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Review

# The Hypothesis of the COVID-19 Role in Acute kidney Injury: A Literatures Review

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## HIGHLIGHTS

- Patients with COVID-19 contamination might have acute kidney injury.
- Death is significantly higher among patients with acute renal failure.
- The main risk factors for acute kidney injury are male sex, diabetes mellitus hypertension,cardiovascular disease.

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## ABSTRACT

Coronavirus disease 2019 (COVID-2019) is a viral infection that mainly causes pulmonary infection but mortality usually occurred in patients have comorbidity, such as chronic kidney disease (CKD) that accounts for over 20% of mortalities, morbid obesity, immunosuppression, diabetes mellitus, hypertension, and cancer. Also, the incidence of acute kidney failure reported 5-10% in outpatient series and up to 50% in patients that need to be admitted in the intensive care unit. It is important to know that acute kidney injury (AKI) is associated with increased mortality, so this essay is going to review possible mechanisms that result in AKI. Based on the multifactorial mechanism of AKI, we should have considered probable causes of AKI and act on a stepwise manner to tackle these mechanisms and improve the ultimate prognosis of patients. Although most of the measures are supportive, in some patients such as severely ill cases cytokine storm may be attributed to the severity of symptoms, so immunomodulatory treatments could be considered to decrease AKI and consequently mortality. Among hypotheses that propose AKI; pre-renal and direct renal involvement by virus discussed in detail.

**Keywords:** Acute Kidney Injury; Acute Tubular Necrosis; Chronic Kidney Disease; Covid-2019; Infection

## Introduction

Up to now, two main groups of β-coronavirus has been recognized:1-Human coronavirus that includes 6 types of virus and in most cases result in mild illness without significant complications. The 2-Zoonotic coronavirus consists of 3 types of the virus; severe acute respiratory syndrome (SARS) that recognized in 2003 and Middle East respiratory syndrome (MERS) that introduced in 2012; both of these viruses result in respiratory infection and recently coronavirus disease 2019 (COVID-2019) infection that results in pandemic respiratory infection (1). Bat is the primary host in all three strains. The intermediate host for SARS is civet and for MERS is a camel, but the Intermediate host for COVID-19 is debated and the first suspected origin was seafood market and recently pangolin is suggested as the main intermediate host (2, 3) and the final host for 3 viruses is human. COVID-19 infection is the most virulent strain that resembles up now that emerges in December 2019. According to the last update of the world health organization (WHO), the coronavirus brings up 53,000,000 infected cases and about 1,300,000 deaths up to November 2020 (4).

COVID-19 infection is accompanied by moderate to severe disease in 20% of patients and the remaining have mild symptoms (5). The incidence of acute kidney failures increases with the severity of the disease. The Kidney

disease improving global outcome (KDIGO) definition was used to identify acute kidney injury (AKI); the peak serum creatinine value more than 1.5. The evidence shows that AKI increases mortality 4 to 5 times (5, 6).

**Methods**

Searching in databases such as PubMed, Scopus, Embase, Medline, and Web of science for all retrospective, prospective, and review articles with these keywords; covid-19, coronavirus plus kidney disease or acute tubular necrosis (ATN), or acute kidney injury. We have chosen the English literature, between Nov. 2019 and Nov. 2020.

**Summary of Researches**

In the study by Pie et al., they evaluated 333 patients with COVID-19 contamination and revealed that about 75% of them had acute kidney injury or abnormal tests in their urinalysis. Among those patients, thirty-five patients had acute kidney damage but sixteen of them had finally gained normal renal function. Death was significantly higher among patients with acute renal failure (about 10 times higher) (6).

They concluded that although renal involvement is common in these patients and most of them recovered without any sequel, it can result in increased mortality (7). In an interesting study in the USA (NYC) by Yamada et al., they evaluated 3,391 patients and discovered about 6% had chronic renal failure. In this category of patients need a ventilator and subsequently, the death rate (especially in advanced age above eighty years old) was higher (8).

In another contradictory study by Wung et al., they assessed medical archives of 116 patients from January 14 to February 13, 2020. Incidence of uremia was mentioned about ten percent and only seven percent of patients had proteinuria. They quoted that acute kidney injury is infrequent in these patients and does not accompany a significant sequel (9).

Among patients with AKI exact mechanism of kidney injury is disputed. In the study by Su et al., the autopsy was made on twenty-six patients for renal specimens. Nine patients displayed evidence of acute kidney injury in laboratory assessment. They surveyed the sample by light microscopy, electron microscope, and immunohistochemical (IHC) staining. In light microscopy, they detected proximal tubular damage. In electron microscopy, they detected groups of virus-like spots with distinct spears in the tubular epithelium, and finally, IHC staining was positive in the tubular segment of specimens. They concluded that this virus directly invades the kidney tissue (10).

In a different study by Rossi et al., as a case report in the evaluation of kidney specimens; the only part of the kidney that was involved by the virus was the tubular segment and other parts of the kidney were not involved by the virus. Interestingly no evidence of virus was observed in electron microscope (EM) evaluation. They concluded that ATN is related mainly to pre-renal causes than direct injury to tubule by a viral infection and we should not only rely on morphologic finding (11).

In the study by Diao et al., they hypothesized the combined mechanism of direct kidney injury by a virus and an exaggerated immune response to virus contributed to ATN in infected patients because they find evidence of virus particle and simultaneously the presence of inflammatory cell in renal specimens that result in tubular damage (12, 13).

In a conflicting study by Miller et al., they mentioned that usually direct involvement of kidneys by viral infection associated with viruria but they did not observe this finding in infected patients. Additionally, they mentioned that the manifestation of the virus in kidney specimen only reveal the viral entrance to kidney and does not mean pathologic involvement of renal system, so multifactorial etiology (viral invasion, and pre-renal etiology) may have essential roles (14).

**Discussion**

AKI is prevalent in patients with coronavirus infection (between 5-50% in non-admitted and admitted patients respectively (15). The death rate reported significantly higher among patients with acute renal failure (about 10 times higher) (6). It could be a consequence of severe pulmonary involvement and multiple organ dysfunction. In a study by Cheng et al., they assessed 701 patients and revealed that the incidence of ATN was about five percent. Also, they discovered that AKI is more common in patients with pre-existing renal failure (12% vs. 4%) (6).

In a large study by Richardson (USA-NYC) 5700 cases were assessed and revealed that AKI incidence was 5-7.5%. Incidence of AKI was fifty percent in patients needed intensive care unit. The main risk factors for AKI were male sex, hypertension (HTN), and diabetes mellitus (15). Conditions like HTN, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), chronic kidney disease (CKD), morbid obesity, immunosuppression have been linked with increasing of death (16, 17). Two studies from china declared that the mortality rate will increase with age (about 1.5 percent between 50–60 years to about 15 percent in 80 years) (18, 19).

In the very clarifying study from Italy, data from the Italian Health Institute, specified that about half of the patients had three or more comorbid conditions and the remaining had one or more comorbid diseases and about one percent had no previous illness. The comorbid illnesses were HTN, DM, CKD in decreasing the prevalence. Interestingly prevalence of chronic kidney disease was more common than pulmonary disease among fatal cases

of viral infection (20).

There are some challenges about the pathophysiology of kidney injury, if the mechanism of pathogenesis will be identified, then the protocols and some preventive or therapeutic measures could be designed to care for these patients and decrease mortality.

The exact role of angiotensin-converting enzyme (ACE) in the pathogenesis of infection largely studied and mentioned that the ACE-2 receptor is frequently expressed in the lung, GI system, liver, and kidney and consequently virus can contaminate these organs. In the study by Qi et al., discovered that the most frequent site for this factor was the renal proximal tubular segment (21). It is recommended that there is renal tropism for viruses especially renal tubules that result in ATN. As mentioned earlier some researchers cited that they discovered the virus in kidney tissue analysis by EM and believe in the direct effect of the virus on the kidney that results in AKI. Rossi et al. did not find a virus in the kidney and believed in ATN due to pre-renal cause (11). Diao et al., in their investigation cited that the combined mechanism of viral tissue invasion and exaggerated immune system response (cytokine storm) may lead to AKI (12, 13). It seems that a multifactorial mechanism could be considered for AKI in covid infection.

In patients that require to ventilator due to acute respiratory distress syndrome (ARDS), there is a hypo-perfusion state that results in AKI; in some patients idea of rhabdomyolysis due to cytotoxic effect of the virus on the muscle, tissue hypoxia and drug toxicity proposed (10).

In the study by Batlle et al., quoted that hypercoagulability can result in obstructing microvasculature of the kidney (22). AKI may have made by a cytokine storm. In this situation, the immune system concurrently damages the virus and normal organs such as the kidney.

Based on the multifactorial mechanism of AKI, we should have considered probable causes of AKI and act in a stepwise manner. In critically ill patients that need ventilation support, fever and insensible fluid loss can result in pre-renal volume depletion, so careful monitoring of fluid to prevent hypo-perfusion and rhabdomyolysis is essential. Some studies mentioned that if conventional treatments of acute kidney damage are unsuccessful hemodialysis can be started (23).

## Conclusions

In critically ill patients, the management of hypercoagulability states that can result in complications such as microvasculature thrombosis in the kidney and other organs should be considered. In severe inflammatory response due to cytokine storm in very ill patients, the treatment that lessens the immune system could be considered to decrease AKI and consequently mortality.

## Authors' contributions

AM is the being responsible of study conception and wrote the manuscript and provided data, SMKA supervised the process and edited the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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## Conflict of interest

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## Ethical statement

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## Data availability

Not applicable.

## Abbreviations

| | |
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| ACE | Angiotensin-converting enzyme |
| AKI | Acute kidney injury |
| ARDS | Acute respiratory distress syndrome |
| ATN | Acute tubular necrosis |
| CKD | Chronic kidney disease |
| COPD | Chronic obstructive pulmonary disease |
| CVD | Cardiovascular disease |
| DM | Diabetes mellitus |
| HTN | Hypertension |
| MERS | Middle East respiratory syndrome |
| SARS | Severe acute respiratory syndrome |

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