



Comorbidities and clinical complications associated with SARS-CoV-2 infection: an overview

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Abstract

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes major challenges to the healthcare system. SARS-CoV-2 infection leads to millions of deaths worldwide and the mortality rate is found to be greatly associated with pre-existing clinical conditions. The existing dataset strongly suggests that cardiometabolic diseases including hypertension, coronary artery disease, diabetes and obesity serve as strong comorbidities in coronavirus disease (COVID-19). Studies have also shown the poor outcome of COVID-19 in patients associated with *angiotensin-converting enzyme-2* polymorphism, cancer chemotherapy, chronic kidney disease, thyroid disorder, or coagulation dysfunction. A severe complication of COVID-19 is mostly seen in people with compromised medical history. SARS-CoV-2 appears to attack the respiratory system causing pneumonia, acute respiratory distress syndrome, which lead to induction of severe systemic inflammation, multi-organ dysfunction, and death mostly in the patients who are associated with pre-existing comorbidity factors. In this article, we highlighted the key comorbidities and a variety of clinical complications associated with COVID-19 for a better understanding of the etiopathogenesis of COVID-19.

Keywords COVID-19 · Comorbidity · Cardiovascular disease · Diabetes · Thyroid disorder · Cancer

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is challenging due to the lack of immunity in humans and the generation of novel variants due to frequent mutations in receptor binding domain [1]. According to the World Health Organization (WHO) (as of March seventh, 2022), 445,096,612 confirmed positive cases and 5,998,301 deaths were reported worldwide [2]. COVID-19 patients with co-existing diseases (comorbidities) need special attention and counseling for disease management. The previous meta-analysis studies have shown that the COVID-19 patients who had comorbidities including diabetes, obesity, hypertension, respiratory complications, and acute kidney failure presented severe complications [3, 4].

The elderly cohort is reported to be at higher risk of SARS-CoV-2-mediated severe complications and death, largely due to the presence of age-related co-existing clinical conditions [5, 6]. Recent studies have shown several risk factors associated with poor prognosis of the disease which further increased the mortality rate particularly in elderly patients with pre-existing cardiovascular diseases (CVDs), thyroid disorder, diabetes, renal failure, hypertension, cancer, and respiratory diseases [7, 8]. This comprehensive review aims to provide an overview of comorbidities and clinical complications associated with the severity of SARS-CoV-2 infection. We have also briefly discussed the viral genome and, morbidity, mortality, and management of COVID-19 patients associated with comorbidity factors.

Diagnosis and pathophysiology of COVID-19

Coronavirus is a positive-sense single-stranded enveloped RNA virus, which belong to the family *Coronaviridae* that can infect many animal species and human beings [9]. COVID-19 is an acute respiratory disease caused by SARS-CoV-2 in which viral particles are released in respiratory

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secretions during coughing and sneezing. For diagnosis, nasal secretions, blood, sputum, and bronchoalveolar lavage are collected from suspected COVID-19 patients. The patients' samples are subjected to serological and molecular tests specific for SARS-CoV-2 including real-time-polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA) and western blots. Viral antigens present in clinical samples are detected by direct immunofluorescence assay (IFA), antibody (or serology) tests, or lateral flow tests (LFTs) [10]. The mode of transmission of SARS-CoV-2 is through inhalation of infectious aerosols and close contact with an infected individual. The virus can affect people of any age, however, more severe conditions have mostly been reported in elderly people and immunocompromised patients [11]. In the elderly population, SARS-CoV-2 often infects the lower respiratory tract which often leads to fatal pneumonia with symptoms such as fever, cough, myalgia, dyspnea with or without diarrhea. The

virus first infects the epithelial lining of the throat, trachea and lung, transforming these cells into a virus reservoir that produces huge amounts of viruses and infects more cells [12, 13]. In the second week of infection, it progresses to hypoxemia, difficulty in breathing and acute respiratory distress syndrome (ARDS) where patients require intensive care and are kept on the ventilator [14].

The viral genome

The Coronaviridae family comprises five genera which include alpha, beta, gamma, delta, and omicron coronaviruses [1] (Fig. 1A, B). The viral genome is encapsulated within membrane and envelope proteins, studded with spike glycoprotein enclosed within nucleocapsid protein. The coronavirus genome consists of ORF1 at 5' end which encodes papain-like protease (PLpro) and 3C-like protease (3CLpro or Nsp5). After invading the host cell,

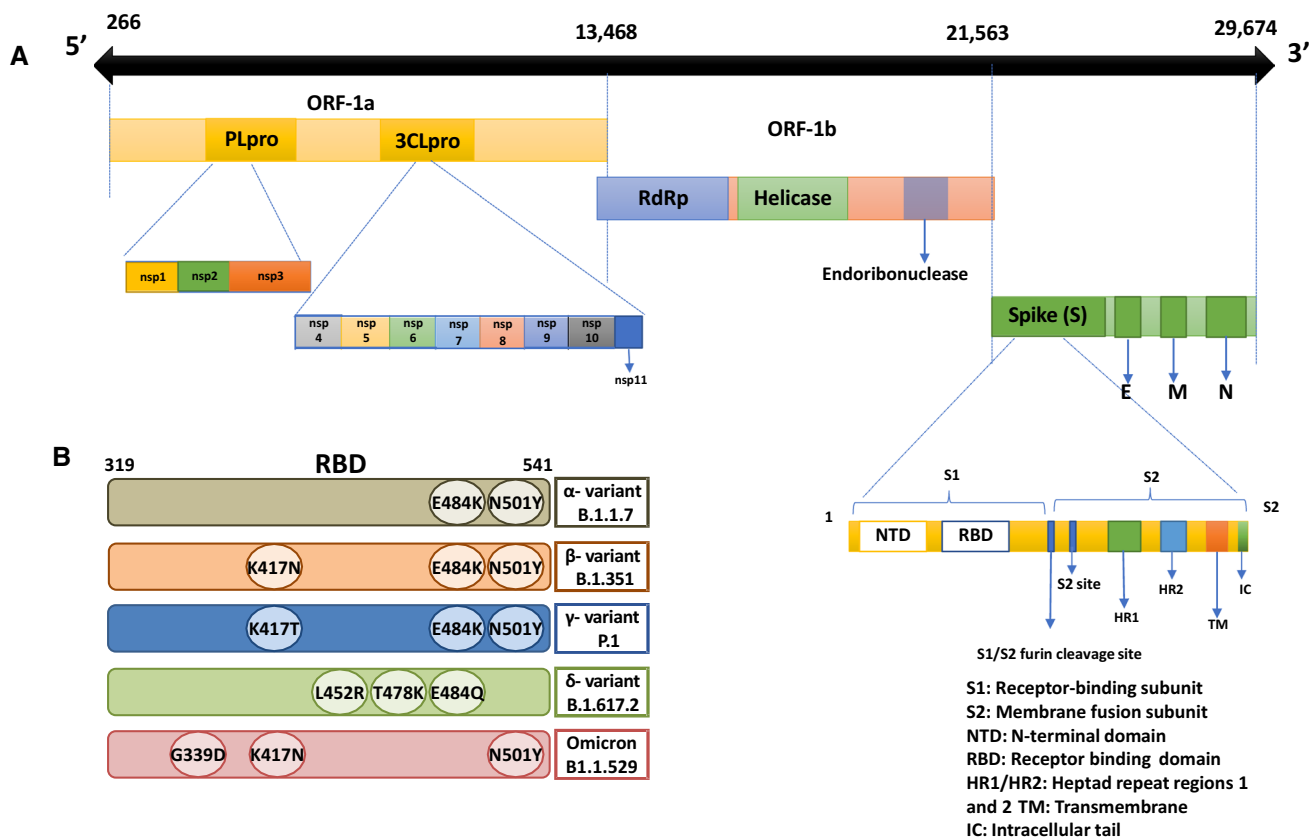


Fig. 1 (A) Schematic representation shows detailed structure of SARS-CoV-2 genome. ORF1a; Open Reading Frame (266–13,468 nucleotide base pair), ORF1b; Open Reading Frame (13,468–21,563 nucleotide base pair), PLpro; Papain-like protease (4955–5900 nucleotide base pair) 3CLpro; 3CL-protease (10,055–10,977 nucleotide base pair), RdRp; RNA dependent RNA polymerase (13,442–16,236 nucleotide base pair), nsp; nonstructural protein, Endoribonuclease (19,621–20,658 nucleotide base pair), Helicase (16,237–18,043

nucleotide base pair), S Protein; Spike Protein (21,563–25,384 nucleotide base pair), E Protein; Envelope Protein (26,245–26,472 nucleotide base pair), M Protein; Membrane Protein (26,523–27,191 nucleotide base pair), N Protein; Nucleocapsid Protein (28,274–29,533 nucleotide base pair). (B) The schematic presentation shows potentially key pathogenic mutations identified in the receptor binding domain (RBD) of different SARS-CoV-2 variants. RBD is the region located between amino acids 319–541

the genome of the virus is translated into viral proteins which are further cleaved into effector proteins by protease 3CLpro and PLpro. PLpro deubiquitinates the interferon regulatory factor 3 (IRF3) and nuclear factor kappa-light chain-enhancer of activated B cells (NF- κ B), thus resulting in the suppression of the host immune system. In addition, RNA-dependent RNA polymerase (RdRp) synthesizes a full-length negative-strand RNA template to make more viral genomic RNA [10]. The interaction between the S-protein of the virus and the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell is the initiation point of viral infection. The viral coat of SARS-CoV-2 expresses the spike protein containing a receptor-binding domain which binds to the ACE2 receptor and facilitates its entry into the host cell. ACE2 receptors are present abundantly on the cell membranes of the heart, lung, kidney, testis, vasculatures and intestine [12].

Impact of comorbidity factors on COVID-19 severity

As the global pandemic has progressed, multiple research reports link several risk factors associated with the disease severity especially higher COVID-19 severity is mostly seen in the elderly population [15, 16]. To date, several research studies published related to comorbidities associated with COVID-19 infection [17]. The presence of comorbidities is associated with the severity of COVID-19 infection and the most common comorbidities include diabetes, CVD, hypertension, cancer, oxidative stress, vitamin deficiency, and kidney disease (Fig. 2). Several reports suggest that post-COVID-19 infection manifests varied clinical outcomes and a few of these are selectively summarized in Table 1.

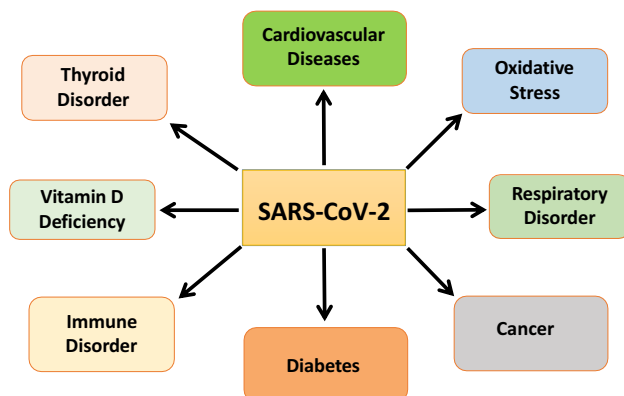


Fig. 2 Schematic diagram shows commonly reported comorbidities associated with SARS-CoV-2 infection

Cardiovascular diseases

COVID-19 has a profound effect on the cardiovascular system (Fig. 3). CVDs are one of the most common causes of immature death and disability in humans and it is gradually rising worldwide. The most common types of CVDs are hypertension, stroke, ischemic heart disease, congestive cardiac failure, sickle cell disease and coagulation dysfunction. According to an epidemiological study, more than 90% of people are at risk of CVDs [28]. People with higher risk factors of cardiac diseases and other proven CVDs are more vulnerable to COVID-19 progression and seem to develop more severe disease with poorer clinical outcomes [29].

The main clinical manifestation of COVID-19 is the presence of respiratory symptoms; however, some patients develop severe cardiovascular and renal complications [30]. The public report released from Wuhan, Lombardy and New York supported that hypertension is the most common comorbidity among the COVID-19 patient admitted to the hospital [3, 4]. An observational study was conducted from different centers in different countries to determine the role of CVDs in COVID-19. In a study, over 3011 patients with an average age of 67 were included [31]. A total of 315 had presented cardiovascular complications like coronary artery disease (15.4%) and arrhythmia (15.1%). In the critical care unit, patients with younger age and comparatively low comorbidity factors presented fewer complications. A total of 349 patients with no co-morbidity during hospitalization, was later found to develop cardiovascular complications. Around 595 deaths were reported, and these patients were having several other complications. This study indicated that COVID-19 severity is often associated with comorbidities and the viral infection further increases the complications in cases with known CVD history [32]. Another study from China reported 44,672 confirmed cases of COVID-19 with a total of 1023 (2.3%) fatalities. Surprisingly, this fatality rate was increased to 6% in patients with hypertension. In this study, 50% of patients were of 70–79 years age group with hypertension and in this group, the fatality rate was 8% [12, 33]. The ACE2 receptor blockers has long been used to treat patients with hypertension and heart failure and ACE2 receptor emerged an important player in COVID-19 pathogenesis.

Role of ACE2 in SARS-CoV-2-induced cardiovascular complication

It is quite evident by now that SARS-CoV-2 entry is facilitated through the ACE2 receptor present on the host cell [34]. ACE2 is a fundamental enzymatic component of the renin–angiotensin–aldosterone system (RAAS). Inhibition of the RAAS plays a key role in reducing morbidity and

Table 1 Major comorbidities associated with SARS-CoV-2 infection

S.No	Country	Population/Cohort	Comorbidity Disease	Clinical Outcome	References
1	South Korea	686 patients with asthma and COVID-19	Asthma	The death percentage was higher in asthmatic patients compared to non-asthmatic patients which was 9.1%	Lee et al. [18]
2	Wuhan, China	52 confirmed diabetes patients with COVID-19	Diabetes	15.4% mortality rate was determined after developing the severe COVID-19 complication	Zhang et al. [19]
3	New York, USA	190 patients with both diabetes mellitus and hypertension along with COVID-19 complication	Diabetes mellitus and hypertension	Out of 10 patients with COVID-19 complications, a total of 8 patients were survived after AT001 treatment and 2 patients were died because of progressive hypoxic respiratory failure and the mortality rate was 20%	Gaztanaga et al. [20]
4	Paris France	57 patients with COVID-19 and pulmonary fibrosis	Diabetes, Hypertension and chronic respiratory disease	Of the total 57 patients, nine were hospitalized in the ICU ward and four required mechanical ventilation and six died during hospitalization because of pneumonia. The fibrocyte percentage was lower (1.6%) as compared to surviving patients (3.7%)	Ghanem et al. [21]
5	Italy, France	4716 patients had COVID-19 infection with and without chronic kidney disease (CKD) complication	Chronic kidney disease	Total 193/4716 COVID19 patients had CKD. Although 184/193 (95.4%) patients were hospitalized due to severe COVID-19 complications. After hospitalization 84/193 (44.6%) died and it was tenfold	Gibbertoni et al. [22]
6	New Delhi, India	1211 patients had COVID-19 infection with or without diabetes mellitus	Diabetes mellitus	The mortality rate was higher in COVID-19 patients with diabetes mellitus which was 2.33% compared to other comorbidities complications	Kantroo et al. [23]
7	Spain	136 patients with chronic kidney disease with COVID-19	Chronic kidney disease	With acute kidney injury (AKI), the mortality rate was higher (40.4%) in COVID-19 compared to patients without AKI or CKD complications (24.3%)	Coca A. et al. [24]
8	Lagos, Nigeria	2075 confirmed COVID-19 adult patients	Hypertension	16.2% mortality rate was determined in COVID-19 patients with hypertension alone whereas 26.4% mortality rate was seen in patients with hypertension along with at least one other comorbidity	Abayomi et al. [25]
9	Philippines	10,881 confirmed COVID-19 patients with diabetes mellitus	Diabetes mellitus	A total of 2191/10881 patients were diabetic. The mortality rate was higher in diabetic patients (26.4%) compared to non-diabetic patients	Espiritu et al. [26]
10	New York, USA	3703 confirmed COVID-19 patients	Hypothyroidism	A total of 68.1% of COVID-19 patients had preexisting hypothyroidism and required hospitalization	van Gerwen et al. [27]

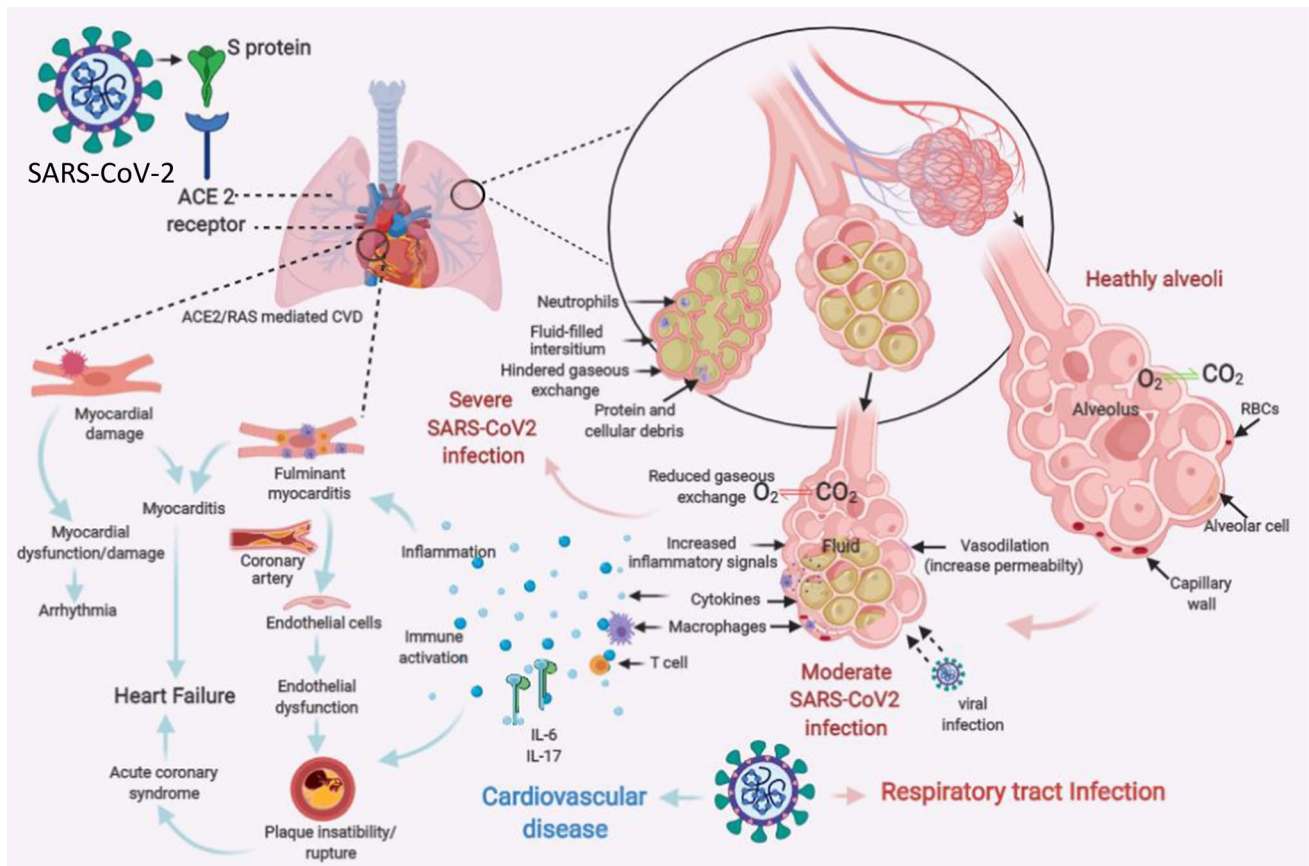


Fig. 3 Cardiovascular manifestation and clinical complications associated with SARS-CoV-2 infection: The figure picturizes how SARS-CoV-2 infection triggers cardiovascular events upon the interaction with ACE2 receptor present on alveolar epithelial and endothelial linings. The binding of SARS-CoV-2 with ACE2 receptors induces an inflammatory reaction in alveoli which leads to compromised gaseous exchange due to fluid accumulation in interstitial space. Severe infection induces robust inflammatory reaction which produces cytokine

storms, and resulting inflammatory mediators exert their adverse effects on several soft tissues including the heart and vasculatures. The SARS-CoV-2-mediated cytokine storms often cause myocarditis-induced cardiomyopathy. Moreover, SARS-CoV-2 infection is largely known to cause endothelial dysfunction that puts the patients, with pre-existing atherosclerotic plaques, at higher risk of acute coronary syndrome and myocardial infarction through destabilizing the plaques

mortality of patients with heart failure (HF) [33]. Renin cleaves hepatic peptide angiotensinogen to produce angiotensin-I (Ang-I). ACE2 hydrolyzes Ang-I and leads to the generation of biological active octapeptide Ang-II which binds with Ang-II type 1 and type 2 receptors (AT1R and AT2R). Ang-II promotes vasoconstriction, inflammation, salt and water reabsorption, and oxidative stress via the activation of AT1R [12]. The Ang-II is a part of RAAS and binds with AT1R and causes increase peripheral vascular resistance resulting in various types of cardiovascular complications such as hypertension, inflammation, coronary heart disease, myocardial fibrosis [35].

The SARS-CoV-2 virus enters the expressing cells such as alveolar cell, type I and type II pneumocytes, and in endothelial cells through the ACE2 receptor [34]. Another study shows that the binding affinity of spike glycoprotein of SAR-CoV-2 is 10–20 fold higher with ACE2 receptors [12]. These studies confirm that ACE2 is the main receptor that

facilitates SARS-CoV-2 virus entry into the host cells. The RAAS plays an important role in pulmonary hypertension and pulmonary fibrosis which are generally seen in chronic obstructive pulmonary disease (COPD). The RAAS also regulates the other types of acute pulmonary disease like ARDS, which is frequently observed in severe COVID-19 patients [36]. ACE2 mediates activation of Ang-II which is a well-known factor for the pathogenesis of pulmonary hypertension. In vitro studies deciphers that the Ang-II directly causes growth/proliferation of pulmonary artery smooth muscle cells through the activation of AT1R [36]. The researchers randomly used different types of therapeutic approaches for maintaining respiratory distress in severe COVID-19. Roelie Asperem et al., investigated the effect of angiotensin receptor blockers (Losartan) with cyclic (c) Ang-II (1–7), a lanthionine-stabilized Ang-II (1–7) analog peptidase-resistant to metabolism [37]. cAng-II (1–7) is a promising clinical cardiovascular therapeutic agent which

acts as a specific agonist for AT1–7/Mas receptors [38]. The lipopolysaccharides (LPS)-induced bronchoalveolar lavage fluid increased the ACE2 activity but administration of cAng-II (1–7), significantly reduced the ACE2 activity in animals. Moreover, Losartan also shows a similar effect and helps to decrease blood pressure. It maintains the PaO₂ level in unexposed ventilated animals. The study indicates that LPS induced pulmonary hypertension was maintained by the losartan but not by cAng-II (1–7) [37]. Since the ACE2 receptor facilitates SARS-CoV-2 entry into the cell, it emerges as a potential target for drug development. Therefore, restoring the balance between the RAAS and the ACE2/angiotensin enzyme could help in limiting the soft organ damage and failure in COVID-19.

Coagulation dysfunction

ACE2 receptors are abundantly expressed in endothelial cells of vasculatures, and it is most likely the cause of increased coagulopathy in the COVID-19. Coagulation dysfunction, thrombosis and thromboembolism (blood clot dissolution), particularly deep vein thrombosis (DVT) are commonly seen in moderate to severe COVID-19 patients and significantly contribute to the severity of the disease [39]. The hospitalized COVID-19 patients showed increased levels of inflammatory and coagulation dysfunction markers

such as C-reactive protein (CRP), ferritin, D-Dimer (DD), fibrinogen and other abnormalities such as anemia, lymphocytopenia, increased troponin I, myoglobin and lactate dehydrogenase (LDH) levels (Fig. 4) [40–43]. Platelets play critical roles in the pathogenesis of thromboembolism in severe COVID-19 [39]. These cell fragments have long been known to play only a pro-adhesive role via granule release and integrin activation [44]; however, later studies uncover the procoagulant roles of platelet in the pathogenesis of thromboembolic disorders [45, 46]. Most importantly, viral infection is often associated with platelet activation either through direct interaction with the virus or via viral-induced antibodies [47]. Platelets contribute to inflammatory reactions through interacting with inflammatory cells [39]. Collectively, these important functions put the platelet at the nexus of inflammation, coagulation dysfunction and thromboembolic complications in severe COVID-19.

The viral particles of SARS-CoV-2 infect the alveolar epithelial lining triggering a rapid immune response, which further leads to dysregulation of the immune system including elevation of a variety of inflammatory markers (cytokine storm) and coagulation dysfunction. The fibrinogen level in COVID-19 patients is increased by 2–3 folds due to cytokine storm, causing thrombus formation, particularly in severe cases [48]. Thrombotic events vary from DVT and pulmonary embolism (PE) to unusual thrombosis of central

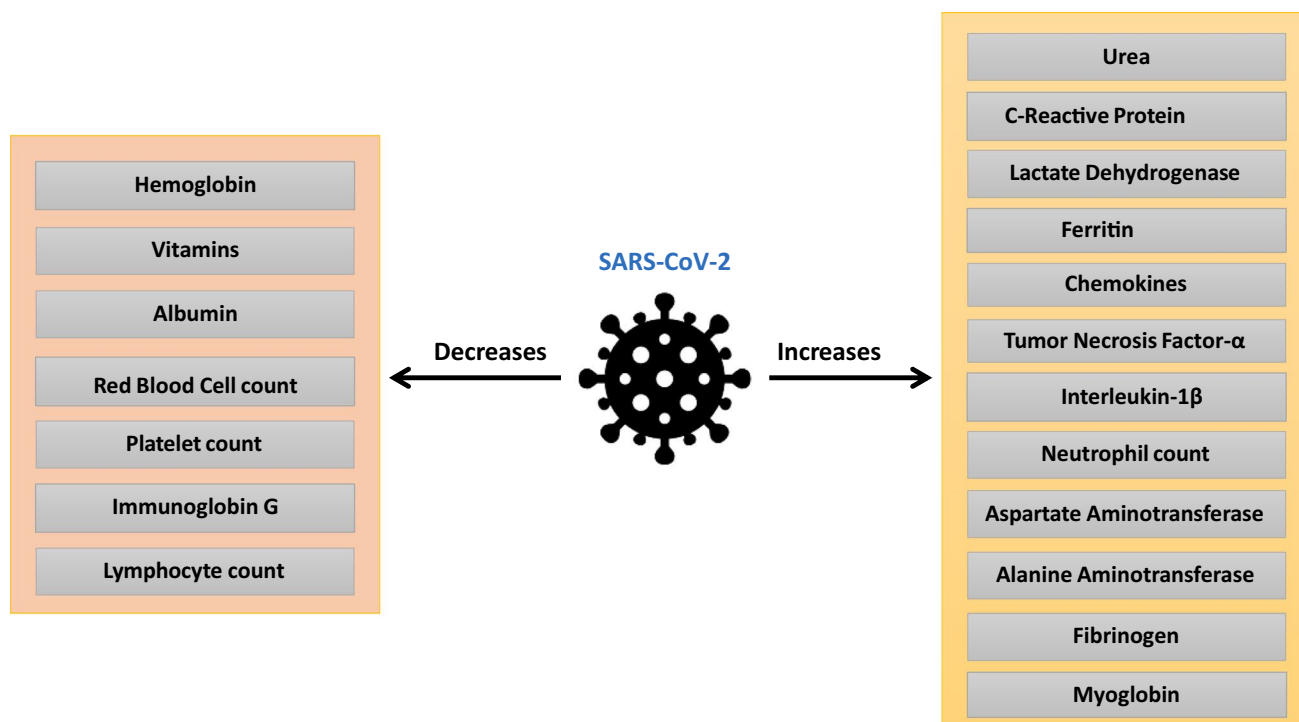


Fig. 4 Dysregulated markers in COVID-19: The diagram shows the key pathophysiological markers identified in the COVID-19. The SARS-CoV-2 infection is mostly linked to increased levels of inflam-

matory and tissue injury markers while decreased levels of other physiological markers

lines or arterial catheters, very early thromboses of extra-renal hemodialysis filters, and ECMO cannulas [49]. We recently reported that induction of soluble P-selectin, soluble CD40 ligand (sCD40L) at the early moderate stage of SARS-CoV-2 infection likely induces platelet activation and, severe COVID-19 patients are at a higher risk of venous, and arterial thromboembolic complications potentially due to acquired FXIII deficiency [50]. A clinical study reported an elevated level of DD in hospitalized COVID-19 patients presenting ARDS symptoms and an increased mortality rate [51]. Other cohort studies reported a correlation between increased levels of DD and COVID-19 severity [52, 53]. Moreover, studies reported the elevation in DD levels and DVT in lower limbs of COVID-19 patients [54, 55]. The radiological investigation revealed PE in severe COVID-19 patients with low oxygen saturation and elevated DD levels [56]. The venous thromboembolism (VTE) was reported to be 15% and 34% at day 7 and day 14 of infection and even higher (48%) in patients admitted to the intensive care unit (ICU) which strongly indicates VTE as a high death risk factor in COVID-19 [57]. Pulmonary CT angiography in patients with ARDS demonstrated that the PE was increased by 23% [58–60]. The VTE impacts not only lung, but it has broader adverse effects on different soft organs including kidney and heart. The PE, myocardial infarction (MI) and stroke are amongst the most serious consequences of thromboembolism which are often seen in severe COVID-19 patients [28]. Thus, in-depth studies of coagulation patterns in COVID-19 may help design therapeutic prophylaxis to limit coagulation dysfunction.

Sickle cell disease

Other than coagulation dysfunctions, sickle cell disease (SCD) is another blood disorder that increases the severity of COVID-19. SCD is an inherited hemoglobin disorder caused by a mutation in the beta-globin gene in which hemoglobin is prone to aggregate in hypoxic conditions [61]. Accumulating evidence suggests that patients with thalassemia and SCD are vulnerable to COVID-19 related severe complications [62]. A study on SCD patients with homozygous sickle mutation (SS) showed lymphopenia, thrombocytopenia and increased CRP levels, which were identified as poor prognostic markers in elderly COVID-19 patients [63]. In addition, another observation study reported the association of SCD trait with PE, VTE, chronic kidney disease (CKD), and exertional rhabdomyolysis [64]. Moreover, studies have suggested that SCD carriers can be considered to have an increased risk of hypercoagulability which may adversely affect clinical outcomes of SARS-CoV-2 infected patients [65]. Acute chest syndrome (ACS) is the major cause of morbidity and mortality in SCD patients and overlapping of COVID-19 and ACS may result in severe complications

in SCD carriers [63, 66]. Consistent with this observation, a study has reported that irrespective of genotype or sex, COVID-19 patients with SCD (Age > 50 years) carrying increased levels of D-dimer, serum creatinine, and lactate dehydrogenase (LDH), are at higher risk of death [67]. These studies strongly suggest that people suffering from SCD are at higher risk of severe COVID-19 complications. Therefore, SCD patients infected with SARS-CoV-2 should be given special considerations and appropriate prophylaxis should be designed accordingly.

Myocarditis

Inflammation of heart muscles called myocarditis is caused due to infections, immune system activation, or exposure to certain medications [68]. Myocarditis leads to cardiomyopathy and triggers extensive scarring followed by left ventricular (LV) adverse remodeling and HF [69]. Viral infections stand out as one of the most common causes of myocardial inflammation. Clinical studies reported the association between SARS-CoV-2 and several complications leading to myocarditis [70, 71]. In a clinical assessment, the Centers for Disease Control and Prevention (CDC) reported the frequency and the risk of patients hospitalized with or without COVID-19 infection. A study on patients associated with myocarditis has reported an increased number of myocarditis cases in 2020 as compared to 2019. The same study also reported that the risk of myocarditis associated with COVID-19 infection was 16 times higher among children and elderly people [72]. Another study revealed that the myocardial muscles injury elevated the troponin I (cardiac injury marker) levels which correspond to an increased risk of mortality by 51.2% when compared to patients without cardiac muscles injury (4.5%).

Increased levels of leukocytes, DD, CRP, ferritin, and interleukin-6 (IL-6), hallmarks of myocarditis, pave the way to ARDS, kidney dysfunction, and coagulopathy [73]. Even though the precise mechanism for myocardial damage caused by SARS-CoV-2 infection is not completely elucidated, myocarditis in COVID-19 patients is an element for poor prognosis and is linked with increased death rate. Systemic inflammation post-SARS-CoV-2 infection promotes myocardium damage/injury [74]. Apart from myocarditis, pericarditis also plays a significant role in defining the cardiovascular comorbidities in SARS-CoV-2 infection. A study reported the severity of fulminant myocarditis (FM), a condition characterized by sudden, severe diffused cardiac inflammation post-SARS-CoV-2 infection. It leads to pericarditis which promotes excess fluid accumulation in the pericardial sac around the heart (pericardial effusion) ultimately leads to cardiac tamponade [75]. Accumulated evidences on myocarditis in COVID-19 demands more screening methods to diagnose and prevent the development

of cardiac complications associated with the viral infection. Complimentary screening can be implemented in infected patients via checking the troponin I levels, electrocardiogram, echocardiography etc. [76].

Diabetes

Diabetes is a metabolic disorder characterized by increased blood glucose levels due to insufficient insulin production from pancreatic β -cells [77]. Several studies reported that chronic diabetes increases the complications of other diseases such as respiratory tract infections [77, 78], cardiovascular complications [79], renal impairment [80], immunosuppressant [81], etc. Immunometabolism indicates the interaction between immunity and metabolism which play an important role in causing immune dysfunction and inflammation. The abnormal metabolic and immune system increases the risk of COVID-19 severity [82].

Hyperglycemia impedes the production of type-1 interferon (IFN) and IL-22. The type-1 IFN has antiviral activity [83]. Although IL-22 reduces chronic inflammation, activates anti-microbial immunity and improves insulin sensitivity. It causes non-enzymatic glycation of several proteins and involves the opsonization of pathogens [84]. Since the condition of diabetes mellitus interfere with the immune system, viral pathogens can easily replicate and survive in the diabetic host body [85]. Patients with SARS-CoV-2 infection along with diabetes mellitus are shown to have an increased mortality rate. Yang et al. conducted a single centered retrospective observational study to determine the complications of patients infected with SARS-CoV-2 who had pre-existing co-morbidities. In this study, a total of 9 COVID-19 patients were reported to have diabetes of which 2 (10%) survived and the other 7 (22%) died [86]. A meta-analysis was performed including 18 clinical reports with a total of 15,558 COVID-19 patients. Among all the illustrated comorbidities, 11.5% were diabetic with a relatively increased mortality rate [87]. Another study included a total of 834 COVID-19 patients of which 64.6% were hypertensive, 28.1% were diabetic with an increased mortality rate [88]. These studies clearly indicate that diabetes is not only the major factor to increase the COVID-19 severity but it also increases the risk of death in COVID-19.

Thyroid disorder

Thyroid gland dysfunction leads to severe health consequences and is more commonly observed in females vs. males. Thyroid glands are responsible for human physiology, growth and homeostasis [89], and produce thyroxine (T4) and tri-iodothyronine (T3) under the control of thyroid-stimulating hormone (TSH). COVID-19 complications may involve metabolic events affected by the thyroid

glands dysfunction which has emerged as a comorbid factor in COVID-19 complications [90]. Thyroid-related events occurring post-SARS-CoV-2 infection cause inflammation of thyroid glands (thyroiditis), or formation of antibodies that can damage the thyroid glands (Hashimoto's disease), thyrotoxicosis, hypothyroidism, hyperthyroidism and Graves' disease. The cytokine storm in COVID-19 activates immune-mediated thyroid disorder [91, 92] resulting in excessive inflammatory signals leading to cell apoptosis, increased vascular permeability which may aggravate multiple organ dysfunction [93, 94]. An amplified expression of Th1/Th17 immune responses and IL-17-related cytokine pathways are reported in COVID-19 [95]. In addition, studies reported the imbalance and hyperactivation of Th1/Th2 and Th1 and Th17, respectively, in patients with an autoimmune thyroid disorder. Increased serum levels of the Th1/Th17-related cytokines have also been reported in patients with COVID-19 [96]. Excessive cytokines circulation causes alteration in thyroid gland function leading to non-thyroidal illness (NTI) [97] which may typically decrease the serum T3, T4 and TSH levels and further reduce the enzymatic activity of 5'-monodeiodinase. In addition, type 3 iodothyronine deiodinase (D3) catalyzes the inactivation of thyroid hormones (T3 and T4). Another study reported that inflammatory cytokines such as IL-1 β , IL-6, IFN- γ , and tumor necrosis factor-alpha (TNF- α) affect the functioning of the hypothalamus-pituitary thyroid (HPT) axis *via* decreasing the TSH secretion. Subacute thyroiditis (SAT), an endocrine complication, is found to be associated with COVID-19 complications. Studies have reported the increased number of SAT patients associated either with COVID-19 complications [98, 99] or post COVID-19 symptoms [100–102]. Viremia is also reported in patients infected with SARS-CoV-2 as ACE2 receptors are highly expressed in thyroid follicles. Moreover, a study reports the expression of ACE2 receptor on thyroid epithelial cells, which could be a potential route of novel coronavirus entry [103]. These studies provide evidence that the SARS-CoV-2 virus causes thyroid inflammation upon interacting with thyroid cells through the ACE2 receptor.

Vitamin D deficiency

Vitamin D is a fat-soluble secosteroid that is produced by the epidermis of skin in response to UV exposure. Vitamin D deficiency has emerged as a cosmopolitan health condition that affects children, young adults and is more persistent in elderly population with an all-cause mortality rate [104]. Vitamin D plays some biological roles such as regulation of bone metabolism, immune system regulation, endocrine control of calcium and phosphorous homeostasis, cardiovascular system, and infectious diseases [15, 16, 105]. SARS-CoV-2 infection cause alveolar type-II pneumocyte dysfunction

which increases the risk of ARDS. Vitamin D in pneumocytes type-II cells attenuates lung injury ultimately ARDS by decreasing the epithelial cell apoptosis and increasing the surfactant synthesis [106]. Nevertheless, patients with a high prevalence of vitamin D deficiency manifested organ failure and chronic renal failure [107, 108]. A study linked the prevalence of vitamin D deficiency with COVID-19 severity and suggested vitamin D deficiency likely increases the death risk in COVID-19 patients [109]. Moreover, vitamin D plays an immune system regulatory role as it suppresses adaptive immune responses in respiratory cells during viral infection [110]. As immune dysfunction is a prominent factor that promotes COVID-19 severity, hemostasis should be maintained to prevent cytokine storms to combat the severity of COVID-19. Since vitamin D prevents viral replication and downregulates the ACE2 receptors, it could be used as a dietary supplement by the COVID-19 patients to limit the progression of disease severity.

Respiratory disease

Respiratory complications directly commensurate the cardiovascular complications and become a perpetual reason of morbidity [111]. Asthma is the most common respiratory disease characterized by chronic airway inflammation [112]. The coexisting respiratory diseases like asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, cystic fibrosis, etc., increase the risks of COVID-19 severity [113]. Previous systemic review and meta-analysis have shown that bronchial asthma increases the severity of COVID-19 patients, and particularly, COPD increases the risk by four times [114, 115]. In chronic SARS-CoV-2 infection, many patients experience post-COVID respiratory complications; thus, the NHS published the guidelines for the patients recovered from COVID-19 to determine the respiratory symptoms and complications like pulmonary fibrosis, pulmonary edema, persistence cough, etc. [116]. The asthma-prone patients are more sensitive to viral infections, thus delaying the antiviral immune response and impaired IFN- λ secretion, which ultimately promotes disease severity [117]. In the same line, a systemic review observed that elderly asthmatic smokers have shown an increased risk of COVID-19 severity [118]. Even though COVID-19 is not directly related to asthma, many other diseases and respiratory complications are more likely to be associated with asthma. About 15–20% of COVID-19 patients experience hypoxia and require a ventilator. The cytokine storm, weak immunity, productive cough, inhalational corticosteroids, and structural destruction of pulmonary tissues develop COPD. The presence of the ACE2 receptor on pneumocytes, the target protein of the SARS-CoV-2 virus, likely increases COPD complications [17].

Oxidative stress exacerbates COVID-19 severity

The reactive oxygen species (ROS) induces oxidative stress that disrupts normal cellular function and promotes cell death [119]. ROS is seen in inflammatory disorders and other infectious diseases caused by different types of pathogens [120]. These are the key factors that connect the COVID-19 with oxidative stress. During infection, cytokine levels are increased and stimulate the immune response. Severe infection causes ARDS and a hypoxic condition that activates macrophages which leads to the induction of proinflammatory cytokines in the pulmonary microvessels [121]. The elevation of inflammatory mediators and hypoxic conditions lead to increased ROS generation and activates hypoxia-induced factor-1 α (HIF-1 α), IL-1 β , IL-18, IL-6 and NF- κ B and ultimately activates caspase-1 and caspase-2 [122, 123].

Immune disorder

The immune system is the first line of defense mechanism implemented by the human body against the invading foreign entity. Upon invasion, viral proteins trigger an immune response in the host which are implemented by host B and T cells, inducing antibodies formation. Therefore, increased levels of cytokines are released in host bodies [124]. The SARS-CoV-2 virus interacts with the immune system of the patient and causes a variety of clinical conditions followed by activation of inflammatory tissue repair response [125]. In addition, these responses may trigger cytokine storms which may severely damage host organs further worsening clinical manifest as discussed earlier [126, 127]. Different types of immune responses are linked to SARS-CoV-2 infection and details of which are listed below.

Innate immune response

An innate immune response is a kind of non-specific immune response that occurs naturally in an individual which involves physical, chemical and cellular defenses against pathogens. Viral invasion is recognized by pattern recognition receptors (PRRs), pathogen-associated molecular patterns (PAMPs), or damage-associated molecular patterns (DAMPs) such as toll-like receptor 7 (TLR7) and TLR8, and node-like receptor (NLR), by macrophages [128, 129]. Upon interaction with viral particle, PRRs triggers the activation of interferon regulatory factor (IRF), NF- κ B, and AP-1 and other cells including polymorphonuclear leukocytes (PMNs), monocytes, natural killer (NK) and dendritic cells (DC) [130–132]. A comparative study of SARS-CoV-1 and SARS-CoV-2 reports the subsequent effects of virus infection on the immune system. It was demonstrated that both viruses infect type I and type II pneumocytes covering

air sacs and modulate the levels of IL-6, MCP1, CXCL1, CXCL5, and CXCL10/IP10 cytokines [133]. In addition, another study reports the induction of proinflammatory chemokines, IL-1 β , IL-6, TNF, and IL1RA in infected human lungs [129].

SARS-CoV-2 gains its entry through respiratory tracts, a mucosa-associated lymphoid tissue (MALT) that acts as a physical barrier to defend foreign entry. The level of mucosal-generated antibody, immunoglobulin A (IgA), increases during the first week of SARS-CoV-2 infection [134]. Autopsy data from virus-infected individuals demonstrated high infiltration of macrophages in hemopoietic organs such as spleen and lymph nodes where ACE2 receptor expressed, contributing to significantly increased levels of IL-6 which further exacerbates inflammation [135, 136]. Such hyperactivation of the immune system leads to cytokine storm which is now evident in severe COVID-19 cases [43]. These findings imply that the inflammatory response is potentially more harmful than the viral direct impact.

Adaptive immune response

If the innate immune system is unable to eradicate the foreign entity, the adaptive immune system takes over which comprises T lymphocytes, B lymphocytes and antibodies in the blood. Both cell-mediated and humoral immunity cell responses are associated with the COVID-19. It is in the limelight that viral infection declines the CD8 + T cells, memory CD4 + T cell and T regulatory cell count in lymph nodes and spleen [137, 138]. Similarly, studies also demonstrated the increased expression of CD94/NK group 2 member A (NKG2A) on natural killer cells (NK) and cytotoxic T cells (CTLs) in patients infected with the SARS-CoV-2 virus which was subsequently reduced in recovered individuals. Infected patients were found to express low cytokine levels such as CD107a, IFN- γ , IL-2, granzyme B, and TNF- α . Therefore, it is equitable that T cells memorized the functional activities after the infection [139]. Memory T cells, upon stimulation, triggers B cells and other immune cells to knock down the infected cells [140]. NK-like T cells express markers CD57 and killer like receptor G1 (KLRG1) which induces inflammatory cytokine production such as IFN- γ and latter controls T cell receptor (TCR) signaling cascade [141–143]. These findings uncovered the facts of abnormal antibodies production in aging individuals suffering from COVID-19. A study reports that human CD26 binds with S protein of SARS-CoV-2 and generates ineffective T cells [144]. CD147 protein is involved in T cell activation and binds to S1 domain of S protein, facilitating its entry into the host cell [145]. The binding of SARS-CoV-2 proteins to CD147 and CD26 forms activation-induced cell death (AICD), which may lead to abnormal T cell function [146].

However, a similar study reports that the T cell apoptosis induces in MERS-CoV and the same was observed in COVID-19 patients [139, 147]. These findings may gather anomalous facts of T-cell functioning in SARS-CoV-2 infected individuals.

Humoral immune response (antibody response)

Once the virus invades the host body, the host immune system recognizes and elicits innate, adaptive or humoral responses. Antibody immune response is characterized by IgG and IgM antibody production within the host body. During the early stage of SARS-CoV-1, B-cells response against nucleocapsid (N) protein is detected, whereas response against spike protein was identified at 4–8 days after infection [148, 149]. Even though N protein is smaller than S protein, it induces antibody production upon infection [150]. Similarly, coronavirus-specific antibodies IgA, IgG and IgM were identified at the beginning of infection where IgG retain for a longer period and IgM declined after 3 months [151, 152]. A study conducted on 16 COVID-19 patients identified serum anti-S-RBD IgG antibodies. Among these patients, 15 were detected with anti-N IgG and anti-S-RBD IgM and 14 patients with serum anti-N IgM only [153]. An ELISA-based time kinetics study demonstrated that IgM and IgA antibodies were detected 5 days after the onset of initial symptoms, whereas IgG was detected after 14 days [154, 155]. In addition, a clinical study from 6 children reported protective serum IgG and IgM antibodies response towards N and S-RBD proteins of SARS-CoV-2 [156]. Such ELISA-based early diagnosis along with qRT-PCR can be employed to detect the severity of COVID-19. Secretory IgA (SIgA) protects respiratory mucosa against viral entry. SIgA neutralizes respiratory tracts of COVID-19 infected individuals where neutralizing IgA was detected in bronchoalveolar lavages of patients [157]. Another study reported the presence of neutralizing antibodies in multisystem inflammatory syndrome in children (MIS-C) which can be utilized to treat COVID-19 as these antibodies stimulate immune cells and ILs such as monocytes, lymphocytes, NK cells, myeloid chemotaxis, and IL-18 or IL-16 [158]. These data provide evidence that antibody titers specific to SARS-CoV-2 can be a source of diagnosis and therapeutic.

SARS-CoV-2 in cardio-oncology

Cancer is one of the most prevalent diseases across the globe. The disease, the treatment and the post-cancer conditions are found to affect several internal organs and hamper the efficiency of the immune system to actively fight infections. The patients with active cancers and those undergoing therapies are more exacerbated with a negative prognosis of viral infection [159, 160]. The magnitude of the problem

may also vary with the type of cancer, chemotherapies/radiotherapy, intake of immunosuppressant and other pre-existing conditions like diabetes or any metabolic syndrome [160, 161]. A study on a Chinese cohort demonstrated that patients with pre-existing comorbidities had a higher risk of death of which 5.6% accounts for cancer [162]. On the bright side, the emergence of recent therapeutic strategies improved the survival rate of cancer patients; the darker side discusses the cardiotoxic side effects which in turn affects the vulnerability to the viral infection [8]. The high risk of SARS-CoV-2 infection and poor prognosis are attributed to the following categories of patients [163]:

- Patients undergoing active chemotherapy
- Patients administering protein kinase inhibitors or poly ADP ribose polymerase (PARP) inhibitors; patients treated with transplants of bone marrow or stem cells (in the last 6 months), or under treatment with immunosuppression drugs.
- Patients with leukemia, lymphoma or myeloma
- Patients undergoing radiotherapy for lung cancer

Damage mediated by SARS-CoV-2 infection is conciliated through inflammation, mainly via IL-6, low albumin level, increase in neutrophils as well as lymphopenia [164]. Lymphopenia is highly related to acute cases of SARS-CoV-2 infection. A cytokine storm prevails largely in COVID-19 patients showing a reduction in the immune cells like CD4 + T cells, CD8 + T cells, and NK cells [165]. Inflammation once elicited, it persists throughout and alters the stromal microenvironment. A loss of balance in the RAAS system combined with the loss of ACE2 in patients with COVID-19 are further contributing factors to tissue and systemic inflammation [166]. Such weakened immune systems are mainly exhibited by cancer patients too; with active cancers or the ones receiving chemo or immunotherapies. SARS-CoV-2 is one such opportunistic pathogen that takes advantage of such hosts and accounts for the major cause of mortality in cancer-related COVID-19 patients [167].

Cancer associated cardiac complications and treatment regimens

Zordoky alluringly described three possible scenarios for increased cardiovascular complications of COVID-19 in cancer survivors. The first one pinpoints the pro-inflammatory, pro-apoptotic and pro-oxidative effect which synergizes myocardial damages with anticancer therapies along with viral infection. Second, the harmful cardiotoxic effect as an outcome of cancer therapies which renders the patients more vulnerable to SARS-CoV-2 infection. The third scenario emphasizes on the cumulative risk factors due to COVID-19 in cancer patients which further

complicates the cardiovascular outcome in such patients [168]. In such situations, certain cancer therapeutics which falls under anthracyclines, anti-growth factors (eg: HER2 blocking antibodies) and inhibitors (tyrosine kinase inhibitors, protease inhibitors, checkpoint inhibitors etc.); which potentially increase apoptosis, oxidative stress or necrosis may affect myocardial cells and compromises the cardiac health leading to cardiomyopathies. A controversial fact exists for the use of checkpoint inhibitors, a drug that is a boon not only for cancer patients but also occasionally for COVID-19 patients [169, 170]. Checkpoint inhibitors are found to stimulate macrophage infiltration and lymphocytes which exerts immune-stimulating response but also activates survival pathways through the inhibition of CTLA-4 and PDL-1 [171, 172]. The combination therapies used with immune checkpoint inhibitors increase the prevalence of myocarditis in cancer patients when compared to monotherapies. For example, Nivolumab treated in combination with Ipilimumab increased the rate of myocarditis in patients from 0.6 to 0.27% when compared to Nivolumab monotherapy [173, 174]. Moreover in lung cancer patients, Nivolumab causes acute lymphocytic myocarditis [175]. Therefore, to compare the clinical benefits of immune checkpoint inhibitor treatment in cancer and COVID-19 patients with respect to the possible after effect such as myocarditis are subjected to further validation using retrospective studies.

Certain types of cancer like lung, brain, gastric, pancreatic, genito-urinal and some metastatic cancers aggravate conditions like bleeding and VTE [176]. Platinum-based anticancer drugs like cisplatin, hormonal therapies like tamoxifen, anti-VEGF therapies like Bevacizumab, immunomodulators like Thalidomide, Bcr-Abl kinase inhibitors like Nilotinib, proteasome inhibitors like Carfilzomib increases the risk factors in cancer patients for elevated coagulation and inhibition of fibrinolysis during SARS-CoV-2 infection [177]. The hyperactivation of T-cytotoxic lymphocytes and NK cells as a secondary inflammatory condition in COVID-19 patients induces the risk for myocarditis and VTE which may lead to death accounted with ARDS. A high level of fibrin degradation was reported in death cases of SARS-CoV-2 infection, especially those cases which were reported to express disseminated intravascular coagulation (DIC) [178, 179]. It is comprehensive that anticancer therapies could aggravate the damages due to intravascular coagulation in COVID-19 patients. In such situations, low molecular weight heparins are best suggested for the treatment of critically ill patients along with a proper thromboprophylaxis regimen [51, 180]. A self-contradiction of increased thrombotic risk parallel to increased bleeding risks is associated with cancer patients. Khorana score is a tool used to address the prophylactic score of VTE in cancer patients [129]. Once records of Khorana score are applied

with COVID-19 patients, the scenario will appear clearer in the context of COVID-19 related thromboembolism in cancer patients.

Myocarditis, type II MI, acute coronary syndrome and stress-related cardiomyopathy are widely categorized into the etiology of myocardial injury in cancer patients [181]. It was reported that cancer patients exhibiting high levels of troponin and possible acute coronary disease are found to have type II MI [182]. This situation can highly be in tune with the fact that COVID-19 patients; (reported from China) who expired without any CVD history; either had elevated cardiac troponin I levels or a cardiac arrest during hospitalization [183]. Thereafter, medical societies across the world recommend the monitoring of troponin I level for patients presented with cancer/cancer history with viral infection having any significant cardiac involvement. Stress cardiomyopathy aka Takotsubo syndrome is well associated with cancer patients with adverse clinical outcomes like thromboembolism, shock and arrhythmias [184, 185]. Such patients are usually given respiratory support. The reason for Takotsubo syndrome mainly being physical and emotional stress is also very much accredited with SARS-CoV-2 infection [186]. Even though the combination of the two- cancer and SARS-CoV-2 infection will increase the incidence of Takotsubo syndrome, a retrospective study is recommended to confirm the occurrence.

Drugs like hydroxychloroquine, azithromycin etc. used against emergencies in COVID-19 situations earlier are known to cause QT prolongation [187]. Similarly, certain anti-cancer drugs like tyrosine kinase inhibitors, HDAC inhibitors and antidepressants are also known to promote QT prolongation [188, 189]. It will be important to learn how COVID-19 treatments in cancer patients are affecting the QT prolongation due to which patients are at increased risk of fatal arrhythmia. Since chloroquine drugs are not in much use for COVID-19 treatment now and drugs like remdesivir are less likely to cause QT prolongation, no arrhythmias were actually reported from COVID-19 cases [190]. However, cancer therapies can potentially be risky and render the patients with viral infection more prone to QT prolongation-induced arrhythmias. Apart from the irregular heartbeat conditions like arrhythmia, certain possibilities are also likely to happen with COVID-19 related cardiac events in cancer patients. One such is a condition affecting the tissues around the heart called as pericarditis as well as a condition of fluid retention around the heart called as pericardial tamponade [191]. It is postulated that SARS-CoV-2 infection can impart myopericarditis in patients with the severity of the disease [74, 192]. Similarly, certain cancers, as well as anti-cancer therapeutics, are also reported to cause myopericarditis which may sometimes be presented with pericardial tamponade [75]. In those patients with active cancer or anti-cancer treatments undergoing SARS-CoV-2 infection, it will

be difficult to predict the cause or occurrence of pericarditis and its aftermath. It is advised to follow the NSAID category of drugs and immediate critical care if a patient is presented with pericarditis upon viral infection.

CVDs stand as the most important cause of mortality in COVID-19 patients. It is absolutely paramount in this situation to increase cardiovascular screening or surveillance in cancer patients. Those patients who are either immunocompromised or have a history of any cardiovascular events or metabolic diseases or are of higher age should be provided with prudent cardiovascular screening. Strict precautions and preventive measures should be adopted to keep cancer patients or post-cancer care patients against contact with the SARS-CoV-2 infection [193]. Once a cancer patient is suspected to come in contact with the virus, immediate medical attention should be given with timely screening of the organ functions. During the SARS-CoV-2 infection, the delayed occurrence of acute MI and subsequent complicated events leading to death has been reported. Even with the end of the third wave of the SARS-CoV-2 infection globally, information is still lacking to deeply excavate the real correlation between COVID-19 and cardio-oncology and more retrospective studies in larger cohorts are in high demand to tailor the treatment strategies (including both supportive and targeted therapies) for COVID-19-cardio-oncology axis.

Alzheimer's disease

Alzheimer's disease (AD), a progressive neurological disorder, has been reported as a clinical complication and, comorbidity in elderly COVID-19 patients [194]. AD is a common cause of dementia where a person loses cognitive function. Accumulating evidence suggests that SARS-CoV-2 enters the brain and makes morphological changes which is the likely cause of cognitive impairment in some COVID-19 patients [195]. A recent study has shown that SARS-CoV-2 infection leads to Alzheimer's-like changes in the brain of some COVID-19 patients [196]. In addition, the central nervous system (CNS) and the peripheral nervous system (PNS) are both damaged by SARS-CoV-2 and also show lengthy impairment [197]. A retrospective cohort study in Spain reported that around 29.1% of COVID-19 patients with AD exhibited further cognitive impairment which significantly increased the morbidity rate in elderly people [198]. Several studies have reported that AD is a common predictive factor to mortality in COVID-19. AD patients infected with SARS-CoV-2 have shorter survival than the COVID-19 patients without AD. Around 54.5% death rates were observed in COVID-19 patients with AD [199]. Another cohort study reports that 25.2% of COVID-19 patients with AD, mainly elderly, died despite active treatment [200]. COVID-19 infection may lead to neurological symptoms as an observational study from China

reported that 14.8% of hospitalized COVID-19 patients suffered from neurological manifestations including impaired consciousness [201]. In addition, similar observations were reported from the European cohort where critical COVID-19 patients showed working memory dysfunction. Around 65% of COVID-19 patients admitted to the ICU showed confusion [202, 203]. ACE2 receptors are highly expressed in different brain regions which provide an initial target for SARS-CoV-2 invasion. A study reported that the pons and medulla oblongata in the human brainstem were more susceptible to virus entry and subsequently caused neurodegenerative disorder [204]. Along with AD, CNS damage results in Parkinson’s disease (PD) and is associated with risk factors such as aging, family history, environment and chemical exposure [205]. A study reported that PD is not a risk factor for COVID-19 [206]. This study suggested that some PD patients with COVID-19 present with worsening

parkinsonian symptoms, requiring increased anti-PD therapy with worse outcomes. These studies suggest that COVID-19 patients need long-term clinical follow-up to avoid further COVID-19 complications.

Conclusions

Treating COVID-19 patients is a crucial task for health-care providers despite few anti-viral medications and, vaccines being available for prevention. COVID-19 causes an endless loop of mortality and morbidity in patients suffering from CVD, diabetes, hypertension, thyroid disorder. These complications ultimately lead to multi-organ failure eventually leading to death. Comorbidities such as CVD, diabetes, thyroid, respiratory, vitamin D deficiency and hypertension (Fig. 5) have been reported as high-risk

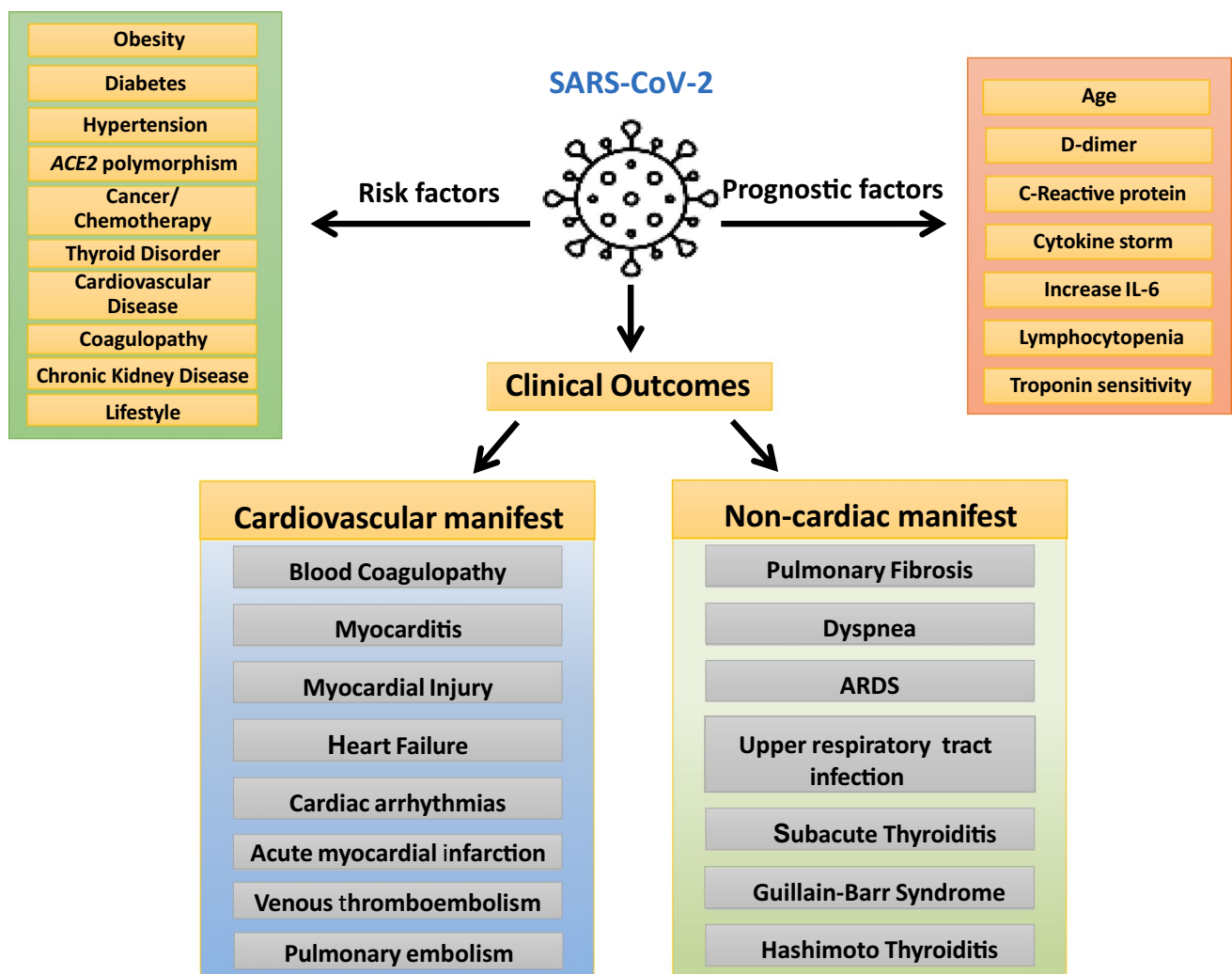


Fig. 5 Schematic diagram summarizes the major risk factors, disease prognosis and cardiovascular and non-cardiovascular clinical manifestation reported in COVID-19 patients

factors in COVID-19 patients and special consideration must be provided to such patients. Since the pre-existing comorbidity is the leading cause of mortality in COVID-19 patients, a thorough clinical assessment is required during hospitalization. Patients with comorbidity factors should take preventive care to safeguard their survival entity and should be prioritized for the vaccination.

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Declarations

Conflict of Interest Authors declare no conflict of interest.

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