CHAPTER

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Acute renal failure in patients with COVID-19: A literature review

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ABSTRACT
Introduction: Acute kidney injury (AKI) is a serious complication of the disease caused by the new SARS-CoV-2 and derives from numerous factors such as direct damage to the renal structures by the virus, the use of nephrotoxic drugs and the cytokine storm in response to the etiologic agent. Objective: In view of the relevance of AKI in the clinical outcome, the present study aimed to list the main aspects of the development of this complication in patients with COVID-19. Methods: A literature review was performed using the Virtual Health Library and Pubmed databases, adopting the descriptors "acute kidney injury" and "coronavirus 19". Results: 635 articles related to the topic were found, of which, after applying the inclusion and exclusion criteria, 23 studies were selected to integrate this review. The articles included were classified as retrospective cohorts and their samples were composed of individuals from Europe, Asia and the Americas. Discussion: Proteinuria, hematuria, leukocyturia and AKI were common clinical findings of renal impairment. AKI is a modifiable and multifactorial risk factor, uncommon in mild and moderate cases and common in severe cases. Age greater than 65 years, presence of comorbidities and laboratory tests with relevant alterations are important risk factors involved in AKI. Patients with stage 3 AKI required renal replacement therapy and were associated with an increased risk of developing chronic kidney disease. Conclusion: In patients with COVID-19 admitted to the ICU, a careful analysis of the clinical history and strict monitoring of laboratory tests are necessary to prevent the development of AKI.

Keywords: COVID-19, Risk factors, Kidney damage.

1 INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic began in 2020 and has represented, in recent years, a leading role in several studies to better understand the pathophysiological repercussions on the human body1. This pathology manifests clinically in an asymptomatic or symptomatic form, with mild or severe respiratory involvement, febrile syndrome, shock, electrolyte disturbances and acute renal failure (ARF) as a result of multiple organ failure2.

Acute kidney injury (AKI), recognized as a morbidity and mortality factor in hospitalized severe COVID-19 patients, presents pathogenesis related to multiple factors, such as the direct cytopathic effect on podocytes and tubules and accessory damage as a result of the use of nephrotoxic drug therapy3. Moreover, the systemic inflammatory response generates a storm of cytokines that activate the complement system and cause endothelial dysfunction4.

Common clinical presentations as a result of renal impairment revolve around hematuria and proteinuria. Studies have shown that more than 40% of patients hospitalized patients manifested the aforementioned symptoms5. Moreover, the microscopic evaluation of the urine of these patients pointed to the presence of acute tubular lesion with granulous and cloudy brown casts, in addition to leukocyturia6.

AKI, as a result of COVID-19, is a disorder associated with a worse clinical outcome in patients with severe SARS-CoV-27. In this context, the present study aimed to analyze the factors involved in the development of acute kidney disease in patients with severe COVID-19 disease.

2 METHODS

This is a literature review in the Public Medline (PUBMED) and Virtual Health Library (VHL) databases, from 2020 to 2022. The following descriptors were used: "acute kidney injury" and "coronavirus 19", in addition to the Boolean operators AND and OR.

The inclusion criteria were original articles published in English, Portuguese and Spanish, full articles and available in full. The exclusion criteria were articles that do not dialogue with the proposed theme, works written in languages other than those mentioned above, literature and/or systematic reviews, case reports and letter to the editor.

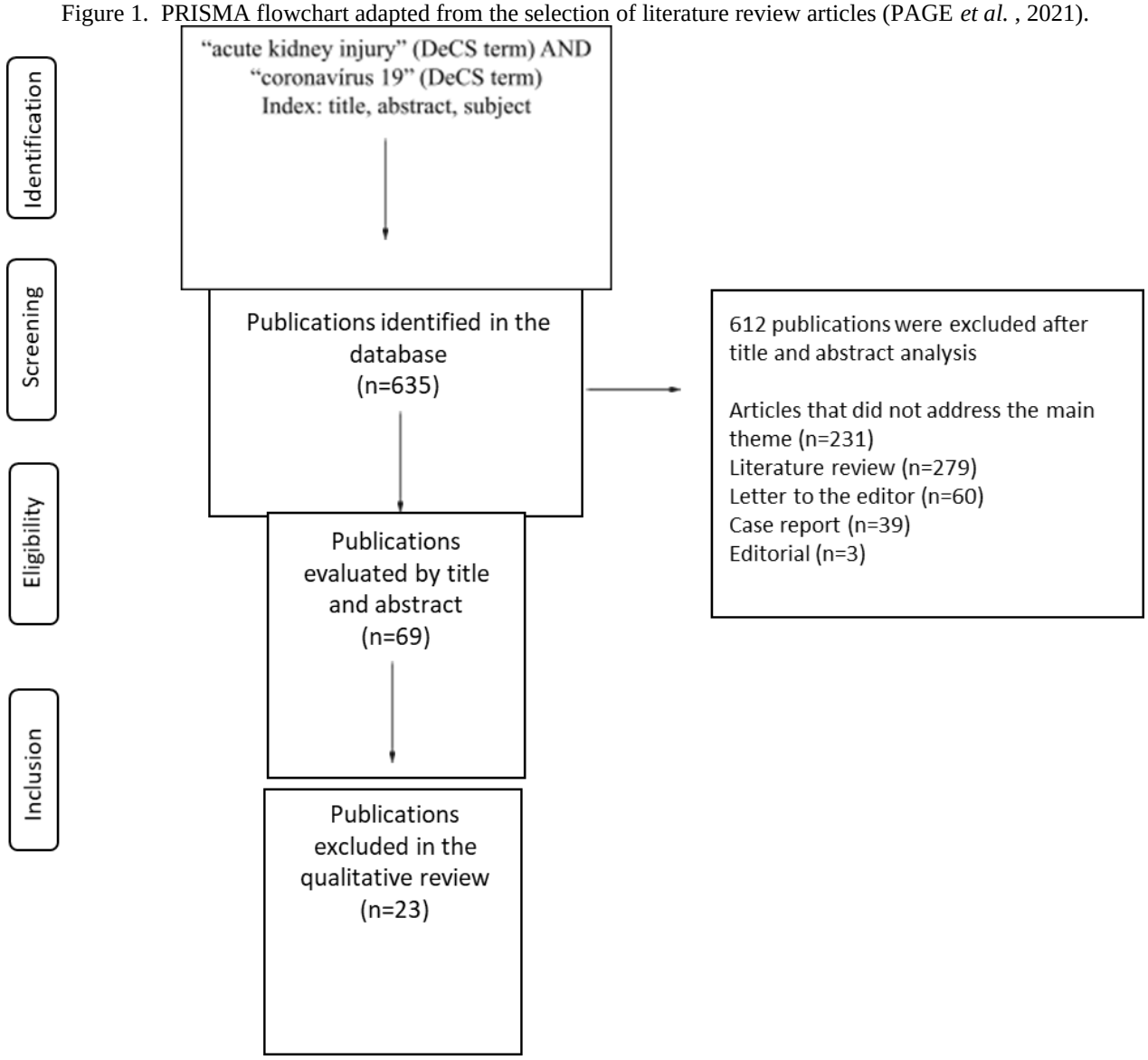
The selection of articles was performed by two independent evaluators and, in case of disagreements, a third examiner was called for the final consensus. The results were arranged in a spreadsheet, including year of publication, authors, databases and journals.

3 RESULTS

The search in the databases identified 635 publications. After the analysis of the title and abstract, only 69 articles had the full text evaluated and the other 566 were excluded. In the end, 23 articles were included and 46 did not meet the eligibility criteria because they did not dialogue with the objective of this review.

Figure 1 presents the flowchart with the inclusion and exclusion criteria specified for the selection of studies according to the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) model (PAGE *et al.,* 2021).

Figure 1. PRISMA flowchart adapted from the selection of literature review articles (PAGE *et al.* , 2021).



All included articles were classified according to the type of study, as retrospective cohorts, published between 2020 (21.73%) and 2021 (78.27%). The study samples included individuals from countries on three continents: Europe, Asia and America. China (5), the United Kingdom (3), the United States (2), Turkey (2) and Brazil (2) were the countries that most repeated themselves in the cohorts included in the qualitative synthesis. No studies on AKI in COVID-19 patients in countries in Africa and Oceania have been identified. Information on the location of the studies and the main results evidenced in the publications are shown in Table 1.

Most studies have shown the number of individuals with COVID-19 who have progressed to AKI. Thus, the highest incidence of AKI in patients infected with SARS-CoV-2 was 71.22%, identified in a Brazilian cohort whose mean age was 60 years1. In parallel, the lowest incidence (1.2%) was reported in a publication that evaluated AKI in children diagnosed with COVID-19 in a Chinese hospital19.

Table 1. Characteristics of the articles included in the qualitative synthesis of the literature review.

Author and Year	Sample Country	Sample	Main Results
Jewell *et al.*, 2021	United Kingdom	1248 adult patients with COVID-19 were enrolled at *King's College Hospital* in London.	The presence of chronic kidney disease (CKD) prior to admission increased the risk of developing AKI in hospitalized patients with COVID-19. Hypertension and diabetes were more frequent among patients with AKI than those without AKI. The use of hospital diuretics was associated with a risk of AKI. Black ethnicity was an independent predictor of AKI2.
Chen *et al.*, 2021	China	823 COVID-19 patients who were treated in Wuhan hospitals.	Hypophosphatemia was an independent risk factor for the development of AKI in hospitalized patients with COVID-19. Patients with AKI were also more likely to die than patients without AKI5.
Naser *et al.*, 2021	Bahrain	353 patients admitted to *Bahrain Defence Force* (BDF) hospital from April 2020 to October 2020.	Diabetes, hypertension, CKD and cardiovascular disease were higher in patients with AKI. Individuals who developed AKI had elevated inflammatory, cardiac or hypercoagulable serum markers and lymphopenia9.
Li *et al.*, 2021	China	223 patients, 52 patients from *Wuhan University'* s Zhaongnan Hospital, 70 from *Leishenshan* Hospital, and 101 patients from *Jiangjunshan Hospital.*	COVID-19 patients with AKI had a higher rate of pre-existing hypertension and cytokine storm compared to patients without AKI. More than half of the patients who received invasive mechanical ventilation developed AKI. Of the COVID-19 patients with ARF, 57.1% were susceptible to bacterial infection10.
Alfano *et al.*, 2021	Italy	307 patients admitted to the *University Hospital of Modena* with SARS-CoV-2 infection.	CKD, evaluation of non-renal sequential organ failure (SOFA), male gender, age over 65 years and glomerular filtration rate (GFR) lower than 45 ml/min were statistically significant risk factors for AKI11.
Chopra *et al.*, 2021	India	105 patients admitted no department of pediatrics from a tertiary care	The presence of sepsis, vasopressor support, hemodynamic instability,

		university hospital in New Delhi.	shock in the time of presentation, need for mechanical ventilation, and nephrotic syndrome were relevant risk factors for the development of AKI in children infected with SARS-CoV-212.
Charoennga m, *et al*., 2021	United States	1424 COVID-19 patients who were hospitalized at *Boston Medical Center* (BMC).	Black patients with COVID-19 were approximately 2.2 times more likely to develop in-hospital AKI and had higher levels of inflammatory markers compared to white patients with AKI13.
Caceres *and al*., 2021	United States	52 patients admitted to *Henry Ford Hospital in Detroit*, Michigan, with a clinical diagnosis of COVID-19.	A higher viral load of SARS-CoV-2 in urinary sediments of patients with COVID-19 correlated with increased incidence of AKI and mortality14.
Almeida *et al.,* 2021	Brazil	278 patients adults Boarding schools.com COVID-19 at the Hospital of the Federal University of São Paulo with COVID-19.	Hematological and inflammatory markers, hypertension, mechanical ventilation, and therapy with vasopressors have been associated with AKI in patients with severe COVID-19. Combined treatment with hydroxychloroquine and azithromycin was associated with renal dysfunction in these patients1.
Mohaved *et al.,* 2021	Iran	854 adult patients admitted with COVID-19 at *Baharloo* Hospital in Tehran were included.	The incidence of AKI in patients with COVID-19 was higher in patients receiving antibiotics against co-infections, in male patients, and in the elderly. The effects were greater in deaths and ICU admission, and AKI was associated with prolonged hospitalization15.
Xu *et al.,* 2021	Sweden	316 seniors with COVID-19 and 875 without COVID-19 were included, all of whom were admitted to two geriatric clinics in two hospitals in Stockholm.	The odds of developing AKI in elderly patients with COVID-19 were higher in those with reduced baseline kidney function and in patients with initial C-reactive protein (CRP) greater than 10 mg/L3.
Lowe *et al.,* 2021	United Kingdom	81 adult patients were admitted to the ICU of the *University Teaching*	The risk factors for the development of AKI were advanced age, diabetes *mellitus* and

		Hospital in Southampton diagnosed with COVID-19.	immunosuppression. AKI was associated with increased disease severity on admission, mechanical ventilation, elevated D-dimer and severe lymphopenia16.
This *et al.*, 2021	Singapore	707 COVID-19 patients admitted to the *National Center of Infectious Disease*.	Advanced age, congestive heart failure, initial use of iACE (angiotensin-converting enzyme inhibitors) or ARB (angiotensin-converting enzyme blockers) or ARB (angiotensin-converting enzyme blockers) angiotensin), initial statin use, exposure to aminoglycoside and vancomycin, use of NSAIDs (nonsteroidal anti-inflammatory drugs) in the hospital, exposure to contrast testing, and hypoxia were associated with an increased risk of developing AKI in SARS-CoV-217 infected patients.
Diebold *et al.*, 2021	Switzerland	188 patients adults Hospitalized No *University Hospital of Basel*, tested positive for COVID-19.	AKI in patients with COVID-19 occurs more in those in need of care and the severity of the condition correlates with the severity of the disease. Risk factors such as age, history of CKD, CRP levels and creatine kinase were identified as independent predictors of AKI6.
Costa *et al.*, 2021	Brazil	114 patients diagnosed with COVID-19 in the ICU of a private hospital in the ityo.	As independent predictors of the occurrence of AKI in patients with COVID-19, age and hypertension were identified7.
Pine *et al.*, 2021	Spain	237 patients who were admitted to the ICUs of the Hospital *Clínic of Barcelona* with a diagnosis of COVID-19 and AKI.	The prevalence of moderate/severe AKI in patients with COVID-19 admitted to the ICU is high and has a strong correlation with mortality and length of hospital stay18.
Wang *et al.*, 2021	China	238 COVID-19 cases admitted not Wuhan Children's Hospital.	Children critically ill with COVID-19 can develop AKI, especially after prodromal gastrointestinal symptoms. An inflammatory storm and complement-mediated injury may underlie the development of AKI in

			children with COVID-1919.
Yan *et al.*, 2021	China	882 patients over 65 years of age hospitalized by COVID-19 were recruited at *Tongji Hospital.*	It has been established that the incidence of AKI in patients with COVID-19 increases with age, due to the decline in renal function with aging, and with the increase in the number of preexisting comorbidities20.
Hamilton *et al.*, 2020	United Kingdom	1032 adult patients were admitted to the *Manchester University Foundation Trust Hospitals* with clinical and/or virological diagnosis of COVID-19.	Independent risk factors related to the development of AKI in patients with COVID-19 were being male or black, having higher serum sodium and baseline CRP, as well as a previous diagnosis of kidney disease4.
Li *et al.*, 2020	China	107 patients Elderly hospitalized with COVID-19 were included.	AKI can be seen as an indicator of poor prognosis, revealing more severe and multi-organ dysfunction. Independent predictors of incident AKI in patients hospitalized for SARS-CoV-2 infection who developed AKI in the ICU were septic shock, invasive mechanical ventilation and the need for vasopressors21.
Trabulus *and to the.*, 2020	Turkey	336 COVID-19 patients admitted to the tertiary university hospital in Istanbul.	AKI was more common in patients with estimated glomerular filtration rate (eGFR) baseline less than 60 mL/min/1.73 m2. At admission, eGFR appears to be a prognostic marker for mortality in patients with COVID-1922.
Oussalah *and al.*, 2020	France	149 patients with a confirmed diagnosis of COVID-19 and ACE inhibitor/ARB use data admitted to *the University Hospital of Nancy.*	The results corroborate the hypothesis of a deleterious effect of long-term therapy with iACE or ARB among patients with severe COVID-19 in relation to the risk of developing AKI23.

4 DISCUSSIONS

Initial reports regarding the current COVID-19 pandemic suggested a limited respiratory condition with little involvement of several organs, however it was evident, with the progression of the disease, the involvement of extra-respiratory organs4. Proteinuria, hematuria, leukocyturia and AKI have been described as common clinical presentations of renal involvement6.

AKI in patients with COVID-19 is an important complication of the disease2, being listed as a modifiable risk factor for mortality in patients with COVID-19, especially in environments with limited resources12. In mild to moderate cases, AKI is not common and is determined by subclinical renal abnormalities, in contrast, it is common in critically ill patients with COVID-19, affecting approximately 20% to 40% of ICU patients1.

The etiological mechanism of AKI in patients with COVID-19 is multifactorial, including direct virus injury, cytokine storm syndrome, antiviral drugs and vasoconstrictors5. Other factors include the use of nephrotoxic agents, such as NSAIDs12, as well as hemodynamic and hypercoagulability changes9. One study demonstrated evidence based on immunodetection of the expression of two SARS-CoV-2 proteins, nucleocapsid and spike in kidney cells from COVID-1914 biopsy samples. The virus also directly infects tubular epithelial cells and podocytes, causing significant structural damage16.

Cytokine storm and complement activation may play key roles in the pathogenesis of AKI in children with COVID-19, and subsequent dehydration with hypoperfusion of the kidneys increases the risk of developing AKI19. Secondary bacterial infections are also responsible for the cytokine storm, especially in individuals with decayed or compromised long-term immunity10. For the treatment of these opportunistic bacterial infections it is necessary to intervene with antibiotics, exposing the patient to nephrotoxic drugs such as vancomycin and amikacin12 that can lead to renal lesions, such as acute tubular necrosis and acute interstitial nephritis, direct cytotoxicity of the proximal tubule. Therefore, appropriate dosing of antibiotics should be administered to COVID-19 patients and monitored frequently to prevent AKI15.

In a cohort study in the United Kingdom, the average age of patients with AKI and COVID-19 was 69 years, 58% were male and 59.1% white and 27.4% black2. Age over 65 years is a strong predictor for AKI11. In children, the median age was 6 years, with the majority (47.6%) in the group of 5 to 13 years12. Age 80 to 90 years was associated with higher odds of AKI in patients with COVID-193. The study by Costa et al. [7] corroborated with age and gender profile, being mostly male (58.5%) and with a mean age of 66.5 years, also addresses that the mean body mass index (BMI) of the patients evaluated was 28 kg/m2.

Although the aforementioned cohort study in the United Kingdom points to a higher prevalence of AKI in COVID-19 in whites, the study by Charoenngam et al. [13] demonstrated that black individuals are more likely than whites to develop AKI. These differences can be explained by genetic particularities, socioeconomic status, access to care, diet, cultures, and other factors, as well as the interaction between them. Levels of inflammatory markers were higher in black patients, suggesting racial differences in the inflammatory burden of COVID-1913.

The main risk factors involved in AKI in patients with COVID-19 include long-term therapy with iACE and ARB23, use of statins before hospitalization, use of nephrotoxic drugs during hospitalization17, presence of comorbidities, glomerular filtration rate on admission22, as well as increased mean initial CRP value3. Critically ill patients with COVID-19 may be at increased risk of AKI due to hypoperfusion of the kidneys as a result of circulatory shock secondary to hypovolemia, sepsis, or cardiogenic shock due to underlying cardiovascular disease or new cardiac event17.

In addition, the laboratory tests that make up risk factors for AKI include thrombocytopenia, hypoalbuminemia, hypophosphatemia, in contrast to higher levels of lactate dehydrogenase (LDH), procalcitonin, CRP, urea and prothrombin time on admission5, as well as D-dimer, troponin I, ProBNP and ferritin. Thus, laboratory tests for serum albumin, hypercoagulability and markers of cardiac injury may be indicative of the development of AKI9. Children with AKI had leukocytosis and thrombocytopenia12, and also had anemia and thrombocytopenia19.

Regarding comorbidities, hypertension was the most common, followed by diabetes mellitus22. In addition, cardiovascular disease, chronic obstructive pulmonary disease (COPD), cerebrovascular disease21, previous diagnosis of kidney disease4, immunosuppression by any reason, including HIV, myelosuppression by hematological neoplasms and immunosuppressive therapy16. In the elderly, there is also a record of dementia3. Comorbidity in children is related to pneumonia, tuberculosis and hematological disorders/malignancy12. The presence of two or more comorbidities substantially increased the risk of developing AKI in patients with COVID-199.

Among patients with COVID-19 AKI, stage 3 received renal replacement therapy (RRT). All surviving patients with stages 1 and 2 and 3 with RRT had complete recovery of baseline renal function16. Normally, in the stage 1 and 2 group of AKI there were no deaths7. Patients with AKI were more likely to be admitted to intensive care, ventilated, more likely to die4, as well as more likely to use vasopressors and had high levels of urea nitrogen in the blood and uric acid21. Sepsis, septic shock, acute respiratory distress syndrome (ARDS), myocardial injury and liver injury were commonly observed complications in patients with AKI20. AKI has been associated with an increased risk of chronic kidney disease (CKD) in individuals with previously normal renal function and acute venous thromboembolism2.

In the cohort study by Piñeiro et al. [18] The treatment protocol for COVID-19 includes antiviral therapy with lopinavir/ritonavir, hydroxychloroquine, and azithromycin. If patients presented clinical deterioration, biological therapy was recommended, which most often included tocilizumab, anakinra, and/or corticosteroids. Corticosteroid use was associated with a 13% reduction in the need for RRT. Favipiravir may be an appropriate therapeutic option in pediatric patients with SARS-CoV-2 with reduced GFR without the need for dose adjustment24.

5 CONCLUSION

Acute kidney injury (AKI) is a common finding of renal involvement related to SARS-CoV-2 infection, being more frequent in severe cases and an important predictor of clinical outcome, especially in patients with stage 3 AKI. Because it has a multifactorial pathogenic mechanism, it is extremely important to pay attention to the treatment used during the hospitalization period, adjusting the dose and carefully monitoring the patient submitted to nephrotoxic drugs, and it is essential to monitor the levels of substances that predict AKI in the blood.

A careful analysis of the patient's clinical history is necessary, considering that the risk factors include several comorbidities and findings in laboratory tests. The advanced age (≥ 65 years) should be seen as a relevant variable for the development and outcome of the case. At the moment, ethnicity should not be listed as a predictor, since there are divergences in the existing literature, evidencing the need for further research on the subject. It is essential to emphasize that patients who survived 3rd stage AKI during the treatment of COVID-19 should have medical follow-up within 6 months of the outcome of the case, which is due to the high risk of developing chronic kidney disease.

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