

## COVID 19 and Acute Kidney Injury

### Abstract

Coronavirus disease 19 (COVID-19) is caused by severe acute respiratory syndrome-coronavirus (SARS-CoV-2), a beta coronavirus, mainly involves the respiratory tract, and the clinical features simulate to a severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) of the past. The genome of the SARS-CoV-2, isolated from a cluster-patient with a typical pneumonia after visiting Wuhan, had 89% nucleotide identical with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. It enters the respiratory tract through angiotensin converting enzyme-2 (ACE2) receptors on alveoli. It may induce lung injury through direct cytopathic effect, involving effector T cells or causing sepsis and inducing cytokine storm. With a similar mechanism, it can cause acute kidney injury (AKI). The overall incidence of AKI is 5.1%, and AKI is an independent risk factor for mortality. The hazard ratio of death increases with the increasing severity of AKI. Management of COVID-19 with AKI is primarily supportive care, and at present, there are no evidence based effective antivirals for the treatment.

**Keywords:** Acute kidney injury, coronaviruses disease, COVID-19, outcomes, severe acute respiratory syndrome

### Introduction

Coronavirus disease-19 (COVID-19) is caused by a beta-coronavirus, which has been named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) on February 11, 2020, by the International Committee on Taxonomy of viruses by the World Health Organisation (WHO).<sup>[1]</sup> It has been called SARS-Cov2 because the primary manifestations of the disease are severe respiratory tract involvement, similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>[2]</sup>

### Worldwide situation

The recent outbreak of COVID-19, in December 2019 in Wuhan City, Hubei province of China, started with a cluster of pneumonia patients gradually gripping the world leading to declaration as a pandemic by WHO in March, 2020.<sup>[1,3]</sup> As of the date on March 25, 2020, WHO reported a total of 3,75,498 confirmed cases, and 16,362 deaths from 196 countries.<sup>[4]</sup> After China, it spread to the United States, Europe, and Asia, and now increasingly cases are being reported from Europe and other parts of Asia outside

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China. A total of 1,990 confirmed cases with 65 deaths have been reported from the South-East Asia Region.

### India specific situation

As of March 23, 2020,<sup>[5]</sup> the Indian Council of Medical Research data showed a total of 18,383 samples from 17,493 individuals had been tested, and 415 individuals were positive for SARS-CoV-2, and 7 deaths have been claimed because of COVID-19 infection. In an opinion by the Director of Center for Disease Dynamics, Economics and Policy (CDDEP), applying mathematical models used in the USA or the United Kingdom to India points to a possible 300 million (30 crore) cases in India, out of which 10 crores will face severe COVID infection,<sup>[6]</sup> if appropriate severe control measures are not taken. Looking at the incidence of 5.1% of AKI in severe cases,<sup>[7]</sup> there may be the potential of 5.1 million AKI patients because of COVID-19, and many of them may require renal replacement therapy (RRT). It is not surprising that if community spread happens in India, with limited resources and health infrastructure, it may be challenging to combat the situation of patients with multiorgan failure and AKI. However, India can handle the COVID-19, and its affects if the disease spreads over a long period of time.

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Moreover, COVID-19 appears more contagious than SARS and MERS, spreads by human-to-human transmission via droplets infections and fomites. The incubation period ranges from 2 days to 2 weeks (usually 3 to 7 days).

### AKI and SARS-CoV-2: Clinical Manifestations

Though COVID-19 manifests primarily as diffuse alveolar damage, interstitial pneumonia, and acute respiratory failure, the involvement of other organs such as the kidney, heart, digestive tract, blood, and nervous system is potentially possible.<sup>[8-10]</sup> It has been reported that SARS-CoV and MERS-CoV had infected more than 10,000 people in the past 2 decades, with mortality rates of 10% and 37%, respectively.<sup>[11,12]</sup> In the previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%–90%) mortality rate.<sup>[13]</sup> A study reported that although AKI was uncommon in SARS but accounted for the fiercely high mortality of 91.7%, notably 33 out of 36 cases died.<sup>[14]</sup> Kidney involvement was a strong and independent predictor of mortality during the SARS and MERS outbreak, suggesting the similar situation for the kidney involvement with COVID-19 infection as well.

The incidence of AKI with COVID-19 has been reported varying from 3%–9%.<sup>[15-18]</sup> A large prospective study has reported the overall incidence of 5.1%.<sup>[7]</sup> In a study of 59 COVID-19 patients with 28 severe cases and 3 deaths, Li *et al.*<sup>[19]</sup> found that 34% of patients had proteinuria on the first day of admission, and 63% developed proteinuria during the hospital stay. Nineteen percent of people showed an elevated level of serum creatinine. Blood urea nitrogen (BUN) was elevated in 27% patients and in two-thirds of patients who died. Each one of those (27/27) who had computerized tomography (CT) abdominal scan showed radiographic abnormalities of the kidneys with reduced density suggesting inflammation and edema. The study also emphasized that renal impairment may be an independent factor of mortality.

In another larger prospective study, Cheng Y *et al.*<sup>[7]</sup> reported 701 patients (median age 63 years with interquartile range, 50–71 years, and 367 males) admitted in a tertiary teaching hospital following the outbreak of COVID-19 in Wuhan city of China. A total of 113 (16.1%) died in the hospital, and the median time to death was 6 days (IQR 3–12) days. On admission, 43.9% of patients had proteinuria, and 26.7% had hematuria. The prevalence of elevated serum creatinine, elevated BUN, and estimated glomerular filtration (eGFR) under 60 ml/min/1.73m<sup>2</sup> were 14.4%, 13.1% and 13.1%, respectively. Overall, AKI was reported in 5.1% of patients. Patients with kidney disease had a significantly higher risk of in-hospital death. Cox proportional hazard regression confirmed that elevated baseline BUN (3.97, 2.57–6.14), and elevated baseline serum creatinine (hazard ratio: 2.10, 95% CI: 1.36–3.26)

was an independent predictor of mortality. It has also been observed that the hazard ratio for mortality also increases with the staging of AKI from 1.9 in stage 1, 3.51 in stage 2, and 4.38 in stage 3 AKI. The hazard ratio of mortality also increased with the degree of proteinuria and hematuria. These factors remain significant factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity, and leukocyte count. The incidence of in-hospital mortality in patients with elevated baseline serum creatinine was 33.7%, significantly higher than patients with normal baseline serum creatinine (13.2%). However, the major limitation of the study was that baseline coexisting chronic kidney disease (CKD) could not be assessed.

### Mechanism of AKI with COVID-19

The mechanism of kidney involvement is at present speculative and appears multifactorial. The susceptible host, particularly elderly and people with underlying diseases like hypertension, cardiac diseases, bronchial asthma, diabetes, etc., are at a risk of severe disease. Like any other viral infection causing kidney injury, the direct viral cytopathic effect on kidney is a postulated mechanism. The virus does not show any evidence of renal tropism. The viral nucleic acid material of CoV in blood and urine in SARS-CoV infection as well as in COVID-19 patients, supports this hypothesis.<sup>[20,21]</sup> Recently, SARS-CoV-2 from the urine sample of an infected patient has been isolated, suggesting the kidney as the target of this novel coronavirus.<sup>[22]</sup>

The molecular study showed SARS CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptor for cell entry like SARS-CoV. ACE2 and dipeptidyl peptidase-4 (DPP4), both expressed on renal tubular cells, were identified as binding partners for SARS-CoV and MERS-CoV, respectively.<sup>[23,24]</sup> ACE2 expression is 100-fold higher in kidney tissues than the lung.<sup>[19]</sup> However, still clinical observation is different that there is more severe lung injury than kidneys in SARS and SARS-CoV-2 as well.

The normal glomerular pathology on microscopy and the absence of electron-dense deposit on ultrastructure microscopy in SARS-CoV patients, do not support the hypothesis of the immune complex-mediated glomerular injury though direct effector T cell-mediated injury could be another postulated mechanism.<sup>[14]</sup> Another important mechanism appears to be virus-induced sepsis and the release of cytokines in circulation leading to severe inflammatory response, hypotension, hypoxia, shock, and the aggravation of target organ injuries, including kidneys as well. The clinical pictures of patients with COVID-19 with sepsis supports this hypothesis.

Most of the patients had mild symptoms with fever, sneezing, cough, sputum, and dyspnea, which indicate severe lower respiratory tract injury. The manifestations

with severe COVID-19 are multi organ involvement, which includes respiratory events such as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status, and functional alterations of other organs. The functional changes were expressed as the laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia. These patients may require intensive care unit treatment. Huang *et al.*<sup>[21]</sup> revealed that all of their 41 patients in the study had pneumonia with bilateral lobular and sub segmental consolidation on CT, and 32% of them required intensive care. The patients requiring intensive care had higher plasma cytokine levels of (interleukin [IL]-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-inducing protein-10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1a, and tumor necrosis factor  $\alpha$ ) on admission. These findings suggest that some of them may benefit from the removal of cytokines during continuous renal replacement therapy (CRRT).

### Diagnosis of AKI

The diagnostic criteria and AKI staging is not different than AKI in other situations.<sup>[25]</sup> The diagnosis of COVID-19 itself is based on the history of contact, clinical and laboratory evidence with hemogram, biochemical parameters, chest imaging with CT and virological examination.<sup>[26]</sup> The confirmation of the diagnosis requires a nucleic acid amplification test with reverse transcriptase polymerase chain reaction (RT-PCR) and other techniques. Many in-house and commercial available nucleic acid detection assays for COVID-19 are available.<sup>[26]</sup> Next-generation gene sequencing can also be used. WHO appointed many referral laboratories in different countries.<sup>[27]</sup> A serological test has also been developed and allowed the detection of a cluster of cases in Singapore.<sup>[28]</sup>

### Treatment

At present, the management strategies of COVID-19 with AKI is primarily conservative in the form of good hydration, nutritional support, paracetamol for fever, headaches and body aches, and antibiotics in the case of secondary bacterial infection only, with aiming for the self-recovery. Along with patient treatment, spread to others also should be given importance. The patient with respiratory distress may require oxygen therapy and intensive care with ventilatory support in the case of acute respiratory distress syndrome. All confirmed COVID-19 patients need to be isolated. An N95 fit-tested respirator and protective clothing and equipment are essential for patients, and the caregivers should also use appropriate approved personal protective equipments (PPEs).

There is no evidence-based effective antiviral therapy available. In a prospective study of AKI with COVID-19, the three most used medicines were antivirals (73.0%),

antibiotics (71.0%), and glucocorticoid (36.9%). Antivirals showed mortality benefit, and the glucocorticoids did not, which is possible because clinicians have used steroids mainly in the terminally sick patients. The varieties of anti virals were used, including arbidolhydrochloride, ganciclovir, interferon, lopinavir and ritonavir, oseltamivir, and ribavirin. However, there was no significant difference on AKI with these therapies.<sup>[7]</sup>

The most recent New England Journal of Medicine (NEJM) study of a randomized controlled trial<sup>[29]</sup> showed no mortality benefit of treatment with lopinavir-ritonavir combination (19.2%) as compared to the standard of care arm (25%). The median time of clinical improvement was only one day shorter in the treatment arm. Lopinavir-ritonavir treatment was stopped early in 13.8% because of adverse events. With some success story with remdesivir in COVID-19 treatment, a clinical trial is currently going on.<sup>[30]</sup> Chloroquine phosphate showed some efficacy against COVID-19 associated pneumonia in a multicentre clinical trial conducted in China.<sup>[31]</sup> The National Taskforce for COVID-19 by the ICMR recommended the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for healthcare workers involved in the care of suspected or confirmed cases of COVID-19 in a dose of 400 mg twice a day on Day 1, followed by 400 mg once weekly for next seven weeks; and for household contacts of laboratory-confirmed cases in the dose of 400 mg twice a day on Day 1, followed by 400 mg once weekly for next three weeks; to be taken with meals. The warning with this advisory also mentioned that the health care workers should not have a false sense of security with this chemoprophylaxis and other preventive measures should remain continued.<sup>[32,33]</sup>

Few retrospective analyses showed benefit with the use of glucocorticoids in SARS-CoV infection.<sup>[34,35]</sup> Metanalysis on the use of glucocorticoids in previous SARS-CoV infection do not support the use of glucocorticoids in COVID-19 as well. In a meta-analysis of corticosteroid use in patients with SARS, four studies showed harm with higher psychosis, diabetes, avascular necrosis, and delayed viral clearance.<sup>[36]</sup> WHO does not recommend the use of steroid expecting potential inhibition of viral clearance and prolongation of the duration of viremia.<sup>[37]</sup>

### Experimental strategies

The use of convalescent plasma showed speedy clinical recovery in some patients with COVID-19 in China.<sup>[21]</sup> Two trials, an open-label, non-randomized clinical trial (NCT04264858) and another multicentre, randomized, and parallel-controlled trial (ChiCTR2000029757) on the efficacy of convalescent plasma in patients with COVID-19, are awaiting results.

In the modern era of monoclonal antibodies directed therapy, the researchers showed encouraging results with



the use of monoclonal antibodies in the treatment of SARS infection as well. An in-vitro study showed neutralizing activity in an assay with a monoclonal antibody directed against the Ras-binding domain of the S- protein of Middle East respiratory syndrome coronavirus (MERS-CoV). However, no such evidence is available against COVID-19.

Inflammatory cytokines levels were extremely high in critically sick patients with infection.<sup>[21]</sup> Tocilizumab, a monoclonal antibody against the IL-6 receptor, may be of benefit; however, its use in treatment requires more evidence. The safety and efficacy of tocilizumab in COVID-19 infection are also under clinical trial (ChiCTR2000029765).

### Extracorporeal therapy

The indication of dialysis remains standard as for any other AKI patients. CRRT, with high volume hemofiltration that will be capable of removing inflammatory cytokines, appears theoretically advantageous. CRRT was successfully used in the treatment of SARS, MERS, and sepsis in the past.<sup>[14,38]</sup> A study showed significant improvement in the Sequential Organ Failure Assessment scores at day 7 in patients with sepsis treated with high-volume hemofiltration and removal of IL-6.<sup>[39]</sup>

In summary, COVID-19 infection may involve kidneys besides the respiratory tract leading to proteinuria, hematuria, and AKI. AKI is an independent risk factor for mortality. With the increasing stage and severity of AKI, the hazard ratio of death of patients with COVID-19 also increases. The management strategies applied for AKI in COVID-19 are supportive only. COVID-19 patients need to be isolated to prevent the spread of infection.

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### Conflicts of interest

There are no conflicts of interest.

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