Review Article

Acute kidney injury in adult patients with COVID-19: an integrative review

Lesão renal aguda em pacientes adultos com COVID-19: revisão integrativa

Lesión renal aguda en pacientes adultos con COVID-19: revisión integradora

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Abstract

Objective: To identify the frequency of acute kidney injury (AKI) in patients hospitalized with COVID-19, associated characteristics, mortality and lethality.

Methods: Integrative review carried out in the databases CINAHL, Embase, LILACS, Livivo, PubMed, SCOPUS, Web of Science and in the grey literature (Google Scholar) on January 12, 2022. Articles were included in English, Spanish and Portuguese, published from November 2019 to January 2022, in hospitalized patients over 18 years old with COVID-19 and AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria. The selected studies were read in full for extraction, interpretation, synthesis and categorization according to the level of evidence.

Results: A total of 699 articles were found and 45 included. Older age, male gender, hypertension, chronic kidney disease, mechanical ventilation, increased C-reactive protein, use of vasoactive drugs and certain classes of antihypertensives were associated with AKI. AKI is related to a higher frequency of mortality. AKI occurred in 30% of patients hospitalized with COVID-19. The mortality rate from AKI was 5% and the case fatality rate was 18%.

Conclusion: These results highlight the relevance of AKI as a significant complication of COVID-19 and suggest that more careful and early control of associated factors could potentially reduce mortality and lethality. It is crucial to intensify research in this field to better clarify the mechanisms involved in kidney injury in COVID-19 patients, as well as to identify more effective therapeutic strategies for its prevention and treatment in this context.

Resumo

Objetivo: Identificar a frequência de lesão renal aguda (LRA) em pacientes hospitalizados com COVID-19, as características associadas, a mortalidade e a letalidade.

Métodos: Revisão realizada nas bases de dados CINAHL, Embase, LILACS, Livivo, PubMed, SCOPUS, Web of Science e, na literatura cinzenta (Google Acadêmico) em 12 de janeiro de 2022. Foram incluídos artigos em inglês, espanhol e português, publicados a partir de novembro 2019 até janeiro de 2022, em pacientes maiores de 18 anos com COVID-19 hospitalizados e LRA conforme critério *Kidney Disease Improving Global Outcomes* (KDIGO). Os estudos selecionados foram lidos na íntegra para extração, interpretação, síntese e categorização conforme nível de evidência.

Resultados: 699 artigos encontrados e 45 incluídos. A idade avançada, sexo masculino, hipertensão, doença renal crônica, ventilação mecânica, aumento da proteína C reativa, uso de drogas vasoativas e de

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determinadas classes de anti-hipertensivos foram associados a LRA. A LRA está relacionada à maior frequência de mortalidade. Em 30% dos pacientes hospitalizados com COVID-19 houve LRA. A taxa de mortalidade por LRA foi de 5% e a letalidade de 18%.

Conclusão: Estes resultados ressaltam a relevância da LRA como uma complicação significativa da COVID-19 e sugerem que um controle mais cuidadoso e precoce dos fatores associados poderia potencialmente reduzir a mortalidade e a letalidade. É crucial intensificar a pesquisa nesse campo para esclarecer melhor os mecanismos envolvidos na lesão renal em pacientes com COVID-19, bem como identificar estratégias terapêuticas mais efetivas para sua prevenção e tratamento nesse contexto.

Resumen

Objetivo: Identificar la frecuencia de lesión renal aguda (LRA) en pacientes hospitalizados con COVID-19, las características relacionadas, la mortalidad y la letalidad.

Métodos: Revisión realizada en las bases de datos CINAHL, Embase, LILACS, Livivo, PubMed, SCOPUS, Web of Science y en la literatura gris (Google Académico) el 12 de enero de 2022. Se incluyeron artículos en inglés, español y portugués, publicados a partir de noviembre de 2019 hasta enero de 2022, con pacientes mayores de 18 años con COVID-19 hospitalizados y LRA de acuerdo con el criterio *Kidney Disease Improving Global Outcomes* (KDIGO). Los estudios seleccionados fueron leídos en su totalidad para extracción, interpretación, síntesis y categorización según el nivel de evidencia.

Resultados: Se encontraron 699 artículos y se incluyeron 45. Los factores relacionados con la LRA fueron: edad avanzada, sexo masculino, hipertensión, enfermedad renal crónica, ventilación mecánica, aumento de la proteína C reactiva, uso de drogas vasoactivas y de determinadas clases de antihipertensivos. La LRA está relacionada con mayor frecuencia de mortalidad. En el 30 % de los pacientes hospitalizados con COVID-19 hubo LRA. La tasa de mortalidad por LRA fue de 5 % y la letalidad de 18 %.

Conclusión: Estos resultados resaltan la relevancia de la LRA como una complicación significativa de COVID-19 y sugieren que un control más cuidadoso y temprano de los factores asociados podría reducir potencialmente la mortalidad y la letalidad. Es crucial intensificar la investigación en este campo para explicar mejor los mecanismos relacionados con la lesión renal en pacientes con COVID-19, así como identificar estrategias terapéuticas más efectivas para su prevención y tratamiento en este contexto.

Introduction

Most individuals with COVID-19, a disease caused by the SARS-CoV-2 virus, have mild and moderate manifestations. It is estimated that 20% of cases progress to the severe form of the inflammatory disease and require hospital care.[1] Of these, 5% develop a critical condition and require care in the Intensive Care Unit (ICU).[1]

The main pathophysiological mechanism of COVID-19 is the overproduction of pro-inflammatory cytokines that triggers an exacerbated inflammatory process, increased vascular permeability and multiple organ failure due to prolonged cytokine effects.[2,3] It is also worth noting that organic dysfunction, especially pulmonary dysfunction, is already a risk factor for AKI.[1] Another clinical aggravating factor is the inflammation-coagulation interaction, with a hyperinflammatory and prothrombotic state.[2,3] This inflammatory process has contributed to the development of Acute Kidney Injury (AKI) in patients with severe COVID-19.[4,5]

The main risk factors for AKI associated with SARS-CoV-2 infection include direct viral damage to the kidneys and the hemodynamic disturbances caused by COVID-19. Angiotensin-converting enzyme 2 (ACE-2) receptors are the main binding pathway for the virus and are widely expressed in the proximal tubules of the kidneys, favoring renal damage.[6] Secondary factors, such as cytokine storm, hypoxia, nephro-toxicity associated with drug use and secondary infection by other microorganisms, can contribute to the development of AKI.[6]

Serum cytokines stimulate renal endothelial cells to secrete more chemokines, thus triggering increased vascular permeability and dysfunction in the renal microcirculation, as well as cell death and renal tissue damage leading to kidney failure.[6] Dysregulation of the complement system and hypercoagulation lead to the formation of microvascular thrombi and the development of sometimes irreversible interstitial damage, such as Acute Tubular Necrosis (ATN) and cortical necrosis. The formation of microthrombi and microangiopathy increase the risk of microinfarctions in different organs, including the kidneys.[6]

Considering that severe COVID-19 has multisystemic repercussions, previous studies have reported that the occurrence of AKI in patients hospitalized with COVID-19 is associated with higher mortality and a worse prognosis.[2,7,8] Therefore, the identification of the characteristics that expose COVID-19 patients to a higher risk of AKI must be known and managed early by the multidisciplinary team. Although previous systematic reviews address the object of study, this review is justified since it

covers more current data, encompasses an additional outcome and additional databases.[9,10]

Thus, the primary objective of this study was to identify the frequency of AKI in patients hospitalized with COVID-19. Secondary objectives were to identify the mortality and lethality of related AKI and to identify the main characteristics described in the literature associated with AKI.

Methods

Type of study and research question

This is an integrative review, with the following guiding question "What is the frequency, mortality, lethality and factors associated with the development of AKI in adults hospitalized with COVID-19?", prepared using the PECO strategy,[11] defined by Patient (hospitalized adult), Exposure (SARS-CoV-2 infection, COVID-19), Comparison (not applicable) and Outcomes (frequency, factors associated with the development of AKI, mortality and lethality).

The review was developed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, comprising a 27-item checklist.[12]

Information sources and search strategy

The search strategy was based on Health Sciences Descriptors (DeCS) and MeSH terms (Medical Subject Headings): "Adult", "Covid-19", "Acute Kidney Injury", "Risk Factors". The descriptors were combined using the Boolean operator AND to cross-reference different descriptors. The search took place on January 12, 2022 in the databases: Cumulative Index to Nursing and Allied Health Literature (CINHAL), EMBASE, Latin American and Caribbean Health Science Literature (LILACS), LIVIVO, PubMed Central, SCOPUS and Web of Science. The detailed search strategy is shown in Chart 1.

Chart 1. Search strategy

Pubmed	"adult" AND "covid-19" and "Acute Kidney Injury" and "risk factors"
Embase	"adult" AND "covid-19" and "Acute Kidney Injury" and "risk factors"
Scopus	"adult" AND "covid 19" and "Acute Kidney Injury" and "risk factors"
Livivo	"adult" AND "covid-19" and "Acute Kidney Injury" and "risk factors"
Web of science	"adult" AND "covid-19" and "Acute Kidney Injury" and "risk factors"
Cinhal	"covid-19" and "Acute Kidney Injury" and "risk factors"
Lilacs	"covid-19" and "Acute Kidney Injury" and "risk factors"
Google scholar	allintitle: "Acute Kidney Injury" "risk factors" "covid 19"

Eligibility criteria

Articles were included in English, Spanish and Portuguese, published from November 2019 to January 2022, with a sample of hospitalized COVID-19 patients over the age of 18, with cases of AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[13,14] (Stage 1: 0.3mg/dL increase or 1.5 to 1.9 times increase in baseline serum creatinine and reduction in urine output to less than 0.5 mL/Kg/h for 6-12 hours. Stage 2: a 2.0 to 2.9-fold increase in baseline serum creatinine and a reduction in urine output to less than 0.5 mL/Kg/h for 12 hours or more. Stage 3: 3.0-fold increase or increase above 4.0 mg/dL in baseline serum creatinine or initiation of renal replacement therapy or patients over 18 years of age with a reduction in estimated glomerular filtration rate to less than 35 mL/min/1.73m^2 and a reduction in urine output to less than 0.3 mL/kg/h for 24 hours or more or anuria for 12 hours or more), whether or not they require dialysis treatment..

We excluded (1) secondary studies, such as reviews and meta-analyses; (2) guidelines, editorials, expert reports; (3) studies on children, kidney transplant recipients and chronic kidney disease; (4) studies that did not address the exposure or outcome of interest. The information regarding the eligibility criteria is in line with the research question, following the PECO strategy, which ensures that the selection of studies is directly related to the research objective.

Selection of studies

The articles found in the search were exported to the reference manager (EndNote Web®), where duplicates were removed, and then the references were exported to the Rayyan® software to screen the studies according to the eligibility criteria. First, the titles and abstracts were read by two independent reviewers. Articles that met the eligibility criteria were read in full by two independent reviewers. Disagreements were resolved by a third reviewer.

Data extraction

The data was collected using a specific tool created by the authors, which included: identification of the publication (authors, year of publication, country in which the study was carried out, language), type of study, sample size with COVID-19, demographic and clinical characteristics, length of ICU stay, frequency of AKI, number of deaths from acute kidney injury and from all causes, mortality rate of AKI in COVID-19 positive patients, lethality of AKI in COVID-19 positive patients and factors associated with AKI. Data extraction was validated by the third reviewer.

Evaluation of included studies

The studies were evaluated and categorized according to the level of evidence (LE),[15] being: I) Systematic reviews or meta-analyses of relevant clinical trials; II) Evidence from at least one well-designed randomized controlled trial; III) Well-designed clinical trials without randomization; IV) Well-designed cohort and case-control studies; V) Systematic review of descriptive and qualitative studies; VI) Evidence derived from a single descriptive or qualitative study; VII) Opinion of authorities or report of expert committees.

Summary of included studies

Quantitative descriptive analysis was carried out using the proportion function in Excel 2013 software. The overall mortality rate was calculated considering the number of deaths from all causes. The AKI mortality rate and lethality was calculated considering the number of deaths of patients diagnosed with AKI, regardless of the stage. Qualitative descriptive analysis was performed to group results related to factors associated with the development of AKI in COVID-19 patients identified in the individual studies.

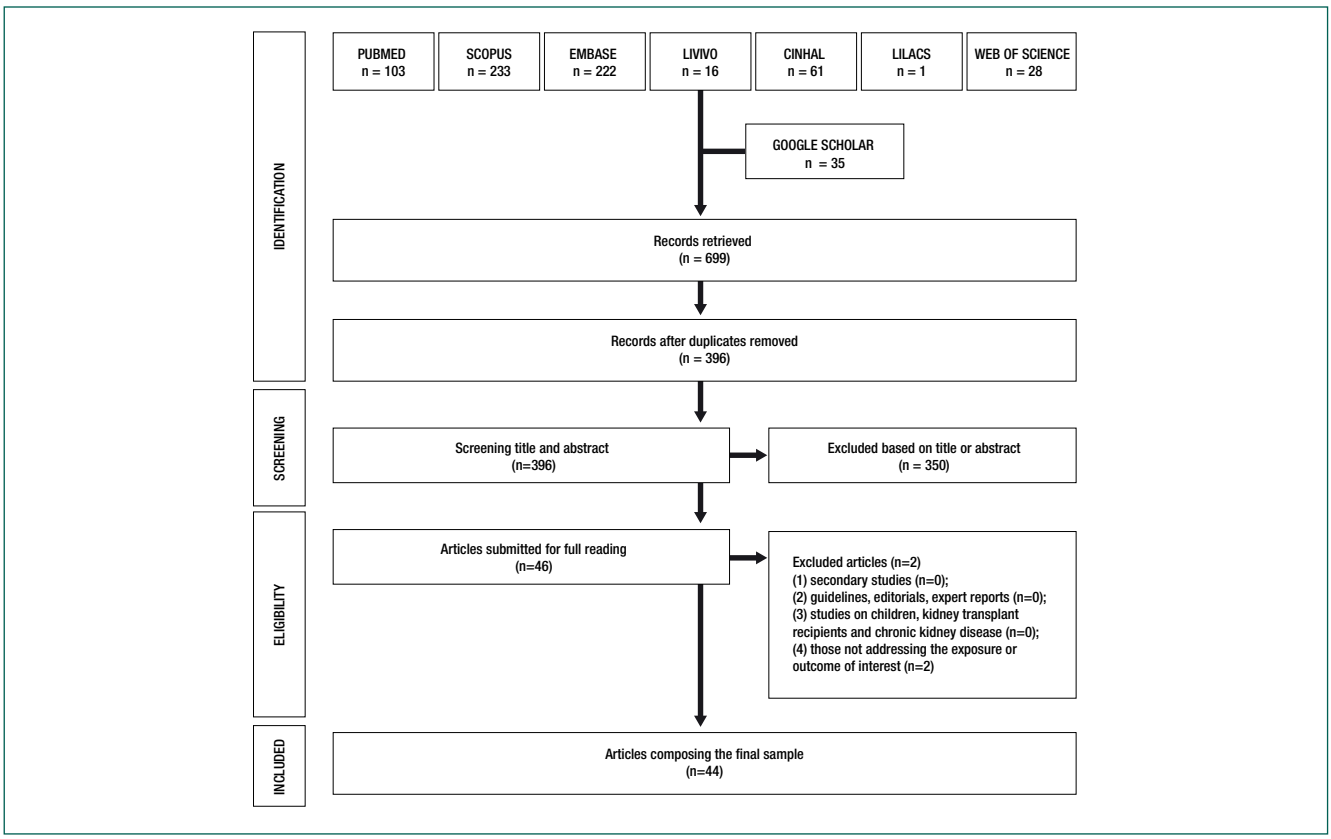
Results

A total of 699 studies were identified using the database search strategy. After removing duplicates, 396 articles remained to be screened by reading the titles and abstracts. 46 studies were selected for exploratory reading and 44 articles were selected for the final sample, as they met the eligibility criteria according to the flowchart. (Figure 1).

All the studies included were published in English, between 2020 and 2022, carried out in South America[16-19] and North America,[20-27] Asia,[28-42] Europe,[43-53] Africa[54] and Middle East.[55-58] The country with the highest number of publications on AKI associated with COVID-19 was China, with 27.3% (n = 12) of the articles.[31-42] All the studies were observational, with a predominance of cohorts 63.6% (n=28),[16,17,20,21,23,28,29,31-33,35-38,40,41,43-46,51-53,55-59] 77,3% (n = 34) retrospective[16-18,20,21,24-28,30-44,46-53,55] and 2,3% (n = 1) prospective.[19] All the included studies had a level of evidence IV. The data extracted from the included studies is shown in Box 2.

The total number of participants included in this review was 78,467 patients, with the smallest sample among the individual studies being 37[30] patients and the highest of 41,294.[45] The median age was over 36 for all the individual studies and males predominated with 79.5% (n=35)[17,18,20-23,25-34,37,39,40,42-44,46-50,52,54-60] (Chart 2). The average length of stay in general was 14.8 days, ranging from 2 to 51 days, with a longer length of stay in patients with AKI, according to the studies that provided this information.[18,28,29,31,35,47,53,54,57-59]

The frequency of AKI ranged from 4%[31] to 81%[49] in the individual studies. Considering the total sample of this review (78467 COVID-19 patients), the frequency of AKI was 30%. The occurrence of AKI was associated with a higher frequency of mortality.[17,18,20,24,28-36,38,40, 42,43,46,48-52,54-56,58,59] All-cause mortality ranged from 1%[31,37] to 60%.[54,56] Mortality from AKI ranged from 1%[28,31] to 43%.[56] Lethality ranged from 3%[37] to 85%.[54] Three studies[22,40,45] did not present death data and so it was not possible to calculate mortality and lethality for these individual studies. Thus, 41 studies[16-21,23-39,41-43] provided data for calculating overall mortality, AKI mortality and lethality for this review. In summary, the all-cause mortality rate in COVID-19 patients was 9%, the AKI mortality rate was 5% and AKI lethality was 18%. Mortality was higher among individuals with stage 3 AKI when compared to stage 1 and 2 AKI.[16,23,27,31,45,57] The factors associated with AKI include: (1) demographic



Source: Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.[12]

Figure 1. Flowchart of the literature search and selection process based on PRISMA

and clinical characteristics, (2) biomarkers and (3) pharmacological treatments (Chart 3).

Discussion

The aim of this review was to identify the frequency, mortality, lethality and main factors associated with the development of AKI in patients hospitalized with COVID-19 in order to strengthen evidence-based practice.

Based on this knowledge, the interdisciplinary team, especially the nursing team, can implement more assertive actions in clinical practice to prevent, diagnose early or even limit the progress of kidney damage, by increasing actions to monitor physiological parameters and renal function, based on the systematization of nursing care aimed at the specific needs of this population.

The frequency of AKI secondary to COVID-19 varied greatly in the articles analyzed, with an overall frequency of 30%. It is possible that this difference is related to the different demographic and clinical characteristics between the samples, including the most prevalent comorbidity, time of serum creatinine measurement, severity of COVID-19, as well as the different proportions of critically ill patients between the studies, including the need for ICU hospitalization and mechanical ventilation. The length of hospitalization described in some studies was variable.[18,28,29,31,35,47,53,55,57-59] This can also be explained in part by the clinical heterogeneity between the samples, as well as by the longer length of stay during AKI.[46,56,60,61]

Several studies have shown that older age is associated with a greater chance of AKI in individuals with COVID-19,[20,22-26,28,30,36-39,41,46-52,55-59] due to the weakening of the immune response, making them more susceptible to viral replication, in addition to the functional decline and histological alterations of the kidneys, accentuated by other comorbidities.[8,60] Male gender has been

Chart 2. Summary of the articles included in the review (n = 44)

Authors, year of publication and country	Type of study	Level of evidence	N COVID-19 patients % AKI (n)	Factors associated with AKI	% mortality in patients with AKI associated with COVID-19	% lethality in patients with AKI associated with COVID-19 (mortality by AKI)
Almeida DC, Franco MCP, Santos DRP, Santos MC, Maltoni IS, Mascotte F, et al., 2021, Brazil.[16]	Retrospective cohort	IV	278 71% (198)	Hypertension and vasoactive drugs	28%	40% (79)
Doher MP, Carvalho FRT, Scherer PF, Matsui TN, Ammirati AL, Silva BC, et al., 2020, Brazil.[17]	Retrospective cohort	IV	201 50% (101)	↑ initial creatinine level, use of diuretics and use of mechanical ventilation	12%	24% (24)
Neves PDMM, Sato VAH, Mohrbacher S, Ferreira BMC, Oliveira ES, Pereira LVB, et al., 2021, Brazil.[18]	Retrospective	IV	95 57% (54)	Hypertension and use of mechanical ventilation	16%	28% (15)
Zamoner W, Santos CAS, Magalhães LE, de Oliveira PGS, Balbi AL, Ponce D, 2020, Brazil.[19]	Prospective cohort	IV	101 50% (51)	Obesity, use of corticosteroids, ↑ APACHE II* and SOFA† scores	34%	67% (34)
Casas-Aparicio GA, León-Rodríguez I, Alvarado-de la Barrera C, González-Navarro M, Peralta-Prado AB, Luna-Villalobos Y, et al., 2021, Mexico.[20]	Retrospective cohort	IV	99 59% (58)	↑ age, obesity and use of invasive mechanical ventilation	38%	66% (38)
Martínez-Rueda AJ, Álvarez RD, Méndez-Pérez RA, Fernández-Camargo DA, Gaytan-Arocha JE, Berman-Parks N, et al., 2021, Mexico.[21]	Retrospective cohort	IV	1170 30% (349)	Chronic kidney disease, hypertension, ↑ CHF‡, ↑ SOFA† score. For hospital-acquired acute kidney injury: mechanical ventilation, ↑ troponin I levels and ↑ glucose admission	16%	52% (182)
Azam TU, Shadid HR, Blakely P, O'Hayer P, Berlin H, Pan M, et al., 2020, United States.[22]	Multicentric	IV	352 26% (91)	↑ age, male gender, ↑ BMI§, diabetes mellitus, hypertension, mechanical ventilation, ↓ GFRǁ, ↑ ferritin, ↑ d-dimer and ↑ LDH¶.	-	-
Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z, 2020, United States .[23]	Cohort	IV	5216 32% (1665)	↑ age, male gender, black ethnicity, diabetes mellitus and hypertension, ↓ baseline GFRǁ, use of iECA** and diuretics	11%	34% (559)
Fisher M, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, et al., 2020, United States.[24]	Retrospective	IV	3345 57% (1903)	↑ age, male gender and black ethnicity	19%	34% (641)
Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al., 2020, United States .[25]	Retrospective	IV	5449 37% (1993)	↑ age, blacks, diabetes mellitus, hypertension, cardiovascular disease, use of mechanical ventilation and vasopressors	13%	35% (694)
Nimkar A, Naaraayan A, Hasan A, Pant S, Durdevic M, Suarez CN, et al., 2020, United States .[26]	Retrospective	IV	327 55% (179)	↑ age, African-American ethnicity, chronic kidney disease and hyperlipidemia	32%	58% (104)
Zahid U, Ramachandran P, Spitalewitz S, Alasadi L, Chakraborti A, Azhar M, et al., 2020, United States .[27]	Retrospective cohort : single center	IV	469 27% (128)	male gender, hypertension, use of iECA**, hemodynamic instability, more severe refractory hypoxemia and mechanical ventilation	19%	71% (91)
See YP, Young BE, Ang LW, Ooi XY, Chan CP, Looi WL, et al., 2020, Cingapure.[28]	Retrospective cohort	IV	707 8% (57)	↑ age, hypertension, dyslipidemia, use of drugs: iECA** or ARB††, vancomycin and NSAID‡‡, severity of COVID {hypoxemia}	1%	12% (7)
Chebotareva N, Berns S, Berns A, Androsova T, Lebedeva M, Moiseev S, 2021, Russia.[29]	Cohort	IV	1280 29% (371)	↑ age, ↓ GFRǁ, ↑ C-reactive protein, ↑ ferritin, ↑ activated partial thromboplastin time, ↑ maximum d-dimer and acute respiratory distress syndrome	9%	31% (114)
Sarkisian DK, Chebotareva NV, McDonnell V, Oganesyan AV, Krasnova TN, Makarov EA, 2021, Russia.[30]	Retrospective	IV	37 46% (17)	Age > 60 years, ↑ C-reactive protein and ↓ platelets. Proteinuria and hematuria.	35%	76% (13)
Chan KW, Hung IF-N, Tsang OT-Y, Wu TC, Tso EY-K, Lung KC, et al., 2021, China.[31]	Retrospective cohort	IV	591 4% (22)	↑ age, smoking, diabetes mellitus, hypertension, use of iECA**/BRA††, ↑ C-reactive protein, ↑ LDH¶ and ↑ creatine kinase, ↓ serum albumin, ↓ GFRǁ, presence of pulmonary abnormality	1%	14% (3)
Chen Z, Gao C, Yu H, Lu L, Liu J, Chen W, et al., 2021, China.[32]	Retrospective cohort	IV	823 5% (44)	↓ platelets, ↓ albumin ↑ phosphate, ↑ LDH¶, ↑ procalcitonin, ↑ C-reactive protein, ↑ prothrombin time and uremia	4%	82% (36)
Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M, et al., 2020, China.[33]	Retrospective cohort	IV	1392 7% (99)	severe COVID-19, ↑ baseline serum creatinine, ↑ d-dimer and lymphopenia	5%	72% (71)
Cui X, Yu X, Wu X, Huang L, Tian Y, Huang X, et al., 2020, China.[34]	Retrospective: multicentric	IV	116 18% (21)	↑ creatinine kinase, ↑ clinical complexity, use of mechanical ventilation, shock state, ↑ SOFA†	10%	57% (12)
Dai Y, Liu Z, Du X, Wei H, Wu Y, Li H, et al., 2021, China.[35]	Retrospective cohort	IV	492 7% (36)	male gender, chronic kidney disease, hypertension, leukocytosis, use of diuretics and use of glucocorticoids	5%	64% (23)
Jin K, Xie T, Seery S, Ye L, Jiang J, Yang W, et al., et al., 2020, China.[36]	Retrospective cohort	IV	342 13% (46)	↑ Age, leukocytosis, ↑ C-reactive protein, ↑ fibrinogen, and severity of pneumonia	10%	76% (35)
Li W-X, Xu W, Huang C-L, Fei L, Xie X-D, Li Q, et al., 2021,China.[37]	Retrospective cohort	IV	1249 7% (91)	Age > 60 years, male gender, obesity, hypertension, diabetes mellitus, ↑ C-reactive protein, use of lopinavir/ ritonavir and ↓ lymphocyte count	0,2%	3% (3)
Peng S, Wang H-Y, Sun X, Li P, Ye Z, Li Q, et al., 2020, China.[38]	Retrospective cohort	IV	4020 7% (285)	↑ Age, hypertension, chronic kidney disease, ↑ inflammatory biomarkers and ↑ ferritin	3%	39% (112)
Sang L, Chen S, Zheng X, Guan W, Zhang Z, Liang W, et al., 2020, China.[39]	Retrospective	IV	210 44% (92)	↑ Age, sepsis, use of nephrotoxic drugs, use of mechanical ventilation and ↑ baseline creatinine	31%	71% (65)

Continue...

Continuation.

Authors, year of publication and country	Type of study	Level of evidence	N COVID-19 patients % AKI (n)	Factors associated with AKI	% mortality in patients with AKI associated with COVID-19	% lethality in patients with AKI associated with COVID-19 (mortality by AKI)
Wang J, Wang Z, Zhu Y, Li H, Yuan X, Wang X, et al., 2020, China.[40]	Retrospective cohort	IV	116 10% (12)	clinical classification of COVID-19, ↑ procalcitonin, ↓ GFR	-	-
Wang RR, He M, Kang Y, 2021, China.[41]	Retrospective cohort	IV	389 7% (28)	↑ age, hypertension, cardiovascular disease, ↑ mean arterial pressure, ↓ SpO2§§, ↑ leukocytes, ↑ neutrophils, ↑ TGO, ↑ C-reactive protein, ↑ serum creatinine, ↑ serum uric acid, ↓ lymphocytes, ↓ platelets and ↓ albumin	4%	61% (17)
Xu J, Xie J, Du B, Tong Z, Qiu H, Bagshaw SM, 2020, China.[42]	Retrospective cohort : 19 hospitals	IV	671 39% (263)	higher severity scores (SOFA† and APACHE II*), longer use of vasopressors, use of mechanical ventilation and extracorporeal membrane oxygenation	28%	71% (188)
Bell JS, James BD, Al-Chalabi S, Sykes L, Kalra PA, Green D, 2021, England.[43]	Retrospective cohort	IV	448 26% (118)	chronic kidney disease, use of mechanical ventilation, ↑ maximum heart rate, atrial fibrillation and ↓ lymphocytes	14%	54% (64)
Parker K, Hamilton P, Hanumapura P, Castelino L, Murphy M, Challiner R, et al., 2021, England.[44]	Retrospective cohort	IV	1032 20% (210)	male gender, hypertension, previous kidney disease and ↑ C-reactive protein	11%	52% (110)
Sullivan MK, Lees JS, Drake TM, Docherty AB, Oates G, Hardwick HE, et al., 2022, England .[45]	Cohort	IV	41294 31% (13000)	admission respiratory rate > 30 rpm/min, chronic kidney disease and black ethnicity	-	-
Lowe R, Ferrari M, Nasim-Mohi M, Jackson A, Beecham R, Veighey K, et al., 2021, United Kingdom.[46]	Retrospective cohort : single center	IV	81 44% (36)	↑ age, ↑ severity of comorbidities, diabetes mellitus, immunosuppression, ↑ APACHE II*, use of mechanical ventilation, vasopressor or inotropic support, ↑ creatinine, ↑ C-reactive protein, ↑ d-dimer, ↑ neutrophil/lymphocyte ratio, ↓ lymphocytes	11%	25% (9)
Lumlertgul N, Pirondini L, Cooney E, Kok W, Gregson J, Camporota L, et al., 2021, United Kingdom .[47]	Retrospective	IV	313 77% (240)	↑ age, ↑ BMI§, ↓ serum bicarbonate (acidosis), ↓ platelets, ↑ C-reactive protein and ↑ serum lactate	26%	34% (82)
Geri G, Darmon M, Zafrani L, Fartoukh M, Voiriot G, Le Marec J, et al., 2021, France.[48]	Retrospective	IV	379 51% (195)	↑ age, male gender, diabetes mellitus, chronic kidney disease, use of mechanical ventilation and vasopressors	19%	37% (73)
Joseph A, Zafrani L, Mabrouki A, Azoulay E, Darmon M, 2020, France.[49]	Retrospective: single center	IV	100 81% (81)	↑ age, SOFA† and use of mechanical ventilation	28%	35% (28)
Alfano G, Ferrari A, Fontana F, Mori G, Magistroni R, Meschiari M, et al., 2020, Italy.[50]	Retrospective	IV	307 22% (69)	↑ age, admission to the intensive care unit, ↑ SOFA†, severe hypoxemia, ↑ interleukin-6, ↑ LDH¶, ↑ d-dimer, ↓ albumin, ↓ platelets and ↓ hemoglobin	13%	57% (39)
Scarpioni R, Valsania T, Albertazzi V, Blanco V, DeAmicis S, Manini A, et al., 2021, Italy.[51]	Retrospective cohort	IV	1701 14% (233)	age, male gender, use of mechanical ventilation	8%	57% (132)
Diebold M, Schaub S, Landmann E, Steiger J, Dickenmann M, 2021, Switzerland.[52]	Retrospective cohort	IV	188 22% (41)	↑ age, male gender, chronic kidney disease, hypertension, ↑ leukocytes, ↑ C-reactive protein, ↑ creatinine kinase and ↑ potassium and use of pre-admission medication: BRA††	6%	27% (11)
Hardenberg J-HB, Stockmann H, Aigner A, Gotthardt I, Enghard P, Hinze C, et al., 2021, Germany.[53]	Retrospective cohort	IV	223 52% (117)	hypertension, mechanical ventilation, vasopressor, leukocytosis and ↑ procalcitonin	15%	28% (33)
Trifi A, Abdellatif S, Masseoudi Y, Mehdi A, Benjima O, Seghir E, et al., 2021, Tunise.[54]	Case control	IV	109 44% (48)	↑ D-dimer and sepsis	38%	85% (41)
Rahimzadeh H, Kazemian S, Rahbar M, Farrokhpour H, Montazeri M, Kafan S, et al., 2021, Ira.[55]	Retrospective cohort	IV	516 38% (194)	↑ age, male gender, COVID-19 severity, hypertension, diabetes mellitus, heart disease, chronic kidney disease, iECA**/BRA†† use, ↑ neutrophil/lymphocyte ratio, ↑ urea and ↑ C-reactive protein	15%	40% (77)
Elkholi MH, Alrais ZF, Algouhary AR, Al-Taie MS, Sawwan AA, Khalafalla AA, et al., 2021, United Arab Emirates .[56]	Retrospective cohort	IV	198 65% (129)	↑ age, ↑ vasopressor dose µg/kg/min, hypertension, CHF‡, ↑ SOFA† and ↑ cardiovascular SOFA†, ↓ mean arterial pressure	43%	66% (85)
Ghosn M, Attallah N, Badr M, Abdallah K, Oliveira B, Nadeem A, et al., 2021, United Arab Emirates .[57]	Retrospective cohort	IV	110 54% (59)	↑ age, use of mechanical ventilation, ↑ admission creatinine and use of extracorporeal membrane oxygenation	21%	39% (23)
Kanbay M, Medetalibeyoglu A, Kanbay A, Cevik E, Tanriover C, Baygul A, et al. 2021, Turkey.[58]	Retrospective cohort : 2 university centers	IV	770 12% (92)	↑ age, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure and cancer, ↑ urea, ↑ glucose, ↑ gamma glutamyl transferase, ↑ alkaline phosphatase, ↑ LDH¶, ↑ C-reactive protein, ↑ d-dimer, ↑ troponin, ↑ brain natriuretic peptide, ↑ international normalized ratio, ↑ activated partial thromboplastin time, ↑ creatinine and ↓ hemoglobin.	5%	46% (42)
Kolhe NV, Fluck RJ, Selby NM, Taal MW, 2020, United Kingdom.[59]	Retrospective cohort : 2 hospitals	IV	1161 26% (304)	age > 65, congestive heart failure, chronic liver disease, chronic kidney disease, use of mechanical ventilation	16%	61% (184)

*APACHE II - Acute Physiology and Chronic Health Evaluation; †SOFA - Sequential Organ Failure Assessment; ‡ICC - Charlson Comorbidity Index; §IMC - Body Mass Index; ||GFR - Glomerular Filtration Rate; ¶LDH - Lactate Dehydrogenase; **iECA - Angiotensin Converting Enzyme Inhibitor; ††BRA - Angiotensin Receptor Blocker; ‡‡AINES - Non-Steroidal Anti-Inflammatory Drugs; §§SpO2 - Oxygen Saturation

Chart 3. Factors associated with AKI reported in the articles included in the review (n = 44)

Demographic and clinical characteristics	Demographic: Older age ,[20,22-26,28-30,36-39,41,46-52,55-59] male,[22-24,27,35,37,44,48,51,52,55] black ethnicity,[23-25,45] and African-American.[26] Clinics: ex-smoker,[31] body mass index <25 kg/m²,[19,20,37,47] diabetes mellitus,[22,23,25,31,46,55] hypertension,[16,18,21,23,25,28,31,35,37,38,41,43,52,53,55,56,58] greater severity of comorbidities (ICC*),[46,56] chronic kidney disease,[21,26,35,43,45,48,52,55,59] pre-existing kidney disease,[25] cardiovascular disease,[25,41,55] coronary artery disease,[58] congestive heart failure,[21,59] chronic liver disease,[21] immunosuppression,[46] cancer[58] presence of serious illness.[33] Severity: severity of COVID-19,[28,40,55] hemodynamic instability,[27] sepsis,[39,54] shock,[34] greater clinical complexity,[34] SOFA†[21,34,42,46,49,50,56,60] and APACHE II‡ higher,[46,60] Acute Respiratory Distress Syndrome,[29] greater severity of pneumonia,[36] lung abnormality,[31] intense hypoxemia,[27,50] intense hypoxemia O2,[41] high respiratory rate on admission,[45] admission to the intensive care unit,[50] need for mechanical ventilation[17,18,20,22,27,34,40,43,46,48,49,51,57,59] and extracorporeal membrane oxygenation.[41,57]
Biomarkers	Inflammatory: increase in interleukin-6,[50] lactate dehydrogenase ,[22,31,32,50,58] d-dimer ,[22,29,33,50,54,58] C-reactive protein,[29-31,37,41,44,46,47,52,55,58] fibrinogen,[36] procalcitonin[32,40,53] and ferritin.[22,29,38] Coagulatory: increase in prothrombin,[32] activated partial thromboplastin time[29,58] and the INR§,[58] reduction in platelets.[30,32,41,47,50] Hematological and immunological: reduction in hemoglobin,[50] lymphopenia,[33,37,41,46] leukocytosis,[35,36,52,53] increased neutrophils and neutrophil/lymphocyte ratio[46,55] Renal: reduction in estimated glomerular filtration rate,[22,23,29,31,40] increase in serum creatinine,[17,33,39,41,57,58] uremia,[32,55,58] increased uric acid[41] and reduced albumin.[31,32,41,50] Other: decrease in serum bicarbonate,[47] increased creatine kinase,[31,34,52] phosphate,[32] potassium[52], serum lactate,[47] glucose,[21,58] triglycerides,[58] dyslipidemia,[26,28] alkaline phosphatase,[58] troponin,[21,58] glutamic-oxalacetic transaminase[41] and BNP‖.[58]
Drugs	Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker,[23,27,28,31,52,55] diuretics,[17,23,35] vasoactive drugs,[16,25,42,46,48,53,56] glucocorticoids[35] and corticosteroids,[60] non-steroidal anti-inflammatory drugs,[28] nephrotoxic drugs,[39] lopinavir/ritonavir[37] and vancomycin.[28]

*ICC - Charlson Comorbidity Index; †SOFA = Sequential Organ Failure Assessment; ‡APACHE II - acute physiology and chronic health evalution; §INR - international normalized ratio; ‖BNP - brain natriuretic peptide

reported in several studies as a factor associated with AKI,[22-24,27,35,37,44,48,51,52,55] its association can be explained by the lower elimination capacity of the SARS-CoV-2 virus, higher prevalence of bad lifestyle habits (alcohol consumption and smoking) and higher expression of ACE-2, which can contribute to worsening symptoms and increasing the incidence of complications such as AKI.[8,61]

Black/African-American populations have higher rates of SARS-CoV-2 infection.[23-26,45] Research indicates that genetic polymorphism of the ACE2, IL-6 and AChE genes are more prevalent in black populations and these factors generate unfavorable responses to COVID-19 infection, making them more susceptible to developing complications.[62,63]

The severity of the clinical picture is associated with multiple organ dysfunctions and the need for life-sustaining support.[17,18,20-22,25,27,34,40,42,43,46,48,49,51,57,59] COVID-19 can trigger a deregulated immune response associated with a storm of pro-inflammatory cytokines, with altered renal vascular permeability and dysfunction of the renal microcirculation.[64,65] The cytokine storm assessed through inflammatory biomarkers such as increased C-reactive protein (CRP), d-dimer, ferritin and lactate dehydrogenase were associated with a higher occurrence of AKI in COVID-19 patients.[22,29-33,37,38,41,44,46,47,50,52,54,55,58]

The progression of the respiratory condition from COVID-19 to Acute Respiratory Distress Syndrome can affect the kidneys through lung-kidney crosstalk.[2,6,66] Mechanical ventilation (MV) has a negative impact on renal oxygenation and is a risk factor for AKI due to decreased renal perfusion secondary to reduced cardiac output and exacerbation of renal edema.[2,6,66]

Pre-existing comorbidities are associated with AKI, especially in patients with severe COVID-19.[46,56] Diabetes mellitus and hypertension generate functional and structural alterations in target organs, including the kidneys, and these factors can increase the risk of developing AKI.[67,68]

Considering the pathophysiological aspects of COVID-19, the use of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drugs increases susceptibility to AKI in COVID-19.[23,27,28,31,52,55] IECAs and ARBs affect intrarenal hemodynamics and are included in the prerenal etiology of AKI.[69] To compensate for decreased renal perfusion, the kidneys activate mechanisms to maintain the glomerular filtration rate[69] prostaglandins act as vasodilators and thus increase renal perfusion. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit this mechanism and alter renal hemodynamics, so their use is a factor associated with AKI. Patients with chronic renal impairment are at greater risk of worsening the disease.[69]

Mortality rates varied between the articles analyzed in this review and this difference may be due to the different stages of severity of AKI, the availability of renal replacement therapy resources, the time of diagnosis of AKI and pre-existing comorbidities.[70] Other studies have reported an association between AKI and hospital deaths among patients hospitalized

with COVID-19.[71,72] The worse results in patients with AKI secondary to COVID-19 may be related to the impairment of acid-base, fluid and electrolyte homeostasis generated by kidney disease in association with COVID-19.[70] AKI mortality was 5% and AKI lethality was 18%.

Finally, it should be noted that the SARS-CoV-2 virus causes indirect damage to the kidneys, both by triggering an exacerbated immune response and by the associated circulatory and hypoxemic dysfunctions, causing direct damage to kidney tissue. Considering that some factors such as pre-existing comorbidities, gender and ethnicity can exacerbate these dysfunctions, it is important for nurses to assess the presence of these associated factors and prevent AKI by providing care aimed at preventing, minimizing and hindering the progression of the condition, and constantly reassessing the effectiveness of the care implemented. It is essential for the nursing team to know that patients with COVID-19 are vulnerable to developing AKI.[73]

Limitations of this review include: (1) research mostly based on cases and data from the first wave of the pandemic, a period in which knowledge of the virus was incipient and (2) little data on the impact of the new strains of SARS-CoV-2 on the development of AKI, (3) the overload of health systems and human resources, (4) the different realities of health systems and finally (5) the impossibility of inferences about causal relationships between risk factors and AKI, due to the design and timing of the studies.

Conclusion

The frequency of AKI in COVID-19 patients ranged from 4% to 81% in individual studies and in this review it was 30%. AKI mortality ranged from 1% to 43% in individual studies and in this review it was 5%. AKI lethality ranged from 3% to 85% in the individual studies and in this review it was 18%. The main factors associated with AKI were advanced age, male gender, hypertension, chronic kidney disease, need for MV, increased CRP, use of vasoactive drugs, iECA and ARBs. Acute kidney involvement in patients hospitalized for COVID-19 was related to an increased mortality rate, especially in those with stage 3 AKI. This review presents a compilation of studies from different countries on different continents. It includes a large number of patients with AKI diagnosed by KDIGO. Thus, the research findings help to map the factors related to the development of AKI, considering all the peculiarities of COVID-19. It encourages the development of more targeted and advanced studies into the variables that make a specific individual or population more susceptible. It contributes to health teams by understanding risk factors and providing care aimed at monitoring the most relevant factors.

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