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Incidence of acute kidney injury in critically ill patients with COVID-19 and 90-day survival: Retrospective Cohort of a Public Intensive Care Unit, Joinville/Brazil

Fernanda Perito de Aguiar[1] **Bruna de Albuquerque Catelano**[1] **Emelli Louise Runcus Kanzler**[1] **Renata Chimelli Pegoraro**[1] **Vinicios Biff**[1] **Pedro Amorim Tabert**[1] **Paulo Henrique Condeixa de França**[1] **Helbert do Nascimento Lima**[1]

[1]Universidade da Região de Joinville – UNIVILLE. Joinville/SC, Brasil.
E-mail: fernandaperitodeaguiar@gmail.com

Abstract

About one third of patients with COVID-19 in intensive care units (ICU) have acute kidney injury (AKI) requiring dialysis. Few studies have evaluated the survival ratel of patients with AKI in exclusively public ICUs. The aim of this study was to evaluate the 90-day in-hospital survival of patients with and without AKI requiring dialysis hospitalized with severe COVID-19. This is a historical cohort of a general hospital in Joinville, Santa Catarina/Brazil. All patients admitted to the ICU between March and December of 2020 with a confirmed diagnosis of COVID-19 were included. AKI was defined by the presence of acute renal function alteration requiring hemodialysis. A multivariate Cox regression model was used to assess the survival of patients with and without AKI requiring dialysis. The results of the study showed that, of the 187 patients included (55.5% men) with a mean age of 62.8±13.6 years, 37.4% had AKI requiring dialysis. Patients with AKI requiring dialysis used more vasoactive drugs, had greater severity on admission and higher mortality rate (84.3% vs. 63.2%; p=0.002) compared to those without AKI. The risk of death in patients with AKI was higher (crude RR= 1.60; 95% CI 1.13-2.26; p= 0.007). After adjustments for age, sex, comorbidities and clinical severity, the presence of AKI requiring dialysis remained associated with a higher frequency of 90-day mortality (RR= 1.49; 95% CI 1.03-2.15; p=0.032). The survival of patients with severe COVID-19 and AKI requiring dialysis in the studied sample was lower compared to private ICUs in Brazil, which suggests inequalities in the public system.

Keywords: Survival. Hemodialysis. COVID-19. Acute Kidney Injury.

INTRODUCTION

Brazil was one of the countries most affected by COVID-19, totaling more than 702,907 thousand deaths and 37,600 million infected in the year 2023[1]. It is estimated that approximately 15% of patients diagnosed with COVID-19 required hospitalization in the country[2], and almost 20% of those hospitalized required admission to an intensive care unit (ICU)[3]. The presence of acute kidney injury (AKI) has been reported in almost one third of cases requiring intensive care[5,6], leading to higher mortality in these patients[7].

According to a meta-analysis that included more than 16,000 patients with COVID-19 who required an ICU, mostly in developed countries, 76% had acute respiratory distress syndrome (ARDS), 68% were supported with invasive mechanical ventilation, and 17% re-

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quired acute dialysis therapy[8]. AKI has been a frequent complication in patients critically affected by COVID-19 who need support in the ICU[9] and has been found around 25% to 27% of patients requiring ICU in developed countries[10]. In addition, the presence of AKI is associated with higher mortality in these patients, estimated at between 29% and 33.7%[4,5,6,11].

In developing or underdeveloped countries, the incidence of AKI in the same context has been higher, being around 58.6% to 60.7%[7]. In Brazil, data from mixed hospitals (public and private health care) have indicated a prevalence of AKI in critically ill patients between 15.7% and 23.2%[12,13].

Considering that 65% of patients hospitalized for COVID-19 in Brazil were over 55 years old, 66.6% had previous cardiovascular diseases and 54.5% had diabetes[14] - both risk situations for AKI[15] -, the incidence of AKI may still be underestimated in hospitals that are mainly public.

Considering the important impact of AKI on patients with COVID-19 and that two-thirds of the Brazilian population depends on public health care (Unified Health System - SUS), studies that investigate the outcome of patients who required dialysis therapy in designated public hospitals for the care of patients with COVID-19 can contribute to the assessment of the quality of these services. The present study aimed to evaluate the incidence of AKI in patients with COVID-19 who required hemodialysis when admitted to a public ICU of a referral hospital for COVID-19 care in the largest city of Santa Catarina.

MATERIALS AND METHODS

This is a retrospective cohort study carried out between March and December of 2020 in an ICU at a public hospital in the city of Joinville, Santa Catarina, Brazil. The local hospital targeted by this study is a general hospital, with exclusive assistance to the public health system, with medical and multidisciplinary residency programs for various specialties, including intensive care. At the beginning of the COVID-19 pandemic, the hospital was assigned to care for the entire Joinville macro-region, with approximately 600,000 inhabitants.

The study was approved by the local Ethics Committee (Opinion 4,702,508), and the free and informed consent form was waived due to the retrospective nature of the study and because it was non-sensitive epidemiological data. All patients aged 18 years or older admitted to the ICU due to COVID-19 were included. Such diagnosis was confirmed via RT-PCR in samples collected through oropharyngeal swab, following standards of the World Health Organization[16]. Patients who died within the first 48 hours after admission to the ICU, who were already on hemodialysis before admission to the ICU, and those with creatinine ≥ 4 mg/dl or on a chronic dialysis program at the time of hospital admission were excluded.

The following information was collected from the electronic medical record: age, gender, previous comorbidities reported by the patient or family member: diabetes mellitus, systemic arterial hypertension, cardiovascular disease (infarction, myocardial revascularization or coronary angioplasty), chronic lung disease (asthma or obstructive pulmonary disease chronic) and cancer. Obesity was defined via the body mass index (BMI) and verified on admission. The Simplified Acute Physiology Score (SAPS 3) and the Sequential Organ Failure Assessment (SOFA) were used in the first 24 hours of admission to the ICU to assess the clinical severity. Arterial blood gases and inspired oxygen fraction rate in the first 24 hours of arrival at the ICU were used to define acute respiratory distress syndrome

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(ARDS)[17]. The presence of AKI was defined by the acute need for hemodialysis prescribed by a nephrologist at the hospital[12]. Other variables considered were length of stay, duration of mechanical ventilation, use of vasoactive drugs and use of non-invasive ventilation.

Categorical variables are presented by their frequency and percentage and numeric variables by their mean and standard deviation. The chi-square test was used to compare the categorical variables and the Student's t test to compare the means of the quantitative variables after verification of their normality by the *Kolmogorov-Smirnov* test, regarding the presence or absence of AKI. The occurrence of in-hospital death within 90 days of admission was defined as the main outcome. The analysis of the survival curve in relation to death between patients with and without AKI is presented using the *Kaplan-Meier* method and the difference is evaluated using the *Log-Rank* test.

The univariate and multivariate analyzes were carried out using Cox regression after verifying the assumptions of proportionality by graph and by proportionality test. The presence or absence of AKI was evaluated in terms of crude 90-day survival and bivariately adjusted for other variables using the same method. All variables that modified the association of the main variable with the study outcome by more than 10% or considered as potential confounders were progressively included in the multivariate models (sociodemographic variables, comorbidities and variables associated with severity).

Although higher scores on severity scales (SAPS-3) have been associated with a worse prognosis for patients admitted to the ICU[18], their use in multivariate models in patients with COVID-19 has been questioned, since many of these patients have not been admitted directly to the ICU, reducing the exact correlation of the score with mortality when performed only on admission to the ICU[19]. Thus, the need for vasoactive drugs and the presence of ARDS in the multivariate model used in this study were considered as variables related to the severity of the patient[20]. The likelihood test was used to assess any interaction factor between the main exposure variable and the other variables. For the multivariate analysis, linear effects were considered for categorical variables on the level of ARDS and length of stay in the ICU after verification using the linear trend deviation test. All data were analyzed using STATA/IC 15.1 software.

RESULTS

During the period of this study, 202 patients were admitted to the ICU of the aforementioned hospital with a confirmed diagnosis of COVID-19. After excluding 15 patients (7 due to death < 48 hours, 3 because they were already on acute hemodialysis before ICU admission and 5 because they had creatinine > 4 mg/dl on admission), a final sample of 187 patients was obtained (Figure 1).

Table 1 presents the main characteristics of the total sample and stratified by the presence or absence of AKI. Of the 187 patients, the mean age was 62.8±13.6 years, 102 (55.5%) men and 133 (71.1%) dying within 90 days of hospitalization. The presence of AKI requiring dialysis was observed in 37.4% (n=70) of the sample. Among the patients evaluated, 120 (64.2%) had criteria for moderate to severe ARDS at the time of admission to the ICU. Patients with AKI requiring dialysis used vasoactive drugs more frequently and had a higher clinical severity score, assessed using the SAPS-3 and SOFA indices, as well as higher mortality (84.3% vs. 63.2%; p=0.002) in comparison to patients without AKI.

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When the 90-day survival curve was evaluated, patients with AKI requiring dialysis had lower survival compared to those without AKI requiring dialysis (Figure 2; p=0.006). When assessing the impact of AKI requiring dialysis on 90-day survival, patients who required hemodialysis had a 60% higher risk of death (crude RR= 1.60; 95% CI 1.13-2.26; p= 0.007). After bivariate adjustments for other variables (Table 2), the effect for increased risk of death among those who required hemodialysis remained similar and significantly for all studied variables, except when adjusted for age, in which it was attenuated (RR adjusted=1.38; 95% CI 0.98-1.96; p=0.067).

Table 3 presents three multivariate models to assess the effect of AKI requiring dialysis on the 90-day survival of patients with COVID-19 in the ICU. When adjusted for age and gender, there was no strong evidence for shorter 90-day survival among patients who required hemodialysis. After adjustments for the assessed comorbidities (model 2) and clinical severity criteria (model 3), the presence of AKI requiring dialysis remained as a factor associated with lower 90-day survival.

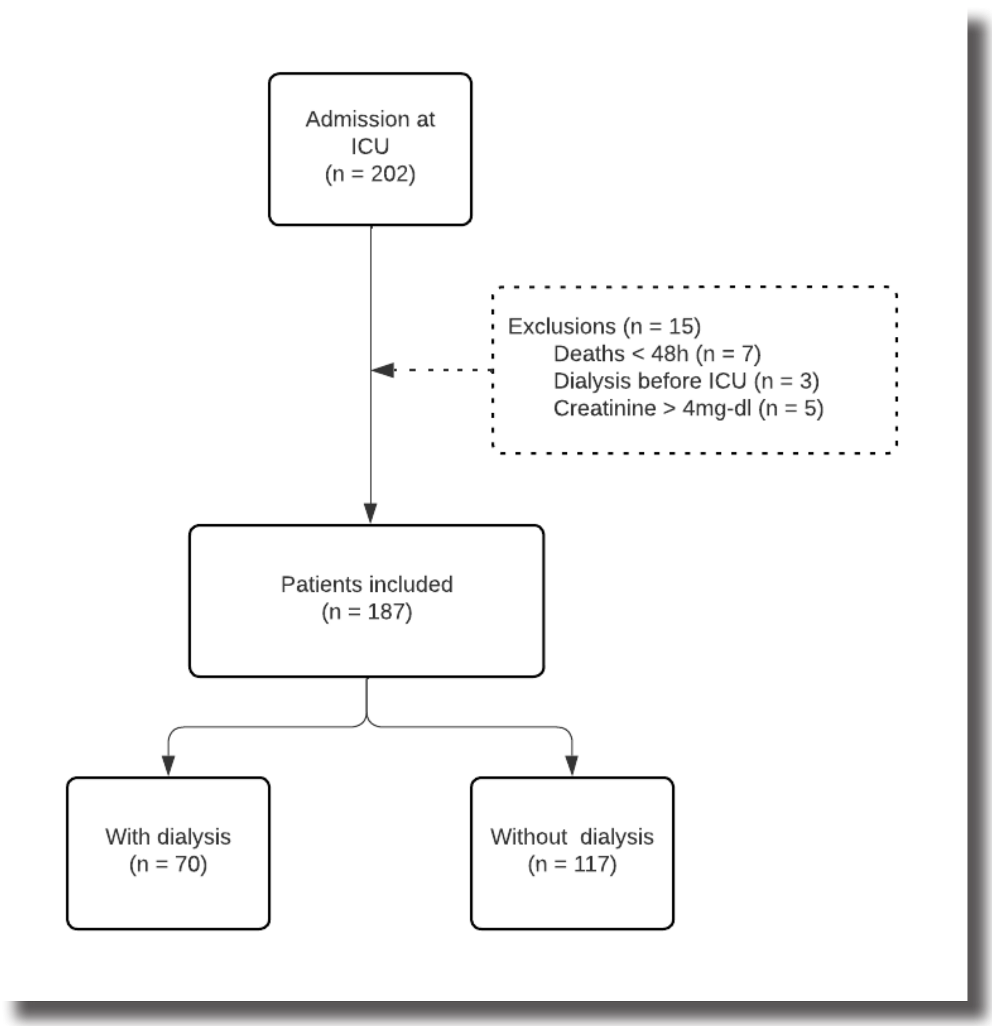

Figure 1 - Study sampling flowchart.

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Table 1 – General characteristics of patients admitted to the intensive care unit diagnosed with COVID-19 and who required hemodialysis (n=187). Joinville-SC, 2020.

Variable	Total Sample n = 187	No hemodialysis n = 117 (62.6%)	With hemodialysis n = 70 (37.4%)	p value
Age, years, mean (SD)	62.8 (13.6)	62.4 (14.3)	63.6 (12.4)	0.563
Sex, n (%)				**0.392**
Women	85 (45.4)	56 (47.9)	29 (41.4)	
Men	102 (55.5)	61 (52.1)	41 (58.6)	
Comorbidities, n (%)				
Hypertension	93 (49.7)	56 (47.9)	37 (52.9)	0.509
Diabetes	63 (33.7)	38 (32.5)	25 (35.7)	0.651
Cardiovascular disease	18 (9.6)	10 (8.5)	8 (11.4)	0.518
Lung disease	14 (7.5)	10 (8.5)	4 (5.7)	0.476
Obesity	42 (22.5)	29 (24.8)	13 (18.6)	0.324
Smoker or ex-smoker	22 (11.8)	11 (9.4)	1 1(15.7)	0.195
Cancer	13 (6.9)	9 (7.7)	4 (5.7)	0.607
Respiratory parameters at ICU admission				
Fi02, median (IQR)	100 (84.2/120)	59.4 (40/75)	60 (48.2/80)	0.390
PaO2, median (IQR)	60 (40/80)	103 (86/120)	103.5 (83.4/120)	0.744
ARDS, n (%)				0.472
Low	67 (35.8)	46 (39.3)	21 (30.0)	
Moderate	75 (40.1)	42 (35.9)	33 (47.1)	
Severe	45 (24.1)	29 (24.8)	16 (22.9)	
OTI, n (%)	11 (5.9)	6 (5.2)	5 (7.1)	0.581
Prone Position, n (%)	111 (59.4)	60 (51.3)	51 (72.9)	0.004
Mechanical ventilation, n (%)	177 (94.6)	108 (92.3)	69 (98.6)	0.065
Mechanical ventilation, days, median (IQR)	14 (9/25)	13 (7/25)	17 (10/24)	0.072
Use of VAD, n (%)	103 (55.1)	55 (47.0)	48 (68.6)	0.004
SAPS 3, median (IQR)	69.5 (56/76)	67 (52/74)	73.5 (64/78)	0.002
SOFA, median (IQR)	7 (3/9)	6.5(3/8)	8.5(6/10)	<0.001
Time in ICU, days, median (IQR)	16 (10/27)	15 (9/26)	18 (10/27)	0.368
Acute HD, n (%)	70 (37.4)			
Death, n (%)	133 (71.1)	74 (63.2)	59 (84.3)	0.002

Caption: N = sample; SD = Standard deviation; IQR = Interquartile range; HD= hemodialysis; ARDS = acute respiratory distress syndrome; OTI = orotracheal intubation; VAD = Vasoactive drug; lung disease = chronic obstructive pulmonary disease and/or asthma; cardiovascular disease = heart failure and/or previous acute myocardial infarction and/or angioplasty and/or coronary artery bypass grafting. SAPS-3= Simplified Acute Physiology Score; SOFA=Sequential Organ Failure Assessment; FIO2= fraction of inspired oxygen; PaO2= arterial partial pressure of oxygen.

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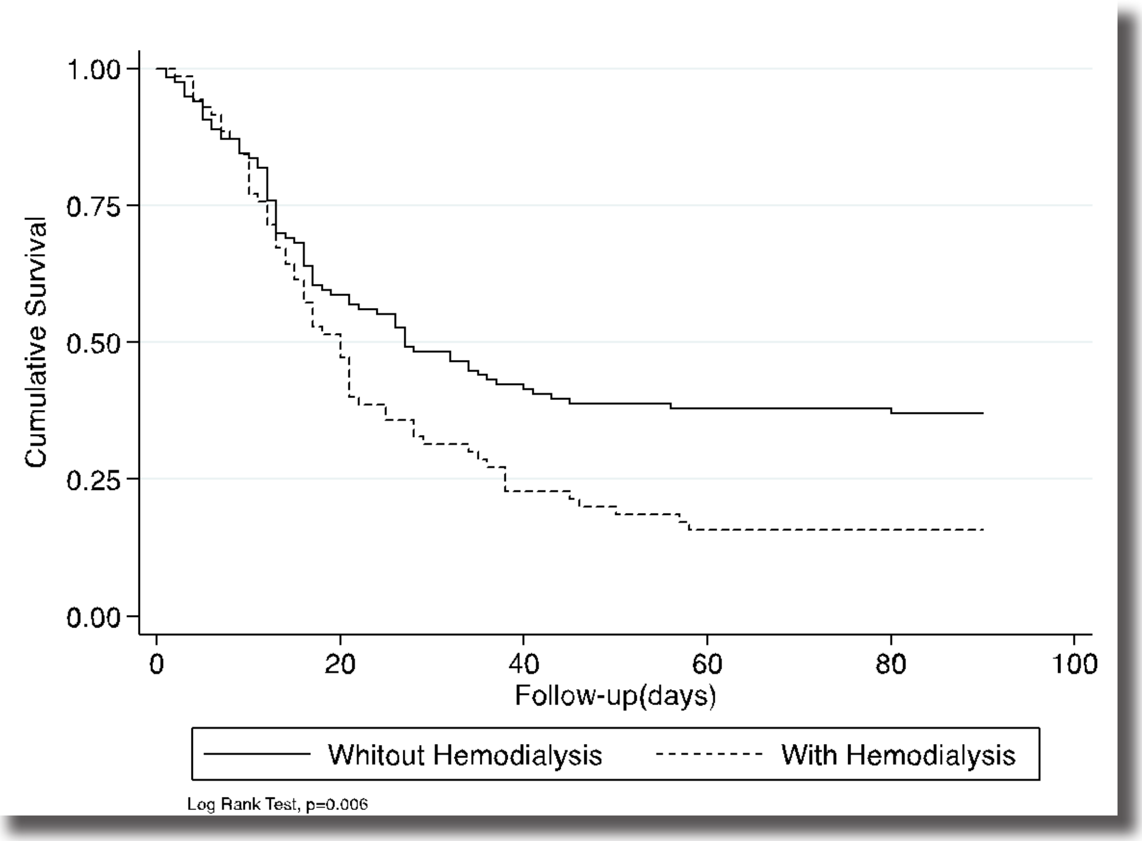

Figure 2 – Cumulative survival with or without acute kidney injury requiring dialysis in patients with COVID-19, by Kaplan Meier. Joinville-SC, 2020.

Table 2 - Analysis of the crude and adjusted association between patients with acute kidney injury requiring dialysis and survival within 90 days after intensive care unit admission due to COVID-19 infection, by Cox regression (n=187). Joinville-SC, 2020.

Variable	Crude HR	95% CI	*p value*	LRT
Hemodialysis	1.60	1.13-2.26	0.007	
Effect of hemodialysis adjusted for	**Adjusted HR**			
Age, years	1.38	0.98-1.96	0.067	<0.001
Sex, male	1.58	1.12-2.24	0.010	0.443
Obesity	1.58	1.11-2.23	0.010	0.386
Hypertension	1.57	1.11-2.22	0.011	0.234
Lung disease	1.62	1.15-2.29	0.006	0.102
previous CVD	1.57	1.11-2.22	0.011	0.155
Cancer	1.63	1.15-2.30	0.006	0.077
Use of vasopressor	1.52	1.07-2.16	0.020	0.141
Previous CVA	1.60	1.13-2.26	0.008	0.868
Diabetes	1.61	1.14-2.27	0.007	0.577

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Variable	Crude HR	95% CI	*p value*	LRT
Smoker or ex-smoker	1.58	1.12-2.23	0.010	0.390
Days in ICU	1.87	1.32-2.66	<0.001	<0.001
ARDS	1.57	1.11-2.23	0.011	0.503

Caption: Lung disease = chronic obstructive pulmonary disease and/or asthma; CVD=Cardiovascular disease (heart failure and/or previous acute myocardial infarction and/or angioplasty and/or myocardial revascularization); ARDS = Acute Respiratory Distress Syndrome.

Table 3 - Cox multivariate regression analysis for association of acute kidney injury requiring dialysis and survival within 90 days after ICU admission due to COVID-19 infection. Joinville-SC, 2020.

	Model 1			Model 2			Model 3		
Variable	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Hemodialysis	1.38	0.97-1.95	0.071	1.44	1.01-2.05	0.043	1.49	1.03-2.15	0.032
Age, years	1.04	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001	1.04	1.02-1.05	<0.001
Sex, male	1.08	0.76-1.53	0.657	1.06	0.74-1.52	0.762	0.90	0.63-1.30	0.584
Lung disease				1.59	0.88-2.87	0.121	1.70	0.93-3.09	0.082
Diabetes				0.89	0.61-1.32	0.576	0.80	0.54-1.19	0.269
Cancer				2.05	1.08-3.89	0.029	1.83	0.96-3.51	0.068
CVD				1.19	0.69-2.05	0.521	1.39	0.80-2.42	0.237
Vasopressor							1.15	0.79-1.68	0.469
ARDS[1]							0.78	0.65-0.92	0.05
Days in ICU[2]							0.52	0.42-0.65	<0.001

Caption: 1- Considering as a linear effect for each category over the first category (without ARDS) as a baseline (T-test, linear regression, p=0.147)

2- Considering as a linear effect for each category relative to the first category (<14 weeks) as a baseline (T-test, linear regression, p=0.703)

Lung disease = chronic obstructive pulmonary disease and/or asthma; CVD=cardiovascular disease (heart failure and/or previous acute myocardial infarction and/or angioplasty and/or myocardial revascularization); ICU=intensive care unit.

DISCUSSION

In the present study, a high mortality rate was found in patients hospitalized for COVID-19 in a public reference ICU in the south of the country. More than a third of the patients had AKI requiring acute dialysis, and the need for hemodialysis had an impact on the survival of these patients. After adjusting for other variables, the presence of AKI requiring dialysis was associated with a 50% lower 90-day survival when compared to patients not requiring acute dialysis therapy.

According to other studies carried out with patients with COVID-19 admitted to the ICU[14,15], the characteristics of the sample cur-

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rently studied were similar. In patients with COVID-19 admitted to ICUs in São Paulo, the mean age was 64.1 years, with 68.8% being male[12], 62.1% had two or more comorbidities, with high blood pressure (68%) and diabetes (45%) being the most prevalent[12]. In the present study, hypertension and diabetes were also the most prevalent comorbidities. These clinical characteristics of patients requiring ICU due to COVID-19 have also been pointed out in other hospitalizations due to COVID-19 in Brazil[14].

The presence of AKI in patients with COVID-19 has been a common complication, especially among those with more severe conditions[4,5,6,21]. In a study conducted in hospitals in China, where the first cases of COVID-19 were confirmed, 46% of patients presented AKI, with 19% requiring acute dialysis therapy[22]. However, the incidence of AKI has been quite variable, depending on the characteristics of the patients and the type of hospital involved, ranging from 20% to 76%[23,24].

In Brazil, in a cohort study carried out with 102 patients with COVID-19 admitted to a private hospital in Rio de Janeiro, 26.5% of patients had AKI requiring acute hemodialysis[25]. Another study involving 13 ICUs in the state of São Paulo showed an incidence of AKI requiring dialysis around 16%, however, 40% of the sample was from public ICUs and 60% from private ones[12]. In southern Brazil, patients hospitalized for COVID-19 in a public ICU in Paraná, 11.6% had AKI[26].

Part of these variations in the incidence of AKI are related to the severity of the patient, the criteria used to define AKI and the need for an ICU. However, one cannot rule out structural limitations or waiting time until admission to a specialized unit as factors that may impact these incidences.

In the present study, the presence of AKI requiring dialysis in an exclusively public ICU was observed in 37.4% of the cases. In a study carried out in the interior of São Paulo in a public hospital with 243 patients, 34% underwent hemodialysis and of these 92.7% died[27]. A high incidence of AKI was found in a public ICU in Pernambuco, where 40% of patients required renal replacement therapy, and, of these, 80% died[28]. This higher incidence found in a public hospital in Pernambuco may be related to the pulmonary severity of these patients[28].

In the present study, the high incidence of AKI compared to other private hospitals may also be related to the greater severity presented by patients. Almost all required mechanical ventilation and more than half needed to use vasoactive drugs. This fact was also observed in a study in the interior of Amazonas in a public hospital where 63% of patients used VAD and 70% needed mechanical ventilation[29]. The delay in patient access to the ICU may also have contributed to this higher incidence of AKI.

As for the mortality of patients with AKI hospitalized for COVID-19 in the ICU, the death rate has been variable, between 52.6% and 88% in international studies[23,30]. In Brazil, the mortality of patients with AKI requiring dialysis in private or mixed ICUs has been around 35%2 to 55.5%[31]. In 2 studies of essentially public ICUs in the states of Rondônia and Goiás, the mortality of patients with COVID-19 who underwent dialysis was approximately 93% in both studies[32,33]. In our study, approximately 80% of the patients who required dialysis died within 90 days.

Although, this high mortality rate has been pointed out in other studies that evaluated the survival of patients with severe COVID-19 in need of RRT outside Brazil[22,34], it seems to be higher in relation to essentially private hospitals. In a study with 101 patients admitted to the ICU of a private hospital in Brazil, 50.2% had AKI, with 33.6% requiring dialysis. The 60-day mortality rate among patients who required dialysis was 35.3%. Possible reasons for this lower mortality could be the lower prevalence of KDIGO stage 3 AKI, the short time interval between the onset of COVID19 symp-

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toms and admission to the ICU (only 1 day)[35].

In a study carried out at a public university hospital in São Paulo, the need for RRT reached 61.5% of patients and the mortality of patients admitted to the ICU and who received RRT was 55.3%, with cardiovascular diseases, obesity, need of mechanical ventilation and prognostic indices APACHE and SOFA as associated factors[31]. In the present study, our sample of patients who required dialysis has a high percentage of patients with Hypertension (52.9%) and Diabetes (35.7%), comorbidities that may have contributed to the worsening of the pulmonary condition presented by the patients and greater mortality.

In line with our findings, the high mortality rate in patients admitted to the ICU with AKI was also observed in a study in the northeast of the country in a public hospital, where of the 1,538 patients admitted to the ICU with COVID-19, 329 had AKI during their hospitalization and of these 78.1% died[36].

In the present study, the presence of AKI requiring dialysis increased the unadjusted risk of death by 60% in the univariate analysis. When considering other confounding variables, the presence of AKI requiring dialysis remained associated with higher mortality in the studied sample. In the sample studied, patients who required dialysis had a higher severity score (SAPS 3), longer mechanical ventilation and more frequent use of vasoactive drugs. Similar findings have also been found in another public ICU in northeastern Brazil, where the need for mechanical ventilation, use of vasoactive drugs and the need for dialysis were associated with higher mortality[28].

In addition to the clinical and severity characteristics found in the present sample, which could explain the high mortality rate among patients who required hemodialysis, structural and specialized care difficulties may have impacted this rate. At the start of the pandemic, the world faced a critical shortage of hospital beds and supplies, especially in ICUs[37,38]. This scenario was no different in Brazil and this cohort covers exactly this period. The hospital where this study was conducted usually had two ICUs before the pandemic and increased their number to eight during the peak of the health crisis. Although the physical structural expansion is possible, the assistance staff trained in intensive care and for the care of critically ill patients does not happen quickly, similar to other locations in the country. Thus, such an impact on the care of these patients cannot be ruled out, especially in the context of a public hospital[39].

Our study has some limitations that must be considered. This is a study conducted in only one public ICU and may not necessarily reflect the reality of other public ICUs in Brazil, especially in hospitals without a medical and multidisciplinary residency program. Furthermore, it was not possible to characterize the stages of AKI. In this way, patients without the need for hemodialysis could have AKI in the early stages, but also with an impact on higher mortality[40]. Even so, this is a study carried out in an exclusively public hospital in the largest city of Santa Catarina. The present findings may corroborate the need to expand the search for factors related to the high mortality of patients with AKI with COVID-19 admitted to a public ICU compared to mixed or private ICUs, in addition to those directly related to the severity of the patients.

CONCLUSION

The presence of AKI requiring dialysis was observed in more than a third of the studied sample, as well as a high 90-day mortality of patients with COVID-19 admitted to a public

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ICU. The presence of AKI requiring dialysis showed 50% lower survival at 90 days compared to patients who did not require dialysis after adjusting for other variables. In addition to the clinical and severity characteristics of these patients with COVID-19, the findings may indicate the possibility of greater structural and care difficulties associated with higher mortality in public ICUs compared to other private ICUs in Brazil.

Author Statement CREdiT

Conceptualization: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Methodology: Aguiar, FP; France, PHC; Lima, HN. Validation: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Statistical analysis: Aguiar, FP; France, PHC; Lima, HN. Formal analysis: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Research: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; Lima, HN. Resources: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Preparation of the original draft: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Writing and review: Aguiar, FP; France, PHC; Lima, HN. Visualization: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN. Supervision: Aguiar, FP; France, PHC; Lima, HN. Project administration: Aguiar, FP; Catelano, BA; Runcus, E.L.; Pegararo, RC; Biff, V; Tabert, PA; France, PHC; Lima, HN.

All authors have read and agree with the version published in the manuscript.

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