Complications of Corona Virus Disease

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8.1 Introduction

The coronavirus disease of 2019 (COVID-19), characterized as a pandemic by the World Health Organization in March 2020, has infected over 30.3 million people and caused 948,147 deaths globally, 134,935 of them in Brazil, as of September 18, 2020 [1]. It can lead to severe pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), and many extrapulmonary complications. These include thrombotic events and cardiovascular, neurological, renal, endocrine, hepatic, and gastrointestinal manifestations, as well as musculoskeletal, ocular, and dermatological symptoms [2]. In this chapter, we will overview some of these complications, reported until now, and some treatment-related and possible long-term sequelae.

8.2 COVID-19-Related Pulmonary Complications

Undoubtedly, the foremost feared complication related to COVID-19 is the development of respiratory failure due to lung involvement. Since the beginning of the pandemic, it has been evident that the mortality was directly related to a viral

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H. Prabhakar et al. (eds.), *Clinical Synopsis of COVID-19*,
https://doi.org/10.1007/978-981-15-8681-1_8

pneumonia that leads to severe hypoxemia, often requiring invasive mechanical ventilation that is, in many occasions, irresponsive to standard ventilatory strategies. The distinctive acute respiratory distress syndrome (ARDS) related to COVID-19 occurs in roughly up to 20% of hospitalized patients [3].

The first cohorts provided a clinical picture of patients being admitted to the hospital with clinical and radiological features of pneumonia, with somehow rapid deterioration, i.e., with severe hypoxemia in the context of an inflammatory syndrome. From the beginning, a clear pattern of ground-glass opacifications on lung CT scans was evident in most patients, ranging from mild to severe extensions. From the clinical standpoint, patients often presented cough and dyspnea, a clear and unequivocal sign of pulmonary involvement. Patients may present a progressive dyspnea or sudden deterioration of the ability to tolerate exercise, depending on the extension and rate of inflammation that varies from each individual. Cough is usually dry and persistent [4]. We have also learned that those patients with pre-existing lung conditions, such as COPD, or smoking habit are at a higher risk for increased mortality [5].

From pathology case series, lung involvement is characterized by distinctive features both from the epithelial and vascular standpoints. Diffuse alveolar damage and/or hyaline membranes, along with desquamation and/or reactive hyperplasia of pneumocytes, are present in most of 70% of analyzed specimens. On the vascular front, presence of capillary congestion, microthrombi deposition, and alveolar hemorrhage was the most frequent findings. Interstitial and fibrotic findings, such as fibrosis of fibroblast hyperplasia, are also present in roughly 33% of the specimens [6]. Nevertheless, we must consider that most analyses are from autopsies, i.e., neither from mild nor moderate or even severe cases of living patients, since lung biopsies are not used to gauge patient management, providing a possible severity bias for these findings.

From the specific pulmonary circulation standpoint, it is acknowledged that the incidence of venous thromboembolism (VTE) is frequent and higher than expected when compared to other viral syndromes such as influenza infection [7]. However, there are no specific recommendations so far for the use of routine screening or use of full anticoagulation as a routine use in the absence of a definite VTE diagnosis [8]. As it will be discussed further in this chapter, thrombotic complications are rather common in COVID-19, and there is an evolving and exciting field of research in this particular realm.

Finally, the last particular aspect of COVID-19 pulmonary complications may be explored by the mechanical ventilation standpoint. From previous ARDS studies, this condition is defined as a severe hypoxemia with low respiratory system compliance. However, in many COVID-19 ARDS cases, despite the ARDS hypoxemia criterion, lung mechanics is somehow preserved, with patients showing normal or near-normal lung compliance, leading to an interesting discussion on the existence of different COVID-19 phenotypes [9]. For this reason, mechanical ventilation needs special attention from healthcare providers to support patients in the way they need and not necessarily in the way guidelines suggest we should treat the so far "standard" ARDS.

In the lungs, air meets blood. In the context of a rather new clinical condition, we were able to understand in a very short period of time that SARS-CoV-2 damages the lungs in distinctive ways, causing at the same time epithelial and endothelial impairments that in conjunction will be responsible for a great deal of early mortality for COVID-19 patients. We still need more laboratorial, clinical, and pathological data to understand how to support our patients through the most critical phase of the disease.

8.3 COVID-19-Related Extrapulmonary Complications

Direct viral toxicity, endothelial cell damage, immune response impairment, and dysregulation of the renin-angiotensin-aldosterone system seem to be related to these complications [10]. SARS-CoV-2 has a spike protein surface unit with a high binding affinity to the human receptor angiotensin-converting enzyme 2 (ACE2). These receptors are highly expressed in many tissues in humans, such as airway epithelia and lung parenchyma, which may be responsible for the pulmonary manifestations, and also in the cardiovascular tissue, central nervous system, kidney cells, small intestine, and vascular endothelium throughout the body, which account for the many extrapulmonary manifestations of this disease [11].

8.3.1 Hematological

Endothelial cell damage caused by ACE-2-mediated entry of SARS-CoV-2 leads to subsequent inflammation and generates a prothrombotic milieu. Therefore, infection-mediated endothelial injury (with elevated levels of von Willebrand factor) and "endothelialitis" (inflammation of the endothelium, characterized by the presence of activated neutrophils and macrophages) occur in multiple vascular beds. Excessive production of thrombin, diminished fibrinolysis, and activated complement pathways, all lead to thrombo-inflammation, microthrombi deposition, and microvascular dysfunction [12].

Platelet-neutrophil cross-communication and macrophage activation cause an inflammatory response, with release of cytokines, and production of neutrophil extracellular traps (NETs). NETs further damage the endothelium and activate extrinsic and intrinsic coagulation pathways [13]. Hypoxia-mediated hyperviscosity and upregulation of the HIF-1 (hypoxia-inducible factor1) signaling, along with direct coronavirus-mediated effects, cause an imbalance of pro- and anticoagulant pathways [14].

Patients with the severe presentation of COVID-19 have an overactivation of their innate immunity and T cell lymphodepletion, with dysregulation of the immune response and cytokine release syndrome (cytokine storm), characterized by high-grade fever, hypotension, and multi-organ dysfunction [2].

High rates of thrombotic events occur because of hypoxia, inflammation, and direct viral-mediated effects. Besides, the increased expression of ACE2 in

endothelial cells after infection with SARS-CoV-2 may perpetuate this vicious cycle of "endothelialitis," endothelial activation, and microvascular dysfunction [15].

Autopsy studies have shown high rates of microvascular and macrovascular thrombosis, especially in the pulmonary circulation. Thrombosis is found either in arterial or venous sites as well as in invasive catheters or extracorporeal circuits [2].

Other reported hematological complications are immune thrombocytopenia, autoimmune hemolytic anemia, and disseminated intravascular coagulation [16].

8.3.2 Cardiovascular

The pathophysiology of cardiac complications related to COVID-19 is probably multifactorial. ACE2 receptors are hyper-expressed in the cardiovascular tissue, including cardiac myocytes, fibroblasts, and endothelial cells, which points to a direct viral injury. Other possible mechanisms are endothelial cell damage and systemic inflammatory response syndrome with cytokine storm [16].

Acute heart failure may be the initial presentation of the disease in 23% of patients, and cardiomyopathy is present in up to 33% [5]. Many patients seek medical care because of cardiovascular symptoms, from mild chest pain without ejection fraction compromise to severe cardiovascular collapse that may require extracorporeal membrane oxygenation (ECMO). Echocardiography findings vary from regional wall motion abnormalities to global hypokinesis with or without pericardial effusion [17]. Electrocardiogram usually shows low-voltage QRS complexes in the limb leads; ST segment elevations in leads I, II, aVL, and V2–V6; and PR elevation and ST depressions in aVR [17]. It is currently unknown if heart failure is due to a new cardiomyopathy or exacerbation of previously undiagnosed heart failure [18].

Chronic cardiovascular diseases with a reduced cardiac reserve may become unstable in the setting of this viral infection due to an imbalance caused by an increase in metabolic demand [19]. This imbalance, summed to an accentuated inflammatory response and myocardial damage, increases the risk of acute coronary events, heart failure, and arrhythmias [20].

Moreover, acute "cor pulmonale" may occur due to elevated pulmonary vascular pressures secondary to ARDS, pulmonary thromboembolism, or potentially virus-mediated injury to vascular endothelial and smooth muscle tissue [2].

Elevated troponin levels as a sign of myocardial injury occur in 7–17% of hospitalized patients and up to 22–31% of those admitted to the intensive care unit (ICU). Myocardial mononuclear infiltrates leading to myocarditis have been identified on the autopsy of patients with high viral loads. Indeed, one study suggested that up to 7% of COVID-19 related deaths were due to myocarditis [21].

Acute coronary syndromes may be due to severe systemic inflammation and hypercoagulability and should be differentiated from acute myocarditis [18]. Moreover, patients with pre-existing coronary artery disease may develop a supply-demand mismatch in the setting of severe hypoxia and hemodynamic instability, which can lead to myocardial ischemia [2].

Patients can refer palpitations in 7% of cases [22]. Many arrhythmias have been reported, most commonly sinus tachycardia, due to multiple and simultaneous reasons, like fever, hypoxia, anxiety, and hypoperfusion [23]. Hypoxemia can also trigger atrial fibrillation, especially in elderly patients. It can become persistent even after the correction of the pulmonary conditions [20]. Another critical issue is the finding of prolonged QTc (corrected QT > 500 ms), which was reported in 6% of 4250 patients with COVID-19 in a multicenter New York city cohort at the time of admission to the hospital [24]. There is a report of new-onset atrial fibrillation, heart block, and ventricular arrhythmias in up to 17% of hospitalized patients and in 44% of those under intensive care [19].

Even after hospital discharge, we should consider that myocardial injury might result in atrial or ventricular fibrosis, the substrate for subsequent cardiac arrhythmias. Future studies may assess the extent of myocardial scar using magnetic resonance or other methods, in order to identify long-term cardiac complications in patients recovered from COVID-19 [20].

8.3.3 Neurological

A high proportion of patients with SARS-Cov-2 develop neurological symptoms. Data series from Wuhan, China, found neurological abnormalities in 36.4% of hospitalized patients [25]. Many of these manifestations have an early onset, suggesting that direct involvement of the nervous system by the virus is an essential factor.

The physiopathology of neurological injury seems to be heterogeneous and multifactorial. Besides direct viral neuroinvasion, autoimmune factors, inflammation ("cytokine storm"), drug side effects, metabolic disturbances, and critical care neuropathy may be involved [26].

Viral neuroinvasion can occur through the olfactory nerve or by leukocyte migration across the blood-brain barrier, infecting the vascular endothelium. It has also been described transsynaptic transfer between infected neurons [11].

ACE2 receptors are highly expressed in the ventrolateral medulla and the nucleus of the tractus solitarius, both areas involved in respiratory cycle regulation, as well as in the ventricles, olfactory bulb, middle temporal gyrus, posterior cingulate cortex, and substantia nigra [11].

Once the virus establishes in the brain, there is evidence that it can disseminate along some neurotransmitter pathways, such as the serotonergic dorsal raphe system or by hematogenous route, through the Virchow-Robin spaces [27].

Symptoms like headache, anosmia, and ageusia are very common. Other neurological findings are impairment of consciousness, seizures, and stroke [11].

Anosmia is the absence of the sense of smell, whereas ageusia is the loss of taste. Both conditions may occur in isolation or be associated with a structural damage to the nervous system and are more frequent in patients with SARS-CoV-2 compared to other upper airway infections. Recovery is variable but usually occurs after 2 or 3 weeks. Follow-up reassessment will be needed to determine if these symptoms are transient findings or permanent sequelae of SARS-CoV-2 infection [28].

Headache is reported in up to 34% of patients. In most of these cases, it is a non-specific symptom, without features suggestive of meningeal irritation [26]. An observational study with 138 patients with COVID-19 showed that, on admission, 69.6% of patients reported fatigue, 34.8% had myalgia, and 6.5% complained of headache [19]. However, patients with refractory or persistent headache should be investigated for meningoencephalitis and cerebral venous thrombosis [26].

Data from a retrospective study with 214 patients showed 36.4% of nervous system-associated manifestations, divided into three subgroups: central nervous system (CNS), peripheral nervous system, and skeletal-related injury. CNS involvement was present in 53 patients (24.8%), with the report of the following signs and symptoms: dizziness (n = 36; 16.8%), headache (n = 28; 13.1%), impaired consciousness (n = 16; 7.5%), acute cerebrovascular disease (n = 6; 2.8%), ataxia (n = 1; 0.5%), and seizure (n = 1; 0.5%). The definition of impaired consciousness by the authors was very broad, since it included any change in level or content of consciousness [25].

Possible mechanisms are direct viral infection and damage to the cerebral parenchyma, toxic-metabolic encephalopathy, seizures, or even demyelinating disease [11].

There is a case report of a middle-aged female with COVID-19 who presented with cough, fever, and altered mental status and, after 3 days, had the diagnosis of necrotizing hemorrhagic encephalitis. MRI showed hemorrhagic lesions within the bilateral thalami, medial temporal lobes, and sub-insular regions [29]. In another case report, a 24-year-old man initially complained of headaches, generalized fatigue, and fever. Later, he developed generalized seizures and altered mental status that progressed to impaired consciousness. Clinical and laboratory evidence was suggestive of a viral meningoencephalitis, and SARS-CoV-2 was detected in the CSF through an RT-PCR analysis. A brain MRI revealed changes in the right wall of the lateral ventricle, the right mesial temporal lobe, and hippocampus, probably due to meningitis. Interestingly, the nasopharyngeal swab specimen for RT-PCR of this patient was negative for SARS-CoV-2, raising awareness of COVID-19 possible independent mechanisms of neuropathogenesis [30].

Despite postulated mechanisms of neuronal colonization and clinical reports, more robust evidence for the association between COVID-19 and encephalitis is needed [27]. Other possible mechanisms for encephalic compromise are hypoxic injury, toxic-metabolic encephalopathy, and vascular damage to the endothelium [26].

Toxic-metabolic encephalopathy may be triggered by numerous toxic-metabolic derangements, including cytokine storm, severe inflammation, sepsis, and renal dysfunction [11].

As previously mentioned, seizures can also lead to consciousness impairment. Subclinical seizures are reported in up to 10% of patients with critical illnesses. There is a case report of a patient with no history of epilepsy who had multiple apparent tonic-clonic seizures. Indeed, if this patient had no formerly undiagnosed seizure disorder, it may represent a clue to a direct effect of SARS-CoV-2 in the CNS [28].

Experimental models performed in susceptible strains of mice inoculated with the coronavirus JHMV strain resulted in an acute encephalomyelitis followed by a chronic demyelinating disease. Despite evidence showing the persistence of CoV RNA in the nervous system after the acute phase of infection, more clinical research is required to evaluate the risk of developing demyelinating diseases chronically [27].

Acute autoimmune polyneuropathy is also a concern, since it was already postulated to be triggered by other kinds of coronavirus infection. As found in case report publications, most of these patients were observed in a critically ill context. Therefore, critically ill polyneuropathy (CIP), prolonged neuromuscular blockade, vitamin deficiencies, electrolyte disturbances, and drug-related neuromuscular disorders should be included in the differential diagnosis [28].

Guillain-Barré syndrome (GBS) has also been reported as expected, since it occurs in association with many viral diseases. Until now, to our knowledge, 12 cases were described. Some of them required mechanical ventilation, and the interval for the development of the symptoms was around 10 days. Clinical features included paresthesia and progressive, flaccid quadriparesis. CSF study showed albuminocytologic dissociation. The most commonly observed subtype was acute inflammatory demyelinating polyneuropathy, and immunoglobulin was the treatment of choice in all these reports [31].

Strokes have also been reported more frequently, specially in younger patients, which points toward a possible association to COVID-19. Evidence of occlusion of large vessels treated with endovascular therapy was documented in all of them [31].

However, it can be only an association without causality, since both conditions share similar risk factors, such as systemic hypertension, diabetes, and atherosclerosis. Moreover, these patients are more prone to develop hypotension and cardiac arrhythmias, which can potentially lead to hypoperfusion, embolic mechanisms of stroke, and large vessel occlusion [32]. Data from an observational study showed acute cardiac injury in 7.2%, arrhythmia in 16.7%, and shock in 8.7% of 138 hospitalized patients [19]. Another observational study showed an incidence of 23% of heart failure, 20% of septic shock, 19% of coagulopathy, and 17% of acute cardiac injury [5]. All of them are factors that can potentially predispose patients to stroke. Hopefully, future research will discover if there are specific viral factors responsible for hypercoagulability, arteritis, and endothelial dysfunction, which can lead to ischemic stroke or brain bleeding in these patients [27].

Neurological injury caused by SARS-CoV-2 may lead to an impairment in respiratory regulation, with consequent breathing-related sleep disorders. In this scenario, long-term worsening of sleep quality may occur, as well as neurocognitive and neuropsychiatric impairment [33]. Patients can also develop posterior reversible encephalopathy syndrome, which causes headache, confusion, seizures, and visual loss [34].

Psychosis, neurocognitive disorders, and other psychiatric disorders (personality change, catatonia, mania, anxiety or depression, chronic fatigue syndrome, and post-traumatic stress disorder) have also been reported, especially in younger

patients [27]. Although many case reports described neurological complications, it is still unknown whether there is a direct viral damage to the central nervous system or if these complications occur due to secondary mechanisms [11]. Future longitudinal studies with patients recovered from COVID-19 will be needed to understand the natural history of this disease and monitor for potential neurologic sequelae, as well as psychological and psychiatric long-term complications.

8.3.4 Renal

Acute renal dysfunction in COVID-19 was initially reported in about 15% of the patients, with a high mortality rate of 60–90%. Higher rates of acute kidney injury (AKI) were furtherly reported in other studies, like the one in New York City with nearly 5500 patients. They found it in 37% of all patients, and 14% of them required dialysis. It was an early finding since one third were diagnosed within 24 h of admission to the hospital [35]. These rates are much higher compared to those reported during the SARS-CoV epidemic [36].

Hematuria has been reported in nearly 50% and proteinuria in up to 87% of critically ill patients with COVID-19. Hyperkalemia and acidosis are also common, even among patients without AKI [2].

Several possible mechanisms may be related to AKI, including direct viral infection of renal cells, microvascular dysfunction, and cytokine storm. Histopathological findings include lymphocytic "endothelialitis" in the kidney and viral inclusion particles in glomerular capillary endothelial cells [10].

8.3.5 Endocrine

SARS-CoV-2 may directly attack the endocrine glands, causing disorders that worsen prognosis of these patients, but there are still few studies regarding it.

Besides worsening glycemic control in diabetic patients, ongoing data has shown that coronavirus increases the rate of hyperglycemia and ketosis in patients with no previous diagnosis of diabetes. Ketoacidosis coexisting with COVID-19 is particularly hazardous to treat, because of the risk of pulmonary fluid accumulation [37].

Mild pancreatic injury has been reported in 17% of patients in one case series. It was defined as elevated serum amylase or lipase [19]. The possible mechanisms are either a direct viral effect or an exaggerated immune response that occurs in some patients [28].

There is a possibility that SARS-CoV-2 can directly affect thyroid tissue. Therefore, thyroid function should be monitored, especially in patients complaining of neck or ear pain, since thyrotoxicosis can worsen cardiovascular conditions [28, 37].

Adrenal gland aggression has not been reported yet, but it may hypothetically occur due to a thrombotic event. This could lead to an acute adrenal insufficiency with impaired hormone production with refractory hypotension. The prompt

recognition of this condition is necessary to allow adequate replacement therapy in order to avoid shock and impaired reaction to severe respiratory distress [38].

8.3.6 Hepatic and Gastrointestinal

Mild to moderate liver injury, with elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation, has been reported [39]. Differently from SARS, COVID-19 seems to cause hepatotoxicity through direct damage to intrahepatic bile ducts instead of hepatocytes [5].

A study taken in Shanghai Public Health Clinical Center reported abnormal liver function in more than one third of patients. Their degree of hepatic dysfunction had direct correlation with the length of hospitalization [40]. It seems that cholangiocytes (the lining epithelial cells in bile duct) are directly damaged. These cells have a high expression of ACE2 receptors, which determines viral cellular tropism [28].

Abdominal pain, diarrhea, inappetence, nausea, and vomiting are also reported in patients with COVID-19 [41]. Recent bioinformatics analysis showed that ACE2 receptors are also expressed in the upper esophagus, stratified epithelial cells, and absorptive enterocytes from the ileum and colon, which can be an evidence for enteric infectivity [39]. The clinical relevance of the persistence of the virus on stool is not yet defined. It is speculated that it may lead to re-admission of patients that were discharged after the resolution of pulmonary symptoms and possibly a fecal-oral route transmission [42].

8.3.7 Others (Musculoskeletal, Ophthalmological, Dermatological)

Musculoskeletal pain may occur in up to 34% of patients during their illness, and elevated creatinine kinase (CK) levels are present in 14–33%. Rhabdomyolysis has also been reported, with myoglobin levels >12,000 μg/L and CK levels >11,000 U/Ls [19].

Regarding dermatological features, there are many described lesions. These findings are mostly due to diffuse microvascular thrombosis and viral exanthem and may include maculopapular rash, urticaria, vesicular rash, petechia, purpura, chilblains, livedo racemosa, and distal ischemia. The most common is maculopapular eruptions, urticaria, or the acral vasculopathic rashes (pseudo-chilblains, pernio-like lesions) recognized as the "COVID toe." There are also dermatosis treatment-related drug reactions, like the generalized pustular rash due to hydroxychloroquine. Lastly, there is a concern that many pre-existing chronic dermatoses may worsen due to circumstances like stress and delayed or interrupted treatment. Besides, physical and environmental and behavioral issues such as wearing masks and latex gloves, frequent washing, and disinfectants could possibly lead to dermatological complications [43].

Ocular manifestations may resemble a common viral infection of the ocular surface, with conjunctival hyperemia and watery discharge. They were reported in up to 31.6% of patients and more commonly in those with severe disease [44]. SARS-CoV-2 has been isolated from conjunctival swabs in patients with ocular symptoms for as many as 27 days after symptom onset [28].

8.4 Long-Term Complications

- Since COVID-19 was first reported on December 31, 2019, we still don't have much knowledge about its sequelae and long-term outcomes. Complications can be related to the disease itself, the combination of the disease with previous comorbidities that the patients may present, and also the treatment, including the hospitalization, medications, and invasive procedures.
- In the Table 8.1, we list some of the complications directly related to COVID-19 infection and their possible long-term outcomes.
- Subacute cardiac complications are beginning to appear. In a recent cohort study, cardiac involvement was revealed by magnetic resonance in 78%, and ongoing myocardial inflammation was present in 60% of patients that had already recovered from COVID-19 with complete resolution of respiratory symptoms and negative results on a swab test at the end of the isolation period [45].
- The long-term impact of COVID-19 is still under investigation, and little is known about how the immune system recovers after infection. There is compelling evidence of persistent viral shedding in nasopharyngeal secretions and also in stool for more than 2 weeks after resolution of symptoms [46].

Table 8.1 COVID-19 complications

	Clinical manifestations	Possible chronic complications
Pulmonary	Acute pneumonia ARDS Pulmonary embolism	Pulmonary fibrosis Chronic respiratory insufficiency
Hematologic	Arterial thrombotic complications: Acute limb and mesenteric ischemia Venous thrombotic complications: Deep vein thrombosis Catheter-related thrombosis Cytokine release syndrome: High-grade fevers, hypotension, multi-organ dysfunction	Limb amputation Chronic venous insufficiency

(continued)

Table 8.1 (continued)

	Clinical manifestations	Possible chronic complications
Cardiovascular	Myocardial ischemia and myocardial infarction Myocarditis Arrhythmia: Atrial fibrillation and flutter, sinus tachycardia, and bradycardia, QTc prolongation Cardiomyopathy: Biventricular, isolated right or left ventricular dysfunction	Myocardial fibrosis Arrhythmias Chronic cardiac insufficiency
Neurologic	Headache, dizziness Anosmia, ageusia Stroke Encephalopathy, encephalitis, Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalopathy	Chronic anosmia and ageusia Neurologic deficits Posterior reversible encephalopathy syndrome Cognitive impairment Chronic neuropathy Chronic neuropathic and non-neuropathic pain Breathing-sleep disorders
Neuropsychiatric	Altered mental status New-onset psychosis Dementia-like syndrome Affective disorders	Chronic anxiety and affective disorders
Renal	Acute kidney injury Electrolyte abnormalities Proteinuria Hematuria Metabolic acidosis Clotting of extracorporeal circuits used for RRT	Chronic renal insufficiency
Endocrine	Hyperglycemia and ketoacidosis, even in patients without the previous diagnosis of diabetes	Diabetes Other endocrine diseases
Hepatic and gastrointestinal	Nausea and/or vomiting, diarrhea, abdominal pain Elevated hepatic transaminases and bilirubins, low serum albumin	Chronic hepatic insufficiency
General manifestations	Anorexia, myalgias, fatigue	Chronic fatigue and musculoskeletal pain
Ophthalmological	Conjunctivitis	Chronic conjunctivitis
Dermatological	Petechiae, livedo reticularis, erythematous rash, urticaria, vesicles, pernio-like lesions	Chronic dermatosis

- In relation to the interaction between the disease and comorbidities, it is important to emphasize that the most frequent comorbidities are hypertension (55%), coronary artery disease, stroke (32%), and diabetes (31%). Patients with COVID-19 are less likely to have the following chronic illnesses: liver diseases (9%), chronic obstructive pulmonary disease (7%), malignancy (6%), chronic renal failure (4%), gastrointestinal diseases (3%), central nervous system diseases (<1%), and immunodeficiency (1%) [47]. Therefore, survivors requiring prolonged rehabilitation are more likely to be older and to have a pre-existing cardiovascular and cerebrovascular disease, which may influence their rehabilitation and outcomes [34].

8.4.1 Treatment-Related Complications

8.4.1.1 Medications

- Medications under study include antivirals (e.g., remdesivir, ribavirin, lopinavir/ritonavir, favipiravir), antimalarials (e.g., chloroquine, hydroxychloroquine), azithromycin, corticosteroids, and biologics (tocilizumab) [48]. They may interfere with other frequently used drugs, like antihypertensives, antiarrhythmics, anticoagulants, antiplatelets, and statins, causing significant pharmacokinetics and pharmacodynamical interactions.
- Many antiviral drugs can cause cardiac insufficiency, arrhythmia, or other cardiovascular disorders [49]. Remdesivir is a polymerase inhibitor of viral RNA and showed in vitro effect against SARS-CoV-2. However, it may cause neurological and cardiovascular adverse effects that are still under investigation [50]. Lopinavir/ritonavir may cause QT and PR prolongation [51].
- Chloroquine and hydroxychloroquine have been used even without clinical benefit evidence and may be responsible for cardiotoxicity, prolonged QT intervals, and also electrolyte and acid-basic intracellular abnormalities [52]. They can also lower the seizure threshold; cause irritability, peripheral neuropathy, and neuromyopathy, and even be associated with psychosis [11].
- Tocilizumab is a monoclonal antibody to the IL-6 receptor and may attenuate the "cytokine storm." However, it may cause neurological adverse effects, like headache, dizziness, and multifocal cerebral thrombotic microangiopathy [11].
- Osteonecrosis of the femoral head and osteoporosis may be a concern in patients treated with high doses of corticosteroids, since many patients recovered from SARS developed it [53]. Patients using supraphysiological doses of corticosteroids are also more prone to develop metabolic and cardiovascular complications (hypertension, obesity, and diabetes) [54].

8.4.1.2 ICU-Related Complications

Early complications related to ICU admissions are acute respiratory distress syndrome (ARDS) and sepsis, multi-organ failure, acute kidney injury, and cardiac injury [47]. Other important concerns are secondary bacterial and fungal infections.

A recent prospective multicentered study has found an incidence of 27.7% of invasive pulmonary aspergillosis among intubated patients with COVID-19 [55].

- Other complications related to prolonged mechanical ventilation are tracheal stenosis, heterotopic ossification, muscle contractures with associated myofascial pain, adhesive capsulitis, decubitus ulcers, hoarseness, tooth loss, sensorineural hearing loss, tinnitus, brachial plexus injuries, and entrapment neuropathies (peroneal and ulnar) [56]. Since COVID-19 patients have higher rates of thrombotic events, they are more prone to develop catheter-related thrombosis. It can occur in either the arterial or venous catheter and also inside extracorporeal circuits [2].
- Prone positioning (PP) is a supplementary strategy to improve oxygenation in patients with acute respiratory distress (ARDS). It has been used in up to 28% of patients admitted to ICU with COVID-19 [57]. Some related complications are transient desaturation, transient hypotension, accidental extubation, and catheter displacing. Besides increased intracranial and intraocular pressure, compression of nerves and pressure ulcers can occur accordingly to the duration of staying prone. A recent study [58] found pressure ulcer incidence in prone positioning of 14% in the following locations: 5% face and chin, 6% face/cheekbones, 6% thorax, 1% trochanter, and 5% other sites. Pressure ulcers occur due to a pressure applied to a specific area over a period of time. This continued pressure leads to tissue ischemia, in addition to an impairment of nutrition and oxygen supply [59].

8.4.1.3 Post-ICU Discharge Syndrome

- Post-intensive care syndrome is characterized by a reduced pulmonary function (restrictive pattern), diminished inspiratory muscle strength, poor knee extension, reduced upper extremity and grip strength, and low functional capacity. Improvement occurs over a year or more [60].
- Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) may occur after COVID-19 and cause weakness, loss of function and quality of life, as well as poor endurance that may persist for up to 2 years or longer. CIP is characterized by a generalized and symmetrical weakness due to a mixed sensorimotor neuropathy that leads to axonal degeneration. It can be difficult wean from mechanical ventilation, since diaphragmatic weakness may also be present. Other clinical findings are distal weakness (more significant than proximal) and sensory loss, atrophy, and decreased or absent deep tendon reflexes. The incidence of CIP is dependent on the patient population, diagnostic criteria, and timing of the examination. Long-term sequelae may be pain, loss of range of motion, fatigue, incontinence, dysphagia, anxiety, depression, post-traumatic stress disorder (PTSD), and cognitive impairment [60].
- Critical illness myopathy (CIM) is a non-necrotizing diffuse myopathy with fatty degeneration, fiber atrophy, and fibrosis. It may occur in up to 50% of patients under mechanical ventilation for more than 7 days and is likely to be underdiagnosed because of the lack of early and accurate diagnostic tools, since a muscle

biopsy is necessary for definite diagnosis. The clinical presentation is similar to CIP, but sensory is well preserved, and weakness is more proximally located. The physiopathology of this syndrome includes extended periods of immobilization, sepsis, and exposure to corticosteroids. Cranial nerves and facial muscles are usually preserved in both syndromes, and recovery is faster than from neuropathies. There is no correlation between these features and any residual loss of pulmonary function [61].

8.5 Other Possible Long-Term Complications

- Cognitive impairment is also a concern in critically ill patients. In one study of patients with respiratory failure or shock, after ICU admission, median global cognition scores (measured by a neuropsychological battery of tests) were significantly lower than the age-adjusted population mean. Among these patients, 26% had scored 2 SD below the population mean, similar to scores for patients with mild Alzheimer's disease. Repeated testing after 12 months showed no recovery, raising the concern that cognitive impairment can persist [62]. Indeed, cognitive impairment can be present in 70–100% of patients at discharge; 46–80% still have it 1 year later, and 20% still have it after 5 years. All components of cognition may be affected, including attention, visual-spatial abilities, memory, executive function, and working memory.
- In research regarding ICU admissions for ARDS, many adverse psychological impacts have been reported. Even after 2 years, post-traumatic stress disorder PTSD (22–24%), depression (26–33%), and general anxiety (38–44%) were prevalent [56]. Risk factors were premorbid psychiatric illness, younger age, female sex, unemployment, alcohol use, and greater use of opioid sedation. Family members may also suffer from PTSD, anxiety, and depression, and they may have difficulty managing their new caregiver roles.
- Further research will be needed to assess the impact on the mental health of COVID-19 pandemic for the whole society, related to its socioeconomic effects and the quarantine experience, as well as for healthcare professionals who worked in the front line.

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