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COVID-19-INDUCED ACUTE KIDNEY INJURY IN CRITICAL PATIENTS: WHAT DOES THE LITERATURE SAY?

Lesão aguda induzida pela covid-19 em pacientes críticos: o que diz a literatura?

Lesión renal aguda inducida por covid-19 en pacientes críticos: ¿qué dice la literatura?

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ABSTRACT

Objective: to identify through the literature the relationship between acute kidney injury (AKI) and COVID-19 in critically ill patients. **Method:** integrative literature review, with selection of articles published between 2020 and 2021 in the Virtual Health Library databases: LILACS, SCIELO, PUBMED. Through the descriptors "Acute Kidney Injury" AND "Coronavirus-19" AND "Intensive Care Unit". **Results:** the study consisted of a cut of 12 publications. Studies in general point out that AKI in the context of COVID-19, is of multifactorial cause, however there is no consensus on this statement, since some studies point out that COVID-19 directly contributes to new cases of AKI in critically ill patients due to to the cytokine cascade present in the pathology, which was not confirmed by all studies. **Conclusion:** this review showed that AKI is a complication present in critically ill patients with Covid-19. The studies found demonstrate that the subject still needs to be further explored so that the relationship between COVID-19 and AKI is definitively clarified.

DESCRIPTORS: Acute kidney injury; Coronavirus-19; Intensive care unit.

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RESUMO

Objetivo: identificar por meio da literatura a relação entre lesão renal aguda (LRA) e COVID-19, no paciente crítico. **Método:** revisão integrativa da literatura, com seleção dos artigos publicados entre 2020 e 2021 nas bases de dados da Biblioteca Virtual da Saúde: LILACS, SCIELO, PUBMED. Por meio dos descritores "Lesão Renal Aguda" AND "Coronavírus-19" AND "Unidade de Terapia Intensiva". **Resultados:** o estudo foi composto por um recorte de 12 publicações. Os estudos em geral apontam que a LRA no contexto da COVID-19, é de causa multifatorial, entretanto não há consenso sobre essa afirmativa, uma vez que alguns estudos apontam que a COVID-19 contribui diretamente para novos casos de LRA em pacientes críticos devido à cascata de citocinas presente na patologia, o que não foi confirmado por todos os estudos. **Conclusão:** esta revisão evidenciou que a LRA é uma complicação presente em pacientes críticos com Covid-19. Os estudos encontrados demonstram que o assunto ainda precisa melhor explorado para que a relação entre o COVID-19 e a LRA seja definitivamente esclarecida.

DESCRITORES: Lesão renal aguda; Coronavírus-19; Unidade de terapia intensiva.

RESUMEN

Objetivo: identificar a través de la literatura la relación entre insuficiencia renal aguda (IRA) y COVID-19 en pacientes críticos. **Metodo:** revisión integrativa de la literatura, com selección de artículos publicados entre 2020 y 2021 en las bases de datos de la Biblioteca Virtual en Salud: LILACS, SCIELO, PUBMED. A través de los descriptores "Daño Renal Agudo" Y "Coronavirus-19" Y "Unidad de Cuidados Intensivos". **Resultados:** el estudio constó de un corte de 12 publicaciones. Los estudios en general señalan que el IRA en el contexto del COVID-19, es de causa multifactorial, sin embargo no existe consenso sobre esta afirmación, ya que algunos estudios señalan que el COVID-19 contribuye directamente a nuevos casos de IRA en pacientes críticos por a la cascada de citocinas presente en la patología, que no fue confirmada por todos los estudios. **Conclusión:** esta revisión mostró que el DRA es una complicación presente en pacientes críticos com Covid-19. Los estudios encontrados demuestran que el tema aún necesita ser más explorado para que la relación entre COVID-19 y AKI se aclare definitivamente.

DESCRIPTORES: Daño renal agudo; Coronavirus-19; Unidad de cuidados intensivos.

INTRODUCTION

Beginning in December 2019 in Wuhan City, China, Coronavirus Disease 2019 (COVID 19), has caused significant changes in the lives of the human population. Responsible for major physical and mental changes, COVID-19 triggers a severe systemic inflammatory process, leading several patients to require hospitalization and even the need for more advanced support in an intensive care unit (ICU),[1] a place intended for critically ill patients and allowing them to receive individualized care focused on local and systemic pathologies.

COVID-19 is a pathology that is currently feared and discussed worldwide, because its severe form causes important complications leading to a rapid worsening of the patient's clinical condition, and even death, and is the subject of study, discussion, and tireless debate in the scientific community.

Some proven complications have called the attention of health professionals to the management and therapy of these patients. Such complications may include thrombosis, pneumonia, and severe acute respiratory failure.[2] However, other pathologies, such as Acute Kidney Injury (AKI), often acquired after infection by the virus, still generate doubts and debates about its real pathophysiology and etiology.

The diagnosis of AKI in the context of COVID-19 should be clearly associated with the outcome, besides including prognostic estimates. Therefore, the use of international creatinine-based scoring scales, such as RIFLE, AKIN and KDIGO, can assist in the diagnostic criteria, but these scales allow only a delayed severity classification.[2]

The incidence of AKI may range from 2,147 to 4,085 cases per million population per year in developed countries, with a rate of 3.2% to 9.6% of hospital admissions, with in-hospital mortality totaling 20% of patients, and in up to 50% of ICU patients.[3]

An overall incidence rate of AKI of approximately 3% to 18% was found.4 In the ICU, when analyzing AKI induced by COVID 19, studies point to an incidence rate of 4% to 71.2%[5-6] and mortality that can reach up to 50%.[4] The studies point to a long hospital stay rate in relation to the increased incidence of cases.

In Brazil in the year 2017, AKI accounted for an incidence of 44.7% of patients admitted to the ICU, while some studies found a lower incidence, the study ranged from 29%-35.7%, and one study that obtained a higher incidence (76.5%).[7] These findings are attributed in several studies to the difficult and late diagnosis of AKI, presence of comorbidities, intense use of invasive procedures, and the severe complications that leverage the poor prognosis of ICU patients.

Because it is an important disease, high prevalence and incidence, AKI in the ICU context should be constantly discussed and studied since it increases mortality, length of hospital stay and hospital costs. Thus, this study is justified by the exponential increase of new cases of AKI in critically ill patients affected by COVID-19. Therefore, this study was based on the following guiding question: What is the relationship between Covid-19 and AKI in critically ill patients?

Thus, this study aimed to identify through literature the relationship between acute kidney injury (AKI) and COVID-19 in critically ill patients.

METHODS

This is an integrative literature review study, developed with the purpose of gathering and synthesizing findings of studies conducted using different methodologies, in order to contribute to the deepening of knowledge on the investigated topic.[8] Therefore, to carry out this study, the following steps were taken: definition of the theme, identification of the research question; definition of eligibility criteria; database search; selection of selected studies; preparation of the data collection instrument by means of a synoptic table, extraction of the results by means of a summarized summary, organization of the data in a specific table; analysis and discussion of the results.

In order to build a complete search, a strategy based on the PICO elements was defined, which consists of an acronym for Patients; Intervention; Comparison; Outcome. Where Patients are those affected by Covid-19 associated with AKI, Intervention were strategies to identify patients who had a diagnosis of Covid-19 as an assessment of tests to identify the risk of developing AKI, Comparison between those who developed versus those who did not have AKI, and Outcome were those found through this study.

The search for the studies was performed in 2 distinct moments. In the first moment, the search was made by one of the authors. After the selection of the studies, a second search was made by a second author who was a specialist in the research area, in order to confirm the selected studies and guarantee a better selection of the studies.

The search and selection of the included studies occurred between August 2021 and March 2022 in the following databases: Latin American and Caribbean Literature on Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (MEDLINE) via PUBMED. The keywords used in the search were: Acute Kidney Injury, Covid-19, and Intensive Care Units. For a broader search of the literature, the descriptors were combined using the Boolean terms "AND and OR". Thus the search was performed by the following grouping: ("Acute Kidney Injury" AND "Covid-19" AND "Intensive Care Units") OR ("Acute Kidney Injury" AND "Covid-19") the same groupings were used for the English language.

The method of study eligibility was carried out in three phases: Thematic; reading the Abstract and reading the full text of the pre-selected articles. The inclusion criteria of this study consisted of: articles available in full that portrayed the proposed theme, observational, descriptive and intervention studies, that referred to AKI in the context of COVID 19, published in English, Portuguese or Spanish between 2020 and 2021 and that answered the proposed objective. Abstracts, theses, and dissertations, articles that were not available in full, that did not mention AKI in the context of COVID 19, that eluded the COVID 19 topic, or that did not answer the proposed objective were not considered. Studies available in 2 or more databases were considered only once; review articles were used in this study.

Data extraction consisted of reading the selected articles in their entirety, summarizing the main ideas and results, and then digitizing and organizing the main results in a Microsoft Office Excel® (2019) spreadsheet.

In order to organize the included articles, the results were presented in 2 tables, where items such as: authors and year of publication, design of the selected studies, number of study participants, gender, incidence of AKI in the context of COVID-19 and the mortality of these patients were addressed (Table 1). In a second table (Table 2), the main considerations about AKI induced by COVID-19 were presented. After data collection, the analysis, presentation and discussion of the results found were performed.

It is worth mentioning that because this is a literature review, the present study is exempt from being evaluated by the Research Ethics Committee, according to Resolution 510 of the National Health Council.

Chart 1 – Flowchart of the study selection process.

Total studies identified with the descriptors (N: 642)
PUBMED: 412 SCIELO: 28 LILACS: 202
SELECTION
N° of excluded studies (N: 159) Excluded after applying filters CKI (Chronic Kidney Injury): 159
ELIGIBILITY
Eligible articles (N: 483) Articles considered only once per publication in 2 or more databases: 152 Excluded for not answering the objective: 309 Excluded due to unavailability: 11
INCLUSION
Analyzed articles included (N: 12) PUBMED: 9 SCIELO: 2 LILACS: 1

Source: Prepared by the authors themselves.

RESULTS

In an initial screening, 642 articles were identified. After applying the filters (original articles and articles available in full), 494 articles were identified. After applying the second filter (published between 2020 and 2021), a total of 483 articles were identified. These were submitted to title reading, which resulted in 226 articles. These were then subjected to abstract reading, which resulted in a total of 86 articles. After the 86 remaining articles were completely read, 74 articles were excluded. Thus, 12 articles were selected to compose the corpus of this research. These articles were evaluated in detail and their characteristics and main findings are described in Table 1. It is worth noting that they all used the quantitative method.

AKI in patients with COVID-19 represents a major management challenge for healthcare professionals. It is responsible for increased mortality, hospital costs, and length of hospital stay in patients infected with SARS-COV-2.

When the age range of patients with COVID 19 associated with AKI was analyzed, studies pointed out that age is a poor

Table 1 – Synthesis of the study. Brasília, DF, 2021

Authors	Type of study	Sample (n)	Gender (%)	Incidence of AKI in COVID-19	Mortality
Ng 2020[9]	Retrospective study	9.657 Patients	SM= 5.747 SF= 3.910	AKI after COVID 3.216 (33,3%)	1.491 (46,4%)
Hirsch 2020[10]	Retrospective study	5.449 Patients	SM= 3.317 (60,9%) SF= 2.132 (39,1%)	AKI after COVID 1.993 (36,6%)	694 (35%)
Sang 2020[11]	Retrospective study	210 Patients	SM=131(62,4%) SF= 79 (37,6%)	AKI after COVID 210 (100%)	93 (44,3%)
Zahid 2020[12]	Coorte Retrospective cohort	469 Patients	SM= 268 (57,14%) SF= 201 (42,86%)	AKI after COVID 128 (27,3%)	91 (71,1%)
Costa 2021[1]	Retrospective cohort	102 Patients	SM= 60 (58,8%) SF= 42 (41,2%)	AKI after COVID 57 (55,9%)	23 (22,5%)
Yang 2020[13]	Retrospective cohort	882 Patients	SM= 440 (49,9%) SF= 442 (50,1%)	AKI after COVID 115 (13%)	68 (59,1%)
Paek 2020 [6]	Retrospective study	704 Patients	SM= 16(57,1%) SF= 12(42,9%)	AKI after COVID 28(4,0%)	13 (46%)
Kolhe 2020[14]	Retrospective study	1.161 Patients	SM= 657 (56,6%) SF= 504 (43,4%)	AKI after COVID 304 (26,2%)	184 (60,5%)
Almeida 2021[5]	Retrospective study	278 Patients	SM= 93(32,3%) SF= 185(67,7%)	AKI after COVID 198(71,2%)	95(34,17%)
See 2021[15]	Retrospective study	707 Patients	SM= 405(57%) SF= 302(43%)	AKI after COVID 57(8,1%)	7(12%)
Charytan 2021[16]	Retrospective study	4.732 Patients	SM= 2.702(57,10%) SF= 2.030(47,90%)	AKI after COVID 1.386(29,3%)	710(51,6%)
Piñeiro 2021[17]	Prospective Study	237 Patients	SM= 182(76,9%) SF= 55(23,1%)	AKI after COVID 52(21,4%)	26(50%)

Legend: Male gender (SM); Female gender (SF); Results.

Table 2 – Main results and considerations

Author, Year	Main results/considerations
Ng et al., 2020[9]	The most common cause of kidney damage in patients with COVID-19 is acute tubular injury. However, it has not been conclusive whether SARS-CoV-2 directly infects the kidney.
Hirsch et al., 2020[10]	The etiology of AKI in cases of COVID-19 has not been fully elucidated, but the clearest risk factors for developing AKI were found to be indicators of severe COVID-19, specifically the need for ventilatory support or treatment with vasopressor drugs.
Yang et al., 2020[13]	The renal tubule has been identified as the main part of injury in patients with COVID-19.However, AKI in patients with COVID-19 is probably diverse and multifactorial, as direct attack by SARS-CoV-2, hypoxia and hypercoagulability arising from COVID-19 may also contribute to the occurrence of AKI.
Sang et al., 2020[11]	Age, sepsis, nephrotoxic drugs, invasive mechanical ventilation, and baseline serum creatinine were strongly associated with the development of AKI in critically ill patients affected by COVID-19.
Zahid et al., 2020[12]	Coronavirus 2019 (COVID-19) in addition to causing diffuse alveolar damage, also causes changes in other organs, among them the kidneys.
Costa et al., 2021[1]	The pathophysiology of AKI in Covid-19 patients is still unclear, but appears to be complex and multifactorial.
Paek et al., 2020[6]	Although the lungs are the main targets of COVID-19 invasion, other organs, such as the kidneys, are also affected. However, the kidney complications of COVID-19 are not yet well explored.
Kolhe et al., 2020[14]	The causes of AKI in COVID-19 may not be predominantly classical pre-renal causes. Direct effects of SARS-CoV-2 on the kidneys and the inflammatory effect of high cytokine levels (cytokine storm) may be additional relevant factors.

Table 2 – Cont.

Almeida et al., 2021[5]	The development of AKI in patients with severe COVID-19 was related to inflammatory blood markers and hydroxychloroquine/azithromycin therapy. The need for vasopressor and hypertension in critically ill patients were also considered potential risk factors.
See et al., 2021[15]	Severe COVID-19 is independently associated with increased risk of AKI in addition to premorbid conditions and age.
Charytan et al., 2021[16]	AKI affects a high proportion of patients with COVID-19 and is associated with increased mortality in this population, especially when subistive renal therapy is required.
Piñeiro et al., 2021[17]	Severe AKI is part of the multiple organ failure that occurs in the context of the cytokine storm present in patients with COVID-19.

predictor and, as in other diseases, was responsible for the increased severity and mortality of patients.

In general, the studies point out that the inflammatory process associated with the cytokine storm released by COVID-19 appears to be the main responsible for systemic complications. Among the most common complications are ARDS (acute respiratory distress syndrome), pneumonias, endocarditis, and AKI, the latter often requiring renal replacement therapy.

Severe respiratory syndrome is the most common complication in the studies. This complication, associated with the need for invasive mechanical ventilation (MV), further increased the cases of AKI in critically ill patients with COVID-19 when compared to patients who did not develop severe respiratory disease.

When analyzing AKI as a direct complication due to COVID-19, studies still do not express clarity about this evidence, since, besides the inflammatory process caused by COVID-19 being an important nephrotoxic factor, other complications and the therapy itself used in the treatment of these complications as MV, antibiotic therapy, vasoactive drugs among others, also appear to be important causative factors of AKI, and when associated with pre-existing comorbidities, the mortality rate and length of ICU stay are considerably increased.

DISCUSSION

COVID-19 had its start in Wuhan-China in early December 2019 and to date is in a worldwide pandemic affecting over 200 countries. With 84,464 confirmed cases, 4,644 deaths in China and 4,174,203 cases with 289,546 deaths outside China these data as of May 15, 2020.[18]

This highly infectious and highly pathogenic pathology infects various systems of the human body such as the respiratory, gastrointestinal, liver and central nervous systems. It can be of abrupt or persistent onset, transmitted primarily by the respiratory route.[19]

The severity of COVID-19 can often be related to the signs and symptoms presented, which makes it necessary to pay more attention to these symptoms through systematized evaluation for early diagnosis and targeted treatment of the disease.

At the beginning of the Covid-19 pandemic, AKI had an incidence of approximately 3%-18% of patients in hospital settings and is related to 10%-20% of deaths, and can reach up to 50% in critically ill patients. However, there are still few studies and evidence to define the real relationship of COVID-19 in association with AKI.[4]

In the sample of 102 patients, an incidence of 55.9% was found; 38 patients evolved to stage 3, and 70% required renal replacement therapy such as hemodialysis.[1]

One study pointed out that symptoms can be classified into non-severe and severe. In the non-severe symptoms, the patients presented mild symptoms and often presented radiographic alterations, such as signs of pneumonia, or when present, the alterations were considered of little relevance. Patients with severe symptoms developed signs of respiratory failure with a frequency greater than or equal to 30 breaths per minute (bpm), partial oxygen saturation (Spo2) less than or equal to 93% at rest, ventilation-perfusion ratio (Po2/Fio2) less than or equal to 300 mmHg, need for MV in some cases, shock or failure of other organs.[20] Among them, the kidneys, leading to the need for admission to the ICU, more detailed monitoring of renal function and even the need for renal replacement therapy.

Nogueira and other authors,[21] point out that there are common clinical changes identified in patients with initial symptoms, such as fever, cough, fatigue, and dyspnea. However, many presented alterations in organic functions, with respiratory and cardiac alterations being the most frequent alterations. However, the study points out that a relevant number of patients may present or develop signs of acute kidney injury.[21]

Yang and collaborators,[22] conclude that AKI is constant in critically ill patients. And that patients who do not seek early care, who only seek health care when the disease presents signs of exacerbation, may have greater complications, which demonstrates that early diagnosis has positive results when compared to patients who are diagnosed later.

The pathophysiology of COVID-19 is still unknown, but when analyzing AKI induced by COVID-19 there are hypotheses about this cause, where there is a possible direct viral infection in the kidneys that causes AKI. Other analyses show that altered cellular respiration due to respiratory failure causes injury to the heart where renal ischemia will occur and consequently the development of AKI due to hypoperfusion. An additional hypothesis may be related to the high burden of inflammatory processes caused by cytokine release from the COVID-19 infection. And finally the hypothesis that the toxins released by continuous medication use cause microthrombosis and rhabdomyolysis, which can also lead to AKI.[23]

Ostermann et al,[24] describe that AKI associated with COVID-19 stems from several causes. These causes comprise critical elements grouped as: hemodynamic changes, inflammation, cytokine release, microcirculation alteration, nephrotoxic exposure. Another factor already confirmed is the impact of invasive

mechanical ventilation, since there is evidence that SARS-COV-2 associated with the need for MV worsens renal function and increases the risk of developing AKI.

These findings are similar to those found in the study by Ronco, Reis and Husain-Syed,[25] who also report AKI as a consequence of several alterations developed in critically ill patients with COVID-19, among them the cardiorenal dysfunction, right ventricular failure caused by the pneumonia caused by COVID-19, which will lead to renal overload and dysfunction due to the low cardiac output resulting from this process, with consequent alterations in blood pressure and renal perfusion.

In the study by Ng et al,[9] it points out that in AKI in patients with COVID-19, acute tubular injury, ischemia, and tubular toxicity occur as a result of the virus infection. Another study,[10] describes that tubular injury occurs possibly due to respiratory failure caused by COVID-19, as a result of hypoxemia and cellular hypoxia. These authors also state that there is a thrombotic component caused by COVID-19 which can also lead to AKI, but which are pre-renal findings. These data are in agreement with the findings of Yang et al,[13] who also refer to renal tubular injury as a consequence of COVID-19 infection due to tissue hypoperfusion and coagulation alterations.

CONCLUSION

COVID 19 is a highly complex disease of great impact worldwide. Its severe form can cause important alterations in the organism varying from worse prognosis to intensive care unit discharge. This disease shows an important factor responsible for damage to the renal system and consequently a contributing factor to the development of AKI. This may be attributed to the cytokine cascade released during the inflammatory process of COVID-19. However, the included studies point out that complications with respiratory failure, and heart diseases, associated with the need for MV, also present impacting factors on the rate of AKI and consequently mortality in critically ill patients.

It is important to know that the relationship between severe COVID and the development of AKI exists so that the nursing staff is aware of the early signs of renal failure in critically ill patients, and interventions can be performed as early as possible, which improves the patient's prognosis.

And finally, because the AKI induced directly by COVID 19 is multicausal, there are no studies proving that the disease attacks the kidneys directly. This leads us to conclude that this topic should be further debated and analyzed. Thus, we suggest new analytical studies of patients infected from the onset of symptoms, in order to detect the impact on glomerular filtration during the course of the disease, before the onset and other complications already described in the literature.

A limitation of the study is the restricted number of articles reviewed. Thus, the results and discussions presented in this article are limited for generalizations to be established.

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