

# COVID-19 AND KIDNEY INJURY: A LITERATURE REVIEW

COVID-19 E LESÃO RENAL: UMA REVISÃO DA LITERATURA

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## ABSTRACT

**Introduction:** Although the kidney injury associated with COVID-19 is not yet fully elucidated, it is recognized as a complex and multifactorial condition. Studies indicate that the prevalence of associated risk factors increases the propensity for kidney injury. Additionally, the early assessment and detection of kidney injury have been emphasized as crucial for predicting prognosis and clinical outcomes during the COVID-19 treatment. **Objective:** Discuss the association between kidney injury and COVID-19 infection, highlighting potential risk factors and clinical implications. **Materials and methods:** This literature review obtained data from studies published in the Scielo and PubMed databases between December 2019 and September 2020. **Results and discussion:** Multiple factors contribute to kidney injury in COVID-19, ranging from direct viral damage to nonspecific mechanisms that hinder overall health. Furthermore, preexisting conditions, such as advanced age and hypertension, have been associated with a higher risk of kidney complications and increased mortality. Therefore, a thorough investigation of the kidney stress induced by the virus (SARS-CoV-2) is essential to enable early diagnosis and prevent severe outcomes. Nevertheless, kidney function recovery remains challenging and requires specialized medical follow-up. **Conclusion:** Despite the growing evidence on the theme, further studies are needed to elucidate the pathophysiological mechanisms underlying COVID-19-related kidney injury, improve early detection strategies, and establish management protocols.

**Keywords:** COVID-19; Acute kidney injury; Pathophysiology; Mortality

## RESUMO

**Introdução:** A lesão renal na COVID-19 ainda não está totalmente elucidada, mas sabe-se que ela é diversa e multifatorial. Os estudos realizados apontam a prevalência de alguns fatores de risco associados a uma maior propensão para o desenvolvimento da lesão renal. Além disso, tem sido discutida nesse cenário a importância da avaliação e detecção precoce da lesão renal, o que auxiliaria na predição de prognóstico e, ainda, no desfecho clínico durante o tratamento da infecção pelo vírus. **OBJETIVO:** Discutir a relação entre o desenvolvimento da lesão renal em pacientes que foram infectados pelo vírus da COVID-19. **Materiais e métodos:** O presente estudo trata de uma revisão da literatura. Os dados apresentados provêm de artigos científicos publicados entre dezembro de 2019 e setembro de 2020. A busca de artigos científicos foi realizada nos bancos de dados SCIELO e PUBMED. **Resultados e discussão:** Sabe-se que vários são os fatores envolvidos na relação entre COVID-19 e lesão renal, desde danos diretos causados pelo vírus até mecanismos inespecíficos que desencadeiam uma série de prejuízos à saúde. Além disso, quando associada a fatores de risco como idade avançada e hipertensão, a infecção pelo coronavírus pode ocasionar complicações renais e aumento da mortalidade. Desse modo, mostra-se essencial o desenvolvimento de mecanismos para realização de uma investigação minuciosa do estresse renal causado pelo vírus com o intuito de auxiliar no diagnóstico precoce e na prevenção de quadros mais graves. Ainda assim, a recuperação da função renal é difícil e precisa de um acompanhamento com especialista para monitoramento da sua evolução. **Conclusão:** Por mais que diversos artigos tenham sido publicados, ainda se faz necessário o desenvolvimento de estudos que determinem com segurança os mecanismos fisiopatológicos, a detecção precoce da lesão renal e o seu manejo específico.

**Palavras-chave:** COVID-19; Lesão renal aguda; Fisiopatologia; Mortalidade.

## INTRODUCTION

Kidney injury associated with COVID-19 is not yet fully elucidated. However, this injury is known to be diverse and multifactorial, resulting from specific and nonspecific mechanisms. These mechanisms include the synergism effects of the direct cytopathic action of the virus (SARS-CoV-2) and the indirect cytokine-mediated damage caused by the systemic inflammatory response in patients with COVID-19.<sup>2,3,7,6</sup>

Studies have identified several risk factors associated with an increased susceptibility to kidney injury in infected patients, particularly chronic conditions, such as metabolic and cardiovascular diseases.<sup>1,2,8,10</sup>

Additionally, early assessment and detection of kidney injury have been recognized as crucial in patients with COVID-19, as those who develop early kidney injury tend to have a high risk of severe outcomes, increased mortality, and a low probability of kidney function recovery.<sup>4,5,9</sup>

The clinical outcome of kidney injury during COVID-19 infection has not yet been elucidated. While some patients experience kidney recovery, others do not, particularly those with preexisting comorbidities that predispose them to further kidney injury.<sup>3,7</sup>

Moreover, acute kidney injury (AKI) in COVID-19 infection has been associated with high mortality rates in intensive care units (ICU), and other conditions (e.g., proteinuria and hematuria) have also been related to increased mortality in patients with COVID-19.<sup>2,3,4,7</sup>

This study aimed to reinforce current knowledge and contribute new insights into the relationship between kidney injury and COVID-19, including its pathophysiology, risk factors, renal biomarkers, recovery potential, and associated mortality rates.

## METHODS

This literature review presented data obtained from studies published between December 2019 and September 2020.

The search was conducted in the SCIELO and PUBMED databases, using the following descriptors: “Kidney”, “Injury”, “COVID-19”,

“Pathophysiology,” and “Mortality”. Titles and abstracts were screened, and those that met the inclusion criteria (i.e., publications available online in English or Portuguese) were selected.

Five thematic areas emerged from this selection: pathophysiology of kidney injury, associated risk factors, renal stress markers, kidney function recovery, and relationship with increased mortality. Among the 292 studies initially identified, 10 were selected in this review.

## RESULTS AND DISCUSSION

### Pathophysiology of kidney injury

Although the mechanisms underlying kidney injury in COVID-19 are unclear, the condition is recognized as diverse and multifactorial. Current evidence suggests that kidney injury results from specific and nonspecific mechanisms, including the synergism effects of direct viral cytopathic on the renal glomeruli and tubules and indirect cytokine-mediated injury due to the systemic inflammatory response in patients with COVID-19.<sup>2,3</sup>

The intracellular infection mechanism of SARS-CoV-2, although not fully elucidated, involves angiotensin-converting-enzyme 2 (ACE2) as a primary receptor facilitating viral entry into human cells. Similar to SARS-CoV, the Spike protein of SARS-CoV-2 binds to the ACE2 transmembrane protein on the host cell, enabling viral entry. This process enables the virus to release fusion peptides, allowing it to attach to the host cell membrane (i.e., a central mechanism in determining tissue tropism) and enter the cell. Notably, studies analyzing RNA sequencing data from patients with COVID-19 and AKI have revealed that ACE2 expression in the kidney is nearly 100 times higher than in the lung. Furthermore, SARS-CoV-2 exhibits an affinity for ACE2 receptors that is 10 to 20 times greater than that of SARS-CoV. Consequently, the SARS-CoV-2 can invade renal tubular cells by binding to ACE2, triggering cytotoxicity effects and impairing kidney function.<sup>3,7</sup>

The literature showed that patients with severe COVID-19, particularly those admitted to ICU, exhibit elevated levels of inflammatory cytokines. This cytokine storm, characterized by significantly increased levels of inflammatory mediators, aims to combat the virus by attack-

ing infected cells. However, the immune system fails to distinguish infected and healthy cells, leading to collateral tissue injury. In the kidney, these cytokines contribute to kidney injury by interacting with resident cells, promoting endothelial and tubular dysfunction.<sup>2,3,6</sup>

### **Risk factors associated with kidney injury**

Risk factors for AKI in patients with COVID-19 include advanced age, diabetes mellitus, cardiovascular diseases, hypertension, black race, and the need for mechanical ventilation and vasopressor support.<sup>1,2,8</sup>

AKI frequently occurs in patients with COVID-19, with an early presentation in the disease course and temporal association with respiratory failure, and it is associated with a poor clinical prognosis.<sup>1,10</sup>

### **Markers of renal stress**

Studies have established a strong association between kidney injury and COVID-19 infection. Identifying the risk of developing AKI in infected patients is crucial for prognosis and treatment optimization, as AKI in this context is a marker of poor clinical outcomes.<sup>5,9</sup>

Currently, AKI diagnosis relies on serum creatinine levels and urine output; however, these markers indicate kidney injury only after its occurrence. Therefore, newer biomarkers have received greater attention, including tissue inhibitors of metalloproteinase-2 and insulin-like growth factor-binding protein 7. These markers, the only renal stress indicators approved by the Food and Drugs Administration, can predict AKI onset by detecting tubular stress and injury.<sup>4,5</sup>

### **Kidney function recovery**

Evidence suggests that most patients with severe COVID-19 experience some degree of kidney injury, with some progressing to kidney failure.<sup>3,7</sup>

Studies on AKI outcomes and management of patients with COVID-19 are scarce. However, renal replacement therapy (RRT) has been widely employed, with some patients exhibiting partial recovery of renal function following viral and inflammatory responses. Despite this, the mortality rate remains high among patients requiring RRT, and the extent of renal

function recovery remains uncertain.<sup>3,7</sup>

Studies emphasize that after the critical phase of infection and kidney injury, nephrological follow-up is essential to monitor the condition of the patient and prevent the recurrence of kidney injury.<sup>7</sup>

### **Increased mortality in patients with kidney injury**

Studies already show that preexisting comorbidities have been strongly associated with a higher mortality rate in patients with COVID-19, with kidney disease being a significant contributor.<sup>7,4</sup>

Besides the AKI during SARS-CoV-2 infection being associated with a high mortality rate in the ICU, other conditions also contribute to increased mortality.<sup>2</sup>

Stage 2 or higher AKI, along with the presence of proteinuria and hematuria and elevated baseline serum creatinine and urea levels, are factors associated with increased mortality in patients with COVID-19 with renal involvement.<sup>3</sup>

## **CONCLUSION**

Although patients with kidney injury present several defense mechanisms to counteract COVID-19 infection, the prognosis remains unfavorable when risk factors are present. In these cases, recovery rates decline while complications and mortality rates increase.

Therefore, despite the existing knowledge on the theme, systematic studies and analyses are needed to develop tools for the early detection of kidney injury. Additionally, establishing a standardized protocol for managing affected patients may help mitigate disease sequelae and reduce associated complications and mortality rates.

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