Kidney Diseases and COVID-19 Pandemic – A Review Article

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Abstract

In December 2019, first cases of a novel coronavirus were identified in Wuhan, China. A state of global pandemic was shortly declared among a very rapid contagious spread of the virus. The causative virus was identified as the SARS-CoV-2 viruses and is genetically related to the previous SARS outbreak in 2003. The virus causes a wide clinical spectrum from mild flu-like symptoms to adult respiratory distress syndrome. Kidney involvement has been reported in several reports in patients with various degrees of severity of SARS-CoV-2 infection. As knowledge is evolving, the accurate incidence of acute kidney injury (AKI) is not known. Many questions are yet to be answered regarding the effect of epidemiological variables and comorbidities on the occurrence of AKI. Some reports have observed the occurrence of hematuria and proteinuria in a percentage of infected patients. Moreover, chronic kidney disease has not been found, in some reports to add to the adverse outcomes, an aspect that merits further exploration. Patients on regular hemodialysis may be vulnerable to coronavirus infection due to the lower status of immunity and the need for frequent attendance at health-care facilities. Due to the previous factors, prevention and mitigation of the SARS-CoV-2 virus, in this vulnerable population, constitutes a major challenge.

Introduction

Origin and epidemiology

SARS-CoV-2 is a novel mutant of the coronavirus family that is causing the most recent and ongoing pandemic. The coronavirus is thought to have been transmitted at first instance from bats to humans. A wet wild animal market is likely considered to be the primary focus. The first cases of human infections were then reported in the city of Wuhan, the capital of Hubei Province of China. This was followed by widespread of the pandemic to many countries around the globe. Until the time of writing this paper (April 6, 2020), the number of infected people around the globe exceeded 1,300,000 patients with mortality over 74,000 [1].

Pathogenesis

COVID-19 primarily targets the respiratory system, causing a wide clinical spectrum from mild symptoms to adult respiratory distress syndrome. The pathogenesis is mediated in severe cases through the so-called cytokine storm (Figure 1). This involves the secretion of large amounts of pro-inflammatory cytokines and chemokines including IL8, IL 6, IL9, IL10, and many others. Pathogenic mechanisms in the kidneys are not fully elucidated, but the suggested mechanisms are through attachment of the virus to ACE2 receptors. Excess secretion of cytokines leads to multiorgan failure in a percentage of patients, including acute kidney injury (AKI), through tissue hypoxia [2].

Figure 1: Renal complications of SARS-CoV-2 virus

Chronic kidney disease (CKD) as a predisposing comorbidity in the event of COVID-19

A number of studies have analyzed patients' comorbidities. The prevalence of CKD was variable across studies, ranging from 0.7 to 6.5% [3]. Only one cohort of 710 patients reported that 40% of patients had CKD in the form of deranged kidney function, hematuria, or proteinuria [4]. Most studies that used regression analysis to predict poor outcome have not identified chronic kidney disease as an important prognostic factor [5]. The lack of stratification of CKD among the prognostic factors of SAR-CoV-2 denotes that patients with CKD are not particularly at a higher risk of SAR-CoV-2 infection [3], [5].
Patients with end-stage renal disease (ESRD) on hemodialysis have a lower immunity status to various types of infections. The impact of COVID-19 infection on hemodialysis patients merits further investigation. In a study of 230 patients on hemodialysis in Wuhan, during the COVID-19 outbreak, 37 patients and 4 health-care providers became infected. The clinical features of hemodialysis patients reported in this cohort were mild. Seven deaths occurred among dialysis patients during the outbreak; however, causes of death were not attributed to COVID-19 [6].

AKI as a complication of COVID-19

Acute kidney injury is a common complication of several infections. In the previous SARS-CoV-2 outbreak in 2003, the incidence of AKI was as low as 6% [2], [7]. Nevertheless, AKI case fatality rate was high [8]. As for SARS-CoV-2, the exact incidence of AKI is not well known. Cohorts that reported AKI incidence are summarized in Table 1 [9],[10], [11], [12], [13], [4], [3], [14], [15], [16], [17], [18], [19], [20], [21], [5].

There is heterogeneity among studies regarding the reported incidence of AKI. This may be attributed to inconsistencies in applying AKI definitions or due to genetic variability that merits further studies.

Some reports have shown that the incidence of AKI is significant, while others report that the incidence is marginal. Guan et al. have shown, in a large cohort of confirmed COVID-19 cases that the prevalence of AKI was as low as 0.5%. This increased in patients with severe COVID-19 to 2.9% [5]. In other cohorts, the incidence of AKI in confirmed cases of COVID-19 was higher.

In two cohorts, the reported incidence of AKI was notably higher. In a cohort of 193 patients, the overall incidence of AKI was 28% and the incidence in severe cases was 66% [18]. In another cohort of 191 patients, the incidence of AKI in non-survivors was 50% [19]. In the study by Hu et al., AKI was present in 17 of all 323 patients (5.3%); however, the incidence of AKI in patients with critical COVID-19 was 38.5%. Furthermore, in this cohort, most patients who had AKI (14 out of 17) had unfavorable outcomes [17].

Interestingly, one retrospective study of 116 patients showed that the changes in kidney function throughout the disease course were subtle [13]; this study included five patients on maintenance hemodialysis, all of whom had severe disease but survived. Despite the subtle changes in kidney function, none of patients in this cohort met the defining criteria for AKI, including seven deaths that were reported [13]. This report concluded that AKI and other kidney diseases are not of paramount clinical significance in patients with COVID-19 [13].

During a previous SARS outbreak in 2003, a study of postmortem kidney biopsies examined using electron transmission microscopy, failed to detect any viral particles in kidney tissues. This finding supports the theory that most of the kidney pathogenesis in the earlier SARS outbreak was in the context of multiorgan failure. The pathogenesis of AKI may be multifactorial. Suggested mechanisms are direct cytopathic effects on kidney tissues, as denoted by the retrieval of the viral RNA from urine samples [4]. The direct cytopathic effect of COVID-19 on kidneys is now more evident, as it has been shown that there is overexpression of both ACE2 receptors and a cleavage spike protein in podocytes and proximal tubular cells [22]. This experimental evidence is of paramount importance and can explain proteinuria in patients with COVID-19. Interestingly, the latter experiment reports variable expression of cleaved S protein such that there is low expression in the Chinese race as compared to Caucasians. Important pathological evidence was reported by Diao et al. The pathology team managed to confirm the visualization of the SARS-CoV-2 viral particles in the renal tubular cells of postmortem kidney biopsies [23], [24]. The difference in kidney tropism between SARS-CoV and SARS-CoV-2 may be attributed to the affinity to ACE2 receptors in the kidneys.

Tissue hypoxia, in the context of massive cytokine secretion, is a key renal pathogenic mechanism. Rhabdomyolysis and raised creatinine kinase have been observed in a few cases [5]. It was also noticed in one cohort that AKI occurred later to acute cardiac injury, suggesting a temporal relationship between cardiac injury and AKI and the possible occurrence of cardiorenal syndrome [19]. In a recent single case report, collapsing variant of focal segmental glomerulosclerosis was diagnosed in renal biopsy of African-American woman, who tested positive to COVID-19. The patient presented with confusion and rapidly deteriorating kidney function, she improved markedly with the initiation of dialysis [25].

Hematuria and proteinuria

In the largest prospective cohort of kidney diseases in COVID-19, it was found that hematuria occurred in 26% of patients and proteinuria occurred in about 43% [4]. Large prevalence of proteinuria could be explained by the finding of the above-mentioned experimental study that showed expression of ACE 2 receptors in podocytes and proximal tubular cells [22]. However, quantification of proteinuria, using 24 h urinary collection or protein to creatinine ratio, was not done within the investigation battery. Kidney biopsy has not been attempted in any patient. In this prospective report, the presence of hematuria or proteinuria signaled poor outcome, as measured by in-hospital mortality.

Effect of dialysis modalities on survival in patients infected with COVID-19

Continuous renal replacement therapy (CRRT) is a modality of dialysis that implies increasing the clearance of solutes through convection, diffusion, ultrafiltration,
Table 1: Characterization of renal complications in several cohorts

| Author Name | Number of patients | Study design | AKI percentage (all) | AKI percentage (non severe cases) | AKI percentage (severe cases) | significance | CKD at baseline | Baseline BUN (non severe cases) | Baseline creatinine (non severe cases) | Baseline creatinine (severe cases) | significance | mean BUN (non severe cases) | mean creatinine (non severe cases) | mean creatinine (severe cases) | significance | comment |
|-------------|--------------------|--------------|----------------------|-----------------------------------|-------------------------------|---------------------------|--------------|----------------|-------------------------------|-----------------------------------|-------------------------------------|----------------|--------------------------|-------------------------------|-------------------------------|----------------|---------|
| Luwen Wang et al | 116 | retrospective | 7/116 | Not reported | Not reported | NA | 4.3% | 4.3% on CRRT | 7 deaths had no AKI 5 patients on CRRT survived |
| Shijiao Yan et al | 168 | retrospective | 3.6% | 0% | 8.30% | 0.6% | Not reported | Not reported | |
| Yi Yang | 36 | retrospective | 22.0% | Not reported | Not reported | Not reported | 3.9 | 5.8 | 66 | 81 | AKI was the 3rd leading cause of death CRRT made no difference of death at 3 days |
| Guo-Qing Qian Yang, Zonghao Wang | 91 | retrospective | 3.0% | Not reported | Not reported | Not reported | 3.93 | 4.99 | 55 | 74 | significant |
| Yi Yang | 36 | retrospective | 22.0% | Not reported | Not reported | NA | 5.3% | 7 deaths had no AKI 5 patients on CRRT survived |
| Guo-Qing Qian Yang, Zonghao Wang | 75 | retrospective | 20.0% | Not reported | Not reported | NA | 5.3% | CRRT made no difference of death at 3 days |
| Guan et al*** | 1099 | 5% all and 2.9% in severe cases | 0.1 | 2.9 | NS | 0.7% | Abnormal kidney function in about 40% |
| Yichun Cheng | 710 | Prospective | 5.1% | 3.8 | 3.8 | NS | Hematuria (26%) and proteinuria (40%) |
| Wen Zhao | 168 | retrospective | 2.6% NS between severe and non severe | NS | 63 | NS | No significant difference between severe and non severe cases as regard baseline serum creatinine cutoff value of serum creatinine 77 was associated with 2.9 odds mortality |
| Jiatao Lu | 577 | retrospective | 3.0% | 2.8 | 3.3 | NS | Hematuria (26%) and proteinuria (40%) |
| Huang Jianfeng Xie | 444 | Retrospective | Not reported | Not reported | 66 | 85 | 0.001 | There was significant difference in baseline creatinine between patients who survived and patients who died |
| Ling Hu Zhen Li Fei Zhou | 193 | retrospective | 5.3% | 6.9 | 3.8 | 0.007 | 2.2% | 73 | 63 | 10 patients had renal replacement therapy and they all did not survive |
| Kun-Long Ma | 84 | retrospective | 7.1% | 1.60% | 25% | 0.03 | 1.2% | No significant difference between severe and non severe cases as regard baseline serum creatinine cutoff value of serum creatinine 77 was associated with 2.9 odds mortality |

and adsorption. The modality has benefits in critically ill patients, including the removal of septic toxins in addition to correction of the uremic status. There is accumulating evidence that critically ill patients who develop AKI may have lower mortality if they are treated using CRRT [26].

As knowledge is evolving about the SARS-CoV-2 virus, the benefit of CRRT in the management of critically ill patients with COVID-19 is much less clear. One retrospective study was conducted in China on 36 confirmed COVID-19 cases who have been admitted to the intensive care unit [10]. All patients were mechanically ventilated; the aim was to compare the effect of CRRT as compared to conventional dialysis. Patients were followed up for an average time of 10.4 days. The mean serum creatinine was slightly higher in patients who received CRRT than in patients who did not receive CRRT (94.5 mmol/L vs. 72 mmol/L, p=0.017). There was a marginally a favorable effect of CRRT in terms of adjusted mortality (54.4% in CRRT group vs. 78% in the conventional hemodialysis group).

On the contrary, another analysis of risk factors and survival in critically ill patients found that non-survivors received more treatment with CRRT than survivors.

Another study of 101 case fatalities in China, five cases had CRRT. Two patients died within 3 days and three patients died after 3 days. The mean baseline serum creatinine was 139.8 µmol/L [27]. In another large retrospective analysis by Guan et al., nine patients were treated with CRRT, eight of whom died suggesting that CRRT had no mortality benefit [5]. In a cohort of 191 patients, 10 patients received renal replacement therapy, and all did not survive, suggesting that renal replacement therapy in severe cases of COVID-19 may not have any survival benefit [19].

Renal-specific mortality due to COVID-19

The leading causes of mortality in COVID-19-infected patients are sepsis and ARDS. This has been observed in several cohorts. A large prospective study showed that the development of AKI in patients infected with COVID-19 was associated with four-fold increase in the mortality [4]. In other reports, renal-specific causes were not the most common or the second most common of mortality in COVID-19. In a retrospective study of 101 non-surviving COVID-19 patients, the incidence of AKI was 23%, there was no significant difference between patients who died within 3 days and patients who died later with regard to AKI incidence (25% vs. 21%, p=0.611) [27]. In this cohort, AKI was the 3rd leading cause of death after respiratory and cardiovascular causes. In a single-centered study in China, chronic kidney disease was present in 7 out of 323 patients (2%). Four patients had severe disease while the other three patients had non severe disease. Elevation of BUN > 88 mmol/L was associated with a two-fold increase in the chance of poor clinical outcomes. Baseline serum creatinine of <88 mmol/L was associated with 63% reduction in the development of poor outcomes. In another report of 82 non-surviving patients with confirmed COVID-19, the AKI percentage was 31% [28].

**Prevention and mitigation of COVID-19 among dialysis patients**

Until the time of writing this paper, there is no consensus or formal approval of any medication for COVID-19. This fact mandates the exhaustion of all measures to prevent the transmission of infection. In this respect, the Centers for Disease Control and Prevention (CDC) has issued an interim guideline for hemodialysis centers. The guideline emphasizes the importance of early recognition and isolation of cases while attending their scheduled sessions [29]. This mandates treating confirmed cases of COVID-19 hemodialysis in designated rooms with droplet infection prevention precautions; patients with confirmed of suspected COVID-19 should be separated by 6 feet distance. The instructions for hemodialysis patients should be centralized around reporting any new symptoms of fever or cough. Patients should be instructed on the proper use of face masks and using tissues when sneezing or coughing to prevent spread of infections [30], [29]. There is an anticipated extraordinary strain on hemodialysis facilities. In parallel, there are a number of suggestions to match the resources. These practical suggestions aim at reduction of the strain on hemodialysis units [29].

Summary and Conclusion

SARS-CoV-2 (COVID-19) virus pandemic constitutes a global health threat. The disease spectrum caused by the virus flu-like symptoms to adult respiratory distress syndrome. Kidney involvement in COVID-19 has been reported in previous cohorts. Acute kidney injury is a complication of COVID-19, either as part of multiorgan failure caused by excess cytokine production or through direct cytopathic effect on renal tissue. Overexpression of ACE2 receptors in podocytes and proximal tubular cells has been observed in patients with COVID-19. Other renal manifestations include proteinuria and hematuria. The true incidence and outcome of AKI in COVID-19 is not entirely clear and merits further studies. Continuous renal replacement therapy (CRRT) benefits in case of AKI are controversial. Patients on hemodialysis may be at increased risk of COVID-19 due to the nature of renal replacement therapy that requires 3 times weekly attendance at dialysis facilities. This necessitates the application of meticulous measures to prevent and mitigate the outbreak in patients on hemodialysis.