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# COVID-19 and renal involvement; evolving role of thromboinflammation, vascular and glomerular disease in the pathogenesis

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## ABSTRACT

Coronavirus disease 2019 (COVID-19), the currently prevailing pandemic that has besieged the whole world, is caused by a novel coronavirus, named as, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initially, there was a focus on respiratory disease, which was and is the most predominant presentation. However, with increasing spread of the infection and consequent increasing knowledge and experience about the disease, it has become apparent that the virus has wide-ranging effects on other organs and systems, including heart, blood, kidney and gastrointestinal tract. A variety of mechanisms are involved in viral damage of these organs. Blood vessels, particularly the microvasculature, and blood clotting systems are also frequently targeted by the virus, especially in severe cases. This review narrates the available evidence on the mechanisms underlying hypercoagulability and thrombotic tendency in COVID-19 disease.

Review

*Implication for health policy/practice/research/medical education:*
Coronavirus disease 2019 (COVID-19) is a newly emerged pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was initially reported from Wuhan, China, in late 2019 but soon spread to affect the whole world. Although primarily thought to involve the respiratory system, the disease appears to involve many other organs/systems including kidneys. A variety of mechanisms is involved in causing damage to these organs by the SARS-CoV-2 infection. Increased coagulopathy is also being reported in COVID-19 patients, which may contribute to multi-organ damage and failure. There is a need for more studies on this subject to better understand and manage this complication in COVID-19 disease.

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## Introduction

Coronavirus disease 2019 (COVID-19) is a new pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initially, there was a focus on respiratory disease as the most predominant target of the illness. However, with increasing knowledge and experience about the infection, attention was also directed towards potential injury of other organs, including heart, blood, kidney and gastrointestinal tract (1). Recent investigations show that SARS-CoV-2 migrates from nasopharyngeal mucosal cells to the alveolar epithelium and endothelium of the lungs, is

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taken up via angiotensin-converting-enzyme 2 (ACE-2) receptors to be released into the blood stream. Subsequently, organs with high expression of ACE-2 receptors take up the virus resulting in local infection in the endothelium. Some of the commonly affected organs include vascular system, myocardium, brain and kidney, which finally result in multiple organ dysfunction, which may prove fatal (2). Furthermore, in kidney, in addition to damage of renal epithelial and endothelial cells, COVID-19 also disturbs renal endocrine function of vitamin D and erythropoietin production, which impairs blood pressure regulation. The incubation time varies from one to ten days. In the majority of individuals, the infection presents with a flu-like syndrome including high-grade fever, myalgias, cough, diarrhea, and shortness of breath. However, in some patients, COVID-19 disease manifests serious signs and symptoms. Nearly, 16 to 20% of patients are affected by a severe form of the disease, characterized by pneumonia and diminished oxygen saturation, requiring admission to intensive care unit (ICU). The median time taken from the first appearance of symptoms and admission to ICU is 10.5 days. Preliminary studies show that this condition is associated with high plasma levels of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-2, IL-6, IL-7 and IL-10 that is a result of the absence of regulatory control, commonly referred to as cytokine storm (2,3). Besides, the dynamic interplay of COVID-19 and ACE2 has been suggested as a potential pathophysiological basis for variable expression of the infection. The pulmonary tract is the most common organ affected presumably due to the high quantity of ACE2 receptors.

## Materials and Methods

Articles related to this topic were searched in PubMed, Scopus, Web of Science, Embase, Directory of Open Access Journals (DOAJ) and Google Scholar, using the following keywords or their combinations: SARS-CoV-2, ACE-2, COVID-19, coagulopathy, acute tubular damage, acute kidney injury, renal proximal tubular damage, sepsis-induced coagulopathy, APOL1-related renal disease, platelets, fibrin, thromboembolism, Kawasaki disease, APOL1 kidney risk alleles, collapsing glomerulopathy, vasculopathy, COVID-19-coagulopathy, fibrin thrombi, plasminogen activator inhibitor-1, fibrinogen degradation products, acute kidney damage, chronic kidney disease, podocytes, D-dimer, intravascular coagulation, adult respiratory distress syndrome, Cytokine release syndrome, multisystem organ dysfunction, thromboinflammation, renal failure, thrombotic microangiopathy and acute kidney failure. The returned searches were carefully scanned for relevant case reports, case series, original articles, and review articles relevant to the topic and selected articles were carefully studied to draw the contents of this narrative review. In particular information related to the role of thromboinflammation, vasculopathy and glomerulopathy in causing kidney damage in COVID-19 was extracted and is presented to increase the understanding of the complex pathogenesis of this disease.

## Renal involvement in SARS-CoV-2 infection: an overview

Renal involvement is not uncommon in patients with COVID-19 infection and is particularly associated with higher morbidity and death. Initial studies reported kidney involvement in 3% to 9% of individuals with COVID-19 infection (4). Acute tubular damage was presumed to be the most plausible cause of acute renal failure; however, it could not explain hematuria or proteinuria in a subgroup of COVID-19 patients. Occasionally, the later manifestations were severe and required kidney biopsy to understand the underlying kidney pathology (5). Acute renal damage can lead to impaired acid-base balance, and altered electrolyte and fluid homeostasis, which could lead to worse outcomes for individuals with COVID-19 (6). In a recent systematic review and meta-analysis to find outcomes for patients with COVID-19 and acute kidney injury (AKI), Robbins-Juarez et al, showed that AKI occurs in a considerable number of SARS-CoV-2 patients. Notably the occurrence of acute renal damage was associated with significantly worse outcomes for individual with SARS-CoV-2, this observation has been complemented by higher risk of mortality (6). A recent report by Rabb showed an elevated risk of AKI associated with age more than 60 years. Concomitant coronary artery disease and high blood pressure are additional risk factors for acute kidney damage (7).

A recent study by Hu et al, utilizing light microscopy, immunostaining and ultrastructural observation in 26 autopsies of cases dying of COVID-19 found diffuse renal proximal tubular damage, effacement of brush borders, vacuolization of tubular epithelial cells and in some cases, a significant necrosis of tubular cells. Furthermore, pigmented casts and hemosiderin granules were detected. There also were some features of vascular involvement affecting microvascular component and characterized by significant erythrocyte aggregates, which occluded the capillary lumen without platelets or fibrinous substance. However, there were no features of vasculitis (8). In general, viral infection-induced thrombotic lesions are not common in human disease. However, in COVID-19 disease,

viral disease-induced thrombosis is being increasingly reported. First, pneumonia due to COVID-19 leads to sepsis-induced coagulopathy, which may progress to disseminated intravascular coagulation (DIC) as a severe complication, and the coagulopathy associated with COVID-19 has been widely demonstrated (9). The process begins with severe hypoxia, which is followed by inflammation and finally intravascular coagulation sets in (10,11). In these conditions, there is a rapid deterioration of organ function by intravascular thrombin production and formation of micro-thrombi with coagulation disturbance and parenchymal hemorrhage by endothelial disruption. Accordingly, venous thromboembolism may develop in SARS-CoV-2 patients due to toxic reaction or immunologic activation of intravascular mediators and platelet-released thrombin. Recent case reports or case series regarding the thromboembolic complications in SARS-CoV-2 patients show various presentations consisting of pulmonary embolism, femoral vein thrombosis, cerebral venous sinus thrombosis, aorto-iliac thrombosis, strokes in young patients and acro-ischemic presentations (12). Likewise, a serious SARS-CoV-2-related cardiovascular presentation has been reported recently form a number of children from UK with multi-system inflammatory syndrome, that resembled the features of Kawasaki disease (13). Similar cases were also reported from New York and other countries of Europe. These cases presented with skin rash and symptoms of typical Kawasaki disease or incomplete Kawasaki disease (14). The recent study by Varga et al showed that vascular injury may occur in addition to pulmonary disease during COVID-19 infection. When SARS-CoV-2 infects the individuals, it binds to ACE2 receptors, which are expressed both on the pulmonary epithelium and on the endothelium of various other organs, including the kidney (15). The endothelial involvement may be the mechanism through which the virus enters the cells. Indeed, several studies have documented that during COVID-19 disease, several organs may be affected in addition to lungs, such as the myocardium and the kidney (15). The probability of direct kidney tubular injury by SARS-CoV-2 is also likely given the recent demonstration of COVID-19 in the urine specimen of an infected case (16).

## Collapsing glomerulopathy and APOL1 kidney risk alleles in COVID-19

The recent case report by Kissling et al, concerning a COVID-19 black male patient, whose condition deteriorated by the development of AKI has some interesting implications regarding the mechanisms of kidney injury in COVID-19. The patient had past medical history of high blood pressure that was under treatment. During hospitalization, the patient experienced an acute renal impairment, with massive proteinuria. In the kidney biopsy, they detected morphologic lesion resembling collapsing glomerulopathy by the light microscopic (LM) and immunofluorescence (IF) findings. Most important was the electron microscopic (EM) study, which showed podocytic vacuoles comprising abundant spherical particles indicative of viral inclusion bodies resembling SARS-CoV-2. They concluded that collapsing glomerulopathy could be a consequence of direct viral infection of podocytes, possibly connected to the spectrum of coronavirus-related kidney involvement. The renal biopsy showed no evidence of hilar variant of focal segmental glomerulosclerosis, which may be detected in hypertension (17). Likewise, Larsen et al, also presented a case of collapsing glomerulopathy in a 44-year-old African American woman, who presented with cough, fever and vomiting. Patient also developed AKI superimposed on known previous chronic kidney disease (CKD) due to diabetes. The patient also had proteinuria. The kidney biopsy in this case also showed the typical glomerular collapse with podocytic epithelial cell hypertrophy and hyperplasia in the Bowman's space. In this case, like the previous one, the direct IF study was negative for antibodies for IgG, IgM, IgA, C3, C1q, kappa and lambda. On EM study, no immune-type electron-dense deposits were detected. While the patient was diabetic, none of the morphologic lesions of diabetic kidney disease was found on renal biopsy. A review of the two cases revealed that both were African-Americans, and around 39% of African-Americans carry one APOL1 risk allele and 13% show homozygosity for APOL1 risk alleles, which predisposes them to increased risk of renal disease. Since, APOL1 is a well-known risk factor for the occurrence of collapsing glomerulopathy in human immunodeficiency virus (HIV)-infected individuals; COVID-19 may also trigger the risk of development of APOL1-related renal disease by the same mechanism. Therefore, collapsing glomerulopathy may be a presentation of COVID-19-associated nephropathy in African American people who have APOL1 risk alleles (18).

## SARS-CoV-2 and thrombotic tendency

Among various viruses that cause hemorrhagic fever, few lead to thrombosis. SARS-CoV-2 or COVID-19 mainly involves lungs and respiratory tract. There are some features of COVID-19, which were not commonly observed in previous coronavirus diseases like SARS and MERS, including cardiomyopathy or stroke. These are most probably due to vasculopathy and coagulopathy

induced by COVID-19 (19). Therefore, these special aspects of SARS-CoV-2 infection are of particular interest. The initial autopsies from COVID-19 cases showed pulmonary vascular microthrombi (20). Most of the case reports on COVID-19 and thrombotic disease showed increased occurrence of deep vein thrombosis and pulmonary embolism, with a few cases of arterial thrombosis. Some of these cases occurred while patients were prophylactically treated with anticoagulants (21). Recent case reports showed the occurrence of thrombotic events in kidney and other vasculature beyond the lungs. Generally, viral infections cause vascular dysfunction and distorted hemostasis predisposing patient to either hemorrhage or thrombosis (22). Cytokine release syndrome, as a result of hyper-immune response, is linked to elevated morbidity and mortality in various viral illnesses. During the ongoing pandemic of COVID-19, various case reports highlighted the presence of thrombotic events mostly manifest by venous thromboembolism and acute ischemic heart disease as a result of severe inflammation, endothelial dysfunction and platelet activation and blood stasis (20-23). Recent evidence shows that coagulopathy by COVID-19 and the resultant ischemic arterial disease may be detected by elevated levels of d-dimers. As mentioned previously, coronavirus infections provoke release of various inflammatory mediators such as, IL-1β, IL-6, and interferon (IFN)-γ and TNF-α (23). Additionally, there is some evidence on the presence of antiphospholipid antibodies in some cases of COVID-19-coagulopathy. This complication will aggravate the clinical condition of these patients (24). Studies regarding the lung damage in COVID-19 showed fibrin thrombi, elevated d-dimer levels, and skin lesions in their extremities indicative of morphologic lesions of thrombotic microangiopathy. It is possible that DIC and thrombosis in the medium-size vessels lead to multisystem organ dysfunction (25).

## Mechanisms of thrombosis by COVID-19

Recent studies have demonstrated that almost all cases with critical SARS-CoV-2 infection had major coagulation disorders, and around 20% of SARS-CoV-2 patients had severe coagulation disorders (26). The term thromboinflammation (coagulation and inflammation) accurately describes the pathophysiology of hypercoagulability occurring in SARS-CoV-2 infection. The inflammatory response to pneumonia causes coagulopathy, which shows good correlation with disease severity. This condition is detected by noticeably raised Factor VIII, von Willebrand factor, D-dimer and fibrinogen. Furthermore, excessive elevations of fibrinogen and D-dimers at the time of admission are accompanied by increased mortality and ICU admissions (27). Recent studies have also shown that the hyper-inflammatory state in individuals with severe COVID-19 is associated with the development of acute respiratory distress syndrome (ARDS) and multi-organ dysfunction (28). It is noteworthy that disturbed coagulation indices in critical cases of SARS-CoV-2 infection might have a prognostic implication (26). A recent investigation found that significantly high fibrinogen degradation products (FDPs) were related to mortality in SARS-CoV-2 infection (26). A decrease of circulating protein C and anti-thrombin and an increase of plasminogen activator inhibitor-1 (PAI-1) are other promoting mechanisms, as they ultimately inhibit fibrinolytic reaction and activate coagulation cascade (26).

## Involvement of renal vasculature by COVID-19-thrombopathy

One of the poorly understood complications of COVID-19 is the microvascular thrombosis in kidney, lungs and other organs, and arterial and venous thrombotic events, possibly due to intense inflammation, endothelial dysfunction, platelet activation, immobilization, and stasis (27-29). All these factors predispose patients to a pro-thrombotic state (28). In addition, other risk factors like dehydration due to fever and gastrointestinal complications including diarrhea or anorexia, insufficient fluid replacement and hemoconcentration, can lead to increased blood viscosity. The coagulopathy of COVID-19 begins with marked elevation of fibrin/fibrinogen and FDPs, with co-existence of diminished platelet counts, disturbances in prothrombin time and partial thromboplastin time, and schistocytes in peripheral blood smears (22). Hypoxia due to COVID-19 pneumonia directly augments blood viscosity and by hypoxia-inducible transcription factor-dependent signaling pathway, therefore leading to thrombosis (30). In addition, extreme hypoxia aggravates inflammation and DIC, other possible mechanisms for thrombosis (10), while coagulopathy secondary to the presence of antiphospholipid antibodies has also been reported (31). Philipponnet et al (29) reported a 52-year-old male who presented with abdominal pain and was admitted to ICU. The patient had intra-stent thrombosis of the left renal artery with massive ischemic lesions of the kidney parenchyma. SARS-CoV-2 RNA was also detected in nasopharyngeal swabs (29). Additionally, Jhaveri et al, reported TMA in a SARS-CoV-2 case. Their case had disturbed renal function which required continuous renal replacement therapy. Kidney biopsy showed significant acute TMA and cortical necrosis. The patient also had elevated β-2 glycoprotein-1 IgM (β2GP-1) levels (10).

Regarding the pathophysiologic mechanisms of thrombotic events in COVID-19, one cannot ignore the role of angiotensin II also. The pro-inflammatory, pro-thrombotic, pro-apoptotic and vasoconstrictive effects of angiotensin II may be promoting factors for thrombotic disorders (19).

## Conclusion

In conclusion, the emerging evidence suggests that coagulopathy, particularly involving the microcirculation, is common in patients with COVID-19 and the prevalence of the complication is related to the severity of disease**.** The available data suggests that the coagulopathy in COVID-19 disease is a result of the inflammatory response to SARS-CoV-2 infection resulting in thromboinflammation and promoting thrombosis. It is more pronounced in those presenting with more severe disease symptoms, and in those who develop sepsis-induced coagulopathy and overt DIC. Further studies are needed on this aspect of COVID-19 disease to fully elucidate the pathogenesis of this enigmatic viral illness.

## Authors' contribution

TS prepared primary draft. MM conducted the first edit. PS, FK and SS conducted the second scientific edits. All authors read and signed the final manuscript.

## Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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