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Editorial

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ACUTE KIDNEY INJURY IN COVID-19 INFECTION: A QUALITATIVE REVIEW OF LITERATURE

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ABSTRACT

COVID-19 is a coronavirus infection of the respiratory system, with multiorgan involvement. Acute kidney injury (AKI) is one of the complications of covid-19 infection. This review explored the epidemiology, pathophysiology, risk factors, and outcome of AKI in Covid-19 infection. There is huge variability in the incidence of AKI among COVID-19 patients from different regions of the world. Some modifiable and non-modifiable risk factors that can increase a patient's risk of developing AKI have been identified. Mortality is significantly increased if a COVID-19 patient develops AKI. Avoidance of risk factors and improve survival and reduce morbidity among patients. Long term follow up is recommended for survivors with AKI to monitor for future kidney disease.

Keywords: *Acute kidney injury, COVID-19*

INTRODUCTION

COVID-19, which was first described in December 2019, has since been declared a pandemic in March 2020 by the WHO, and has caused a significant worldwide morbidity and mortality. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The gold standard for diagnosing infection is by identification of SARS-CoV-2 RNA in respiratory tract secretion saliva by real-time polymerase chain reaction, but other methods such as detection of viral antigen and antibody production against the virus have been used for diagnosing COVID-19 infection as well [1, 2, 3]. The route of human-to-human transmission is through inhaled respiratory droplets and direct contact [4, 5, 6]. The median incubation period for the virus is 5.1 days, with symptoms mostly developed within 11.5 days [7]. Clinical features of the disease have been reported as a wide spectrum, from asymptomatic infection to mild respiratory tract symptoms to viral pneumonia, and finally multiorgan failure and death at the end of the spectrum.

The main system implicated in this disease is the respiratory system, but other systems such as the kidneys are also affected, especially in severe diseases. Epidemiological studies have pointed out several factors which increased one's susceptibility to symptomatic and severe disease, such as older age, metabolic syndrome, diabetes and cardiovascular disease [8]. The presence of end-organ damage such as lungs or kidneys increased the risk of mortality [8]. Patients with COVID-19 develop more severe acute kidney injury (AKI), require more dialysis and are less likely to have inpatient renal recovery compared to patients without COVID-19 [9], hence predisposing them to new onset or progression of chronic kidney disease [10]. This review study aimed to explore in-depth and to bridge the knowledge gap regarding AKI in COVID-19 disease.

METHODOLOGY

The aim of this systematic literature review was to review evidence regarding AKI in COVID-19, focusing on incidence, pathophysiology, risk factors, and outcome. A systematic search was conducted in PubMed/MEDLINE, Scopus and Cochrane Center Trials databases to identify all

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publications on AKI in COVID-19 patients. Search terms such as "COVID-19", "Coronavirus", "SARS-CoV-2", "Severe Acute Respiratory Syndrome Coronavirus 2", "acute kidney injury", "acute renal impairment", and "acute renal failure" were used. All articles from 1st December 2019 to 12th January 2022 were included. All relevant literature and their reference lists were reviewed by two independent reviewers using inclusion and exclusion criteria. The inclusion criteria included case reports, case series, prospective and retrospective cohort studies, systematic reviews, and meta-analyses assessing AKI in adult COVID-19 patients. Animal studies, letters, studies on kidney transplant patients, studies with only abstract published, and studies not in English were excluded. As this is a qualitative review, there is no statistical method involved.

EPIDEMIOLOGY

There are variable ways studies define AKI in COVID-19 patients. AKI is defined by Kidney Disease Improving Global Outcomes (KDIGO) as an increase in serum creatinine by > 26.52umol/L or increase in serum creatinine > 1.5 times from baseline, or a reduction in urine to < 0.5 mL/kg/hour for six hours [11]. It is further divided into Acute Kidney Injury Network (AKIN) stages based on serum creatinine level changes. Another way of defining AKI is using the Acute Dialysis Quality Initiative (AQDI) RIFLE criteria, which specify degree of kidney impairment (risk, injury and failure), and outcome (loss and end stage kidney disease). Some studies defined AKI based on two-fold increase in serum creatinine between baseline and peak level during hospitalisation.

A meta-analysis consisting of 39 clinical studies on AKI n COVID-19 infection reported incidence of 15.4%, which increased to 53% among patients with severe COVID-19 infection, and 4.3% of these patients required some form of kidney replacement therapy (KRT) [12]. Another larger meta-analysis consisting of 79 studies from Asia, North America and Europe described an incidence rate of 10.6%, and that those with more severe disease were more likely to require continuous KRT [13].

A systematic review of sixty studies from China, the USA, Korea and Europe recorded a 19.45% pooled incidence of AKI in COVID-19 patients, and KRT requirement incidence among COVID-19 patients with AKI at 39.04% [14]. In a separate systematic review, which included

Study	Type of study	Region	Studies number	Sample size	Median age (years)	CKD included?	AKI
Fabrizi et. al.,[12] 2020	Systemic review & meta-analysis	China, USA, Korea	39	25566	61	Yes	15.4%
Lin et.al.,[13] 2020	Meta-analysis	China, USA, Europe, Kuwait, Mexico, Iran, Hong Kong	79	49692	N/A	N/A	10.6%
Raina et. al.,[14] 2021	Systemic review	China, USA, Korea, France, UK	60	42612	61.1	Yes	19.45%
Xu et.al.,[15] 2021	Systemic review	China, USA, Korea, Europe, Singapore, Japan	22	16199	61.2	N/A	10%
Zheng et.al.,[16] 2020	Systemic review	China	25	10419	56	Yes	6.5%
Sundaram et. al.,[17] 2021	Retrospective cohort	India	1	110	61	N/A	28.2%
Hirsch et. al.,[18] 2020	Retrospective cohort	USA	1	6477	AKI: 69 Non AKI: 61	N/A	36.6%
See et. al.,[19] 2021	Retrospective cohort	Singapore	1	707	46	N/A	8.1%
Chan et. al.,[20] 2021	Retrospective observational	USA	1	3993	64	Yes	46%

Table 1: Incidence of AKI in COVID-19 patients.

N/A = Not available

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22 studies from China, the USA, East Asia, Europe and Singapore, the incidence rate of AKI was recorded at 10% and among these patients, 4% required KRT [15]. Another systematic review including 25 studies only from China showed a pooled incidence of AKI in COVID-19 patients at 6.5%, with increased incidence in intensive care units at 32.5% [16].

A retrospective cohort study consisting of 110 hospitalised COVID-19 patients in South India reported a 28.2% incidence of AKI [17]. This is lower than that found in a retrospective cohort study conducted in the USA, which reported an incidence of 36.6%, among which 14.3% required KRT [18]. This study also showed an increased rate of AKI among ventilated patients at 89.7%, versus non ventilated patients at 21.7%. Nearer to home, a retrospective cohort study from Singapore recorded an even lower incidence of AKI among COVID-19 patients at 8.1%, possibly due to younger median age among the patients [19]. A retrospective observational study conducted in the USA showed that the incidence of AKI was 46% among COVID-19 patients [20].

In Malaysia, the average 7-day incidence rate of COVID-19 was reported to be at 26.6 per 100000 population [21]. AKI was reported at 4% among COVID-19 patients in Malaysia [22].

From these studies and analyses as summarized in Table 1, we know that the incidence of AKI among COVID-19 patients were between 6.5% to 46%, with a lower incidence among Chinese patients and highest among those in the USA. This can be explained by the different criteria for hospitalisation, by which the China healthcare system isolated and hospitalised all positive patients whereas the USA healthcare system admitted those who are significantly more ill and require intervention or treatment.

PATHOPHYSIOLOGY

Coronaviruses are enveloped RNA viruses with a nucleocapsid. SARS-CoV-2 is made up of four main structural proteins, namely the surface spike which resembles a crown, envelop glycoprotein, nucleocapsid and membrane proteins, as well as 16 non-structural proteins [23]. The virus enters the host cell via the binding of its spike protein to the host angiotensin 2 (ACE2) receptors and then priming by the host transmembrane serine protease 2 (TMPRSS2). After entry, the virus is replicated by endocytosis and virion assembly [24]. There are two stages of SARS-CoV-2 pathogenesis, namely the earlier viral replication phase, followed by host cell immune response to the infection via inflammatory cells recruitment and cytokine release.

1. Direct tissue invasion and role of ACE2

Various studies implicated the effect of direct viral invasion and injury to the renal tissue. In a post-mortem biopsy of a COVID-19 patient with renal failure, there was virus visualization and isometric vacuolization of proximal tubules [25]. Post-mortem renal biopsy of 26 patients found SARS-CoV-like particles and its positive antibody staining in the renal tubules, supporting the pathophysiology of direct viral invasion to renal tissues [26]. An autopsy of nine patients in the UK reported acute tubular injury in all biopsies, real-time PCR targeting viral E gene was found positive in three patients, and one sample showed positive sub-genomic viral RNA [27, 28]. Renal tissue viral tropism is further supported by a study that isolated SARS-CoV-2 from post-mortem kidney tissue, demonstrating the virus ability to replicate in non-human primate kidney tubular epithelial cells [29]. This same study identified a higher frequency of viral RNA in kidney tissue among patients with AKI compared to those without. Another post-mortem renal biopsy of six patients reported acute tubular necrosis, sloughing of luminal brush border, vacuole degeneration and detection of viral antigen via immunohistochemistry [30]. SARS-CoV-2 particles have been found in urine samples [26, 31], which could be explained by the viral release into the tubular lumen from the damaged tubular epithelial cells, as the large virus size reduces the likelihood that it underwent glomerular filtration [32].

ACE2 receptors and the host TMPRSS2 play a significant role in the pathogenesis of AKI in COVID-19 infection by serving as a target for viral attachment. In vitro cell study demonstrated the attachment of glycoprotein spikes on the surface of SARS-CoV-2 to ACE2 and entry into cell; the spike protein is cleaved by cellular TMPRSS2 causing the release of fusion peptides leading to membrane fusion [33, 34]. Co-expression of ACE2 and TMPRSS genes in the kidneys has been reported in proximal tubule brush border apical membrane and podocytes in the kidney [35, 36]. Post-mortem renal biopsy results of 26 patients showed diffuse acute tubular injury as evidenced by the loss of brush border, vacuolar degeneration, and tubular lumen dilatation containing cellular debris, besides endothelial injury and distinct expression of ACE2 in proximal tubular cells especially around areas of severe injury [26]. Diffuse polymorphonuclear casts in the tubule lumens and multiple bacterial foci. Erythrocyte stagnation in glomerular capillary loops and peritubular areas without fragmentation of red cells or thrombi was also described [26].

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In COVID-19 infection, angiotensin II is increased [37] causing downregulation of ACE2, which leads to activation of type 1 angiotensin receptor activation, decreased formation of angiotensin 1-7 and worsening of AKI [38]. Angiotensin II reduction, with its subsequent increase in renin through a positive feedback loop, has been demonstrated in COVID-19 patients with AKI [39, 40], leading to poor outcomes in critically ill patients [41, 42]. However, inhibition of the renin-angiotensin-aldosterone system (RAAS) is not associated with an increased risk of hospitalisation or severe disease in COVID-19 patients [43].

2. Systemic inflammation and role of cytokines

Systemic inflammation and cytokine storm have been described to be another mechanism through which AKI develop in COVID-19 patients. Patients with AKI showed increased inflammatory markers such as ferritin, D-dimer, erythrocyte sedimentation rate, procalcitonin and C-reactive protein, signifying the role of inflammation in kidney injury [44, 45, 46]. In severe disease, immune overactivation leads to cytokine storms, causing systemic inflammation [47]. COVID-19-associated macrophage activation and cytokine storm lead to tissue factor release and coagulation factor activation, resulting in a hypercoagulable state [48]. A study also reported strong complement C5b-9 (membrane attack complex) deposition in the renal tubules of COVID-19 patients, suggesting the role of complement pathway activation in inflammatory cascade and procoagulant state [30]. Another study detected C3c and C3d in glomerular capillaries and renal arteries, C3d in the tubular compartment, as well as C5b-9 in peritubular capillaries tubular basement membrane and arterioles [49]. Activation of the complement system leads to inflammatory response, vascular damage and coagulation. However, the cytokine storm mechanism has been challenged by shreds of evidence of lower interleukin-6, interleukin-8 and TNF levels in COVID-19 patients compared to sepsis patients and those with non-COVID ARDS [50, 51], which suggest that inflammation is a contributory factor in kidney injury rather than the main mechanism.

3. Glomerulonephritis

Renal biopsy data from 47 patients in a study based in France reported that the majority of AKI in critically ill patients were of tubular origin, and who were not critically ill had collapsing glomerulopathy and focal segmental glomerulosclerosis [52]. Although the pathophysiology of collapsing glomerulopathy in COVID-19 is unknown, it has been postulated to be similar to HIV-associated nephropathy, via podocyte injury through autophagy and mitochondrial disturbances [53]. Collapsing glomerulopathy and thrombotic microangiopathy have also been reported in COVID-19 patients by others [54, 55].

Some of these histological abnormalities are found in patients without an increase in serum creatinine or oliguria, signifying a cellular level of injury occurring in COVID-19 patients without disrupting clinical renal function. Besides increases in serum creatinine, other reported renal manifestations include proteinuria, hematuria, hyperkalemia, hyponatremia and metabolic acidosis [56, 57, 58]. A systematic review reported pooled proportion of proteinuria among COVID-19 patients at 52.47% and that of hematuria in the patients at 35.89% [14]. However, low molecular weight proteinuria rather than albuminuria has been reported by a study, signifying tubular injury instead of glomerular [59].

4. Prothrombotic state and other contributing factors

A few other publications reported that besides the mechanisms of AKI described above (cytokine storm, complement dysregulation, activation of angiotensin II pathway), nephrotoxic treatments, respiratory distress causing hypoxia, hypovolemia, prothrombotic state of the disease and nosocomial sepsis could contribute to the development of renal injury among COVID-19 patients [38, 60, 61, 62]. Renal artery thrombosis has been reported in some case studies [63, 64]. To summarize, the pathophysiology of AKI in COVID-19 is multifactorial and often, injury begins at the cellular level before renal function impairment clinically.

RISK FACTORS AND PREDICTORS

Various studies and analyses have described some risk factors for the development of AKI among COVID-19 patients. A meta-analysis study reported that age 60 years and above had a higher risk of AKI with an odds ratio of 3.53 and the risk of AKI with the severe disease showed an odds ratio of 6.07 [13]. Listed here are some factors that predisposed patients to higher risk of developing AKI in the course of the disease.

1. Baseline characteristics

Older age [12, 13, 18, 65, 66, 67, 68], male gender [18, 68, 20], and black race [18] have been associated with higher risk of developing AKI in COVID-19 disease.

2. Comorbidities

COVID-19 patients were reported to be at higher risk of developing AKI if they have following comorbidities such as increased body mass index [68, 69], chronic habit of cigarette smoking [68], hypertension [18, 65, 68], diabetes mellitus [18, 68], cardiovascular disease [18, 65, 68, 69], premorbid respiratory disease [18], premorbid chronic kidney disease [66, 67, 68, 20, 70, 71, 72], arterial hypertension [12] and cancer [68].

3. Disease characteristics

Some of the predictors of the development of AKI in COVID-19 disease include disease severity [13, 19, 65], higher baseline inflammatory markers [67, 72, 73] and usage of mechanical ventilation [18, 68, 72]. Concurrent presence of hematuria and proteinuria are strong predictors of the development of AKI [17], and the more severe these urinary abnormalities were, the higher the mortality rate [38, 45].

4. Medications

Medications usage that were associated with higher risk of AKI are vasopressor medication [18, 68], baseline usage of medications inhibiting the renin-angiotensin-aldosterone system [19] and nephrotoxic medications (vancomycin and nonsteroidal anti-inflammatory drugs) [19]. However, the discontinuation of inhibitors of renin-angiotensin-aldosterone system did not affect the disease severity of COVID-19 or renal functions [74].

Treatment in a tertiary hospital was found to imperceptibly reduce the risk of AKI [18]. The presence of AKI increases the risk of requiring mechanical ventilation [75]. Some of the predictors of mortality include age, male gender, diabetes, cerebrovascular disease, more than two-fold increase in serum lactate dehydrogenase, and degree of severity of AKI [76].

OUTCOME

There are three main outcomes of AKI in COVID-19 patients, namely recovery of renal function, progression to chronic kidney disease and death.

One study reported that only 30% of patients with AKI had renal recovery at discharge [20]. Complete renal recovery of 81.7% and partial recovery of 17.2% upon discharge among patients with AKI in COVID-19 was reported, with worse outcomes in more severe kidney injury and those with premorbid chronic kidney disease [76]. Another study found that among the survivors, the incidence of chronic kidney disease was 15% three months after suffering AKI during COVID-19 infection [77]. A retrospective cohort study consisting of 1612 patients documented that the patients with COVID-19 who developed AKI during hospitalisation had estimated glomerular filtration rate decline by 11.3 mL/min/1.73m2 per year faster compared to non-COVID-19 patients who had AKI from other illnesses [78].

Meta-analysis involving 49692 patients reported an increased risk of death in COVID-19 patients with AKI, with an odds ratio of 11.05. Continuous KRT is predictably required significantly more in severe disease, with an odds ratio of 6.6 [13]. Another meta-analysis also showed the increased mortality among patients with AKI, with an odds ratio of 15.4 [12]. One systemic review found that the mortality among patients with acute renal impairment to be higher at 54.24% versus 17.71% overall [14]. Similarly, in another study mortality was reported to be at 50% among hospitalised COVID-19 patients with AKI [20]. Ninety-day mortality of 31% was documented in a prospective cohort study, with increased mortality among the elderly, obese, diabetic, and severe ARDS patients [79]. A retrospective cohort study in India of 110 patients reported a mortality rate of 24.5% with a strong association between AKI and death [17], whereas a study in Turkey demonstrated a mortality rate of 38.9% [76].

DISCUSSION

COVID-19 is a worldwide pandemic disease with AKI as a significant complication that increases mortality risk. Vaccination and reduction in human contact are among the current prevention measures for COVID-19. The incidence of AKI among COVID-19 patients varied from 6.5% to 46%. This huge variation can be attributed to the patients selected for studies; the degree of disease severity among the hospitalised patients has to be taken into account. The majority of the publications reviewed reported the incidence of AKI in hospitalised COVID-19 whereas a significant proportion of patients who underwent non-healthcare setting quarantine or self-monitoring were under-represented by these data.

SARS-CoV-2 has been shown to directly invade and cause injury to the renal tissues with predilection at the tubular cells. Other mechanisms of injury include inflammation, cytokine storm, complement dysregulation, activation of angiotensin II pathway, nephrotoxic agents, hypoxia due to respiratory distress, hypovolemia, prothrombotic state of the disease and nosocomial sepsis. The list is non-exhaustive and is still under study.

Several risk factors have been identified to predispose

COVID-19 patients to AKI. Identification of the non-modifiable risk factors such as older age, male gender and black race increases the awareness among the healthcare provider towards population at risk. The increased mortality among elderly patients and in those with premorbid illnesses can be due to reduced renal functional reserve, decreased functioning renal mass and diminished stress-induced renal capacity to increase its glomerular filtration rate [80]. Modifiable risk factors such as pre-morbidities especially chronic kidney disease and nephrotoxic treatment or medications should be avoided especially among the at-risk patients, to lower the chances of developing AKI. Future studies on the early markers of AKI in COVID-19 will be required to identify patients with renal cellular injury from the disease before it progresses to clinical renal function impairment.

Treatment for COVID-19 has not been reviewed in this publication due to its ever-evolving nature involving various ongoing clinical studies. The mainstay treatment for COVID-19 disease is a steroid, and a study showed that steroids improved the chances of renal function recovery after an acute injury [81, 82]. Besides steroids, current management for AKI in COVID-19 is mainly supportive, with the use of KRT when indicated which is tailored to the haemodynamic status of the patients [83]. Volume repletion, avoidance of nephrotoxic medications and treatment of sepsis are among the supportive management given to these patients. When required, standard protocol and prescription for continuous KRT can be given to the COVD-19 patients with AKI as per those without COVID-19 as studies have shown no difference in circuit patency and effectiveness of the therapy, with personal protective equipment and proper disinfection between use [84, 85, 86]. Clinical trials on extracorporeal cytokine removal treatment are ongoing.

From our review, only a portion of AKI patients recovers to baseline creatinine before discharge, with some reported delayed renal recovery during outpatient follow up [68]. There were a number of these survivors who went on to develop chronic kidney disease and renal failure. Failure of renal function recovery to baseline has been associated with increased mortality and subsequent chronic kidney disease [87]. This highlights the importance of long term follows up for the patients who developed AKI during COVID-19 disease regardless of renal function upon discharge.

Vaccination efforts against SARS-CoV-2 have been made worldwide as a preventive measure to limit COVID-19 contagion and mortality. Several case reports found de novo minimal change disease (MCD) and AKI following vaccination [88, 89, 90, 91], as well as relapse of MCD post vaccination [92, 93]. Besides MCD, other glomerulonephritis with AKI has been reported following COVIDd-19 vaccination include IgA nephropathy, focal segmental glomerulosclerosis, anti-glomerular basement membrane nephritis and NELL-1-associated membranous nephropathy [94, 95, 96]. AKI associated with PR3-ANCA vasculitis [97] and MPO-ANCA vasculitis [98] have also been reported following vaccination. These reports involved both messenger RNA-based and adenovirus vector-based vaccines, and it has been postulated that immune mediated mechanisms mimicking natural response to COVID-19 infection may have lead to the injury, although there is no concrete evidence available currently on the pathophysiology of vaccine-related AKI. As current evidence shows overwhelming benefits of COVID-19 vaccination in preventing severe disease and death, nevertheless, physicians should be aware of the possible rare association between the acute flare of renal disease and vaccination.

The strength of this review is that it contains a summary of various aspects related to AKI in COVID-19 disease. The weakness of this review is that it is a qualitative review that did not involve statistical analysis of the data. We also did not review treatment of AKI in COVID-19 in detail, as there is sparse variability of evidence-based treatment besides that discussed above. COVID-19 has been a worldwide disease burden since the end of December 2019, and there is much room for improvement in terms of knowledge for this disease.

CONCLUSION

COVID-19 pandemic worldwide has led to significantly high morbidity and mortality. AKI is prevalent among hospitalised patients, especially among those critically ill. Studies have shown worse outcomes among patients with adverse kidney involvement. Risk factors have been identified, which may help stratify at-risk patients, prioritize monitoring and initiate preventive measures. Long term follow-up among the survivors with or without renal recovery is advocated because of their increased risk for subsequent chronic kidney disease and worsening of premorbid renal impairment.

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