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Covid-19 and Acute Kidney Injury: Recent Updates

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Abstract:
In January 2020, the pathogen was identified and named by the World Health Organization as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2). The consequent SARS-CoV-2-related disease was defined as coronavirus disease 2019 (COVID-19). As data emerged about characteristics of the disease, it was found to be associated with increased risk of acute kidney injury (AKI). We explore the recent literature and reports emerging from the epicenters of the pandemic to help our viewers understand the nature of AKI among these patients.

Key words: *SARS virus, COVID-19, Pandemic, AKI, acute kidney injury, pneumonia, acute tubular injury, ARDS.*

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Introduction

A series of unexplained pneumonia cases were reported in the city of Wuhan, the capital of Hubei province in central China in December 2019. In January 2020, the pathogen was identified and named by the World Health Organization (WHO) as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2). The consequent SARS-CoV-2-related disease was defined as coronavirus disease 2019 (COVID-19)[1]. On March 11, 2020 it was declared as pandemic by WHO and so far has affected over 1 million people across the globe[2]. As data emerged about characteristics of the disease, it was found to be associated with increased risk of acute kidney injury (AKI)[3,4]. The purpose of this review is to explore recent literature on epidemiology, pathogenesis and outcomes of patients with COVID-19 and AKI. Of note, the information is preliminary and rapidly evolving with emerging publications.

Epidemiology

Several studies with the exception of few have reported increased incidence of AKI in patients with COVID-19 infection. Reported incidence of AKI in various studies including unpublished literature is listed in Table 1. Of note, there is wide variation in reported incidence of AKI ranging from 0-29%. This is partly explained by mostly single center studies from China with limited sample size with the exceptions of studies from Guan and Cheng et al. In addition, difference in severity of illness at different centers may be a plausible explanation for difference in incidence of AKI among different reports.

The study by Cheng et al. was specifically focused on incidence of AKI and its impact on outcomes of Covid-19 patients. There were two additional important observations in this study. First, among patients with elevated baseline creatinine, AKI was more common (9.1 vs. 2.0%), more severe (Stage III AKI - 3.6% vs. 0.7%) and happened sooner (2 vs. 6 days) compared to those with normal baseline creatinine. Second, abnormal renal parameters were noticed even on admission with proteinuria, hematuria, elevated blood urea nitrogen (BUN) and creatinine were present in 44%, 26.9%, 15.5% and 14.1% respectively[10].

In another data by Zhen Li et al (unpublished), a similar remarkable proportion of patients exhibited abnormalities of renal parameters at admission to the hospital, including 59% with proteinuria, 44% with hematuria, 14% with elevated BUN and 10% with elevated serum creatinine. Most of these abnormalities were mild. However, overall elevation of BUN and creatinine was found in 31% and 22% of all patients during hospital stay[17].

Pathogenesis of AKI

Pathogenesis of AKI in patients with COVID-19 is likely multifactorial[10,18]. The plausible mechanisms and supporting evidence or rationale is listed in table 2. Of note, presence of viral RNA in urine has not been linked to AKI and is only sporadically demonstrated. Wang L et al found viral RNA in urine in 7.5% of 53 tested patients of whom none developed AKI[5]. In another study, none of the 72 tested patients had viral RNA in urine[8], while Guan et al found viral RNA in one urine specimen but it is not clear how many patients were tested[6].

Table 1: Incidence of acute kidney injury in COVID-19 patients as presented in the recent literature.

Author	Location & Number of Patients	Incidence of AKI	CRRT*
Wang L Am J Nephrol March 2020[5]	Wuhan N=116	0%	
Guan NEJM Jan 2020[6]	30 Regions in China N=1099	0.5%	0.8%**
Chen et al Lancet Jan 2020[7]	Wuhan N=99	3%	9%**
Wang et al JAMA Feb 2020[8]	Wuhan N=138	3.6%	1.45%
Zhang et al Med Rxiv Feb 2020[9]	Wuhan N=221	4.5%	2.3%
Cheng et al Kidney Int. March 2020[10]	Shanghai N=701	5.1%	
Huang et al Lancet Jan 2020[11]	Wuhan N=41	7%	
Chen et al BMJ March 2020[12]	Wuhan N=274, 113 (Deceased)	11%, 25% in deceased	1%
Zhou et al Lancet March 2020[13]	Wuhan N=191	15%, 50% in deceased	5%
Arentz et al JAMA March 2020[14]	Seattle USA N=21	19%	
Diao et al MedRxiv March 2020[15]	Wuhan N=85	23%	
Yang et al Lancet Resp Med Feb 2020[16]	Wuhan N=52 (ICU)	29% (ICU)	17%

*CRRT – Continuous Renal replacement therapy
**Higher utilization of CRRT compared to incidence of AKI may reflect an attempt to achieve negative fluid balance in patients with Adult respiratory distress syndrome (ARDS) or remove inflammatory mediators in septic patients, though it was not clearly documented in respective papers. Possibility of typographic error cannot be excluded either.

Table 2: Possible mechanisms of acute kidney injury in patients with COVID-19 infection.

Mechanisms	Rationale/Evidence
Direct viral cytopathic effect	Abundant expression of angiotensin converting enzyme II (ACE II) receptor in kidneys which is used by Novel corona virus for cell entry[1,19]. Demonstration of SARS-CoV-2 nucleocapsid (NP) protein on immunohistochemistry in renal tubules in an autopsy study[15].
Acute tubular necrosis	Contributing factors may include volume depletion, cytokine storm, hypoxia, shock or rhabdomyolysis[6,10,20]. Demonstration of acute tubular necrosis with CD68+ macrophage infiltration of the tubulointerstitium and C5b-9 deposition on tubules in an autopsy study[15].
Immune complex mediated mechanism due to deposition of viral antigens (less likely)	Findings of proteinuria and hematuria in two studies[10,17]. However, these findings are non-specific. Finding of normal glomerular histology on autopsy in patients affected by Covid-19[15] and a related SARS-CoV in 2003[21] argues against this mechanism.

Management of AKI

There is not much details in published literature regarding strategies for management of AKI. It is likely that these patients were managed in standard way like any other critically ill patient in ICU. Fluid conservative strategy (or negative fluid balance strategy) was likely employed especially in patients with ARDS[22]. This is supported by data from Guan et al and Chen et al, in which 9 patients had CRRT despite only 6 and 3 patients developing AKI respectively (likely to achieve negative fluid balance) [6,7]. Choice of renal replacement therapy appears to be CRRT in various studies.

Guidelines mainly based on opinion and existing evidence for other critically ill patients have emerged for patients with COVID-19 in intensive care unit (ICU)[23] who are more likely to develop AKI. Key features of these guidelines which may be relevant to the practice of nephrologists are listed as follows:-

1) Strict infection control practices
2) Conservative fluid strategy
3) Use of crystalloids rather than colloids and avoidance of hydroxyethyl starch
4) Use of nor-epinephrine for shock followed by vasopressin or epinephrine and avoidance of dopamine
5) Use of steroids for refractory septic shock.

Indications of hemodialysis are likely be standard with utilization of CRRT wherever available. Others can use prolonged intermittent renal replacement therapy. In patients with ARDS and AKI, RRT may be required sooner if unable to achieve conservative fluid balance. Strict adherence to recommended infection control practices should be observed during dialysis treatment.

Prognosis

There is very limited information on impact on AKI on patient outcomes in published literature. In a study by Cheng et al, AKI was independently associated with increased mortality (Hazard ratio 2.2, 95% CI 1.1-4.4). Of significance, among those with elevated baseline creatinine, development of AKI resulted in increased incidence of death (30.9% vs. 9.2%) compared to those with normal baseline serum creatinine. In addition, elevated BUN, creatinine, proteinuria and hematuria at admission were also found to be independent predictors of mortality.[10,24] Zhen Li et al (un-published) also found that AKI was associated with ~5.3 times increased risk of mortality in an unadjusted analysis [17]. Similarly, Zhou et al found association of serum creatinine > 133 µmol/L with increased mortality in an unadjusted analysis but not in a multivariate model [13].

Conclusion

The research on COVID-19 and especially on its renal implications is still evolving. Based on limited literature, it appears that patients with COVID-19 and especially those needing intensive care are susceptible to renal injury due to either or combination of direct viral cytopathic effect or inflammatory response and its consequences. Management strategies will include monitoring of renal function, optimization of hemodynamic parameters, tailoring fluid balance strategies based on respiratory status, avoidance of nephrotoxic medications and initiation of renal replacement therapy for standard indications.

Conflict of Interest: None declared

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