Review

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Organ system effects and reinfection of COVID-19: A review

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its effects on the organ systems have been summarized in recent literature with predominant pulmonary characteristics as a hallmark of the COVID-19 virus. Considering its accelerated appearance from Wuhan, China, in December 2019, extrapulmonary effects have been reported globally of SARS-CoV-2 involving the central nervous system (CNS), cardiovascular, gastrointestinal, renal, and hematologic systems; thus, the potential mechanisms, pathophysiology, clinical characteristics, management, outcome, and case reports per organ system are summarized in depth. The authors interpreted articles composed of case reports, case-series, meta-analysis, cohort studies, retrospective studies, and narrative reviews focusing on COVID-19 confirmed cases and their effects on the organ systems. Prevalent clinical organ system complexities include pneumonia, acute respiratory distress syndrome (ARDS), pulmonary hypertension, pulmonary embolism, hypertension, cardiac arrhythmias, myocarditis progressing to fulminant myocarditis, anorexia, nausea, vomiting, diarrhea, liver dysfunction, encephalopathy, encephalitis, meningitis, intracerebral hemorrhage, acute kidney injury, and hypercoagulability causing stroke and disseminated intravascular coagulation (DIC). This comprehensive literature review article will help clinicians and researchers gain insight about SARS-CoV-2 and its diverse effects on multiple organ systems involved, therefore help implement prospective management and preventative measures.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the deadly COVID-19 disease, was first reported in Wuhan, China, in December 2019 and the World Health Organization (WHO) declared a pandemic on March 11, 2020, affecting over 200 countries worldwide. As of November 30, 2020, there have been over 62 363 527 confirmed cases and 1 456 687 deaths to date worldwide.[1] Pulmonary manifestation has been a hallmark of the deadly disease since its development. As the instances increase and more studies are being published, extrapulmonary manifestations affecting various organ systems have been reported. The susceptibility of acquiring SARS-CoV-2 affects all age groups, with organ systems' disease development and severity varying amongst subjects. The elderly population and subjects with underlying disease states have been reported to have a more rigorous disease course with a probability of more than one organ system involvement and increased risk for mortality. This article aims to identify and understand the potential mechanisms and pathophysiology of SARS-CoV-2 affecting the reported organ systems, clinical features, management, and outcomes based on published literature reports.

Methods

This review conducted a thorough search using electronic databases such as PubMed, Google Scholar, and PubMed Central to obtain comparative research studies published from February 2020 to September 2020. Selection of articles depended on keywords such as: "COVID-19," "SARS-CoV-2," "Coronavirus," "Pulmonary," "Pneumonia," "Extrapulmonary," "Cardiovascular," "CVS," "myocarditis," "vasculitis," "Gastrointestinal," "Liver Dysfunction," "Central Nervous System," "CNS," "Encephalopathy," "Encephalitis," "Renal," "Acute Kidney Injury," "AKI," "Renal failure," "Hematologic," "multi-systemic disease," "clinical characteristics," "pathology," "pathophysiology," "infectious disease," "systematic literature review," "literature review," Articles were then

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analyzed and incorporated based on the applicability to the subject of study.

Pulmonary System

Mechanism

SARS-CoV-2 gains viral entry through direct contact with saliva and respiratory droplets via coughing and sneezing, which subsequently binds to angiotensin-converting enzyme 2 (ACE2) receptors; thus, it is imperative to examine the location of these receptors to comprehend the magnitude of its effects, as increased expression of ACE2 is thought to be related to disease severity such as pneumonia, acute respiratory distress syndrome (ARDS), and mortality (Figure 1). The lungs have substantial ACE2 expression present on type II epithelial cells. Pulmonary involvement is primarily due to ACE2 receptor degradation by the binding of SARS-CoV-2 followed by an overwhelming inflammatory response in the lung interstitium and damage to the alveolar space eliciting the systemic release of cytokines, chemokines such as interleukin 1 beta (IL-1B), Tumor necrosis factor alpha (TNF-α), IL-6, and IL-7. Cytokine storm is the pathogenesis known to cause immunologic changes seen in patients infected with this virus. This inflammatory response has the propensity to cause hypoxia leading to respiratory failure and potentially death. Direct endothelium damage seems to play a role in causing massive coagulopathy, constriction of the blood vessels, and inflammation in COVID-19 induced lung injury.[2]

Increased MAS-like (macrophage activating system) activity due to cytokine-induced endothelial damage is evident in many studies regarding COVID-19 induced pneumonia, cytokine storm, and increased ferritin levels can activate the coagulation cascade resulting in thrombosis and small blood vessel diseases affecting the pulmonary system. The combination of endothelial damage and concurrent hypoxia causes an overbearing inflammatory response and activation of the coagulation cascade causing extensive damage to the lung architecture, thereby compromising its respective function.[2]

Clinical characteristics

Mild pulmonary effects of COVID-19 positive patients present with clinical features such as fever, cough, sore

Figure 1. Multisystemic overview and effects of COVID-19

throat, fatigue, and dyspnea, whereas a severe disease course presents with pneumonia, ARDS, shock potentially leading to respiratory failure and multi-organ failure, thus, requiring immediate intensive care unit (ICU) admittance.[2-5] A study found that 20% of the COVID-19 infected patients had a severe disease course requiring ICU admittance; patients under the age of 18 showed a lower mortality rate of 0.3/1000 cases compared to a mortality rate of 305/1000 cases in patients over the age of 85.[2] COVID-19 cases do not have a typical presentation of ARDS such that the compliance of the lungs is maintained and tachypnea that occurs due to hypoxia permits increased volume, decreased levels of carbon dioxide without triggering shortness of breath sensation.[3] Interestingly, hypoxia experienced in hypobaric high altitude environments exhibits the same clinical presentation as COVID-19 patients.[3] In a study conducted by Chen et al, it was found that 17% of COVID-19 patients showed ARDS. In contrast, the other 65% experienced a rapid deterioration of their health and succumbed to their death due to detrimental multi-organ response.[5] Also, findings suggest that the elderly (>65) and preexisting comorbidities such as hypertension and diabetes are predisposing factors causing disease exacerbation to ARDS.[5] Patients during the early stages of the disease do not present with disseminated intravascular coagulation (DIC); instead, this presentation occurs during disease progression commonly seen simultaneously with ARDS.[3] The development of microthrombi in vascular beds can cause a pulmonary infarction, pulmonary hypertension, and hemorrhage.[3]

CT pulmonary angiography of COVID-19 infected patients in the ICU most commonly showed ground-glass opacities located near the lower lobe and peripheral regions of the lungs, with consolidation occurring in several lobules.[4,5] The number of segments of the lungs affected directly reflects disease complexity.[4] To date, chest X-ray (CXR) findings in most cases have shown bilateral consolidation of the lower lobes in 10-12 days following the onset of symptoms.[5] CT scan of the lungs is the screening test of choice, due to its high sensitivity (97%), following a positive reverse-transcription polymerase chain reaction (RT-PCR). In contrast, CXR has shown little diagnostic benefit in COVID-19 affected patients.[3] Ultrasounds are used to observe single or multiple-merging B lines and consolidations situated under the pleura, in either the inferior or posterior regions of the lungs, to detect further development of the disease.[4] Autopsy studies of COVID-19 patients showed significant interstitial pneumonia and extensive damage to the alveolar space resulting in the presence of alveolar macrophages, alveolar edema, and hyaline membranes.[2]

Management

Initial management in any suspected or diagnosed COVID-19 patient includes isolation to prevent disease
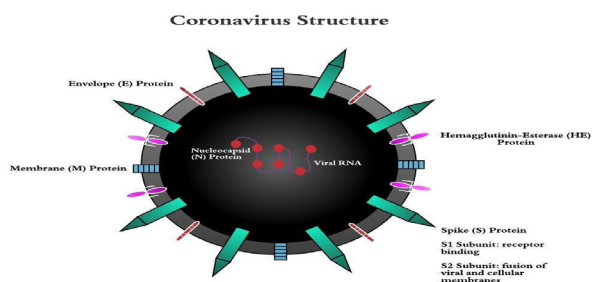
spread to other patients, hospital visitors, and staff.[4] Management is based on the timing of a patient's clinical presentation and the stage of disease progression.[4] Low molecular weight heparins (LMWHs) are administered to all suspected and diagnosed COVID-19 cases regardless of the risk score.[6] A high positive end-expiratory pressure on the ventilator by itself has not shown considerable improvements in COVID-19 patients; however, the combination of proning has led to avid improvement by using gravity as a tool to allow adequate perfusion and oxygenation.[3] Anticoagulants should be administered if the D-dimers are substantially higher (4x) than the reference value in infected COVID-19 patients resulting from inflammation-induced activation of the coagulation cascade.[4] Routine monitoring of D-dimer and lung CT scan is essential during hospitalization.[6] To date, IL-6 inhibitors such as tocilizumab, JAK kinase inhibitors such as baricitinib, and corticosteroids have shown significant improvements in COVID-19 patients.[3]

Case Report

A case report by Lee et al reported a 46-year-old female with a past medical history of hypertension presenting to the emergency department on February 5, 2020, with complaints of cough and fever for two days. The patient recently returned from a trip to Macau seven days ago. Given her travel history and respiratory symptoms, the patient was isolated and tested for SARS-CoV-2, which confirmed positive via reverse-transcription polymerase chain reaction (RT-PCR) of a throat swab. Chest imaging displayed patchy densities in the middle lung field and left upper lobe. The patient was managed with empiric oseltamivir and levofloxacin for pneumonia. On day 14, chest imaging revealed resolving infiltrates of the left upper lobe. The patient made a full recovery and was discharged on day 26 after three consecutive negative SARS-CoV-2 nasopharyngeal swabs (Figure 2).[7]

Cardiovascular

Mechanism

The proposed cardiac pathophysiology of SARS-CoV2 2 involves utilizing the transmembrane ACE2 and the innate immune response system known as the Contact System (CS). CS is linked with various proteolytic defense systems operating in human vasculatures, such as the Kallikrein–Kinin (KKS), the Coagulation/Fibrinolysis.[8,9] Infection of host cells with SARS-CoV-2 requires the expression of both the transmembrane ACE2 protein and the transmembrane protease serine 2 (TMPRSS2) in the same cell type.[10,11] SARS-CoV-2 enters type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes via ACE2 membrane proteins.[12]

In times of oxidative stress, such as with the COVID-19, endogenous molecules named 'Damage-associated molecular patterns' (DAMPs) are released from dying cells. During viral infections, DAMPs initiate defense reactions such as membrane and endosomal Toll-like receptors, which are the primary line of defense for pathogen sensing.[9] During the immune response to infection, the CS's main molecules are Factor XII (FXII), the prekallikrein, and the high-molecular-weight kininogen (HK), which are produced by the liver and can be found in circulation.[9] By activating FXII, DAMPs initiate a cascade of intrinsic coagulation, fibrin formation (microthrombosis), and fibrinolysis, resulting in increased D-dimer levels.[9] In a powerful positive feedback loop, KAL activates more FXII, and the intrinsic coagulation pathway may begin.[9] The fibrinolytic pathway is also influenced by KAL, which activates plasminogen into plasmin, ultimately leading to fibrin degradation and elevated D-dimer levels.[13] The FXII induced coagulation pathway is associated with pathologic thrombus formation, and COVID-19 has been characterized by coagulopathy based on the reported lung autopsies and the high level of D-dimers.[9-11,13,14]

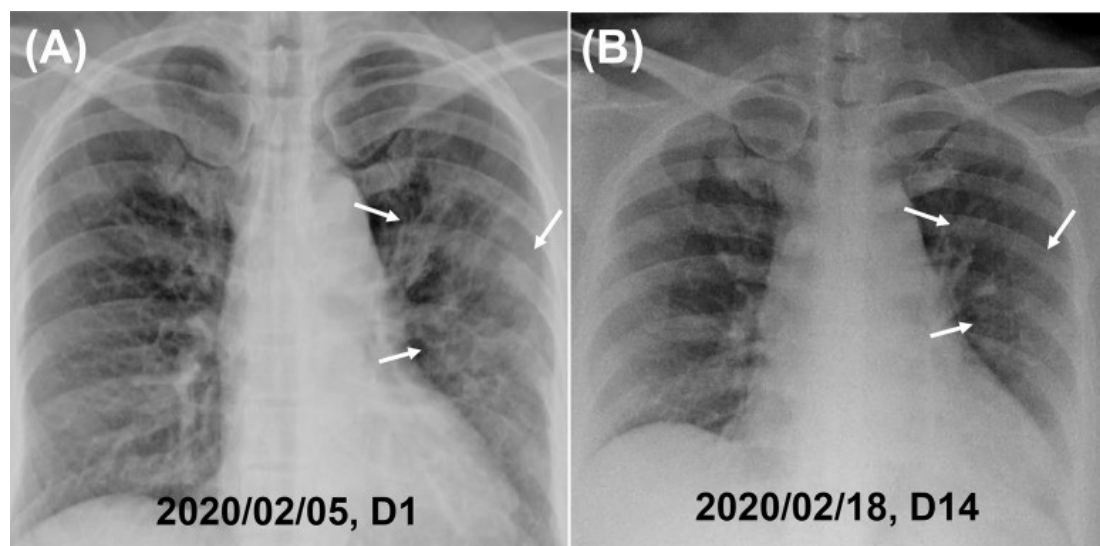There seems to be a relationship between hypertension

Figure 2. Chest imaging displays increased pulmonary infiltrations, notably in the left upper lung field. (B) Chest imaging on day 14 with the resolution of the pulmonary infiltrations. Note: Chest radiograph from a confirmed COVID19- subject, consideration of Lee et al.[7]

and COVID-19 that may relate to the role of ACE2, making it useful in predicting potential pathology. ACE2 is specifically highly expressed in pericytes, leading to microvascular dysfunction that could explain the greater risk for acute coronary syndromes.[10,14] Failing human hearts have an upregulated ACE2 expression, which may lend credibility to the virus's higher infectivity and higher mortality in heart failure patients.[9,10] Moreover, cellular entry of coronaviruses through ACE2 has implications for vascular instability and hypotension and increased mortality of infected patients with pre-existing hypertension.[9,12,13] These findings also have therapeutic implications, as inhibition of viral entry may prevent or attenuate COVID-19.

Clinical characteristics

The clinical association of respiratory manifestations with COVID-19 has been primarily studied; however, the viral impact needs a more robust examination. Patients with pre-existing cardiovascular disease have shown to have higher complication and fatality rates associated with SARS-CoV-2 infection.[11] The most prevalent cardiac complications in patients with COVID19 infection include hypertension, cardiac arrhythmia, fulminant myocarditis, and heart failure.

The clinical presentation of COVID-19 in symptomatic patients is analogous with symptoms like fever, cough, shortness of breath, fatigue, diarrhea, and myalgia. The cardiac manifestations have been quite extensive and are discussed regarding each presentation. Patients infected with COVID-19 have reported having higher cases of either new-onset hypertension or episodes of hypertension in patients with a past medical history of hypertension. In a study conducted by the China CDC, 44 672 patients were analyzed and 12.8% presented with a prior history of hypertension, with a 39.7% mortality in these patients. However, the study reported that due to the higher prevalence of hypertension in older patients; the results were not indicative of hypertension being the cause of increased susceptibility to COVID-19. Also, patients with hypertension did appear to progress to a more severe form of the disease, even though patients with ARDS presented with a higher risk of disease progression.[11]

The impact of SARS-CoV-2 infection on the myocardium has been shown to accelerate myocardial injury and inflammation and activate the cytokine system.[12] All of these actions have predisposed patients to cardiac arrhythmias, including atrial fibrillation, tachyarrhythmias, ventricular fibrillation, and conduction block.[12] Additionally, some patients have presented with chest pain and palpitations before developing respiratory systems.[12] The mechanism of how SARS-CoV-2 causes myocardial injury is still being studied. However, the suggested mechanism includes systemic inflammation causing direct damage to cardiomyocytes, interferon related immune response, hypoxic damage to the myocardium, and cytokine storm

related damage.[12] Additionally, a study that observed 187 patients with COVID-19 displayed 27.8% of patients with myocardial injury, leading to cardiac arrhythmia and conduction abnormalities.[13] The study concluded that the onset of arrhythmias was directly correlated with an increase in -terminal pro-B-type brain natriuretic peptide (NT-ProBNP) levels, suggesting a relationship between arrhythmias and acute myocarditis.[13]

The progression of myocarditis to fulminant myocarditis has been observed in some patients. The development of atrial and ventricular arrhythmias can lead to severe necrosis in patients presenting with cardiogenic shock and fulminant myocarditis.[12] This occurrence can potentiate new re-entry points in the electrical circuit and lead to atrial and ventricular fibrillation.[12] A case study was conducted on a 63-year-old COVID-19 confirmed patient in China presented with complicated pneumonia and cardiac manifestations.[15] Laboratory examination on this patient showed high troponin I up to 11.37 g/L, elevated MYO myoglobin and NT-ProBNP levels, and increased IL-6 levels up to 272.40 pg/mL.[15] On echocardiogram, this patient displayed an enlarged left ventricle and decreased left ventricular ejection fraction (LVEF).[15] The line chart that emphasizes the effect of myocardial injury in this patient is shown below in Figure 3 for his admission duration.[15] The study concluded that COVID-19 patients could develop severe cardiac manifestations related to the myocardial injury that can significantly increase mortality rates (Figure 3).[15]

Lastly, the association of heart failure with COVID-19 has been prominent in many studies. Most patients diagnosed with COVID-19 displayed high serum creatine kinase and lactate dehydrogenase (LDH) levels indicating possible injury to the myocardium.[16] In a recent study of 191 patients in Wuhan, 23% of COVID-19 patients presented with heart failure.[16] Although 30% of these patients had a prior history of hypertension, and 19% of patients had diabetes, heart failure was the third most common comorbidity.[16] Additionally, 52% of non-survivors due to COVID-19 had heart failure, further emphasizing severe disease progression with heart failure.[16] Evidence of myocardial injury was prominent in the elevated biomarkers high-sensitivity cardiac troponin I levels and NT-proBNP.[16] The need for intense ICU care is directly associated with patients who present with elevated cTn1 and NT-proBNP levels to delay the progression of severe disease.[16] This can be achieved with frequent patient monitoring, daily laboratory exams, and symptomatic management.

Management

The current management of COVID-19 has mainly been supportive care with no approved treatment. Patients with preexisting cardiac-related comorbidities, such as hypertension and diabetes, are at an increased risk for deterioration of a COVID-19-related infection; these
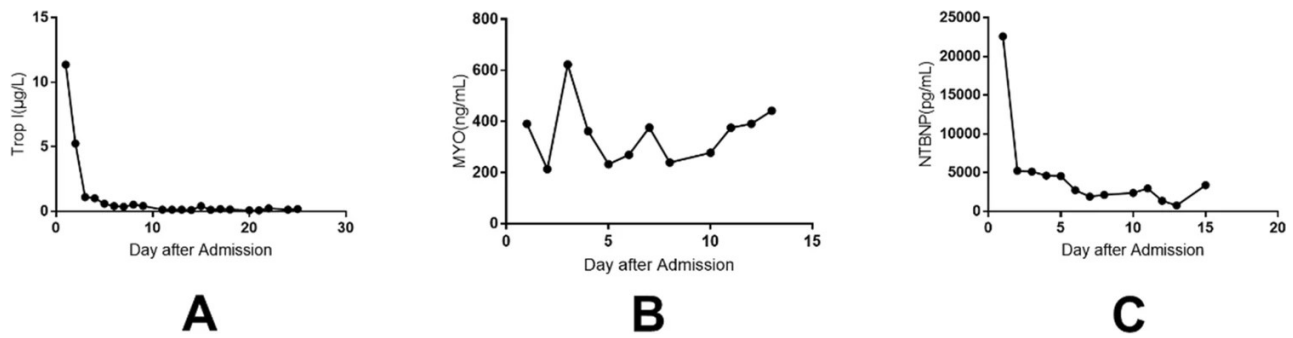
Figure 3. A line chart depicts myocardial injury markers, Trop I troponin I, MYO myoglobin, and NT-ProBNP N-terminal brain natriuretic peptide. Throughout admission, Trop I and NT-ProBNP decreased gradually, but MYO stayed elevated.[15]

patients are usually prescribed ACE inhibitors, which leads to a higher number of ACE receptors prevalent in the bloodstream. The hypothesis by health professionals states that the excess ACE receptors could be the reason for these patients to have an increased risk of contracting COVID-19. However, it is still unknown whether it is the use of ACE-inhibitors or hypertension alone that leads to the progression of the disease, and due to this uncertainty, patients are recommended to continue prior medication regime.[17]

Patients that suffer from an acute myocardial injury and are infected with COVID-19 are assessed based on their hemodynamic stability, thus fundamentally undergo various tests and procedures; cardiac biomarkers such as troponins are initially screened, and patients are subsequently admitted for further monitoring.[18] A rapid rise in troponins, a decline in hemodynamic stability, shock, ventricular tachycardia, or ventricular fibrillation requires management with anti-viral, anti-cytokine, and experimental therapies.[19] A focused transthoracic echocardiogram is done to assess if the LVEF is less than 55% unless the patient has a rapid decline in instability.[19] Patients with an LVEF of less than 55% are assessed for cardiogenic shock or ventricular tachycardia/ventricular fibrillation.[19] LVEF greater than 55% is managed with supportive care and monitoring.[19] Patients have further cardiac tests deferred and discharged appropriately with cardiac follow up scheduled. These patients are diagnosed with the placement of a pulmonary artery catheter and values recorded, lab values with serum lactate and central venous saturation monitored, as well as possible cardiac MRI/CT with or without a cardiac biopsy.[19] Management of these patients constitutes of vasopressors, inotropic agents, as well as mechanical ventilation, if needed.[19]

No specific therapy has shown clear signs of efficacy in these patients. In addition, many of the treatments have shown signs of cardiogenic side effects. Patients have shown improvement in COVID-19 symptoms with the combined use of azithromycin and chloroquine.[18] However, azithromycin has shown signs of QTc prolongation and progression to ventricular arrhythmia in some patients.[18] Chloroquine, and the potent synthetic form hydroxychloroquine, have led to cause

atrioventricular block and QTc prolongation.[20] Patients are closely monitored with an electrocardiogram (ECG) and electrolytes (including magnesium and potassium) to limit further complications.[20] This combination therapy, including calcium channel blockers or beta-blockers, has developed sinus bradycardia with possible hypoperfusion and syncope.[20]

Another therapeutic regime consists of lopinavir/ritonavir combined with ribavirin. Lopinavir/ritonavir has shown the ability to cause atrioventricular block and possibly, torsades de pointes. In addition, lopinavir/ritonavir, a CYP3A4 inhibitor, interacts differently with various drug metabolites, increasing the risk of rhabdomyolysis due to enhancing levels of statins. Conversely, ribavirin does not have any cardiogenic side effects; however, it can increase lopinavir/ritonavir levels, which is directly cardiotoxic.[21]

Furthermore, other medications being used for COVID-19 symptoms that can cause cardiogenic side effects are methylprednisolone, interferon, remdesivir, and tocilizumab. Methylprednisolone has shown to cause fluid retention and hypertension in the patients. During the SARS-CoV-1 outbreak in 2002-2003; patients showed higher levels of viral particles in their system directly related to the use of methylprednisolone. Interferon has been shown to harm cardiac myocytes and cause conduction abnormalities directly. Remdesivir was used to treat the Ebola virus and caused bradycardia in a patient. The use of remdesivir with COVID-19 and possible cardiogenic side effects is unknown. Lastly, tocilizumab has shown to cause hyperlipidemia in several patients, which can worsen or lead to an acute coronary syndrome in predisposed patients.[22]

Case report

A case report conducted by Zeng et al summarized the first case of COVID-19 associated myocarditis on April 10, 2020. A 63-year-old male presented to the hospital with a complaint of fever, productive whitish sputum, shortness of breath, and sensation of his chest tightening upon exertion. The patient did not have a past medical history of cardiac ailments. He was a smoker and had allergies producing cough upon exacerbation. The patient had

newly traveled to Hubei province, China. Upon admission, the patient was confirmed for COVID-19 via sputum testing. Chest imaging exhibited ground-glass opacities characteristic of viral pneumonia. Cardiac biomarkers of injury were present with elevation in troponin I (11.37 g/L), myoglobin (390.97 ng/mL), NT-BNP (2 2600 pg/mL). ECG demonstrated sinus tachycardia but no ST-segment variations. An echocardiogram exhibited left ventricular enlargement, which a decreased LVEF of 32%, further complicated via elevations in pulmonary pressures (44 mm Hg). The hematologic analysis showed elevated alanine transaminase (97 U/L) and creatinine (157 μmol/L). The patient was diagnosed with fulminant myocarditis, multiple organ dysfunction syndrome, severe pneumonia, and ARDS. The patient was managed according to his numerous diagnosis with fluctuations in his disease state but developed a secondary infection on the 29th day and succumbed to his condition on the 33rd day of hospitalization.[15]

Gastrointestinal
Mechanism
SARS-CoV-2 utilizes the host ACE2 and TMPRSS2 for entry into the host cell.[23] TMPRSS2 is thought to be responsible for cleaving the S-Spike from SARS-CoV-2, facilitating fusion and access into the host cell.[24] In addition to being expressed in the lungs, ACE2 and TMPRSS2 are also expressed in the gastrointestinal tract and small intestine.[3,23] Structural studies indicate ACE2 receptors in the upper esophagus, liver, and colon.[25] Not only ACE2 receptors were located in multiple organs throughout the gastrointestinal tract, but they were also found to have significantly increased expression.[3] Ong et al. suggest that the increased expression of ACE2 receptors within the enterocytes specific to the ilium and colon may result from the increased affinity of SARS-CoV-2 to these receptors.[26] SARS-CoV-2 RNA has been isolated from patients' stools, indicating potential fecal-oral transmission and a more significant role of gastrointestinal involvement than initially anticipated.[3,24,27] The exact clinicopathological mechanism by which diarrhea, the main gastrointestinal symptom of SARS-CoV, is not fully understood; however, typical viral changes to intestinal permeability potentially causing intestinal malabsorption are thought to be the cause.[3]

As a consequence of the prothrombotic state after COVID-19, microemboli may obstruct hepatic vasculature resulting in hepatic injury. Hepatic injury may also pursue as adverse effects of medication used to treat COVID-19. Remdesivir, hydroxychloroquine, chloroquine, ribavirin, lopinavir/ritonavir, and oseltamivir have been used in the management and inherent treatments of COVID-19, all of which are subject to hepatic metabolism. The mechanism of hepatic injury is unclear, whether primarily due to the SARS-CoV-2 or the adverse effects of therapy.[28]

Clinical characteristics
Overall, the most common gastrointestinal clinical manifestations concerning SARS-CoV-2 are anorexia, nausea, vomiting, and diarrhea.[29] Of these, diarrhea has been reported to be the most prevailing gastrointestinal related symptom, even though gastrointestinal symptoms are thought to represent an atypical presentation of the virus.[30] Mildly elevated transaminase has also been found in a significant proportion of patients, with a potential correlation of a worsening clinical outcome.[29,31] While SARS-CoV-2 is still regarded as predominantly respiratory disease, gastrointestinal symptomatology is becoming more prevalent.[32] Considering viral particles have been shown to shed through feces long after viral symptoms have concluded.[30-32] Lastly, the timeline of severe gastrointestinal symptoms warranting hospitalization has been longer on average than the hallmark respiratory symptoms. Patel et al noted that the time discrepancy between the onset of symptoms and hospital presentation was more prolonged than respiratory symptoms.[31]

Management
Initial management concerning addressing the gastrointestinal symptoms of SARS-CoV-2 would not be specific to the virus. However, instead, it would focus on supportive management.[3] Fecal viral particles have been consistently detected in a majority of patients, even well after they had recovered from respiratory symptoms.[30,31,33] As most gastrointestinal related symptoms related to SARS-CoV-2 are mild; a greater focus is on the potential diagnostic and screening utility of fecal testing for RNA viral particles.[30,31,33]

Case report
A case report conducted by Mackett et al reported a 74-year-old male admitted to the hospital with complaints of diarrhea and vomiting for three days. The patient had a past medical history of quiescent ulcerative colitis and hypertension. He had not had an ulcerative colitis flare-up in 15 years. The patient recently returned from a trip to Scotland one week before the onset of his symptoms. The patient reported episodes of watery brown stools and vomiting occurring three times a day. His sodium levels were 122 mmol/L initially upon admittance and were managed intravenously with 0.9% saline over eight hours. He was discharged within 24 hours once his sodium levels had increased >125 mmol/L. Seventy-two hours later, he was re-admitted with new-onset delirium and functional decline and recurring diarrhea and vomiting. During his admittance, the patient felt feverish and developed a dry cough. The patient was examined for SARS-CoV-2 via throat swab, tested positive via RT-PCR, and was further transferred to the COVID-19 cohort ward. The patient was managed via 1.5 L fluid restraint, normalizing his sodium levels within three days. The patient made a full recovery and was discharged after 72 hours.[34]

Central nervous system

SARS-CoV-2 has been shown to cause central nervous system (CNS) and peripheral nervous system (PNS) disturbances; to date, common symptoms include headaches, dizziness, seizures, decreased awareness, and ataxia.[35-37] More serious CNS manifestations include cerebral vascular events such as acute ischemic stroke, intracranial hemorrhage (ICH), and cerebral venous sinus thrombosis.[35-38] In addition, encephalopathy, acute necrotizing encephalopathy (ANE), encephalitis, cerebral edema, vasodilation in the meninges, and acute demyelinating lesions are also neurological disturbances seen in COVID-19 patients.[38,39] The possible mechanisms causing these neurological complications are hypoxia, disruption of ACE2, immune-mediated responses, hypercoagulability, and trans-synaptic transfer.[40,41]

Mechanism

In response to SARS-CoV-2, the body kick starts a strong immune-mediated reaction in an attempt to eliminate the foreign agent from causing additional harm; however, the protective intention of the immune-mediated response to infection leads to further damage. The CD8+ T cells, Th1-Th2, eosinophils, specific antibody levels (IgM and IgG), cytokine storm, and positive acute phase reactants such as C-reactive protein (CRP) and ferritin, and an increased neutrophil to lymphocyte ratio (NLR) are the immunological changes noted in COVID-19 patients.[40,42] Autopsy brain studies of COVID-19 patients showed markedly increased levels of cytokines, interferon gamma (IFN-y), T-cells, monocytes, and macrophages confirming viral entry into the CNS.[40] In addition, pro-inflammatory markers such as cytokines and chemokines were significantly increased in multiple cohort studies reflecting disease severity.[40] Th1 and Th2 responses are evident in COVID-19 patients due to the increased levels of IL6, IL2, IL7, IL10, granulocyte stimulating factor, IFN-y, and TNF.[40] Viral infections are known to access the brain via disruption of the blood-brain barrier; the probable mechanism of SARS-CoV-2 entering the CNS is due to the presence of ACE2 receptors found on the endothelium of the blood vessels; the presumably binding of SARS-CoV-2 to ACE2 receptors on the endothelium destroys the protective function of the blood-brain barrier and blood-CSF barrier, allowing the virus and the activated inflammatory mediators and cytokines such as monocytes, macrophages, interferons, interleukins and chemokines to hematogenously enter the CNS.[24,38,41,43-45] This increased permeability of the blood-brain barrier and an overwhelming cytokine storm results in COVID-19 induced viral encephalitis, acute necrotizing encephalopathy, and mortality.[3,38,41,43] Expression of ACE2 is high in some regions of the brain such as the piriform cortex; other areas of the human brain such as the posterior cingulate cortex, middle temporal gyrus, inhibitory and excitatory neurons, as well as oligodendrocytes and astrocytes also consist of ACE2 receptors but with lower expression than piriform cortex.[24] A study conducted by Qi et al identified ACE2 and TMPRSS2 expression in the human brain's substantia nigra and cortex; the Gene Expression Omnibus (GEO) database indicated that this expression exists in the precursor cells of the oligodendrocytes and the astrocytes of these specified brain regions.[24]

COVID-19 induced pneumonia and severe respiratory distress can cause cerebral hypoxic events leading to neurological complexities; systemically, hypoxic events result in metabolic acidosis resulting in additional intracellular accumulation of lactic acid, increased free radicals, and decreased ATP production of neuronal cells.[41] Decreased oxygen in the blood causes intracranial blood vessels to dilate; in doing so, the neuronal cell tissue fluid composition increases causing swelling of the neurons, interstitial brain edema, encephalopathy, and injury.[41,43,46]

Clinical characteristics

Patients with decreased mental status, hypertension, malnutrition, and other pre-existing medical conditions and the elderly are at greater risk for exhibiting altered levels of consciousness when infected with COVID-19.[47] Patients with pre-existing neurological conditions before a COVID-19 infection are more likely to have encephalopathy during the earlier stages of the disease course.[47] Patients with altered mental status due to COVID-19 have increased levels of IL-6, IL-8, IL-10, and TNF-α.[47] Besides, electrolyte imbalances due to metabolic, endocrine, renal, and liver dysfunction also increase the chances.[47] Cerebrovascular events in COVID-19 patients with preexisting medical conditions are at a higher risk of experiencing further cerebrovascular related complications.[41,47] There are many risk factors associated with COVID-19 induced strokes; subjects with an average age of 71.6, hypertension, diabetes, increased CRP and D-dimer, neutrophils, WBCs, and a history of cerebrovascular events are more likely to have a severe disease course.[41,47] A study found that five patients who had a stroke during an exacerbated COVID-19 infection also had increased D-dimers, abnormally decreased number of platelets, and multi-systemic failure.[47] New findings from a study conducted in the USA indicated that even patients younger than the age of 50 had a likelihood of experiencing a stroke during a COVID-19 infection.[47]

ANE has been seen in COVID-19 infected patients in response to an induced cytokine storm and subsequent damage to the blood-brain barrier.[48-51] ANE is commonly seen in children; however, this is also evident in COVID-19 infected adults.[49] CT scan of the brain shows symmetric, multifocal lesions in the thalamus, cerebral white matter, brain stem, and cerebellum.[49,51]

COVID-19 induced ICH is presumed to be due to the binding of SARS-CoV-2 to ACE2 receptors on the endothelial cells of blood vessels.[49,50,52] Decreased

expression of ACE2 receptors due to its degradation by COVID-19 can compromise the renin-angiotensin system's functionality, disrupting the CNS and PNS system via dysregulation of blood pressure causing intracerebral hemorrhage.[49,52] A retrospective case series conducted by Benger et al on five subjects between the ages of 41 and 64 infected with COVID -19 found that all had developed ICH, on average 32 days after the onset of their disease course; all patients had underlying comorbidities, with hypertension being the most prevalent.[52] Also, all COVID-19 patients had multiple organ involvement before the development of ICH.[52]

Patients that developed meningitis and encephalitis due to COVID-19 had clinical characteristics of altered consciousness, generalized convulsions, and nuchal rigidity. [53] A case study was conducted on a patient with meningitis amid a COVID-19 infection showing signs and symptoms of encephalitis and having inflammation in the hippocampal region and the right mesial lobe on brain imaging.[48,53] Cerebrospinal fluid was tested to rule out HSV and VZV infections; these differential diagnoses were ruled out due to the absence of HSV and VZV antibodies, confirming its occurrence due to RT-PCR positive COVID-19.[53] It is suspected that the virus's neurotropic effects increase following the immune system's disruption due to the SARS-CoV-2- ACE-2 binding complex activity.[54]

Management

Management for COVID-19 is rapidly changing as there is no definitive treatment available due to its novel nature. However, many supportive therapies have been administered for symptomatic relief; thus, antiviral, anti-inflammatory, and subjective antithrombotic drugs have been the mainstay of treatment.

In COVID-19 patients, chloroquine and hydroxychloroquine have been used for management; it is crucial to consider the CNS drug permeability before drug administration as the level of penetrance differs in non-COVID-19 patients versus COVID-19 patients due to a weakened blood-brain barrier in the latter population, allowing greater concentration of the drug to access the CNS potentially causing more harm than good. Of the two antimalarial drugs, hydroxychloroquine has increased CNS penetrance and should be administered with caution. Also, 71 clinical trials have tested hydroxychloroquine in conjunction with baricitinib (Olumiant) to observe its anti-inflammatory effects. Studies have confirmed that the combination of these drugs for 10-12 days provided symptomatic relief, a decrease in SARS-CoV-2 titer noted in nasopharyngeal swabs and laboratory testing, and decreased IL-6. Another drug that has been tested in clinical trials for potential administration to COVID-19 positive patients is Ruxolitinib, a JAK inhibitor; this drug has reduced penetrance in the CNS.[55]

Another drug combination that has been widely used in COVID-19 patients is lopinavir and ritonavir, which also has decreased CNS drug permeability. IL-6R antibody, tocilizumab, and the modified nucleoside remdesivir also have low CNS penetrance. An RNA-dependent RNA polymerase inhibitor is currently being tested in multiple clinical trials to observe the drug's efficacy in COVID-19 patients; to date, it shows a low CNS penetrance. An antibiotic, azithromycin, has undergone 17 clinical trials and has demonstrated sufficient CNS penetration.[55]

It has been determined that SARS-CoV-2 binds to ACE2 receptors on the endothelial cells, which causes a massive inflammatory response increasing blood vessel constriction, leading to end-organ damage and stroke; ACE2 recombinant therapy is a potential treatment for COVID-19 related stroke.[45]

Although there are several medications taking precedence for the management of COVID-19, drug interactions need to be reckoned with. Numerous COVID-19 cases often have previous medical conditions. Hence, careful past medical history and medication use are crucial in the management process; azithromycin, corticosteroids, plasma exchange, tocilizumab, remdesivir, ribavirin, lopinavir/ritonavir, favipiravir, hydroxychloroquine, and chloroquine are currently being extensively examined.[56]

The drug duo lopinavir and ritonavir and the antibiotic azithromycin commonly interact with stroke-related therapies such as antihypertensives, antiplatelets, statins, and anticoagulants. Azithromycin, a 50s ribosome protein synthesis inhibitor, interacts with anticoagulants, statins, and antiarrhythmics. Ribavirin also interacts with anticoagulants and has the propensity to cause neuropathy. Methylprednisolone, an anti-inflammatory drug, interacts with anticoagulants and can cause delirium. Chloroquine and hydroxychloroquine are known to cause neuropsychiatric side effects as well as ataxia and seizures. Interferon, responsible for activating the immune system, typically causes neuropsychiatric effects, retinopathy, and neuropathy. Tocilizumab, an IL-6 inhibitor, may increase the metabolism of statins.[56] Knowing the drugs' mechanism and several drug interactions can help find suitable treatments for COVID-19 patients with diverse comorbidities.

Case report

A case report conducted by Lameijer et al reported an 81-year-old male with a past medical history of monoclonal gammopathy of unknown significance presented to the hospital on March 22, 2020, with a complaint of fever, back pain, and malaise for seven days. The patient was tested for SARS-CoV-2 and confirmed positive via RT-PCR. Extensive bilateral consolidations were observed via chest imaging.[57] The patient was further managed with LMWH dalteparin 2500 IU subcutaneously and chloroquine orally with an initial loading dose of 600 mg, accompanied by 300 mg two times a day. On the fifth day following his admission, the

patient's disease course further progressed, prompting admission to the ICU where intubation and ventilation were implemented due to respiratory insufficiency. Once discontinuing all sedatives, an abnormal breathing pattern was observed, and the patient was not responsive. For brain imaging, a head CT was conducted, which displayed prominent ischemia bilaterally, further complicated by the hemorrhagic transformation (Figure 4). Brain edema in the vascular region of the MCA (middle cerebral artery), PCA (posterior cerebral artery), and superior cerebellar arteries bilaterally was also present. After discontinuation of all therapies, the patient had succumbed to his disease.[57]

Renal
Mechanism
In recent literature, the SARS-CoV-2 is reported to have direct interaction with the ACE2 receptors. The ACE2 protein is the primary binding site for SARS-CoV-2, expressed much more in the kidneys than the lungs.[58] There are several cells within the kidney where ACE2 is expressed and co-localizes with an ACE, such as the proximal tubule's brush border apical membrane. It is also noted that there is decreased ACE2 expression in the podocytes.[58,59] Several factors can alter the expression of ACE2 receptors; for instance, it is presumed that the use of RAAS inhibitors may change the expression of ACE2, which may be responsible for the disease virulence.[60,61] Initially, the virus could enter the kidney by invading the
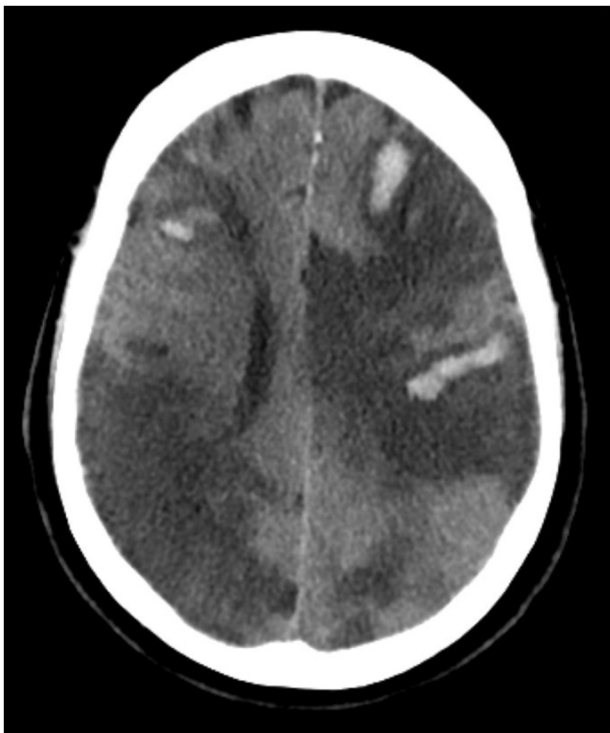

Figure 4. CT-Scan imaging of the brain displays dispersed ischemia bilaterally in various vascular regions with hemorrhagic transformation. Note: CT Scan image of a confirmed COVID19-subject, consideration of Lameijer et al.[57]

podocytes and gain access to the tubular fluid where it will subsequently bind to ACE2 in the proximal tubule.[58] Also, a potential risk factor that has been proposed is the infectivity caused by the interaction of the SARS-CoV-2 with ACE2 receptors.[58,60]

ACE2 is present in several cells in the kidney, such as proximal cells of the brush border, podocytes, epithelium of the Bowman's capsule, collecting ducts, and mesangial cells.[3,58] Regarding COVID-19 induced renal injuries, a frequent abnormality of mild-to-moderate proteinuria is noted, which is mediated via several mechanisms.[3,59] IL-1β, IL-8, IFN-γ, and TNF-α on laboratory reports collected from patients in the ICU reflected higher levels.[3] Thus, these inflammatory markers reflect the proposed mechanism of cytokine storm in COVID-19 patients; thus, this is comparable with sepsis-associated acute kidney injury (AKI), suggesting an overwhelming inflammatory response leading to kidney injury.[3] Alterations in renal hemodynamics can cause further dysfunction. Although AKI is not common in patients with mild-to-moderate COVID-19 disease (5%), it is vital to study the mechanisms and manifestations to potentially prevent or reduce renal complications arising amid a severe COVID-19 infection.[3,59]

Clinical characteristics
Patients with COVID-19 may have various renal dysfunction levels, characterized by increased blood urea nitrogen (BUN), creatinine, proteinuria, and renal structural changes.[62,63] A study consisting of 59 patients with COVID-19 found that 34% of patients had excessive albumin levels in urine on the first day of admission.[62] Also, 63% of patients presented with proteinuria during their stay in the hospital.[62] These findings suggest the presence of renal impairment before or at the moment of admission.[62] BUN was also found to be elevated in 27% of the patients, and more importantly, two-thirds of the patients who died presented with increased BUN and serum creatinine over 200 μmol/L.[62,63] Kidney CT scans showed the density was in the range of 19.5–34.97 HU, significantly lower than the value in patients without kidney disease (i.e., 35 HU); these results indicate that inflammation and edema of the renal parenchyma may occur in patients with COVID-19.[62]

Moreover, patients with an elevated baseline serum creatinine demonstrated a higher leukocyte count and lower lymphocyte and platelet counts.[34] Also, coagulation pathway abnormalities, including prolonged activated partial thromboplastin time and higher D-dimer, were more common in patients with elevated baseline serum creatinine.[34] The percentage of patients with increased procalcitonin, aspartate aminotransferase, and lactose dehydrogenase was also higher in patients with elevated baseline serum creatinine.[34] Additionally, it is reported that the gap between peak and baseline serum creatinine was also much more significant in patients with high baseline

serum creatinine.[34] Recent autopsy data demonstrated that tubular epithelial cell necrosis and degeneration, with interstitial hyperemia, microthrombus, or focal fibrosis, were the main pathological characteristics, while glomerular lesions were less frequent.[34]

Another renal manifestation of COVID-19 is the collapsing focal segmental glomerulosclerosis (FSGS).[34] This finding insinuates that FSGS could account for the heavy proteinuria reported in a notable proportion of patients with COVID-19.[34] The receptor for SARS-CoV-2, membrane-bound ACE2, is expressed on podocytes. However, the polymerase chain reaction for SARS-CoV-2 was adverse in kidney biopsy samples.[34] Still, the technique has a notoriously low rate of detection in nonrespiratory instances (including blood and urine), and the quality of the extracted RNA material is lacking.[34,58] A collapsing FSGS, with or without acute tubular necrosis, may also hamper the course of the hemophagocytic syndrome.[34] This disorder is distinguished by an increased release of a wide range of cytokines.[34,58] In the patient, normal levels of cytokines, particularly IL-6, while inflammation markers were still raised, plead against this hypothesis.[58] However, a potential virus-driven intrarenal cytokine release cannot be excluded.[58] This observation suggests that collapsing FSGS, possibly resulting from a direct viral effect on podocytes, may belong to the vast array of COVID-19–associated renal involvement.[34,63]

Management
Due to the novel nature of COVID-19, a definitive course of treatment is not available. During the management of COVID-19 induced AKI, it is imperative to routinely monitor serum creatinine levels and urine output, and avoid the administration of nephrotoxins in patients who have preexisting kidney abnormalities, which can be exacerbated during a covid-19 infection.[64] In doing so, this promotes more remarkable perseverance of the kidney's structure and corresponding function due to proactive measures taken to conclude a favorable prognosis potentially.[64] Also, clinicians should measure biomarkers that detect kidney damage such as serum creatinine and BUN during hospitalization due to a COVID-19 infection.[63] Past medical history of coronary heart disease, hypertension, and chronic kidney disease should also be examined in the intensive care unit.[63] Risk screening could predict the progression of COVID-19 to minimize patients' in-hospital fatality and improve their long-term prognosis.[63]

An alternative method to manage COVID-19 induced AKI is by assessing the volume responsiveness and tolerance upon admittance and adjusting accordingly; assessment followed by adjustment results in volume homeostasis, regulating volume overload, preventing pulmonary edema, right ventricular overload, congestion, and concurrent AKI. Positive COVID-19 patients are often hypovolemic prompting adequate fluid restoration to prevent AKI.[64]

Inflammatory responses mediated by COVID-19 causing a cytokine storm can directly damage the kidney's architecture due to a robust immune response; this can be treated via hemoperfusion, an extracorporeal therapy.[65,66] This therapy can prevent cardiorenal syndrome (CRS), which has the propensity to cause multi-organ system failure and mortality due to the overwhelming inflammatory response.[65,66] IL-6 is the primary culprit causing excessive production of cytokines in COVID-19 positive patients, which can cause CRS[65-67]; thus, anti-IL-6 monoclonal antibody, tocilizumab, can be administered to manage CRS in susceptible COVID-19 patients.[65]

The heart and kidney are in constant communication with one another; thus, a COVID-19 patient can experience AKI. CRS, cardiomyopathy, and acute viral myocarditis can contribute to congestion of the renal veins, hypotension, and renal hypoperfusion leading to decreased glomerular filtration rate.[65,66] Extracorporeal membrane oxygenation supports both the heart and lungs and can be used in conjunction with continuous renal replacement therapy.[65]

Case report
A case report conducted by Larsen et al reported a 44-year-old African American female with a past medical history of type 2 diabetes mellitus, hypertension, and chronic kidney disease who presented to the hospital with flank pain and progressive cough accompanied by fever and vomiting. The patients' urinalysis was positive for blood and proteinuria when measured upon presentation. Urine protein/creatinine ratio was reported as 3.9 g/g, and serum creatinine of 4.0 mg/dL, which was significantly higher than her baseline of 1.4 mg/dl, last measured six months prior. Physical examination was notable for a temperature of 102°F (38.9°C), blood pressure of 140/90 mm Hg, heart rate of 107 beats per minute, and mild costovertebral angle tenderness. The patient's CXR demonstrated subsegmental atelectasis and a small pleural effusion both on the right lung. Her renal ultrasound was insignificant. The patient was suspected of acute pyelonephritis, sepsis, and COVID-19 during admission. The patient was managed with IV fluids, ceftriaxone, and vancomycin. She was further admitted for a thorough investigation of her AKI. During her admittance, the patient's respiratory status significantly worsened alongside developed confusion requiring management with supplemental oxygen. A repeat CXR was ordered, revealing her respiratory state's progression with new-onset diffuse patchy opacities bilaterally, prompting a change of her ceftriaxone to cefepime. On her eighth day since admission, the patients' renal function also progressively declined, urging management with dialysis. Serum creatinine levels also increased to 11.4 mg/dL during this time, and urine output remained stable. A renal biopsy was conducted, and the patient was also tested for COVID-19 via PCR,

and the results remained pending. The biopsy yielded sclerotic changes, with injury to tubular epithelium most noticeable in the proximal tubules and interstitial edema with inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils. The results for RT-PCR for COVID-19 also returned positive. The patient was diagnosed with collapsing glomerulopathy. She continued management with dialysis, which significantly improved her initial state, and was weaned off oxygen support. Due to her standard urine output of >1 l/d but inadequate clearance, she was discharged from the hospital, and outpatient dialysis was initiated.[68]

Hematologic
Mechanism
In recent literature, the SARS-CoV-2 is reported to exert its effects via direct communication with the ACE2 receptors on various organ cells.[3] As the immune lymphocytes express these receptors, the SARS-CoV-2 can target these cells leading to the possible hematologic effects of the COVID-19 infection.[3] An excessively increased inflammatory response known as a "cytokine storm" may also trigger the lymphocytes' cellular apoptosis, further resulting in lymphopenia.[3]

Hypercoagulability with elevations in D-dimer and LDH and decreases in platelet count has been commonly reported in COVID-19 subjects.[3,69] The hypercoagulable state is thought to occur from the aggravated inflammatory response, which results in increased inflammatory mediators, TNF-α, and IL-6. This action further promotes the synthesis of the acute phase reactants, CRP, amyloid, and fibrinogen.[70] The excessive production of fibrinogen provokes a procoagulant state within the body.[70] However, the mechanism of SARS-CoV-2 induced hypercoagulability to date has not been fully understood, leading to limited treatment options.[69]

Clinical characteristics
During the initial phase of the COVID-19 infection occurring in approximately 3 to 7 days, the hematological effects manifestations are relatively mild.[71] Once the SARS-CoV-2 spread further via the bloodstream, in around 7 to 14 days, lymphopenia is clinically evident with a notable decrease in B lymphocytes and T lymphocytes.[71] The inflammatory and hypercoagulable responses in COVID-19 lead to many thrombotic complexities, such as DIC, ARDS, stroke, heart disease, and pediatric multisystem inflammatory Syndrome (PIMS). A case series study reported by Wang J et al. regarding three cases of COVID-19 subjects summoned prothrombotic complexities as patients who displayed microthrombi on autopsy reports insisting a prothrombotic occlusive etiology preferably over characteristic findings of ARDS.[69,72] These findings were further supported by transient symptomatic clinical improvements when the patients were administered a tissue plasminogen

activator.[72] A study conducted by Rico-Mesa et al also reported hypercoagulable states as etiologies for COVID-19 associated with pneumonia and ARDS by thrombin formation and fibrin deposition observed with bronchoalveolar lavage.[69]

The increased D-dimer levels are regularly observed clinically, with their levels correlating to disease severity.[3,73] A study conducted by Yang Liu et al. reported inflammatory biomarkers such as prothrombin time (PT), fibrin degradation products (FDP), and D-dimer, LDH, CRP, and IL-6 to serve as prognostic values during the disease course.[3,74,75] The study reported PT, FDP, and D-dimer as prognostic values for individuals with increased ICU mortality and antithrombin III (ATIII) as a biomarker for subjects with increased ICU survival.[74,75]

Management
The excessive inflammatory and hematologic effects of COVID-19 may prompt IVIG and LMWH therapy, respectively.[71] The use of IVIG may help decrease the inflammatory mediators responsible for the cytokine storm, and LMWH can help mitigate the hypercoagulable state in subjects.[71] Tissue plasminogen activator has also been reported to benefit patients experiencing pathologic manifestations from hypercoagulable etiologies.[72] Immediate management with anticoagulant therapy can prevent clot and microthrombi formation and reduce end-organ damage.[71]

Pediatric inflammatory multisystem syndrome
The PIMS has clinical presentations similar to Kawasaki disease and toxic shock syndrome and is temporally associated with SARS-CoV-2. Fever, abdominal pain, and cardiovascular involvement are common clinical characteristics. Overall, children seem to be less affected by COVID-19 than adults. In a study conducted by Ramcharan et al, 15 pediatric patients were between the ages of 6.4 to 11.2, with an average age of 8.8. Of these pediatric populations, 93% (14/15) was above the age of 5 years old, while 73% (11/15) were male. Two of 15 patients had previous exposure to COVID-19 two months before the onset of PIMS, and three children had family members with COVID-19 symptoms two months before the onset of PIMS symptoms. All of the patient population experienced a fever that lasted for five days. Gastrointestinal manifestations were seen in 87% (13/15) of the children. In contrast, 8 of the 15 experienced Kawasaki-like symptoms but did not meet the diagnosis criteria. Lethargy was noted in 27% (4/15) of the patients. Abnormal ECG findings were reported in 60% (9/15) of the patients, with six showing normal ECG findings before discharge from the hospital. In 93% (14/15) of the patients, coronary artery involvement was seen in electrocardiography. Coronary artery abnormalities were prominent; dilation or aneurysm was exclusively seen in either the left anterior descending artery, left

main coronary artery, or the right coronary artery. Atrioventricular valve regurgitation was present in 87% (13/15) of the patients during hospitalization. Of the 13 patients that exhibited atrioventricular valve regurgitation, ten patients experienced mitral valve regurgitation. Symptoms resolved two days after the complications. Nine of 15 patients experienced tricuspid regurgitation; of these nine patients, five patients completely recovered with appropriate management after day one of disease.[76]

Management

Ten of 15 patients were treated with IVIG. The remaining five patients were treated with IV methylprednisolone. All patients were treated with antibiotics for five days. Ten patients (65%) required ICU admission. Eight patients required respiratory support, of which four needed mechanical ventilation, and the other four patients required high flow nasal cannula support. Of the patient population that experienced PIMS induced cardiovascular events, 65% (10/15) were managed with an intravenous fluid bolus. Another 10/15 were managed with vasopressors for approximately three days to treat hypotension. Three patients experienced systemic hypotension requiring norepinephrine and vasopressors for management. Nine patients required epinephrine for left ventricular dysfunction. Patients that exhibited refractory hypotension were treated with intravenous hydrocortisone. All patients were prescribed low dose aspirin to prevent coronary artery events.[76]

Discussion

The pathogenesis of the SARS-CoV-2 virus has been evident in causing severe respiratory illness and affecting many other organ systems. Knowing the extent of the damage caused by the virus in affected individuals can help develop vaccines and prevent further transmission. The first step in preventing the virus's spread to other organ systems is determining the virus's incubation period. A study conducted by researchers in China showed a mean incubation period of 5.2 days (95% CI, 4.1 to 7.0), while another study displayed a mean incubation period of 6.4 days (95% CI, 5.6-7.7). Physicians can use the incubation period to adjust screening protocols and therapeutic modalities based on the patient's duration of infection. Based on actual reported data, the set quarantine time is 14 days to ensure appropriate infection and resolution of the virus.[77]

Current diagnostic testing of COVID-19 consists of RT-PCR, real-time RT-PCR (rRT - PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). Although rRT-PCR and RT-LAMP are highly specific, most institutions are using the RT-PCR for diagnostic testing. Current recommendations by the Centers for Disease Control and Prevention (CDC) consist of obtaining laboratory examinations, nasopharyngeal and oropharyngeal swab tests, and RT-PCR assays if

earlier detection is needed. The RT-PCR assays that have been developed focus on three separate regions, such as RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2. Among the three assays, the SARS-CoV-2 RdRp/helicase assay showed the lowest detection rate in vitro, making it highly sensitive and specific. Additionally, the SARS-CoV-2 RdRp/helicase assay did not cross-react with other human pathogenic coronavirus or respiratory viruses, further creating the protocol for its use to confirm a positive result.[78] Based on a clinical study of 4880 cases from one hospital in Wuhan, 53.3% of patients had a positive oropharyngeal test, whereas 71% were positive when using RT-PCR, further expressing the need for confirmatory testing.[79]

To confirm COVID-19 in symptomatic patients with cough, fever, sore throat, etc., obtaining a chest computerized tomography (CT) is recommended, despite the RT-PCR results. In a study based on 1014 patients in Wuhan, China, only 59% of patients had a positive RT-PCR result. However, 88% of those patients had positive findings on their CT scan. These patients presented with possible CT findings of bilateral pulmonary parenchymal ground glass and consolidative pulmonary opacities, with possibly appearing in the periphery of both lungs, as seen in Figure 5. It was further noted that abnormalities on CT scans of patients were more evident in the initial course of COVID-19 infection. In retrospect, patients presenting with signs and symptoms related to specific organ systems are assessed with a CXR, CT scan, ECG, as well as extensive laboratory examinations as needed.[80] The combination of symptomatic clinical presentation, laboratory findings, and imaging results can aid in the early diagnosis and management of COVID-19 patients.

Preliminary results have shown a varied prognosis among patients depending on the country and the management of their COVID-19 infection. The reported death rate ranges from 1% to 2%, with most fatalities occurring in patients 50 years and older. Additionally, the younger population has lower fatality rates across all studies; however, they have the highest number of asymptomatic carriers with an increased rate of transmission.[81] The COVID-19 overactivation of immune responses, cytokine storm, and increased coagulable states may produce inflammatory and coagulation biomarkers predictive of prognosis. Coagulation markers; PT), FDP, D-dimer, and ATIII have been reported to serve as prognostic biomarkers predicting ICU mortality in a study conducted by Liu et al. In this study, PT, FDP, and D-dimer were predictive in subjects with increased ICU mortality, while ATIII was prognostic of increased survival in ICU patients.[74] Inflammatory biomarkers; IL-6 and CRP may also serve as prognostic values in subjects predictive of COVID-19 disease severity. In a retrospective study of 140 confirmed cases conducted by Liu et al, 67.9 % of patients had elevations in IL-6 with levels greater than 32.1 pg/mL predicting a more
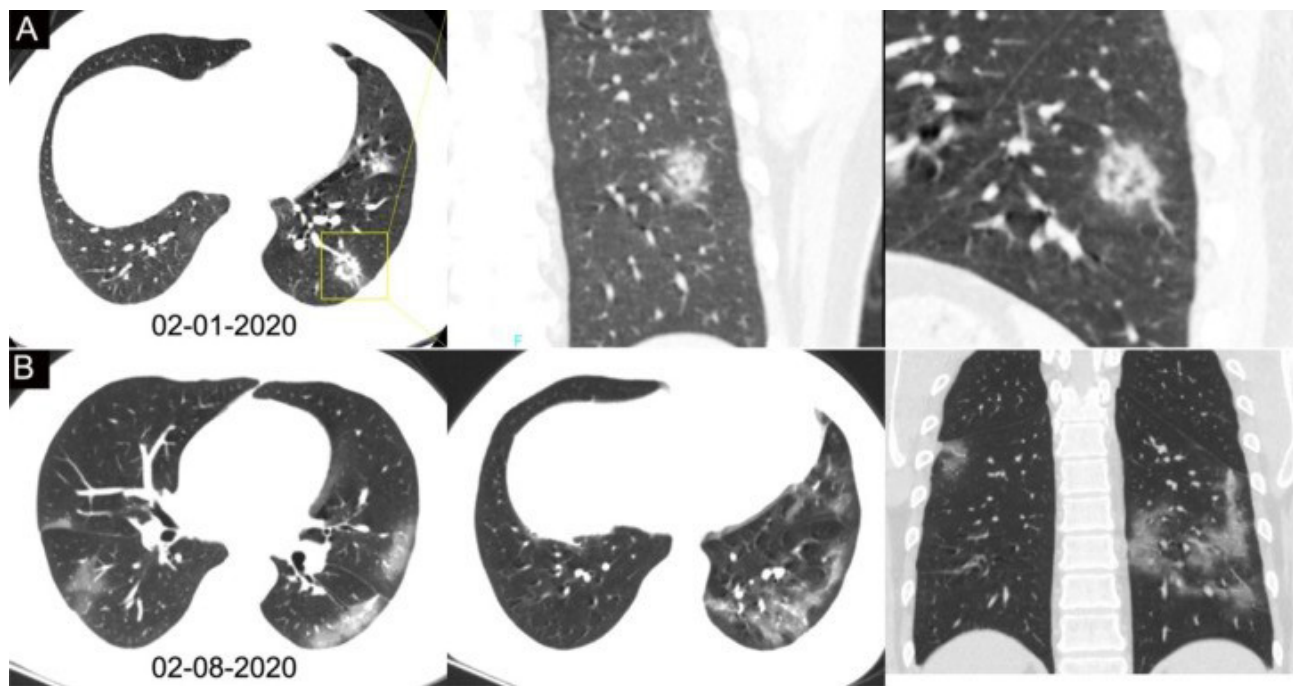
Figure 5. Chest CT of a patient presenting with a positive RT-PCR result. CT scan shows bilateral multifocal ground-glass and consolidative opacities. *Note*: CT Scan image from a confirmed COVID-19 subject, consideration of Ai et al.[80]

severe disease state. The study also reported that 65% of the subjects showed increases in CRP with levels greater than 41.8 mg/L, predicting a more severe disease state.[82] A meta-analysis conducted by Pourbagheri-Sigaroodi et al. on laboratory findings of 2988 COVID-19 confirmed patients concluded that increased NLR, D-dimer, PT, LDH, alanine transaminase, aspartate aminotransferase, and decreased lymphocytes and platelet count reflected a poor prognosis.[83]

Reinfection/Reactivation

The possibility of reinfection with the SARS-CoV-2 after recovery has been in question in recent literature. Studies have shown a drop in neutralizing IgG antibodies in confirmed COVID-19, raising the concern and susceptibility to reinfection and reactivation. During infections, the antibody levels regularly diminish after the acute phase as the B lymphocyte "effector" response is brief. Plasma cells in the bone marrow sustain serological memory as they secrete immunoglobulins without the presence of an antigen after the initial conversion. The plasma cells generating significant antibody titers after a SARS-CoV-2 infection may protect against reinfection. Subjects overcoming asymptomatic or mild COVID-19 disease, approximately one-third, have demonstrated low anti- receptor-binding domain titers and low viral neutralizing activity, with the highest observed in severe disease.[84] A study conducted by Yuan et al reported 25/172(14.5%) discharged subjects that returned to the hospital with newly positive RT-PCR results. The 25 patients were discharged accordingly, meeting the hospital criteria for clearance. Yuan et al concluded that

two apart negative RT-PCR analyses in one day may not be adequately evaluating patients for viral clearance and approval for discharge.[85] Other reasonable explanations include false-negative RT-PCR testing and reactivation of the virus. A false-negative result on a persistent infection may later be confirmed as an existing infection displaying a reoccurrence. A high false-positive rate (48/384, 12.5%) has also been reported validating the possibility.[86] Li et al reported prolonged viral shedding of the virus which had been reported in 36 patients with a median span of 53 days and a peak of 83 days.[87] The possibility of reinfection of a true-negative result with a different SARS-CoV-2 strain should not be dismissed. The importance of understanding the potential recurrence and reactivation of COVID-19 thoroughly is vital in controlling the global pandemic.

Limitations

This literature review focuses on the organ system signs and symptoms and the reinfection of COVID-19. This study poses some limitations as it is also unclear whether the organ system manifestations are a primary infection or secondary characteristics to systemic causes of illness. The SARS-CoV-2 viral mechanism of action on some organs to date has not been fully understood and poses limitations for definitive treatment and prognosis. As we are still amidst the COVID-19 pandemic, reinfections are recently being reported, and more case studies and research data are required to support existing findings further.

Conclusion

During this study, the authors conducted a systematic

literature review of over 300 articles and used 96 published reports of COVID-19 and their respective organ system manifestations, complications, and management. Within these systems, clinical developments include pneumonia, ARDS, dysrhythmias, myocarditis, cerebrovascular disease, encephalopathy, encephalitis, diarrhea, vomiting, AKI, DIC, and lymphopenia, respectively. Several research studies have validated the presence of multiple COVID-19 associated organ system complexities occurring in diverse subjects. This study also affirmed subjects with comorbidities are more susceptible to being infected with SARS-CoV-2 and developing a COVID-19 organ system complexity. Knowledge of pre-existing comorbidities aids in a suitable and well-tailored treatment plan subjective to each patient's needs. Many ongoing clinical trials are underway to find optimal management for patients suffering from COVID-19 to better comprehend the disease's pathophysiologies and drug interactions of the available treatments currently being administered to patients. The authors of this systematic literature review hypothesized that there might be an association with COVID-19 induced long term complications that are not presently evident yet and should be studied to take proactive steps in preventing later disease progression and severity, particularly in susceptible patients who have predisposing medical conditions such as neurodegenerative diseases. With the gradual increase of the COVID-19 pandemic and rising numbers of cases and mortality, further studies and published articles are of great importance to better understand disease presentations, treatment, and outcomes. A need for a vaccine is highly urged, as learned from previous pandemics, to put a cessation to the COVID-19 disease globally.

Conflict of Interest
None declared.

Ethics Approval
Not applicable.

Authors' Contribution
IP: Drafting of the review article, editing, interpretation of data, revision, supervision of the manuscript writing process. NK: Editing, drafting the review article, and interpretation of data. UJ, DM, HA, AM: Drafting the review article and interpretation of data. SB: Interpretation of data.

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