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.

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 Reported incidence of AKI in various studies including unpublished literature is listed in Table 1.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.

Pathogenesis of AKI
Pathogenesis of AKI in patients with COVID-19 is likely multifactorial15,19. 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 AKI17. In another study, none of the 72 tested patients had viral RNA in urine, while Guan et al found viral RNA in one urine specimen but it is not clear how many patients were tested16.
COVID-19 and AKI

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Location &amp; Number of Patients</th>
<th>Incidence of AKI</th>
<th>CRRT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang L, Am J Nephrol</td>
<td>Wuhan N=116</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Am J Nephrol March 2020</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guan NEJM Jan 2020</td>
<td>30 Regions in China N=1099</td>
<td>0.5%</td>
<td>0.8%**</td>
</tr>
<tr>
<td>Chen et al Lancet Jan 2020</td>
<td>Wuhan N=99</td>
<td>3%</td>
<td>9%**</td>
</tr>
<tr>
<td>Wang et al JAMA Feb 2020</td>
<td>Wuhan N=138</td>
<td>3.6%</td>
<td>1.45%</td>
</tr>
<tr>
<td>Zhang et al MedRxiv Feb 2020</td>
<td>Wuhan N=221</td>
<td>4.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Cheng et al Kidney Int. March 2020</td>
<td>Shanghai N=701</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Huang et al Lancet Jan 2020</td>
<td>Wuhan N=41</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Chen et al BMU March 2020</td>
<td>Wuhan N=274, 113 (Deceased)</td>
<td>11%, 25% in deceased</td>
<td>1%</td>
</tr>
<tr>
<td>Zhou et al Lancet March 2020</td>
<td>Wuhan N=191</td>
<td>15%, 50% in deceased</td>
<td>5%</td>
</tr>
<tr>
<td>Arentz et al JAMA March 2020</td>
<td>Seattle USA N=21</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Diao et al MedRxiv March 2020</td>
<td>Wuhan N=85</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Yang et al Lancet Resp Med Feb 2020</td>
<td>Wuhan N=52 (ICU)</td>
<td>29% (ICU)</td>
<td>17%</td>
</tr>
</tbody>
</table>

*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.

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

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. 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). 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) 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 non-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 to 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.
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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. Zheng et al (unpublished) also found that AKI was associated with ~5.3 times increased risk of mortality in an unadjusted analysis. 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.

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

References