

ORIGINAL ARTICLE

# COVID-19 and its relationship with kidney diseases: a scope review

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**Abstract**

**Background:** COVID-19 is an acute respiratory disease originally from China that emerged in December 2019 and quickly spread around the world, affecting 230,418.415 people, and causing 4,724,876 deaths. Coming from the coronavirus family, SARS-CoV-2 is a new subtype of virus that affects the respiratory tract in different levels and can spread and affect other vital structures in the body.

**Objective:** to identify the risk factors that lead patients infected by the new coronavirus to develop kidney disease.

**Methods:** this is a systematic review of the Scoping Review type (scope review), according to the method proposed by the Joanna Briggs Institute, with the implementation of a checklist structured by PRISMA-ScR that contains 22 mandatory items. The following descriptors were used: coronavirus infection, acute kidney injury and risk factors in five databases, namely PubMed, Scopus, Embase, Virtual Health Library and Web of Science.

**Results:** while reading the studies, it was concluded that Acute Kidney Injury was the main renal finding in patients contaminated by SARS-CoV-2. The risk factors for developing renal worsening in patients with COVID-19 were the extremes of age, race, sex, pre-existing diseases, and the disease evolution.

**Conclusion:** it is assumed that renal involvement does not occur only for an exclusive reason, but as a set of factors. It is up to the health team to pay constant attention to the warning signs by monitoring the contaminated patient.

**Keywords:** Coronavirus infection, acute kidney injury, risk factors.

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## Authors summary

### Why was this study done?

This study conducted was made thinking about the level of incidence and registration of kidney comitment in patient with COVID-19 and what was the cause as well, considering that this disease affects majoritaryly the respiratory tract.

### What did the researchers do and find?

The aims of this study is identify the risk factors that lead patients infected by the new coronavirus to develop kidney disease. A review was carried out based on the literature available in the databases. The majoritary findings concluded that Acute Kidney Injury (AKI) was the main renal finding in patients contaminated by SARS-coV-2, follow by the risk factors identified for developing renal worsening in patients with COVID-19, like the extremes of age, race, sex, pre-existing diseases and disease evolution.

### What do these findings mean?

The renal involvement does not occur only for an exclusive reason, but as a set of factors surrounding the course of the disease and the biological profil of the patient.

## INTRODUCTION

COVID-19 is an acute respiratory disease caused by SARS-CoV-2 that has spread rapidly around the world, originating in Hubei Province, Wuhan, China, in December 2019. This new disease is not the first of its family, but a variation of the coronavirus family that rarely affects humans, being confined only to animals such as bats, cattle, cats, and camels, such as MERS-CoV and SARS-CoV. Although the exact origin of SARS-CoV-2 is not known, it is understood that its viral structure is 96.2% similar to CoV-RaTG13, which mainly affects bats and is 79.5% like SARS-CoV than the other presented forms of the coronavirus family<sup>1-3</sup>.

In January 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 as the sixth public health emergency of international attention, in which health workers, governments and the general population in order that the spread of the disease was prevented. As of February 2020, WHO reported 45,171 cases and 1,114 deaths, of which 99% of cases and 99% of deaths were related to COVID-19 in China. The spread of the disease occurred rapidly and exponentially, reaching almost all countries and, even with the attempt to contain the disease, the WHO declared in March 2020, a pandemic caused by SARS-CoV-2<sup>2-4</sup>.

SARS-CoV-2 is the virus that causes the COVID-19 disease, which mainly affects the respiratory tract initially with a flu-like condition, with the most common symptoms such as dry cough, runny nose, fever, headache, myalgia, sore throat and, later, anosmia (loss of smell), ageusia (taste alteration), which lead to hyporexia (decreased appetite), with the possibility of progressing to severe pneumonia, with difficulty breathing, dyspnea (shortness of breath), and asthenia (tiredness). Among the symptoms presented by people infected by SARS-CoV-2, many may present gastrointestinal disorders (diarrhea, nausea/vomiting), even though they are not the most common. The transmission of the new virus occurs through the respiratory tract and/or mucous membranes, with dispersion by droplets, respiratory secretions, and direct contact<sup>3,5</sup>.

COVID-19 can present itself in 80% of cases in an asymptomatic or oligosymptomatic form (mild symptoms) and, in 20% of cases, it evolves to the severe form of the disease, requiring respiratory support in 5% of cases. Acute respiratory failure syndrome is a complication resulting from COVID-19, which occurs more often in

the elderly, immunosuppressed people, or those with other comorbidities, such as hypertension, diabetes, neurological and respiratory diseases. These risk factors, or their accumulation, are the main findings in the emergence of complications and mortality rate<sup>6</sup>.

SARS-CoV-2 is found in the respiratory tract secretions, saliva, feces and urine in patients with diarrhea. The onset of symptoms occurs from the 3rd to the 14th day after infection. Its diagnosis is given through laboratory, clinical-imaging, clinical-epidemiological and clinical tests, however, there is no treatment, only vaccines control the disease<sup>4,6</sup>.

Renal function is a fundamental part of the functioning of the human body; any injury can harm this cycle and disrupt human metabolism. With acute kidney injury (AKI) as a multifactorial impairment of rapid evolution in renal filtration function, the factors that lead to the development of AKI revolve around preexisting clinical diseases, susceptibility and some therapeutic interventions, however its appearance may vary between stages, such as pre-renal, renal and post-renal, caused by decreased renal perfusion or hypotensive drugs, direct damage to glomerular, tubular or tubulointestinal structures, and obstruction of the flow of urine in renal structures to the urethra, respectively<sup>7-9</sup>.

Thus, the study problem is: What are the risk factors that lead the relationship of patients with COVID-19 to develop kidney disease? Thus, the objective of the study is to identify the risk factors that lead the patient contaminated by SARS-CoV-2 to develop kidney diseases.

It is believed that this study becomes relevant, as it makes known the current studies on the subject, defining the reason why so many patients with COVID-19 evolve to some level of renal involvement and enabling the guidance of professionals on the necessary management.

## METHODS

This is a systematic review of the Scoping Review type in accordance with the review method proposed by the Joanna Briggs Institute (JBI). The scope review is intended to map, through a transparent and rigorous method, the main concepts of a given area of knowledge, bringing a complete view, to compile and disseminate the data obtained and identify gaps in existing research without evaluating them critically<sup>10</sup>.

The research question was made using the PCC acronym (Population, Concept, Context): Population – people affected by COVID-19; Concept – kidney disorders; Context - relationship of COVID-19 with kidney diseases.

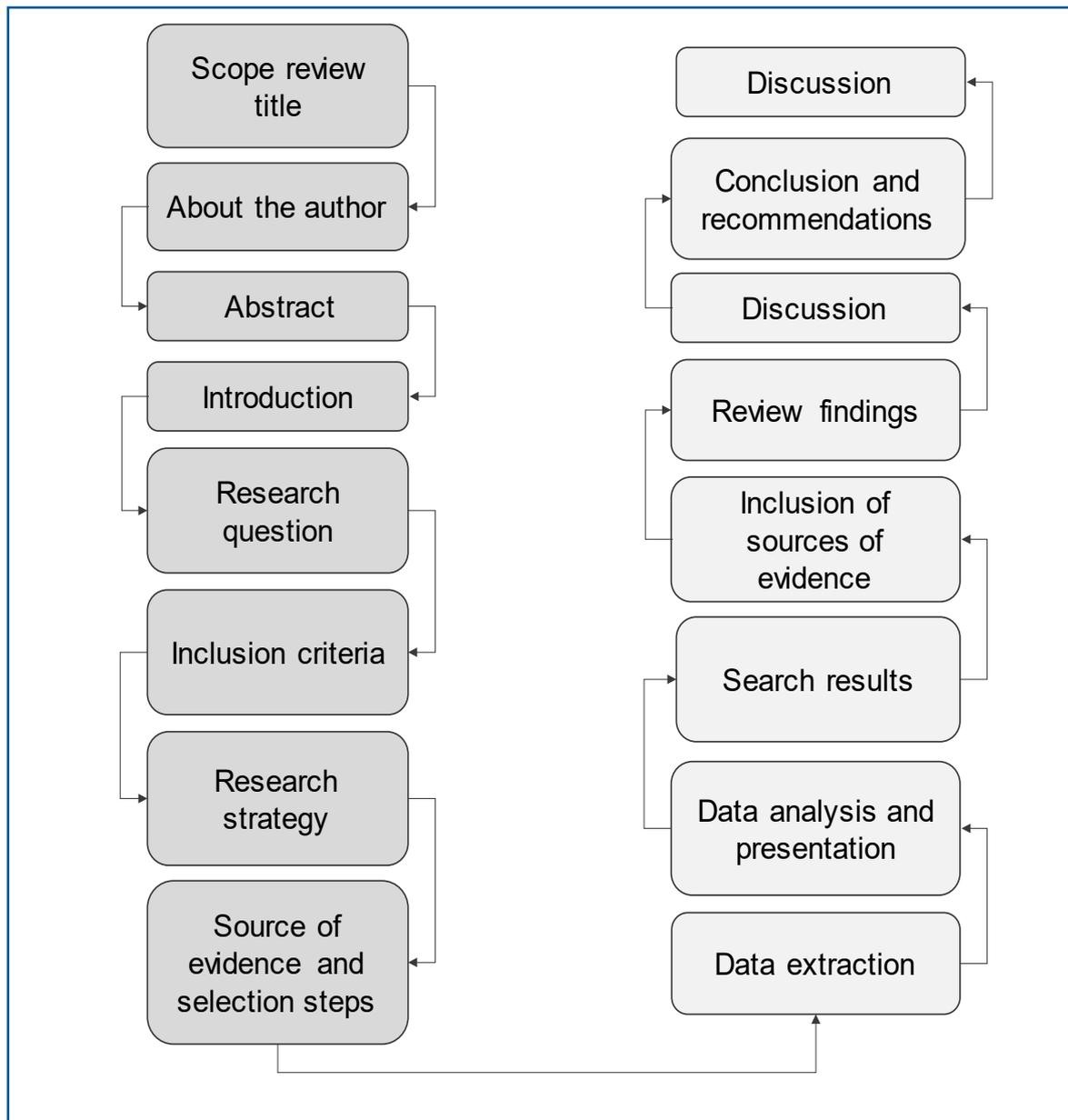
The study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review (PRISMA-ScR) Checklist, a guiding script to carry out a scope review built through the guidelines of the Joanna Briggs Institute (JBI). PRISMA-ScR presents 22 separate items according to the mandatory chapters in the review, such as: title, abstract, introduction, method, results, discussions and funding<sup>11</sup>.

Thus, the search for relevant studies was carried out through the PubMed, Scopus, Embase, VHL (Virtual Health Library) and Web of Science databases. The

bibliographic survey took place from April to July 2021, using the double-checking method.

Descriptors were identified according to the research theme, delimited through MeSh (Medical Subject Headings) and DeCS (Descriptors in Health Sciences). The search strategies were used in English and Portuguese “coronavirus infection AND acute kidney injury AND risk factors”.

To carry out the search in the databases, studies in English and Portuguese were included, in which review studies, case studies, experience reports, editorials, letters, theses, dissertations and course conclusion studies were excluded. The research followed the flow exemplified below (figure 1):

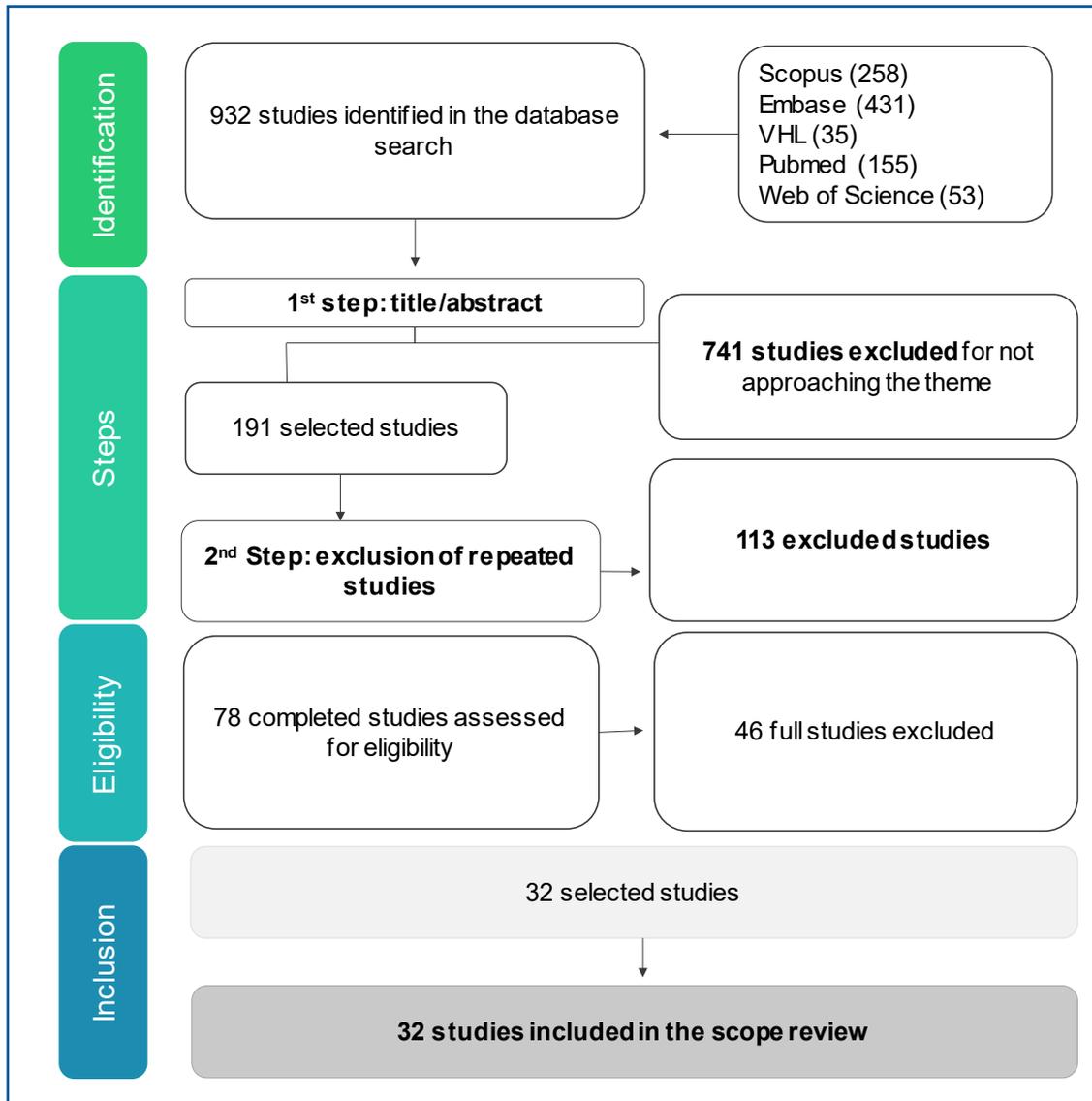


**Figure 1:** Steps for formulating a Scope Review based on the Joanna Briggs Institute (JBI)

**RESULTS**

A total of 32 studies were selected, which underwent the process of reading titles, abstracts, application of eligibility criteria and full reading. Initially, 932 studies

were identified and 690 of these were excluded by title reading, 51 by abstract reading and 46 by full reading, as shown in the figure below.



**Figure 2:** Search strategy based on PRISMA-ScR (2018)

According to the survey in the databases, 32 articles that addressed risk factors related to kidney disease in patients with COVID-19 were part of this review. The first 20 articles were published in 2020, showing the impact of this new disease and the efforts of the scientific community to understand it.

Most articles addressed the disease evolution process in patients affected by COVID-19, as well as the management and identification of the virulent condition, in addition to highlighting possible causes that would lead to the development of Acute Kidney Injury (AKI). The articles also address risk factors for kidney involvement, bringing a discussion focused on possible biomarkers of some degree of kidney injury, such as: laboratory test results, immunological markers, pre-existing diseases, and the individual's biological characteristics.

Thus, for a better organization of this review, it was decided to separate the main findings by topics, following the logic of the individual's trajectory in the disease.

**Laboratory findings signaling of kidney injury**

Table 1 shows the results that addressed the laboratory analyses. Most authors agreed that the findings represent markers for renal involvement during COVID-19, namely: systemic inflammation markers (serum procalcitonin and blood leukocytes); Estimated Gromerular Filtration Rate (GFR); low serum albumin; lymphopenia; high D-dimer; C-reactive protein (CRP); proteinuria; Soluble urokinase-type plasminogen activator receptor (suPAR); high platelet count; hyperinflammation; tendency to coagulopathy; high lactose dehydrogenase levels; and elevated serum creatinine.

**Table 1:** the AKI and COVID-19 athwart laboratory findings. Brazil, 2021

Article	Objective	Methods	Main Findings
A <sup>12</sup>	To review data to analyze the incidence of severe AKI, its predictors, and its association with mortality in critically ill patients with COVID-19 in the ICU at the Cleveland Clinic Abu Dhabi.	Retrospective monocenter study including all adult patients (age ≥18 years) admitted to the ICU between March 1 and May 29, 2020, with confirmed SARS-CoV-2 infection.	AKI is not associated with inflammatory processes as identified in tests of IL-6, ferritin and C-reactive protein or thromboembolism markers (D-dimer and fibrinogen).
A <sup>13</sup>	To identify the detailed clinical courses of patients with COVID-19 to identify additional important clues to the pathophysiology of the association of COVID-19 and AKI.	Retrospective observational cohort study that took place between March 1, 2020, and June 3, 2020. Adult patients symptomatic for COVID-19 with positive result who were admitted to any of the 3 hospitals of the Charité – Universitätsmedizin Berlin were included in the survey.	Increased blood levels of systemic inflammation markers (serum procalcitonin and blood leukocytes) emerged as variable risk factors for severe AKI.
A <sup>14</sup>	Identify the clinical characteristics and highlight potential risk factors for ARI related to COVID-19, to facilitate the clinical management of COVID-19.	Retrospective cohort study that took place between March 9 and 17, 2020. Hospital patients with COVID-19 were included.	Estimated glomerular filtration rate (GFR) and procalcitonin can help clinicians identify patients with COVID-19 who have early-stage kidney damage.
A <sup>15</sup>	To share the clinical characteristics and treatment experience of patients with COVID-19 who developed AKI.	Retrospective study that took place from February 17 to March 22, 2020. All patients with COVID-19 who were admitted to this study entered this study.	Among patients with AKI, those who had low serum albumin on admission, among other factors, had a higher incidence of severe AKI.
A <sup>16</sup>	To assess the impact of AKI on mortality and renal prognosis of patients with SARS-CoV-2 infection.	Retrospective single-center study that took place from February 28 to May 4, 2020. Adult patients admitted to the ICU of Hospital Alemão Oswaldo Cruz, Brazil were included in this study.	Lymphopenia, elevated D-dimer, and C-reactive protein (CRP) levels have been associated with an increased risk of developing AKI.
A <sup>17</sup>	To identify involvement prospectively, most especially of proteinuria (quantitative) at baseline and its prognosis in patients with severe or moderate SARS-CoV-2 infection.	Multicenter, prospective observational study from March 15 to April 19, 2020. All patients aged 18 years with proven symptomatic of moderate to severe COVID-19 were included.	Proteinuria is an easily measurable marker to predict outcome and can be used to assess the severity of SARS-CoV-2 infection, in addition to being an independent predictor of length of stay and ICU admission.
A <sup>18</sup>	To characterize the levels of various biomarkers of inflammation and their association with hospital outcomes in patients with COVID-19.	Multinational observational study of adult patients hospitalized for COVID-19.	Glomerular Filtration Rate (GFR) has been independently associated with LRA. Among the biomarkers associated with the emergence of AKI, only suPAR (soluble urokinase-type plasminogen activator receptor) and C-reactive protein were relevant.
A <sup>19</sup>	To analyze the incidence, etiologies and results of AKI in patients contaminated by SARS-CoV-2.	Retrospective single-center study conducted in an ICU assigned to critically ill patients with COVID-19 between February 5th and March 20th, 2020.	Lower lymphocyte level, serum IL-6 level, sepsis, and high platelet count are related to the development of AKI.

**Continuation - Table 1:** the AKI and COVID-19 athrow laboratory findings. Brazil, 2021

Article	Objective	Methods	Main Findings
A <sup>20</sup>	To assess the incidence, risk factors and prognosis of AKI in adult patients with COVID-19 at a tertiary university hospital designated for severe cases of COVID-19 by the local government.	Retrospective study performed at Tongji Hospital (Wuhan, China), a hospital designated for the treatment of patients with severe COVID-19.	Lymphopenia, D-dimer, high-sensitivity C-reactive protein, and high lactate dehydrogenase levels were the most common findings in AKI patients, in addition to higher serum creatinine.

**Immunological manifestations related to SARS-COV-2 contamination**

Table 2 shows the results that addressed immunological markers in patients affected by COVID-19.

The main findings are: Elevated levels of IL8, IL10 and IL2R.

**Table 2:** reaction of the Immune System to COVID-19 and AKI. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>21</sup>	To assess the incidence and risk factors of AKI and its impact on hospital and intensive care unit (ICU) hospital mortality.	Retrospective observational study conducted at Tongji Hospital, from January 28 to March 29, 2020. Patients diagnosed with COVID-19 who were admitted to the intensive care unit (ICU) were included in this study.	High levels of IL8, IL10 and IL2R were associated with a high risk of developing severe AKI in critically ill patients with COVID-19.

**Pre-existing diseases as a bad prognosis in kidney injury during covid-19**

The results that mostly addressed pre-existing diseases of patients who were affected by COVID-19 are shown in table 3. During the data analysis, it was evident that the pre-existing conditions that most cause the development of some type of injury kidney disease

in the onset of that disease are: hypertension; diabetes; cardiac insufficiency; peripheral vascular disease; other cardiovascular diseases; Chronic Kidney Disease (CKD); other pre-existing kidney diseases; high body mass index (BMI); hematologic malignancy; immunosuppression in general; and cerebrovascular diseases.

**Table 3:** risk of pre-existing diseases during the COVID-19. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>22</sup>	To examine and to validate the identified risk factors, as well as explore any potential correlation between AKI biomarkers in COVID-19 infection and discuss the possible implications of these findings.	Retrospective analysis of AKI-related biomarkers and comorbidities associated with COVID-19 infections in 632 patients from March 1 to June 10, 2020.	Elevated systolic and diastolic blood pressure is associated with the severity of AKI, supporting the theory that hypertension plays a role in AKI in COVID-19 positive patients, as diabetes, heart failure increases.
A <sup>23</sup>	To characterize the clinical outcomes of critically ill patients with COVID-19 and some preexisting chronic kidney disease and/or Early Suppression and Rapid Response.	Retrospective study in three teaching hospitals which included adult patients (aged ≥18 years) admitted to the ICU with a confirmed diagnosis of COVID-19 in the period between March 10 and July 23, 2020.	Surprisingly, the mortality rates of patients with CKD stages 1-4, and new renal impairment were comparable, although they were more than double the mortality rate seen in patients without renal impairment.

**Continuation - Table 3:** risk of pre-existing diseases during the COVID-19. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>24</sup>	To analyze factors associated with AKI in hospitalized patients to identify factors that can be potentially used for the early identification of patients with COVID-19 who are at high risk of developing AKI.	Retrospective observational single-center study conducted at Hankou Hospital in Wuhan, China. Only patients with confirmed COVID-19 were included in this study.	Pre-existing cardiovascular and renal diseases are potential risk factors for AKI in patients with COVID-19.
A <sup>25</sup>	To examine and validate the identified risk factors, explore any potential correlation between biomarkers and AKI in COVID-19 infection, and discuss the possible implications of these findings.	Retrospective study of data from March 1 to June 10, 2020. All inpatients who tested positive for SARS CoV-2 in polymerase chain reaction (PCR) tests were included.	Diabetes and heart failure increase the risk of AKI in patients with COVID-19 infection. Other additional risk factors were identified in this analysis, such as hypertension, obesity, peripheral vascular disease, and hematologic malignancy.
A <sup>26</sup>	To characterize risk factors for AKI in intensive care patients with Covid-19, their incidence, and patient outcomes.	Single-center cohort study that took place between March 14 and May 12, 2020. All adult patients (>18 years) admitted to the ICU with a confirmed diagnosis of COVID-19 from University Hospital in Southampton (UHS).	Pre-existing diseases that qualify as risk factors for the development of AKI were diabetes mellitus, hypertension, and immunosuppression for any reason.
A <sup>27</sup>	To investigate the incidence and diagnosis of AKI on admission to the ICU in patients with COVID-19, examine the possible association between AKI and hospital mortality with different severities, and generate a nomogram model to predict AKI.	Retrospective study of all patients diagnosed with COVID-19 hospitalized from February 4, 2020, to April 16, 2020.	High BMI (Body Mass Index), cardiovascular and cerebrovascular diseases and CKD are diseases that are at risk for the development of AKI in patients contaminated by SARS-CoV-2.

**Biological aspects facing kidney injury at covid-19**

Table 4 presents results of biological factors that cause the development of some stage of Acute Kidney

Injury (AKI) during the onset of COVID-19. They are elderly, male and African descent.

**Table 4:** biological aspects, a factor to consider. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>28</sup>	To determine the incidence of AKI in patients hospitalized with COVID-19 infection and to assess demographic factors and comorbidities that portend an increased risk of AKI in these patients, in addition to evaluating the association between AKI and mortality in these patients.	Retrospective case study between March 10, 2020, and May 13, 2020.	We found significantly greater odds of AKI with increasing age, among African-Americans, among others.
A <sup>29</sup>	Determine risk factors associated with AKI on admission with confirmed or clinically diagnosed COVID-19.	Single-center retrospective study from January 29 to February 25, 2020. All clinical or confirmed diagnoses of COVID-19 hospital admissions were eligible for inclusion in this study.	Male gender, secondary bacterial infection and use of diuretics were identified as independent risk factors for AKI in patients infected with SARS-CoV-2.

**Continuation - Table 4:** biological aspects, a factor to consider. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>30</sup>	To determine the incidence of in-hospital AKI in patients with COVID-19 and to study the baseline characteristics and laboratory data associated with its development. The secondary objective of the study was the in-hospital mortality associated with AKI in patients with COVID-19.	Retrospective study. All adult patients >18 years of age admitted to Brookdale University Hospital and Medical Center with COVID-19 infection between March 18 and April 23, 2020, were entered into this study.	AKI patients were more likely to be male and older, among other factors.

**Trajectory of the patient with covid-19, its evolution and renal impact**

According to table 5, the results address the evolution of the disease as a causative factor for kidney injury. It is a fact that AKI is the most recurrent involvement in patients affected by COVID-19. This fact is associated with the use of invasive mechanical ventilation (IMV); vasopressor drugs; nephrotoxic drug; high APACHE II score; diuretics; heart failure; drop in PaO<sub>2</sub>/FiO<sub>2</sub>; sepsis; and renal replacement therapy (RRT) of some kind, such as dialysis. This direct relationship with the evolution to LRA is indicated.

Another data identified corresponds to the period of hospitalization and diagnosis of AKI in patients positive for COVID-19. Most individuals admitted to the ICU with some degree of renal impairment do not survive after a period of 28 days, in part due to the virulent power of SARS-CoV-2, or due to missed diagnoses. As for the raised histopathological finding, AKI may occur due to acute tubular injury, possibly caused by the direct virulence of SARS-CoV-2 in the proximal tubular epithelium, since virus particles were observed in the tubular epithelium and podocytes.

**Table 5:** the approach in the management of patients with COVID-19 and the evolution to AKI. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>31</sup>	Define the rate of AKI among patients hospitalized with COVID-19 and describe the various aspects of AKI phenomenology in this patient population.	Retrospective observational cohort study of a large New York healthcare system. All adult patients (<18 years) who tested positive in the nasopharyngeal PCR-RT test for COVID-19, hospitalized between March 1 and April 5, 2020, were included.	The need for Renal Replacement Therapy (RRT) and hospital disposition (discharge or death) were the most common outcomes for those who developed AKI. In our analysis, the clearest factors for the development of AKI in severe COVID-19 patients were specifically the need for ventilatory support or treatment with vasopressor drugs.
A <sup>32</sup>	To allow an insight into the clinical impact of AKI associated with SARS-CoV-2.	This is a retrospective cohort study analyzing the electronic medical records of patients with COVID-19 hospitalized in AKI, from March 1st to May 31st, 2020.	Most of the AKI developed in the community were of pre-renal origin, while most of the AKI developed in the hospital were intrinsic. The need for RRT (Renal Replacement Therapy) was significantly more common in intrinsic AKI.
A <sup>33</sup>	To report the incidence, hospital recovery rate, risk factors and mortality of AKI associated with COVID-19 and share our experience in a tertiary hospital in Switzerland.	Retrospective observational cohort study at the University Hospital of Basel. All adult patients hospitalized with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 between February 1 and June 30, 2020, were eligible for this analysis.	AKI is common in patients hospitalized with COVID-19, and is mainly reversible in mild cases, however cases of in-hospital recovery were unsatisfactory in advanced stages of AKI. Severe AKI occurs in critically ill patients with COVID-19 and may also imply that acute tubular injury in the context of multiple organ failure.

**Continuation - Table 5:** the approach in the management of patients with COVID-19 and the evolution to AKI. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>34</sup>	To describe the clinical characteristics, correlates and outcomes of critically ill patients with COVID-19 and AKI complications.	Retrospective, observational, multicenter study conducted at 19 COVID-19 designated hospitals in Wuhan. All adult patients with COVID-19 who were admitted to the ICUs of participating hospitals between January 1 and February 29, 2020, were included if they met the inclusion criteria.	AKI was quite common in severe cases of pneumonia caused by COVID-19, being associated with higher mortality. Most of COVID-19 patients in our study did not survive to day 28, which is worse than the median survival of patients on Continuous Renal Replacement Therapy (CRT) critically ill.
A <sup>35</sup>	To assess the incidence of acute kidney injury (AKI) in hospitalized patients diagnosed with COVID-19 and to identify the risk factors associated with its onset and those associated with its prognosis during the first 90 days of the pandemic in a Brazilian public and tertiary university hospital.	Prospective cohort study of the first 90 days of the pandemic, starting on March 25, 2020. Hospitalized patients diagnosed with COVID-19, confirmed by the PCR-RT molecular test for SARS-CoV-2, in wards and intensive care units (ICUs) of a public and tertiary university hospital in São Paulo, Brazil.	The high APACHE II score is one of the risk factors associated with developing AKI, however, when indicated at the beginning, renal replacement treatment (RRT) may be associated with better patient survival, as it would provide a removal of cytokines or excess fluids.
A <sup>36</sup>	To strictly analyze hospital mortality and renal outcomes among patients with COVID-19 and AKI.	Retrospective observational cohort study of a large New York healthcare system. All adult patients (aged ≥18 years) with positive results for COVID-19 who were hospitalized from March 1, 2020, to April 27, 2020, were eligible.	The development of AKI during hospitalization for COVID-19 was associated with a substantial increase in the risk of death. This risk was amplified when AKI resulted in dialysis. The incidence rate of in-hospital death was higher among patients with stage 3 AKI on dialysis, followed by stages 1-3 AKI and those without AKI.
A <sup>37</sup>	To identify the incidence of AKI in patients with COVID-19 and assess the clinical features of AKI and its impact on patient outcomes.	Retrospective cohort study that ran from February 19 to March 31, 2020. All patients who tested positive for COVID-19 who were admitted to two hospitals in Dongsan were included in this study.	Renal involvement has been associated with poor prognosis, including admission to the ICU, use of MV (Mechanical Ventilation) and hospital mortality.
A <sup>38</sup>	To investigate the incidence and diagnosis of AKI among patients with COVID-19 admitted to the ICU.	Retrospective study that took place from February 4th to April 16th, 2020. All patients admitted to the ICU who had a confirmed diagnosis of COVID-19 were included.	Among all AKI patients, only 54% were recognized by physicians during their ICU stay, and the rate of missed diagnoses was 46%, which may result in a higher mortality rate.

**Continuation - Table 5:** the approach in the management of patients with COVID-19 and the evolution to AKI. Brazil, 2021

Article	Objective	Methods	Main findings
A <sup>39</sup>	Describe the incidence, risk factors and impact of AKI and RRT on clinical outcomes in patients with COVID-19 admitted to the ICU.	Retrospective study that took place between March 4 and May 13, 2020. All adult patients ( $\geq 18$ years of age) with severe acute respiratory syndrome confirmed as COVID-19 infection admitted to the ICU of Hospital Israelita Albert Einstein were included (HIAE), a quaternary private university hospital in Brazil.	The development of AKI was independently associated with the use of diuretics and Invasive Mechanical Ventilation (IMV). AKI develops temporarily after starting VMI.
A <sup>40</sup>	To investigate and compare the clinical features of AKI and their association with overall mortality among different phenotypes.	Retrospective study that took place from January 1 to March 23, 2020. We identified all national electronic medical records of patients with recorded COVID-19 test results.	Findings suggest that AKI may be a sentinel of sequential organ dysfunction or the consequence of multiple organ dysfunction.
A <sup>41</sup>	To assess the incidence, risk factors and prognosis of AKI in critically ill and critically ill patients with Covid-19.	Retrospective study of medical records of patients admitted to the ICU at Wuhan JinYinTan and Guangzhou Medical University Hospitals. All adult patients ( $> 18$ years) with laboratory-confirmed Covid-19 who were admitted to the intensive care unit (ICU) between January 23 and April 6, 2020.	The time to hospital admission, diagnosis of AKI, heart failure and drop in $\text{PaO}_2/\text{FiO}_2$ is strongly associated with the potential for renal recovery. Stage 3 AKI independently predicted the risk of death within 28 days of admission to the ICU. Sepsis, nephrotoxic drugs and invasive mechanical ventilation, among others, were strongly associated with the development of AKI.
A <sup>42</sup>	To report the experience of renal autopsy findings in patients with severe COVID-19.	Kidney samples were obtained from autopsies of 26 COVID-19 cases with a post-mortem interval ranging from 1 to 6 hours during the period February 18 to March 27, 2020.	Diffuse acute proximal tubular lesion with brush border loss and non-isometric vacuolization, which may be partially caused by direct virulence of SARS-CoV-2, had been observed. Some spherical viral particles characteristic of the coronavirus were found in the proximal tubular epithelium. Virus infection was confirmed by staining using an antibody. Virus particles were also identified in the tubular epithelium and podocytes, known sites for ACE-2 expression.

## DISCUSSION

COVID-19 is considered a respiratory disease caused by the SARS-CoV-2 virus, which leads the individual to develop an acute respiratory syndrome. With its spiral shape and the presence of Spike (S) protein around it, SARS-CoV-2 attacks alveolar epithelial cells through the angiotensin-2 converting enzyme (ACE-2) through the protein<sup>43,44</sup>.

Although COVID-19 mainly affects the lungs, other organs are affected in the course of the disease, especially the heart, liver, intestine, brain, testicles, and kidneys. The reason why other organs are equally attacked is because of the presence of ACE-2 in cells, such as the continuous circulation of this enzyme in the bloodstream<sup>43</sup>.

In the case of kidney disease, according to the data obtained, its identification as Acute Kidney Injury (AKI) was unanimous in the studies analyzed, considering that the kidneys are one of the main organs affected by SARS-CoV-2. For a better understanding of this comorbidity, it is important to mention that the diagnosis of AKI is given by the criteria described in the manual of the organization Kidney Disease Improving Global Outcomes (KDIGO)<sup>45</sup>.

AKI is an acute kidney disease that is divided into 3 stages, identified through the quantification of serum creatinine and excreted urine. The stage 1 patient has 1.5-1.9 times the baseline or  $\geq 0.3\text{mg/dl}$  ( $\geq 26.5\text{mmol/l}$ ) increase in serum creatinine, and urine quantitation  $< 0.5\text{ml/kg/h}$  between 6-12 hours; stage 2, which presents 2.0-2.9 times

the baseline serum creatinine and  $<0.5\text{ml/kg/h}$  for  $\geq 12$  hours of quantified urine; stage 3, for those who present serum creatinine in 3.0 times the baseline or increase in serum creatinine to  $\geq 4.0\text{mg/dl}$  ( $\geq 353.6\text{mmol/l}$ ) and urine quantification  $<0.3\text{ml/kg/h}$  for  $\geq 24$  hours or anuria for 12 hours<sup>46</sup>.

It is noteworthy that patients starting renal replacement therapy or those under 18 years old who show a decrease in GFR to  $<35\text{ml/min per }1.73\text{m}^2$  also fall into stage 3 of AKI<sup>46</sup>.

Regarding the importance of laboratory findings for diagnosing acute kidney injury, tests performed for the analysis of some biological materials, such as blood and urine, in order to make a diagnosis or just monitor the functioning of the body<sup>47</sup>. Considering that physiological changes often alter laboratory patterns, with patients affected by COVID-19, it is no different.

According to the results obtained, it is possible to affirm that patients contaminated by SARS-CoV-2 have some laboratory alterations that can serve as indicators of an AKI, namely: serum albumin  $<3.5\text{g/dl}$ , lymphopenia, thrombocytosis, hyperferritinemia, serum creatinine  $>1.3\text{mg/dl}$ , proteinuria, glomerular filtration rate (GFR)  $<60\text{ml/min/1.73m}^2$ , elevated C-reactive protein (CRP) level, D-dimer  $>0.500\mu\text{d/ml}$  and lactate dehydrogenase  $246\text{ IU/L}$ <sup>15-17,19,20,40</sup>.

Still thinking about the laboratory alterations presented by patients with COVID-19, it is known that the soluble urokinase-type plasminogen activator receptor (suPAR) and serum procalcitonin, among others, are also biomarkers associated with the onset of AKI<sup>18,13</sup>.

Among the laboratory changes to be observed, it is important to highlight the role of thrombocytosis, fibrinogen and D-dimer in the prognosis of patients affected by COVID-19, as this finding is important when identifying several cases of thromboembolism, which comes as a possible factor for the LRA<sup>20,48</sup>. Still, other studies address the disagreement with the role of ferritin, CRP, D-dimer and fibrinogen in the role of identifiable measurable markers for the detection of AKI<sup>12</sup>.

Such findings contribute to the primary signaling of physiological changes in the patient's body, requiring the attention of active health professionals.

Although COVID-19 is a new disease, the way the body behaves is no different. With the activation of the immune system at the first sign of an "invader". The identification of interleukins at an increased level in patients who presented AKI is responsible for the pro-inflammatory action against SARS-CoV-2, presented by IL-6, IL-8, IL-2R, and later IL-10, IL-1 $\beta$ <sup>19,21</sup>. Such identification leads one to believe that these proteins command the immune system and cause a storm of cytokines, which reflects in an exacerbated action of the individual's immune system, causing a protective factor to become harmful, thus interfering with good patient recovery. Cytokine storms, together with other factors such as elevated D-dimer, are related to the formation of blood thrombi, which act as a potential cause of AKI against the complication and evolution of COVID-19 in infected patients<sup>49,50</sup>.

Other studies claim that immunobiological identification does not always come as a biological marker

signaling the decline in renal function, but only as a clinical finding of the human body's reaction to viral infection<sup>12</sup>. These high levels of protein concentration are important indicators in the follow-up of patients in severe cases of the disease.

It is understood that some chronic diseases already act as a risk factor in infectious diseases in general. In the COVID-19 pandemic, this fact was increasingly discussed, making it clear that care for these people should be redoubled<sup>5</sup>. This relationship happens because patients with chronic diseases have a greater amount of the ACE-2 enzyme expressed in their body. Thus, due to the great affinity of SARS-CoV-2 with this enzyme, the high risk that carriers have is understandable<sup>51</sup>.

Based on the findings during the searches, some pre-existing diseases are a risk during the evolution of COVID-19, such as cardiovascular diseases (heart failure and peripheral vascular disease), hypertension, diabetes mellitus, immunosuppression by any factor, chronic kidney disease, cerebrovascular diseases, and high body mass index (BMI)<sup>22-27</sup>. There are also other conditions that qualify as a risk factor, but which were not identified in the studies evaluated, which are: smoking, pregnancy, asthma, chromosomal diseases in a state of immunological weakness, chronic obstructive pulmonary disease (COPD) and hematological diseases (anemia)<sup>5</sup>.

The relationship between pre-existing diseases and COVID-19 is due to the way in which the body responds to contamination by SARS-CoV-2, considering that an individual who has a chronic disease, or factors that compromise full functioning immune system, are more vulnerable to a poor prognosis during contamination and recovery. The fact to be raised is not only about the risk that this individual is predisposed to, but about how the body will respond to the new virus and, consequently, how the disease evolves. The more vulnerable the patient, the more likely he is to develop a more severe condition in COVID-19 and the greater the risk of developing AKI<sup>25,52</sup>.

Therefore, it is important to maintain close surveillance for this type of patient, as they are more likely to develop kidney damage from COVID-19.

It is known that biological aspects can influence the onset of AKI in patients infected with SARS-CoV-2. Age, gender and ethnic characteristics may be the characteristics of those who demonstrate a great impact in the search for factors that permeate AKI patients in COVID-19.

According to the data obtained, individuals over 60 years of age and male are the most affected. Being elderly has always been a vulnerability factor, as the body no longer has the same appearance as youth, the physiological course no longer works as it used to and chronic diseases arrive, and by itself the body loses a little more of its defense<sup>53,54</sup>. COVID-19 presents itself more aggressively in older people, its relationship may be linked to a decline in the immune system, as younger patients infected by the virus have a better prognosis and a lower rate of AKI development<sup>55</sup>.

The relationship between the prevalence of males in AKI cases in patients contaminated by SARS-CoV-2 is not clear, although studies show that males take care less of their own health, arriving at the health service most of the

time with a more advanced disease picture<sup>56</sup>.

When related to the fact that people of African descent are more likely to have an increased risk for AKI during COVID-19. This is because the individual is structurally more likely to have hematological diseases, hypertension and diabetes<sup>28,31,56,57</sup>. Also regarding ethnic characteristics, within the samples of selected studies, there was a discrepancy in the percentage of people who developed AKI during COVID-19. Those coming from the West had almost three times more individuals with some degree of AKI than those from the East. This may be related to the fact that there is a greater expression of the ACE-2 enzyme in the podocytes and proximal tubule of individuals from the West<sup>58</sup>.

In general, all factors lead to some pre-existing disease in the infected patient, thus explaining why people with such characteristics are more likely to develop AKI during COVID-19.

AKI does not always start in a hospital setting. There are some acute kidney injuries of pre-renal origin, that is, that developed in a community, either by dehydration or other factors, but which became more significant when combined with COVID-19. Through the study, the equivalence between pre-renal and intrinsic AKI (which originated in a hospital environment) was evident, with an equal risk of mortality for both<sup>32</sup>.

Of all stages of AKI, stage 3 is the most dangerous, as it is when there is no possibility of renal capacity returning, unlike stages 1 and 2. Patients who have AKI 3 concomitantly with COVID-19 do not showed improvement in renal function and/or did not survive a period of more than 28 days of hospitalization, with variable outcomes between Continuous Renal Replacement Therapy (TSRC), organ transplantation and death<sup>31,34</sup>.

The use of early RRT in patients with developing AKI can bring benefits, as substances harmful to the body will be removed and the amount of excess fluid in that body will decrease<sup>35</sup>. On the other hand, there is a significant increase in the risk of death in patients who underwent dialysis<sup>36</sup>.

There are some factors that increase the patient's chance of developing AKI, such as: drop in PaO<sub>2</sub>/FiO<sub>2</sub>, cardiopulmonary arrest, secondary infections, as well as the necessary approaches during the care of patients affected by COVID-19 that become risk factors for the emergence of AKI, such as: Invasive Mechanical Ventilation (IMV), admission and stay in the ICU, use of diuretics, vasopressor drugs and other nephrotoxic drugs<sup>31,37,41,39</sup>. In contrast, although IMV is a potential risk factor for the development of AKI and, consequently, death, the "delay" in performing the intubation would be the most harmful for these patients<sup>59</sup>.

As kidneys have a large amount of the ACE-2 enzyme in their tissue, the histopathological findings of the presence of the virus itself in the proximal tubule are a possible migration of SARS-CoV-2 through the bloodstream, facilitated by the circulating ACE-2<sup>24,42</sup>.

It is important that AKI is identified early, in order to intervene and interrupt the progressive worsening trajectory of renal involvement. It is worth considering a worrying factor that provides an increase in the mortality

rate: the lack of diagnoses in patients admitted to the ICU who already show signs of acute renal failure. The body demonstrates the signs of AKI and it is up to the professional to investigate and draw a line of care in order to increase the life span of this patient, as well as to preserve as much as possible the renal function of that individual hospitalized for COVID-19<sup>27</sup>.

The occurrence of Acute Kidney Injury (AKI) in patients contaminated by SARS-CoV-2 is still not clear, however, it is believed that this pathology will present itself as a sentinel factor signaling a sequential failure of organs, or the consequence itself of a multiple organ failure<sup>40</sup>.

Through the analysis of the articles, it was possible to understand that the critical condition of patients with COVID-19 is one of the main factors for renal impairment.

Although some studies address the formation of blood thrombi as one of the main causes of AKI in patients affected by COVID-19, the direct action of the virus on the renal epithelia must be considered. Thus, the need for further studies is clear. It is important to consider the hypothesis that renal impairment does not come from an exclusive reason, but as a combination of factors, such as the drug approach, physiological changes and other factors that harm the renal system.

The healthcare team must be constantly on the lookout for all warning signs for a patient in serious condition due to COVID-19. Early diagnosis can abruptly change the course of the disease and allow the best possible intervention for the individual.

## ■ CONCLUSION

It was evidenced that the risk factors that lead the patient contaminated by SARS-CoV-2 to develop kidney diseases were age, male gender, hypertension, diabetes, heart failure, immunosuppression, cerebrovascular diseases, chronic kidney disease, obesity, African descent, use of mechanical ventilation, sepsis and use of diuretics.

Regarding the relationship of patients with COVID-19 and the development of kidney diseases, the age and gender factor of individuals affected by the disease indicate a higher incidence of AKI. This is followed by the observance of pre-existing diseases, such as hypertension and diabetes, which call for attention in monitoring the evolution of the disease. The use of mechanical ventilation and sepsis are also highlighted as preponderant factors in the development of AKI and/or death.

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JSM, Project and manuscript elaboration; MASO, data collection and organization; IMPB, final review of material.

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## Conflicts of Interest

no conflicts of interest.

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## Resumo

**Introdução:** COVID-19 é uma doença respiratória aguda original da China que surgiu em dezembro de 2019 e se alastrou rapidamente pelo mundo, atingindo 230.418.415 pessoas e levando 4.724.876 pessoas a óbito. Vindo da família do coronavírus, o SARS-CoV-2 é o novo subtipo de vírus que afeta o trato respiratório em diversos níveis, podendo se alastrar e afetar outras estruturas vitais do corpo.

**Objetivo:** identificar os fatores de risco que levam o paciente contaminado pelo SARS-CoV-2 a desenvolver afecções renais.

**Método:** trata-se de uma revisão sistemática do tipo Scoping Review (revisão de escopo), de acordo com o método de revisão proposto pelo Joanna Briggs Institute (JBI), com a implementação de um check-list estruturado pelo PRISMA-ScR que contém 22 itens de carácter obrigatórios na revisão. Utilizado os descritores: infecção por coronavírus (coronavírus infection), lesão renal aguda (acute kidney injury) e fatores de risco (risk factors) em cinco bases de dados, sendo elas PudMed, Scopus, Embase, BVS (Biblioteca Virtual em Saúde) e Web of Science.

**Resultados:** durante a leitura dos estudos, chegou-se em conclusão de que a Lesão Renal Aguda (LRA) fora o principal achado renal em pacientes contaminados pelo SARS-Cov-2. Os fatores de risco para desenvolver o agravamento renal em pacientes com COVID-19 foi o extremo da idade, raça, sexo, doenças pré-existentes e a evolução da doença.

**Conclusão:** supõe-se que o acometimento renal não ocorra apenas por um motivo exclusivo, mas como uma conjuntura de fatores. Cabe a equipe de saúde se atentar de forma constante para os sinais de alerta mediante o acompanhamento do paciente contaminado.

**Palavras-chave:** infecção por Coronavírus, lesão renal aguda, fatores de risco.

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