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Complications of COVID-19 infection: A narrative review

Kirthika Venkatesan, Faatir Chaudhry, Zayd Mughal, Sruti Patel

ABSTRACT

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in 2020. Millions of people die every day due to a lack of oxygen, hospital beds, and vaccines necessary to alleviate the disease burden. The virus has developed the ability to infect other bodily systems leading to anosmia, cerebrovascular disease, preterm birth, intrauterine growth restriction, venous thromboembolism, renal defects, and much more. In this narrative review, we aim to address the complications from COVID-19 infection and identify any prospective studies. Published papers between 2020 and 2021 relevant to the topic were obtained through extensive search using major databases and relevant keywords. Inclusion criteria included studies that directly related to the complications from COVID-19 in adults. Exclusion criteria included studies involving medication complications as a result of COVID-19 treatment. Identifying the mechanisms behind these complications offers a basis to further understand the nature of COVID-19, which has implications for treatment and prevention.

Keywords: Arrhythmias, Cardiovascular, COVID-19, Liver failure, Neurologic, Pregnancy, Pulmonary, Renal failure

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INTRODUCTION

COVID-19 first emerged in Wuhan, China and was declared a pandemic by the WHO in 2020 [1]. The virus has spread to multiple countries causing mass deaths or rendered individuals with severe complications. COVID-19 spreads through fomites and air particles. Common symptoms of the virus include mild dry cough, fever, shortness of breath, severe debilitating pneumonia, and anosmia. Individuals above the age of 65, diabetics, pregnant women, and those who are immunosuppressed are at a greater risk of contracting the infection and more hospitalizations and complications [1].

The use of personal protective equipment, quarantine/lockdown, border and travel restrictions have helped to prevent transmission. The development of vaccinations has helped to further reduce hospitalizations. The emerging variants of the virus pose another major challenge in the fight against the pandemic [2].

The disease burden has increased all over the globe and some countries, like India, are experiencing an uncontrolled amount of hospitalizations resulting in a shortage of hospital beds and oxygen tanks. Millions of people all over the world have died from the complications of COVID-19. Apart from pneumonia, the virus is known to affect the brain, kidneys, heart, and blood. In this literature review, we aim to address the complications of COVID-19 infection, identify barriers, and suggest future studies. We aim to provide a platform that highlights the

mechanisms behind these complications necessary to establish effective preventative and treatment measures.

MATERIALS AND METHODS

This is a narrative review of the existing studies investigating the complications of COVID-19. All published papers between 2020 and 2021 relevant to the topic were obtained through extensive search using databases such as Google Scholar, PubMed, and ScienceDirect. Relevant keywords were used in different orders: "coronavirus," "COVID-19," "complications," "neurologic symptoms," "venous thromboembolism," "renal failure," "hepatic failure," "arrhythmia," "pregnancy," and "pulmonary." Inclusion criteria included studies that directly related to the complications from COVID-19 infection. Exclusion criteria included studies involving medication complications from COVID-19 infection treatment. The following topics were investigated: pulmonary complications, neurologic complications, pregnancy and neonatal complications, hematologic complications, cardiovascular complications, renal complications, dermatologic complications, and gastrointestinal (GI) complications.

Pulmonary complications

COVID-19 primarily affects the respiratory system [3]. Transmission occurs through coughing, sneezing, inhalation of respiratory droplets, contact with oral, nasal, and eye mucous membranes [4, 5]. Symptoms of the virus include cough, pneumonia, fever, sneezing, fatigue, and muscle weakness. Some individuals may not experience any symptoms at all [4]. Individuals who are immunosuppressed (i.e., diabetes, cancer) tend to have more severe symptoms and poorer outcomes compared to healthy adults. The virus utilizes a protein spike necessary for evaluating tropism and virus transmission. The virus also enters the host cell via the angiotensin-converting enzyme-2 (ACE-2 receptor). This receptor provides entry for the virus into the host cells, allowing for viral replication. Then, host cell-surface proteases, like transmembrane serine protease 2, interact with cell membrane proteins resulting in binding and infection [6]. These mechanisms allow the virus to go unrecognized by the host's immune system, creating the perfect environment for replication [6]. Once the progeny virus is released from the host cell, it invades pulmonary cells leading to inflammation, vasoconstriction, fibrosis, and atrophy of the lungs [7].

COVID-19 can lead to lymphocytic pneumonia, acute fibrinous and organizing pneumonia, or acute respiratory distress syndrome. Lung autopsies in infected patients demonstrate various findings including severe neutrophilic capillaritis extending in the alveolar space and tracheal mucosa, severe mucous tracheitis/tracheobronchitis, patchy/diffuse areas of consolidation, aspiration pneumonia along with foreign bodies, squamous cells, and vegetable particles in the airways [3, 8].

A common finding is diffuse alveolar hemorrhage, accompanied by interstitial and endothelial inflammation [9]. This alveolar damage is associated with perivascular T cell infiltration [10]. In addition, patients with COVID-19 infection have a higher rate of microthrombi in alveolar capillaries than patients with the Influenza virus. Another finding is intussusceptive angiogenesis, a process in which one blood vessel splits into two vessels [10]. This is thought to occur due to the proliferation of endothelial cells and associated increased ACE-2 receptor expression in pericytes [11]. Hence, a loss of pericytes in patients with COVID-19 may explain the pathogenesis of microangiopathies [9].

A study by Fox et al. examined the autopsies of lungs in patients between 44 and 78 years of age who died from COVID-19 [12]. The authors reported the production of immunopositive megakaryocytes inside alveolar capillaries. These cells are known to generate fibrin thrombi in mass quantities. In addition, respiratory failure occurs in severe cases of COVID-19 which may warrant lung transplantation [12]. Bharat et al. (2020) performed lung transplantation in three patients with severe COVID-19 infection. They found that the lung autopsy in these patients shared similar pathological and molecular features with pulmonary fibrosis, ultimately supporting that lung transplantation is the only alternative for survival [13].

Neurologic complications

Pulmonary complications of COVID-19 have received the foremost attention; however, the neurologic manifestations are more disabling, persistent, and common in patients with COVID-19. Studies show evidence that COVID-19-related neurologic manifestations are because of direct and indirect neurotropism, suggesting that the virus enters the nervous system via ACE-2 receptors, which are also present in neurons and glial cells within the brainstem [14]. On the contrary, other studies state that the virus is not neurotropic, similar to rabies or poliovirus, and it is proposed to invade via a trans-neuronal spread making its way to the brainstem [15]. The latter statement is supported by a case series done by Matschke et al. [16] in Germany that demonstrated autopsy findings showing invasion in perivascular and brain parenchyma by immune cells particularly macrophages and lymphocytes [16].

Studies report nearly 10–36% of survivors complain of disabling and persistent neurological symptoms after COVID-19 infection [15, 17]. These complications are described in three categories: central nervous system (CNS) encephalopathy (presenting as dizziness, headache, impaired consciousness, delirium, acute cerebrovascular disease, ataxia, or seizures); peripheral nervous system manifestations such as taste, smell, and vision impairment; and skeletal muscle injury manifestations [17, 18]. Patients with severe COVID-19

infection are more likely to experience a stroke (6%), impaired consciousness (15%), and skeletal muscle injury (19%) [17]. These patients are usually older with preexisting comorbidities and display atypical symptoms of COVID-19 symptoms [17].

Encephalopathy can present as alteration in consciousness to delirium and seizures [14]. The most common neurological manifestation of COVID-19 infection is anosmia due to olfactory dysfunction. Encephalopathy is the most common neurological manifestation in hospitalized patients, which can be seen in up to one-third of hospitalized patients [15]. According to Nath and Smith (2021), patients presenting with altered mental status are hospitalized three times longer and two-thirds of patients are unable to manage activities of daily living at the time of discharge. Helms et al. (2020) conducted a case series where they performed brain magnetic resonance imaging (MRI) of patients with COVID-19 exhibiting unexplained encephalopathy. They noted frontotemporal hypoperfusion in 11 out of 13 patients and leptomeningeal enhancement in eight out of 13 patients. Appropriate neurologic workup, and having a high suspicion for COVID-19-related CNS encephalopathy are pertinent to prevent irreversible damage [19].

Cerebrovascular events occur in 1–5% of hospitalized patients with COVID-19, and patients with underlying risk factors for stroke are at a greater risk [15]. A study was done on hospitalized patients in Wuhan, China by Li et al. [20] showed those who suffered an acute stroke during hospitalization were most likely older, presenting with severe infection, and have cardiovascular risk factors, including a prior history of stroke. In addition, these patients were more likely to have an increased inflammatory response and a hypercoagulable state with an increase in both D-dimer and C-reactive proteins. There are more reported ischemic strokes than hemorrhagic strokes [15]. These patients should be monitored for rapid clinical deterioration, as it can lead to worsening of neurological function and high mortality rates.

Anosmia in COVID-19 patients is due to olfactory dysfunction and invasion of the support cells. The virus binds to the ACE-2 receptor on the olfactory nerve [15]. Nearly 60% of patients develop loss of smell, and upon testing nearly 90% have an alteration of smell [21]. The loss of taste (ageusia) is thought to be secondary to the loss of smell but can lead to loss of appetite and weight loss. A different study reported anosmia in 86% and ageusia in 88% of patients with mild-moderate COVID-19 symptoms [14].

An analysis done by Patel et al. (2020) showed that 55% of patients reported anosmia and ageusia. The median onset of anosmia concerning the onset of COVID-19 symptoms was four days and the median duration was eight days. The relatively short period of onset concerning other COVID-19 symptoms suggests that anosmia could also be a useful early diagnostic factor in non-tested household close contacts of confirmed COVID-19 patients to aid in self-isolation [22]. Most patients recover their sense of taste and smell within a couple of weeks but some may develop parosmia or permanent anosmia [14, 15].

Another neurologic manifestation is critical illness polyneuropathy and myopathy, most commonly seen in patients who are in the intensive care unit (ICU) for prolonged periods with the reported incidence as high as 33% [14]. It is not clear if this is due to COVID-19 or simply due to prolonged mechanical ventilation in the ICU. Clinicians should suspect this in cases presenting with myalgias and increase creatine kinase levels.

Guillain-Barre syndrome (GBS), also known as acute inflammatory demyelinating polyneuropathy (AIDP), is documented as one of the many complications of COVID-19. Previously with SARS and MERS-CoV, both AIDP and acute motor axonal neuropathy (AMAN) have been seen. Although the most common is AIDP (70%), Miller-Fisher syndrome (12%), AMAN (6%), and acute motor-sensory axonal neuropathy (AMSAN; 12%) can be seen as well [23]. Hence, more studies are needed to focus on those variants and their relation to COVID-19.

GBS usually presents with acute flaccid paralysis with or without respiratory compromise, ascending weakness, and areflexia. Among the neurological findings from GBS, paresthesia was the most common symptom (48.9%), with the mean age being 56 (±16) years, and the majority being males (64.5%) [23]. Cerebrospinal fluid (CSF) typically shows increased protein concentration with a normal white blood cell count [23]. Several mechanisms of GBS have been postulated, and the mechanism is considered to be an inflammatory cytokine surge produced in response to COVID-19 infection resulting from the activation of CD4 T cells [24]. This explains the indirect damage to the neuronal pathways that manifest diffuse muscle weakness [23].

A small case series in Italy described five patients with COVID-19 GBS. Three patients presented with a pathognomonic increase in CSF protein. All the patients reported resolution of symptoms after being treated with immunoglobulins [14]. Another meta-analysis of 64 studies demonstrated that two-thirds of the patients improved after treatment with immunoglobulins [23]. The majority of the patients (53.2%) had been treated on an inpatient basis, and some patients (28.7%) had to be transferred to the ICU based on isolation or oxygen requirements. The management options include immunoglobulins, plasmapheresis, steroids, and antivirals. The majority of patients received and recovered from immunoglobulins (77.66%).

Mental fatigue and inattention are also reported more frequently in COVID-19 patients [14]. 59% of hospitalized patients had neurocognitive impairments post-recovery, affecting verbal memory (38%), verbal fluency (35%), and executive function (6.1%). Neurocognitive impairments are associated with severe COVID-19 infection, including those who require mechanical ventilation. Minimizing the risk factors is as important in the prevention of such impairments. Providing neurorehabilitation programs

for treating sleep problems, improving alertness, and behavior problems may aid in the recovery of such neurological consequences in patients with COVID-19 [14].

Pregnancy and neonatal complications

Pregnancy is a state of immunosuppression that predisposes women to viral infections [25, 26]. Prior research suggests that coronaviruses in pregnant women place them at a higher risk for severe illness, morbidity, and mortality compared to the general population. Specifically, SARS during pregnancy is associated with a higher risk of spontaneous miscarriage, preterm birth (the most common), intrauterine growth restriction, admission to ICU, renal failure, and disseminated intravascular coagulopathy [27, 28]. The clinical scenario of these infections in this cohort can be deadly; however, with regard to COVID-19, the prognosis seems to be less severe. Nevertheless, they are a fragile cohort that needs to be managed with caution due to fatal complications in the mother and child [29].

Vertical transmission from the mother to the fetus is a major concern of COVID-19 [30]. Stillbirths, miscarriages, and intrauterine growth restriction are some of the adverse events. Early symptoms of infants with infected mothers include abnormal liver function, thrombocytopenia, gastrointestinal hemorrhage, multiple organ failure, and refractory shock.

The main receptor that COVID-19 uses to enter a cell is the ACE-2 receptor, found in the syncytiotrophoblast, cytotrophoblast, and villi of the placenta, ovaries, uterus, and vagina [31, 32]. Further evidence of vertical transmission comes from serological analysis of the placenta and the neonate. Studies have found the presence of both IgM and IgG SARS-CoV-2 antibodies in neonates. IgG antibodies crossing the placenta is an established phenomenon; however, the transfer of IgM cannot be explained by placental transfer [33]. These IgM antibodies do not appear until three to seven days after infection. It is surprising to note that reverse transcriptase-polymerase chain reaction (RT-PCR) tests of these infants were negative for COVID-19. One study investigated immunological studies in 51 neonates born to COVID-19 infected mothers. Results revealed that none of the babies had significant changes in cellular or humoral immunity including differentiation of lymphocyte subsets [34]. Nevertheless, the immunological description suggests fetal exposure to COVID-19 in utero [30]. It is uncertain if COVID-19 is transmitted via breast milk. The guidelines recommend that COVID-19 positive women continue breastfeeding with the use of a medical mask to avoid transmission via respiratory droplets.

A retrospective analysis by Chen et al. analyzed the clinical history of nine pregnant women with COVID-19 in China. Results revealed all nine women underwent cesarean section in their third trimester. None of the patients developed severe COVID-19 pneumonia or died. Contrary to the above-mentioned evidence, there was no evidence of intrauterine infection, including amniotic fluid, cord blood, and breast milk samples. The results of this study could have been affected by the small sample size. Moreover, since the study had pregnant women in their third trimester, the transmission of the virus during the first or second trimester may have been plausible. Since all these pregnant women underwent cesarean section, it is not known if vaginal birth may have altered these results. Further research is necessary to establish the exact mechanisms for vertical transmission [35].

A case report by Mohammadi et al. (2020) investigated a rare case of ovarian venous thrombosis in a 26-year-old obese pregnant woman infected with COVID-19 in Iran. The eight-week pregnant woman presented with abdominal pain, nausea, and vomiting for one week. As per hospital protocols, she was tested for COVID-19. Qualitative real-time RT-PCR was positive for COVID-19. A subsequent computed tomography (CT) scan of the chest supported a diagnosis of COVID-19. Due to persistent abdominal pain, ultrasound, and MRI of the abdomen and pelvis were done. Results confirmed the presence of an ovarian venous thrombosis. It must be noted that the patient did not have a family history or personal history, including her prior pregnancies, of thrombosis or clotting disorders. Her obesity, chronic COVID-19, along with prolonged bed rest in the hospital are all risk factors for her thrombosis. Using Doppler ultrasound, it is possible to diagnose the clot; however, CT and MRI are confirmative [36].

A case report from Switzerland of a 26-year-old pregnant woman with COVID-19 had preterm labor and fetal demise at 19 weeks of gestation. Although PCR of maternal blood, vaginal secretions, and urine were negative for COVID-19, the fetal surface of the placenta tested positive. Pathology of the placenta showed areas of inflammation, increased fibrin deposition, and funisitis. It must be noted that fetal tissue was negative for COVID-19 [37].

A study analyzing 15 placentae of COVID-19 infected mothers showed increased maternal vascular malperfusion compared to mothers who were not infected with COVID-19 [38]. Pathological findings of the placenta included fibrinoid necrosis, amniotic membrane arteriole hypertrophy, and decidual arteriopathy. Research also documents intramural and nonocclusive thrombus, villitis, chorioamnionitis, and funisitis [39]. These vascular and endothelial changes are associated with impaired blood flow to the fetus leading to neural inflammation [40]. These results illustrate that COVID-19 can cause vascular and inflammatory changes in the placenta which can have serious effects on the mother and the fetus.

Hematologic complications

During the COVID-19 pandemic, several hematologic complications have been identified among patients.

Blood clotting is a known method of the body to be protective in cell injury. However, many patients infected with COVID-19 have had unusual clotting events. Biswas et al. (2021) have hypothesized that the binding of a spike protein in COVID-19 with the ACE-2 receptor on the endothelial cells of blood vessels may result in the activation of the coagulation pathway and eventual formation of blood clots. Furthermore, a study in Italy consisting of 362 COVID-19 patients attributed high mortality rates due to pulmonary embolism (PE), venous thromboembolism (VTE), ischemic stroke, and disseminated intravascular coagulation. Results revealed that thromboembolic events occurred in 28 cases. Specifically, there were 16 cases of VTE, 10 cases of PE, and eight cases of disseminated intravascular coagulation [41]. Walid (2021) finds similar associations as Biswal et al. (2021), which note that COVID-19 binds to CLEC4M, a receptor that clears von Willebrand factor (VWF) and factor VIII (FVIII). There is limited research in this specific area [42].

Multiple studies have looked at the relationship between COVID-19 patients and intracranial hemorrhage. Mishra et al. (2021) investigated 324 patients who presented with stroke and found that eight of those patients had confirmed COVID-19, and three were at risk. The mechanism behind intracranial hemorrhage is attributed to the activation of cytokine cascade by the virus [43].

Older age, respiratory failure, and non-Caucasian race are risk factors for intracerebral hemorrhages in patients [44]. Furthermore, patients with a prior history of anticoagulation use have approximately a five-fold increased risk of intracerebral hemorrhage [44].

Respiratory tract infection is a known risk factor for the development of PE. One study found that COVID-19 patients that underwent pulmonary CT angiography had an incidence rate for PE of approximately 22%, while another study found corresponding elevated C-reactive protein and D-dimer values [45]. Thus, it can be interpreted that patients with higher levels of inflammation and D-dimer levels are more susceptible to developing pulmonary embolism or vice versa.

Martinelli et al. (2020) looked at a COVID-19 positive pregnant woman who developed a PE. While this young woman had no personal or family history of blood disorders, it was a combination of obesity and pregnancy that put her in a prothrombotic state that resulted in the PEs. These risk factors should be taken into consideration when tailoring antithrombotic prophylaxis and treatment [46].

In a related and much broader study, Fauvel et al. (2020) looked at 2878 hospitalized COVID-19 positive patients and found the following risk factors for PE: male gender, elevated C-reactive protein, and time from symptom onset to hospitalization. On the other hand, the following protective factors were also identified for PE: anticoagulation with therapeutic dose before admission and anticoagulation with prophylaxis dose during hospitalization. Contrary to the findings by Martinelli et al. (2020) obesity was not a risk factor for PE. Furthermore, older age, history of malignancy, smoking, and history of the venous thromboembolic disease also did not have any association with PE [47].

Hypercoagulability is noted in some patients due to abnormalities of the coagulation cascade, causing thrombocytopenia, elevated D-dimer, prothrombin time, fibrinogen, and VWF. This is thought to occur as a result of the inflammatory response, endothelial damage, and cytokine storm, along with the patient's comorbidities. These may result in deep venous thrombosis, PE, ischemic stroke, cerebral venous thrombosis, and peripheral arterial thromboembolism. Using lower molecular weight heparin is also associated with a better prognosis in those with severe infections and elevated D-dimer levels [48].

Cardiovascular complications of COVID-19 infection

Cardiovascular system failure is a reported consequence of COVID-19 infection [48]. Some studies have shown up to 7% of COVID-19-related deaths are a result of myocardial injury [49]. Viral illnesses such as the Middle East respiratory syndrome coronavirus (MERS-CoV) and influenza have been associated with myocardial injury [49]. This primarily occurs through the release of cytokines, hypoxia, or direct myocardial injury, documented by the elevation of cardiac markers (i.e., troponin) [49]. Similarly, the influenza virus has been associated with an increased risk of acute myocardial injury in the first seven days of infection with a ratio of 6.1% for influenza compared to 2.8% for other viruses [49]. Patients with preexisting risk factors for heart disease such as diabetes, obesity, male sex, hyperlipidemia, hypertension, or coronary artery disease may have underlying heart failure which is uncovered by COVID-19 infection [48]. Thus, it can be challenging to determine if heart failure is due to new-onset cardiomyopathy or an exacerbation of a previously undiagnosed heart failure [49].

The proposed mechanism for COVID-19-related cardiovascular diseases is likely through the disruption of immune system regulation, increased metabolic demand, and increased procoagulant activity [49]. Proinflammatory cytokines such as interleukins and tumor necrosis factors are elevated in severe cases of COVID-19 infections [50]. Patients with preexisting risk factors for heart disease such as diabetes, hyperlipidemia, hypertension, or coronary artery disease may have underlying heart failure uncovered by COVID-19 infection [48].

The etiology of heart failure in COVID-19 patients is unclear. On one hand, it could be a direct result of SARS-CoV-2 on the myocardium or it could be caused by hypoxia, volume overload, renal failure, and stress [48]. Few studies have reported Takotsubo cardiomyopathy, which is a type of stress-induced

cardiomyopathy [48]. Most of these cases occurred in women older than 65 years of age. In one case series, an autopsy from 12 confirmed cases of COVID-19 deaths showed SARS-CoV-2 RNA in the lungs of all patients, with five showing high viral titers in the heart. Endomyocardial biopsy showed myocardial inflammation with viral particles [48]. Patients with COVID-19-associated myocarditis present with chest pain, dyspnea, dysrhythmia, and acute left ventricular dysfunction [49]. Electrocardiogram (ECG) abnormalities including ST-segment and T wave abnormalities, T wave inversion, and PR segment and ST-segment depression or elevation have been reported, along with elevation of troponin levels [49].

SARS-CoV-2 has a spike protein that allows it to bind ACE-2 receptors expressed on type 1 and type 2 pneumocytes and other cells which facilitate viral entry [48]. ACE-2 is an inverse regulator of the renin-angiotensin-aldosterone system. Consequently, due to this interaction of SARS-CoV-2 with this system, hypokalemia can occur, which may precipitate an arrhythmia [48]. The most common arrhythmia associated with COVID-19 is sinus tachycardia as a result of fever, hypoxia, hypoperfusion, and/or anxiety [49]. The arrhythmia can lead to underlying cardiac tissue damage; thus, it is important to rule out secondary causes such as direct myocardial injury, myocarditis or acute coronary syndrome.

In the pediatric population, 4–6 weeks post-COVID-19 the development of a multisystem inflammatory syndrome (MIS-C) may occur [51]. MIS-C is a pediatric hyper inflammation disorder associated with severe COVID-19 and its clinical manifestations mimic that of Kawasaki disease (KD) [51]. Although this is a multisystem involvement, it primarily affects the cardiovascular system [51]. This is a new disease manifestation, so the underlying pathogenesis is not fully clear. Current treatment includes immunoglobulin and high-dose corticosteroids [51].

Multisystem inflammatory syndrome in adults presents with tachycardia, tachypnea, hypotension, bilateral conjunctivitis, mucositis, peripheral edema, palmar erythema, and maculopapular rash [52]. These symptoms are identical to KD except for gastric complications, coagulopathy, and shock occurring more with MIS-C [51]. KD is more common in children younger than five years, as opposed to MIS-C which is more common in older children [51]. It is still uncertain whether MIS-C immunological mechanism is similar to the cytokine storm-induced hyper inflammation found in adult COVID-19 as it is usually seen within two weeks, whereas MIS-C occurs between 4 and 6 weeks post-COVID-19 [51].

Dermatologic complications of COVID-19 infection

Although relatively rare, many dermatologic manifestations have been recorded and studied in patients with COVID-19. Bouaziz et al. (2020) investigated 14 patients from France who had confirmed COVID-19 via PCR samples collected using nasopharyngeal swabs. Of these 14 patients, seven had inflammatory skin lesions, specifically exanthema, chickenpox-like vesicles, and cold urticaria. The remaining seven patients had vascular lesions such as violaceous macules, livedo, purpura, chilblain, and eruptive cherry angioma. The pathophysiology of these lesions is unclear; however, it is hypothesized that immune dysregulation, vasculitis, and vessel thrombosis may play a significant role [53].

Freeman et al. (2020) documented 505 patients across eight countries that had been afflicted with COVID-19 or had contact with individuals who had the virus. 318 patients were found to have pernio-like lesions, presenting as painful, pruritic, and/or violaceousacral lesions typically found on the hands and feet, and lasted on average 14 days [54].

An interesting dermatologic finding among two patients from the Middle East was also recently identified. Both patients were female and initially presented with the chief complaint of a skin rash. They had red-purple papules on the fingers bilaterally. One patient also had diffuse erythema on the subungual region of her right thumb. While neither patient presented with any of the typical symptoms of COVID-19, both had confirmed COVID-19 after conducting a required RT-PCR test before travel. It is believed that these findings are the result of COVID-19, with ischemia being the underlying process [55].

Another study looked at seven COVID-19 positive patients in Wuhan, China that had varying levels of limb ischemia. Among these patients, three had underlying conditions of diabetes, hypertension, and coronary heart disease. Furthermore, all seven patients had D-dimer levels that were nearly 20 times the upper normal limit. Although they were started on anticoagulation therapy, the treatment was not effective since five of these seven patients died. Of the remaining two patients, one had improvement with the anticoagulation therapy, while the other had worsening of digital ischemia. The conclusion of this study was to closely monitor patients with digital ischemia and begin anticoagulation therapy promptly [56].

Similar findings have been reported in pediatric populations. At one hospital, 20 pediatric patients were treated for COVID-19 [57]. Of these patients, nine were treated with hydroxychloroquine (HCQ). It was observed that two patients had developed cutaneous involvement at the onset of diagnoses, while one patient developed cutaneous involvement after HCQ treatment during hospitalization. One 8-month-old girl had a rash similar in appearance to roseola which lasted for two days. Another 11-year-old girl had a pruritic maculopapular rash present before hospital admission which lasted for 5 days. Finally, a 17-year-old patient developed a mildly pruritic maculopapular rash on the third day of HCQ treatment. For all three patients, the rash resolved after discontinuation of HCQ. It was concluded that skin rash

may occur in pediatric patients with or without using HCQ for the treatment of COVID-19 [57].

Renal complications of COVID-19 infection

The kidney is one of the most frequent organs affected in patients with severe COVID-19 [58]. Patients with chronic kidney disease (CKD) including those on dialysis or renal transplant patients represent a particularly vulnerable population for COVID-19 [59]. those on dialysis or renal transplant patients represent a particularly vulnerable population for COVID-19 [59].

Early reports have identified CKD as a risk factor for severe COVID-19 with increased mortality rates [59]. A study from the United Kingdom showed patients with a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 and organ transplantation had a higher risk of mortality [59]. In renal transplant patients who are on immunosuppressive (IS) therapy may benefit from a reduction of IS medications [60]. In addition, patients who were receiving in-center dialysis had a higher incidence of community exposure to COVID-19 [59]. The 28-day mortality among patients on dialysis aged >75 years was as high as 31.4% [59].

The kidney is the most prevalent extrapulmonary organ affected in patients with acute respiratory distress (ARDS) [61]. More commonly, acute kidney injury (AKI) is mild to moderate with increasing creatinine level, hematuria, and proteinuria, which is self-limiting in most patients [59]. In severe cases of AKI, dialysis is often required, and it is often seen in severely ill patients receiving mechanical ventilation [59].

The mechanisms resulting in AKI secondary to COVID-19 are multifactorial, including the severity of septicemia, endothelial damage, hypercoagulability, myocardial dysfunction, respiratory dysfunction, drug-induced nephrotoxicity, and the effects of hypoxia and dehydration on renal perfusion [59]. The renal system is highly dependent on the hemodynamic status governed by the respiratory and cardiac systems. This bidirectional concept is known as a cardiorenal syndrome [61]. On the microvascular level, cytokines released in response to inflammation increase vascular permeability and the formation of renovascular microthrombi [61]. This results in intravascular fluid depletion or venous congestion secondary to volume overloading from intravascular fluid therapy [61]. Together these effects may contribute to kidney dysfunction. Patients with CKD with preexisting low renal perfusion are more vulnerable due to hypoxia secondary to ARDS [60].

Both direct viral effects through the ACE-2 receptor expressed on epithelial cells of kidney tubules, and indirect effects could contribute to the development of AKI [58]. Biopsy samples from patients with COVID-19 have shown collapsed glomerulopathy, but the extent to which direct versus indirect tropism associated glomerular injury is still undetermined [59].

Gastrointestinal complications of COVID-19 infection

Patients with COVID-19 may experience GI symptoms like diarrhea (9–34%), nausea and vomiting (7–16%), abdominal pain (3–11%), and loss of appetite [62–65]. Apart from respiratory droplets, fecal-oral transmission is also possible. Considering that stools can test positive for SARS-CoV-2 nucleic acids even when respiratory samples are negative, the preventive management of fecal-oral transmission deserves close attention [63].

In a study of 318 confirmed COVID-19 cases, 61.3% of patients reported a minimum of one GI symptom, with loss of appetite (34.8%), diarrhea (33.7%), and nausea (26.4%) being the most common [66]. Across the board, multiple studies done in multiple countries showed similar manifestations. However, the prevalence of GI symptoms at diagnosis varies across studies, ranging widely from 2% to 57% [64].

Some patients may have abnormal liver function tests or liver injury (14.8–53%) [64, 67]. Critically ill patients with COVID-19 have a higher rate of GI complications than those without COVID-19 (74% vs. 37%) [68]. These patients develop more severe forms of GI complications during their hospital stay such as bowel ischemia, GI bleeding, pancreatitis, Ogilvie syndrome, and severe ileus. These complications are rare and are currently being investigated.

Prior research shows that SARS-CoV viruses share similar cellular entry mechanisms [69]. It is proposed that COVID-19 infects the gastrointestinal tract via the ACE-2 receptor. This receptor is expressed in colonic enterocytes, where it can be found with up to 100-fold higher concentrations than in the respiratory tract [70].

Acute liver injury in patients with COVID-19 is thought to be idiopathic. Transient elevation of serum aminotransferases and impaired markers of liver function have been observed in up to 58% of patients with severe COVID-19 [64]. The exact mechanism is unclear, but it is hypothesized that liver injury may be due to factors such as systemic inflammatory responses and direct virus-related liver toxicity, drug toxicity, microbiome alterations, impairment of gut barrier and progression of preexisting liver disease [64]. Incidence of liver injury in COVID-19 ranges from 2–53%, with hepatitis involving mild to moderate elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) as the most common finding [62, 67, 71].

Guan et al. (2020) demonstrated elevated AST and ALT levels of patients with mild COVID-19 infection and 39.4% of patients with severe disease. Elevated ALT levels were observed in 19.8% of patients with non-severe disease and 28.1% of patients with severe disease [72]. Huang et al. (2020) reported elevation of AST in eight of 13 patients in the ICU compared to seven of 28 patients who did not require care in the ICU [73]. These studies suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19. However, another study

reported that patients without preexisting chronic liver disease were characterized by higher rates of liver injury than non-severe patients [64].

Prospective studies

The pulmonary complications of COVID-19 infection are well known since it is the primary organ to be affected by the virus. Prospective research can further evaluate these complications to identify people at greater risk for infection.

Neurologic manifestations of COVID-19 can lead to short-term and long-term complications. Prospective studies can analyze the pathophysiology and therapeutics of acute cerebrovascular events. Further studies are needed to evaluate the long-term complications, especially the GBS variants that can lead to long-term disability if adequate treatment is not given appropriately. Limited research has been conducted on pregnant women due to ethical reasons. Even though IgM antibodies are found in infants of COVID-19 infected mothers, the long-term complications are unknown. Although investigations in this population are challenging, further research is necessary to understand the behavior of COVID-19 between the mother and fetus.

There is limited evidence for dermatologic manifestations of COVID-19. Further investigation is required to analyze the pathophysiology of dermatologic manifestations and associated histopathological findings. Many patients who suffered hematologic complications as a result of COVID-19 were treated with anticoagulation therapy. The long-term effects of anticoagulation therapy in this population as well as the recurrence of any hematologic complications post-treatment need to be investigated.

The cardiovascular system as a whole is bidirectional with the continuous communication between the respiratory, renal, and cardiovascular systems. With ARDS being the most common complication of COVID-19, the resulting hypoxia affects both the renal and cardiac system resulting in overt heart disease, arrhythmias, myocardial infarction, and acute renal injury. Further research should include screening methods for at-risk individuals with the overall goal of reducing mortality from cardiac complications.

The mechanisms of COVID-19-associated GI complications are multifaceted. These complications are not alarming or life-threatening from what we know thus far. Prospective studies should look into long-term manifestations of COVID-19 concerning preexisting GI disorders (i.e., colon cancer, Crohn's and ulcerative colitis). Further research is required to better understand the fecal-oral viral transmission and the correlation of viral load and severity of GI symptoms. Such research is necessary to uncover the intrinsic relationship of COVID-19 with these gastrointestinal manifestations to develop effective therapeutic strategies.

CONCLUSION

In conclusion, complications associated with COVID-19 infection are vast and affect almost every organ system. These effects can have lasting detrimental effects on the body. It is unclear if extrapulmonary manifestations of the virus are a direct result of the infection or due to a secondary process such as over-exaggeration of immune responses, treatment effects, or ischemia from respiratory tract impairment (Calabres et al., 2020). Given the complexity of this virus, further research is necessary to understand these mechanisms to develop effective therapeutic measures.

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Data Availability

All relevant data are within the paper and its Supporting Information files.

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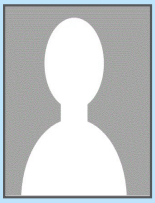

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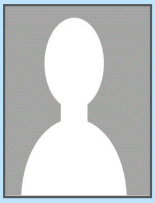

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