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COVID-19 and kidney failure; a mini-review to recent evidence

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ABSTRACT

In COVID-19 infection, most of the renal disturbances are due to acute tubular necrosis. Renal dysfunction occurs in severe COVID-19 infection and is usually secondary to sepsis, cytokine storm, and hypotension. Other conditions, such as exacerbated inflammatory responses, dehydration, hypoxia, hypercoagulability, endothelial damage, pneumonia, septicemia, drug nephrotoxicity, and myocardial dysfunction also contribute to renal failure.

Keywords: COVID-19, Acute renal failure, Collapsing glomerulopathy, SARS-CoV-2, Thrombotic microangiopathy, Angiotensin-converting enzyme 2, Acute tubular necrosis, Acute respiratory distress syndrome, COVID-19-associated glomerulopathy

Mini Review

Implication for health policy/practice/research/medical education:
Acute kidney injury occurs in patients with COVID-19 infection and has been reported to be associated with in-patient hospital mortality.

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Introduction

It has gradually become apparent that COVID-19 infection is not restricted to the lung system as the kidney also appears to have a considerable effect on the consequences of the disease (1). Acute renal damage that occurs in COVID-19 patients is related to in-patient hospital death (2). Acute kidney injury (AKI) is correlated with the intensity of the coronavirus disease and increased mortality and morbidity rates. Despite early studies, which addressed the negligible incidence of acute renal impairment, recent reports show that AKI is a common finding in COVID-19 patients admitted in the intensive care units (ICUs) (3). Elderly individuals with COVID-19 infection and comorbidities, such as diabetes and hypertension, are at a greater risk of mortality (4). Early findings demonstrated that acute renal impairment is a critical complication of severe SARS-CoV-2, since most renal failures are mild to moderate, presenting by an elevation in serum creatinine (5). Renal tubules are the major part of the cytopathic injury caused by SARS-CoV-2; however, the etiologies of kidney injury in COVID-19 cases, are probably diverse and have multi-etiopathological factors that involve the interstitium and glomeruli. In this mini-review, we aimed to explain the most recent information on renal diseases in COVID-19 infection.

Search strategy

For this mini-review, we searched the Web of Science, Scopus, Embase, PubMed, and Google Scholar using the keywords; COVID-19, acute renal failure, collapsing glomerulopathy, SARS-CoV-2, acute kidney injury, thrombotic microangiopathy, angiotensin-converting enzyme 2, acute tubular necrosis, cytokine storm, acute respiratory distress syndrome, and COVID-19 associated glomerulopathy.

Acute kidney injury in SARS-CoV-2 patients

To investigate the characteristics, prevalence, risk factors, and consequences of acute renal injury among COVID-19 patients on ventilators, Fominskiy et al conducted an observational study in Milan, Italy. Among the patients, 75.0 % (72 individuals) suffered from acute renal failure, and 17.7% (17 patients) of these patients required continuous renal replacement therapy. Most

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patients experienced stage one AKI only, while 15 patients developed stage two of acute renal impairment, and finally, 33.4% (24 individuals) had stage three of this disease. Their study showed that hospital death was 38.9% for acute renal impairment and 52.9% for those that required continuous renal replacement therapy (4). In another study, Ng et al conducted a retrospective cohort investigation to detect the outcome and survival of hospitalized patients with COVID-19 and acute renal injury. The participants were older than 18 years and the primary outcome was in-hospital death. Among the 9657 participants admitted with SARS-CoV-2 infection, the rate of AKI was 38.4/1000 patients/day. They reported that the incidence rate of in-patient hospital mortality in patients without renal failure and in patients with renal failure without receiving dialysis (AKI stages 1-3), and also in acute renal failure patients requiring dialysis (AKI stage 3D) were 10.8, 31.1, and 37.5/1000 patient/days, respectively. Their study showed an elevated risk for in-hospital mortality in subjects with AKI with stages I to III and in individuals with stage 3D AKI (6). Likewise, an observational and retrospective study by Chan et al on 3993 COVID-19 patients who were hospitalized in the Mount Sinai Health System (February 27 to May 30, 2020), showed AKI in 46% (1835 patients), while 19% (347 patients) of AKI patients required dialysis. The rate of insufficiency with stages I, II and, III of AKI were 39%, 19%, and 42%, respectively. Their study demonstrated that higher serum potassium, male gender, and history of pre-existing chronic kidney disease (CKD) were the independent factors of severe AKI. Additionally, their study indicated that in-hospital mortality was 50% in individuals with AKI compared to 8% in patients without AKI. Notably, 35% of AKI survivors that were discharged from the hospitals had not fully recovered to their baseline renal function (7). In addition, a study by Gupta et al on 3099 severe COVID-19 patients showed that 637 cases suffered from acute renal impairment within 14 days of admission. Furthermore, around 54.9% of the patients expired within 28 days of admission. Similar to the previous study, the risk factors included a history of chronic renal failure, male gender, diabetes mellitus, non-White ethnicity, hypertension, higher level of D-dimer, and higher intensity of hypoxemia, and higher BMI (body mass index) on admission. Consequently, the 28-day mortality with acute kidney impairment in this study was associated with severe oliguria and older age. Their investigation showed that 403 of 637 patients with AKI expired (8).

Yang et al conducted a systematic review and meta-analysis on the incidence of AKI and kidney replacement therapy in COVID-19 subjects. They revealed that the pooled incidence of acute renal impairment in 51 investigations that included 21 531 participants was 12.3% (9). In another meta-analysis on the incidence, risk factors, and effect of AKI on the prognosis of individuals with SARS-CoV-2 infection, around 79 original articles, containing 49 692 individuals with COVID-19 infection were included. They showed that the death rate and occurrence of AKI in patients with SARS-CoV-2 infection in China were meaningfully lower compared to COVID-19 patients outside China. Additionally, a considerably higher ratio of COVID-19 patients from North America that were older than 65 years, developed AKI. European COVID-19 patients had a considerably greater mortality and a higher continuous renal replacement therapy rate than the non-European COVID-19 patients. They also reported that severe SARS-CoV-2 infection and age more than 60 years were independent risk factors for AKI. In addition, their meta-analysis showed that there is a risk of mortality in cases with COVID-19 (10). During COVID-19 infection, most of the renal disturbances are due to ATN (acute tubular necrosis) caused by sepsis, cytokine storm, and hypotension that result in severe COVID-19infection. Other conditions, such as an exacerbated inflammatory response, dehydration, hypoxia, hypercoagulability, endothelial damage, pneumonia, septicemia, drug nephrotoxicity, and myocardial dysfunction are associated with severe COVID-19 infection as well (5). Furthermore, the hyper-activation of the immune system against SARS-CoV-2 may also be responsible for renal dysfunction (11). Consequently, a massive influx of cytokines can trigger serious inflammation and damage the kidney structure; a condition named 'cytokine storm'. Moreover, SARS-CoV-2-associated ARDS (acute respiratory distress syndrome) is initiated by local inflammation in association with infiltration of various immune cells consisting of polymorphonuclear neutrophils, various T-cells, and macrophages. Furthermore, the release of cytokines in the pulmonary tissue mediates effector T-cells and injury-related molecular patterns which may cause additional migration of inflammatory cells and intensify the tissue injury. ARDS may mediate the occurrence of AKI by hypoxia, reduced cardiac output, venous congestion, and the presence of intrathoracic pressure (12). Additionally, in the process of COVID-19 infection, small clots may be formed in the bloodstream and occlude the small vessels which, in turn, further disturbs the renal function (11). Recent studies have shown that direct viral invasion through ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane serine proteases 2), hypercoagulability, and hypoxia may also attribute to kidney disturbance (8). The pathological features of renal biopsy in most cases are vascular and tubular injury. However, a significant percentage of individuals may develop hematuria as well as some virus-resembling particles in renal cells; although it is still not proven that they are true viral inclusions. Recent studies have shown direct viral infection (cytopathic effect) to the renal structure occurring during COVID-19 infection. However, some studies insist that the viral-like particles in renal failures are induced by COVID-19 (13). In general, the three most common morphologic lesions consist

of collapsing glomerulopathy, AKI, and thrombotic microangiopathy (14). Collapsing glomerulopathy is a condition that is accompanied by severe podocytopathy, nephrotic-range proteinuria, and AKI (15). This condition has been reported to be associated with the high-risk APOL1 genotype (5,16). Akilesh et al conducted a multicenter study in living cases who underwent kidney biopsies to find the spectrum of the morphologic lesions of renal diseases in COVID-19 infection and their association with SARS-CoV-2. Their study consisted of fourteen native and three transplant renal biopsies in the United States. The pathology study of the cases showed acute tubular necrosis in 14 individuals, seven cases of collapsing glomerulopathy, and seven patients with endothelial injury/thrombotic microangiopathy. They also detected a higher incidence in individuals with Black and Hispanic ethnicity (17,18). In addition to the three pathologic aspects of COVID-19, there have been some case reports of Kawasaki disease among COVID-19-positive children; however, their presentations were atypical (18). This disease is a type of vasculitis that is frequently detected in children less than 5 years of age (19). As mentioned before, the most possible mechanism of renal damage in SARS-CoV-2 patients has been explained by the direct viral invasion of the intrinsic renal structure. The cytopathic effect of the virus is conducted through the ACE2-membrane protein. There is a massive presentation of ACE2 in the renal proximal tubular cells; therefore, this may be a potential target for renal damage. Moreover, TMPRSSs are cellular transmembrane serine proteases that act as co-receptors and stimulate the spike protein on the coronavirus surface, leading to membrane fusion into the kidney cells. Recent studies showed that ACE2 and TMPRSSs are expressed on podocytes, implying that renal structures are exposed to the virus. The main morphological features of renal tubular cells invaded by this virus are vacuolar degeneration, swelling, shedding, and visible pigmented casts in the lumen. Furthermore, raised kidney interstitial pressure due to renal edema may also be responsible for the increased intensity of tubular injury (20,21). Recently, Tarragón et al conducted a study on 41 COVID-19 patients to detect the etiology of renal impairment. Their study demonstrated that the etiology of acute renal failure was pre-renal in 61%, glomerular in 7.3%, and AKI with underlying sepsis in 24.4% of the patients, respectively; however, toxicity-related ATN was detected in 7.3% of the individuals (22). More recent studies showed that the virus itself contaminates glomerular endothelial cells, podocytes, and other kidney tubular cells, mainly causing acute tubular damage and occasionally, collapsing glomerulopathy (10,23).

COVID-19 associated glomerulopathy

The majority of individuals with COVID-19-associated glomerulopathy present with proteinuria and significant acute renal dysfunction leading to dialysis in most cases and failure of renal function recovery. The cases of collapsing focal segmental glomerulosclerosis had significant tubular involvement as well as microcystic tubular dilation (24).

Conclusion

In summary, various parameters are associated with renal failure in COVID-19 patients. Renal impairment initiates with the direct viral invasion of the kidney tissue facilitated by ACE2, which functions as a receptor for SARS-CoV-2. Renal damage can present with acute tubular injury, glomerular disease, and vasculopathy.

Authors' contribution

Conceptualization: DJ. Methodology: DJ and MRM. Validation: ZM. Formal Analysis: MRM. Investigation: DJ. Data Curation: DJ. Writing—Original Draft Preparation: DJ and MRM. Writing—Review and Editing: ZM. Visualization: DJ. Supervision: MRM. Project Administration: MRM

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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

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