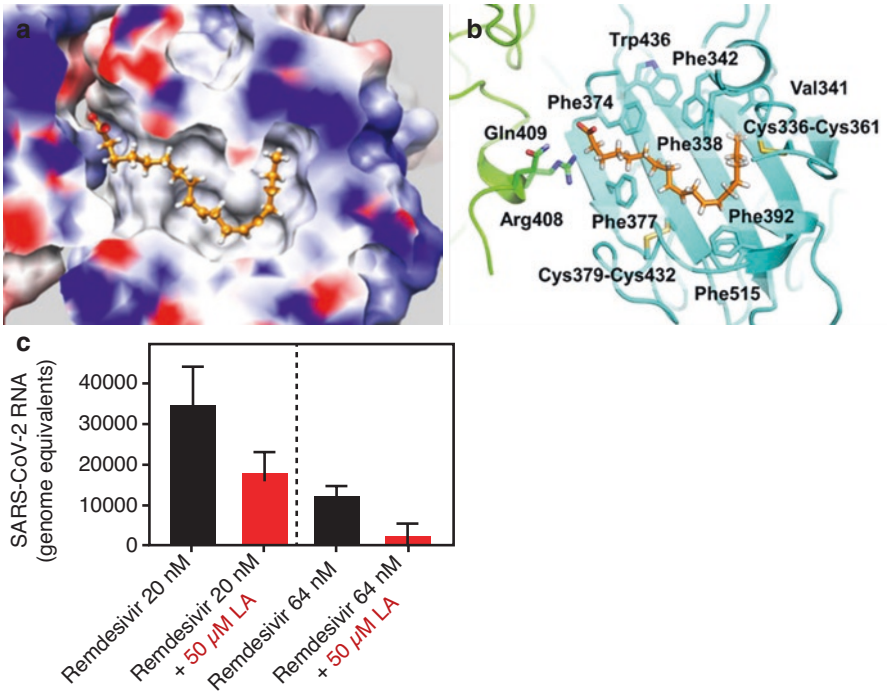

Fig. 16.5 Cryo-EM structure of SARS-CoV-2 spike linoleic acid complex. (**a**) Hydrophobic LA-binding pocket in a surface representation illustrating excellent fit of bound LA. (**b**) LA interactions with amino acids in the binding pocket. The acidic LA headgroup is in the vicinity of an arginine (408) and a glutamine (409) (This data is taken from Ref. 12). (**c**) The amount of extracellular virus ($n = 3$) at the dose combinations shown was determined by qRT-PCR (This data is taken from Ref. 12). Synergistic effect of LA and remdesivir on SARS-CoV-2 viral replication. Effects of varying doses of remdesivir ±50 μM LA on virus infection are shown. Human Caco-2 ACE2+ cells were infected with SARS-CoV-2 and then treated with varying doses of remdesivir ±50 μM LA

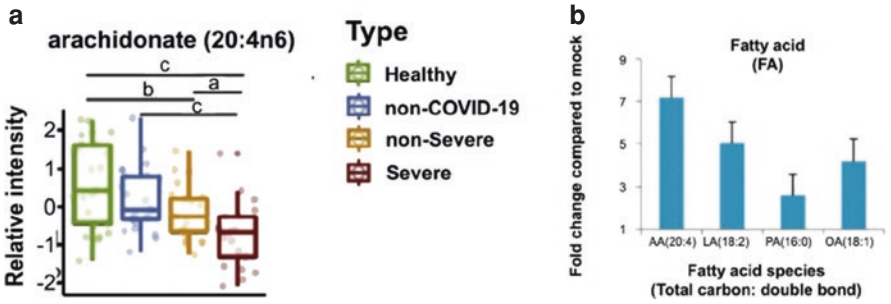

Fig. 16.6 (**a**) Plasma levels of AA in those infected with SARS-CoV-2. These results show that those infected with the virus have low levels of AA. (**b**) Analysis of HCoV-229E-infected cells (this virus is a close cousin of SARS-CoV-2 and is used to study the effects of SARS-CoV-2 on cells in vitro) revealed a change in lipid levels. Huh-7 cells infected with HCoV-229E released high amounts of AA suggesting a role for this lipid in the pathobiology of COVID-19. AA, arachidonic acid; LA, linoleic acid; PA, palmitic acid; OA, oleic acid. $^{a, b, c}P < 0.05$ compared to respective controls as shown in the figure (This data is taken from Ref. 13)

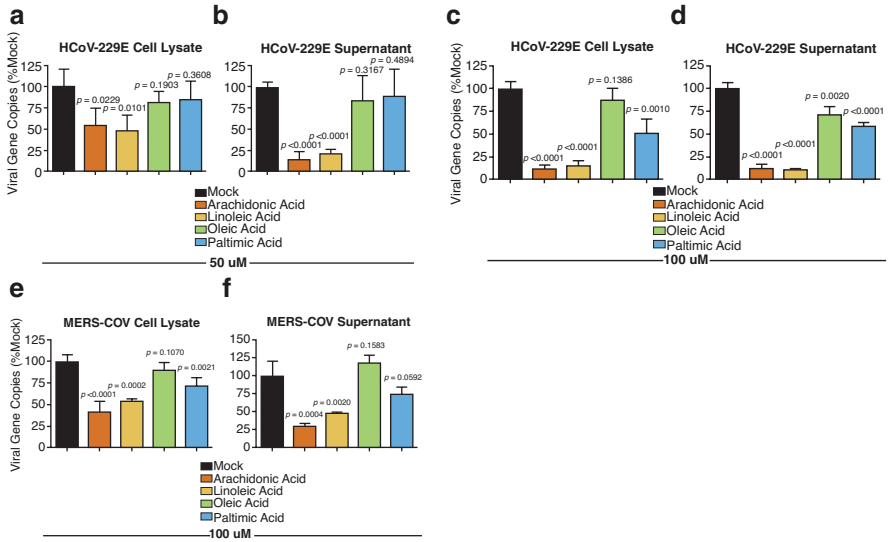

Fig. 16.7 Ability of LA and AA and other fatty acids to inactivate HCoV-229E and MERS-CoV viruses. HuH-7 cells were infected with HCoV-229E or MERS-CoV viruses. After 1 h of inoculation with the virus, the cells were treated with 50 or 100 uM of fatty acids for 24 h. Both supernatant and cell lysates were collected and analyzed by RT-qPCR technique. $P < 0.05$ (This data is taken from Ref. 13)

Immunocytes and AA

Humans are constantly exposed to various microbes through inhaled air. Hence, efficient alveolar macrophages are needed to protect from various microbial infections. Cytokine-activated macrophages release LA, GLA, and AA that are capable of inactivating various bacteria, viruses, and fungi [1–13]. This suggests that macrophages and other cells need to secrete adequate amounts of various PUFAs to prevent respiratory infections.

In this context, it is noteworthy that NK cells, cytotoxic tumor lymphocytes: CTL (cytotoxic lymphocyte) cells, lymphokine activated killer cells, dendritic cells, and leukocytes, in general, release perforin and granzyme, IL-6, TNF-α, and IFN-γ to eliminate infected and cancer cells. But NK cells and CTLs kill tumor cells even in the absence of perforin and granzyme by augmenting the expression of soluble PLA2 (sPLA2) that induces the release of AA and other fatty acids [41–49] from the cell membrane lipid pool. These unsaturated fatty acids also form a constitutive component of cytolytic granules of CTL, NK, and γδT cells [49] that seem to induce apoptosis of tumor cells [46]. This emphasizes the importance of PLA2 and other phospholipases and their action to induce the release of unsaturated fatty acids and their cytolytic action on microbes, microbe-harboring cells, and cancer cells.

It is noteworthy that macrophages and tissue-resident memory CD8+ T cells interact and cooperate with each other to sense pathogens, eliminate them and thus, protect the tissues from microbial infection including SARS-CoV-2 [50]. These resident memory T cells are dependent on and need fatty acids for their survival and function and, in turn, transport specific fatty acids to the T cells by employing the specific fatty acid binding proteins (FABPs). It is interesting to note that the type of FABPs expressed by the T cells depends on the tissue in which they are resident that, in turn, is determined by tissue-derived factors. To meet the fatty acid demands of the tissue-resident memory T cells (and possibly other immunocytes including macrophages), the immunocytes modify their FABPs expression depending on the tissue in which they are located [51], suggesting that each tissue and their resident memory T cells and macrophages need unsaturated fatty acids not only for their survival but also to bring about their specific action(s) that is tailored to their location as dictated by the local milieu. These results [50, 51] imply that each tissue or cell needs very specific fatty acids that is met by specific FABPs. The need for such specific fatty acids and their respective FABPs suggests that each cell/tissue has some very specific requirement of fatty acids that is dictated by their function and milieu, which could include their exposure to specific microbes and their participation/role in inflammation and its resolution.

M1 and M2 Macrophages and Lipids

Macrophages that are needed to kill various microbes and clear the debris during the resolution of inflammation and infection are of two types: M1 and M2. M1 type are pro-inflammatory in nature whereas M2 type are anti-inflammatory. M1 kill the invading microbes including SARS-CoV2, whereas M2 resolve inflammation and restore homeostasis (see Fig. 16.8). PGE2 and leukotrienes (LTs) derived from AA facilitate the generation of M1 macrophages and they, in turn, release pro-inflammatory PGE2 and LTs. On the other hand, the generation of M2 macrophages is facilitated by anti-inflammatory cytokines IL-4 and IL-13 and lipoxin A4 (LXA4) (which is derived from AA), resolvins from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and protectins and maresins from DHA [14–20]. Hence, availability of adequate amounts of DGLA, AA, EPA, and DHA is essential (from which PGE1, PGE2, LXA4, resolvins, protectins, and maresins are derived) for the smooth transition from pro-inflammatory events to resolution of inflammation and restoration of homeostasis (see Fig. 16.8).

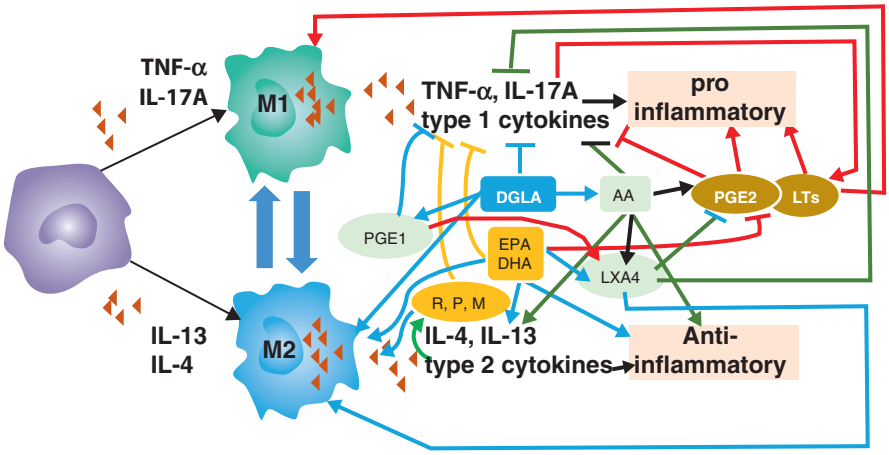

Fig. 16.8 Scheme showing the function of M1 and M2 macrophages and various cytokines secreted by them and their respective actions. DGLA, AA, EPA, and DHA have anti-inflammatory actions and inhibit the production of pro-inflammatory TNF-α, IL-2, and IL-1 and facilitate the generation of M2 macrophages. PGE1 formed from DGLA, LXA4 from AA are anti-inflammatory in nature. Resolvins (R), protectins (P), and maresins (M) formed from EPA and DHA are anti-inflammatory and block the production of TNF, IL-1, IL-2. PGE2, Leukotrienes B4, D4, and E4 formed from AA are pro-inflammatory in nature. LXA4, resolvins, protectins, and maresins inhibit the production of PGE2 and LTs. PGE2 can initiate the production of LXA4 from AA. Leukotrienes (of 5 series) are also formed from EPA that have pro-inflammatory action but are much less potent compared to LTs formed from AA. EPA and DHA inhibit the production of PGE2

Interaction(s) Among Desaturases, COX, LOX, n-3, and n-6 Fatty Acids and Their Metabolites and Cytokines

Pro-inflammatory cytokines TNF-α and IL-6 block the activities of desaturases which are needed for the conversion of dietary LA and ALA to their respective long-chain metabolites AA and EPA and DHA, respectively (see Figs. 16.2, [52]). Because of this, GLA, DGLA, AA, EPA, and DHA deficiency occurs leading to reduced generation of LXA4, resolvins, protectins, and maresins that inhibit IL-6 and TNF-α formation. This crosstalk between cytokines and various PUFAs and their metabolites is needed for optimizing the inflammatory process and its orderly resolution and re-establishing homeostasis after injury and infection. Hence, in instances wherein there is a deficiency of DGLA, AA, EPA and DHA excess generation of IL-6 and TNF-α occurs that results in cytokine storm as seen severe COVID-19 patients. This excess production of pro-inflammatory cytokines may at least, in part, is due to deficiency of GLA, DGLA, AA, EPA, DHA, LXA4, resolvins, protectins, and maresins (reviewed in [14]). In this context, the relationship between PGE1/PGE2 and LXA4 is interesting. During the process of inflammation, local tissue concentration of PGE2 need to reach its optimum levels so that PGE2 can trigger the generation of LXA4 (both PGE2 and LXA4 are derived from AA and LXA4 is an anti-inflammatory molecule whereas PGE2 is pro-inflammatory in nature) so that resolution of inflammation is initiated. Thus, local concentrations of PGE2 are critical to trigger the anti-inflammatory process. Like PGE2, even PGE1, derived from DGLA, also triggers the generation of LXA4 but is less effective compared to PGE2 (see Figs. 16.9, [53]). These results emphasize the crosstalk between DGLA/AA and PGE1/PGE2/LXA4 and how the inflammatory process is

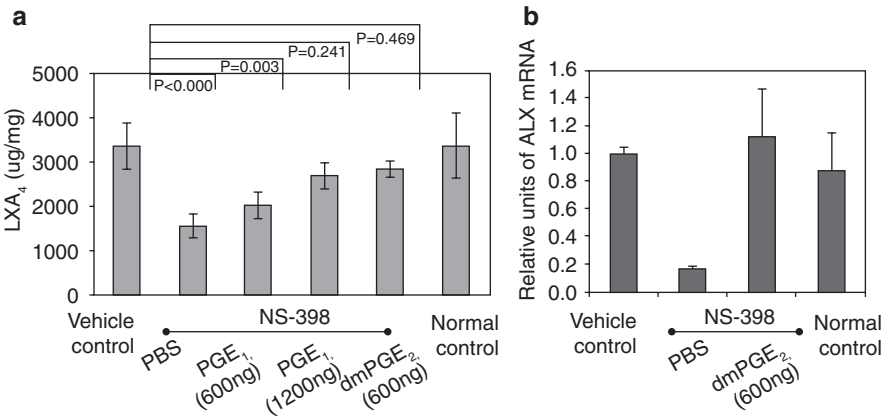

Fig. 16.9 Effect of various concentrations of PGE1 and PGE2 on the generation of LXA4. The result of this study shows that though both PGE1 and PGE2 can augment LXA4 generation from AA, PGE2 is more potent compared to PGE1 in inducing the generation of LXA4 from AA (This data is taken from Ref. 54)

interwoven with the anti-inflammatory events. Based on these evidences, it is reasonable to suggest that the activities of Δ^5 desaturase (that is needed for the conversion of DGLA, the precursor of PGE1, to AA, the precursor of PGE2 and LXA4) is critical to both inflammation and its resolution. Thus, it can be said that decreased activity of Δ^5 desaturase may hamper resolution of inflammation since its (Δ^5 desaturase) deficiency/low activity results in decreased formation of AA and consequently insufficient generation of PGE2 and LXA4 could occur (see Fig. 16.4 for the metabolism of essential fatty acids). It is also important to note that both IL-6 and TNF-α can also suppress Δ^6 desaturase activity that is needed for the conversion of dietary LA and ALA to their respective long-chain metabolites GLA and 18:4 n-3 (octadecatetraenoic acid) that are needed for the formation of AA and EPA, the precursors of LXA4 and resolvins. Thus, it is likely that the activity of Δ^6 desaturase is as important as that of Δ^5 in the pathobiology of inflammation and its resolution. Since IL-6 and TNF suppress desaturases activity and in turn, their products (desaturases) GLA, DGLA, AA, EPA, and DHA (and their metabolites LXA4, resolvins, protectins, and maresins) suppress the production of IL-6 and TNF, it is imperative that a delicate balance is maintained between and among them in order to regulate inflammation and its resolution (see Figs. 16.4, 16.8, 16.9, and 16.10). In addition, both EPA and DHA inhibit the activity of Δ^5 desaturase that can also lead to decreased formation of AA. This implies that increased intake of EPA and DHA may, in fact, lead to decreased formation of AA (EPA and DHA can also displace AA from the cell membrane lipid pool) and so a deficiency of LXA4 could occur. It is interesting to note that EPA and DHA are the precursors of resolvins, protectins, and maresins that have anti-inflammatory actions like LXA4. But there is evidence to suggest that resolvins, protectins, and maresins bring about their actions, at last in part, by enhancing the formation of LXA4 (see Fig. 16.10 and Refs. 54 and 55). It is evident from the data shown in Fig. 16.10 that LXA4 suppresses the production of IL-6 and TNF-α and its (LXA4) synthesis and secretion is enhanced by resolvins D and E, which are derived from EPA and DHA respectively [54, 55]. These results imply that both EPA and DHA derived products (resolvin E is derived from EPA whereas resolvin D is derived from DHA, respectively) including but not limited to resolvins, protectins, and maresins bring about their anti-inflammatory actions at least, in part, by enhancing the production of LXA4 from AA. This once again emphasizes the close interaction among EPA, DHA, and AA and their respective metabolites. In addition, it was observed by us that LXA4 is more potent than resolvins and protectins in suppressing STZ-induced diabetes mellitus in experimental animals and is more potent than resolvins and protectins (and possibly, maresins) in suppressing IL-6 and TNF-α generation ([55, 56], and unpublished data). Based on these results, it is reasonable to propose that LXA4, resolvins, protectins, and maresins possess anti-inflammatory actions but their degree of effectiveness differ with LXA4 being the most potent (LXA4 > resolvins ≥ protectins ≥ maresins) and resolvins, protectins, and maresins bring about their anti-inflammatory action to some extent by enhancing LXA4 formation. Thus, there is a very intricate and delicate positive and negative interaction(s) among n-6 and n-3 fatty acids and their metabolites and enzymes

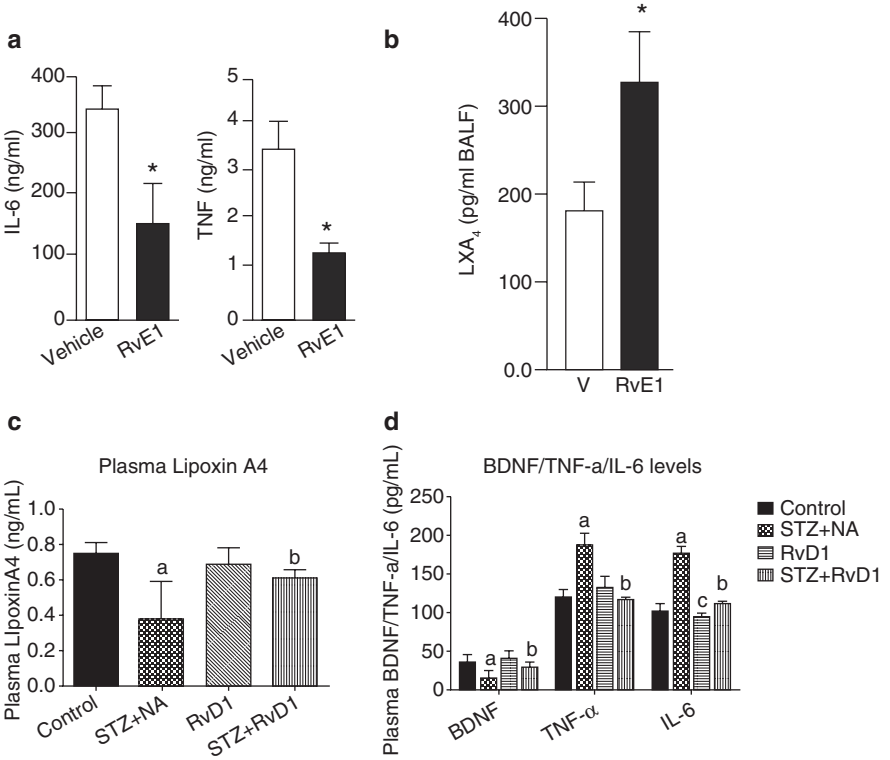

Fig. 16.10 (a) Effect of resolvin E1 on IL-6 and TNF-α levels and LXA4 formation (from Ref. 54). $^{*}P < 0.05$ compared to vehicle (V). In this study, the animals received 50 or 100 ng/day intravenously. (**b**) Effect of PGE1 on the geenration of LXA4. It is evident that PGE1 is less potent compared to PGE2 in inducing the generation of LXA4. Fig. 16.11. (**a**) Effect of resolvin E1 on IL-6 and TNF-alpha production. Resolvin E1 (RvE1) inhibited the production of IL-6 and TNF compared to vehicle. (**b**) RvE1 increased the formation of LXA4 compared to vehicle suggesitng that resolvin E1 brngs about some, if not all, of its anti-inflammatory actions by enhancing the formation of LXA4. (**c**) Effect of resolvin D1 (60 ng/animal by intraperitoneal route) on STZ-induced type 2 diabetes mellitus. Resolvin D1 enhanced the formation of LXA4 that is inhibited by STZ. (**d**) RvD1 prevented the development of STZ-induced diabetes and inhibited STZ-induced increase in plasma IL-6 and TNF-α levels and restored plasma LXA4 and BDNF to normal. This data is taken from Ref. 55). In **a** part of the Fig. 16.10: (**a**) $^{a}P \leq 0.001$ compared to untreated control; $^{b}P \leq 0.01$ compared to streptozotocin + nicotinamide (STZ + NA) group. In **d** part of the Fig: $^{a}P \leq 0.01$ compared to STZ + NA and $^{b}P \leq 0.01$ compared to untreated control

COX-2, LOX, desaturases (see Figs. 16.4, 16.8, 16.9, and 16.10) in inflammation and its resolution. Furthermore, there is a close interaction among COX and LOX enzymes and the formation of PGE2 and LXA4 as shown in Fig. 16.11. Hence, it is necessary to measure all these enzymes and various eicosanoids in the pathobiology of COVID-19 and other similar infections to understand their role and develop suitable therapeutic strategies.

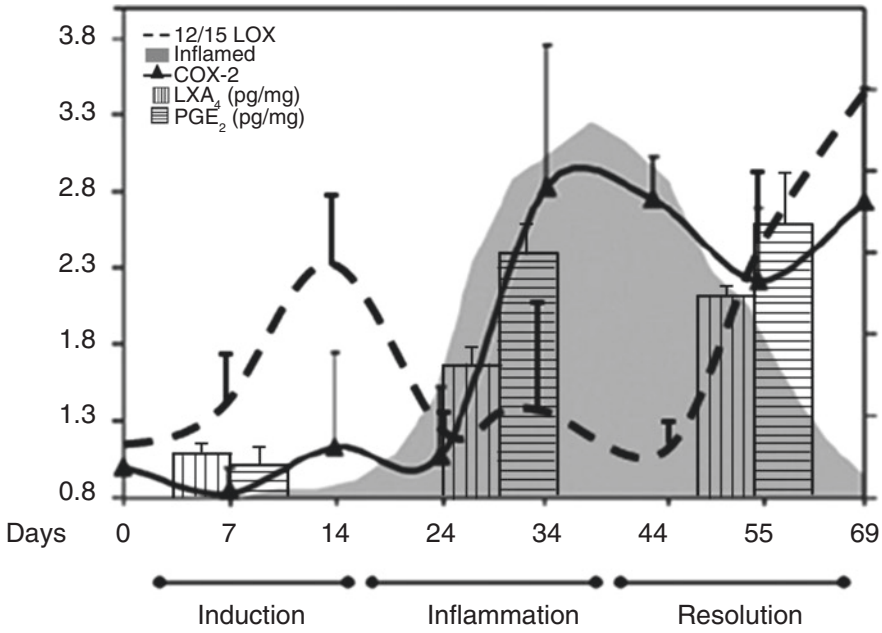

Fig. 16.11 A summary scheme showing potential relationship among COX-2/LOX enzymes, PGE2/LXA4 and their relationship to inflammation and its resolution

PGE2 and LXA4 Interact with each Other to Control Inflammation and Its Resolution

As already discussed above, PGE2 and LXA4 derived from the common precursor AA are necessary for inflammation, its resolution and to reestablish tissue homeostasis. PGE2 has both pro-inflammatory and anti-inflammatory actions whereas LXA4 is anti-inflammatory in nature. PGE2 facilitates development of M1 macrophages whereas LXA4 enhances M2 macrophage generation. PGE2 triggers the generation of LXA4 once its (PGE2) concentrations reach optimum levels (the optimum levels may vary from tissue to tissue and type of inflammation) and suppresses LTB4 (a pro-inflammatory molecule derived from AA) production by modulating 5- and 15-lipoxygenase expression events that enable suppression of inflammation and initiation of anti-inflammatory pathway. This redirection of generation of PGE2 from AA to LXA4 to resolve inflammation is attributed to the biphasic release of AA from the cell membrane lipid pool.

This redirection of AA metabolism from PGE2 to LXA4 is needed not only to induce timely resolution of inflammation but also to augment tissue regeneration and reestablish homeostasis. This is supported by the observation that 15-PGDH–(15-prostaglandin dehydrogenase, a prostaglandin degrading enzyme) deficient mice showed a twofold increase in bone marrow, colon, and liver PGE2 levels accompanied by increased fitness of these tissues with augmented hematopoietic

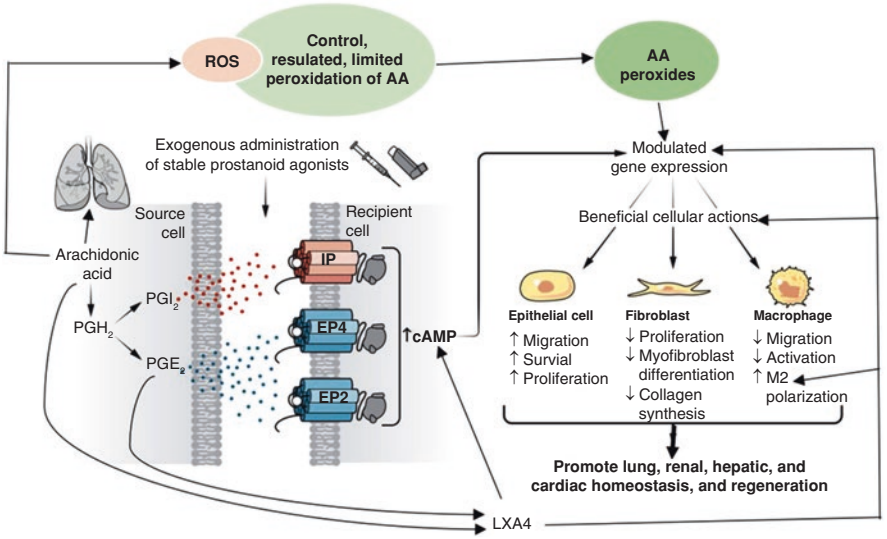

Fig. 16.12 Scheme showing potential beneficial action of AA metabolites PGE2, PGI2, and LXA4 in tissue regeneration (Modified from Ref. 58)

capacity and enhanced liver regeneration and recovery of neutrophils, platelets, and erythrocytes [57]. This beneficial action of PGE2 regarding tissue regeneration is supported by the recent report that PGE2 and PGI2 (both derived from AA) have the potential to augment lung regeneration ([58, 59], see Fig. 16.12). In a previous study [60], we observed that PGI2 prevents radiation, benzo(a)pyrene (BP), and cis-platinum (cis-DDP)-induced genetic damage to the bone marrow cells of mice and enhances the recovery of hematopoiesis. Since PGE2 and LXA4 interact with each other and LXA4 augments PGI2 production [61], it is likely that LXA4 plays a significant role in lung regeneration that is relevant to repair, regenerate, and restore lung function to normal in those with COVID-19. These results [57–61] emphasize the critical role of AA and its metabolites PGE2, PGI2, and LXA4 in tissue regeneration (see Fig. 16.12). Even bone marrow derived mesenchymal stem cells (MSCs) seem to reduce the severity of acute lung injury by secreting LXA4 and by downregulating TNF-α, IL-6, IL-8, and IFN-γ [62]. Thus, LXA4 is critical to prevent and restore tissue damage that occurs in severe COVID-19 patients.

Subjects who are obese, have type 2 diabetes mellitus, hypertension, and coronary heart disease and elderly subjects have high degree of mortality due to COVID-19 can be related to low plasma levels of AA/EPA/DHA seen in them [63]. As a result of deficiency of AA/EPA/DHA, these subjects are likely to show enhanced production of pro-inflammatory cytokines leading to cytokine storm due to the absence of negative feedback regulation exerted by these lipids on IL-6 and TNF-α production.

Conclusions and Therapeutic Implications

It is evident from the preceding discussion that AA and other PUFAs and their metabolites especially, LXA4 and PGE2 have the potential to inactivate SARS-CoV-2, regulate inflammation and its resolution, suppress IL-6 and TNF-α and prevent or ameliorate cytokine storm, enhance tissue regeneration, possess cytoprotective actions, and mediate the beneficial actions of mesenchymal stem cells. This implies that administration of AA/LA could be of significant benefit in COVID-19, especially when the SARS-CoV-2 is showing innumerable number of mutations and as a result the vaccines are proving to be relatively ineffective. Hence, serious consideration on the potential use of LA, AA, and other PUFAs in the prevention and management of COVID-19 and other similar infections [8–15] is recommended since, these lipids can be administered orally and parenterally without any significant side effects. In view of the pleiotropic actions of AA and its metabolites PGE2, PGI2, and LXA4 as discussed above, it is likely that these bioactive lipids especially, AA, could be of benefit in the prevention and management of post-COVID-19 and post-COVID-19 vaccine side effects.

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Chapter 17
Statins and COVID-19 (Mechanism of Action, Effect on Prognosis)

Joanna Lewek, Stanislaw Surma, and Maciej Banach

Abbreviations

ACE2	Angiotensin-converting enzyme-2
AP-1	Activating protein-1
Apo A1	Apolipoprotein A1
Apo CIII	Apolipoprotein C-III
Apo E	Apolipoprotein E
ARDS	Acute respiratory distress syndrome
ASA	Acetylsalicylic acid
CMV	Cytomegalovirus

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CNS	Central nervous system
COVID-19	Coronavirus disease 2019
eNOS	Endothelial nitric oxide synthase
EPCs	Endothelial progenitor cells
GR	Glucocorticoid receptor
GRE	Glucocorticoid response elements
HDL	High-density lipoprotein
hs-CRP	High-sensitivity C-reactive protein
HSV	Herpes simplex virus
ICAM-1	Intracellular adhesion molecule-1
IL	Interleukin
IR-6R	Interleukin-6 receptor
LDL	Low-density lipoprotein
MCP1	Monocyte chemoattractant protein-1
MIP	Macrophage inflammatory proteins
MIS	Multisystem inflammatory syndrome
MMP	Metalloproteinases
NF-κB	Nuclear factor-κB
NO	Nitric oxide
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SAA	Serum amyloid A
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMC	Smooth muscle cells
TC	Total cholesterol
TF	Tissue factor
TG	Triglycerides
TLR	Toll-like receptor
TMPRSS2	Transmembrane serine protease 2
TNF-α	Tumor necrosis factor-α
t-PA	Tissue-type plasminogen
TXA2	Thromboxane A2
VCAM-1	Vascular cell adhesion molecule-1
VLDL	Very-low-density lipoprotein
vWF	von Willebrand factor

Statins, which are widely used not only in dyslipidemia, but also in coronary syndromes, work by inhibition of the rate-controlling enzyme from mevalonate pathway - 3-hydroxy-3methyl-glutaryl-coenzyme A reductase. The blockade of metabolic pathway leading to the production of cholesterol and isoprenoids lowers cholesterol level [1]. Besides lipid lowering abilities, this group of drugs has been linked to many pleiotropic effects reducing the risk of heart diseases or stroke. Most

Table 17.1 Pleiotropic effects of statins

Pleiotropic effects of statins	
Concerning lipids	Concerning intracellular signaling pathways
Cholesterol synthesis inhibition	↑ endothelial NO synthesis
↑ LDL uptake and degradation	↑ t-PA expression
Lipoprotein secretion inhibition	Endothelin-1 expression inhibition
LDL oxidation inhibition	Antioxidant effect on endothelium
The expression of scavenger receptors inhibition	↑EPCs inducing neovascularization
	Angiogenesis induction
	Vascular SMC proliferation inhibition
	↓ thrombogenic potential of platelets
	Plaque size reduction
	↓ macrophage accumulation in atherosclerotic lesions
	↓ MMPs expression
	↓ inflammatory cells in plaques
	↓ hs-CRP
	Direct beneficial effect on myocardium
	Cardiac hypertrophy inhibition
	↓risk of ischemic stroke
	Protection for dementia

LDL low-density lipoprotein, *NO* Nitric acid, *t-PA* tissue-type plasminogen, *EPCs* endothelial progenitor cells, *SMC* smooth muscle cells, *MMP* metalloproteinases, *hs-CRP* high-sensitivity C-reactive protein

of the pleiotropic statins effects are mediated by the inhibition of isoprenoid synthesis. Those effects include two main categories: directly lipids and intracellular signaling pathways (Table 17.1) [1, 2].

Due to the wide range of beneficial effects, statins are widely used not only in patients with dyslipidemia. Therefore, many patients with COVID-19 had a previous history of lipid lowering treatment with statins. On the other hand, numerous studies indicate that cardiovascular diseases worsen the prognosis of patients with COVID-19. Simultaneously, among SARS-CoV-2 infection complications there are cardiovascular diseases. The interconnectedness of those factors was the reason for many studies assessing the role of statins which are widely used in cardiovascular diseases. In addition it should be mentioned that the viral replication during COVID-19 is followed by the host inflammatory response combined with cytokine storm and SARS-CoV-2 evasion of cellular inflammatory response [3].

Statins, which are non-specific immunomodulators, play a role in COVID-19, and can be used as treatment in cytokine storm due to the ability to cytokines inhibition (Fig. 17.1).

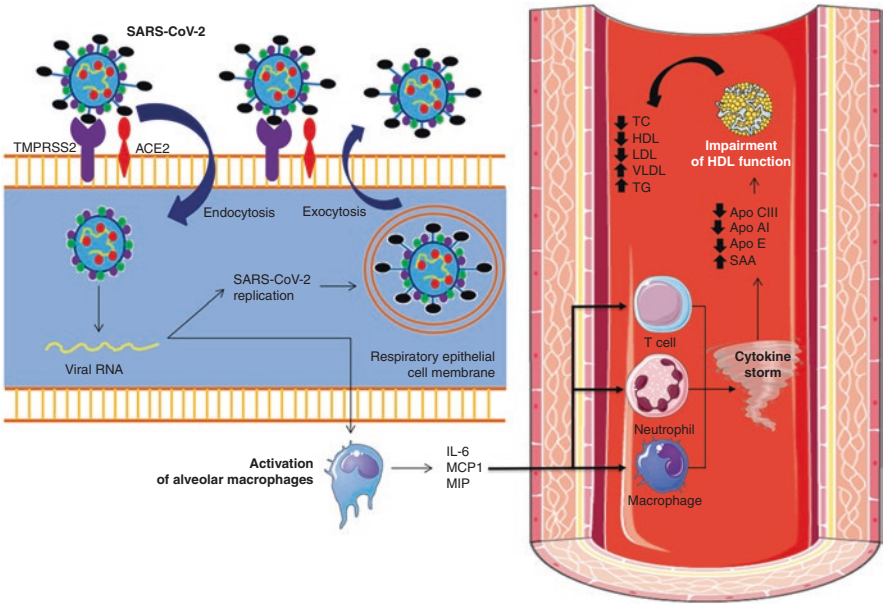

Fig. 17.1 Statins and COVID 19—pathomechanism (prepared using Servier Medical Art) [4–6]. *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TMPRSS2* transmembrane serine protease 2, *ACE2* angiotensin-converting enzyme 2, *RNA* ribonucleic acid, *IL-6* interleukin 6, *MCP1* monocyte chemoattractant protein-1, *MIP* macrophage inflammatory proteins, *Apo CIII* apolipoprotein C-III, *Apo A1* apolipoprotein A1, *Apo E* apolipoprotein E, *SAA* serum amyloid A, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *VLDL* very-low-density lipoprotein, *TG* triglicerydes

Statins and COVID-19: Mechanism of Action

Among beneficial statins effects which may be helpful in COVID-19 infections there are pleiotropic effects of statins, including anti-inflammatory and antithrombotic effects. During the course of COVID-19 infection statins can modify cellular pathways. The mechanisms of statins action in the course of COVID-19 can be divided into direct and indirect mechanisms [7].

Direct Effect of Statins

The penetration of SARS-CoV-2 into the cells requires the presence of ACE2 protein in cellular membranes, which are built from lipid rafts. Lipid rafts serve as subdomains of the cell membranes and contain cholesterol and sphingolipids. Their presence is linked with endocytosis of the virus into cells, therefore promoting viral infection [4]. They also play a role in the interaction between the spike protein of

SARS-CoV-2 and angiotensin-converting enzyme-2 (ACE-2) [4]. ACE-2, a transmembrane metallocarboxypeptidase type I, serves as the main receptor for SARS-CoV-2. ACE-2 exposes its enzymatically active domain on the surface of cells. It binds with virus spike protein, which initiate attachment and transmembrane fusion. Human cellular ACE2 receptor role has already been demonstrated in ACE2-knockout mice with SARS-CoV-1 infection, who presented with lower viral replication, decreased levels of spike protein RNA, and less significant lung damage in comparison to normal ACE2 expression mice [8]. The significant role of lipid rafts mediating SARS-CoV-2 entry into cells was also confirmed by Lu et al. [9]. Moreover, the reduction of cholesterol level in lipid rafts was linked with ACE-2 transfer to an environment outside lipid rafts [9]. Another functional role of lipid rafts is associated with their ability to facilitate both mechanisms of coronaviruses entry into host cells: direct membrane fusion and receptor-mediated endocytosis [9]. They provide a platform concentrating components crucial for membrane docking, fusion, and endocytosis, at the same time enabling intermolecular interactions [10]. Thus, lipid rafts may serve as membrane reservoirs able to concentrate host cell ACE-2 receptors where the interaction with spike protein is facilitated [10]. The process of SARS-CoV-2 penetration to the cells can be mediated by accumulated in lipid rafts caleolins, clathrins, and dynamin [11].

It has been shown that the reduction of cholesterol level during COVID-19 was associated with lower amounts of viral mRNA in host cells [9]. By reducing endogenous cholesterol synthesis, statins cause disruption of lipid rafts, which limits the SARS-CoV-2 adhesion and binding, consequently impairing their penetration into the host cell [4].

Another mechanism of statins is directly linked with ACE-2 protein. Besides being the receptor for SARS-CoV-2, ACE-2 protein is associated with blood pressure regulation via renin angiotensin aldosterone system (RAA). Simultaneously, it has a significant role in inflammatory response leading to conversion of angiotensin II to angiotensin 1–7 with well-known anti-inflammatory, vasodilatatory, and antifibrotic capacities through the ACE2/Ang-(1–7)/Mas [12]. Statins were proved to counter-balance inflammation, due to the ability to enhance ACE2. Another possible explanation is that they have a potential to up-regulate ACE-2 supported by the ability to be agonists for the peroxisome proliferator γ receptor (PPPAR-γ) [5, 13].

Another entry route to host cells for SARS-CoV-2, with lesser affinity compared to ACE2 is a cluster of differentiation 147 (CD147), which is a transmembrane protein. Treatment with statins has a wide range of mechanisms leading to CD147 downregulation by the inhibition of N-glycosylation and isoprenylation processes. Statins are able to modify structure and to change function and expression of CD147, thus leading to the shift in the level of N-glycosylation of CD4 promoting its less glycosylated form accompanied by a decrease in function and production of MMP-2 and MMP-9 [14]. As a consequence, statin treatment disturbs next possible entry way for SARS-CoV-2 to the host cell [15].

Next direct antiviral mechanism of statins is the attenuation of SARS-CoV-2 replication via RNA-dependent RNA polymerase (RdRp) and the main protease called M^{pro} or $3CL^{pro}$. RNA-dependent RNA polymerase is the major polymerase

taking part in SARS-CoV-2 RNA replication. Recent study by Baby et al. showed that pitavastatin has strong affinity to the active site of RdRp leading to the attenuation of the replication process [6]. The main protease cuts translated from RNA polyproteins into the functional viral proteins. A recent study by Reiner et al. showed that statins exert inhibitory effect on M^{pro}—the affinity to M^{pro} was at least similar to antiviral drugs. The study compared seven statins (rosuvastatin, atorvastatin, pitavastatin, simvastatin, pravastatin, lovastatin, and fluvastatin) and three antiviral drugs (two protease inhibitors—lopinavir and nelfinavir and one the RNA-dependent RNA polymerase inhibitor—favipiravir). Binding energies of statins were similar to antiviral drugs [16].

However, direct effects of statins on SARS-CoV-2 regarding penetration to the cell and replication process have been proved, the results of those studies need confirmation in further analyses.

Indirect Effect of Statins

Indirect effects of statins can be expressed in a few ways and are mainly associated with their pleiotropic effects [17]. It should be mentioned that COVID-19 is a complex disease with numerous symptoms and complications, thus statins may exert their indirect activity in many ways, depending on the clinical manifestation of the disease.

COVID-19 is an infectious and inflammatory disease in which cytokines play the main role leading to cytokine storm and macrophage activation syndrome (MAS) manifested by coagulopathy, cytopenia, fever, hyperferritinemia, and hypofibrinogenemia. Therefore, the reduction of inflammation via depletion of pro-inflammatory cytokines by statins is especially beneficial. The inflammatory activity of statins was proved in meta-analysis of 19 randomized clinical trials including 6214 patients with heart failure. The study showed effectiveness of lipophilic statins compared to placebo or standard treatment in reduction of hsCRP (SMD; −0.90, 95%CI; ((−1.22)-(−0.58)), p = 0.00), IL-6 (SMD; −1.02, 95%CI; ((−1.96)-(−0.16)), p = 0.02), and TNF-α (SMD; −1.36, 95%CI; ((−2.49)-(−0.23)), p = 0.02). Hydrophilic statins reached statistically significant reduction of hsCRP vs placebo or standard therapy (SMD; −0.79, 95%CI; ((−1.06)-(−0.54)), p = 0.00) [18]. Another meta-analysis of 17 publications including 3766 patients with impaired glucose homeostasis showed a significant reduction in CRP after atorvastatin administration (WMD, −0.35; 95%CI, ((−0.54)-(−0.17)) and simvastatin therapy (WMD, −0.66; 95%CI, ((−0.79)-(−0.54)). Additionally, it has been shown that atorvastatin leads to statistically significant reduction in IL-6 (WMD, −0.44; 95%CI, ((−0.65)-(−0.22)) [19].

Interleukin-6 plays the main role in inflammatory process in COVID-19 with strong correlation with the disease severity [20]. The reduction of IL-6 and CRP by statins is associated with their pleiotropic effects [21] and can be reached by inhibiting Toll-like receptor 4 (TLR-4). Studies on murine showed that the inhibition of

TLR4 protects against acute lung injury [22]. Inflammatory response may be blocked via two pathways: the myeloid differentiation primary response 88 (MyD88) and Toll/IL-1R domain-containing adaptor-inducing IFN-β (TRIF) dependent pathway [7]. Both of those ways are related to NF-kB [23]. TLRs from the surface of the cell seem to be involved in inducing inflammation and may take part in recognizing SARS-CoV-2 molecular patterns [24].

Besides cytokine storm, severe systemic inflammation in COVID-19 may manifest as macrophage activation syndrome, a life-threatening condition combined with hyperproduction of pro-inflammatory cytokines: IL-1, IL-6, and TNF-α. Large scale activation of macrophages leads to fever, coagulopathy, cytopenia, hyperferritinemia, and hypofibrinogenemia [25]. Although the statin influence on MAS remains controversial and has not been proved, available studies confirm inhibition of macrophages migration and thus their proliferation in atherosclerosis process [26]. The treatment with rosuvastatin affects the expression and activates PPAR- γ in human monocytes, which results into transformation of monocytes to anti-inflammatory M2 macrophages. Such an effect was proved in both in vivo and in vitro studies, confirming the anti-inflammatory activity of statins [27]. The other way of affecting macrophages properties is conducted through the depletion of the geranylgeranylation of the isoprenoid way and following Rac1 activation. It results in enhanced immunocompetency of macrophages, which may remain in activable state [28].

Another clinical manifestation of COVID-19 is linked with thrombotic complications with the relatively high rate of incidence of 9.5% (95% CI 6.8–12.8) [29]. The anticoagulant effects of statins may reduce the risk of pulmonary embolism during the acute phase of the disease and post the disease. The potential mechanism of such an activity of statins can be explained by their ability to the inhibition of plasminogen activator inhibitor-1 (PAI-1), which leads to the increased degradation of fibrin clots mediated by plasmin [30].

It has also been shown that statins have the potential to improve the function of vascular endothelium. SARS-CoV-2 infection affects endothelium by its pro-inflammatory and pro-thrombotic activity [31, 32]. The post-mortem studies revealed higher expression and activation of complement components, which together with ACE2 reduction may promote the disease progression by the development of thrombosis and microvasculopathy [33]. Among other pleiotropic effects of statins, it has been shown that they can reduce the reactive oxygen species (ROS). ROS lead to progression of atherosclerosis plaques and cause endothelial dysfunction [34, 35]. Statins exert their action against ROS in a very complex way: they stimulate the Kruppel-like Factor 2 (KLF-2) and cystationine γ-lyase (CSE) [36, 37], act against disturbed blood flow effect and decrease endothelial shear stress, activate PXR, which in turn leads to the activation of NLRP3 inflammasome [38]. Another valuable mechanism of statins is the increase the number of human endothelial progenitor cells (EPCs) which are able to replace dysfunctional and damaged endothelial cells therefore regenerate endothelium in patients with ischemic heart failure [39]. Last, but not least, statins are able to stimulate pregnane X receptor (PXR) and can debilitate pyrin domain-containing protein 3 (NLRP3) Inflammasome by TNFα or oxidized LDL [40].

Statins have been shown to exert anti-fibrotic effects. It is of utmost importance, taking into consideration the fact, that COVID-19 is often complicated by pulmonary fibrosis, preceding the development of acute respiratory distress syndrome. The fibrosis can be developed during acute phase of the disease, as well as can complicate the out of hospital phase. Le et al. included 107 COVID-19 patients and proved that after 3–6 months post the disease there is a risk of pulmonary fibrosis development [41]. It is calculated that it may affect up to one-third of all patients requiring hospitalization [42], while ARDS may be diagnosed in about 40% op COVID-19 patients [43]. Animal studies on mice showed that atorvastatin reduced the alpha-smooth muscle actin (α-SMA), p-Src, lysyl oxidase-like protein 2 (LOXL2), as well as accumulation of collagen and fibrosis in an interstitial tissue. Moreover, through the inhibition of transforming growth factor beta (TGF-β), it limits the level of fibronectin and α-SMA [44]. Simvastatin also was proved to be effective in preventing pulmonary fibrosis. One of the potential mechanisms is the ability to increase fibroblast apoptosis [45]. What is more, it has been postulated that by inhibiting the TGF- β1 it blocks epithelial-mesenchymal transition (EMT) [46]. Simultaneously, TGF-β signaling attenuation is associated with pulmonary fibrosis caused by remodeling and the deposition of connective tissue among epithelial cells and fibroblasts [47].

In inflammatory diseases, including COVID-19, a 40–70% reduction in HDL lipoprotein levels was observed, which may further exacerbate disease progression [48]. As it was mentioned before, statins exert an indirect antiviral effect due to their pleiotropic effects. One of the postulated mechanisms is conducted via high-density lipoprotein (HDL), which have been shown to bind lipopolysaccharides and lipoteichoic acids [49, 50]. Furthermore, the binding of HDL to lipopolysaccharide protects animals from the toxicity of this endotoxin [51]. In addition, HDL can prevent some viruses from entering cells, reducing infection, and proliferation in various tissues [52]. Moreover, HDL lipoproteins have antioxidant, anticoagulant, immunomodulatory, and anti-inflammatory properties, and are also involved in the regeneration of vascular endothelium [48]. It has been proved that not all statins exert the same effect, with the predominance of simvastatin and rosuvastatin [53].

A very interesting indirect antiviral mechanism of action of statins is the effect of these drugs on arachidonic acid levels. Hoxha's review of the literature concluded that deficiency of arachidonic acid may increase the risk of COVID-19 [54]. Das' review of the literature even pointed to a potential role for arachidonic acid in the prevention and treatment of COVID-19 [55]. Statins have been shown to significantly increase plasma arachidonic acid concentrations in hypercholesterolemic patients [56]. In an in vitro study by Goc et al. the effect of omega-3 polyunsaturated fatty acids, including arachidonic acid, on the penetration of SARS-CoV-2 into cells was investigated. These acids have been shown to disrupt the binding of SARS-CoV-2 to cell surface ACE2 [57], thus impeding its' entry to the cells, which is conducted via increased synthesis of arachidonic acid.

To conclude, statins present numerous effects, both direct and indirect, with the potential to improve the prognosis of COVID-19 patients (Fig. 17.2).

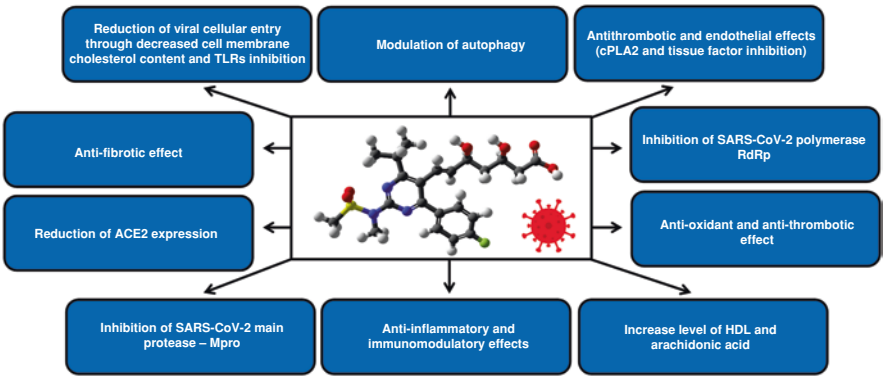

Fig. 17.2 Direct and indirect effects of statins in COVID-19 patients [4–6, 17, 25, 29, 41, 54]. *TLRs* toll like receptors, *ACE2* angiotensin converting enzyme 2, *cPLA2* phospholipase A2, *TLR* toll-like receptor, *HDL* high-density lipoprotein

Statins and COVID-19: Effect on Prognosis

The impact of statin use on the severity and prognosis of COVID-19 has been the subject of multiple meta-analyses (Table 17.2). In a study by Lee et al. the effect of statins on COVID-19 mortality was examined in 10,448 COVID-19 patients. In addition, the effect of statins on mortality risk was compared between two groups: patients with COVID-19 and a retrospective group of patients with pneumonia. The researchers demonstrated a significantly lower hazard ratio (HR) associated with statin use (HR = 0.637; 95% CI: 0.425–0.953; $p = 0.0283$). Furthermore, statin use showed similar benefits when comparing HR between a retrospective cohort of COVID-19 patients and hospitalized pneumonia patients. Thus, statin use was significantly associated with lower mortality in patients with COVID-19, consistent with the findings in patients with pneumonia [71]. Meta-analysis of Diaz-Arocutipa et al. on 147,824 patients showed that the statin therapy was linked to lower mortality risk in patients with COVID-19—for adjusted odds ratio (11 studies, adjusted OR 0.67, 95%CI 0.52–0.86) and adjusted hazard ratio (10 studies, adjusted HR 0.73, 95%CI 0.58–0.91). What is more, it proved that the chronic statin use was also associated with lower mortality. In contrast, when applying the unadjusted risk ratio analysis of 19 studies showed no association between mortality and the statin use (unadjusted RR 1.16, 95%CI 0.86–1.57) [59].

Next meta-analysis showed no statistically significant risk reduction of mortality in patients who used statins (OR = 0.97; 95% CI: 0.92–1.03) and no statistically risk reduction of severe course of COVID-19 (OR = 1.09; 95% CI: 0.99–1.22). However, when applying adjustment for confounders, a 27% decrease in the risk of severe course of the disease and mortality in COVID-19 was demonstrated (adjusted OR 0.73 ± 0.31 vs. unadjusted OR 1.44 ± 0.84; $p = 0.0028$) [67].

Another huge meta-analysis, including 11,930,583 patients with COVID-19 based on 35 studies proved that statin use did not cause significant reduction of the

Table 17.2 Meta-analyses assessing the statin effect on the outcome in COVID-19 patients

Author/year	Number of patients	Number of included studies	Results of statins	Conclusions (in patients with COVID-19)
Chow et al. 2021 [58]	110,078	13	Pre-hospitalization statin use: no significant change in the risk of death (OR = 0.62; 95% CI: 0.38–1.03) Statin use since COVID-19 diagnosis: reduced risk of death (OR = 0.57; 95% CI: 0.43–0.75) Statin use in patients admitted to ICU: no significant change in mortality (OR = 0.65; 95% CI: 0.26–1.64) Statin use in non-ICU patients: lower risk of death (OR = 0.64; 95% CI: 0.46–0.88) No change regarding the risk of ICU admission	Lower mortality risk in patients who received statins since the diagnosis of COVID-19 and non-ICU
Diaz-Arocutipa et al. 2021 [59]	147,824	25	In-hospital statin use: no change in the risk of mortality (adjusted HR = 0.74; 95% CI: 0.49–1.10). Chronic statin use: Significant reduction of the risk of mortality (aHR = 0.71; 95% CI: 0.56–0.91)	Lower risk of death with statin use
Hariyanto and Kurniawan et al. 2021 [60]	11,930,583	35	Statin use: No significant reduction in the risk of COVID-19 (OR = 1.09; 95% CI: 0.58–2.03) and the risk of severe course of COVID-19 (OR = 1.07; 95% CI: 0.86–1.33)	Lack of improvement of prognosis with statin use
Kollias et al. 2021 [61]	114,688	22	Statin use vs. *no* statin: Reduction of the risk of mortality (HR = 0.65; 95% CI: 0.53–0.81 and OR = 0.65; 95% CI: 0.55–0.78)	Lower risk of death with statin use
Kow et al. 2020 [62]	8990	4	Severity and mortality: 30% reduction of risk (HR = 0.70; 95% CI: 0.53–0.94)	Improvement of prognosis with statin use
Kow et al. 2021 [63]	138,402	35	Statin use: reduction of the risk of mortality from any cause (OR = 0.63, 95% CI: 0.51–0.79), and the risk of severe course of COVID-19 (OR = 0.80, 95% CI: 0.73–0.88)	Improvement of prognosis with statin use

Table 17.2 (continued)

Author/year	Number of patients	Number of included studies	Results of statins	Conclusions (in patients with COVID-19)
Onorato et al. 2021 [64]	2398	7	Severity and mortality: risk reduction by 41 (OR = 0.59; 95% CI: 0.35–0.99). Chronic statin use: greater benefits of their use (OR = 0.51; 95% CI: 0.41–0.64)	Improvement of prognosis with statin use
Pal et al. 2021 [65]	19,988	14	Severity and mortality: no significant risk reduction (OR = 1.02; 95% CI: 0.69–1.50). Reduction of the risk of adverse outcomes by 49% after adjustment (OR = 0.51; 95% CI: 0.41–0.63)	Improvement of prognosis with statin use
Permana et al. 2021 [66]	52,122	13	In-hospital statin use: decreased risk of mortality by 56% (RR = 0.54; 95% CI: 0.50–0.58). Chronic statin use: no change in the risk of mortality (RR = 1.18; 95% CI: 0.79–1.77)	Reduction of mortality with in-hospital statin use
Scheen 2020 [67]	42,722	13	Mortality: no significant risk reduction (OR = 0.97; 95% CI: 0.92–1.03) Severity: no significant risk reduction (OR = 1.09; 95% CI: 0.99–1.22) 27% reduction in the risk of severity of the disease and mortality adjusted for confounders (adjusted OR = 0.73 ± 0.31 versus unadjusted OR = 1.44 ± 0.84; $p = 0.0028$)	Improvement of prognosis with statin use
Vahedian-Azimi et al. 2021[68]	32,715	24	Significant reduction in the risk of ICU admission (OR = 0.78; 95% CI: 0.58–1.06) No significant change in the risk of tracheal intubation (OR = 0.79; 95% CI: 0.57–1.11) Significant reduction in the risk of death (OR = 0.70; 95% CI: 0.55–0.88) In-hospital statin use: decrease of mortality (OR = 0.40; 95% CI: 0.22–0.73), compared with chronic use (OR = 0.77; 95% CI: 0.60–0.98)	Reduction of ICU admission and total mortality with statin use

(continued)

Table 17.2 (continued)

Author/year	Number of patients	Number of included studies	Results of statins	Conclusions (in patients with COVID-19)
Wu et al. 2021 [23]	63,537	28	Statin use was: reduction in the risk of mortality (OR = 0.71, 95% CI: 0.55–0.92) and for the need for ventilation (OR = 0.81, 95% CI: 0.69–0.95). Statin use: no significant reduction of the risk of ICU treatment (OR = 0.91; 95% CI: 0.55–1.51)	No need to withdraw statins after hospital admission in patients with COVID-19 Improvement of prognosis in COVID-19 after statin use
Yetmar et al. 2021 [69]	395,513	16	Chronic statin use: reduction of the risk of mortality (adjusted RR = 0.65; 95% CI: 0.56–0.77) and severe course of the disease (aRR = 0.73; 95% CI: 0.57–0.94).	Lower risk of death or serious illness in COVID-19 patients using statins. Importance of statin continuation
Zein et al./2021 [70]	14,446	8	Statin use: reduction of the risk of mortality (RR = 0.72; 95% CI: 0.55–0.95) Chronic statin use: reduction of the risk of mortality (RR = 0.71; 95% CI: 0.54–0.94)	Reduction of mortality risk in COVID-19 with the use of statins

ICU intensive care unit, *RR* risk ratio, *OR* odds ratio, *95% CI* 95% confidence interval, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

risk of COVID-19 (OR 1.09; 95%CI: 0.58–2.03). No effect on the severity of COVID-19 was also observed (OR 1.07; 95% CI: 0.86–1.33) [60].

Overall, the results of meta-analyses evaluating the impact of statins on improving outcomes in patients with COVID-19 remain inconsistent. It may be explained by confounding factors including, age, sex, concomitant diseases, pharmacotherapy, environmental factors, genetic susceptibility, and lifestyle. What should be emphasized, different types of statin were analyzed. It was confirmed by Rossi et al. who showed reduced mortality in patients with COVID-19 treated with simvastatin and atorvastatin. Such an effect was not observed among patients treated with pravastatin and rosuvastatin [72]. Another possible explanation was presented by Cariou et al. who noted that the effect of statins can depend on the cardiovascular burden (severity of underlying disease, stage, and concomitant diseases) in patients with COVID-19 [73]. Therefore available papers should be carefully interpreted taking into consideration the fact that such type of research may be burdened with errors [74]. In addition, some of the methods used in the meta-analyses are discussed [75, 76].

Future studies should provide more information on the potential benefits of statin therapy for patients with COVID-19. However, it is known that patients with

COVID-19 should not discontinue statin therapy [77]. The causal relationship between statin use and outcomes in COVID-19 patients can only be confirmed by the results of randomized controlled clinical trials (RCTs).

A comprehensive literature review by Talasaz et al. compiled the ongoing RCTs on the use of statins (mainly atorvastatin and rosuvastatin) in pharmacotherapy of COVID-19. In addition, the authors noted that the role of OMEGA-3 fatty acids, fibrates, and niacin in the treatment of COVID-19 is also under investigation [78].

Recently published randomized clinical trial by Ghafoori et al. performed on hospitalized patients suffering from COVID-19 assessed atorvastatin. A group of 156 patients were randomly assigned to one of two group: receiving standard therapy against SARS-CoV-2 and the intervention group with atorvastatin added to standard therapy. Statin therapy in comparison to standard group was associated with longer duration of hospital stay (7.72 days vs. 5.06 days, $p = 0.001$), higher pulse rate (94.26 per minute vs. 87.87 per minute, $p = 0.004$) and increased frequency of admissions to intensive care units (18.4% vs. 1.3%, $p = 0.001$). Moreover, patients who used atorvastatin were less likely to recover from COVID-19 than those who did not use statin (93.4% vs. 97.4%, $p = 0.0001$) [79].

On the other hand, Davoodi et al. showed that addition of atorvastatin to standard therapy was more effective than standard therapy in hospitalized adult patients with COVID-19. The trial was performed on 40 hospitalized patients with COVID-19 randomized to intervention group with atorvastatin added to lopinavir and ritonavir vs. standard group with lopinavir and ritonavir. Statin therapy was associated with shorter duration of hospital stay (7.95 ± 2.04 days vs. 9.75 ± 2.29; $p = 0.0120$). No significant difference between groups was observed regarding reception of the invasive mechanical ventilation (0% vs. 5%) and the use of interferon and immunoglobulin (15% vs. 20%, $p = 0.5$) [80].

Possible explanation to the conflicting results of above mentioned studies are combined with the low number of patients, lack of definitively effective therapy against SARS-CoV-2, and short duration of the study and the therapy.

Moreover, it should be emphasized that statins do not replace other drugs used to treat patients with COVID-19. In some patients, statins may accompany the proper treatment against SARS-CoV-2. It appears that the use of statins in COVID-19 patients may also help reduce the risk of lipid disorders during long-term observation of patients with infections caused by other SARS coronaviruses [81].

COVID-19 and Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) (heterozygous and homozygous) is related with higher risk of severe course of SARS-CoV-2 infection, with greater risk of acute myocardial infarction [82]. The pandemic and the decline in preventive ambulatory care also may result in higher risk of ASCVD and concomitant complications, which is even more dangerous in patients with FH. Recently, a brief recommendation for treatment of patients with FH during COVID-19 pandemic was

Table 17.3 Recommendations regarding the dyslipidemia treatment in COVID-19 patients according to polish guidelines [84]

Recommendations	Class	Level
In patients with COVID-19, the treatment of elevated LDL cholesterol levels should be optimized as soon as possible, especially in people with high or very high cardiovascular risk, who should use the highest recommended doses of statins	IIa	C
The initiation or intensification of lipid lowering therapy and its monitoring is also possible during the e-visit/e-advice	I	C
Optimal control of CVD risk factors, including in particular achieving therapeutic targets for LDL-C, during a pandemic is of special importance due to the need to reduce the risk of cardiovascular events and death in patients with COVID-19, in conditions of limited availability of health resources	I	C
In people with COVID-19, optimal statin treatment should be continued, also during hospitalization, as it may be associated with an improved prognosis	IIa	B

developed. The authors of the recommendation point this out that a vast range of papers confirm scientific evidence that statins have potential to decline severity of COVID-19 among patients with familial hypercholesterolemia. Therefore, social distancing and therapeutic rules should be especially respected among that group of patients. Statin use in patients with FH and COVID-19 is generally safe and according to European Society of Cardiology guidelines it may improve prognosis in majority of patients. Thus, statin therapy should not be discontinued [83], but rather intensified. Polish guidelines regarding diagnosis and therapy of dyslipidemia presented recommendations regarding statin therapy in COVID-19 patients for the first time in the world [84] (Table 17.3).

Clinical Implications

According to available data on statin use in patients with COVID-19, there are some rules which we should follow:

1. Statins should be continued in all COVID-19 patients already treated with statins.
2. Statins should be initiated in all COVID-19 patients who require such therapy according to current guidelines on cardiovascular diseases.
3. COVID-19 itself is not a reason to statin therapy.

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Chapter 18
COVID-19 and Antihypertensive Treatment

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Introduction

This chapter will focus on the relationship between blockers of the renin-angiotensin-aldosterone system (RAS) and the risk of COVID-19 infection as well as the progression of the infection to severe disease and lethality. This will be complemented by brief descriptions of, (1) the relationship between COVID-19 and hypertension, (2) the influence of antihypertensive agents other than RAS blockers on the infection, and (3) the influence that the COVID-19 pandemic might have had on blood pressure (BP) values and the related cardiovascular risk via alterations of the environment, people habits, social factors, and the efficiency of the healthcare system.

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COVID-19 and Hypertension

In the early phase of the COVID-19 pandemic a large number of studies reported that a history of hypertension was extremely common in patients with the COVID-19 infection. For example, in March 2020 the Italian National Institute of Health (Istituto Superiore di Sanità) released the information that, among people deceased for the COVID-19, 73% had a chronic BP elevation. However, the mean age of the deceased people was 81 years, i.e. an age in which hypertension is very common. Furthermore, prevalence of hypertension and patients' age has been extremely variable in studies that have addressed the clinical characteristics of COVID-19 infected patients [1]. This makes it difficult to reach a conclusion on whether a chronic BP elevation is accompanied by a greater risk of COVID-19 or rather than the association between these conditions originates from the inevitable but casual coexistence of two highly prevalent conditions, especially in the aged population.

This is probably not the case, however, for the severity of the COVID-19 infection because in a large number of studies, evidence has been obtained that, in patients hospitalized, admitted to Intensive Care Units or deceased for COVID-19, a history of hypertension is particularly common [2, 3], and greater than that seen in patients with a less severe infection, the greater prevalence compared to less severe patients ranging from about +50% to more than +200% [4–7]. Although an adverse independent role of hypertension for the COVID-19 severity has been denied by some studies [8], in several other studies the severity of COVID-19 (lethal outcome, admission to Intensive Care Units or development of heart failure) has been found to be related to hypertension and even to the BP levels, after adjustment for confounding [3, 9–13]. More recently, this has received support also from the results obtained in a large fraction of the Italian population (about 20 million), in which hypertension was found to be one of the conditions independently related to the severity of COVID-19. This has led to the development of a score that has been found to be predictive of the severe or lethal forms of COVID-19 more accurately than comorbidity scores based only on age or not specifically addressing the COVID-19 infection [14].

Why hypertension is likely to increase the risk of COVID-19 to progress towards a more severe disease is still a matter of speculation. In some studies, a chronic BP elevation has been associated with alterations of immunological defenses and inflammatory processes, i.e. factors that play an obvious important role for COVID-19 outcome [15]. A simpler explanation, however, is that hypertension is associated with subclinical damage of a variety of organs, as recently shown by the PAMELA population study, in which subclinical alterations of cardiac or renal structure and function were detected in about 43% of hypertensive individuals [16]. This is probably an underestimation of the hypertension/subclinical organ damage association because (1) the average age of the hypertensive individuals (64 and 58 years in those with and without organ damage, respectively) was not particularly advanced and (2) the study did not measure hypertension-related organ structural and functional alterations in the brain, the eye, and the peripheral arteries. In

particular, it did not assess alterations of endothelial function, which are common in hypertension [17] as well as a target of the SARS-CoV-2 virus [18]. Indeed, background organ damage may represent the common mechanism that favors a greater severity of COVID-19 infection, which has been reported not only in people with hypertension but also in type 2 diabetes mellitus and dyslipidemias [19, 20] two conditions that also silently deteriorate organ structure and function before emerging with clinically overt events.

COVID-19 and Antihypertensive Drug Treatment

Confirming the results of a study performed at the time of the first SARS virus infection about 20 years ago [21], studies performed during the current COVID-19 pandemic have shown that the SARS-COV-2 virus enters the cells via the ACE-2 enzyme, i.e. an enzyme located at the cell surface which is also involved, albeit collaterally, in the mechanisms of action of the renin-angiotensin system by favoring, among other actions, degradation of angiotensin II [15]. Although some investigators speculated that RAS blockers could be beneficial by protecting against acute lung injury (including injury by infections, e.g. by SARS) [22], others emphasized the possibility that these drugs might support cell entry of the SARS-CoV-and thus enhance the risk and severity of the infection [23]. The latter was based on the observation that RAS blockers may upregulate the ACE-2 enzyme in cells [15] in both experimental animals and humans, although this had not been shown in cells of the respiratory tract [15] A potentially harmful effect of RAS blockers was given a wide echo by the press [24], generating concern among the scientific societies that, despite absence of specific evidence, this would result into a large-scale discontinuation of these drugs. Concern was entirely justified because RAAS blockers are lifesaving drugs not only in hypertension but also in heart failure and coronary diseases, their discontinuation leading to a marked rebound increase of morbid and fatal cardiovascular events [25].

After a period in which no evidence was available, the above possibilities were tested by a number of studies and two especially large-scale ones were published in the same issue of the New England Journal of Medicine on May first, 2020 [24, 25]. One study [26] was based on the analysis of the Healthcare Utilization Databases of the Lombardy region (Northern Italy) to determine the antihypertensive drugs prescribed to 6272 patients infected by the SARS-COV-2 virus in February and March 2020 (average age 68 years, 37% women) during the preceding year, having 30,759 individuals matched for age, sex, and municipality of residence as controls. As reported in Fig. 18.1, the results showed that previous use of ACE inhibitors, ARBs or mineralocorticoid receptor antagonists (MRAs) was more common in COVID-19 infected people than in controls. This was the case, however, also for all other major antihypertensive drugs, suggesting that this greater use did not reflect a specific adverse influence of these drugs on the risk of COVID-19 infection, but rather an adverse effect of the diseases for which RAAS blockers are prescribed, i.e.

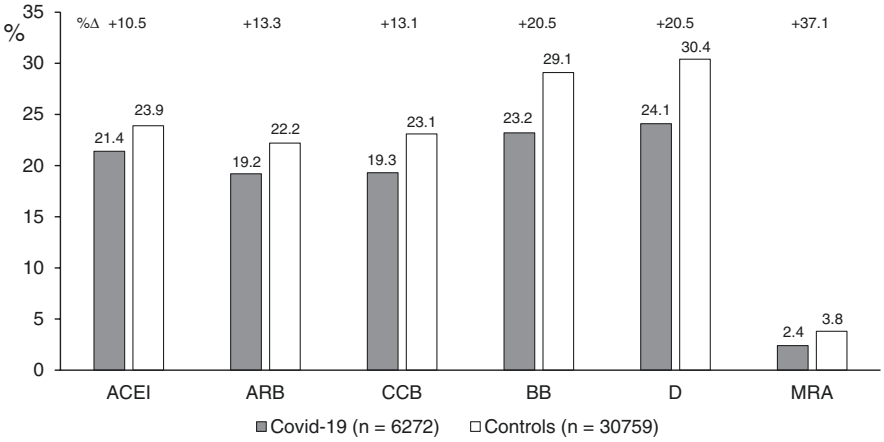

Fig. 18.1 Use of ACE inhibitors (ACEI), angiotensin receptor antagonists (ARB), mineralocorticoid receptor antagonists (MRA), calcium channel blockers (CCB), beta-blockers (BB), and diuretics (D) during 2019 in patients with COVID-19 during the first pandemic wave. Data are shown in comparison to controls matched for age, sex, and municipality of residence in Lombardy. D include thiazide and thiazide like diuretics (modified from ref. 26)

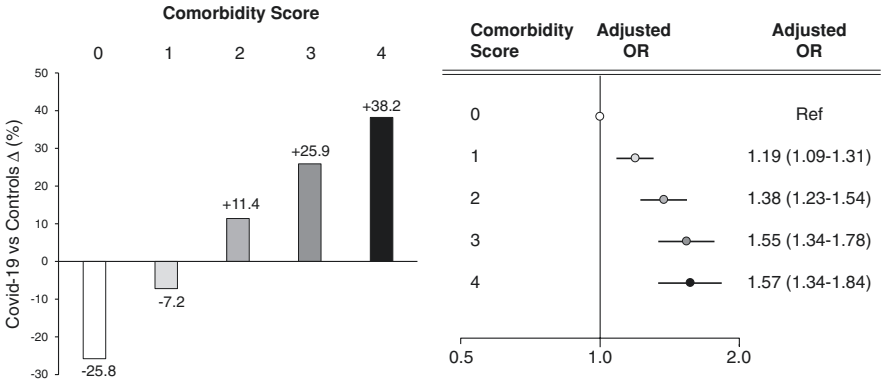

Fig. 18.2 The left panel shows the relative difference between COVID-19 and Controls according to a comorbidity score, i.e. a score based on a large number of associated diseases which was found to predict the risk of hospitalization and mortality in the Lombardy population. The right panel shows the risk of COVID-19,after adjustment for confounders, according to the above-mentioned score. Score 0 was taken as reference. Abbreviations as in Fig. 18.1 (modified from ref. 26)

hypertension but also heart failure, coronary diseases and renal diseases. This interpretation was supported by the evidence that, (1) the relative difference between COVID-19 infection and controls increased progressively with the increase of the chronic comorbidity score (Fig. 18.2, *left panel*), i.e. a score based on a large number of background diseases that was found to accurately predict hospitalization and mortality in the Lombardy population [27], (2) this was the case also for risk of

COVID-19 after adjustment for confounding variables, which increased progressively for the minimal to the maximal score (Fig. 18.2, right panel), and (3) when adjusted for confounding variables no RAAS-based drug class (ACE inhibitors, ARBs or MRAs) exhibited a significant alteration in the risk of COVID-19, this being the case also for other antihypertensive agents in all instances either in the context of monotherapy or combination therapy (Fig. 18.3). Similar conclusions were reached when the analysis addressed separately men and women and people aged less than 60 years or 60 years and beyond. As shown in Table 18.1 they were also reached when data were analyzed according to the severity of the infection, i.e. separately in mild and severe or lethal forms. Most importantly, they were reached by the second large study, which found that in COVID-19 infected patients there was no difference in the use of different antihypertensive drugs, this being the case

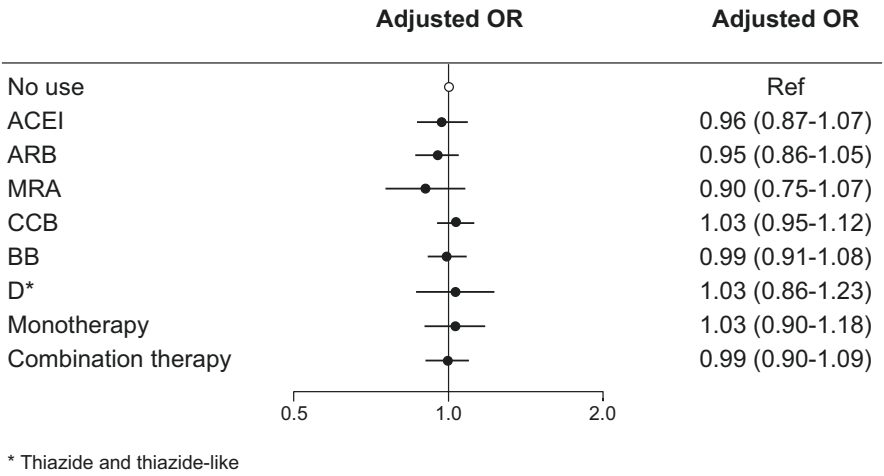

Fig. 18.3 Odds ratios (OR) and 95% confidence intervals (CI) of COVID-19 in 2020 (February and March) according to pretreatment with different antihypertensive drugs in 2019.OR were adjusted for confounders (modified from ref. 26)

Table 18.1 Adjusted odds ratios, and 95% confidence intervals, of COVID-19 infection associated with use of blockers of the renin-angiotensin system and other antihypertensive drugs, according to the severity of clinical manifestations (Modified from ref. 26)

	Severity of clinical manifestations	
	Mild-moderate (5655 cases/27,790 controls)	Critical/fatal (617 cases/2969 controls)
ACEIs	0.97 (0.88 to 1.07)	0.91 (0.69 to 1.21)
ARBs	0.96 (0.87 to 1.07)	0.83 (0.63 to 1.10)
CCBs	1.01 (0.92 to 1.10)	1.15 (0.91 to 1.44)
Diuretics	1.07 (0.97 to 1.19)	0.96 (0.74 to 1.26)
Beta-blockers	0.98 (0.89 to 1.07)	1.07 (0.84 to 1.37)

ACEIs angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *CCBs* calcium channel blockers

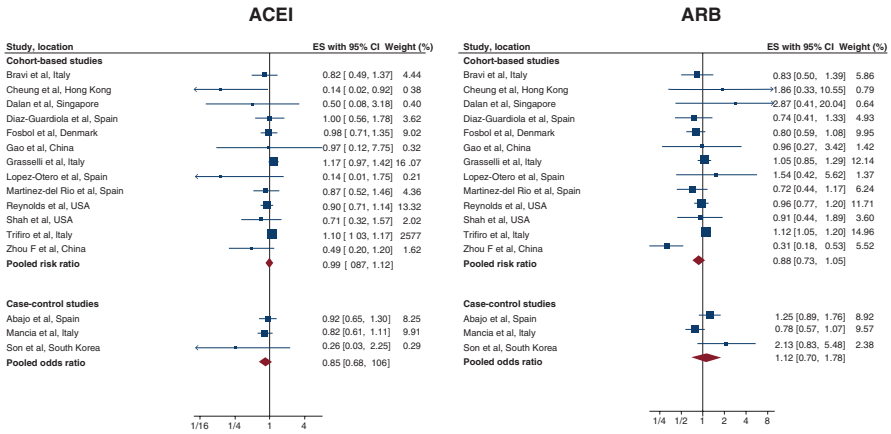

Fig. 18.4 Forest plot of the association between ACE inhibitors (ACEI) or ARB treatment and all-cause mortality/severe disease in 87,951 patients hospitalized with COVID-19 infection. Abbreviations as in preceding Figures and Tables. (From ref. 29, by permission)

also when the analysis focused on severe COVID-19 cases and addressed hypertensive individuals only [28]. Although with some rare exceptions, these conclusions have been supported by the following long series of studies as well as by large meta-analyses, one which has shown no alteration in the risk of mortality or severe disease by pretreatment with ACE inhibitors or ARBs in almost 90.000 COVID-19 hospitalized patients (Fig. 18.4) [29]. This is against the rare reports that there can be some difference between ACE inhibitors and ARBs the former drug class displaying a protective effect that is not displayed by the latter [30]. Some large studies that supported this conclusion have been retracted and to-date the European Medical Agency (EMA) "*reiterates its previous advice that (during the* COVID-*19 pandemic) patients should continue to use ACE inhibitors or ARBs as advised by their doctors*" [31].

Study Limitations

A limiting aspect of the evidence reported in the previous subsection is that the studies on which the evidence is based had an observational nature, which does not allow to completely exclude confounding and alternative explanations. However, the relationship between blockers of the RAS and COVID-19 has been more recently investigated also via a randomized trial design in which a comparison was made between continuation or discontinuation of ACE inhibitors or ARBs in COVID-19 patients. In all trials no difference in the progression of COVID-19 to more severe clinical conditions has emerged between the two groups. For example, in the trial known by the acronym of BRACE-CORONA the number of days alive

and out-of-hospital from the hospital admission date was similar in patients (median age 55.1 years) discontinuing ($n = 334$) vs. those continuing ($n = 325$) ACE inhibitor or ARB treatment (21.9 ± 8.0 vs 22.9 ± 7.1 days), the incidence of death at the 30th day being 2.7% vs. 2.8% [32]. In a second trial both death rate and a score based on sequential organ failure did not differ between the 104 and 100 COVID-19 patients (median age 75 years), respectively, discontinuing or continuing a treatment based on RAS blockers [33]. This was the case also in a third trial on a total of 152 patients aged 62 years in whom the study cohort had a large prevalence (52%) of diabetes mellitus [34]. This reinforces the conclusion reached by the observational studies and, overall, reassures that RAS blockers can be safely used, (1) in non-COVID-19 infected people to treat the diseases for which they are indicated, and (2) during a COVID-19 infection when these drugs are needed because of a BP elevation, a loss of BP control by preceding treatment, heart failure or coronary disease.

Two notes of caution are appropriate, however. One, available trial evidence on RAAS blockers has important limitations such as the small number of patients, the low risk of progression of the disease and the insensitive nature of the selected endpoint [35]. In addition, in these trials ACE inhibitors were used much more frequently than ARBs, for which trial-based evidence is thus particularly limited. Finally, no randomized trial has addressed the role during a COVID-19 infection of MRAs or of other antihypertensive drugs. Thus, the possibility of some role of BP-lowering agents in the complex and variable treatment strategies that are adopted in COVID-19 patients, according to their clinical characteristics and severity, cannot at this stage be completely excluded. Two, no matter how carefully designed and conducted, observational studies are open to potential confounding that no adjustment procedure can completely eliminate. In the previously mentioned study from the Lombardy Health Utilization database [26], we observed that some drugs remained independently associated with an increased risk of COVID-19 after adjustment for confounders. One was the use of anticoagulants (+16% risk) while another was the use of immunosuppressants (+30% risk). Among antihypertensive agents loop diuretics were associated with a 46% increased risk of COVID-19 infection which persisted after adjustment for confounders. We interpreted this finding as probably due to conditions such as severe heart failure or advanced renal disease, which were underestimated by the adjusting procedures we used. Alternative explanations are possible, however, and should be addressed by specifically designed and more controlled research approaches. In this context, beta-blockers deserve attention because of especially promising evidence. In a study published in Spain i.v. metoprolol was associated with improved oxygenation of COVID-19 patients compared to controls [36]. Furthermore, other studies have shown that beta-blockers may reduce not only SARS-CoV-2 cell entry but also interlukein-6 and other components of the cytokine storm, hypercoagulation, mucus hypersensitivity as well as be beneficial in skeptic shock. All these features may translate into clinical benefits in severe forms of COVID-19 [37, 38].

Blood Pressure Values, Blood Pressure Control, and COVID-19 Pandemic

Available studies provide a limited amount of data on the BP values during the COVID-19 infection, which means that to-date the changes and prognostic impact of intra-infection BP can count on only scattered observations [13, 39–41]. The issue is extremely difficult to be properly investigated because during COVID-19 BP can be modified in either direction by a number of factors, e.g. stress, anti-inflammatory drugs including corticosteroids medical maneuvers, alterations of the hydration state, as well as other ill measurable factors.

It is, on the other hand, likely that during the COVID-19 pandemic, and especially during the lockdowns there were some changes in the BP values of the population as well as of hypertensive patients. As shown in Fig. 18.5 several factors were likely to influence BP during the pandemic and related lockdown. In few instances, e.g. reduced pollution and environmental noise (because of a reduction in traffic), these factors may have favored a BP decrease. However, any depressor influence might have been masked and superseded by pressor-genic factors such as, to mention a few, a reduction of mobility and physical exercise, an increase of caloric intake and perhaps of alcohol consumption, a state of fear and anxiety generated by the unpredictable evolution of the disease and the uncertainty about the job and the future [42]. This might have increased BP values and reduced the number of hypertensive patients in whom treatment had achieved BP control, i.e. the BP value at which patient protection is maximized [43]. Indeed, an overall increase in the BP values during the COVID-19 pandemic has been reported by a recent study which has found a several mmHg increase of BP in 2020 compared to 2019, at variance

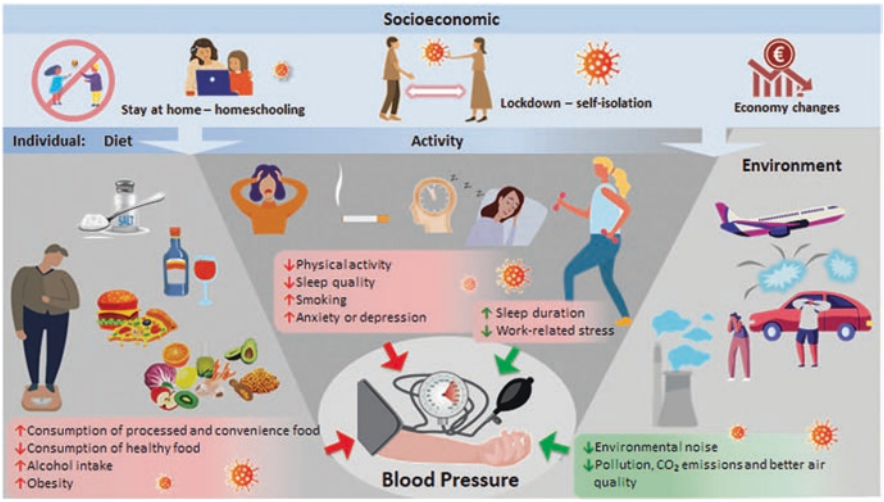

Fig. 18.5 Influence of the lockdown during the COVID-19 pandemic on lifestyle and environmental risk factors probably involved in blood pressure changes and hypertension. (From ref. 42, by permission)

from the only slightly different BP values in 2019 compared to 2018 [44]. This may have been seriously favored also by the dramatic reduction, during the pandemic, of the ability of healthcare systems to cope with diseases other than COVID-19. This has been documented by a study which has reported in 2020 a striking reduction of hospitalizations and other medical services for cardiovascular diseases in different countries and continents [45]. It has also been documented for European countries with regard to hypertension. In an interview of the Excellence Hypertension Centers of the European Society of Hypertension, it was reported that during the first pandemic-related lockdown medical services stopped entirely in most centers and no visits were made in 90% of the patients [46], a rarefaction of medical assistance with obvious detrimental consequences for the detection of hypertension-related complications, loss of BP control, need of treatment changes because of side effects, and in general quality of hypertension care. Lack of medical services may also have negatively affected adherence to the prescribed drugs, which is favorably influenced by the doctor's availability and good relationship with the patient. As it can be seen in Fig. 18.6, a similar drastic loss of cardiovascular care during the 2020 pandemic

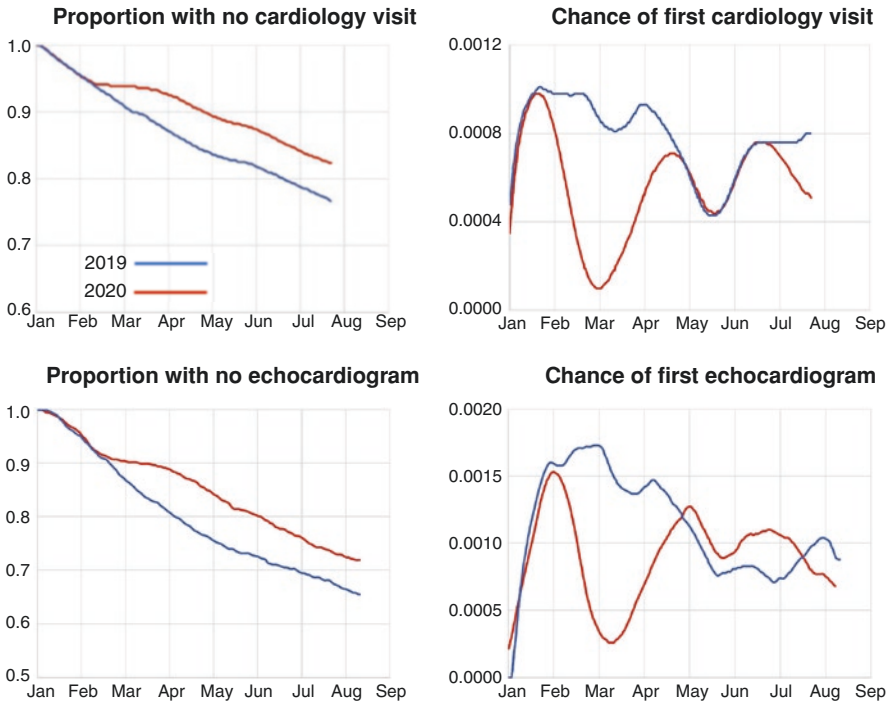

Fig. 18.6 The top left and right panels show the proportion of patients under antihypertensive drugs who had access to a cardiology visit during 2020 (January to September) and the patient's chance (estimated by means of hazard functions) to have a cardiology visit during the pandemic wave and lockdown in early 2020. Comparisons are made with the corresponding periods of 2019. The bottom left and right panels show the analogous data for an echocardiogram in patients under antihypertensive drugs who had a previous hospitalization for heart failure. The blue color indicates 2019 and the red color 2020

occurred in Italy. Using the Lombardy database mentioned above we have seen that in patients under prescriptions of antihypertensive drugs the chance of having a cardiology visit was less during the first 9 months of 2020 compared to a similar period during 2019. Furthermore, during the first COVID-19 pandemic wave and lockdown (early 2020) the chance of having a medical visit showed a striking reduction (more than 80%) compared to the corresponding 2019 period. This was the case also for the chance of having an echocardiogram in patients under antihypertensive drugs who had a history of hospitalization for heart failure.

COVID-19 and Hypertension Guidelines

The evidence reported above suggests that there is no need to substantially modify the choice of antihypertensive drugs or treatment strategies recommended by the European hypertension guidelines [43] because of the COVID-19 pandemic. That is, the same major drug classes recommended by the guidelines before the pandemic (ACE inhibitors, ARBs, Beta-blockers, CCBs and Diuretics) should continue to be used for achieving BP control during the pandemic. The same is true for use of these drugs in combination treatment as well as for the guidelines important recommendation to start treatment with two drugs in the majority of hypertensive patients. It seems appropriate, however, for guidelines to further recommend that, during the pandemic, patients pay closer attention to BP values by regular self-measurements in the home environment to capture possible trends to a BP increase or loss of BP control. This should be accompanied by attention to and correction of inappropriate lifestyles, e.g. reduction of caloric intake, appropriate vegetable content of the diet, avoidance of alcohol, and increase or maintenance of physical activity. Guidelines should also made clear that treatment changes should not be self-decided and implemented but established with the doctor's participation. To face a rarefaction in the number of doctor's visits telematic consultations and other forms of telemedicine approaches should be implemented and this should be favored by appropriate facilitations and reorganizations of the healthcare systems. The priority goal should be to avoid the dramatic breakdown in the medical assistance of diseases other than COVID-19 that has occurred in the past.

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Chapter 19
Colchicine in COVID-19 (Mechanism of Action, Effect on Prognosis)

Ibadete Bytyçi and Maciej Banach

Introduction

The current coronavirus disease 2019 (COVID-19) is ongoing global pandemic and a major public healthcare problem worldwide [1]. Despite the extensive work of scientists in last 2 years, the optimal treatment against COVID-19 is still under investigation and there are still relatively limited therapeutic options that offer direct clinical benefits for COVID-19 patients. Moreover, the mortality rates still remain high [2, 3]. The disease can have a wide variety of clinical manifestations from mild, moderate to severe-life threating conditions ranging from acute respiratory distress syndrome (ARDS), sepsis, arrhythmia, coagulopathy, acute coronary syndrome, multiorgan dysfunction (MOD), and death [4, 5].

Systematic inflammation or cytokine storm/cytokine release syndrome (CRS) is the hallmark of COVID-19's severity. Immune-mediated inflammatory process plays a crucial role in the pathophysiology of COVID-19 with an overproduction of early response proinflammatory cytokines, namely interleukin (IL)-1, IL-6, IL-9, IL-10, IL-1β, tumor necrosis factor alfa (TNF-α), and interferon (IFN) [6–9]. Thus, it has been hypothesized that drugs that present potent anti-inflammatory and

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immunomodulatory actions may be effective therapies against COVID-19 and its complications [10, 11]. Colchicine is an old drug that for many decades has been successfully used in the treatment of inflammatory diseases (mainly the rheumatological ones), thus, it has been also proposed as a possible treatment option for COVID-19 [12, 13]. Recently, many studies have been shown the positive effect of colchicine in reduction the mortality and other clinical complications in COVID-19 patients [14–18].

COVID-19 and the Role of Inflammation

In many cases COVID-19 is manifested as asymptomatic or mildly symptomatic course, however, the infection may evolve into uncontrolled and a generalized hyperinflammatory state causing multiorgan damage that can be fatal in 2–3/100 patients [19]. The progression of COVID-19 can be divided into three phases:

(a) *Early infection phase*: the virus contacts and infiltrates the lung cells causing initial symptoms. During this phase, an adaptive immune response is required to destroy the virus and prevent the virus progression.
(b) *Pulmonary phase*: during this phase the viral replication and spread causes lung injury through compromise protective immune response and the inability of immune system to defeat the virus.
(c) *Inflammatory phase*: In this stage there is an overproduction of proinflammatory cytokines called as cytokine storm. During this phase the patients may have severe respiratory failure and multiorgan dysfunction [20, 21].

Patients with severe COVID-19 might have an abnormal or exaggerated inflammatory response, which is responsible for multiorgan injury. Particularly this response is characterized by a massive production of cytokines as mediators in inducing an inflammatory or immune response to effectively fight the virus [22]. Cytokines including IL-1β and IL-6 stimulate neutrophils for activation through chemoattractants and upregulate intercellular adhesion molecules on endothelial cells [22]. This leads to neutrophils adhesion to the vasculature, diapedesis, and infiltration into the affected tissues in COVID-19 patients, initially into lung parenchyma, but later into other organs. After neutrophils have migrated to sites of inflamed tissue, they degranulate and release proinflammatory cytokines and chemokines, proteases, and toxic radicals of oxygen [22, 23]. Furthermore, activated neutrophils and other leukocytes aggregate directly with platelets to further exacerbate inflammation-induced thrombosis [24]. Activated neutrophils adhere directly to each other, producing transient vascular occlusions. They also contribute to thrombosis via cytokine-induced release of α-defensin from neutrophil granules. The pyrin domain-containing protein 3 (NLRP3) is another critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines (pro-IL-1β and pro-IL- 18) to their active form. Both

products activate B, T, and NK cells in addition to stimulating of the release of other inflammatory cytokines, in response to microbial infection and cellular damage [25, 26].

Colchicine

Colchicine is a pharmacological agent, originally extracted from the plant family *Colchicum autumnale* or *Gloriosa superba*, a plant used by the ancient Greeks and Egyptians [27]. Although colchicine first received approval from the US Food and Drug Administration (FDA) in 2009, its modern use dates some centuries ago. In contrast to other anti-inflammatory drugs, colchicine has broad cellular effects via inhibition of tubulin polymerization and alteration of leucocyte responsiveness. Today it is used effectively in the treatment of pericarditis, rheumatic diseases, systemic vasculitis, periodic febrile illnesses, Sweet's syndrome, and others [12, 13, 27]. Nowadays, clinical studies also support its cardioprotective effects and its beneficial effect in atherosclerosis, myocardial infarction, and other anti-atherothrombotic effect [27–29]. Based on this data, the recent European Society of Cardiology guidelines for cardiovascular prevention for the recommended colchicine as the first anti-inflammatory agent to reduce the (residual) cardiovascular risk (with the IIbA recommendation) [30].

Mechanism of Action

Colchicine has different mechanisms of action through modulating of multiple anti-inflammatory pathways [31]. The anti-inflammatory effect of colchicine associated with the interruption of the microtubule filaments is believed to be one of the most important mechanisms. Colchicine prevents microtubule assembly that are responsible for cellular division, migration, signaling, and transport, and thereby disrupts activation of inflammation, chemotaxis/adherence, generation of leukotrienes and cytokines, and the process of phagocytosis as well [31, 32]. Moreover, colchicine can interfere with neutrophils as the primary cells involved in the inflammation phase through altering the distribution of adhesion molecules on the surface of neutrophils and endothelial cells, leading to inhibition of the interaction between endothelial cells and white blood cells by interfering with their migration to infected tissue. The main mechanism of action of colchicine against the cytokine storm is the inhibition of interleukins (IL-1β and IL-18) release through interfering with the NLRP3 inflammatory protein. The interfering of colchicine with inflammasomes interrupts their activation and reduces IL-1β production, which in turn prevents the induction of IL-6 and TNF and the recruitment of additional neutrophils and macrophages [31, 32].

In addition, colchicine displays anti-inflammatory effect by suppressing the radicals of superoxide and in that way, it inhibits mast cell degranulation [32, 33]. Available studies have shown that viroporin E, an envelope protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and viroporin 3a can induce NLRP3 inflammation pathway [34]. Hance targeting the NLPR3 inflammatory pathway with colchicine may be considered as a novel approach for the prevention of cytokine storm in SARS-COV-2 infection (Fig. 19.1). Murine models have also showed that colchicine inhibits neutrophil release of α-defensin, preventing large thrombus burden. Colchicine via its microtubule effect, converts the geometry of platelets and inhibits platelet activation by decreasing calcium entry, thereby, diminishing in vitro platelet-to-platelet aggregation [34].

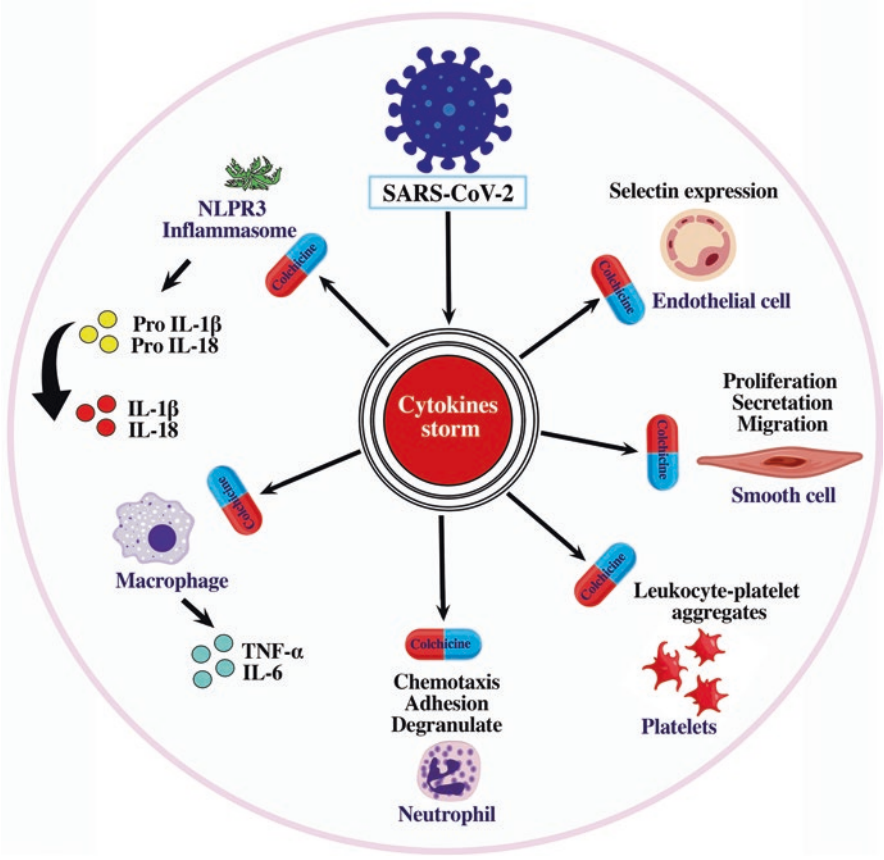

Fig. 19.1 The effect of colchicine on cytokine storm

Colchicine Pharmacokinetics

Colchicine is a lipophilic drug with mean oral bioavailability about 45% and despite it binds to albumin in the plasm, it quickly enters the peripheral leucocytes where it accumulates. This is the reason that pharmacological effects of colchicine are related to the concentration in leukocytes rather than in the plasma [35]. Colchicine is metabolized in the liver and intestine by cytochrome P450 (CYP3A4) and its half time is 1–2.7 h. It is primarily eliminated through the hepatobiliary extraction while about 10% through renal extraction, so the dose reductions may only be necessary in patients with severe renal dysfunction.

Despite the narrow therapeutic index of colchicine, it is relatively well tolerated, and the most common side effects are gastrointestinal disturbances that can occur in more than 20% of patients, while the neuromyopathy as side effect is more expected with chronic daily use of colchicine. Medications that strongly inhibit CYP3A4 metabolism (e.g., atorvastatin, simvastatin, ritonavir, clarithromycin, cyclosporine, ketoconazole, diltiazem, verapamil) pose a risk of drug-drug interactions, therefore in these cases monitoring is needed [36, 37].

Impact of Colchicine on Mortality and Morbidity on COVID-19

Many studies have recently reported the effectiveness of colchicine in reduction the mortality and other clinical complications in COVID-19 patients [14–18]. The first clinical trial (The Greek Effects of Colchicine in COVID 19-GRECO-19) evaluating the colchicine versus standard of care (SOC) in hospitalized patients found a significant reduction of clinical events including ordinal scale clinical deterioration (OSCD; 1.8% vs. 14%) [17]. Lopes et al. reported reducing the length of hospital stay (LOS: 7.0 days vs. 9.0 days; $p = 0.003$) and need for supplemental oxygen therapy (4.0 days vs. 6.5 days; $p < 0.001$) in patients receiving colchicine (0.5 mg 3× daily for 5 days and then the same dose twice daily for another 5 days) compared to SOC [18].

Recently, the results of a large double blinded clinical trial (COLCORONA) with 4888 patients were presented where patients were randomly assigned to receive orally administered colchicine 0.5 mg/twice per day for 3 days then once per day for 27 days thereafter. At 30-day follow-up, the clinical events (composite of death and hospitalization) were significantly lower in patients receiving colchicine compared to control (4.6% vs. 6%; $p = 0.04$) [26]. In contrast, another large clinical trial (RECOVERY) did not find survival benefit among colchicine treated patients [38]. In addition, more recently, many available meta-analyses of COVID-19 studies have also reported benefits of colchicine administration on mortality [14, 16, 39–41]. A meta-analysis by Lien et al. with a total 17,205 participants has showed the significant mortality reduction by 43% with numerical 33% reduction of subsequent mechanical ventilation [41]. Another important evidence from the available studies,

that strengthens the benefit of colchicine in patients with COVID-19, is the benefit of colchicine treated patients for other clinical events, including hospitalization, length of hospital stays (LOS), and need for mechanical ventilation [14].

Role of Colchicine in Cardiac Protection

Cardiovascular disease (CVD) remains the leading cause of death worldwide, despite current optimal therapy, lifestyle changes, and risk factors control [42]. Concomitant CVDs are present in about 25% of overall COVID-19 infected population and in higher proportion of those who die [43]. Although, the primary cause of death in COVID-19 infection is respiratory failure and the disease is often discussed in a pulmonary context, patients develop the cardiac manifestations that may contribute to overall mortality and be the primary cause of death in these patients [43]. The cardiac involvement in SARS-CoV2 infection could be multifactorial, which include coronary spasm, atherosclerotic plaque rupture, endothelial injury, microthrombi formation, etc. Different mechanisms responsible for cardiac involvement can occur directly or indirectly and there are at least several confirmed mechanisms responsible for cardiac injury [44]. The SARS-CoV-2 can entry into cardiac cells leading to endothelial dysfunction and direct cardiac injury. In situ labeling of viral RNA, has detected a viral tropism for cardiac myocytes [45]. In addition, an interaction between viral spike protein and target cell angiotensin-converting enzyme 2 (ACE2) receptor facilitating membrane fusion was also found [45]. Myocardial injury and fulminant myocarditis can occur from direct viremic effect on the myocardial cells [46, 47].

In addition to direct mechanisms the indirect mechanisms of cardiac injury are mainly due to inflammation. The cytokine storm or hyperimmune response can trigger arrhythmias, plaque destabilization cardiomyopathies, and myocardial cell injury [23]. The myocardial injury including degeneration of myocardial cell, necrosis, interstitial hyperemia with infiltration of lymphocytes, and other inflammatory mediators but without component of virus in the myocardial tissue were also reported [48, 49]. In addition, SARS-CoV-2 can activate the coagulation cascade leading to thromboembolic events [49].

Cardiovascular manifestations of SARS-CoV-2 variate from mild to severe myocardial injury including coronary ischemia, acute coronary syndrome (ACS), myocarditis, myocardial fibrosis, cardiomyopathy, heart failure, and cardiogenic shock.

Atherosclerosis involves a complex interplay between different mechanisms. It is also well recognized that inflammation has a central role in the pathogenesis and clinical manifestations of atherosclerosis. Therefore, the colchicine has been shown to modulate and inhibit the NLRP3 through multiple pathways, which is responsible for maturation of the pro-inflammatory cytokines IL-1β and IL-18. Furthermore, this inflammasome has been implicated as a key mediator in the cascade of inflammatory pathway in atherosclerosis [29, 50]. In another hand, the cholesterol crystals as part of atherosclerotic plaque, also activate the NLRP3 inflammasome leading to instability of plaque [51].

The positive effect of oral colchicine was also confirmed in coronary artery disease (CAD). Oral colchicine was shown to inhibit cleaved caspase-1 protein expression and downstream mature IL-1β and the positive effect of colchicine was confirmed in patients with CAD, including in stable patients and ACS patients undergoing angiography [51, 52]. In addition to cytokines, the monocytes also produce a range of inflammatory chemokines such as CCL-2, CX3CL1 and CCL5, which play important role on atherosclerotic plaque progression. While colchicine demonstrated decrease the levels of those chemokines in patients with ACS [50]. Moreover, the colchicine effect also was shown on another part of cascade of inflammation through neutrophils as first line of defense of the immune system against microorganisms and important component of atherosclerosis [53, 54]. Thus, the inhibition of neutrophil adhesion and its interaction with endothelial cells via inhibiting expression of L-selectin are some mechanisms of colchicine demonstrated experimentally in vitro. Another important effect of colchicine is modulation of the formation of leukocyte-platelet aggregates, which have a major impact to atherothrombosis conditions via microtubule inhibition, leading to a reduction in procoagulant activity [51].

Recently, colchicine's effects on circulating microRNAs, which are noncoding RNA molecules that regulate gene expression at the post-transcriptional level, were recently studied in ACS patients [50]. Finally, increased cytokine secretion during COVID-19 infection, can lead to apoptosis or necrosis of myocardial cells, nonischemic myocardial injury and impaired cardiac function through multiple mechanisms of response of hyperactivated immune system (Fig. 19.2) [23].

Colchicine Dosage for Cardioprotection in Patients with COVID-19

Despite the effective dose of colchicine in plasma concentration was proposed to be 0.5–3.0 g/l, because of pharmacodynamic effects of colchicine is closely related to concentrations in leukocytes, many studies suggested that doses of 0.5–2.0 mg/day are considered relatively safe and without major gastrointestinal adverse effects [54–56].

Colchicine is a drug with narrow therapeutic index and the dosing regimens needs to be carefully designed. During the early infection phase of COVID-19, a practical approach could be to use with low initial dose (0.5 mg/day) as a preventive method to prevent progression into second/third phase. Low dose of colchicine has a good tolerability, and the immunosuppressive effect is not expected, but it is not recommended to be administered in the same time with other immunosuppressants or glucocorticoids to avoid possible decreased of the immune system [25, 55–57].

In contrast to first phase that colchicine can be used as a preventive drug, in the second phase the therapy is crucial and colchicine dose can be increased to 0.5 mg/twice daily for adult with a body weight greater than 70 kg. Despite the low dose, liver and kidney function should be monitored and attention is needed in the case of

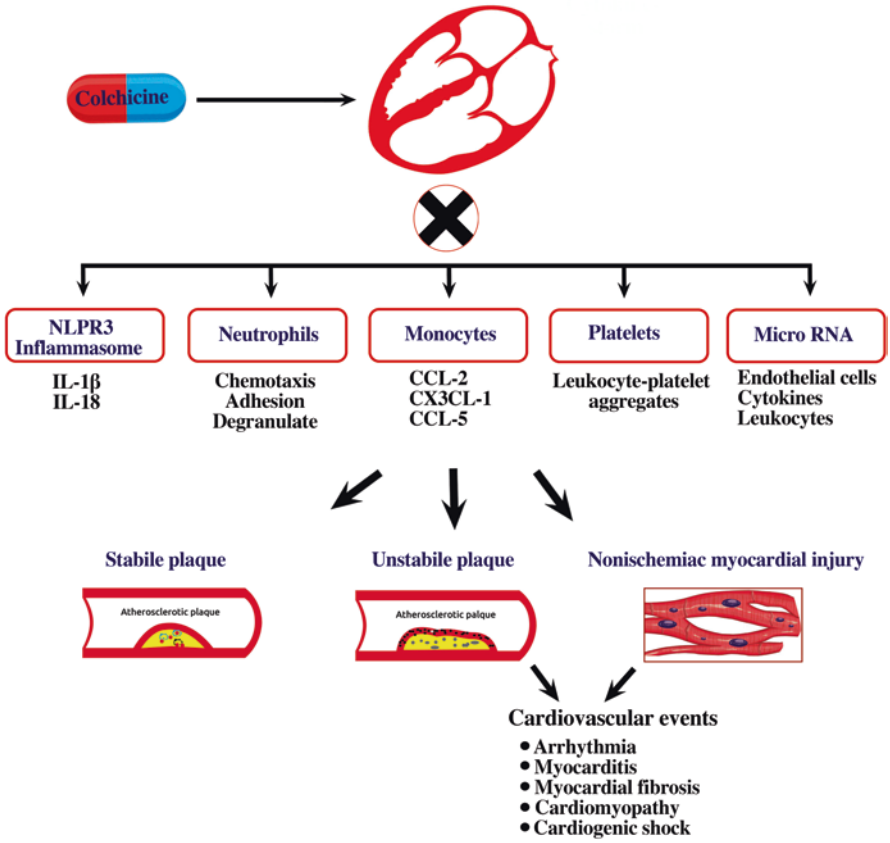

Fig. 19.2 Cardioprotect effects of colchicine

possible interaction with other drugs in use. At the third stage administration of colchicine (0.5 mg/once or twice daily), in monotherapy or in combination with glucocorticoids to control the cytokine storm is recommended [55–57].

Role of Colchicine in Glycemic Level

Many available studies emphasized the evidence that SARS-CoV-2 infection can lead to hyperglycemia through suppressing insulin secretion and lowered sensitivity to insulin, worsening COVID-19 severity not only in diabetic patients but also in the absence of diabetes, that later may complicate COVID-19 with superinfection and poor prognosis [58, 59]. Furthermore, patients with COVID-19 who were hyperglycemic had higher incidence of severe disease compared normoglycemic patients

[58]. Colchicine at maximum daily doses of 1.5 mg has been associated with lower incidence of diabetes and improving the fasting insulin resistance [60].

Although, the true mechanisms of improving the glycemic level through colchicine treatment are still not fully understood, IL-1 receptor antagonist has demonstrated an improvement in beta-cell secretory function and decrease hemoglobin A1c in adults with diabetes. In addition, decrease the IL-6 in colchicine treated patients, has shown high correlation with first phase of insulin secretion [61].

Role of Colchicine on Furin Level

Furin is an enzyme that belongs to the pro-protein convertase subtilisin/kexin (PCSK) family. Several bacterial toxins and viral envelopes including human immunodeficiency virus, Ebola as well as SARS CoV-2, need cleavage of furin for their functionality. Obese and diabetic patients, males, and the elderly, have increased serum levels of furin, that might explain why these subgroups are at an increased risk of COVID-19 related complications and deaths [62]. Furin has been found to play a role in redirecting lipid deposition in adipose tissue. In addition, it has a role in increasing interaction between adipocytes and mononuclear inflammatory cells that latter can lead to vascular remodeling, atherosclerosis, and chronic inflammation [63].

Colchicine acts by targeting several inflammatory pathways and has been found to target specifically endothelial inflammation and vascular degeneration through furin. Screening serum levels of furin early in positive SARS-CoV2 patients might serve as an important strategy to anticipate COVID-19 poor outcomes, and preventing them [62, 63].

Conclusions

Colchicine is an inexpensive, well-known immunomodulatory drug with acceptable safety profile that has different mechanisms of action through modulating of multiple anti-inflammatory pathways. Its atheroprotective properties are thought to be mainly related to its effect on tubulin polymerization. However, most of the available clinical trials did not confirm (or is inconsistent) its effectiveness in different patients' groups with COVID-19, and therefore as for now it cannot be recommended as a targeted therapy for this group of patients [64]. Further data on the patients that might benefit the most (e.g., those with high levels of inflammatory biomarkers, with underlying CVD, and others) are necessary to have final indications on its utilization in coronavirus infected patients [65].

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Chapter 20
Antiplatelet Drugs in COVID-19: Mechanism of Action and Effect on Prognosis

Jack S. Bell, Gregory Y. H. Lip, and Riccardo Proietti

Key Points

1. Platelets from patients with COVID-19 disease are hyperactivated and show increased aggregation and platelet-leukocytes interactions. SARS-CoV-2 can directly invade platelets leading to digestion of the virion and destruction of the platelet.
2. Aspirin is theoretically an attractive therapeutic agent for COVID-19 disease due to its anti-thrombotic, anti-inflammatory, and anti-viral properties.
3. The RECOVERY trial is a large randomised controlled trial that showed no difference in mortality or progression to invasive mechanical ventilation in hospitalised COVID-19 patients treated with aspirin 150 mg once a day until discharge compared to usual care alone.
4. The results from several randomised controlled trials investigating antiplatelets in COVID-19 disease are awaited.
5. At this point in time, there is no evidence for starting antiplatelets in the treatment of COVID-19 disease.

Introduction

As we learn more about COVID-19 disease it has become increasingly apparent that there is an excess of thrombotic events compared to other viral pneumonias [1, 2]. While venous thromboembolism (VTE) appears to be the most significant burden,

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there also appears to be an excess of arterial thromboembolism (ATE), including acute coronary syndrome (ACS), stroke, and peripheral arterial thrombosis, and post-mortem studies have revealed extensive microvascular thrombosis [1–3]. Consequently, antiplatelet drugs were quickly identified as potential therapeutic agents to reduce the burden of thrombotic disease. In particular, aspirin has been a subject of much interest as it is cheap, generally well-tolerated and effective for secondary prevention of cardiovascular disease at low doses [4]. Furthermore, at higher doses aspirin has anti-inflammatory and even anti-viral properties, which makes it a theoretically attractive candidate for treating COVID-19 disease. In this chapter, we will explore relevant pathophysiological and clinical perspectives on thrombosis in COVID-19 disease before exploring the mechanism of action of antiplatelets in COVID-19 disease and evaluating the clinical evidence for effect on prognosis. We will focus on aspirin as this is where the majority of the COVID-19 literature is concentrated.

Thrombosis in COVID-19: Pathophysiological Perspectives

The pathophysiology driving the COVID-19-associated coagulopathy is complex and yet to be fully delineated. While SARS-CoV-2 is not inherently thrombogenic, it generates a coagulopathy through induction of a profound inflammatory response and widespread endothelial activation, which may in part be via direct viral invasion of the vascular endothelium [5, 6]. Early stages of the coagulopathy are characterised by an isolated rise in D dimer, with higher levels portending a worse prognosis [7]. Here, localised lung inflammation may trigger the formation of lung microthrombi through immunothrombosis: the physiological process by which the haemostatic and innate immune systems coordinate localised thrombosis to contain infection [8]. In a subgroup of patients, localised pulmonary inflammation progresses to a cytokine storm and a systemic coagulopathy [9, 10]. Immunothrombosis becomes dysregulated leading to widespread pulmonary microthrombi which may coalescence to form clinically detectable thrombus. This may manifest clinically with increasing oxygen requirements and injury to other organ systems, and biochemically with increasing D dimer, mild thrombocytopenia and mildly prolonged PT [11]. As systemic inflammation and coagulopathy develop further there may be progression to multiorgan failure with laboratory features trending towards overt disseminated intravascular coagulation [12].

Platelets in COVID-19

Platelets are a bridge between the haemostatic and innate immune systems and appear to undergo several changes in COVID-19 disease which antiplatelets could theoretically influence. First, platelets from COVID-19 patients are more activated,

as measured by granule release and P-selectin expression, and aggregate faster compared to healthy donor platelets [13]. The typically mild thrombocytopenia seen in COVID-19 disease likely reflects this enhanced platelet activation and consumption, and is associated with worse prognosis [14]. Platelet activation is associated with increased activity in the MAPK pathway and increased thromboxane A2 production [13]. In critically ill COVID-19 patients, platelet hyperreactivity, as measured by ex vivo aggregation in response to a thrombin stimulus, could be diminished to the levels of healthy controls following pre-treatment with high dose aspirin [13].

Second, flow cytometry reveals significantly elevated platelet-neutrophil, −monocyte, and -T cell aggregates in COVID-19 patients compared to healthy controls [13]. The platelet-neutrophil interaction is thought to be particularly relevant to immunothrombosis in COVID-19 through the formation of neutrophil-extracellular traps (NETs). NETs are extra-cellular web-like structures of DNA decorated with cytotoxic histones and antimicrobial proteins that are expelled from neutrophils to physically trap and destroy microbes [15]. While there are myriad triggers for NET formation including microbes, cytokines, and endothelial damage, the platelet-neutrophil interaction appears to be crucial for the formation and propagation of NETs [16, 17]. As well as their antimicrobial effects NETs are a nidus for thrombosis—free DNA activates the intrinsic coagulation pathway and histones activate platelets [18]. While NETosis is a physiological process, with prolonged inflammation it can become dysregulated leading to neutrophil-mediated endothelial damage and extensive microvascular thrombosis. Post-mortem histology from patients with COVID-19 disease has shown colocalisation of platelets and NETs in microthrombi in the lungs, kidneys, and heart [19]. Furthermore, levels of circulating NETs correlate with COVID-19 disease severity and thrombosis [20], and levels of platelet-derived factors that trigger NETosis, such as platelet-derived factor 4, are significantly higher in COVID-19 patients compared to controls [21]. As the platelet-neutrophil interaction is important for NET formation antiplatelets may be able to reduce NETosis and therefore dysregulated immunothrombosis. Indeed, aspirin pre-treatment has been shown to reduce NET release and microvascular occlusion in a mouse model of *Staphylococcus aureus* bacteraemia [22].

Platelet-monocyte interactions are also relevant for immunothrombosis. In severe COVID-19 patients, platelet–monocyte interactions were strongly associated with monocyte tissue factor expression, which activates the extrinsic coagulation pathway [23]. Platelet activation and monocyte tissue factor expression correlated with soluble markers of coagulation such as fibrinogen and D-dimer, invasive mechanical ventilation, and in-hospital death [23]. Incubation of platelets from COVID-19 patients with healthy monocytes induced monocyte tissue factor expression, an effect which was blocked with pre-incubation with a P-selectin neutralising antibody, but not with aspirin or clopidogrel [23]. As aspirin and clopidogrel were delivered ex vivo to highly active platelets extracted from severe COVID-19 patients, this may not represent the physiological effects of these antiplatelet agents in vivo.

Third, electron microscopy has shown that SARS-CoV-2 virions incubated with platelets are rapidly internalised, leading to programmed cell death and

microvesicle release within 30 min [24]. RNA sequencing of platelets from patients with COVID-19 shows evidence of fragmented SARS-CoV-2 genome alongside gene expression changes in pathways associated with protein ubiquitination and mitochondrial dysfunction [24]. Interestingly, it has been suggested that platelets may be a dead end for SARS-CoV-2 with virions in the plasma being rapidly internalised and digested [25]. However, this process leads to platelet destruction with release of inflammatory mediators and microvesicles that contribute to a pro-inflammatory and pro-thrombotic milieu [26]. The effect of antiplatelet agents on this phenomenon, whether positive or negative, remains unclear.

Thrombosis in COVID-19: Clinical Perspectives

Thrombosis in COVID-19 can be broadly categorised into venous thromboembolism, arterial thrombosis, and microvascular thrombosis. A recent meta-analysis examining 102 studies found that overall incidence of COVID-related VTE was 14.7% (95% CI 12.1–17.6), rising to 23.2% in critically ill patients (95% CI 17.5–29.6) [27]. A separate meta-analysis of studies comparing VTE incidence between COVID-19 and non-COVID-19 respiratory infections, particularly H1N1 influenza, determined that there was a 6% increased risk of VTE in COVID-19 compared to non-COVID-19 cohorts, which rose to 15% in critically ill patients [1].

In comparison, the reported rates of arterial thromboembolism are considerably lower. One meta-analysis estimated an overall incidence of arterial thromboembolism of 4.0% (95% CI 2.0–6.5, $I^2 = 95\%$; 19 studies; 8249 patients). The most common arterial event was ischaemic stroke occurring in 1.6% (95% CI 1.0–2.2, $I^2 = 93\%$; 27 studies; 40,597 patients), followed by ACS in 1.1% (95% CI 0.2–3.0, $I^2 = 96\%$; 16 studies; 7939 patients), and other arterial thromboembolic events, such as limb or mesenteric ischaemia, in 0.9% of patients (95% CI 0.5–1.5, $I^2 = 84\%$; 17 studies; 20,139 patients) [27]. These figures are consistent with a Cochrane systematic review which reported a weighted mean incidence of 1.7% for ACS (range 0–3.6%, 16 studies) and 1.2% for stroke (range 0–9.6%, 20 studies) [28]. We note that the Cochrane review authors decided to carry out a narrative review rather than a meta-analysis due to high variation in study design and reported outcomes. A retrospective study conducted across four New York hospitals appeared to show an excess of arterial thrombosis in COVID-19 when comparing 3334 COVID-19 patients with 954,521 patients hospitalised with viral pneumonia between 2002 and 2014. When comparing COVID-19 to viral pneumonia the prevalence of myocardial infarction (MI) was 8.9% vs. 2.8%, the prevalence of ischaemic stroke was 1.6% vs. 0.7%, and the prevalence of other systemic embolism was 1% vs. 0.1% [2]. Please note that the rates of MI reported in this COVID-19 cohort were considerably higher than in other studies and therefore these results should be interpreted with caution.

Alongside macrothrombi, autopsy studies have shown that alveolar capillary microthrombi are nine times more prevalent in patients who have died from COVID-19-associated respiratory failure compared to those who have died from influenza-associated respiratory failure [3]. Platelet-rich microthrombi are also seen in the kidneys and myocardial vessels and are likely a driver of multiorgan failure in COVID-19 patients [19, 29].

Aspirin in COVID-19

Acetylsalicylic acid, originally marketed under the brand name aspirin in 1899, has anti-thrombotic, anti-inflammatory, and anti-viral properties that make it an attractive candidate for treating COVID-19 disease (Fig. 20.1).

Anti-thrombotic Effects of Aspirin

At low doses (e.g., 75–81 mg/day) aspirin acetylates and irreversibly inhibits cyclo-oxygenase-1 (COX-1) enzymes and thereby reduces the production of thromboxane A2, a potent platelet agonist. This is the primary mechanism by which aspirin exerts its anti-thrombotic effects. While much of the evidence is being re-examined recently [30], low dose aspirin appears to be effective for secondary prevention of cardiovascular disease [4] and could therefore be expected to reduce arterial thrombosis in COVID-19. Furthermore, low dose aspirin could in

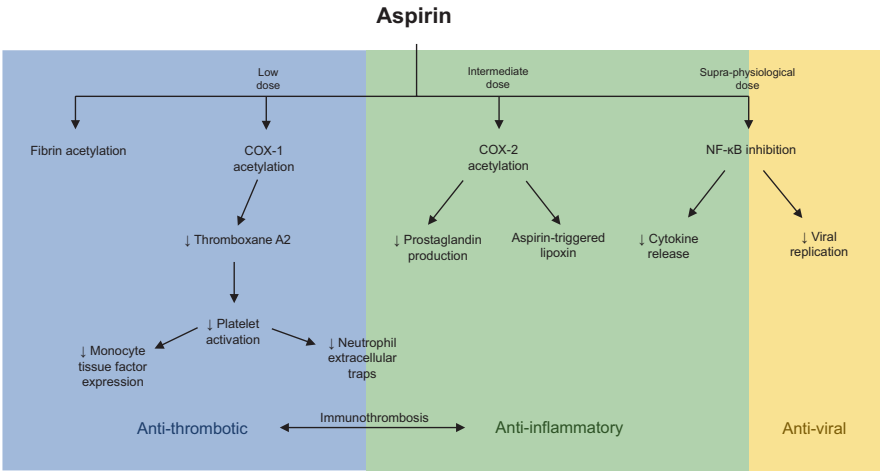

Fig. 20.1 Potential mechanisms of action of aspirin in COVID-19 disease

theory mitigate some of the pathological platelet changes seen in COVID-19 disease, as described previously. Independent of antiplatelet effects, aspirin also appears to have some direct effect against fibrin-rich venous thrombus and has been shown to be effective in secondary prevention of VTE [31]. One mechanism is through direct acetylation of fibrin which has been shown to increase fibrin clot permeability and clot lysis [31].

Anti-inflammatory Effects of Aspirin

At higher doses (e.g., 650 mg–4 g/day), aspirin acetylates inducible COX-2 which reduces production of pro-inflammatory prostaglandin mediators and thereby exerts an anti-inflammatory effect. Acetylated-COX-2 also diverts arachidonic acid into forming 15-epoxy-lipoxin A4, also known as aspirin-triggered lipoxin (ATL). ATL exerts an anti-inflammatory effect in the endothelium, through reduced reactive oxygen species production and increased nitric oxide synthesis, and across virtually all immune cell types. This is explored in detail elsewhere [32]. While COX-2 acetylation is traditionally thought to occur at higher doses of aspirin, a randomised controlled human trial found that ATL is optimally induced with aspirin 81 mg once daily, compared to 325 mg or 650 mg once daily [33].

Anti-viral Effects of Aspirin

Independent of COX inhibition, very high doses of aspirin exert anti-inflammatory and anti-viral effects via inhibition of the key nuclear transcription factor nuclear factor-κB (NF-κB). NF-κB is essential both for transcription of a range of anti-viral cytokines and for viral replication during hostile takeover of host cells. D, L-lysine acetylsalicylate + glycine (LASAG), a licensed derivate of aspirin with increased solubility, can reduce in vitro viral replication of both low and highly pathogenic human beta coronaviruses (HCoV-229E and MERS-CoV, respectively) via an NF-kB-dependent mechanism [34]. Studies of influenza viruses have shown similar findings [35]. We note that high concentrations of aspirin, which would be toxic through oral administration, were required to generate these anti-viral effects in vitro. Instead, some groups have suggested that aerosolised aspirin could be used to deliver high local concentrations into the lungs, the primary site of viral replication and inflammation [36]. Inhaled aerosolised LASAG has been shown to reduce duration of symptoms in a randomised placebo-controlled trial of 41 hospitalised patients with severe influenza [37]. We note that no studies to date have investigated the effect of aspirin or its derivates on SARS-CoV-2 replication, although severe COVID-19 is associated with high levels of NF-κB activity [38].

Mechanism of Action of Other Antiplatelets in COVID-19 Disease

Dipyridamole has garnered some attention as an anti-COVID-19 therapeutic for similar reasons to aspirin. It has both antiplatelet and anti-inflammatory activity alongside some direct in vitro activity against SARS-CoV-2 at physiological concentrations [39]. Furthermore, dipyridamole may have additional action against NETosis through agonism of adenosine A_{2A} receptors on neutrophils [40]. Consequently, there are three small randomised controlled trials investigating the effect of dipyridamole, either alone or in combination with aspirin, on outcomes in COVID-19 disease (see Table 20.2). P2Y12 inhibitors are posited to influence prognosis in COVID-19 through more potent platelet inhibition. Similar to dipyridamole, ticagrelor appears to inhibit cellular adenosine uptake and may therefore have pleiotropic anti-inflammatory properties [41]. Indeed, in the randomised placebo-controlled XANTHIPPE trial (Examining the Effect of Ticagrelor on Platelet Activation, Platelet-Leukocyte Aggregates, and Acute Lung Injury in Pneumonia) patients with pneumonia receiving ticagrelor had reduced oxygen requirements, reduced platelet-leukocyte aggregates, and reduced IL-6 levels compared to placebo [42].

Clinical Studies of Aspirin in COVID-19

Despite aspirin being a theoretically attractive drug for treating COVID-19 disease, robust evidence for a beneficial effect on prognosis is lacking.

There have been numerous retrospective observational studies which have sought to establish an association between aspirin use and clinically relevant outcomes (Table 20.1). Most of these studies investigate the impact of a pre-admission aspirin prescription on outcomes for hospitalised COVID-19 patients and are therefore prone to significant confounding. For example, patients receiving pre-admission aspirin are more likely to be elderly, more comorbid, and have a higher baseline risk for thrombotic disease. Patients prescribed aspirin are also more likely to be prescribed other cardiovascular medications, such as a statin or an ACE-inhibitor, which may influence prognosis in COVID-19 disease. Furthermore, there is large heterogeneity in study design and reported outcomes which limits the interpretation of these studies. Meta-analyses of these observational studies appear to show reduced mortality with aspirin although with a low certainty of evidence [43–45].

To date there has only been one published randomised controlled trial investigating the effect of aspirin on outcomes in hospitalised COVID-19 patients. The RECOVERY trial is a randomised, controlled, open-label platform trial which has evaluated multiple potential treatments for hospitalised COVID-19 patients across 177 hospitals in the UK, 2 hospitals in Indonesia, and 2 hospitals in Nepal. In this arm of the trial, 7351 patients were randomly allocated to receive usual care plus

Table 20.1 Trials of antiplatelet agents in COVID-19 disease

Study name	Patients	Study design	Intervention	Primary outcomes	Secondary outcomes	Comments
RECOVERY group, 2021	Hospitalised patients *N* = 7351 standard of care + aspirin 150 mg OD until discharge *N* = 7541 standard of care only	Randomised open-label controlled trial 177 hospitals in UK, 2 in Indonesia, and 2 in Nepal	Aspirin 150 mg OD until hospital discharge	28-day mortality: 17% in both groups (rate ratio 0.96; 95% CI 0.89–1.04; $p = 0.35$)	Composite endpoint of invasive mechanical ventilation or death for patients not on invasive mechanical ventilation at randomisation: Aspirin 21% vs. control 22% (risk ratio 0.96, 95% CI 0.90–1.03; $p = 0.23$) Length of stay: Aspirin (median 8 days, IQR 5 to >28) vs. control (9 days, IQR 5 to >28) Discharged alive within 28 days: Aspirin 75% vs. control 74% (rate ratio 1.06, 95% CI 1.02–1.10; $p = 0{\cdot}0062$) Thrombotic events: Aspirin 4.6% vs. control 5.3% (SE 0.4%) Major bleeding events aspirin 1.6% vs. control 1.0% (SE 0.2%)	Large sample size Randomised controlled trial Patients on pre-admission aspirin or other antiplatelets were excluded
ACTIV-4B trial	Symptomatic outpatients *N* = 657	Randomised controlled trial USA	Aspirin 81 mg OD vs. apixaban 2.5 mg BD vs. apixaban 5 mg BD vs. placebo for 45 days following positive COVID-19 test	Composite of all-cause mortality, symptomatic venous or arterial thromboembolism, MI, stroke, or hospitalisation for cardiovascular or pulmonary cause		Trial stopped early due to low event rate

Health outcome predictive evaluation (HOPE) COVID-19 registry Santoro et al. 2021	Hospitalised patients *N* = 6986 no antiplatelet therapy *N* = 730 single antiplatelet on hospital admission *N* = 50 dual antiplatelet on hospital admission	Prospective cohort study Multinational registry	N/A	All-cause mortality: Antiplatelets 18% vs. control 19% ($p = 0.64$) On multivariate analysis mortality risk ratio 0.29 (95% CI 0.22 to 0.38, $p < 0.0001$) in favour of antiplatelets	Invasive mechanical ventilation: 8.7% antiplatelet vs. 8.5% no antiplatelet Embolic events: 2.9% antiplatelet vs. 2.5% no antiplatelet Bleeding events: 2.1% antiplatelet vs. 2.4% no antiplatelet	Retrospective study
Sahai et al. 2021	Symptomatic PCR-positive ambulatory and hospitalised patients *N* = 248 no antiplatelet therapy *N* = 248 aspirin	Propensity-matched retrospective study Multi-Centre, USA	N/A	All-cause mortality: No difference between aspirin and control (13.3% vs. 15.3%, $p = 0.53$)	MI, VTE, and thrombotic stroke: Aspirin 9.3% vs. control 2.8% ($p = 0.005$)	Retrospective study Patients already on aspirin are more prone to thrombotic events
Chow et al. 2021	Hospitalised patients *N* = 314 no aspirin *N* = 98 aspirin 81 mg OD	Retrospective cohort study Multi-Centre, USA	N/A	All-cause mortality: Aspirin 26.5% vs. no aspirin 23.2% ($p = 0.51$) Multivariable analysis: Adjusted HR for mortality 0.53 (95% CI, 0.31–0.90, $p = 0.02$) in favour of aspirin	Invasive mechanical ventilation: Aspirin 35.7% vs. no aspirin 48.4% ($p = 0.03$). Adjusted HR 0.56 (95% CI 0.37–0.85, $p = 0.007$) ICU admission: 38.8% aspirin vs. 51.0% no aspirin ($p = 0.04$). Adjusted HR 0.57 (95% CI 0.38–0.85, $p = 0.005$) There were no differences in major bleeding ($p = 0.69$) or overt thrombosis ($p = 0.82$)	Retrospective study Aspirin and non-aspirin group poorly matched. Reduced O_2 requirements in aspirin group on admission—53% vs. 45% patients maintaining oxygen saturations on room air; 3% vs. 6% requiring non-rebreathe mask

(continued)

Table 20.1 (continued)

Study name	Patients	Study design	Intervention	Primary outcomes	Secondary outcomes	Comments
Meizlish et al. 2021	Hospitalised patients not receiving pre-admission antiplatelets *N* = 319 de novo in-hospital aspirin 81 mg OD *N* = 319 no in-hospital aspirin	1:1 propensity-matched retrospective study Multi-Centre, USA	N/A	In-hospital mortality: On multivariate regression HR 0.522 (95% CI 0.336–0.812, $p = 0.004$) Controlled for age, anticoagulation other than prophylactic dose, male sex, obesity, cardiovascular disease, African-American race, maximum D dimer during admission, and admission Rothman index (disease severity), ICU admission		Retrospective study What influenced clinician decision to start certain patients on aspirin? Doesn't present unadjusted mortality rates in propensity-matched groups
Osborne et al. 2021	Veterans Outpatients with active prescription of aspirin at time of PCR diagnosis of COVID-19 14-day mortality cohort: *N* = 6814 aspirin *N* = 6814 no aspirin 30-day mortality cohort: *N* = 6300 aspirin *N* = 6300 no aspirin	1:1 propensity-matched retrospective study National veterans' network, USA	N/A	In-hospital mortality: At 14-days aspirin 2.5% vs. no-aspirin 6.3% (OR 0.38, 95% CI 0.32–0.46) At 30-days aspirin 4.3% vs. no aspirin 10.5% (OR 0.38, 95% CI 0.33–0.45) Propensity matched for age, gender, and care assessment needs score (1-year mortality		Based on active outpatient prescription of aspirin Unclear which patients were admitted to hospital and may have received other antithrombotics Large number of patients across diverse populations. However, generally older and overwhelmingly male

Sisinni et al. 2021	Hospitalised COVID-19 patients *N* = 253 pre-admission aspirin *N* = 731 no pre-admission aspirin	Retrospective cohort study Two hospitals, Italy	N/A	Composite of in-hospital mortality and respiratory support upgrade at 30 days: Aspirin 63% vs. no aspirin 75% (HR 0.788, log-rank $p = 0.013$)	In-hospital mortality: Aspirin 52% vs. no aspirin 53% (HR 1.042, log-rank $p = 0.653$) Upgrade in respiratory support: Aspirin 33% vs. no aspirin 49% (HR 0.640, log-rank $p = 0.008$)	Reduction in primary endpoint in aspirin group driven by reduced respiratory support upgrade rather than reduced mortality Baseline characteristics of aspirin and no aspirin group were significantly different in many variables Reduced respiratory support upgrade in aspirin group may reflect the fact that this more comorbid group would be less likely to be deemed suitable for NIV or IMV
Yuan et al. 2021	Hospitalised patients with coronary artery disease *N* = 53 pre-admission aspirin use *N* = 131 no aspirin use	Retrospective cohort study Single Centre, China	N/A	In-hospital mortality: No significant difference between aspirin and non-aspirin group (21.2% vs. 22.1%, $p = 0.885$)		Retrospective Data only available for pre-admission aspirin use No data on use of other antiplatelets

(continued)

Table 20.1 (continued)

Study name	Patients	Study design	Intervention	Primary outcomes	Secondary outcomes	Comments
Liu et al. 2021	Hospitalised patients Total sample = 232 *N* = 24 aspirin 100 mg OD *N* = 24 no aspirin	1:1 propensity-matched retrospective cohort study Single Centre, China	N/A	30-day mortality: Aspirin 4.17% vs. controls 29.2% 60-day mortality: Aspirin 8.3% vs. control 33.3%		Small study Not clear whether aspirin was an existing prescription or whether it was started in hospital
Liu et al. 2020	Hospitalised patients *N* = 14 dipyridamole 50 mg TDS *N* = 17 usual care	Randomised open-label trial Two centres, China	Dipyridamole 50 mg TDS for 14 days	Mortality: Dipyridamole 7.1% vs. control 23.5% Discharged alive: Dipyridamole 78.6% vs. control 11.8%	Rise in D dimer levels: Less with dipyridamole	Small study Poorly defined outcomes No information about randomisation process Unblinded

aspirin 150 mg once a day until discharge and 7451 patients received usual care alone [46]. Exclusion criteria included patients with a history of aspirin hypersensitivity or recent major bleeding and patients taking pre-admission antiplatelet agents. There was no difference in the primary outcome of 28-day mortality which was 16.6% in the aspirin group and 17.2% in the control group (rate ratio 0.96, 95% CI 0.89–1.04; $p = 0.35$). This lack of mortality benefit was consistent across all prespecified subgroup analyses: age, sex, ethnicity, duration of symptoms before randomisation, amount of respiratory support at randomisation, and use of corticosteroids. In patients who were not receiving invasive mechanical ventilation (IMV) at the time of randomisation, aspirin had no effect on the proportion of patients reaching the composite endpoint of IMV or death (21% aspirin vs. 22% control; risk ratio 0.96, 95% CI 0.90–1.03; $p = 0.23$). Patients randomised to aspirin had a slightly shorter length of hospital stay (median 8 days (IQR 5 to >28) vs. 9 days (IQR 5 to >28)) and a small but significantly increased likelihood of being discharged from hospital alive within 28 days (75% vs. 74%; rate ratio 1.06, 95% CI 1.02–1.10; $p = 0.0062$) compared to patients receiving usual care alone. As expected, aspirin was associated with a reduction in thrombotic events (4.6% vs. 5.3%; absolute risk decrease 0.6%, SE 0.4%), which was driven by a reduction in both venous and arterial events, but was associated with an increased risk of major bleeding events compare to usual care alone (1.6% vs. 1.0%; absolute risk increase 0.6%, SE 0.2%). This was such that for every 1000 patients treated with aspirin there were approximately six fewer thrombotic events but six more major bleeding events.

Taken together, this large, randomised, and well-controlled trial shows no effect of aspirin over standard care in terms of mortality or progression to invasive mechanical ventilation. With regards to study limitations, the open-label nature of the trial may have led to clinician bias. Exclusion criteria included patients receiving pre-admission antiplatelet therapy and who are likely to have higher baseline thrombotic risk. The effect of aspirin in this population is yet to be determined.

Why was aspirin ineffective in hospitalised COVID-19 patients? First, there may be lack of an additive effect of aspirin on top of the anticoagulant effects of low-molecular weight heparin (LMWH) treatment (60% of patients received standard prophylactic dose LMWH; 34% received higher dose LMWH), and the anti-inflammatory effects of dexamethasone (received by 87% of patients) in the RECOVERY trial. For example, dexamethasone may attenuate the cytokine storm and immunothrombosis [47] and may even act on similar antiplatelet mechanisms as aspirin. In community-acquired pneumonia, treatment with glucocorticoids reduces platelet thromboxane A2 production in vitro, and is associated with lower levels of urinary 11-dehydro thromboxane B2, a reliable marker of platelet activation, in vivo [48]. Second, platelet pathways may be less relevant in the pathophysiology of COVID-19 coagulopathy, with inflammation and the coagulation cascade instead being the key drivers of thrombosis. It is possible that thromboxane-A2-independent platelet pathways may still be relevant in COVID-19 disease as has been shown in ex vivo studies of *Streptococcus pneumoniae* infection [49]. In this case, antiplatelets targeting the ADP receptor, such as P2Y12 inhibitors, may yet show clinical benefit. Third, low dose aspirin may be insufficient to achieve effective COX

inhibition in the context of the profound inflammation and hypercoagulability seen in COVID-19 disease. In a small cohort of largely African American COVID-19 patients, measuring urinary 11-dehydro thromboxane B2 levels showed inadequate therapeutic response to aspirin in 91% of patients on 81 mg daily aspirin and 50% of patients on ≥ 162 mg daily aspirin [50]. Increased oral doses of aspirin would have to be balanced against bleeding risk, particularly with concomitant LMWH administration. An alternative approach could be to achieve high local concentrations of acetylsalicylate in the lungs through nebulised LASAG. While LASAG is approved for IV administration in Germany there is no license for aerosolised LASAG and this is therefore unlikely to present a viable treatment option in the near future.

Aspirin in Patients with COVID-19 in the Community

The role of aspirin in patients with COVID-19 in the community was investigated in the ACTIV-4B COVID-19 Outpatient Thrombosis Prevention Trial [51]. This was a randomised controlled trial in which symptomatic but clinically stable outpatients with COVID-19 were randomised to receive either aspirin 81 mg once daily, prophylactic-dose apixaban (2.5 mg twice daily), therapeutic-dose apixaban (5 mg twice daily), or placebo for 45 days following a positive COVID-19 PCR or antigen test. The primary outcome was a composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalisation for cardiovascular or pulmonary cause. A total of 657 of the anticipated 7000 patients were recruited and randomised before the trial was prematurely terminated due to low event rates. Despite the broad composite primary endpoint, this only occurred in 1 of the 164 patients in the aspirin group (0.7%), 1 of the 165 patients in the prophylactic apixaban group (0.7%), 2 of the 164 patients in the therapeutic apixaban group (1.4%), and 1 of the 164 placebo patients (0.7%) in the placebo group. This suggests that the burden of thromboembolic disease is not clinically relevant in symptomatic outpatients and that in this population the risks of using anti-thrombotic agents likely outweigh the benefits.

Trials of Other Antiplatelet Drugs

There has been one small proof-of-concept open-label randomised trial investigating the effect of dipyridamole on COVID-19 outcomes [39]. A total of 31 hospitalised COVID-19 patients were randomised to receive usual care plus dipyridamole 50 mg TDS orally for 14 days or usual care alone. Higher clinical remission and cure rates were reported in the dipyridamole group although the definitions of these outcomes were not clearly described in the manuscript. Mortality was lower in the dipyridamole group compared to controls (7.1% vs. 23.5%). Increases in D-dimer levels were also smaller in the dipyridamole group compared to controls. There is insufficient

information in this manuscript regarding the randomisation process and outcome definitions of the trial. In conjunction with the small sample size and unblinded nature of the trial, these results should be interpreted with extreme caution.

Future Trials

There are several randomised controlled trials yet to be published that are investigating the prognostic benefit of aspirin, P2Y12 inhibitors, and antiplatelet-anticoagulant combination therapy in COVID-19 disease across both community and hospital settings (Table 20.2) [52]. We note that none of these trials include as many patients as the RECOVERY trial. The largest of the awaited trials is REMAP-CAP which has a similar adaptive open-label platform design to the RECOVERY trial. A preliminary press release has indicated that in the subset of 1467 critically ill COVID-19 patients there was no effect from either aspirin or P2Y12 inhibitors in reducing mortality or increasing organ support-free days [53]. We eagerly await the full results of this trial.

Table 20.2 Awaited randomised controlled trials for antiplatelet agents

Therapeutic agent	Trial name	Setting	Intervention	Estimated enrolment
Aspirin	REMAP-CAP	Inpatients Multinational	Aspirin 75–100 mg OD for 14 days Vs P2Y12 inhibitor (clopidogrel 75 mg OD or ticagrelor 60 mg BD or prasugrel 60 mg stat then 5-10 mg OD) for 14 days Vs Usual care	10,000 (across entire adaptive trial)
	ACTCOVID-19	High risk outpatients (either >70 or < 70 + risk factor for thrombotic disease) Multinational	Aspirin 75–100 mg OD for 28 days	4000 (across both inpatient and outpatient arms)
	RESIST	Non-ICU inpatients Single centre India	Aspirin 75 mg OD for 10 days	900 (including separate arm evaluating atorvastatin 40 mg OD)
	PEAC	Inpatients Single centre China	Aspirin 100 mg OD + 14 days after discharge	128

(continued)

Table 20.2 (continued)

Therapeutic agent	Trial name	Setting	Intervention	Estimated enrolment
P2Y12 inhibitors	REMAP-CAP	Inpatients Multinational	Aspirin 75-100 mg OD Vs P2Y12 inhibitor (clopidogrel 75 mg OD, ticagrelor 60 mg BD, prasugrel 60 mg stat then 5-10 mg OD) Vs Usual care	10,000 (across entire adaptive trial)
	COVID-PACT	Critically ill patients Multi-centre USA	Clopidogrel + full dose anticoagulation Vs clopidogrel + prophylactic dose anticoagulation Vs full dose anticoagulation Vs prophylactic dose anticoagulation	750
	PARTISAN	Inpatients Single centre Italy	Prasugrel 10 mg OD for 15 days Vs placebo	128
Dipyridamole	DICER	Inpatients Single centre USA	Dipyridamole 100 mg QDS for 14 days Vs placebo	100
	TOLD	Inpatients Single centre USA	Dipyridamole 100 mg TDS for 7 days	100
Aspirin + dipyridamole	ATTAC-19	Inpatients Single centre USA	Dipyridamole 200 mg + aspirin 75 mg BD for 14 days	132
Aspirin + rivaroxaban	ACTCOVID-19	Inpatients Multinational	Aspirin 75-100 mg OD + rivaroxaban 2.5 mg BD vs. rivaroxaban 2.5 mg BD alone	4000 (across both inpatient and outpatient arms)
Combination therapy	C-19-ACS	Inpatients Multi-centre UK	Aspirin 75 mg OD + clopidogrel 75 mg OD + rivaroxaban 2.5 mg BD + atorvastatin 40 mg OD + omeprazole 20 mg OD	3170
	NAAC	Inpatients Single centre India	Aspirin 325 mg stat then 75 mg OD + atorvastatin 80 mg stat then 40 mg OD + nicorandil 10 mg stat then 5 mg BD for 10 days Vs usual care	300

Conclusion

While aspirin is theoretically an attractive candidate for treating COVID-19 disease due to its anti-thrombotic, anti-inflammatory, and anti-viral properties, there is no evidence to support its use. The large, randomised, and well-controlled RECOVERY trial showed that aspirin has no effect on mortality or progression to IMV in hospitalised COVID-19 patients. However, this trial excluded the high-risk population of patients on prior antiplatelets, and no randomised controlled trials have explored the effect of other antiplatelet agents, such as P2Y12 inhibitors and dipyridamole, on prognosis in COVID-19 disease. We eagerly await the results of several ongoing randomised trials before entirely dismissing antiplatelets as a potential treatment for COVID-19 disease.

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Chapter 21
Antidiabetic Drugs in COVID-19

Niki Katsiki and Maciej Banach

Introduction

Patients with diabetes mellitus (DM) are more prone to COVID-19 infection and may exhibit more severe outcomes in terms of both morbidity and mortality [1]. Potential pathophysiological mechanisms linking DM with COVID-19 prevalence and prognosis may include a higher affinity for cellular binding and virus entry, T-cell dysfunction, reduced viral clearance, and susceptibility to inflammation and cytokine storm syndrome, mainly due to dysregulated innate immunity and maladaptive inflammatory responses [1, 2]. Insulin resistance, glucotoxicity, vascular endothelial damage, increased blood viscosity (leading to deep vein thrombosis and pulmonary embolism), tissue hypoxia, and interstitial lung damage (leading to acute respiratory distress syndrome), as well as activation of the renin–angiotensin–aldosterone system (RAAS), increased oxidative stress, and enhanced cytokine production are also involved in the predisposition of COVID-19 infected DM patients to increased severity and mortality [2]. Furthermore, cardiometabolic morbidities (e.g., obesity, hypertension, cardiovascular disease, dyslipidemia, smoking, chronic obstructive pulmonary disease) that frequently co-exist with DM can contribute to the increased susceptibility to and adverse outcomes from COVID-19, and other viral, bacterial, parasitic, and mycotic infections in DM patients [1].

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Glycemic control may affect COVID-19 prevalence and prognosis in DM patients [3]. Indeed, tight control of glucose has been suggested in order to keep susceptibility low and prevent severe courses of COVID-19 [2]. Of note, inpatient hyperglycemia has been associated with a longer hospital stay and a higher mortality rate in hospitalized COVID-19 patients [4]. Apart from glucose levels, certain cytokines, including interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α, may also be linked to the worst prognosis or fatality among COVID-19 infected DM patients [5].

Antidiabetic drugs have been suggested to affect COVID-19 outcomes both via their effects on glycemia and their potential anti-inflammatory and/or anti-oxidant properties [6]. This chapter focuses on the impact of different antidiabetic drugs on COVID-19 prognosis.

Metformin

Overall, both preadmission and in-hospital metformin use has been shown to reduce mortality risk in COVID-19 DM patients [7, 8]. In this context, in a cohort study of 31,966 DM patients positive for COVID-19, metformin use was related to a significantly reduced risk of COVID-19 hospitalization (OR 0.86, 95%CI 0.81–0.91), ICU admission (OR 0.81, 95%CI 0.69–0.94), in-hospital mortality (OR 0.68, 95%CI 0.63–0.73), and all-cause death (OR 0.70, 95%CI 0.66–0.75) [9]. The CORONADO nationwide observational study (n = 2449 French DM patients hospitalized for COVID-19) showed that in patients taking metformin before hospitalization (n = 1496), mortality rate was significantly lower both on day 7 (8.2 vs. 16.1%, $p < 0.0001$) and day 28 (16.0 vs. 28.6%, $p < 0.0001$) [10]. Similarly, among 775 nursing home residents infected with COVID-19, 30-day mortality was significantly decreased (by more than half; OR 0.48, 95%CI 0.28–0.84) in those on metformin compared with those not taking this drug [11]. In another retrospective analysis of electronic health record data on 25,326 subjects tested for COVID-19, DM was linked to increased rates of positive cases (OR 2.11, 95%CI 1.78–2.48; $p < 0.0001$) [12]. Furthermore, the presence of DM more than triple the risk of mortality (OR 3.62, 95%CI 2.11–6.2; $p < 0.0001$) but metformin-treated patients had a significantly lower death rate (OR 0.33, 95%CI 0.13–0.84; $p = 0.021$) [12]. A nationwide observational cohort study in England (n = 2,851,465 DM patients) recorded 13,476 COVID-19-related deaths and found that metformin use was related to decreased mortality risk (HR 0.77, 95%CI 0.73–0.81) [13].

In-hospital metformin use has also been linked to lower mortality among 355 DM patients hospitalized for COVID-19 [14]. Of note, this protective effect of metformin was found regardless of daily dosage from 500 mg to 2 g daily, although the greatest benefit was seen with doses between 1000 to <2000 mg daily [14]. In another retrospective cohort analysis (n = 6256 DM patients hospitalized for

COVID-19), metformin was effective in reducing in-hospital death rate only in women (52.8% of the study population), but not in men [7]. Overall, a recent meta-analysis, involving 2,916,231 COVID-19 patients with DM ($n = 32$ cohort studies), found that metformin was associated with significantly lower mortality (OR 0.78, 95%CI 0.69–0.88; $p < 0.00001$, I^2 67%) [15].

The above-mentioned benefits of metformin use in relation to COVID-19 susceptibility and prognosis could be attributed to improved glucose metabolism, insulin sensitivity, immuno-modulation, anti-inflammatory, and anti-oxidant effects [14, 16].

Sulfonylureas (SUs)

In the English nationwide cohort study mentioned above [13], SUs use was marginally related to a lower mortality rate (HR 0.94, 95%CI 0.89–0.99). In contrast, SUs were associated with increased risk for ICU admission, requirement of invasive mechanical ventilation and/or in-hospital mortality (HR 1.55, 95%CI 1.07–2.24; $p = 0.022$) in a retrospective cohort study involving 1220 DM patients admitted for COVID-19 (385 patients were treated with SU prior to hospitalization) [17]. Similarly, in a retrospective cohort study of 1323 hospitalized COVID-19 patients (393 patients had DM), preadmission use of SUs was related to a non-significant increase of in-hospital adverse outcomes, including death [18]. Another retrospective US study ($n = 36{,}364$ COVID-19 positive or hospitalized patients) showed in subgroup analyses that SUs were linked to a greater odd of hospitalization for COVID-19 (OR 1.19, 95CI 1.03–1.37; $p = 0.019$) [19].

However, a meta-analysis involving DM patients with COVID-19 ($n = 18$ studies) showed that SU-treated patients had reduced death risk (OR 0.80, 95%CI 0.66–0.96; $p = 0.016$) [20]. Interestingly, in all SU trials included in this meta-analysis (i.e., three retrospective studies with 445 patients [21–23] and two prospective studies with 4111 patients [24, 25]), SUs use tended to decrease mortality rate but this trend did not reach statistical significance. Only when all data was pooled and analyzed, SUs therapy was found to significantly lower death risk by 20% ($p = 0016$), as previously mentioned [20].

Overall, the impact of SUs on COVID-19 infection and outcomes remains controversial. For a pathophysiological point of view, SUs promote the secretion of insulin, an anabolic hormone which could be beneficial in severe infections [26]. Furthermore, glibenlamide was identified as a potential inhibitor of the main viral protease, which is essential for viral replication [27], whereas gliclazide can inhibit the ion channel in the envelope protein of coronaviruses [28]. However, it should be noted that SUs can easily cause hypoglycemia and therefore, their use in severe COVID-19 patients requires careful blood glucose monitoring.

Pioglitazone

Peroxisome proliferator-activated receptor (PPAR)-γ, apart from regulating glucose and lipid metabolism, can also repress the inflammatory process [29]. In this context, pioglitazone, a PPAR-γ agonist, has been shown to exert anti-inflammatory properties by reducing the expression of pro-inflammatory cytokines (e.g., IL-1b, IL-6, and IL-8 in monocytes, IL-2, IL-6, and IL-8 in lymphocytes, as well as CRP and IL-6 in the circulation) and increasing the secretion of anti-inflammatory ones (e.g., IL-10 and IL-4 in astrocytes) [30]. Furthermore, animal studies reported that pioglitazone could suppress acute lung injury and fibrosis [31, 32]. Therefore, it has been suggested that pioglitazone may protect against SARS-CoV-2 driven hyperinflammation [33]. This drug can also upregulate the expression of angiotensin converting enzyme 2 (ACE2) and consequently decrease the levels of angiotensin II, thus potentially protecting against acute lung injury [33]. Of note, there is no data that pioglitazone upregulates ACE2 expression in the alveolar cells [33].

In an English nationwide cohort study (n = 2,851,465 DM patients), 13,476 COVID-19-related deaths were recorded; the adjusted HR for mortality was 0.94 (95% CI: 0.82–1.07) for recorded versus no recorded prescription of thiazolidinediones [13]. Another multinational retrospective cohort study (n = 64,936,797 patients with COVID-19 diagnosis or positive results for SARS-CoV-2) showed that pioglitazone was associated with significantly reduced hospital admissions (RR 0.71, 95% CI 0.54–0.93; $p = 0.01$) [34]. Interestingly, pioglitazone was found, in a computer-based bioinformatic analysis, to target 3-chymotrypsin-like protease (3CLpro) and inhibit SARS-CoV-2 RNA synthesis and replication [35]. However, this finding has not been confirmed in other studies yet.

It should be pointed out that there is a paucity of data regarding the effects of pioglitazone on COVID-19 clinical outcomes and thus further research is needed [36]. Furthermore, pioglitazone may cause weight gain and oedema, as well as aggravate heart failure, thus limiting its use during acute illness, including COVID-19 [37]. Ongoing clinical trials (e.g., https://clinicaltrials.gov/ct2/show/NCT04604223) will shed more light into this field.

Dipeptidyl Peptidase 4 Inhibitors (DPP4i)

The enzyme DPP4 has been implicated not only in glycaemia regulation, but also in immuno-modulation and subclinical inflammation [38]. Furthermore, it has been recognized that DPP4/CD26 is the receptor for the MERS-CoV (Middle East Respiratory Syndrome-Corona Virus) [39] and that DPP4 is a co-receptor of COVID-19 for entering host cells [38]. Therefore, DPP4i have been regarded as potential modifiers of monocyte/macrophage, neutrophil, and endothelial mediated immunity, thus being helpful in the COVID-19 setting [39].

In this context, DPP4i use at admission was linked to a significant lower rate of in-hospital death (adjusted HR 0.13, 95%CI 0.02–0.92; $p = 0.042$) among 90 T2DM

patients hospitalized for COVID-19 [23]. Furthermore, in a multinational retrospective cohort study involving 64,936,797 COVID-19 positive patients, DPP4i use was related to a significant decrease in respiratory complications (RR 0.82, 95% CI 0.74–0.90; $p < 0.001$) [34]. Of note, if DPP4i use was continued after hospital discharge, this led to a significantly lower risk of death compared with those who discontinued use (RR 0.45, 95% CI 0.28–0.72; $p < 0.001$) [34]. Another cohort study ($n = 1220$ DM patients admitted for COVID-19; 199 on DPP4i) found that DPP4i use prior to hospitalization was associated with reduced rates (adjusted HR 0.46, 95%CI 0.29–0.71; $p < 0.001$) of the composite endpoint (defined as ICU admission, requirement of invasive mechanical ventilation and/or in-hospital mortality) compared with non-users [17]. However, among 2,851,465 DM patients included in a nationwide observational cohort study in England (with 13,476 COVID-19-related deaths), the adjusted HR of mortality for DPP4i recorded versus no recorded prescription was 1.07 (95%CI 1.01–1.13) [13]. A recent meta-analysis of 16 studies ($n = 549,817$ participants) showed that DPP4i use was significantly related to a 17% decrease in COVID-19 mortality risk (RR 0.83, 95% CI 0.71–0.98, $p = 0.023$) compared with non-DPP4i use [40]. Previous meta-analyses also provide similar results [41, 42], although there are also neutral findings [43].

With regard to sitagliptin, this drug exerts multidimensional anti-inflammatory actions mostly by affecting the NF-kappa-B signaling pathway; such effects can be of great benefit in individuals with COVID-19 [44]. In this context, a single-center clinical trial involving 89 non-DM COVID-19 patients, found that the addition of sitagliptin to standard therapy during hospitalization was linked to improved radiological scores, clinical outcomes and inflammatory biomarkers [45]. Another multicenter, retrospective, observational study ($n = 338$ T2DM patients admitted to hospital due to COVID-19) showed that sitagliptin use at the time of hospital admission was related to significantly lower mortality (HR 0.44, 95%CI 0.29–0.66; $p = 0.0001$), better clinical outcomes (60 versus 38% improved patients; $p = 0.0001$) and more hospital discharges (120 versus 89 of discharged patients; $p = 0.0008$) compared with standard of care [46]. The efficacy of the sitagliptin + melittin complex against infection from the SARS-CoV-2 virus has been evaluated in computational studies with promising results [47]. Similar findings have been reported by applying an integrative bioinformatics approach, suggesting DPP4 as a putative target for treating COVID-19 and sitagliptin as a potential therapeutic option against viral entry and infection [48].

With regard to linagliptin, in a randomized, double-blind, clinical trial, 73 hospitalized patients with SARS-CoV-2 infection and hyperglycemia were divided into two groups: 35 receiving linagliptin + insulin and 38 receiving only insulin [49]. Average hospital stay was 12 ± 1 days for the insulin therapy group and 10 ± 1 days for the linagliptin+insulin group. Compared with insulin monotherapy, linagliptin and insulin combination was associated with a significantly lower (by 74%) risk of assisted mechanical ventilation (HR 0.258, 95%CI 0.092–0.719; $p = 0.009$), as well as improved fasting and postprandial glucose levels, with reduced insulin requirements and no increased risk of hypoglycemia [49]. An open-label, multicenter, prospective, randomized clinical trial was also conducted to evaluate the impact of

linagliptin, compared with standard of care, on clinical outcomes in 64 Israeli T2DM patients hospitalized for COVID-19 [50]. There was a trend of more rapid clinical improvement in linagliptin-treated patients (7 versus 8 days in the linagliptin versus standard of care group, respectively; HR 1.22, 95%CI 0.70–2.15; $p = 0.49$), as well as a trend towards lower in-hospital mortality with linagliptin (OR 0.56, 95%CI 0.16–1.93) [50]. However, the trial was prematurely terminated due to the control of the COVID-19 outbreak in Israel [50] and this may explain the non-significant results. Interestingly, computational studies identified linagliptin as a potential inhibitor of SARS-CoV-2 Mpro viral cysteine protease, as well as other viral cysteine proteases from the beta coronavirus family (e.g., MERS-CoV CLpro and SAR-CoV Mpro), thus suggesting its potential role as a broad-spectrum antiviral agent [51]. Studies evaluating the effects of other DPP4i (i.e., alogliptin, vildagliptin, and saxagliptin) separately on COVID-19 are lacking.

Overall, DPP4i exert anti-inflammatory and immune-modulatory effects that suggest a potential beneficial role in COVID-19 prevention and treatment. Data from clinical trials are promising, especially for sitagliptin and linagliptin, but further evidence is needed before any recommendations can be made for clinical practice. The results of ongoing clinical studies (e.g., https://clinicaltrials.gov/ct2/show/NCT04542213; https://clinicaltrials.gov/ct2/show/NCT04365517) will further elucidate the impact of DPP4i on COVID-19. However, we should also consider that, although the use of DPP4i is safe, these drugs have shown neutral effects on cardiovascular outcomes, which could be a limiting factor for their use in COVID-19 patients.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

There are experimental data showing that GLP-1 RAs can attenuate pulmonary inflammation, decrease cytokine production and thus, preserve lung function in animal models of lung injury [52]. GLP-1 RAs can exert anti-inflammatory properties (via reducing TNF-α and IL-1β secretion), anti-apoptotic and immuno-modulatory effects on several organs, including the cardiovascular, endocrine, renal, and respiratory systems [2, 53].

Among 64,892 veterans with DM and COVID-19, those treated with GLP-1 RAs had significantly lower risk for hospitalization (OR 0.92, 95%CI 0.85–0.99) [54]. In a retrospective, multinational, cohort study (involving 64,936,797 COVID-19 patients), GLP-1 RAs therapy was related to significant decreases in hospital admissions (RR 0.67, 95%CI 0.57–0.79; $p < 0.001$), respiratory complications (RR 0.62, 95%CI 0.52–0.73; $p < 0.001$), and death rate (RR 0.58, 95%CI 0.35–0.97; $p = 0.04$) [34]. A recent meta-analysis (61 studies, $n = 3{,}061{,}584$ T2DM patients infected by COVID-19) evaluated the effects of preadmission use of antidiabetic drugs on mortality rates; GLP-1 RAs use was protective against COVID-19 related death (OR 0.51, 95%CI 0.37–0.69) [55]. Similarly, another meta-analysis (involving six studies and 140,859 participants) showed that GLP-1RA users had a 25% significant

reduction in COVID-19 mortality risk (RR 0.75, 95% CI 0.60–0.94, $p = 0.013$) compared with non-users [40].

Interestingly, the US National COVID Cohort Collaborative (N3C) Consortium analyzed observational data from 12,446 SARS-CoV-2-positive adults and found that GLP-1 RAs users (within 24 months before a positive SARS-CoV-2 PCR test) had a significantly lower risk of 60-day mortality compared with DPP4i users (OR 0.54, 95%CI 0.37–0.80), as well as lower odds of emergency room visits (OR 0.81, 95%CI 0.69–0.96), hospitalization (OR 0.73, 95%CI 0.62–0.87), and need for mechanical ventilation (OR 0.73, 95%CI 0.55–0.97) [56].

It should be noted that overall, GLP-1 RAs exert anti-hypeglycemic, anti-inflammatory, anti-thrombotic, and anti-obesity effects, as well as cardiorenal benefits, thus protecting COVID-19 patients from several adverse outcomes [57]. Therefore, GLP-1 RAs represent a valuable asset in the treatment of non-critically ill COVID-19 patients with DM. The results of ongoing clinical trials (e.g., https://www.clinicaltrials.gov/ct2/show/NCT04615871) will further elucidate the impact of GLP-1 RAs on COVID-19 outcomes.

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2i)

SGLT2i have shown important cardiorenal benefits both in the presence and absence of DM [58, 59]. Furthermore, SGLT2i have been reported to exert anti-inflammatory effects [60, 61]. Preclinical data also suggest a potential role for SGLT2i in lung protection [62]. For example, empagliflozin was reported to promote apoptosis and inhibit proliferation in pulmonary vessels, thus preventing adverse pulmonary arteriole remodeling [62]. On the other hand, dapagliflozin was found to prevent cytosolic pH lowering and reduce the viral load, thus potentially protecting against the severe course of COVID-19 infection [63]. Finally, in computational analysis, canagliflozin emerged as a promising inhibitor of SARS-CoV-2 Mpro viral cysteine protease, thus affecting the course of COVID-19 [64].

Among 64,892 veterans with DM and COVID-19, those on SGLT2i had significantly lower odds of hospitalization (OR 0.92, 95%CI 0.85–0.99) and death (HR 0.82, 95%CI 0.74–0.92) [54]. Similarly, in a nationwide cohort study ($n = 2{,}851{,}465$ DM patients, 13,476 COVID-19-related deaths), the adjusted HR for COVID-19 mortality for recorded versus no recorded SGLT2i prescription was 0.82 (95%CI 0.74–0.91) [13]. Furthermore, a recent meta-analysis (6 studies with 275,468 participants) showed that SGLT2i use led to a 22% decrease in COVID-19 death risk (RR 0.78, 95%CI 0.61–0.98, $p = 0.035$) compared with non-use [40]. The US National COVID Cohort Collaborative (N3C) Consortium ($n = 12{,}446$ SARS-CoV-2-positive patients) reported that SGLT2i users had a significantly lower risk of 60-day mortality compared with DPP4i users (OR 0.66, 95%CI 0.50–0.86), as well as lower odds of other adverse outcomes, such as emergency room visits (OR 0.90, 95%CI 0.81–0.998) and hospitalizations (OR 0.82, 95%CI 0.73–0.91) [56].

However, there are also a few neutral results. For example, the DARE-19 was a randomized, placebo-controlled, double-blind, trial in 1250 patients hospitalized with COVID-19, treated with either dapagliflozin or placebo for 30 days [65]. Dapagliflozin was associated with a non-significant lower rate of the primary composite outcome (organ dysfunction or death) compared with placebo (HR 0.80, 95%CI 0.58–1.10; $p = 0.17$) [65]. Furthermore, a propensity-score-matched cohort study involving a large UK-based primary care dataset ($n = 9948$ patients on SGLT2i and 14,917 patients on DDP4i) reported no effect of either drug category to COVID-19 incidence, thus highlighting the safety of these drugs during the COVID-19 pandemic [66].

Overall, SGLT2i exert both anti-inflammatory and cardiorenoprotective effects, thus representing an attractive therapeutic option for non-critically ill COVID-19 patients. However, we should keep in mind that COVID-19 induced "cytokine storm" can lead to peripheral lipolysis and ketosis, which can subsequently increase the risk euglycaemic diabetic ketoacidosis, when coupled with the dehydration that typically occurs in acute illnesses [67]. Therefore, SGLT2i should be used with caution in T2DM patients with severe forms of COVID-19 requiring hospitalization. Needless to mention that insulin therapy is the preferred antidiabetic treatment during hospital stay in critically ill patients. There are ongoing clinical studies (e.g., https://clinicaltrials.gov/ct2/show/NCT04381936 with empagliflozin) which may shed more light into the potential role of SGLT2i in preventing COVID-19 infection and progression.

Insulin

The effects of insulin therapy on COVID-19 incidence and outcomes should be looked at from different aspects. For example, insulin use can significantly contribute to achieving glycemic control, which can be clinically important in the COVID-19 setting by minimizing hyperglycemia [68, 69]. On the other hand, insulin therapy represents a marker of frailty in T2DM patients; such patients may be more prone to COVID-19 infection and worse outcomes [70]. Furthermore, it has been speculated that insulin treatment may participate in COVID-19 development by aggravating systemic inflammation disorder, pulmonary disease and injuries of vital organs, as well as promoting weight gain and obesity [71, 72]. Finally, insulin-treated patients are more prone to hypoglycemic episodes [71], thus predisposing to adverse outcomes, including the cardiovascular system [73].

Several studies have found a significant association between insulin treatment and COVID-19 severity and prognosis. In the CORONADO (CORONAvirus and Diabetes Outcomes) study, among 2951 DM patients hospitalized for COVID-19, insulin therapy prior to admission was linked to an increased mortality risk (OR 1.44, 95%CI 1.01–2.06) [70]. Similar results have been reported in a nationwide observational cohort study in England ($n = 2{,}851{,}465$ DM patients); the adjusted HR for mortality was 1.42 (95%CI 1.35–1.49) for insulin users compared with non-users

[13]. In another study involving 64,892 veterans with DM and COVID-19, insulin therapy was related to increased risks of hospitalization (OR 1.12, 95%CI 1.07–1.18), ICU admission (OR 1.12, 95%CI 1.04–1.22) and death (OR 1.18, 95%CI 1.09–1.27) [54]. Among 1220 DM patients admitted for COVID-19, those on insulin prior to hospitalization had an increased HR for the composite endpoint of ICU admission, requirement of invasive mechanical ventilation and/or in-hospital (HR 6.34, 95% CI 3.72 to 10.78, $p < 0.001$) was [17].

The link between insulin therapy and COVID-19 related mortality has been confirmed in meta-analyses. For example, in a recent meta-analysis (six studies, $n = 1338$ DM patients with COVID-19), insulin-treated patients were 2.5 times more prone to death compared with non-treated ones (OR 2.59, 95%CI 1.66–4.05; $p < 0.0001$) [74]. Similarly, another meta-analysis (18 studies, $n = 17{,}338$ patients) showed that insulin use was associated with a greater mortality (pooled OR, 2.20; $p = 0.002$) [20]. Apart from COVID-19 related death, insulin treatment has been correlated to an increased risk of severe COVID-19 complications (OR 2.56, 95%CI 1.18–5.55) and in-hospital admission (OR 1.31, 95%CI 1.06–1.61), as shown in a meta-analysis involving 18 studies and 12,277 DM patients with COVID-19 [71]. Of note, insulin use has also been related to COVID-19 incidence (OR 1.70, 95%CI 1.40–2.08) and COVID-19 severe form (OR 2.30, 95%CI 1.60–3.30) [75].

Overall, insulin treatment has been linked to COVID-19 incidence and worse outcomes, including death. However, we should highlight the importance of insulin use during hospitalization, especially in critically ill patients. Dedicated prospective studies are needed to clarify whether insulin per se is harmful in the COVID-19 setting or whether it is the frailty of the insulin-treated patients that is mainly responsible for the adverse outcomes.

Conclusions

DM has been linked to COVID-19 infection and poor prognosis. Certain antidiabetic drugs were reported to protect from worse COVID-19 outcomes, whereas insulin use has been linked to COVID-19 related death, but this evidence comes mainly from observational data. We should also remember that association is not causation. Therefore, prospective, interventional trials are needed to address this issue [76]. The results of such ongoing studies, when available, will further elucidate the effects of antidiabetic therapy on COVID-19 prognosis.

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Part IV
Cardiovascular Complications on Long COVID-19

Chapter 22
Long-COVID-19: Definition, Epidemiology, and Clinical Implications

Alice P. McCloskey and Peter E. Penson

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak first occurred in late 2019 in China. The associated condition, coronavirus disease 2019 (COVID-19), causes a range of symptoms including fever, cough, loss of taste and smell, fatigue, headache, and breathing difficulties [1–3]. Although symptoms are mild in most affected individuals, COVID-19 is associated with severe illness in some patients, and has a case-fatality rate of around 1% [4]. In the absence of a specific cure for the condition, the initial management of patients consisted of symptomatic management, and the use of supportive technology available in the clinic such as ventilators [5, 6]. Although only a small proportion of infected individuals are severely affected, the widespread and rapid transmission of COVID-19 resulted in immense acute pressure on healthcare systems throughout the world. Various infection control measures, such as the mandatory wearing of face coverings, school closures, and lockdowns were implemented, in part to reduce this acute pressure on health systems.

Whilst the initial phases of the response to COVID-19 naturally focused on refining the acute management of the disease (lasting no more than 3 weeks in most

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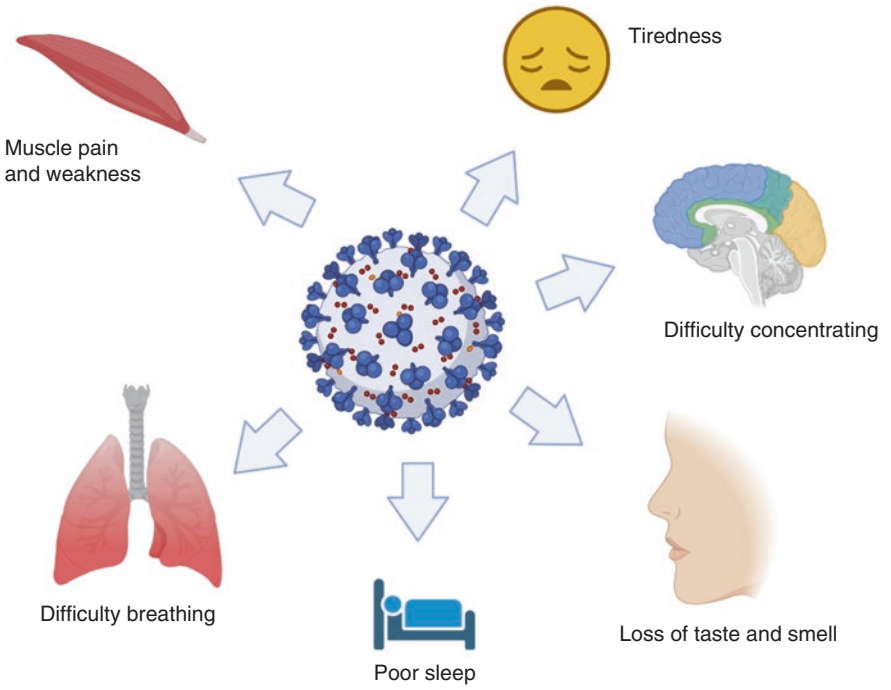

Fig. 22.1 Commonly reported symptoms of long-COVID. (Image created using Biorender.com)

individuals [7]), it quickly became apparent that, in common with many other viral diseases, recovery from COVID-19 was extremely delayed in some individuals [7], a phenomenon described as 'post-acute sequelae of COVID-19 (PASC)', 'post-COVID-19 condition', 'post-COVID-19 syndrome', 'chronic COVID syndrome (CCS)' or simply 'long-COVID' [8–12]. This syndrome affects multiple organs and systems, and symptoms include tiredness, weakness, shortness of breath, muscle aches and pains, prolonged loss of taste and smell, and difficulty concentrating (Fig. 22.1). Owing to the very high prevalence of COVID infections worldwide, long-COVID is likely to have substantial impacts on morbidity, and healthcare resource use for the foreseeable future. This chapter will summarize the current state of knowledge with respect to long-COVID, with a particular focus on the definition, epidemiology, and clinical implications of the condition.

Biological and Historical Context

Long-COVID must be understood in the context of the wider body of knowledge about recovery from viral illness, and, of post-viral syndromes [13]. The similar condition Severe Acute Respiratory Distress Syndrome (SARS), also caused by a

coronavirus is associated with long terms symptoms characteristic of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) (fatigue, myalgia, and depression) [13]. Importantly, these symptoms are persistent and severe—preventing individuals from returning to work for up to 20 months post-infection. The mechanism behind these adverse effects is imperfectly understood, however, for SARS it was demonstrated that the virus could enter the brain via the olfactory route, resulting in activation of inflammatory pathways. Long-COVID has also been likened to post-Ebola syndrome which also manifests with joint and muscle pain, and fatigue [14].

Definitions of Long-COVID

Owing to the syndromic nature of long-COVID, its complex pathophysiology, variety of symptoms (in terms of nature, onset, and duration), and the absence of a biological test, long-COVID essentially becomes a diagnosis of exclusion in patients who have had a confirmed or suspected COVID-19 infection, and for which other causes for the clinical presentation cannot be found [15]. Formal definitions of long-COVID have been proposed by the National Institute for Health and Care Excellence (NICE) [11] in the United Kingdom (UK) and by the World Health Organization (WHO) [8] (Table 22.1). Importantly the definitions make clear that symptoms may be ongoing and unresolved from the initial infection or may recur (or appear for the first time) at some point after apparent recovery from the acute infection.

Table 22.1 Summary of international definitions of Long-COVID

Organization	Country	Definition	Reference
NICE	UK	*The term 'long-COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)*	[11]
WHO	International	*Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time*	[8]

Symptoms and Pathophysiological Mechanisms in Long-COVID

Whilst the pathophysiology of a diverse and complex syndrome is likely to be difficult to fully elucidate, it is nevertheless helpful to undertake efforts to understand the condition with a view to developing diagnostic tests and treatments for long-COVID. It has been suggested that the symptoms of long-COVID may result from direct damage to tissues as a result of the infection, thrombolysis, excessive unregulated inflammation or virus-induced activation of autoreactive T and B cells [16]. Recent investigations into viral persistence in COVID-19 and immune responses to infection have been extremely instructive in shedding light on mechanistic aspects of long-COVID.

Recent autopsy studies have clearly demonstrated widespread and persistent systemic infection with SARS-CoV-2. A study of 44 COVID-19 patients demonstrated that SARS-CoV-2 RNA could be detected in a range of anatomical sites (including the brain) for as long as 230 days. Interestingly, the study found little evidence of inflammatory responses to infection outside of the lung, and thus further investigation is necessary to better understand the causal links between prolonged infection with SARS-CoV-2, and the clinical symptoms of long-COVID [17].

Further light on the immune response to COVID-19 was shed by a larger prospective multicentre cohort study of 215 patients which compared immunoglobulin signatures in COVID-19 patients and healthy controls [16]. The investigators found that the development of long-COVID was associated with a distinct immunoglobulin signature (based on IgM and IgG3); and when this was combined with clinical and demographic information, it contributed to an effective risk stratification scoring system. This has important implications for identifying patients most likely to suffer from long-COVID but is also informative with respect to pathophysiological mechanisms—particularly with respect to specific inflammatory mediators which might prove to be therapeutic targets.

The wide range of symptoms reported and associated with long-COVID clearly demonstrates the systemic nature of the condition, and the range of organs affected. Studies of COVID-19 in large populations have reported a wide range of reported symptoms including tiredness, weakness, shortness of breath, muscle aches and pains, loss of taste and smell, and difficulty concentrating (Fig. 22.2).

Clearly, different patients experience different symptoms, and the pathological mechanisms accounting for the symptoms are likely to represent a variety of responses to persistent SARS-CoV-2 infection in different organs and tissues.

It has been suggested that chronic fatigue following COVID-19 may result from inflammation and congestion in the glymphatic system, resulting in reduced drainage of cerebrospinal fluid within the central nervous system [19]. Dyspnoea is likely to result from damage to the lung tissues (particularly endothelial cells) during the acute infection, particularly in individuals with existing respiratory disorders. Loss of taste and smell may result from viral entry (via non-neuronal ACE2) into cells of the olfactory system, causing inflammation and impairing olfactory nerve function.

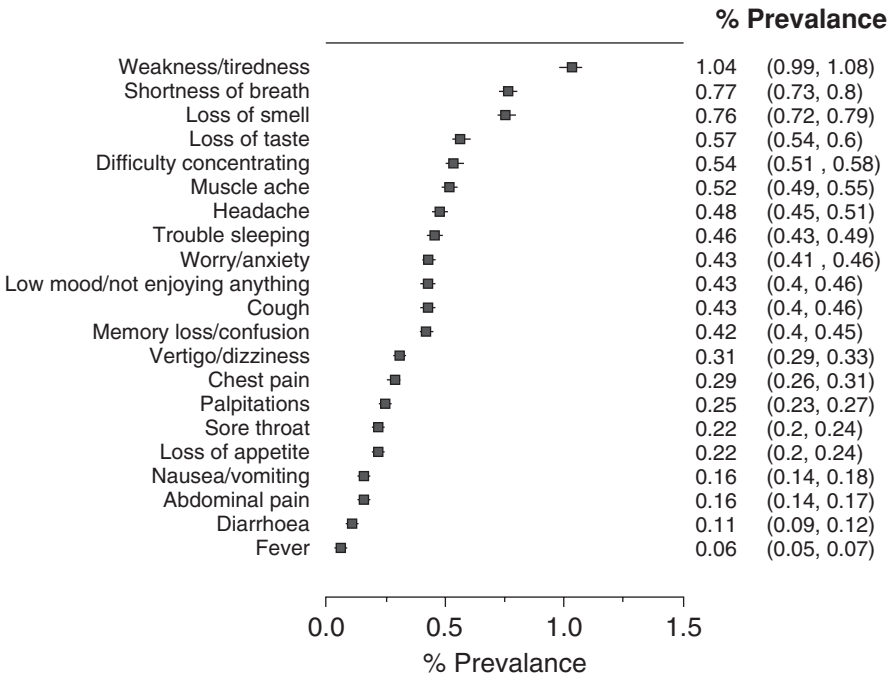

Fig. 22.2 Prevalence of long-COVID symptoms in the United Kingdom: Estimated percentage of people living in private households with self-reported long-COVID by symptom. Data current at February 2022, plotted using data released from the UK Office of National Statistics [18]

Cardiovascular abnormalities following COVID are clearly an important cause for concern in the management of patients [19], and biomarker manifestations of cardiac damage can be detected many weeks after infection [20]. However, as this topic is the subject of specifically focused chapters within this volume, the mechanisms will not be discussed further here.

Epidemiology of Long-COVID

As time has progressed, and more of the world's population has been exposed to COVID-19 it is to be expected that the prevalence of long-COVID will increase proportionally. Indeed, this has been seen in health surveillance data. Interestingly, in the United Kingdom, data from the Office of National Statistics suggests that the incidence of reported long-COVID syndromes is increasingly steadily, both for individuals who have had a relatively recent COVID-19 infection (within 12 weeks), but also for those with much more temporally distant infections—up to 12 months previously (Fig. 22.3).

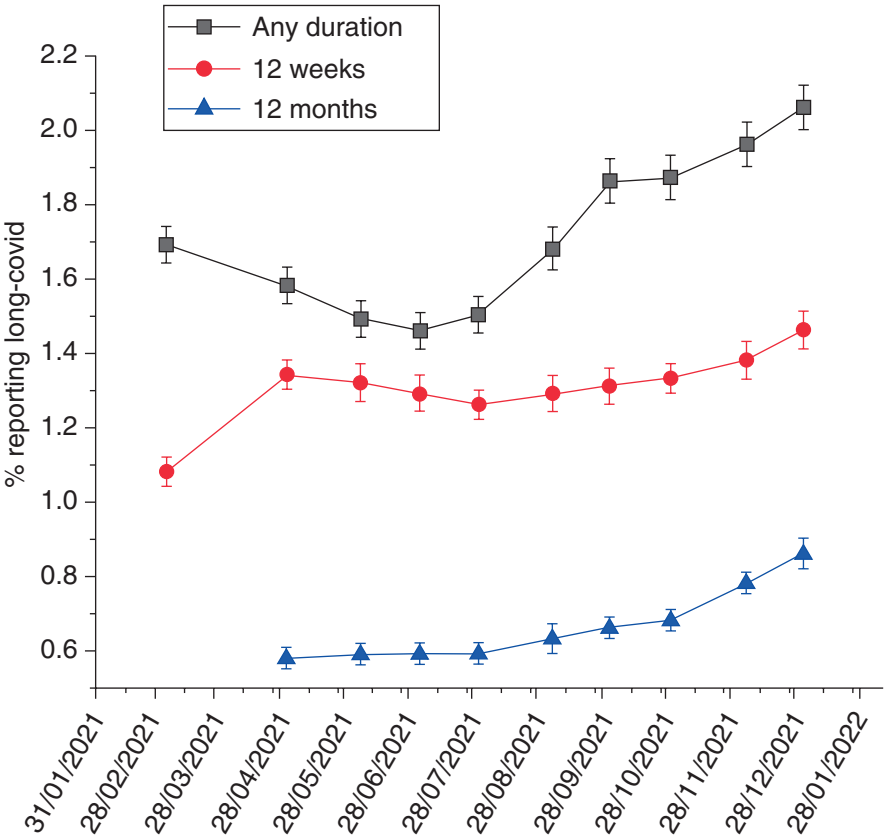

Fig. 22.3 Time course of the prevalence of long-COVID symptoms in the United Kingdom. Black Squares: Estimated percentage of people living in private households with self-reported long-COVID of any duration (4-week period prior to reporting date). Red Circles: Estimated percentage of people living in private households with self-reported long-COVID who first had (or suspected they had) COVID-19 at least 12 weeks previously (4-week period prior to reporting date). Blue Triangles: Estimated percentage of people living in private households with self-reported long-COVID who first had (or suspected they had) COVID-19 at least 12 months previously (4-week period prior to reporting date). Data current at February 2022, plotted using data released from the UK Office of National Statistics [18]

Clearly these data must be interpreted with caution, as symptoms are largely self-reported, and causality cannot be ascribed, nevertheless, the data do support the expected rise in the long-term complications of infection over time.

The REACT-2 study in the UK provided the opportunity for a large and detailed study of long-COVID symptoms. The investigators recruited over half a million participants and asked about their previous history of COVID infection and questioned in detail about 29 symptoms associated with long-COVID by previous researchers. The results highlighted the high prevalence of ongoing morbidity following acute COVID infection—nearly 15% of participants experienced at least

one symptom which lasted 12 weeks or more. Multivariate analysis was conducted to identify independent predictors of long-COVID following acute infection. Long-COVID appeared to be associated with a more severe initial infection, female sex, increasing age, obesity, and smoking [21].

A smaller study of 4182 users of the 'COVID Symptom Study' app compared the attributes of patients with COVID symptoms which resolves in less than 10 days, with those whose symptoms lasted at least 28 days, 8 weeks, and 12 weeks. The findings were in accordance with the REACT-2 trial. Long-COVID symptoms included fatigue, headache, dyspnoea, and anosmia and were associated with severe acute illness (>five symptoms in the acute phase), and demographics outlined above female, older age and obesity. The authors were able to validate their findings by developing a predictive model and testing it in an independent sample, which was modestly predictive (area under the receiver operator characteristic curve was 76%) [22].

Importantly, it appears that vaccination reduces the reported incidence of long-COVID. A large cross-sectional study of 951 patients with PCR-confirmed COVID infections (67% of whom were vaccinated, predominantly with the BNT162b2 mRNA vaccine [23]) and 2437 controls allowed for the study of association between vaccination status and the development of long-COVID. Following adjustment for time and measured confounding demographic variables, there was a substantial and statistically significant reduction in a range of long-COVID symptoms: fatigue (RR = 0.36), headache (RR = 0.46), weakness (RR = 0.43), and persistent muscle pain (RR = 0.32). The effect was strongest in double-vaccinated individuals. The authors concluded that vaccination may prevent against the development of long-COVID. Clearly these results (which are currently only available as a pre-print) cannot tell us about the effects of other vaccines in different populations, but they clearly add another important piece of evidence supporting the overwhelming benefit/risk ratio for vaccination [24].

Clinical Implications of Long-COVID

The implications of long-COVID must be considered both on an individual and a population level. The most commonly reported symptoms (described above) are likely to have implications for individuals' ability to work in the short term, and (based on the high reported prevalence) may have significant implications for healthcare resources. However, in otherwise healthy individuals, common long-COVID symptoms are unlikely to be life threatening. Nevertheless, particular consideration should be given to outcomes of long-COVID in particular at-risk groups.

The impact of COVID (and long-COVID) on individuals at high risk of cardiovascular disease is covered at length elsewhere in this volume, so will not be discussed in detail here. However, it is important to note that multiple factors related to COVID (ranging from direct cardiac damage in acute infections, thromboembolism, and delayed routine care) are likely to result in poor outcomes for those

patients at high risk of cardiovascular events [25, 26]. Indeed, a large cohort study (153,750 individuals with COVID-19 and 5,637,647 non-infected controls), has demonstrated a substantial increase in the incidence of a range of cardiovascular events in the 12 months following acute infection with COVID-19 [26]. These findings are biologically plausible if widespread SARS-CoV-2 infection results in systemic inflammation, in light of recent advances in knowledge of the contribution of inflammation to the aetiology of atherosclerotic cardiovascular disease [2, 27–33].

As the likelihood of long-COVID has been shown to increase with age [21, 22], the implications of the condition requires careful consideration in older adults. Indeed, the complications of long-COVID appear to be more severe in those aged over 65 years, than for other lower respiratory tract infections, with an increased risk of respiratory failure, dementia, and post-viral fatigue [34]. Therefore, older adults may require close monitoring and care following COVID to spot the early signs of clinical deterioration.

At the other extreme of life, the impact of long-COVID in children also requires specialist consideration. In many children, COVID is asymptomatic or mild, and symptoms are short-lived. In one large study, less than 2% of children reported symptoms after 56 days [35, 36]. However, rarely, children experience severe and life-threatening late effects of COVID, such as paediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-TS) which can even occur after a mild or asymptomatic index infection [37]. Urgent attention is required in order to better predict those at risk of this devastating condition, and to manage recovery. Recent findings from the LATE-COVID-Kids study have identified younger age, higher levels of antithrombin III, and higher heart rate as being associated with increased risk of developing PIMS-TS [38]. These findings require validation in a range of populations to reach further conclusions and consensus.

Beyond the level of individual patients, long-COVID clearly has implications on the delivery of healthcare, from the specific management of patients with the condition, and that fact that healthcare professionals throughout the world are struggling to ‘catch up’ with routine healthcare screening and interventions which ceased or were dramatically scaled back during the pandemic [1]. Data on the prevalence of long-COVID suggests that health and social workers are more likely to be affected than individuals in any other professional group [18] (almost certainly reflecting the very high rates of COVID infection acquired by these individuals as a result of their patient-facing contact). Severe long-COVID (as with other post-viral conditions) clearly impacts upon an individual’s ability to return to work, therefore it is to be expected that a larger than usual level of illness absence of healthcare professionals will persist for the foreseeable future.

Inevitably in the context of a rapidly-developing body of knowledge, guidelines, and treatment recommendations will be continuously developed and refined. However, current guidelines mainly focus on the reactive management of specific symptoms, and supporting the patient to return to their activities of daily life [11, 12].

Conclusions and Future Directions

The ubiquitous worldwide spread of COVID-19 has resulted in an inevitable growing problem of the post-viral syndrome, known as long-COVID. The syndrome manifests in a variety of ways, but common symptoms include tiredness, weakness, shortness of breath, muscle aches and pains, loss of taste and smell, and difficulty concentrating. These symptoms result in significant morbidity, and there is, as yet, not cure for the condition. Whilst careful studies have shed some light onto the potential mechanisms of the disease (which may involve persistent systemic infection and the activation of specific inflammatory pathways), a much greater understanding of the pathophysiology of long-COVID, and of post-viral syndromes in general is necessary to allow fully validated risk prediction scores to be developed. This will enable identification of patients most at risk and inform optimal management of such patients. In the meantime, it must be remembered that *'prevention is better than cure',* and promising data suggest that individuals who are vaccinated are less likely than unvaccinated individuals to experience long-term sequalae of COVID if they later develop an infection.

Declaration of Interest P.E.P. owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Mylan, Napp, Sanofi.

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Chapter 23
Cardiovascular Complications of Long COVID-19: Prevalence, Diagnosis, and Risk Factors

Michał Chudzik and Joanna Kapusta

Introduction

Long COVID-19 Epidemiology

The first cases of infection with SARS-CoV-2, belonging to the betacoronavirus genus and causing the coronavirus disease 2019 (COVID-19), were reported in the city of Wuhan in China. The disease spread rapidly around the world, significantly changing the lives of millions of people [1]. Patients who have recovered from COVID-19, regardless of whether the infection was mild or severe, often experience long-term complications. These complications are collectively referred to as "long COVID-19", "post-COVID-19 syndrome", or "post-acute COVID-19 syndrome" [2, 3].

The term "long COVID-19" was initially used by an internet user on one of the social networking sites to describe her prolonged symptoms related to COVID-19 infection. Subsequently, the term quickly found its way to the medical world [4].

In the guidelines of December 18, 2020, the British National Institute for Health and Care Excellence (NICE) with the Scottish Intercollegiate Guidelines Network (SIGN) and The Royal College of General Practitioners (RCGP) were the first to define the respective forms of COVID-19 adopting the duration of symptoms as a classification criterion (Fig. 23.1) [5].

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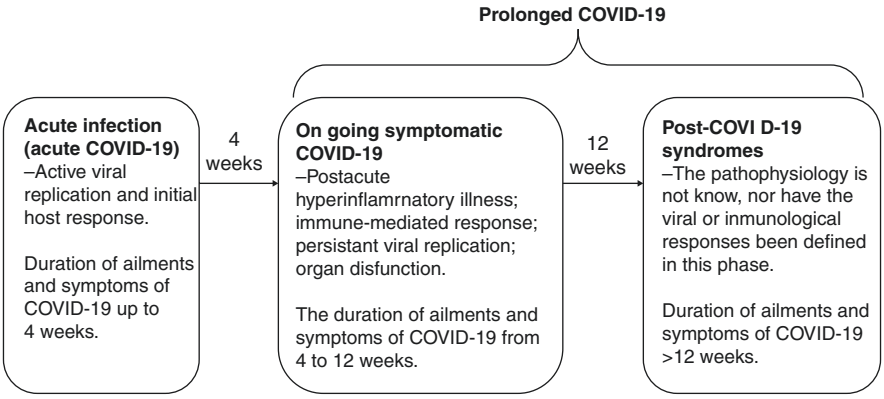

Fig. 23.1 Physiopathological characteristics of the evolutionary phases of SARS-CoV-2 infection [7]

Although there is no commonly accepted definition, according to the World Health Organization (WHO)–"Post-COVID-19 condition occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within 3 months from the onset of COVID-19, with symptoms and effects that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive impairment, and also other symptoms that lead to difficulty functioning in everyday life. Symptoms of post-COVID-19 condition can persist from the initial illness, or begin after recovery from an acute COVID-19 episode. Symptoms may come and go or relapse over time" [6].

From the beginning of the pandemic, scientists have been closely monitoring the effects of COVID-19 and issuing preliminary reports on the persistent symptoms. A study, conducted at the turn of April and May 2020 in Italy, in a group of 143 people following hospitalization, demonstrated that as many as 87.4% of patients experienced persistent fatigue and shortness of breath 60 days after the occurrence of the first symptom. Only 12.6% of patients had no symptoms related to COVID-19, 32% had 1 or 2 symptoms, and 55% had 3 or more symptoms. The most frequently reported symptoms were fatigue (53.1%), dyspnoea (43.4%), arthralgia (27.3%), and chest pain (21.7%). No persistent fever or any symptoms occurring in the acute phase of the disease were noted in the study group, but there was a disturbing observation of decreased quality of life in 44.1% of patients [8].

The prevalence of long COVID-19 varied considerably due to a number of factors [9–12], including the subjects' age and gender, presence of comorbidities, vaccination and vaccine type, study group size, various criteria and tools used in the studies. Differences in the prevalence of long COVID were also demonstrated in many countries and regions, including Great Britain 1.6–71% [13], Germany 35–77% [14], China 49–76% [15], Africa 68% [16], India 22% [17], Bangladesh 16–46% [18], Denmark 1% [19], Italy 5–51% [20], the USA 16–53% [21], or

Norway 61% [22]. This observation may indicate a large influence of socio-demographic factors. The time point of patient evaluation is also an important factor, as the frequency of symptoms begins to decline over time following the infection. In a study by Hossain et al. [23] *conducted among outpatients,* the prevalence of long COVID-19 symptoms was initially 22.5% after 4 weeks and 16.1% after 12 weeks since the diagnosis. A recurrent pattern of long COVID-19 symptom remission from week 13 to week 31 was also observed in the study. A similar temporary improvement in the occurrence of symptoms was also demonstrated in the studies by Wu et al. [24] and Cassar et al. [25].

The lack of uniform long COVID-19 definition is another factor contributing to the varied reporting of this syndrome worldwide. Mahmud et al. [18] established the prevalence of long COVID-19 symptoms at 46%. They assessed the occurrence of symptoms lasting over 2 weeks, in contrast to the criteria used by the British Bureau of Statistics, where it was additionally necessary to exclude the correlation between the occurring symptoms and comorbidities. The introduction of this additional criterion has led to a reduction in the estimated prevalence of long COVID-19 [26].

Early studies estimated the prevalence of chronic COVID-19 at 30–80%, but these calculations were mostly for inpatients [27]. In a study conducted in the USA in a group of outpatients ($N = 272$), the lack of complete recovery within 2–3 weeks from the diagnosis of COVID-19 was observed in 35% of subjects. This study demonstrated that, in addition to elderly patients with multiple comorbidities, approximately 20% of long COVID-19 cases occurred in 18–34 years old subjects without comorbidities, meaning that SARS-CoV-2 can cause the long-term disease even among young adults without chronic conditions. These observations constitute are important for understanding the effects of COVID-19 disease, even in a group of outpatients with mild symptoms [28].

Risk Factors for Developing Severe and Long-Lasting COVID-19

According to the available literature, risk factors contributing to the severity of COVID-19 and increasing mortality in patients infected with SARS-CoV-2 include older age, gender, non-white origin, disability, and pre-existing comorbidities, including obesity, cardiovascular diseases, respiratory diseases, and hypertension. The role of immunosuppression is still subject to discussion [29].

The risk factors for long COVID-19 appear to be more consistent. They include: female gender, older age, obesity, asthma, poor physical and mental health before the pandemic, and socio-demographic factors [26]. The introduction of remote work and reduction in physical activity adversely affected the society in terms of higher prevalence of overweight and obesity [30]. According to the available data from Great Britain (2019) [31], as many as 68% of men and 60% of women aged 16 and older were overweight or obese. In a report by the UK's National Child

Measurement Scheme, one in three children leaving primary school was overweight or obese [32]. Similarly, the American Heart Association (AHA) [33] published data demonstrating high prevalence of obesity, metabolic syndrome, poor eating habits, and lack of physical activity among children and adults in the US. Obesity and other cardiometabolic risk factors promote vascular endothelium inflammation and dysfunction [34], which may result in the development of long COVID-19. In a prospective study in 6907 patients, Thompson et al. [35] found that female gender, mental disorders, poor general health, asthma, as well as overweight or obesity increased the risk of developing chronic COVID-19. Similar results were obtained by Sudre et al. [13, 26].

To investigate the characteristic features associated with long COVID-19 symptoms, Tenforde et al. conducted a study covering a period between days 14 and 21 after the diagnosis of COVID-19 in a group of 274 outpatients. It was demonstrated that the risk factors associated with the development of long COVID-19 were age over 50 ($p = 0.01$) and comorbidities ($p = 0.003$). Among comorbidities, the most common were: hypertension (OR = 1.3, $P = 0.018$), obesity (OR = 2.31, $P = 0.002$), mental disorders (OR = 2.32, $P = 0.007$), and immunosuppression (OR = 2.33, $P = 0.047$) [28].

Multiple studies (observational and prospective) conducted in China, France, Spain, the United Kingdom, the United States, and Italy that assessed the long-term effects in patients with acute COVID-19 have demonstrated that admission to the ICU and/or ventilatory support are associated with increased risk of developing long COVID-19 [36].

Similarly, a study by Kamal et al. [37] demonstrated a correlation between the acute course of COVID-19 and the occurrence of symptoms following recovery. Only 10.8% of subjects did not experience any symptoms after recovery, while the rest of the patients complained of persistent symptoms. The most commonly reported symptom was fatigue (72.8%), while more critical conditions such as stroke, kidney failure, myocarditis, and pulmonary fibrosis were reported in several percent of the study subjects. The study demonstrated a correlation between the presence of comorbidities and severe course of COVID-19. The severity of COVID-19 correlated with the severity of symptoms following COVID-19. Moreover, in a study by Sudre et al. in patients with severe COVID-19 requiring hospitalization, long-term symptoms were observed more commonly [13].

The UK Office for National Statistics (ONS) informed that the prevalence of any long COVID-19 symptoms is higher in women than in men (respectively: 23.6% vs. 20.7%). Moreover, it has been demonstrated that the patients most often experiencing long-term effects of the disease are aged 35–49 (26.8%), followed by 50–69 age group (26.1%), and ≥70 years old patients (18%) [38].

Data assessing racial and ethnic aspects in the post-COVID-19 syndrome are limited. In a study by Halpin et al. [39] assessing symptoms occurring 4–8 weeks after discharge from hospital, it was found that 42.1% of black subjects reported moderate to severe dyspnoea, while only 25% of white patients experienced this symptom.

Characteristic Symptoms of Long COVID-19

Up to 40–45% of SARS-CoV-2 infections remain asymptomatic [40]. However, most patients (60–80%) who were hospitalized due to COVID-19 report the occurrence or persistence of at least one symptom 50 days after receiving a positive test result [39, 41]. Symptoms persisting 14–21 days after the initial diagnosis were also reported among patients who had not been hospitalized (35%) [28].

Symptoms can develop in the course of COVID-19 diagnosis and persist, or they may not occur until after the recovery [5]. Long COVID-19 can occur in all patients, regardless of the severity of symptoms in the acute phase of the disease [12]. It is characterized by symptoms and ailments within any system, including cardiovascular, respiratory, neurological, digestive, endocrine, urogenital, and musculoskeletal systems [5]. The symptoms most commonly occurring in patients with long COVID-19 are fatigue, musculoskeletal pain, dyspnoea, smell and taste disorders, cognitive dysfunction, the so-called brain fog, sleep disorders, cough and chest pain [42]. The characteristics of long COVID-19 symptoms associated with individual body systems is presented in Fig. 23.2. Persistent symptoms have a significant

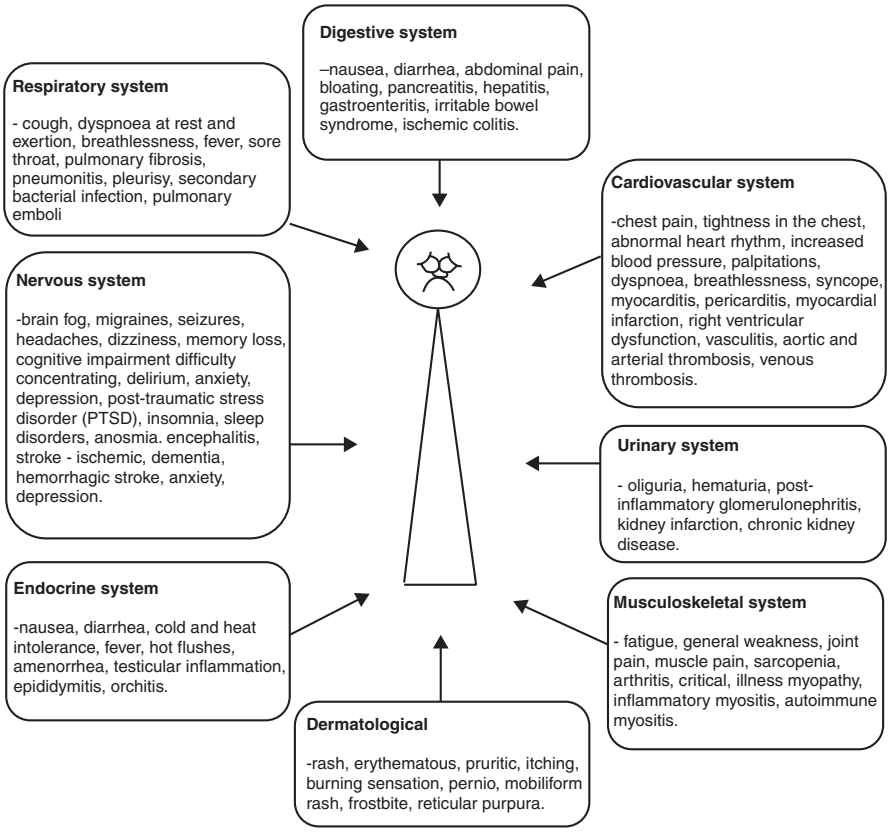

Fig. 23.2 Characteristics of symptoms from individual systems and organs in long COVID-19 [26]

impact on the patients' quality of life and their return to normal activities. In a review by Jennings G et al., reduced quality of life was reported in 57% of patients with symptoms lasting over 12 weeks [43].

Overview of Long COVID-19 Symptoms and Possible Mechanisms Leading to Their Development

Fatigue is one of the most commonly reported symptoms in long COVID-19, regardless of the acute disease severity [8]. It adversely affects muscle strength, concentration, and motivation to act. The UK Office for National Statistics (ONS) estimated the incidence of fatigue among people who contracted COVID-19 at 11.9% within 5 weeks after diagnosis [38]. A study by Goërtz et al. demonstrated that 92.9% of inpatients and 93.5% of outpatients reported chronic fatigue even 79 days after the infection with SARS-CoV-2 [44]. Halpin et al. [39] also observed that fatigue was the most frequently reported symptom (72%) in the group of patients treated in the intensive care unit (ICU) and 60.3% in the group of patients treated in hospital wards not requiring ICU care.

Currently, it is believed that several factors and mechanisms may be responsible for the development of fatigue following COVID-19. Possible mechanisms include disturbed communication in the inflammatory response pathways [45]. However, cross-sectional analytical studies are available that failed to demonstrate a correlation between pro-inflammatory markers and persistent fatigue in patients with long COVID-19 [46]. According to another hypothesis proposed by Wostyn, chronic fatigue syndrome following COVID-19 may result from damage to olfactory sensory neurons, causing decreased cerebrospinal fluid flow through the cribriform plate, which subsequently leads to lymphatic system congestion and toxic accumulation in the central nervous system [47]. Hypometabolism in the frontal lobe and cerebellum is also associated with fatigue reported in COVID-19 patients and is likely due to systemic inflammation and cell-mediated immune mechanisms rather than direct viral neuroinvasion [48]. Moreover, it is believed that the negative psychological and social factors associated with the outbreak of the COVID-19 pandemic [49], as well as direct infection of skeletal muscles with SARS-CoV-2, which causes damage, weakness and inflammation of muscle fibres, and neuromuscular connections, can lead to chronic fatigue, even weeks or months after the infection [29, 50].

Dyspnoea is another symptom frequently reported in patients after COVID-19. The UK Office for National Statistics (ONS) estimated that the dyspnoea occurs in approximately 4.6% of patients 5 weeks following SARS-CoV-2 infection, regardless of the severity of the acute disease [38]. In a study by Halpin et al., it was found that dyspnoea is a common symptom after COVID-19, occurring even 4–8 weeks after discharge from hospital. In the group of patients treated in the intensive care unit (ICU), this symptom was observed in 65.6% of patients, while in the group of inpatients who did not require ICU care, it occurred in 42.6% [39]. A study by Carfi et al. carried out in a group of 143 patients demonstrated that in 43.4% of patients dyspnoea had persisted for even 60 days since COVID-19 diagnosis [29, 41].

In survivors of SARS-CoV-2 infection, endothelial damage and intense immune and inflammatory response contribute to pulmonary tissue and airway dysfunction leading to dyspnoea [51]. Elderly people with acute respiratory distress syndrome, as well as those with longer hospitalization periods and pre-existing lung disease, are at an increased risk of developing fibrotic lesions in the lung [52]. Pulmonary thromboembolism has also been observed in patients after COVID-19. The mechanism of disease development is related to persistent inflammation resulting in the continued production of pro-inflammatory cytokines and reactive oxygen species (ROS) that are released into the bloodstream and surrounding lung tissue. Endothelial damage activates fibroblasts, which deposit collagen and fibronectin, forming fibrotic lesions. Endothelial damage, platelet activation, and platelet-leukocyte interactions, as well as the release of pro-inflammatory cytokines, disruption of normal clotting pathways, and hypoxia generate prolonged hyperinflammation and hypercoagulability, thereby increasing the risk of thrombosis in pulmonary vessels [53].

Cognitive impairment and negative impact of the disease on the mental health is another post-COVID-19 complication. Among patients hospitalized due to infection with SARS-CoV-2, a number of ailments related to the neurological system were observed, including encephalopathy, cognitive impairment, cerebrovascular diseases, brain damage due to hypoxia, seizures, corticospinal symptoms, neurological dysfunction, and mental disorders [54]. What is more, the publications on long COVID-19 also described a phenomenon called “brain fog” as a common and debilitating symptom [29, 55].

The acute course of COVID-19 and prolonged mechanical ventilation adversely affect the mental health of patients and increase the risk of impairment of cognitive functions such as memory, attention, sensory perception of the environment, and thinking. A study by Pandharipande et al. demonstrated that 40% of patients treated in the intensive care unit, 3 months after being diagnosed with COVID-19, had cognitive impairment similar to patients with moderate traumatic brain injury, and 26% had results similar to patients with mild Alzheimer’s disease [56]. Another retrospective study of 1040 ICU patients with respiratory failure and/or shock demonstrated persistent delirium in 71% of patients, 16 weeks after discharge [57].

Headache and stroke are common post-COVID-19 complications. The UK Office for National Statistics (ONS) estimated the incidence of headache in patients after COVID-19 within 5 weeks of infection at 10.1% [13, 28, 29, 38, 58].

The excessive release of cytokines, observed in some patients in the form of “cytokine storm”, apart from activating glial cells, increases the likelihood of neurological symptoms including encephalitis and stroke [51]. People with acute COVID-19 infection also demonstrated long-term psychiatric symptoms, such as post-traumatic stress disorder (PTSD), depression, anxiety, and obsessive-compulsive symptoms [59–61]. In a study by Creese et al., it was observed that mental health in the elderly population was strongly affected by quarantine and social distance. Experiencing loneliness and decreased physical activity are risk factors for mental health deterioration during the pandemic [62]. Moreover, Manca R. et al. have demonstrated increased rates of neuropsychiatric and behavioural

disorders, including apathy, anxiety, depression, agitation, and irritability, as well as confusion, in elderly care home patients with and without dementia. These changes were observed not only as a consequence of SARS-CoV-2 infection, but also as a consequence of prolonged forced social isolation [63].

Neuroinfection with SARS-CoV-2 can result in neuritis, neurodegenerative, and psychiatric disorders [64]. An analysis by Young Lee et al. demonstrated that in the course of COVID-19 pandemics, the most commonly prescribed drugs, apart from antipyretics and medications used to treat the typical disease symptoms (cough, runny nose), were psychiatric drugs for problems related to sleeping, and symptoms of anxiety and depression [65]. Many studies have demonstrated that symptoms such as poor sleep quality and sleep disturbances are common after the recovery from the acute phase of COVID-19 [29].

Smell and taste disorders are common symptoms during acute COVID-19 and may persist long after the initial phase of the disease has subsided. They mainly include impairment of the sense of smell (hyposmia or anosmia) and taste (hypogeusia or ageusia), abnormal chemesthesis (i.e., mucosal sensitivity to irritants), and/or qualitative changes in chemosensory perception (phantosmia and parosmia). The UK Office for National Statistics (ONS) estimated the incidence of smell and taste disorders 5 weeks after COVID-19 diagnosis at 7.9% and 8.2%, respectively [38]. In the available literature, the incidence of smell and taste disorders in patients who have recovered from acute COVID-19 varies from 11% to 45.1% [66, 67].

The most likely pathogenesis of smell disorders in COVID-19 is the impairment of the olfactory sensory neurons in the course of infection and death of airway epithelial cells, accessory cells and pericytes. The pathogenesis of taste disorders in the course of COVID-19 disease may be based on indirect damage to taste receptors due to infection of epithelial cells and, as in smell disorders, the development of local inflammation [68].

The impact of long COVID-19 has also been observed in the scope of multi-organ disorders [29]. Studies by Dennis et al. conducted in a group of 201 patients, 4 months after the initial symptoms of the infection, demonstrated dysfunction in one or more organs in 70% of subjects [58]. The conducted follow-up indicates the occurrence of acute renal failure in patients hospitalized due to SARS-CoV-2 infection [69]. Similarly, Huang et al., who evaluated renal function in patients with COVID-19 demonstrated that 35% of subjects had impaired renal function (eGFR <90 mL/min per 1.73 m^2) 6 months after discharge from hospital [15, 29].

Kidney damage may result from several mechanisms related to SARS-CoV-2 infection. Potential explanations include a deregulated immune response or autoimmunity, chronic inflammation, disorders of the endothelial and clotting system, and disorders of the autonomic nervous system. Chronic systemic inflammation is often observed long after the acute phase of COVID-19 has subsided [58], therefore elevated inflammation is the most likely hypothesis for long-term multi-organ complications in patients with long COVID-19 [29].

The exact pathophysiology of long COVID-19 is unknown. Considering the impact of the disease on many systems and organs, it can be concluded that it is multifactorial [36].

Mechanisms Underlying Cardiovascular Damage in Long COVID-19

The processes underlying the heart muscle injury related to COVID-19 are not fully comprehended, therefore, based on the available studies, several possible mechanisms have been proposed, such as direct cytotoxic damage, dysregulation of the renin-angiotensin-aldosterone system, endothelial inflammation, and dysregulation of the immune response including cytokine release [26, 29].

It has been observed that drugs commonly used in the treatment of patients with cardiovascular diseases, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), may increase the risk of developing COVID-19 and affect the severity of the disease.

Angiotensin converting enzyme 2 (ACE2) plays a key role in the development of cardiovascular complications [70]. Through viral protein to the angiotensin 2 converting enzyme (ACE-2), the virus enters the host cells causing damage to the lung tissue. It also binds to vascular endothelial cells of other organs, such as the kidneys and the heart [71]. It has been observed that the occurrence of cardiovascular events in people with COVID-19 is associated with vascular inflammation and remodelling resulting from endothelial dysfunction [71]. These dysfunctions are caused by the "cytokine storm", which is the immune system overreaction to contact with the pathogen. The result is the secretion of cytokines - proteins that affect the growth, multiplication, and stimulation of cells involved in the body's immune response. The "cytokine storm" violates the integrity and physiological anticoagulant and anti-inflammatory properties of the vascular endothelium [72].

High ACE2 expression in COVID-19 patients leads to over activation of the renin-angiotensin-aldosterone system, which results in electrolyte disturbances and dysregulation of fluid homoeostasis [70]. This mechanism contributes to the development of arterial hypertension, which increases the load on the heart, causing organic pathological lesions in the heart muscle. These lesions can induce heart rhythm disturbances. Studies have demonstrated an increased risk of complications and mortality in people with COVID-19 and pre-existing cardiovascular disease (CVD), as well as in people with 1 or more risk factors such as hypertension, diabetes, hypercholesterolaemia or obesity [73–75] A meta-analysis performed in China demonstrated increased mortality in people with cardiovascular diseases infected with COVID-19; the mortality rate was approximately 11% [76].

In 8–62% of patients hospitalized due to COVID-19, elevated levels of cardiac troponin (cTn) were found, suggesting injury to the heart muscle. It has been found to be associated with higher disease severity, need for mechanical ventilation and mortality [77, 78]. Echocardiographic abnormalities were also observed in COVID-19 patients, including right ventricular dysfunction (26.3%), left ventricular wall motion abnormalities (23.7%), global left ventricular dysfunction (18.4%), diastolic dysfunction (13.2%), and pericardial effusion (7.2%) [78]. Unfortunately, the long-term cardiovascular effects in post-COVID-19 patients are not fully understood. Puntmann et al. [79] have described cardiac involvement in 78% of patients

and persistent inflammation in 60% (n = 100) within several months after SARS-CoV-2 infection. In people with cardiovascular disease, long COVID-19 is of concern due to its association with high morbidity and exacerbation of underlying cardiovascular conditions. Studies in patients with long COVID-19 have shown dyspnoea, chest pain, arthralgia and muscle weakness, difficulty sleeping, and reduced quality of life [15, 72].

The Effect of Long COVID-19 on the Heart Muscle

Based on previous experience with coronavirus infections in 2003 (SARS) and 2012 (MERS), it is believed that inflammation and increased cardiometabolism may responsible for persistent cardiovascular symptoms [2].

The most frequently reported symptoms in the scope of cardiovascular diseases (CVD) in patients with long COVID-19 are chest pain and palpitations. According to Venkatesan and Lopez-Leon et al. [80, 81], they may appear regardless of the severity of the acute phase of the disease and may persist for months [82]. In 2–6 months' follow-up of patients following COVID-19 diagnosis, Carvalho-Schneider et al. [83] and Romero-Duarte et al. [84] established the frequency of chest pain at 5–21%, and heart palpitations at about 10%. With time, the reported symptoms demonstrated a downward trend. Moreover, according to Coromilas et al. [85], patients who required treatment in the intensive care unit showed an increased risk of developing acute arrhythmia. There has also been a correlation between COVID-19 and postural orthostatic tachycardia syndrome (POTS) in a growing number of patients. This syndrome is characterized by changes in heart rate when changing the body position, often accompanied by palpitations and decreased exercise tolerance [27, 86]. Blitshteyn and Whitelaw observed that POTS and other autonomic disorders, i.e. neurocardiogenic syncope or orthostatic hypotension may occur in healthy, nonhospitalized persons even 6–8 months after the acute phase of COVID-19 [87]. The correlation between POTS and COVID-19 is based on a similar interaction with ACE2 protein observed in this syndrome. It is believed that ACE2 mediated dysregulation of blood pressure may result in hypotension and dysautonomia [27, 88].

Preliminary analysis of data from cardiac magnetic resonance imaging (MRI) revealed heart injury (78%) and persistent myocarditis (60%) in post-COVID-19 patients [79]. Heart MRI performed in a group of 26 professional athletes with mild or asymptomatic COVID-19 demonstrated diagnostic features of myocarditis in 15% and heart muscle injury in 30.8% of the athletes [2, 89]. The lesions included increased T1 values (spin-lattice relaxation time) and T2 (spin-spin relaxation time) related to heart injury, as well as late gadolinium enhancement (LGE). Similar observations were made in a study by Knight et al. [82, 90].

Short observation time or a small study group often constituted significant limitation of the analysed studies. In 2021, Joy et al. [91] conducted a study with the longest follow-up of post-COVID-19 patients. The study group included 74 patients who were followed up for 189 days after receiving a positive SARS-CoV-2 test result.

However, the number of patients with cardiac MRI abnormalities was low during this period, so the spin-lattice relaxation time and spin-spin relaxation time, as well as the late post-contrast enhancement, did not reveal significant changes. Athletes constitute a special group of patients that require increased attention. Even a slight disturbance of the haemodynamic parameters, such as impaired heart function, which would be asymptomatic in healthy people, can significantly affect the results obtained in this group of patients. A study by Daniels et al. [92] was conducted on a large number of patients (1597 athletes) and covered 4 weeks after the diagnosis of COVID-19. Myocarditis, in most cases asymptomatic, was detected in 2.3% of the subjects. Singer et al. [93] have analysed the risk of myocarditis caused by COVID-19 approximately 3–12 weeks after the infection. The study was conducted among young Americans, aged 12–19, of both genders. It was observed that young men infected with the virus were six times more likely to develop myocarditis than the vaccinated subjects. In addition, the mean rate of myocarditis was determined to be 0.08%.

Studies conducted in patients hospitalized due to COVID-19 demonstrated increased levels of troponin and other biomarkers (B-type natriuretic peptide, C-reactive protein, ferritin and D-dimers). Manocha et al. [94] also observed that high troponin levels constitute a strong predictor of 30-day in-hospital mortality. Similarly, Caro-Codón et al. [95] demonstrated a correlation between elevated troponin levels and a higher risk of myocardial injury, as well as significantly higher mortality in patients infected with SARS-CoV-2.

In a study by Townsend et al. [96] carried out in a group of 150 patients, roughly 80 days after COVID-19 diagnosis, increased levels of D-dimers were more common in COVID-19 patients who required hospitalization and in patients over 50 years of age ($p < 0.001$). Explaining the mechanisms responsible for the persistence of elevated levels of D-dimers may be important in the pathogenesis of long COVID-19, and observations in this area may significantly change the therapeutic approach to patients [82].

The Effect of Long COVID-19 on Blood Vessels

Some time has already passed since the COVID-19 pandemic began in 2019, but little is known about the long-term effects of SARS-CoV-2 infection on heart and blood vessel function. While SARS-CoV-2 infection was initially thought to be associated with acute respiratory distress syndrome (ARDS), it has been observed over time that the disease it causes, COVID-19, is actually a multi-organ disease that can also induce cardiovascular symptoms, including acute myocardial injury (myocardial infarction) [97], myocarditis [98], stress cardiomyopathy (Takotsubo syndrome) [99], heart failure (HF) [100], and secondary heart injury caused by severe COVID-19 [101, 102].

Studies concerning cardiovascular complications in deceased COVID-19 patients revealed arterial and venous thromboembolism, which may confirm that SARS-CoV-2 virus affects the vascular system throughout the body with previously unknown long-term consequences [82].

Performing autopsies of patients who died from COVID-19, Ackermann et al. [103] demonstrated a correlation between acute COVID-19 and severe pulmonary and extrapulmonary vasculitis, both at the macro- and microvascular levels. Madjid et al. [74] observed that pulmonary and extrapulmonary thromboembolism, a common complication of COVID-19, may determine the short- and long-term effects of SARS-CoV-2 infection. They also pointed out to a link between coronavirus disease 2019 and more severe inflammation leading to vasculitis, myocarditis and arrhythmia.

A study by Roncati et al. [104] was the first one to demonstrate that vasculitis related to COVID-19 causes a life-threatening increase in the type 2 T-helper immune response (humoral immunity) to type 3 hypersensitivity. The subsequent deposition of antigen-antibody complexes, mainly in the vascular walls, induces acute systemic vasculitis. Moreover, in a study by Cao et al. [105], it was found that the damage to the vascular endothelium is caused by a highly pro-inflammatory cytokine response induced by SARS-CoV-2. Due to their pro-inflammatory effect on the endothelium, TNF-α and IL-1β cytokines play a key role in the induction of vascular dysfunction in patients suffering from COVID-19 [82, 106].

Sollini et al. [107] were the first to investigate the long-term effects of COVID-19 on the vascular system. The obtained results suggest that SARS-CoV-2 induces vasculitis, which may be responsible for the symptoms persisting for more than 30 days after the infection. There were also studies by Ratchford et al. [108] and Szeghy et al. [109] assessing the impact of COVID-19 on the vascular system in the upper and lower extremities. The study included 20 young adults, whose vascular function was assessed 3–4 weeks after the infection using Doppler ultrasound. The results demonstrated significantly impaired vascular function in the systemic circulation as well as arterial stiffness in COVID-19 positive patients compared to the control group. These observations confirm the occurrence of cardiovascular disorders among young adults recovering from SARS-CoV-2 infection. In a study by Nandadeva et al. [110] 16 young adults, followed up for 3 months after the diagnosis of COVID-19, were subjected to ultrasound assessment of brachial artery dilatation in response to ischaemia (flow-mediated dilatation - FMD), cerebral vasodilation and arterial stiffness [82]. In subjects with long-term symptoms, the analysis demonstrated a reduction in peripheral vasodilation, while in asymptomatic subjects the vascular function was similar to the control group. Moreover, the study demonstrated that the function of the studied blood vessels did not change significantly, regardless of the persistence of COVID-19 symptoms.

Diagnosis and Treatment of Cardiovascular Effects in Long COVID-19

The diagnostic procedure regarding cardiovascular conditions associated with long COVID-19 includes high risk patient screening for myocardial injury. High risk patients include people with: abnormal cardiological examination results in the acute phase of the disease, a newly diagnosed cardiovascular disease following acute infection and athletes. High risk patient screening should consist of a careful interview, clinical examinations, blood tests including: C-reactive protein, troponin, N-terminal pro B-type natriuretic peptide (NT-proBNP), glycated haemoglobin and lipids,

electrocardiography (ECG), and transthoracic echocardiography, performed 8–12 weeks after infection. In the case of patients with clinically significant abnormalities after screening, additional testing is recommended. Following screening, non-invasive examinations, such as cardiac magnetic resonance (CMR), positron emission tomography, 24 h Holter ECG, and computed tomography angiography (CTA) may be considered, and in high risk patients, coronary angiography or endomyocardial biopsy (EMB). In some cases, consideration should be given to referring to specialist clinics, e.g. clinics treating heart rhythm disorders or psychological clinics. In patients with chronic cardiovascular conditions visiting medical facilities to undergo a prophylactic medical check up, an interview regarding the history of COVID-19 infection and vaccination status should be conducted. In the case of patients reporting persistent symptoms following COVID-19, it is necessary to perform an assessment of physical fitness, mental health, with regard to anxiety and depression, and cognitive functions. This allows early identification of patients who require additional help in their recovery so that they can be referred to appropriate specialist clinics [26].

According to the Sports Cardiology Section of the European Association of Preventive Cardiology opinion of 2019 regarding the recommendations for athletes and their ability to return to sport after SARS-CoV-2 infection [111], gradual resumption of exercise and return to sport is allowed after mild infection, while in the case of patients suspected of having myocarditis, it is advisable to limit exercise for even up to 3 months.

According to ESC [112] and AHA [113], the management of patients with complicated myocarditis unrelated to SARS-CoV-2 infection (i.e. unexplained left ventricular dilatation, severe left ventricular dysfunction, and bradyarrhythmia or tachyarrhythmia) is based on a myocardial biopsy performed to identify the subtype of myocarditis and to determine specific treatment options [26]. In the case of pericarditis related to COVID-19, the efficiency of non-steroid anti-inflammatory drugs and/or colchicine is being studied [114]. Currently, there are no detailed recommendations regarding treatment after COVID-19. In the case of acute coronary syndromes following COVID-19, patients are usually treated according to ESC guidelines [115] of 2020 and AHA guidelines [116] of 2014. Similarly, the management of patients with heart failure is based on the use of modern therapies in accordance with previously developed guidelines [117]. Whereas, in the scope of prolonged antithrombotic prophylaxis following acute COVID-19, two studies are currently under way: HEAL-COVID [118] and STIMULATE ICP [114].

The management of long COVID-19 effects is largely based on conservative treatment, consisting in the elimination of risk factors related to the development of cardiovascular diseases [119]. The association between overweight/obesity and long COVID-19 analysed in the available literature may serve as an example [120]. Evidence indicates the beneficial effects of non-invasive methods of weight loss, i.e., diet, regular physical activity, stress reduction and sleep hygiene on inflammation, vascular dysfunction, and metabolic syndrome [26, 121]. In patients with persistent symptoms of dyspnoea, pulmonary rehabilitation [122] based on breathing exercises is recommended to alleviate symptoms [26, 123]. Also, in people returning to work, struggling with incomplete mental and physical recovery, a referral to mental health assessment/cognitive-behavioural therapy and gradual return to work are recommended [124]. Exercise programmes encouraging patients to be physically active and maintain an upright posture (including upright standing) facilitate

symptom alleviation after staying in bed for a long time during severe illness. In addition, compression stockings may alleviate the symptoms of orthostatic hypotension by reducing venous stasis and peripheral oedema. The presented management of various ailments related to the post-COVID-19 syndrome is supplemented with pharmacotherapy (Fig. 23.3). The most frequently used drugs include: ivabradine, fludrocortisone, midodrine, clonidine, and methyldopa [26].

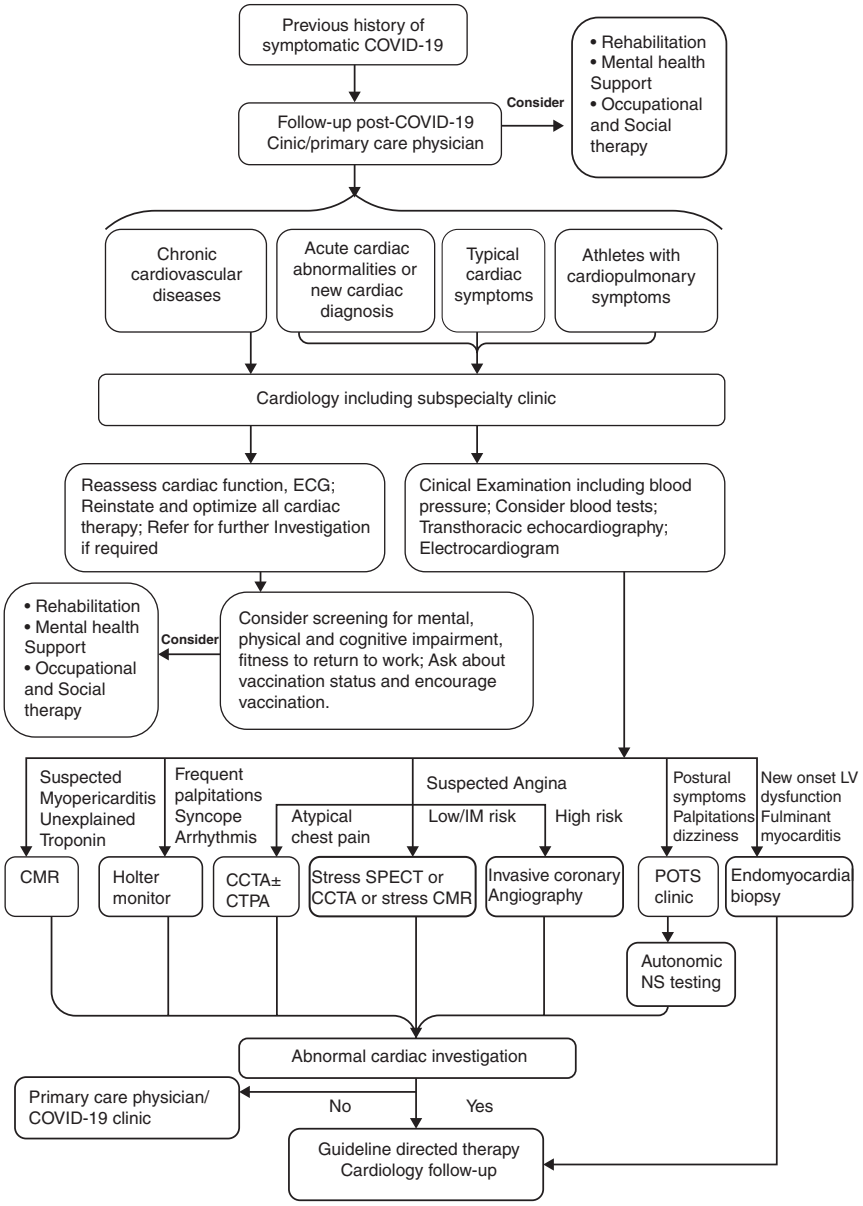

Fig. 23.3 Suggested algorithm for further care and treatment of patients with acute cardiovascular effects of COVID-19 [26]

Many people slowly recover on their own, but some require multidisciplinary rehabilitation. Despite the lack of objective diagnostic criteria, several guidelines for the diagnosis and treatment of chronic COVID-19 have been published, including the ones issued in December 2020 by the National Institute for Health and Care Excellence (NICE) [125]; Permanent Board of the Catalan Society of Family and Community Medicine (CAMFiC) long COVID-19 Study Group from Spain; [126] and French recommendations [127]. The World Health Organization (WHO) guidelines on life and clinical management of COVID-19 also include a section on "Management of COVID-19 Patient Following Acute Disease" [128]. The British Thoracic Society also issued guidelines regarding the follow-up of all patients in week 12, regardless of the severity of COVID-19, by means of chest X-ray and clinical evaluation [129]. People with severe disease are advised to hold the follow-up visit earlier (within 4–6 weeks) in order to assess the need for further tests and rehabilitation [2]. Echocardiography and electrocardiography are recommended for monitoring patients with persistent cardiac symptoms [27].

Cardiovascular complications of long COVID-19 and proposed therapies are presented in Table 23.1.

Table 23.1 Cardiovascular complications of long COVID-19 and proposed therapies

The causes of myocardial injury	Long-term complications	Applied prophylactic therapies	Diagnostic methods
• Direct injury to the heart muscle • Viral infiltration via ACE2 • Microvascular thrombosis • Cytokine storm and systemic inflammation • Antiviral therapies • Oxygen demand exceeds oxygen supply • Acute coronary syndrome	• Arrhythmias • Ventricular fibrillation • Ventricular tachycardia • Atrial fibrillation • Atrial tachycardia • Heart failure • Atherosclerotic cardiovascular disease • cardiovascular death	• Blockade of the renin-angiotensin-aldosterone system (RAAS) • Statins • Antiplatelet therapy • Anticoagulants • Anti-inflammatory agents	• Cardiac biomarkers (troponin, B-type natriuretic peptide (NT-proBNP)) • Echocardiography • Electrocardiography • cardiac magnetic resonance imaging (MRI)

ACE2 angiotensin converting enzyme 2, *BNP* brain natriuretic peptide, *RAAS* renin-angiotensin-aldosterone system, *MRI* magnetic resonance imaging [3]

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Chapter 24
Cardiovascular Complications of Long-COVID: Management

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Introduction

We have been struggling with the coronavirus pandemic for over 2 years. The management of the acute phase of infection has been widely investigated. However, SARS-CoV-2 also affects people beyond the acute phase of the disease, causing numerous of burdensome symptoms [1]. The long-term effects of COVID-19 seem to be complex and heterogeneous, affecting both hospitalized and non-hospitalized patients [2].

According to a clinical case definition developed by World Health Organization (WHO) "post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time" [3].

Cardiovascular complications of COVID-19 may emerge during the acute phase of infection and as a long-term sequelae of post-COVID-19 cardiac syndrome [4]. Chest pain and palpitations are the most commonly reported cardiovascular symptoms [5]. COVID-19 cardiovascular involvement includes heart failure, arterial thrombotic events, arrhythmias, myocarditis, pericarditis, stress cardiomyopathy as well as venous thromboembolism [6]. There is a lack of diagnostic and therapeutic algorithms dedicated to patients with cardiovascular complications of long-COVID.

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This chapter is a proposition of the management of post-COVID-19 cardiovascular complications based on the current literature and our clinical experience from the Silesian study on COVID-19 complications (SILCCOV-19).

Review of Original Studies

The Silesian study on COVID-19 complications (SILCCOV-19) is a prospective observational registry-based cohort study designed to evaluate the prevalence and clinical significance of COVID-19 complications in patients after COVID-19 infection. Two-hundred consecutive individuals who had symptoms of COVID-19 in the acute phase of disease with clinical indications for hospital admission and those without a need for hospitalization (86 individuals, 43%) in the acute phase of disease were included. The interdisciplinary diagnostics during the study visit (the median time from symptom onset to the study visit was 107 days for non-hospitalized and 105 days for hospitalized patients), including cardiovascular, pulmonary, neurological, hepatology, and psychiatric tests, was performed. Abnormal platelet parameters, NT-pro BNP levels, functional and radiological findings in the lungs, and insomnia were the most frequent COVID-19 complications in hospitalized and non-hospitalized patients. Despite frequent occurrence of palpitations (15%), dyspnoea (9%), and chest pain (6%) no significant cardiologic complications were diagnosed (statistical significance defined as $P < 0.05$). Patients' characteristics associated with significantly higher risk of complications after COVID-19 were: older age, longer duration of symptoms, and longer time of hospitalization during the acute phase of COVID-19 infection [7].

In the prospective observational cohort study of 100 patients recently recovered from COVID-19 infection, 78 patients (78%) had abnormal cardiac magnetic resonance (CMR) findings and 60 patients (60%) had ongoing myocardial inflammation, independently of preexisting conditions, severity, and overall course of the acute phase of infection, the time from the original diagnosis as well as the presence of cardiac symptoms [8].

CMR performed in 58 (49%) survivors from the prospective COVID MECH study 6 month after hospitalization for moderate-to-severe COVID-19 revealed pathology in 12 (21%) patients and did not correlate with severity of the disease. Cardiovascular biomarkers (cardiac troponin T and N-terminal pro-B-type natriuretic peptide) during COVID-19 were higher in patients with CMR pathology, but with no significant association after adjusting for confounders [9].

In the qualitative study of 114 individuals with long-COVID, including 43 healthcare workers, a patient-generated panel of principles for long-COVID services was proposed due to improve care of patients with long-COVID. A set of quality standards including access to appropriate care, minimal patient care burden, clinical responsibility and continuity of care, multidisciplinary rehabilitation, evidence-based approach and patient involvement was suggested [10].

Review of Guidelines

The National Institute for Health and Care Excellence (NICE) rapid guideline on managing the long-term effects of COVID-19 emphasizes the absence of evidence for pharmacological treatment of post-COVID-19 syndrome and recommends to follow the current national and local guidance referring to the general population for managing the common symptoms. The guideline suggests to use a holistic, person-centered approach, and multidisciplinary assessment [11].

European Society of Cardiology (ESC) released two-part guidance for diagnosis and management of cardiovascular disease during the COVID-19 pandemic. Second part of guidance advises on the care pathways, treatment, and follow-up of the most commonly encountered cardiovascular conditions and of COVID-19 [12].

The WHO living guidance on COVID-19 clinical management states that patients with a history of suspected or confirmed COVID-19, independently of the infection severity, should have access to follow-up care. The guidance proposes the patient-tailored, coordinated interventions including proper management of life-threatening complications, education, advice on self-management strategies, caregiver support and education, peer-to-peer groups, stress management, stigma mitigation, home modification as well as prescription of rehabilitation programs and/or specialty management [13].

Management

One should remember that the long-term effects of COVID-19 affect both hospitalized and non-hospitalized patients in the acute phase of SARS-CoV-2 infection [14]. Furthermore, the occurrence of the post-COVID-19 condition seems to be independent of the initial illness' severity [15]. Thus, the specific group of patients that could be diagnosed towards the cardiovascular complications of COVID-19 has not been established. Likewise, screening for cardiovascular complications is not recommended. However, the course of the acute phase of infection should be noted, as it seems that experiencing more than five symptoms during the first week of illness can be associated with the development of long-COVID [16].

Based on the analysis of SILCCOV-19 study, diagnostic tests that could be useful in the identification of post-COVID-19 complications were proposed; cardiac troponin T and N-terminal pro-B-type natriuretic peptide as a possible screening markers of cardiac injury; D-dimer-test to identify hypercoagulable states and patients with high risk of thromboembolism; the 6-min walk test to objectify exercise tolerance; morphology test to diagnose post-infectious neutropenia, anemia or abnormal platelet distribution width and mean platelet volume; iron panel to diagnose iron deficiency after COVID-19 infection; high-resolution computed tomography (HRCT) to diagnose lung lesions and transfer factor of the lung for carbon monoxide (TLCO) to diagnose abnormalities in gases diffusion in alveoli; questionnaires to assess patient's psychological state [7].

Currently, there is no specific pharmacological treatment of post-COVID-19 syndrome. Therefore, managing cardiovascular complications of long-COVID should be based on current guidelines referring to the general population. However, taking into account the possible mechanisms of cardiovascular involvement in post-COVID-19 condition, early implementation of symptomatic and cardioprotective treatment in patients with cardiovascular complications of long-COVID according to presented symptoms and comorbidities seems to be appropriate [17].

Multidisciplinary evaluation is necessary because symptoms reported after COVID-19 infection require differential diagnosis and assessment of comorbidities. It is crucial to evaluate the character of presenting symptoms including the relationship to exertion, and other exacerbating or relieving factors. Past medical history should be assessed as SARS-CoV-2 infection may be a triggering factor for pre-existing comorbidities. Therefore, prior diseases, especially those causing overload or cardiac injury (coronary artery disease, hypertension) as well as exposure to toxins and family history are relevant.

Patients with symptoms of a life threating complications should be urgently admitted to the hospital.

Heart Failure

In patients with symptoms and signs of heart failure guideline-directed medical therapy should be initiated and optimized to the maximal tolerated doses. Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) improves survival, reduces the risk of heart failure hospitalizations, and reduces symptoms in heart failure with reduced ejection fraction (HFrEF). There is no clinical evidence of the association between ACE-I treatment and increased susceptibility to the COVID-19 infection [18]. The use of the sodium-glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin and empagliflozin) is recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not. In individuals with signs and/or symptoms of congestion diuretics should be used and modulated according to the patient's clinical status [19].

Coronary Artery Disease

The management of acute coronary syndromes and chronic coronary syndromes in patients with post-COVID-19 condition should be based on the corresponding guidelines [20–22]. According to the ESC guidance for diagnosis and management

of cardiovascular disease during the COVID-19 pandemic, aspirin can be used for secondary prevention of cardiovascular events despite being one of the non-steroidal anti-inflammatory drugs as it is used in low doses that have very limited anti-inflammatory effect [12]. Statin therapy is recommended in patients with coronary artery disease but the measurements of serum transaminases and creatine kinase should be performed because hepatic diseases and severe rhabdomyolysis are gastrointestinal manifestations of long-COVID [17].

Arrhythmia

In case of cardiac arrhythmia in patients with post-COVID-19 syndrome it is necessary to implement proper treatment dependently on type of diagnosed arrhythmia. Supraventricular tachycardia requires therapy with beta-blockers or calcium channel blockers if beta-blockers are contraindicated [23]. In atrial fibrillation and flutter the ventricular rate control, rhythm control as well as therapeutic anticoagulation according to CHA2DS2-VASc score should be considered [24]. In patients with bradyarrythmias the need for permanent pacing should be evaluated after excluding potentially reversible causes of arrythmia [25]. Complex ventricular arrhythmias should be immediately consulted with cardiologist. The indications for catheter ablation, secondary prophylactic implantable cardiac defibrillator (ICD) or wearable defibrillator in ventricular tachyarrhythmia need to be evaluated [26].

Myocarditis

Treatment of patients with myocarditis in long-COVID should be identical to the treatment of patients in general population. Cardiac magnetic resonance, if available, is the preferred method for the diagnosis of acute myocarditis. There are no specific recommendations regarding the treatment of patients with COVID-19 myocarditis [12]. Avoiding physical exertion for 6 months after diagnose of myocarditis is recommended [27].

Venous Thromboembolism

Patients with venous thromboembolism as a possible complication of post-COVID-19 condition should be treated as patients without a history of COVID-19 infection. Proper doses of anticoagulants should be implemented.

Conclusions

The results of original studies present discrepancy in the prevalence of the potential cardiovascular complications in post-COVID-19 syndrome. Increased levels of parameters indicating hypercoagulable states and potential heart failure are observed. Therefore, due to the divergent outcomes and a lack of guidelines on the management of cardiovascular complications in long-COVID, the diagnostic and therapeutic process should be performed using person-centered, multidisciplinary approach. Presented symptoms should be assessed and appropriate laboratory and imaging tests should be performed. A thorough patient's evaluation including psychological state is important because disorders such as anxiety or depression are common in patients with long-COVID and may cause somatic symptoms and worsen cardiovascular prognosis. Symptomatic treatment based on the available guidelines referring to the general population is recommended. Finally, the multidisciplinary rehabilitation in patients with post-COVID-syndrome should be considered. According to NICE guidelines rehabilitation plan should include: providing information, education, supported self-management, peer support, symptom management strategies and physical rehabilitation [11]. Further research on the long-term cardiovascular complications after COVID-19 infection is necessary to develop appropriate management strategies.

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Part V
The Impact of COVID-19 Pandemic on the e-Services and Digital Tools Development in Medicime

Chapter 25
The Impact of the COVID-19 Pandemic on e-Services and Digital Tools Development in Medicine

Sonu M. M. Bhaskar

Introduction

COVID-19, caused by a previously unknown novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a respiratory illness [1]. The World Health Organization (WHO) designated COVID-19 a pandemic on March 11, 2020, just about 3 months after the first cases were identified [2]. As of April 14, 2022, COVID-19 has infected more than 499 million people and caused nearly 6.2 million deaths around the world [3]. COVID-19 has had a significant impact on health systems [4–10], as well as socioeconomic repercussions, particularly among vulnerable and marginalized populations, and indeed in low- and middle-income countries (LMICs) with weaker health systems [11, 12]. Given the high transmissibility, a high case fatality rate of more than 1%, and the absence or limited treatment or vaccines available especially during the early phases of the pandemic, much of the public health response to, and management of, the COVID-19 pandemic have hinged around containment and mitigation [13–15]. However, the efficacy of traditional public health measures, such as detecting and containing clusters of infection and interrupting community transmission to contain infectious disease outbreaks

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and their detrimental impact, have had variable success across nations during COVID-19 [13, 16, 17]. It is poignant that public health measures for epidemic response, such as surveillance, rapid case identification, mitigation and containment of community transmission [18, 19], and robust public communication, are closely monitored for their implementation and impact on incidence and mortality rates [20].

During COVID-19, digital tools have been rapidly incorporated, deployed, and used in pandemic preparedness and response encompassing all aspects such as infection surveillance, screening, quarantine and self-isolation, and clinical management including diagnosis, prevention, and treatment [21]. However, wider variations in its application and deployment across regions exist [22, 23]. There are also significant challenges around its implementation, inequity [24], privacy, and use. This article will discuss the emerging use and scale of digital tools catalyzed by the COVID-19 pandemic. Several key policy issues and barriers will also be discussed. Future perspectives towards improving the availability and access of digital tools and a conceptual framework for robust pandemic preparedness and response are also presented.

COVID-19 as a Catalyst for Research and Innovation on, and Uptake of, Digital Tools

Infectious disease outbreaks have in past led to research and development to build and boost core capacity to aid public health measures [25, 26]. For example, during the Ebola epidemic in West Africa from 2014 to 2016, mobile phone data was used to simulate travel patterns, and hand-held sequencing equipment allowed for more effective contact tracing and greater insights into the Ebola outbreak dynamics [27, 28]. More recently, electronic data systems were used to identify disease clusters during the 2003 outbreak of severe acute respiratory syndrome (SARS) virus in Hongkong [29]. Consistent with previous outbreaks, the COVID-19 pandemic has acted as a catalyst for research and innovation as well as rapid deployment and uptake of digital tools [30, 31]. During COVID-19, digital technologies, or services such as telemedicine have been recognized as a critical part of, and pivotal to, our public health response and systems strategy [13, 32–35]. In ways that are difficult to achieve through conventional means or manually, digital health technologies can aid our pandemic strategy and response in the advent of a future pandemic [13]. Notably, some countries such as South Korea and Singapore have integrated digital technologies into containment and mitigation measures at the systems level [21], including surveillance, testing, contact tracing, and robust quarantine, which could have contributed to the incidence curves flattening early, and consistently lower-case fatality rate of COVID-19 in South Korea and Singapore compared to United States, China, India, European Union, United Arab Emirates, and Australia. Singapore [20] and South Korea offer a model framework for a successful pandemic response for low-resource healthcare settings in Africa, Asia, Latin America, and elsewhere [36]. Taking lessons from the previous SARS outbreak in 2002, 900 rapid

response public health preparedness clinics (PHPCs) were established across Singapore [37], to improve response to pandemics and outbreaks [38]. PHPCs serve as a liaison or intermediary between the community and hospitals, by classifying individuals with flu-like or pneumonia symptoms into low- and high-risk categories. The high-risk patients are referred to an infectious disease hospital for further examination and treatment. Two Bluetooth-operated mobile applications, namely TraceTogether [39] and SafeEntry [40], were developed in Singapore to optimize contact tracing and quarantine compliance [40]. These applications detect people within close distance and duration of encounter with an infected individual. All operational enterprises in Singapore are mandated to have SafeEntry during the pandemic, whereas TraceTogether is available for common citizens to download and use on a voluntary basis [39]. Likewise, a mobile location tracking app was developed by Israel that sends out an alert if users are in close contact with the COVID-19 positive case [41]. Moreover, South Korea has been utilizing ancillary contact tracers such as global positioning system (GPS) phone tracking, credit card records, and surveillance videos. Notably, South Africa is also using GPS-data tracking tools. Open-source technologies and crowdsourcing data [42–45] offer exciting opportunities for spatial disease surveillance, local outbreak monitoring, and public health decisions or interventions that are integral to future pandemic response and its mitigation [46]. Recent efforts on integrating large-scale cohort data are welcome developments [47]. However, despite a flurry of contract tracing apps, in more than 46 countries, the efficacy of these apps has been limited by their low uptake, trust deficit, and privacy concerns [41, 48, 49]. An autonomous governance entity, independent of government, comprised of and led by members of the civil society or broader community, could mitigate such risks, address concerns, and build trust around data use and governance [50]. Besides, sustainable financing is required to make these services more accessible to disadvantaged communities and low-resource settings [51].

Digital Tools for Tracking

Several digital tools, such as big data and artificial intelligence (AI), have been used in the tracking of infected cases and monitoring the spread of infection across locations to build preparedness against COVID-19 [13]. For example, in China, data dashboards and migration apps have allowed the visual display of infection or disease spread and tracking of people's movement [13]. Machine learning models have been trained on real-time data collected using these digital tools [52]. These AI or machine learning models are used to forecast SARS-CoV-2 transmission dynamics and guide border checks and surveillance [53]. Taiwan introduced health screenings for airline travelers from Wuhan as promptly as China announced the outbreak [54, 55]. Healthcare facilities were able to use big data to examine patients' travel history and identify individuals for SARS-CoV-2 testing and tracking by linking these data with immigration records and health insurance databases [13, 54, 56]. The

web-based dashboards such as Johns Hopkins University (MD, USA) COVID-19 dashboard and HealthMap provide real-time visualizations of COVID-19 infections and mortality worldwide [57]. When analyzing projections, the correctness, validity, and reliability of forecasts by AI-based digital tools need thorough evaluation [58, 59]. Besides, given that most of these models have been trained on datasets emanating from specific populations, the generalizability of these AI systems is limited [60]. Novel strategies using federated learning algorithms offer alternative privacy-preserving AI models with good generalizability as they are trained on several datasets from various countries or regions [61–63]. This is especially poignant during a pandemic such as COVID-19 to rapidly develop high-fidelity diagnostic or prognostic models without the constraints associated with the aggregation of datasets [61, 64].

Digital Tools for Infection Screening

Public health officials look for signs of disease to screen for infections in people who appear to be asymptomatic [65]. In China, open-source, online and cloud-based digital tools have been used to identify individuals with COVID-19 infection and facilitate provision of suitable resources to such individuals [66]. High-performance infrared thermal cameras have also been utilized in Taiwan to collect a real-time thermal image of people to quickly identify individuals with fever [67]. In Singapore, temperature data on people taken at entrances to public buildings or transportation are analyzed to locate emerging hotspots and clusters of infections where COVID-19 screening can be undertaken [68]. Other countries such as Iceland, Germany, and South Korea embarked on widespread testing using self-reported symptoms by patients on mobile technology, and various datasets, including clinical and genomic sequencing data, to delineate the virus's pathology and transmission [69]. However, these tools have several limitations. Infection screening technologies are costly and require trained workers, which prevents many countries from adopting them [13]. Because of the long incubation time and the relatively high prevalence of asymptomatic illness with COVID-19 compared to other infectious diseases, the infection screening efficacy of digital tools that monitor vital signs or self-reported symptoms is limited [70].

Digital Tools for Contact Tracing

Digital contact tracing automates tracing on a scale and at a speed that would be difficult to achieve without the use of digital tools [21]. It decreases the dependence on one's memory recall, a challenge when dealing with highly populated areas with mobile populations [71]. Digital contact tracing apps have been developed for use in several countries in response to the COVID-19 epidemic; such apps rely on

innovative solutions that have never been attempted on this scale before [72, 73]. For example, a high-tech technology-enabled surveillance system has been used for contact tracing in Singapore [74, 75]. The Singapore government used a smartphone app, called TraceTogether, that uses Bluetooth to track users' position and vicinity to other individuals, warning those who come into contact with an infected person or are at high risk of carrying it [75]. Besides, Singaporean citizens are also provided COVID-19 related information twice a day via WhatsApp that contains information regarding the overall number of COVID cases, suspected sites of an infection outbreak, and strategies for infection prevention [75]. However, privacy concerns around the use and data storage with these apps have been raised. In contrast to centralized apps such as TraceTogether that share contacts and contact events with a central server, decentralized apps such as Swiss Covid offer an alternative platform as they only upload the anonymous details of the user reporting positive for COVID-19 [76]. It is critical to assess the precision and efficiency of digital tools, as the efficiency of the system in detecting transmission events isn't adequately described. A study from Oxford University found that contact tracing applications would have to be used by 60% of a nation's population to be effective as a mitigation approach [77]. Smartphone ownership, user trust, usability, and device compatibility all limit adoption of contact tracing tools [78]. Identifying contacts deemed close enough for transmission and optimal exposure duration that's appropriate to trigger an alert are other practical and lingering challenges [79].

Digital Tools for Quarantine and Self-Isolation

Several tools have been developed in countries such as Australia, Iceland, China, Taiwan, and South Korea for quarantine and self-isolation that identifies and tracks people infected, as well as implement or enforce quarantine by isolating infected and restricting travel [13, 80]. Such applications use several technologies such as cameras, digital recorders, GPS, mobile phone applications, quick response codes, and artificial intelligence. In Australia, international visitors were confined in hotels, or special quarantine facilities away from the mainland, upon arrival before the international borders became normalized [81]. Individuals who violate quarantine were required to wear tracking devices under new regulations, with fines imposed for subsequent violations. In Iceland, a mobile phone application was developed to track those infected with COVID-19 and ensure that they remain in self-isolation [82]. In Hongkong, people under self-isolation are required to wear a wristband, linked to a database via cloud technology that warns authorities in the event of a quarantine breach [83]. Whereas in Taiwan, home-quarantined individuals were monitored electronically assisted by government-issued mobile phones that are GPS-tracked [84]; in case of a breach, this "electronic fence" quarantine tool automatically sends messages to the individual and fines are levied [54]. Such tools have also been used in South Korea where individuals in self-isolation are mandated to download a mobile phone application that triggers a warning to authorities if the

quarantine is breached [80, 85]. China's rapid response (QR) code system allows government authorities to track health and limit movement by requiring individuals to fill out a symptom survey and register their temperature [86, 87]. This QR code functions as a COVID-19 health status certificate and travel permit [88]. The color codes generated by this system stratified COVID-19 health status as low, medium, and high risk. Individuals with green codes are allowed to travel freely, while those with red codes must self-isolate for 14 days [88]. In addition to QR code systems, portable digital recorders, cameras mounted on drones, big data, robots, the internet of things (IoT) [89], and AI-powered surveillance cameras are also used by authorities in China to monitor and restrict public gathering [88, 90]. These technologies rely upon the accuracy of the self-reporting of symptoms by individuals which may be an issue when individuals infected with COVID-19 are not symptomatic [73, 91]. Moreover, individuals leaving quarantine without their mobile devices or gadgets can bypass the quarantine tracking by such technologies [73].

Concerns around trampling of the right to privacy and violation of civil liberty, with the use of these technologies, and unprecedented surveillance, such as the use of AI, cameras, and recorders in China, have been raised [92, 93].

Digital Tools for Clinical Monitoring

During the COVID-19, telemedicine technologies such as virtual care platforms, which combine video conferencing and digital monitoring to give remote healthcare to patients, have been a cornerstone of patient care, helping to offset the decline in outpatient visits [94], by providing vital patient continuity and limiting exposure to healthcare workers and health systems [95–97]. The use of telemedicine platforms has seen a meteoric rise in Australia, Canada, the United States, and indeed around the world, especially in providing virtual care to patients with chronic diseases during lockdown [98]. Beyond COVID-19, these technologies offer the potential to improve access to healthcare services [13, 32]. Notwithstanding the rapid implementation and wider uptake of telemedicine during COVID-19, systemic problems including organizational readiness (such as licensing, digital maturity, reimbursements, and regulatory hurdles), variations in access and use across marginalized groups and geographical locations, and infrastructural constraints exist [22, 23, 95]. Moreover, risks such as equipment failure, poor services in low-bandwidth areas, misdiagnoses, costs associated with proprietary telemedicine platforms, and data breaches pose as barriers and need to be addressed [99]. Standardization of telemedicine workflows leveraging existing clinical tools could improve its practice, quality of care, and usability [95]. AI and robotics-assisted telemedicine technologies are also promising and show potential for use in pandemics [100, 101]. For example, telepresence robots can provide support to those who are isolated by helping patients communicate with family and doctors, and vice versa. COVID-19 diagnosis and risk prediction can be aided by AI. For instance, in China, COVID-19 pneumonia cases are identified using a cloud-based AI-assisted telemedicine

service that analyses CT scans in seconds, thereby facilitating differential diagnosis of COVID-19 distinct from other respiratory conditions - expediting the diagnostic workflow. Another interesting crowdsourced application that has garnered attention and is available for free use is COVID-Net, an open-source deep convolutional neural network architecture [102]. COVID-Net can swiftly distinguish COVID-19 cases from other lung disorders on chest X-rays. Besides, machine learning algorithms have also been developed to predict COVID-19 severity and mortality after infection [102]. These models show potential for use as clinical decision-making and resource allocation aid. Given the shortage of medical supplies and limited availability of hospitals and healthcare personnel during peak demand, especially during the early phase of the pandemic, such algorithms can help route patients and resources to hospitals and providers in need [45].

Discussion and Future Perspectives

Central to countries that have flattened their COVID-19 incidence curves [103], and achieved sustained low fatality rates, have been the integration of digital technologies into public health or health systems preparedness and response [13]. The deployment of digital tools has facilitated planning, surveillance, screening, contact tracing, quarantine and self-isolation, and remote clinical management [104]. The early adoption of these technologies will have far-reaching consequences in reducing chronic disease burden and preventing high caseload due to COVID-19 infections [12]. Lessons from policy and implementation perspectives from countries such as South Korea and Singapore [20], could help other nations, especially LMICs, to use this as "a pandemic preparedness and response toolkit" for future surges due to COVID variants or in the advent of a future pandemic [36]. We propose a conceptual framework for holistic pandemic preparedness and response encompassing digital tools along with existing public health measures such as handwashing, face masks, vaccines, hand sanitizer, disinfecting high-touch surfaces, and home-based rapid antigen tests (see Fig. 25.1).

However, caution must also be exercised to ensure that digital technologies are made available or used equitably [105], with due respect for justice and ethics [106]. Healthcare inequalities can be exacerbated by digital tools, which can reinforce socioeconomic inequities [12, 13]. There are huge geographical disparities in internet availability and use across the regions, with mobile internet connectivity or penetration being as high as 82% in Europe in contrast to 28% in Africa according to the GSMA report published in 2019 [107]. Moreover, lower socioeconomic groups and remote regions even in high-income countries carry significant disparities in the availability, deployment, and use of digital tools such as high-speed broadband, wearable devices, and 4G/5G capable smartphones [108]. Comprehensive and targeted policy-led resource and funding allocations are required to address these disparities. Governments should consider dedicated funding allocation and resources for digital capacity building as part of broader pandemic preparedness and response

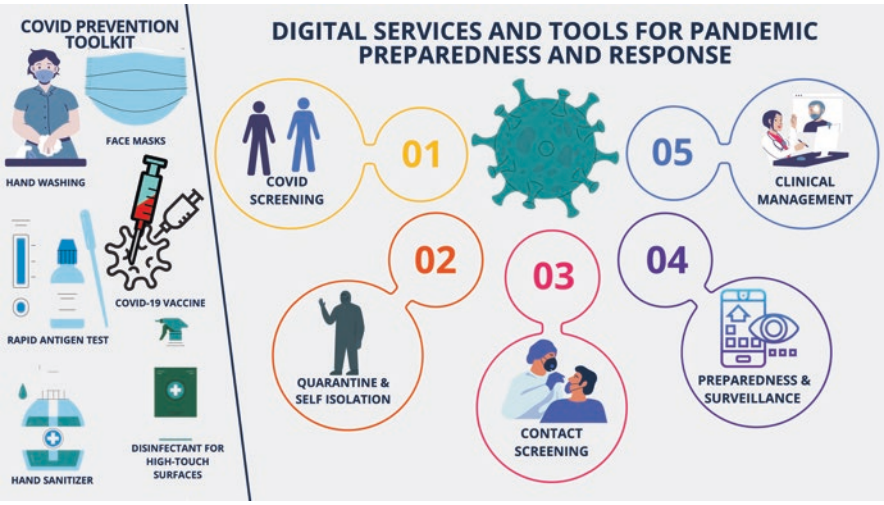

Fig. 25.1 A conceptual framework for pandemic preparedness and response encompassing digital services and tools along with conventional public health measures

initiative [51]. This may require stronger public-private partnerships to boost the penetration of reliable, continuous, and high-speed mobile/broadband networks including provision for subsidized mobile phones or wearable technologies for use by those from vulnerable communities or geographically remote regions [23, 105, 109]. Initiatives such as free or subsidized Wi-Fi hotspots by telecom providers or by city councils in these regions may be pursued. Digital literacy is another important consideration [110]. This needs to be tackled at a systems level by providing linguistically and culturally appropriate education and training to consumers [111]. Data privacy and ethical concerns also merit further debate and consideration [56, 91, 92].

In conclusion, digital tools have shown immense benefit during COVID-19 [112]. Globally, COVID has undoubtedly accelerated the efforts to deliver healthcare digitally [113]. Telemedicine, specifically, has facilitated increasing levels of doctor-patient engagement regardless of geographic location, considerably expanding the global reach of healthcare workers as well as fostering more health-seeking and preventative behaviors [113]. The shift to value-based healthcare using digital technologies or telemedicine holds promise to aid post-pandemic recovery and is likely to benefit millions of people, consistent with the WHO's support for digital health as a strategy toward improving universal health coverage [114] and that of the United Nations' sustainable development goal [113, 114]. Digital health and data-driven care are perceived as drivers of universal health coverage. We should focus on ensuring standardized gathering, tracking, analysis, and reporting of complete and accurate health-outcome data, segmented by groups, to assess the impact of interventions regardless of access. This model of care using telemedicine could optimize care delivery, save costs, and hence improve care and patient outcomes [115]. However, more efforts to address the equity divide are required [12, 24].

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