Acute kidney injury in coronavirus infectious disease: a study of incidence, risk factors, and prognosis during the first wave of the disease in Brazil

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Abstract

Introduction Acute kidney injury (AKI) is one of the main complications of COVID-19 caused by SARS-CoV-2. This study aimed to evaluate the incidence of AKI in Brazilian hospitalized patients diagnosed with COVID-19 and identify the risk factors associated with its onset and those associated with its prognosis.

Methods A prospective cohort study of hospitalized patients diagnosed with COVID-19 at a public and tertiary university hospital in São Paulo from March to December 2020.

Results There were 347 patients hospitalized with COVID-19, 52.4% were admitted to the intensive care unit (ICU) and 47.6% were admitted to the wards. The overall incidence of AKI was 46.4%, more frequent in the ICU (68.1% vs 22.4, $p < 0.01$) and the overall mortality was 36.1%. Acute kidney replacement therapy was indicated in 46.6% of patients with AKI. In the general population, the factors associated with AKI were older age (OR 1.03, CI 1–1.05, $p < 0.05$), mechanical ventilation (OR 1.23, CI 1.06–1.83, $p < 0.05$), presence of proteinuria (OR 1.46, CI 1.22–1.93, $p < 0.05$), and use of vasoactive drugs (OR 1.26, CI 1.07–1.92, $p < 0.05$). Mortality was higher in the elderly (OR 1.08, CI 1.04–1.11, $p < 0.05$), in those with AKI (OR 1.12, CI 1.02–2.05, $p < 0.05$), particularly KDIGO stage 3 AKI (OR 1.10, CI 1.22–2.05, $p < 0.05$) and in need of mechanical ventilation (OR 1.13, CI 1.03–1.60, $p < 0.05$).

Conclusion AKI was frequent in hospitalized patients with COVID-19 and the factors associated with its development were older age, mechanical ventilation, use of vasoactive drugs, and presence of proteinuria, being a risk factor for death.

Keywords COVID-19 · AKI · Cross-talk · Incidence · Mortality

Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-Cov-2 was declared a pandemic by the World Health Organization (WHO) in March 2020. The first Latin American case was reported on February 2020 in Brazil, and by June 2020, Latin America and The Caribbean became the worlds' latest COVID-19 epicenter with the number of deaths in the region exceeding 7 million, or over 27% of the world's COVID-19 deaths [1, 2].

One of the main complications of the infectious condition is acute kidney injury (AKI), a syndrome characterized by a

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rapid decrease in renal function, with consequent accumulation of nitrogenous wastes, hydro-electrolytic, and acid–base disorders [3].

Although there is ample literature on the association between respiratory failure and AKI, within the physiopathological model of cross-talk between the organs, there are still few studies that elucidate the renal repercussions caused by the new coronavirus, in view of its recent discovery.

Diffuse alveolar damage and acute respiratory failure are the main characteristics of the disease in its severe form; however, AKI is very frequent (4–37%) [4, 5], especially among critically ill patients, and is a factor related to worse outcomes.

Therefore, this study aimed to evaluate the incidence of AKI in Brazilian hospitalized patients diagnosed with COVID-19 and to identify both the risk factors associated with its onset and those associated with its prognosis.

Materials and methods

A prospective cohort study of hospitalized patients diagnosed with COVID-19, confirmed by real-time polymerase chain reaction (RT-PCR) for SARS-Cov-2, was performed in clinical wards and intensive care units (ICUs) of a public and tertiary university hospital in São Paulo, Brazil, in the period from March to December 2020. Patients were accompanied from their hospitalization until the clinical outcome (discharge or death), the AKI diagnosis was assessed, and their risk factors were identified through the collection of information in electronic medical records, those being associated with their diagnosis, death, and indication for acute kidney replacement therapy.

We collected clinical and laboratory data during hospitalization. Renal function was evaluated daily by measuring serum creatinine and checking urine output. AKI was identified according to KDIGO definition when occurred an increase in serum creatinine level > 0.3 mg/dL within 48 h or by 50% within 7 days and staged in the three KDIGO categories [6]. For the detection of proteinuria or hematuria, the semiquantitative dipstick test was used; data were requested at admission in all patients and during hospital stay in those patients without proteinuria at admission.

Indications for acute kidney replacememnt therapy were uraemia or azotaemia (BUN > 100 mg/dL), fluid overload (after diuretics use), electrolyte imbalance (K > 6.5 mEq/L after clinical treatment), acid–base disturbances (pH < 7.1 and bicarbonate < 10 mEq/L after clinical treatment), and metabolic and fluid emand to capacity imbalance as defined by Macedo et al. in 2011 and revised by Ostermann et al. in 2016 [7, 8]. The demand is determined by the severity of the acute illness and the solute and fluid burdens. The demand capacity balance is dynamic and varies with the course of

critical illness. When renal capacity decreases and fails to cope with the demands, initiation of acute kidney replacememnt therapy was considered [9].

Patients with chronic kidney disease stages IV and V, kidney transplant patients, and individuals under 18 years old were excluded.

This study was registered in the Brazilian Registry of clinical trials (ReBEC) under number RBR-62y3h7 and was approved by the local ethics committee (CAAE 30451520.6.0000.5411 and report number 4.003.880). All the research was performed following current regulations, and written informed consent was obtained from all participants or their legal guardians.

From the study protocol, the data were entered into an electronic spreadsheet, and any typing errors were eliminated. The analysis was performed with the aid of IBM SPSS 20 or Sigma Stat 3.5. Frequency or central tendency and dispersion measures were calculated for the categorical or continuous variables, respectively, being AKI established as outcome variable. The Chi-square test was used for comparison of categorical variables and the t test for continuous variables.

Afterward, multivariate analysis was performed through the construction of a logistic regression model with calculations of the odds ratio (OR), including in the model all the independent variables that showed association with the outcome, with $p \leq 0.20$. A similar procedure was performed by establishing the occurrence of death and the indication of acute renal replacement therapy as a dependent variable.

Results

During 2020, 347 patients were hospitalized at our HC with confirmed diagnosis of COVID-19. The mean age was 59.8 ± 16.1, with a predominance of males (57.6%), the majority being hypertensive (60.5%), 52.4% admitted to the intensive care unit (ICU), and 47.6% admitted to the wards. The overall incidence of AKI was 46.4%, more frequent among patients admitted to ICU than in those in wards (68.1% vs 22.4, $p < 0.01$). The mean time for the AKI diagnosis was 6 days and KDIGO stage 3 AKI was the most frequent (53.4%). Upon hospital admission, 235 patients underwent Urine I examination, of which 31.1% had proteinuria (43.5% of AKI patients) and 36.9% had hematuria (49.1% of AKI patients). Acute renal replacement therapy was indicated for 75 patients (46.6% of AKI patients).

The factors associated with the development of AKI were mechanical ventilation (11.3 vs 72%, $p < 0.0001$), use of vasoactive drugs (VAD, 12.9 vs 72%, $p < 0.0001$), and ICU admission (31.2 vs 77%, $p < 0.0001$). Based on logistic regression analysis, mechanical ventilation (OR 1.23, CI 1.06–1.83, $p < 0.05$), presence of proteinuria (OR 1.46,

CI 1.22–1.93, $p < 0.05$), VAD use (OR 1.26, CI 1.07–1.92, $p < 0.05$), and older age (OR 1.03, CI 1–1.05 $p < 0.05$) were AKI risk factors. Tables 1 and 2 show, respectively, the factors associated with AKI in the univariate and multivariate analysis.

The overall mortality was 36.1% (125 patients), being higher in ICU patients (32.9 vs 87.2%, $p < 0.0001$). The factors associated with mortality were ICU admission (32.9 vs 87.2%, $p < 0.0001$), the need for mechanical ventilation (14.9 vs 83.2%, $p < 0.0001$), the use of VAD (16.2 vs 83.2%, $p < 0.0001$), and the presence of AKI (26.6 vs 81.6%, $p < 0.0001$), mainly KDIGO stage 3 AKI (9 vs 52.8%, $p < 0.0001$), as identified in Table 3.

Based on logistic regression analysis, the presence of AKI (OR 1.12, CI 1.02–2.05, $p < 0.05$), mechanical ventilation (OR 1.13, CI 1.03–1.60, $p < 0.05$), and KDIGO stage 3 AKI (OR 1.10, CI 1.22–2.05, $p < 0.05$) remained as variables associated with death, with the addition of higher age (OR 1.08, CI 1.04–1.11, $p < 0.05$), as shown in Table 4.

When analyzing only patients admitted to intensive care beds, AKI occurred in 68.3% of patients and the overall mortality was 61.1%. The mean time for the diagnosis of AKI was 5 days and KDIGO stage 3 AKI was the most frequent (57.7%). Acute renal replacement therapy was indicated for 41.6% of patients who were under intensive care.

The factors associated with the development of AKI in ICU patients, as identified in Table 5, were the need for mechanical ventilation (36.8 vs 91.1%, $p < 0.001$), use of VAD (40.4 vs 89.4%, $p < 0.001$), presence of CKD (3.5 vs 13%, $p = 0.048$), hematuria (33.3 vs 52.8%, $p = 0.006$),

proteinuria (28.1 vs 45.5%, $p = 0.022$), increased baseline creatinine dosages (0.72 ± 0.26 vs 0.92 ± 0.44, $p = 0.009$), and D-dimer (5723.3 ± 5013.4 vs 10,249.8 ± 5905, $p < 0.001$), as well as APACHE II and SOFA scores (14.6 ± 6.4 vs 22.3 ± 6, $p < 0.001$ and 5.9 ± 3.9 vs 9.6 ± 3.6, $p < 0.001$, respectively). CPK dosage was also associated with AKI (168 (69.25–688)).

In the logistic regression (Table 6), the risk factors for AKI were the need for mechanical ventilation (OR 1.1, CI 1.02–1.4, $p < 0.05$), older age (OR 1.06, CI 1–1.11, $p < 0.05$), and the presence of proteinuria (OR 1.2, CI 1.06–1.7, $p < 0.05$).

The mortality of ICU patients was 61.1%, being higher in older patients (56.4 ± 14 vs 64.4 ± 13. 7, $p < 0.001$), in those requiring mechanical ventilation (47.1 vs 90.9%, $p < 0.001$), use of VAD (47.1 vs 90.9%, $p < 0.001$), presence of CKD (5.7 vs 12.7%, $p = 0.12$), presence of AKI (38.6 vs 87.3%, $p < 0.001$), mainly KDIGO stage 3 AKI (11.4 vs 57.3%, $p < 0.001$), undergoing acute renal replacement therapy (12.9

Table 2 Logistic regression of variables associated with AKI

Variables	OR	95% IC	*p* value
Age	**1.03**	**1–1.05**	**< 0.05**
Proteinuria	**1.46**	**1.22–1.93**	**< 0.05**
Mechanical ventilation	**1.23**	**1.06–1.83**	**< 0.05**
Vasoactive drugs	**1.26**	**1.07–1.92**	**< 0.05**

Bold values refer to variables that had a *p* value less than 0.05

CI confidence interval

Table 1 Clinical and laboratory characteristics of hospitalized patients regarding the presence or absence of AKI

Variables	General ($n = 347$)	Without AKI ($n = 186$)	With AKI ($n = 161$)	*p* value
Male sex (%)	200 (57.6)	98 (52.7)	102 (63.4)	0.65
Age (years)[a]	59.8 ± 16.1	57 ± 16.6	63.4 ± 14.6	0.088
ACE inhibitors use (%)	144 (41.5)	72 (38.7)	72 (44.7)	0.257
Arterial hypertension (%)	**210 (60.5)**	**103 (55.4)**	**107 (66.5)**	**0.035**
Diabetes mellitus (%)	**125 (36)**	**56 (30.1)**	**69 (42.9)**	**0.014**
Obesity (%)	94 (27.1)	47 (25.3)	47 (29.2)	0.412
CKD (%)	**43 (12.4)**	**16 (8.6)**	**17 (16.8)**	**0.021**
CVD (%)	65 (18.7)	31 (16.7)	34 (21.1)	0.289
Diuretic use (%)	**93 (26.8)**	**41 (22)**	**52 (32.3)**	**0.031**
GFR (mL/min/1.73 m^2)[a]	153 (44)	95 ± 25.3	76.8 ± 26.3	0.827
Mechanical ventilation (%)	**137 (39.5)**	**21 (11.3)**	**116 (72)**	**< 0.0001**
Vasoactive drugs (%)	**140 (40.3)**	**24 (12.9)**	**116 (72)**	**< 0.0001**
ICU admission (%)	**182 (52.4)**	**58 (31.2)**	**124 (77)**	**< 0.0001**
Death (%)	125 (36)	23 (12.4)	102 (63.4)	< 0.0001

Bold values refer to variables that had a *p* value less than 0.05

AKI acute kidney injury, *ACE* angiotensin-converting enzyme, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *GFR* glomerular filtration rate (CKD-EPI), *ICU* intensive care unit

[a]Mean ± SD

Table 3 Clinical and laboratory characteristics of hospitalized patients according to outcome

Variables	No death ($n=222$)	Death ($n=125$)	p value
Male sex (%)	123 (55.4)	77 (61.6)	0.423
Age (years)[a]	**56.88 ± 16.42**	**65.46 ± 13.7**	**0.029**
Arterial hypertension (%)	**124 (55.9)**	**86 (68.8)**	**0.018**
Diabetes mellitus (%)	**69 (31.1)**	**56 (44.8)**	**0.011**
Obesity (%)	56 (25.2)	38 (30.4)	0.298
CKD (%)	28 (12.6)	15 (12)	0.868
CVD (%)	35 (15.8)	30 (24.0)	0.059
Diuretic use (%)	54 (24.3)	39 (31.2)	0.165
GFR (mL/min/1.73m^2)[a]	92.43 ± 26.49	75.74 ± 25.31	0.636
Mechanical ventilation (%)	**33 (14.9)**	**104 (83.2)**	**< 0.0001**
Vasoactive drugs (%)	**36 (16.2)**	**104 (83.2)**	**< 0.0001**
ICU admission (%)	**73 (32.9)**	**109 (87.2)**	**< 0.0001**
AKI (%)	**59 (26.6)**	**102 (81.6)**	**< 0.0001**
KDIGO stage 3	**20 (9)**	**66 (52.8)**	**< 0.0001**
APACHE II[a]	15.55 ± 6.76	23.21 ± 5.44	0.147
SOFA[b]	6.24 ± 3.63	10.12 ± 3.51	0.292

Bold values refer to variables that had a p value less than 0.05

CKD chronic kidney disease, *CVD* cardiovascular disease, *GFR* glomerular filtration rate (CKD-EPI), *ICU* intensive care unit, *AKI* acute kidney injury, *KDIGO* Kidney Disease Improving Global Outcomes criteria, *APACHE II* Acute Physiology and Chronic Health Evaluation score, *SOFA* Sequential Organ Failure Assessment score

[a]Mean ± SD

[b]Median (IQR)

Table 4 Logistic regression of variables associated with death

Variables	OR	95% IC	p value
Age	**1.08**	**1.04–1.11**	**< 0.05**
AKI	**1.12**	**1.02–2.05**	**< 0.05**
Mechanical ventilation	**1.13**	**1.03–1.6**	**< 0.05**
KDIGO stage 3	**1.1**	**1.22–2.05**	**< 0.05**
Vasoactive drugs	1.143	0.99–1.60	0.12

Bold values refer to variables that had a p value less than 0.05

CI confidence interval, *KDIGO* Kidney Disease Improving Global Outcomes criteria

vs 60, $p<0.001$) and with higher APACHE II and SOFA scores (15. 5 ± 6.7 vs 23.2 ± 5.4, $p<0.001$ and 6.2 ± 3.6 vs 10.1 ± 3.5, $p<0.001$, respectively), as identified in Table 7.

At logistic regression analysis, the variables associated with death were older age (OR 1, CI 1.03–1.1, $p<0.0001$), VAD use (OR 1.15, CI 1.05–1.43, $p<0.0001$), need for acute renal replacement therapy (OR 1.26, CI 1.09–1.72, $p=0.01$), and presence of AKI (OR 3.4, CI 1.35–8.6, $p=0.01$), as shown in Table 8.

Discussion

This study describes the first wave of the COVID-19 pandemic in a public university hospital in the inland of São Paulo, Brazil, which is a reference for 28 municipalities in the region with more than 2 million inhabitants. During this period, 347 patients diagnosed with COVID-19 were hospitalized, with a mean age of 59.8 ± 16.1, 52.4% admitted to the ICU and 47.6% admitted to the ward. The overall incidence of AKI was 46.4% with a mean time for diagnosis of 6 days. This incidence of AKI is higher than that reported so far in the literature.

Chinese studies [10–17] have reported a low and variable AKI incidence (0.5–7%), higher in severe COVID-19 cases (2.9–19%). European and North American studies [18–20] have reported an AKI incidence of 20–40% of patients hospitalized with COVID-19. In all cohorts, AKI occurred between the 7th and the 14th day of illness; it was associated with higher hospital mortality and decisive in the prognosis of these patients [9–21]. Brazil is a large country with several vulnerable groups, in addition to an emerging economy and fragile social protection, which may have contributed to more demand for health services and increased development of serious forms of COVID-19 [23].

SARS-CoV-2 has a protein, called Spike (S), which binds to the ACE2 receptor present in host cells, enabling its activation and cleavage by transmembrane proteases and

Table 5 Clinical and laboratory characteristics of patients admitted in ICU regarding the presence or absence of AKI

Variables	General ($n=180$)	Without AKI ($n=57$)	With AKI ($n=123$)	p value
Male sex (%)	108 (60)	30 (52.6)	78 (63.4)	0.17
ACE inhibitors use (%)	77 (42.3)	24 (42.1)	53 (43.1)	0.78
Arterial hypertension (%)	112 (62.2)	35 (61.4)	77 (62.6)	0.77
Diabetes mellitus (%)	67 (37.2)	18 (31.6)	49 (39.8)	0.43
Obesity (%)	49 (27.2)	14 (24.6)	35 (28.5)	0.67
CKD (%)	**18 (10)**	**2 (3.5)**	**16 (13)**	**0.048**
Proteinuria (%)	**72 (40)**	**16 (28.1)**	**56 (45.5)**	**0.022**
Hematuria (%)	**84 (46.6)**	**19 (33.3)**	**65 (52.8)**	**0.006**
Mechanical ventilation (%)	**133 (73.8)**	**21 (36.8)**	**112 (91.1)**	**< 0.001**
Vasoactive drugs (%)	**133 (73.8)**	**23 (40.4)**	**110 (89.4)**	**< 0.001**
Age (years)[a]		59.2 ± 13.6	62.2 ± 14.6	0.19
Basal creatinine (mg/dL)[a]		**0,72 ± 0.26**	**0.92 ± 0.44**	**0.009**
D-Dimer (ng/mL)		**5723.3 ± 5013.5**	**10,249.8 ± 5906**	**< 0.002**
APACHE II[a]		**14.6 ± 6.4**	**22.3 ± 6**	**< 0.001**
SOFA[b]		**5.9 ± 3.9**	**9.6 ± 3.6**	**< 0.001**

Bold values refer to variables that had a p values less than 0.05

AKI acute kidney injury, *ACE* angiotensin-converting enzyme, *CKD* chronic kidney disease, *ICU* intensive care unit, *APACHE II* Acute Physiology and Chronic Health Evaluation score, *SOFA* Sequential Organ Failure Assessment score

[a]Mean ± SD

[b]Median (IQR)

Table 6 Logistic regression of variables associated with AKI in patients admitted in ICU

Variables	OR	95% IC	p value
Age	**1.06**	**1–1.11**	**< 0.05**
Mechanical ventilation	**1.1**	**1.02–1.4**	**< 0.05**
Proteinuria	**1.2**	**1.06–1.7**	**< 0.05**
Basal creatinine	4.2	0.96–18.7	0.057

Bold values refer to variables that had a p value less than 0.05

CI confidence interval

culminating in the release of fusion peptides by the virus. ACE2 is highly expressed in the mouth and tongue, in addition to alveolar epithelial cells. In the kidneys, it is highly expressed in proximal tubule cells and to a lesser extent in podocytes [13, 22–24]. Thus, the higher AKI incidence in western countries could be associated with the higher expression of angiotensin-converting enzyme 2 (ACE2) in podocytes and proximal tubule in western individuals compared with eastern individuals, as identified in normal kidneys and described by Pan et al. [22]. However, other studies did not find the SARS-CoV-2 virus in the renal biopsy/autopsy issue samples [25, 26].

AKI is a complex disorder characterized by the degradation of renal function over a period of hours to days, resulting in a temporary decrease or interruption of the renal capacity to promote the excretion of nitrogenous products

and the hydro-electrolytic homeostasis of the body, also resulting in volume overload [27, 28]. Its incidence in hospitalized patients varies between 5 and 7%; it is higher in ICU patients, around 50%, according to other studies. Despite the technological advances that have occurred and the reduction in the mortality rate in the last decade, the AKI prognosis remains severe and the death rate remains high, especially in patients in need of dialysis (up to 62%) [29–31].

In logistic regression, we identified that the factors associated with the development of AKI in patients hospitalized with COVID-19 were mechanical ventilation, use of VAD, proteinuria, and older age. In the case of ICU patients with COVID-19, the factors associated with the development of AKI were mechanical ventilation, proteinuria, and older age. In this last regression, we removed the APACHE and SOFA scores because of collinearity.

In a Brazilian study, Bucuvic et al. [33] showed that 62% of patients diagnosed with AKI were male, 65.2% were elderly, diabetes mellitus occurred in 61.9%, hypertension in 44.4%, and CKD in 21.9%. Ponce et al. [34] performed a large retrospective observational study that looked into the epidemiology of AKI and its effect on patient outcomes across time periods. For comparison purposes, patients were divided into two groups according to the year of follow up: 2011–2014 and 2015–2018. The authors evaluated 5,428 AKI patients. The AKI stage 3 was 3 (50.6%), and there was a mortality rate of 34.3% (1,865 patients). Dialysis treatment was indicated in 928

Table 7 Clinical and laboratory characteristics in patients admitted in ICU according to outcome

Variables	No death ($n=70$)	Death ($n=110$)	p value
Male sex (%)	38 (54.3)	70 (63.6)	0.21
Age (years)[a]	**56.4 ± 14**	**64.4 ± 13.7**	**< 0.001**
Arterial hypertension (%)	38 (54.3)	74 (67.3)	0.13
ACE inhibitors use (%)	26 (37.1)	51 (46.4)	0.32
Diabetes mellitus (%)	20 (28.6)	47 (42.7)	0.1
Obesity (%)	15 (21.4)	34 (30.9)	0.26
CKD (%)	**4 (5,7)**	**14 (12.7)**	**0.12**
Proteinuria (%)	**21 (30)**	**51 (46.4)**	**0.003**
Hematuria (%)	**27 (38.6)**	**57 (51.8)**	**0.006**
Mechanical ventilation (%)	**33 (47.1)**	**100 (90.9)**	**< 0.001**
Vasoactive drugs (%)	**33 (47.1)**	**100 (90.9)**	**< 0.001**
AKRT (%)	**9 (12.9)**	**66 (60)**	**< 0.001**
AKI (%)	**27 (38.6)**	**96 (87.3)**	**< 0.001**
KDIGO stage 3	**8 (11.4)**	**63 (57.3)**	**< 0.001**
APACHE II[a]	**15.5 ± 6.7**	**23.2 ± 5.4**	**< 0.001**
SOFA[b]	**6.2 ± 3.6**	**10.1 ± 3.5**	**< 0.001**

Bold values refer to variables that had a p values less than 0.05

ACE angiotensin-converting enzyme, *AKRT* acute kidney replacement therapy, *CKD* chronic kidney disease, *AKI* acute kidney injury, *KDIGO* Kidney Disease Improving Global Outcomes criteria, *APACHE II* Acute Physiology and Chronic Health Evaluation score, *SOFA* Sequential Organ Failure Assessment score

[a]Mean ± SD

[b]Median (IQR)

Table 8 Logistic regression of variables associated with death in patients admitted in ICU

Variables	OR	95% IC	p value
Age	**1**	**1.03–1.1**	**< 0.0001**
Vasoactive drugs	**1.15**	**1.05–1.43**	**< 0.0001**
AKI	**3.4**	**1.35–8.6**	**0.01**
AKRT	**1.26**	**1.09–1.72**	**0.01**

Bold values refer to variables that had a p value less than 0.05

CI confidence interval, *AKI* acute kidney injury, *AKRT* acute kidney replacement therapy

patients (17.1%). Patient survival improved along the study periods, and patients treated in 2015–2018 had a relative risk death reduction of 0.89 (95% CI 0.81–0.98, $p = 0.02$). The independent risk factors for mortality were sepsis, > 65 years of age, admission to the ICU, AKI-KDIGO 3, recurrent AKI, no metabolic and fluid demand to capacity imbalance (as a dialysis indication), and the period of treatment.

We already know from the non-COVID-19 literature that AKI is associated with worse clinical outcomes. An international multicenter study from 2015 [35] with 1,032 ICU patients showed that AKI was independently associated with higher mortality at all stages, with the following odds ratios: 1.7 for KDIGO stage 1 and 6.9 for KDIGO stage 3. In ICU patients, AKI is also associated with longer duration of mechanical ventilation, use of vasoactive drugs, and increased length of hospital stay, with acute renal replacement therapy being necessary in 50% of cases.

The data presented by our study identified an overall mortality of 36.1%, being higher in ICU patients (32.9 vs 87.2%, $p < 0.0001$). The factors associated with mortality were the presence of AKI, mainly KDIGO stage 3, older age, use of VAD, and mechanical ventilation. Mortality was 61.1% in ICU patients, higher in individuals with older age, in VAD use, presence of AKI, and need for dialysis.

Many factors contribute to the maintenance of high mortality of AKI in COVID-19 patients, especially the lack of identification of risk factors for the development of this pathology, as well as the lack of knowledge about factors associated with mortality.

Still, it is important to emphasize that mechanical ventilation, mainly associated with renal and/or pulmonary involvement, may predispose hospital infections that contribute to a higher mortality of these patients. When intubated patients are under mechanical ventilation, the lung defense mechanisms are altered by the underlying disease or by the loss of protection of the upper airways, such as the loss of an intact cough reflex, which may result in pulmonary hypersecretion or an increase in the frequency of respiratory infections, with a high morbidity and mortality rate..

Upon hospital admission, 235 patients underwent Urine I, of whom 36.9% had hematuria (49.1% of AKI patients) and 31.1% had proteinuria (43.5% of AKI patients). Data published to date [8–20] reported that, at COVID-19 diagnosis, 27–64% of the patients presented hematuria and/or proteinuria.

It is worth mentioning that proteinuria, as highlighted in our results, showed to be an important risk factor associated with the development of AKI, having as main pathophysiological basis the hypothesis of direct damage of SARS-Cov-2 in tubular epithelial cells and renal podocytes. Therefore, proteinuria in patients with COVID-19 may be associated with the viral cytopathic effects, which reduces filtration and protein reabsorption, as well as results in tubular injury; or even have a glomerular origin, especially in those patients who develop acute glomerulopathies [5].

This study has some limitations: data were collected from a single center, by means of electronic medical records and have included patients only during the first pandemic wave in the country. However, this study represents an important datapoint on the epidemiological profile of AKI associated

with COVID-19 in Brazil, a country with continental characteristics and a heterogeneous and vulnerable population.

Conclusion

Thus, the analysis of our results allows us to conclude that AKI associated with severe COVID-19 is more frequent than the already published data from the Chinese, European, and North American cohorts, and the risk factors associated with the development of AKI are the older age, presence of proteinuria, use of mechanical ventilation, and VAD. Mortality is high in this population, being higher in elderly patients with greater clinical severity, especially in those requiring dialysis and who develop KDIGO stage 3 AKI.

More and larger studies are needed to determine the etiology of AKI in patients with COVID-19, as well as the factors associated with its development and prognosis. The second wave occurred in the country from December 2020 to July 2021 and was even more devastating in both incidence and severity, despite the onset of vaccination. Studies comparing the incidence of AKI during both waves, as well as the risk factors for its development and its impact on patient survival are needed.

Declarations

Conflict of interest None.

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