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Narrative Review

Assessment of Acute Kidney Injury in Critically Ill Sars-Cov-2 Patients: A Narrative Review

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ABSTRACT

Background: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has highlighted acute kidney injury (AKI) as a significant complication among hospitalized patients, with varying incidences reported globally. The pathophysiology of COVID-19 related AKI encompasses direct viral damage, systemic inflammation, and the activation of the renin-angiotensin-aldosterone system (RAAS), among other factors. This complexity underscores the need for a detailed understanding of its epidemiology, clinical presentation, and management strategies to improve patient outcomes.

Objective: To synthesize current knowledge on the epidemiology, pathophysiology, clinical presentation, and management of AKI in COVID-19 patients, aiming to identify key factors influencing incidence rates, patient prognosis, and effective therapeutic approaches.

Methods: A comprehensive review of literature was conducted, examining studies from various geographical regions that reported on the incidence, risk factors, pathophysiological mechanisms, clinical presentation, and management of AKI in COVID-19 patients. Data on renal replacement therapy needs, mortality rates, and outcomes related to different management strategies were also collated.

Results: The incidence of AKI among COVID-19 patients varies significantly, with higher rates observed in critically ill patients. Key risk factors include older age, pre-existing comorbidities (e.g., hypertension, diabetes mellitus), and severe COVID-19 infection. The clinical presentation of AKI in the context of COVID-19 is characterized by abnormalities in urinary sediment, including albuminuria and hematuria. Management strategies largely align with those for AKI due to other causes, focusing on fluid and hemodynamic management, cautious use of nephrotoxic drugs, and consideration of RAAS inhibitors. The mortality rate among COVID-19 patients with AKI is notably high, particularly in those requiring renal replacement therapy.

Conclusion: AKI is a common and serious complication of COVID-19, associated with high morbidity and mortality rates. A multidisciplinary approach, incorporating current guidelines and tailored management strategies, is essential for the care of these patients. Further research is needed to fully understand the pathophysiology of COVID-19 related AKI and to identify effective treatments.

Keywords: COVID-19, SARS-CoV-2, acute kidney injury, epidemiology, pathophysiology, management, renal replacement therapy.

INTRODUCTION

The emergence of the coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, marked a significant pivot in the global understanding of infectious diseases. Originally identified in Wuhan, China, COVID-19 quickly demonstrated its capability to spread rapidly across the globe, leading the World Health Organization to declare it a pandemic by March 2020. Early reports by May of the same year indicated over 6.35 million cases and more than 245,000 fatalities worldwide (1), highlighting the virus's devastating impact. The history of coronaviruses traces back to 1937 with the identification of the infectious bronchitis virus in chickens by Hudson and Beaudette, while human infections with coronaviruses like HCoV-229E and HCoV-OC43 were known since the nineteenth century. However, the appearance of SARS-CoV-2 brought unforeseen challenges due to its severe respiratory manifestations, often leading to acute respiratory distress syndrome (ARDS) and a range of systemic complications including acute myocardial infarction, acute kidney injury (AKI), thrombotic events, and pulmonary embolism (2).

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Observations from clinical practices during the pandemic have underscored the virus's predilection for not only the respiratory system but also for causing severe disruptions across multiple organ systems, including cardiac, digestive, hematological, neurological, and renal functions (3). The association of COVID-19 with kidney involvement, especially among hospitalized patients, has been a significant concern due to its link with increased mortality and morbidity. The progression of the disease in such patients often leads from acute proteinuria and hematuria to acute kidney failure, necessitating renal replacement therapy or kidney transplantation. This kidney involvement is identified as a critical factor influencing mortality rates within hospital settings, with a direct impact observed on kidney cells.

In the context of acute kidney injury (AKI), the correlation with respiratory distress has been particularly noted. The incidence of AKI was found to be markedly higher among patients requiring mechanical ventilation compared to those who did not, with severe AKI occurring in close temporal proximity to the initiation of such ventilation (4). This observation is further supported by data showing an 89.7% rate of AKI among ventilated patients versus a 21.7% rate among non-ventilated patients, and a significant portion of these cases progressing to severe stages (stages 2 and 3) of AKI (5). Such findings suggest a profound link between severe forms of COVID-19 infection and the incidence of AKI, particularly among those in critical care settings.

Despite the initial focus on respiratory and systemic effects, the prevalence and characteristics of AKI in COVID-19 patients have not been fully elucidated, with early reports from China and Italy indicating a variable prevalence ranging from 0.5% to 29% (6). This variability highlights the challenges in obtaining comprehensive data on AKI, including its temporal relationship to respiratory failure, diagnostic criteria, and outcomes following renal replacement therapy. The lack of uniform data from Chinese hospitals points to the complexity of case recognition and patient care practices across different facilities, further complicating the understanding of AKI's impact on COVID-19 patients.

Acute kidney injury is now recognized as a common complication of COVID-19, particularly among those admitted to intensive care units (ICUs), with clinical histories suggesting its likely effect on more than 20% of hospitalized patients and over 50% of those in ICUs (7,8). The identification of predisposing factors and understanding the mechanisms underlying AKI in COVID-19 patients are crucial for the development of effective treatment and management strategies. Observations indicate that severe AKI is present in a significant proportion of ventilated patients, emphasizing the critical nature of renal hypoperfusion in severely ill COVID-19 patients (9). This review aims to explore the mechanisms of AKI development, its pathophysiology, potential treatment approaches, and strategies for early detection and prevention, underscoring the importance of specialized medical attention for affected individuals.

MATERIAL AND METHODS

This systematic review was conducted in adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines, aimed at evaluating the existing literature on the diagnostic biomarkers of Acute Kidney Injury (AKI) in the context of SARS-CoV-2/COVID-19 infection. The literature search and review process were carried out from January 2021 to July 2021, focusing on identifying studies that aligned with our predefined inclusion criteria. For inclusion, we considered cross-sectional, case-control, cohort, and randomized control studies that utilized biochemical markers for predicting AKI, with a reference biochemical marker of Renal Function Test and confirmation of COVID-19 infection through molecular methods. The scope of this review encompassed studies published in English, irrespective of their geographical location, during the pandemic period, including both abstracts and full articles.

We excluded studies focusing on the treatment and management of COVID-19 and AKI, as well as those from which the authors did not furnish the requested data within a four-week period following our inquiry. Additionally, unpublished reports and conference proceedings were omitted from our analysis due to their unreviewed status and the inherent difficulties in data verification.

The literature search was performed using databases such as Midline, Google Scholar, and PubMed, employing search terms such as "Acute Kidney Injury," "SARS-CoV-2," "COVID-19," "Diagnostic markers," and "biochemical markers." This was supplemented by reviewing additional citations not initially identified during the primary search. The study selection process involved an initial screening of titles and abstracts, followed by a full-text examination of those that met the preliminary criteria. Two independent reviewers assessed the studies for quality and relevance, categorizing them as (1) included, (2) not included, and (3) awaiting further review. Any disagreements between the two reviewers were resolved by consulting a third reviewer.

Data extraction was meticulously performed, with relevant information on diagnostic accuracy, sensitivity, and specificity being compiled in a Microsoft Word document to facilitate collaboration among reviewers. This process ensured a comprehensive evaluation of the selected studies, adhering to the principles of systematic review and meta-analysis.

In conducting this review, we also considered the ethical aspects of research involving human subjects. The studies included in our review were expected to comply with the ethical standards delineated in the Declaration of Helsinki, ensuring the protection of participants' rights, safety, and well-being. Although our review did not directly involve human subjects, the ethical integrity and

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compliance of the included studies with ethical standards were of paramount importance in our selection and analysis process. This ethical consideration underscores the commitment to maintaining high standards of research integrity and ethical conduct in the synthesis of evidence from existing literature.

FINDINGS

In the context of the COVID-19 pandemic, acute kidney injury (AKI) has emerged as a significant complication for hospitalized patients, prompting a detailed investigation into its risk factors, prevalence rates, and potential management approaches. The risk factors for COVID-19-related AKI can be broadly categorized into general risk factors, factors present at admission, and those emerging during hospitalization. General risk factors include old age, diabetes mellitus, circulatory disease or congestive heart failure, and excessive body mass index, among others. Upon admission, severe forms of COVID-19, high degrees of viremia, and compromised respiratory status are critical considerations. During hospitalization, exposure to nephrotoxins, the use of vasopressors, and the necessity for mechanical ventilation are key concerns that increase the risk of AKI.

Epidemiological data from various studies highlight the significant impact of COVID-19 on kidney health across different populations. For instance, retrospective and observational studies from China have reported varying rates of AKI and renal replacement therapy (RRT) needs, with mortality rates escalating with the severity of AKI. Similar observations have been made in the United States and the United Kingdom, where the prevalence of AKI among COVID-19 patients has been substantial, especially in those requiring ICU care. These findings underline the importance of early identification and management of AKI in COVID-19 patients to mitigate the risks of severe outcomes.

Management strategies for COVID-19-related AKI entail a combination of standard procedures and experimental approaches. Standard measures focus on the risk stage-based management and prevention of AKI, including monitoring kidney function through serum creatinine and urine output, fluid management with balanced crystalloids, glucose management to counteract insulin resistance and hypercatabolism, and careful assessment of the risk and benefits of nephrotoxic medications. Hemodynamic optimization is crucial for mitigating the risk of renal injury and respiratory failure. Experimental strategies include the use of immunomodulatory agents, systemic anticoagulation, antivirals, NSAIDs, statins, recombinant ACE2, and serine inhibitors. However, the efficacy of these experimental approaches in specifically managing AKI in the context of COVID-19 remains under investigation, with current literature providing limited direct evidence of their impact on AKI progression.

The management of AKI in COVID-19 patients involves a multifaceted approach that includes addressing underlying risk factors, adopting evidence-based clinical management strategies, and exploring new therapeutic options. The high prevalence and association with increased mortality emphasize the need for vigilant monitoring and proactive management of AKI in the context of COVID-19.

Table 1: Risk Factors for COVID-19 Related Acute Kidney Injury

General Risk Factors	At Admission	During Hospitalization
Old age	COVID-19 severe form	Nephrotoxins (medication, contrast exposure)
Diabetes mellitus	Degree of viremia	Vasopressors
Circulatory disease or congestive heart failure	Respiratory status	Mechanical ventilation (Airing)
Excessive body mass index		
Chronic renal disease		
Immunosuppressed state		
Hypertension		
Inherited risk factors (e.g., APOL1, ACE2 polymorphisms genotype)		
Hypovolemia		
Abdomyolysis		
Increased signs of inflammation (e.g., D-dimers, C-reactive protein, ferritin)		
Dehydration		
Exposure to medications such as angiotensin-converting enzyme (ACE) inhibitors (ARBs)		
Non-steroidal anti-inflammatory drugs (NSAIDs)		
Lymphopenia		
Leukocytosis		

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Table 2: Rates of Acute Kidney Injury with COVID-19 in Hospitalized Settings

Location	Study Design	Total Patients	RRT (%)	ICU (%)	HTN (%)	CKD (%)	DM (%)	CVD (%)	ESRD (%)	AKI (%)	Mortality with AKI (%)	References
China	Retrospective	116	4	0	37	4	16			0	NR	(2)
China	Observational	138	2	26		3	10	31		4, 8*	NR	(3)
China	Observational	333	3	17	32		23			11, 43**	57, 25-90***	(4)
China	Observational	701	NR	10	33	2	14			5	34	(5)
UK	Retrospective	2,743 / 10,547****	20 / 27****	100				0.7	2	RRT	80 / 50****	
USA	Observational	21	NR	100		48			10	19	NR	(6)
USA	Retrospective	5,700	4	22	56	5		18		24	NR	(7)
USA	Observational	1,000	14	24	60	14		19		34, 78*	NR	(8)
USA	Observational	575	15	30	72	29	48			28, 61**	50	
USA	Observational	2,215	20	100	60	13		22		43	NR	(9)
USA	Retrospective	257	31	100	63		36	19		NR	NR	(10)
USA	Retrospective	5,449	23	26	56		33	18		37	35	(11)

* In ICU
** In ICU (% of AKI patients)
*** Mortality rate by AKI stage (Stage 1, Stage 2, Stage 3)
**** April / July 2020 data

Table 3: Management Approaches for COVID-19 Related Acute Kidney Injury

Treatment	Rationale	Recommendations
Standard Procedures		
Standard measures	Management and prevention based on the risk stage of AKI.	Adopt strategies from guidelines appropriate for stage-based management and prevention of AKI in COVID-19.
Measurement of kidney function	Essential for clinical assessment of AKI risk and stage; serum creatinine and urine output are standard markers.	Monitor kidney function via serum creatinine and urine analysis.
Fluid management	Crystalloid composition for volume management has shown decreased AKI risk in non-COVID patients, such as in sepsis cases.	Use balanced crystalloids for initial IV volume replacement in patients with COVID-19 AKI.
Glucose management	Insulin resistance and a hypercatabolic state (hyperglycemia) are common in COVID-19.	Implement glucose-lowering strategies in high-risk patients.
Nephrotoxin management	Commonly prescribed in COVID-19 patients; the risk and benefits of medication, including NSAIDs, need assessment.	Limit the use of nephrotoxic drugs.
Hemodynamic optimization	Hypotension and hypovolemia are common; liquid and vasopressor therapy based on active assessment can reduce renal and respiratory complications.	Fluid and hemodynamic management should be tailored to the cardiovascular status.
Experimental Strategies		
Immunomodulatory agents	SARS-CoV-2 infection triggers cytokine release; these agents can inhibit cytokine production and block receptors.	Current evidence does not demonstrate an impact on AKI progression.

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Treatment	Rationale	Recommendations
Systemic anticoagulation	Thrombi in renal circulation can cause AKI.	No direct evidence linking anticoagulants to AKI management.
Antivirals	Viral infiltration of tubular cells affects renal function.	Antivirals may reduce the risk of COVID-19 infection and its renal implications.
NSAIDs	Possess anti-inflammatory properties.	The mechanism regarding AKI remains unclear.
Statins	Inhibit the production of pro-inflammatory cytokines and modulate immune responses.	The effect on AKI management is yet to be determined.
Recombinant ACE2	Deactivates SARS-CoV-2 and reduces ACE cellular activity.	The mechanism in the context of AKI is not well understood.
Serine inhibitors	Block serine protease-2 to prevent viral entry.	Under investigation for potential benefits in AKI management.

DISCUSSION

In the realm of medical research surrounding the SARS-CoV-2 pandemic, acute kidney injury (AKI) has emerged as a consequential concern, particularly among hospitalized patients. This narrative integrates observations from a series of studies conducted in diverse geographical settings, including a noteworthy case series from Wuhan that monitored 116 non-critically ill patients. In this cohort, a modest increase in creatinine and blood urea nitrogen (BUN) levels was identified in 10.8% of the patients, underscoring the incidence of AKI during hospitalization to be approximately 11% (ranging from 8–17%), with a more pronounced prevalence of 23% (14–35%) observed among critically ill individuals (10, 11). A discernible need for renal replacement therapy was identified in 5% of these critical cases. These findings, while instructive, necessitate cautious interpretation due to the constraints imposed by study design and external influencing factors. Additionally, the global illumination of kidney diseases through the lens of the pandemic has revealed significant variability in AKI incidence, further complicated by factors such as patient demographics, comorbidities, and variations in clinical management (12-14).

The pathophysiological underpinnings of COVID-19 related AKI remain incompletely elucidated. The direct viral damage mediated via the ACE2 receptor, excessive activation of the renin-angiotensin-aldosterone system (RAAS), and the surge in pro-inflammatory mediators are thought to play pivotal roles. Critically ill patients, often older individuals with pre-existing conditions like hypertension and diabetes mellitus, are at elevated risk. These conditions, coupled with therapeutic interventions that potentially influence renal hemodynamics, set the stage for a complex interplay of factors leading to AKI (15, 24, 25). The role of nephrotoxic substances, including certain medications and contrast media used in diagnostic procedures, further compounds the risk, although comprehensive analyses in the context of COVID-19 remain sparse (26).

Observations have highlighted a strong association between AKI and mortality among COVID-19 patients, with studies demonstrating a gradation in mortality rates corresponding to the stages of AKI (17, 18, 21-23). This correlation underscores the critical nature of kidney involvement in the prognosis of COVID-19 patients and accentuates the necessity for vigilant monitoring and management of AKI within this patient population.

The clinical presentation of AKI in the context of COVID-19 is notably characterized by abnormalities in urinary sediment, including albuminuria and hematuria, indicative of both tubular and glomerular damage. This renal involvement has been linked to direct viral infiltration, RAAS activation, and systemic inflammation, contributing to the complex pathogenesis of AKI in these patients (50, 51). Furthermore, the detection of SARS-CoV-2 in urine samples raises the possibility of the kidneys serving as viral reservoirs, although definitive evidence through viral culture is requisite for confirmation (5, 6, 29).

Histopathological analyses have unveiled a spectrum of renal abnormalities in deceased COVID-19 patients, ranging from acute tubular injury to glomerular pathology, suggesting direct viral effects and systemic factors contributing to renal damage. Notably, the impact of genetic predispositions, such as APOL1 variants, in exacerbating glomerulopathy among certain demographics warrants further investigation (52, 53, 54).

The management of AKI in COVID-19 patients largely aligns with standard practices employed for AKI arising from other etiologies, emphasizing fluid and hemodynamic management, cautious use of nephrotoxic drugs, and tailored therapeutic interventions based on individual risk profiles (74, 75). The application of RAAS inhibitors and other pharmacologic agents, while theoretically beneficial, remains to be substantiated through empirical evidence within this specific context (76, 77).

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CONCLUSION

In conclusion, AKI associated with COVID-19 presents a multifaceted challenge, with significant implications for patient outcomes. The variability in incidence rates and clinical presentations, coupled with the evolving understanding of its pathophysiology, underscores the imperative for ongoing research. Future investigations should aim to delineate the mechanisms of disease more clearly, identify effective therapeutic strategies, and establish robust guidelines for the management and prevention of AKI in COVID-19 patients. This endeavor necessitates a multidisciplinary approach, integrating insights from nephrology, infectious diseases, and critical care to optimize patient care and outcomes in the face of this unprecedented global health crisis.

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