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(Relationship between covid19 and renal function)

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Introduction

In December 2019 a novel coronavirus (SARS-CoV-2) developed in Wuhan, China, and is expanding as a global outbreak causing Corona virus disease (COVID-19), with over 23 million cases across 188 countries and more than eight hundred thousand deaths [from "COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)".1 SARS-CoV-2 is a positive-sense single-stranded RNA virus that is spread via nose and mouth secretions including small droplets produced by coughing. The standard method of diagnosis is real-time reverse transcription polymerase chain reaction (rRT-PCR) on respiratory samples obtained by a nasopharyngeal swab.2 Heterogeneous clinical manifestations, from mild symptoms of upper respiratory tract illness to severe acute respiratory distress syndrome (ARDS) due to interstitial bilateral pneumonia, multiple organ failure, and death can occur. 3,4 The ability of the virus to bind the ubiquitous angiotensin-converting enzyme (ACE)-2 receptors allow SARS-CoV-2 to target organs other than the lungs, such as the heart, central nervous system, gastrointestinal tract, etc.5,6 At present, the kidney is one of the several targets of COVID-19, but, as initially misdiagnosed, its involvement was considered negligible. However, acute kidney injury (AKI), expressed as high amount of protein excretion and macroscopic hematuria, in patients with COVID-19 is considered a marker of disease severity and a negative prognostic factor for survival.3,7 In fact, a meta-analysis evaluating the outcome of COVID-19 subjects who developed AKI observed that those with severe AKI, defined as Kidney Disease Improving Global Outcome (KDIGO) stage III or need of acute renal replacement therapy (RRT), showed a higher mortality than those with stage I or II stage.

The functions of the kidney include maintenance of acid-base balance; regulation of fluid balance; regulation of sodium, potassium, and other electrolytes; clearance of toxins; absorption of glucose, amino acids, and other small molecules; regulation of blood pressure; production of various hormones, such as erythropoietin; and activation of vitamin D.

Impaired renal function can lead to obstruction of excretion of metabolites and toxins in the body, which will adversely affect the maintenance of the electrolyte and acid-base balance of the human body. In addition, when renal function is severely damaged, uremia will occur, and endanger life. Early detection of evidence

of renal injury and timely effective interventions are of great significance for reducing complications and improving prognosis.

This review will examine renal involvement, both direct and indirect, during SARS CoV-2 infection, in order to manage kidney complications in clinical practice.

Pathogenesis of Kidney Injury

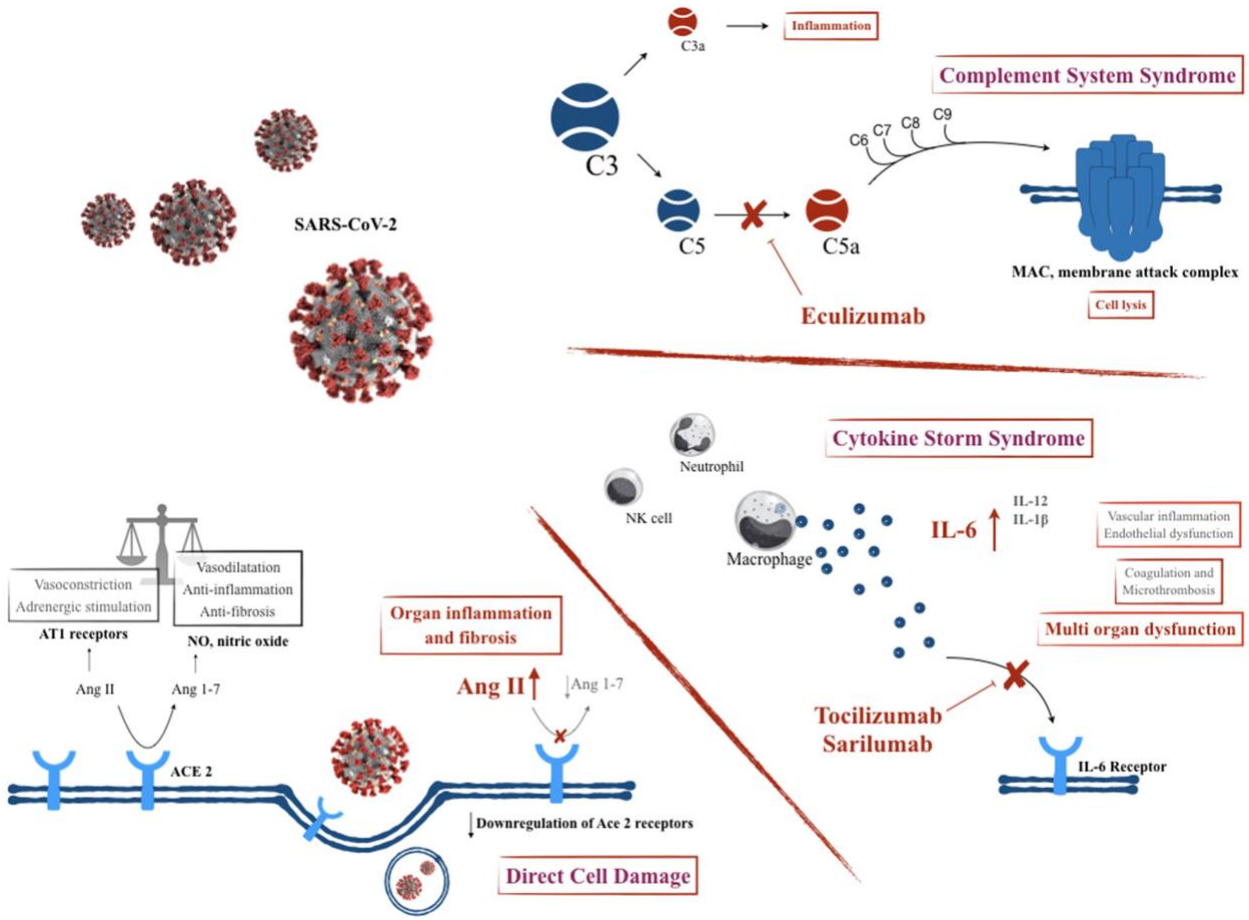
SARS-CoV-2 infects the host using the ACE-2, a membrane-bound peptidase, expressed more in the kidney than in other organs (lung, heart, intestine, and endothelial cells).8-10 While ACE converts angiotensin I (Ang I) to angiotensin II (Ang II), ACE2 degrades Ang II to angiotensin 1–7 [Ang-(1–7)]. Ang II plays a role in vasoconstriction and adrenergic stimulation, binding type 1 Ang II receptors (AT1),27 while Ang-(1–7) opposes the Ang II-AT1 axis through vasodilatation, and anti- inflammatory and anti-fibrotic action, mainly increasing the production of nitric oxide.

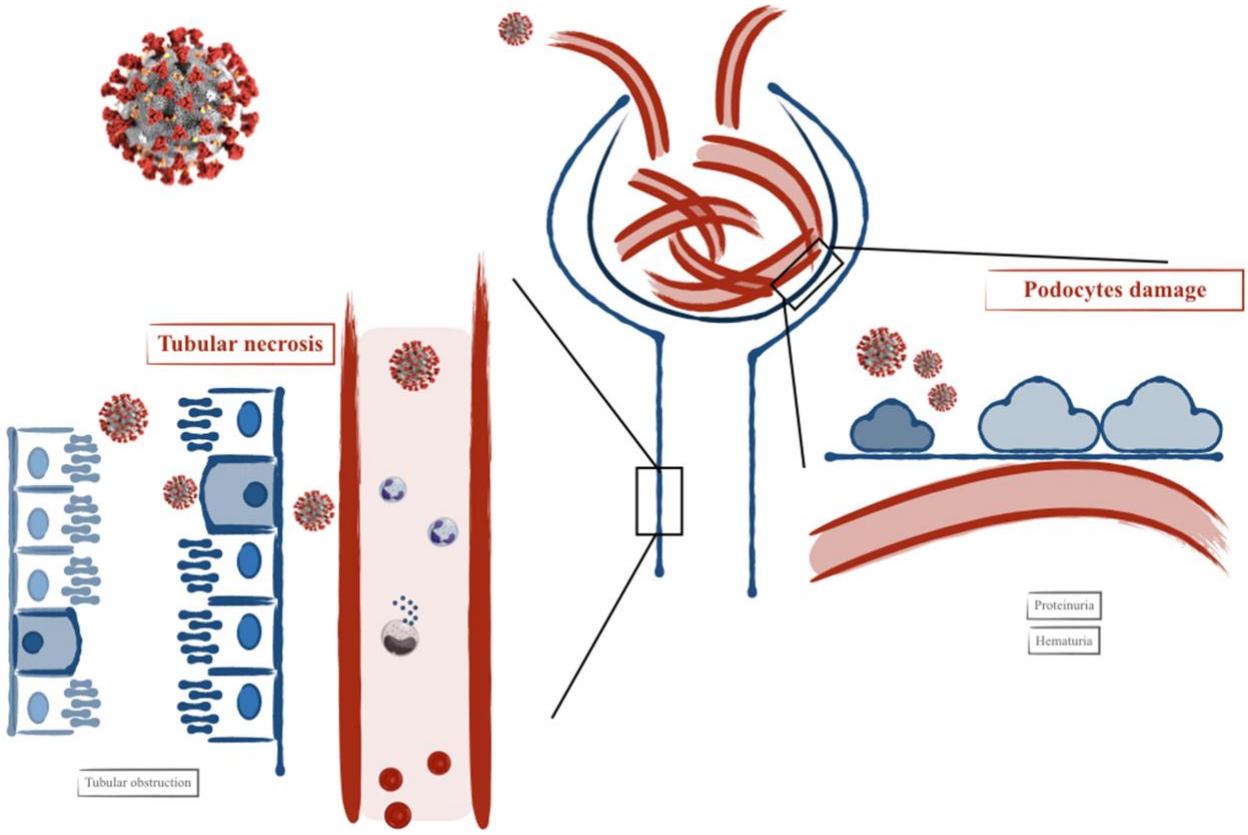
By downregulating ACE2, SARS-CoV2 determines an increase in ACE activity and a shift to overproduction of Ang II.11 This leads to a proinflammatory (including complement activation) and pro-fibrotic state in the kidneys. Renal damage may be due both to primary mechanisms, directly referred to the virus, and secondary mechanisms, linked to the hemodynamic and immune response to the virus.

Direct Mechanisms of Renal Damage

If in an advanced stage of disease, AKI can be ascribed to hypotension and low kidney perfusion due to hemodynamic, haemostatic or infectious factors, viral replication in the kidney parenchyma itself also plays a role. However, an acute proximal tubular injury is described in autopsies of subjects who died of COVID-19, associated with a development of glomerular fibrin thrombi caused by direct endothelial damage.13 In a recent observation, SARS-CoV-2 showed renal tropism, and RNA has been detected in the kidneys, with preferential targeting for glomerular cells.14 Furthermore, as observed in other virus-associated nephropathies, SARS-CoV-2 can directly infect human kidney tubules and also

induce cytoplasmic renal tubular inclusions.15 As mentioned, regardless of the direct viral kidney infection, SARS-CoV-2 determines an increase in the Ang II/Ang-(1–7) ratio. The result is AT1-receptor activation as well as a decrease in vasodilatation Ang (1–7) activity, with a subsequent risk of a worsening of the renal function. Thus, patients with chronic kidney disease (CKD), especially those with diabetic nephropathy, may have a higher risk of AKI because of an already existing upregulation of ACE and downregulation ofACE2.16 A recent analysis including more than 17 million patients in the UK suggested that patients with CKD are at higher risk of mortality than those with other known risk factors, including chronic heart and lung disease.33





Indirect Mechanisms of Renal Damage

In addition to direct pathophysiological mechanisms, renal dysfunction in the context of COVID-19 might also arise through the systemic effects of SARS-CoV-2 infection and critical illness. For example, considerable insensible fluid losses might occur through hyperpyrexia and the gastrointestinal manifestations of COVID-19, such as diarrhea, may result in volume depletion, an important potential contributor to AKI in other settings. Similarly, critically ill patients might be exposed to nephrotoxins as part of their clinical care, in particular, antibiotics, which can cause tubular injury or acute interstitial nephritis19,20. Moreover, individuals who develop secondary infections (regardless of whether they are bacterial, fungal or viral) are at increased risk of secondary sepsis-associated AKI25. Patients with severe COVID-19-associated pneumonia and/or ARDS are also at a high risk of AKI

as a complication of mechanical ventilation. Specifically, COVID-19-associated ARDS is often treated by increasing positive end-expiratory pressure (PEEP), which leads to increased intrathoracic pressure and can ultimately result in increased renal venous pressure and reduced filtration, which may be further amplified if intra-abdominal pressure is elevated (for example, with fluid overload)22. In addition, all forms of positive pressure ventilation can increase sympathetic tone, leading to secondary activation of the renin–angiotensin system23,24. In the setting of ARDS after shock resolution, patients are often managed with a restrictive fluid strategy. However, in the setting of COVID-19, patients may initially present with relative volume depletion due to fever and gastrointestinal losses, and therefore careful attention to volume status is needed to avoid hypovolemia. Organ crosstalk describes the complex and mutual biological communication between distant organs mediated by signaling factors, including cytokines and growth factors, as well as the release of damage-associated molecular patterns (DAMPs) from injured tissue. Such crosstalk has also been suggested to mediate AKI in the setting of ARDS24,25. For example, lung injury in patients with COVID-19 can be severe and abrupt and lead to the release of not only DAMPs but also cytokines, chemokines and vasoactive substances that may continue to AKI. Tissues other than the lung might also serve as sources of DAMPs; for example, rhabdo-myolysis in the setting of COVID-19 would result in the release of myoglobin from muscle20. Available evidence suggests that older age, chronic kidney disease (CKD), and the presence of other comorbidities (for example, diabetes mellitus, hypertension, obesity, heart failure and chronic obstructive pulmonary disease) are associated with worse outcomes and also represent risk factors for the development of AKI in patients with COVID-19. These clinical features are characterized by low-grade inflammation and increased immune senescence, although how these impact the kidney in the setting of COVID-19 is unknown28.

Martials

The data was taken from Al-Mawanaa General Hospital. All the 40 patients were diagnosed with COVID-19 using PCR, CT scan, CRP and D-Dimer, all of them have positive results and we found increasing in urea and creatinine values comparing to the normal range so that mean all patients have renal dysfunction.

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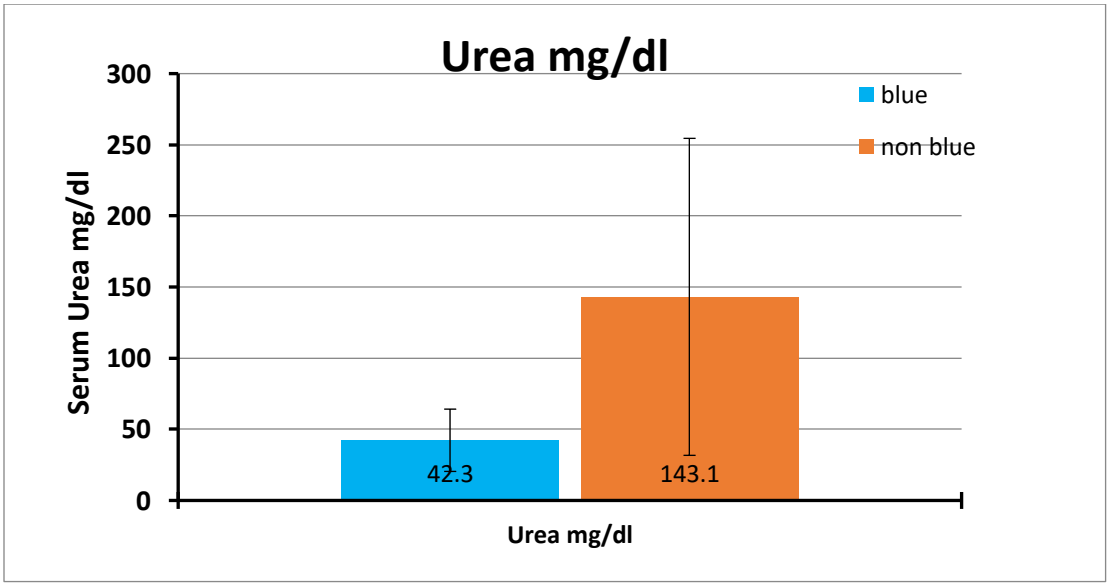
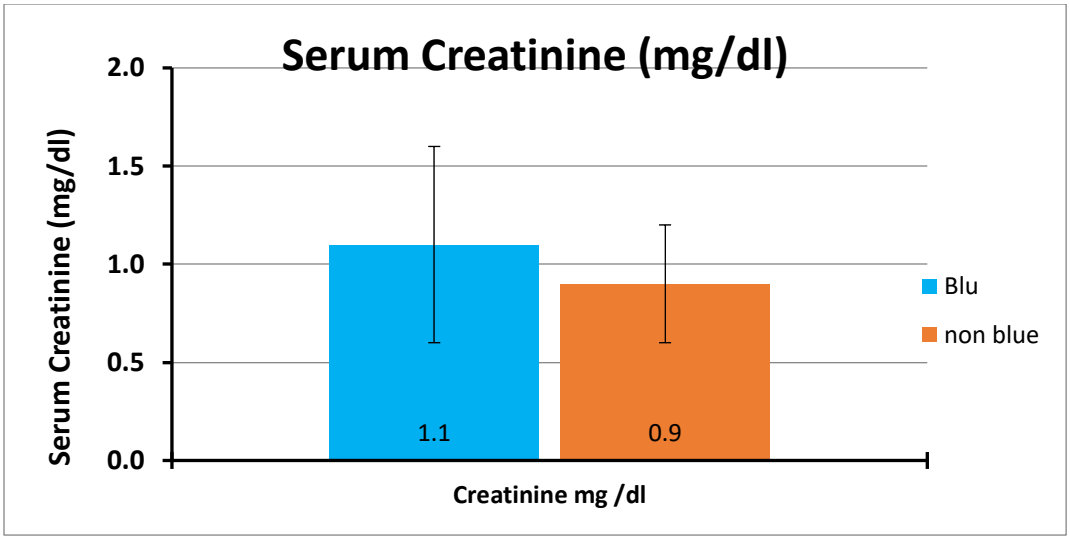
Results

			P values
	Control (blue color)	Study (non blue)	
Serum urea (mg/dl)	42.3 ± 21.9	143.1 ± 111.4[a]	**0.001**
Serum Creatinine (mg/dl)	1.1 ± 0.5	0.9 ± 0.3[a]	**0.225**
P value<0.05 considered significant			





A total of 40 patients were included in the study. The mean of age was 50 years, and 54.7% patients were men. The median duration from onset to admission was 9 days. The prevalence of hypertension and diabetes was 32.2% and 22.9%, respectively. Compared with moderate cases, patients with severe or critically ill COVID-19 pneumonia were older, more likely to experience dyspnea, and more likely to have hypertension, diabetes, and angiotensin- converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) treatment history.

This study found that serum creatinine and blood urea nitrogen were generally increased during the course of COVID-19. Detection of urinary microproteins and application of multiple indicators assessment could be helpful for discovering abnormal renal function in patients with COVID-19. However, this study also has several limitations. First, the number of patients included in this study is limited, and there were some missing data. Second, because of the strain on medical resources in the epicenter of the COVID-19 out- break, we could not get full laboratory support to obtain more sufficient evidence for evaluating the urine. Third, the duration of observation is not long enough to implement survival analysis to predict the probabilities for remission of renal damage in the long term and risks for mortality. Fourth, we did not detect SARS-CoV-2 in urine samples. Therefore, we could not assess correlations between urine virus and renal complications. Fifth, we did not have renal pathology data to assess the direct effect of the virus on renal outcomes. We did not detect biomarkers, such as urinary NGAL and KIM-1, to

accurately distinguish pre-renal AKI from ATN. Sixth, as the admission creatinine was used to define AKI in expanded criteria, some AKI at admission that did not resolve may have not been included, which might potentially overestimate overall recovery as well as underestimate severity in some patients (those with AKI at admission that continued to worsen). In conclusion, despite high morbidity of renal involvement, the short-term renal prognosis of patients is good, as half of them achieved remission in 3 weeks after onset of symptoms. However, adverse short-term outcomes of renal involvement are also associated with mortality in COVID-19. Severity of pneumonia was identified as an independent negative prognostic indicator for renal complications. Therefore, the strategy on treatment and prevention of severe or critically ill pneumonia is appropriate for COVID-19–related renal complications.

Conclusions

COVID-19 is a viral infectious disease mainly presenting with fever and pneumonia. Several data suggest an important role played by the immune system in critically ill patients leading to ARDS, multiple organ failure, and even death. Consequently, different pathways, in addition to viral damage, may contribute to organ damage. Kidney injury may occur and impact the prognosis. Anti-inflammatory and supportive therapies are the cornerstones of treatment for severe cases, while in selected patient's renal replacement therapy and extracorporeal blood purification may be applied.

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