Acute Kidney Injury and Renal Replacement Therapy in Critically Ill COVID-19 Patients: Risk Factors and Outcomes: A Single-Center Experience in Brazil

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Abstract

Background: Critically ill patients with COVID-19 may develop multiple organ dysfunction syndrome, including acute kidney injury (AKI). We report the incidence, risk factors, associations, and outcomes of AKI and renal replacement therapy (RRT) in critically ill COVID-19 patients. ***Methods:*** We performed a retrospective cohort study of adult patients with COVID-19 diagnosis admitted to the intensive care unit (ICU) between March 2020 and May 2020. Multivariable logistic regression analysis was applied to identify risk factors for the development of AKI and use of RRT. The primary outcome was 60-day mortality after ICU admission. ***Results:*** 101 (50.2%) patients developed AKI (72% on the first day of invasive mechanical ventilation [IMV]), and thirty-four (17%) required RRT. Risk factors for AKI included higher baseline Cr (OR 2.50 [1.33–4.69], $p = 0.005$), diuretic use (OR 4.14 [1.27–13.49], $p = 0.019$), and IMV (OR 7.60 [1.37–42.05], $p = 0.020$). A higher C-reactive protein level was an additional risk factor for RRT (OR 2.12 [1.16–4.33], $p = 0.023$). Overall 60-day mortality was 14.4% {23.8% ($n = 24$) in the AKI group versus 5% ($n = 5$) in the non-AKI group (HR 2.79 [1.04–7.49], $p = 0.040$); and 35.3% ($n = 12$) in the RRT group versus 10.2% ($n = 17$) in the non-RRT group, respectively (HR 2.21 [1.01–4.85], $p = 0.047$)}. ***Conclusions:*** AKI was common among critically ill COVID-19 patients and occurred early in association with IMV. One in 6 AKI patients received RRT and 1 in 3 patients treated with RRT died in hospital. These findings provide important prognostic information for clinicians caring for these patients.

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Introduction

The first case of COVID-19 in Brazil was confirmed on February 26, 2020, and 6 months later, Brazil had more than 3,500,000 diagnosed cases and was the country with the second highest number of cases worldwide [1]. The clinical spectrum of COVID-19 ranges from asymptomatic disease to respiratory failure and multiple organ dysfunction syndrome [2], resulting in a large number of intensive care unit (ICU) admissions [3, 4]. Previous studies have shown that about 5% of all cases and up to 30% of hospitalized patients require ICU admission [5, 6].

Acute kidney injury (AKI) is a common clinical problem in critically ill patients, especially in those with acute lung injury receiving invasive mechanical ventilation (IMV) [7, 8]. Initial data showed a variable incidence of AKI in COVID-19 patients, ranging from 0.5 to 23% [2, 9], but more recent reports have shown even higher incidences, with rates of up to 36%, and need for renal replacement therapy (RRT) in 5.2% of patients [3, 10]. The development of AKI was associated with worse outcomes [2, 9, 11, 12]. The aim of our study was to describe the incidence, risk factors, and impact of AKI and RRT on clinical outcomes in COVID-19 patients admitted to the ICU.

Materials and Methods

We included adult patients (≥18 years old) with confirmed severe acute respiratory syndrome coronavirus 2 infection admitted to the ICU of Hospital Israelita Albert Einstein (HIAE), a private quaternary teaching hospital in Brazil, between March 04 and May 13, 2020. A laboratory-confirmed case of severe acute respiratory syndrome coronavirus 2 infection was defined by a positive RT-PCR assay for a specimen collected via nasopharyngeal swab. Patients with CKD on dialysis were excluded from the study.

Demographic and clinical variables included age, sex, chronic medical conditions, regular medications, reason for ICU admission, date of onset of symptoms, and drugs prescribed during hospitalization. Simplified Acute Physiology Score 3 (SAPS3), Sequential Organ Failure Assessment Score (SOFA), and Charlson Comorbidity Index were recorded on the first day of ICU. We also collected data on IMV, extracorporeal membrane oxygenation, vasopressors, and RRT requirement. Laboratory results were gathered at ICU admission.

Baseline Cr was defined as the average of all values observed between 8 and 365 days prior to hospitalization [13]. In the absence of previous serum Cr records, the lowest Cr level during hospitalization was considered [14]. The estimated glomerular filtration rate was calculated using the CKD-Epidemiology Collaboration Cr equation [15]. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [14].

Individuals were initially treated according to the institutional protocol (appendix). Timing of dialysis initiation and the choice of modality were at the discretion of the nephrology team. Regularly at our center, critically ill patients with AKI are initiated on continuous venovenous hemodiafiltration (CVVHDF) at a prescribed dose of 30–35 mL/kg/h of effluent and with regional citrate anticoagulation [16]. The Prismaflex AN69 ST150 set was used with the Prismaflex control unit (Baxter, IL, USA) to perform CVVHDF. We evaluated the delivered dialysis dose, the filtration fraction, and the fluid balance during the first 7 days of therapy. We assessed the filter life span, and the reasons for changing the dialysis set throughout the CRRT time. The local Ethics Committee reviewed and approved this study (CAAE30525320.0.0000.0071). All patients were unable to provide consent themselves, so consent was gained using the appropriate emergency consent mechanisms.

Outcomes

The primary outcome was 60-day mortality after ICU admission. After hospital discharge, the follow-up was made either by accessing the medical records or by telephone contact. The same strategy was applied to 28-day mortality. For all other secondary outcomes, follow-up was made until May 23, 2020 which included the following: Cr at hospital discharge, ICU mortality, in-hospital mortality, duration of mechanical ventilation in survivors, ICU length of stay, hospital length of stay, and dependence on RRT at hospital discharge.

Statistical Analysis

A convenience sample was considered for this analysis, with consecutive patients included until the latest follow-up. There were no missing data for any of the outcomes. Continuous variables are presented as medians (quartile 25%–quartile 75%) and categorical variables as number and percentages. Patients were divided in groups according to development of AKI (AKI vs. non-AKI) and treatment with RRT (RRT vs. non-RRT) until the latest follow-up.

Baseline and clinical characteristics of the patients were compared among the groups using Fisher exact tests and Wilcoxon rank-sum tests. Time until ICU and hospital discharge is presented as Kaplan-Meier plots. The association of AKI or RRT with ICU and hospital mortality was reported as odds ratio with 95% confidence interval from generalized linear modelling with binomial distribution. The association with ICU and hospital length of stay was assessed using the subdistribution hazard ratio derived from a Fine-Gray competing risk model with death before the event treated as competing risk. The association of Cr with hospital discharge and duration of ventilation in survivors was assessed as the median difference from a quantile regression with $T = 0.50$ and results estimated with bootstrap with 1,000 resamples. To account for potential confounders, additional analyses adjusted by SAPS3 and Charlson Comorbidity Index were performed.

Multivariable logistic regression model was used to identify factors independently associated with development of AKI and need of RRT. A list of candidate baseline predictors was determined a priori and included only variables with a known or suspected relationship with outcome. The multivariable model was constructed considering variables with a $p < 0.05$ in the univariable analysis and confirmed using a backward elimination technique and the leaps algorithm to perform a best subset selection including exhaustive search based on the Bayesian information criteria

Table 1. Baseline characteristics of the patients according to development of AKI or need of RRT

	Overall (n = 201)	AKI (n = 101)	Non-AKI (n = 100)	p value	RRT (n = 34)	Non-RRT (n = 166)	p value
Age, years	64.0 (52.0–80.0)	73.0 (56.0–84.0)	60.0 (45.0–72.2)	<0.001	69.0 (57.2–82.0)	64.0 (48.2–80.0)	0.074
Male gender, n (%)	123 (61.2)	67 (66.3)	56 (56.0)	0.174	27 (79.4)	96 (57.8)	0.031
BMI, kg/m^{2,a}	28.2 (24.6–32.1)	28.7 (25.4–33.2)	27.1 (24.3–31.1)	0.114	28.7 (26.1–32.4)	27.9 (24.5–31.9)	0.189
SAPS3	49.0 (42.0–55.0)	52.0 (45.8–57.0)	43.0 (42.0–53.0)	<0.001	52.0 (49.0–57.0)	46.0 (42.0–55.0)	0.008
SOFA	2.0 (0.0–4.0)	3.0 (1.0–6.0)	1.0 (0.0–2.0)	<0.001	4.0 (2.0–8.0)	1.0 (0.0–3.0)	<0.001
Source of ICU admission, n (%)							
Emergency room	96 (47.8)	50 (49.5)	46 (46.0)	0.688	18 (52.9)	77 (46.4)	0.031
Ward	77 (38.3)	35 (34.7)	42 (42.0)		7 (20.6)	70 (42.2)	
Step-down unit	15 (7.5)	9 (8.9)	6 (6.0)		4 (11.8)	11 (6.6)	
Other hospital	13 (6.5)	7 (6.9)	6 (6.0)		5 (14.7)	8 (4.8)	
Coexisting disorders, n (%)							
Charlson Comorbidity Index	1.0 (0.0–2.0)	1.0 (0.0–3.0)	0.0 (0.0–1.0)	<0.001	2.0 (1.0–3.0)	1.0 (0.0–2.0)	<0.001
Hypertension	98 (48.8)	59 (58.4)	39 (39.0)	0.009	21 (61.8)	77 (46.4)	0.148
Diabetes	64 (31.8)	39 (38.6)	25 (25.0)	0.055	19 (55.9)	45 (27.1)	0.002
Heart failure	17 (8.5)	13 (12.9)	4 (4.0)	0.045	9 (26.5)	8 (4.8)	<0.001
Pneumopathy	19 (9.5)	9 (8.9)	10 (10.0)	0.982	2 (5.9)	17 (10.2)	0.639
Coronary artery disease	16 (8.0)	13 (12.9)	3 (3.0)	0.020	6 (17.6)	10 (6.0)	0.054
Arrythmia	25 (12.4)	17 (16.8)	8 (8.0)	0.092	7 (20.6)	17 (10.2)	0.161
Smoking	6 (3.0)	2 (2.0)	4 (4.0)	0.669	2 (5.9)	4 (2.4)	0.596
Solid neoplasia	19 (9.5)	13 (12.9)	6 (6.0)	0.155	4 (11.8)	15 (9.0)	0.862
Hematological neoplasia	12 (6.0)	7 (6.9)	5 (5.0)	0.780	3 (8.8)	9 (5.4)	0.715
At ICU admission, n (%)							
Respiratory failure	139 (69.2)	75 (74.3)	64 (64.0)	0.155	32 (94.1)	107 (64.5)	0.001
Use of noninvasive ventilation	122 (60.7)	65 (64.4)	57 (57.0)	0.356	23 (67.6)	99 (59.6)	0.497
Use of invasive ventilation	87 (43.3)	70 (69.3)	17 (17.0)	<0.001	34 (100.0)	53 (31.9)	<0.001
Hours ICU admission to intubation	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.611	1.0 (0.0–2.0)	1.0 (0.0–2.0)	0.398
Use of vasopressor	82 (40.8)	66 (65.3)	16 (16.0)	<0.001	33 (97.1)	49 (29.5)	<0.001
Use of ECMO	2 (1.0)	2 (2.0)	0 (0.0)	0.482	2 (5.9)	0 (0.0)	0.028
Deep sedation	69 (34.3)	57 (56.4)	12 (12.0)	<0.001	32 (94.1)	37 (22.3)	<0.001
Medications, n (%)							
ACEi and/or ARB	60 (29.9)	34 (33.7)	26 (26.0)	0.302	11 (32.4)	49 (29.5)	0.902
Antibiotics	193 (96.0)	100 (99.0)	93 (93.0)	0.069	34 (100.0)	159 (95.8)	0.480
Steroids	104 (53.3)	64 (67.4)	40 (40.0)	<0.001	19 (67.9)	84 (50.6)	0.137
Lopinavir-ritonavir	25 (12.4)	18 (17.8)	7 (7.0)	0.035	9 (26.5)	16 (9.6)	0.016
Hydroxychloroquine + azithromycin	168 (84.0)	84 (84.0)	84 (84.0)	0.999	30 (88.2)	137 (83.0)	0.620
Tocilizumab	9 (4.5)	7 (6.9)	2 (2.0)	0.177	3 (8.8)	6 (3.6)	0.378
Convalescent plasma	32 (15.9)	19 (18.8)	13 (13.0)	0.351	4 (11.8)	27 (16.3)	0.689
Signs and symptoms, n (%)							
Days symptoms to diagnosis	4.0 (2.0–7.0)	3.0 (1.0–6.0)	5.0 (3.0–8.0)	0.001	3.0 (1.0–7.0)	4.0 (2.0–7.0)	0.076
Days symptoms to hospital admission	6.0 (3.0–9.0)	6.0 (3.0–7.0)	7.0 (4.0–10.0)	0.002	6.0 (4.5–7.0)	6.0 (3.0–9.0)	0.658
Days symptoms to ICU admission	1.0 (0.0–2.0)	1.0 (0.0–3.0)	0.5 (0.0–1.0)	0.303	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.155
Rhinorrhea	51 (25.4)	14 (13.9)	37 (37.0)	<0.001	5 (14.7)	46 (27.7)	0.171
Odynophagia	23 (11.4)	6 (5.9)	17 (17.0)	0.025	2 (5.9)	21 (12.7)	0.405
Anosmia	10 (5.0)	2 (2.0)	8 (8.0)	0.101	0 (0.0)	10 (6.0)	0.300
Cough	175 (87.1)	85 (84.2)	90 (90.0)	0.306	28 (82.4)	147 (88.6)	0.477
Shortness of breath	173 (86.1)	83 (82.2)	90 (90.0)	0.162	28 (82.4)	144 (86.7)	0.688
Fever	174 (86.6)	86 (85.1)	88 (88.0)	0.700	29 (85.3)	144 (86.7)	0.999
Diarrhea	40 (19.9)	20 (19.8)	20 (20.0)	0.999	5 (14.7)	35 (21.1)	0.541
Organ support							
Maximum dose of norepinephrine, μg/kg/min	0.10 (0.06–0.20)	0.12 (0.07–0.23)	0.06 (0.04–0.10)	0.011	0.15 (0.10–0.25)	0.10 (0.05–0.15)	0.002
Use of epinephrine, n (%)	10 (5.0)	9 (8.9)	1 (1.0)	0.024	7 (20.6)	3 (1.8)	<0.001
Use of dobutamine, n (%)	13 (6.4)	11 (10.9)	2 (2.0)	0.023	6 (17.6)	7 (4.2)	0.012
Use of recruitment maneuver, n (%)	34 (16.9)	30 (29.7)	4 (4.0)	<0.001	18 (52.9)	16 (9.6)	<0.001
Use of prone positioning, n (%)	10 (5.0)	9 (8.9)	1 (1.0)	0.024	6 (17.6)	4 (2.4)	0.001

Data are presented as median (quartile 25%–quartile 75%) or n (%). Percentages may not total 100 because of rounding. ACEi, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment. [a] BMI is in kilograms divided by the square of the height in meters.

before undergoing a final assessment for clinical and biological plausibility. Missingness among continuous predictors was present in less than 5% of the patients; thus, these values were imputed using the median value. Subsequent sensitivity to missingness was performed using multiple imputations. The Cox proportional hazard model was used to analyze the effect of AKI and RRT on 28- and 60-day mortality. Time from ICU admission until death at 28- and 60-day was presented as Kaplan-Meier plots. All analyses were conducted in R v.3.6.3 (R Foundation) [17], and significance level was set at 0.05.

Results

A total of 207 patients with COVID-19 admitted to the ICU were evaluated. Six patients on chronic hemodialysis were excluded. Of the remaining 201 patients, 123 (61%) were males with a median age of 64 years (IQR, 52–80) Table 1.

Baseline Cr was available prior to admission in 103 patients (52%). Baseline estimated glomerular filtration rate

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Table 2. Laboratory tests results according to the development of AKI or the need for RRT

	Overall (n = 201)	AKI (n = 101)	Non-AKI (n = 100)	p value	RRT (n = 34)	Non-RRT (n = 167)	p value
Kidney function							
Baseline Cr, mg/dL	0.85 (0.7–1)	0.90 (0.75–1.20)	0.80 (0.68–0.90)	<0.001	1.02 (0.89–1.34)	0.80 (0.66–0.93)	<0.001
Baseline eGFR, mL/min/1.73 m²	89.9 (72.53–105.92)	78.71 (57.98–98.33)	96.75 (83.82–116.31)	<0.001	70.43 (48.64–86.03)	93.19 (76.58–109.98)	<0.001
Cr at hospital admission, mg/dL	0.98 (0.8–1.25)	1.20 (0.90–1.50)	0.86 (0.75–1.00)	<0.001	1.33 (1.10–1.62)	0.91 (0.78–1.13)	<0.001
Cr at ICU admission, mg/dL	0.98 (0.78–1.28)	1.27 (0.93–1.64)	0.85 (0.70–1.00)	<0.001	1.64 (1.33–2.27)	0.90 (0.75–1.17)	<0.001
Highest Cr during ICU admission, mg/dL	1.16 (0.88–1.8)	1.80 (1.34–2.90)	0.90 (0.78–1.07)	<0.001	3.31 (2.44–4.63)	1.05 (0.85–1.36)	<0.001
Urine change, n (%)	49 (24.4)	35 (81.4)	14 (50.0)	0.011	11 (84.6)	38 (65.5)	0.311
Hematuria	35 (17.4)	25 (58.1)	10 (35.7)	0.109	9 (69.2)	26 (44.8)	0.199
Leukocyturia	26 (12.9)	20 (46.5)	6 (21.4)	0.058	7 (53.8)	19 (32.8)	0.268
Proteinuria	38 (18.9)	30 (69.8)	8 (28.6)	0.002	11 (84.6)	27 (46.6)	0.029
Laboratory test at ICU admission							
Hemoglobin, g/dL	12.9 (11.5–14)	12.5 (11.3–13.9)	13.0 (11.9–14.3)	0.266	11.8 (10.8–13.8)	12.9 (11.7–14.1)	0.129
White blood cell count, cells/mm³	6,815 (4,730–8,782.5)	7,210 (4,910–9,960)	6,590 (4,380–8,300)	0.14	7,580 (5,580–9,960)	6,670 (4,625–8,455)	0.141
Lymphocytes, cells/mm³	873.5 (627.5–1,255)	828 (597–1,161)	945 (691–1,264)	0.074	826 (498–1,040)	910 (689–1,257)	0.075
Lymphopenia, n (%)*	118 (58.7)	67 (69.1)	51 (53.7)	0.041	24 (72.7)	94 (56.2)	0.197
Platelets, ×10³ cells/mm³	179 (150–237)	172 (134–235)	185 (159–239)	0.052	183 (146–237)	177 (151–239)	0.701
D-dimer, ng/mL	824 (488–1,245.75)	876.5 (557.5–1,592.0)	685.0 (420.5–1,136.0)	0.009	1,359.0 (838.0–2,236.0)	688.0 (451.5–1,136.0)	<0.001
Ferritin	947 (565.75–1,800.75)	1,091 (616–2,080)	869 (544–1,696)	0.435	1,803 (1,016–3,577)	884 (560–1,625)	0.085
Lactate dehydrogenase	346 (287–442)	354 (292.0–465.0)	341.0 (287.0–424.0)	0.225	376.0 (326.0–495.0)	340.5 (275.8–424.5)	0.043
CRP, mg/dL	97.2 (52.2–158)	104.1 (63.6–194.0)	83.7 (40.4–143.2)	0.012	168.8 (107.0–230.5)	86.3 (49.9–142.5)	<0.001
Pro-calcitonin	0.22 (0.11–0.48)	0.29 (0.14–0.76)	0.15 (0.07–0.22)	0.02	0.55 (0.23–1.70)	0.17 (0.08–0.28)	0.006
Cr phosphokinase	78 (49–161)	86 (49.5–207.0)	69 (49.0–288.0)	0.414	86.0 (66.0–288.0)	76.0 (46.0–142.0)	0.307
Sodium, mEq/L	138 (135–140)	138 (135–140)	138 (135–141)	0.255	137 (135–140)	138 (135–140)	0.718
Potassium, mEq/L	4.05 (3.8–4.4)	4.2 (3.8–4.5)	4.0 (3.8–4.3)	0.046	4.0 (3.6–4.4)	4.1 (3.8–4.4)	0.786
Ionized calcium	1.14 (1.1–1.18)	1.14 (1.10–1.18)	1.16 (1.12–1.19)	0.143	1.15 (1.10–1.18)	1.14 (1.10–1.18)	0.734
Phosphate, mEq/L	3.5 (2.9–4.2)	3.7 (3.0–4.4)	3.4 (2.8–3.9)	0.127	4.2 (3.7–5.0)	3.3 (2.6–3.8)	<0.001
Magnesium, mEq/L	1.7 (1.5–1.8)	1.6 (1.5–1.8)	1.7 (1.6–1.9)	0.002	1.6 (1.5–1.8)	1.7 (1.6–1.8)	0.294
Urea, mg/dL	30 (22–43.5)	39.0 (26.0–65.0)	27.0 (20.0–34.5)	<0.001	44.0 (33.0–68.0)	28.0 (22.0–40.0)	<0.001
Aspartate transaminase, U/L	34.5 (25.25–51)	44.0 (28.0–60.0)	33.0 (24.0–46.0)	0.081	61.0 (44.0–69.0)	31.5 (22.0–46.8)	<0.001
Alanine transaminase, U/L	30.5 (22–48)	31.0 (23.0–45.0)	29.0 (18.0–55.0)	0.924	37.0 (23.5–49.0)	28.5 (22.0–47.2)	0.274
Bilirubin, mg/dL	0.4 (0.2–0.5)	0.4 (0.3–0.6)	0.3 (0.2–0.5)	0.014	0.5 (0.4–0.6)	0.3 (0.2–0.5)	0.002
Interleukin-6	127.1 (55–356.8)	226.9 (81.0–776.0)	89.0 (28.6–140.8)	0.005	776.0 (335.9–981.3)	105.6 (35.6–160.8)	<0.001
Arterial blood gas							
pH	7.41 (7.37–7.45)	7.40 (7.35–7.44)	7.43 (7.39–7.46)	0.001	7.37 (7.32–7.42)	7.42 (7.38–7.46)	<0.001
PaO₂, mm Hg	70.2 (38.2–108.7)	73.0 (41.2–115.5)	58.9 (37.1–101.2)	0.252	80.9 (42.6–124.5)	68.1 (37.9–101.8)	0.21
PaCO₂, mm Hg	38.25 (33.7–44.2)	39.4 (34.2–44.6)	36.8 (33.0–43.6)	0.143	40.0 (37.3–44.7)	37.6 (32.8–43.5)	0.028
HCO₃, mEq/L	23.9 (22.1–25.8)	23.6 (21.6–25.6)	24.6 (22.9–26.2)	0.059	23.3 (21.2–24.7)	24.4 (22.2–25.8)	0.068
Base excess, mEq/L	0.2 (−1.7 to 1.6)	−0.2 (−2.8 to 1.0)	0.6 (−0.6 to 1.8)	0.002	−0.9 (−4.2 to 0.2)	0.4 (−1.5 to 1.7)	0.002
Lactate, mg/dL	12.0 (10–16)	12.0 (10.0–16.0)	12.0 (9.0–16.0)	0.795	12.0 (10.0–12.8)	13.0 (9.8–17.0)	0.288

AKI, acute kidney injury; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; CRP, C-reactive protein. *Lymphocyte count <1,000 cells/mm³.

Table 3. Nephrology processes of care

	AKI (n = 101)	Non-AKI (n = 100)	p value	RRT (n = 34)	Non-RRT (n = 167)	p value
AKI KDIGO stage, n (%)						
1	43 (42.6)	–	–	0 (0.0)	43 (64.2)	<0.001
2	19 (18.8)	–	–	0 (0.0)	19 (28.3)	
3	39 (38.6)	–	–	34 (100)	5 (7.5)	
Nephrology process of care						
Days from ICU admission to nephrology	3.0 (2.0–7.0)	–	–	3.0 (3.0–7.0)	2.0 (2.0–9.5)	0.427
Days from ICU admission to RRT	–	–	–	3.5 (3.0–7.0)	–	–
Days from IMV to RRT	–	–	–	3.0 (2.0–5.75)	–	–
Days from AKI to RRT	–	–	–	2.0 (1.0–5.0)	–	–
Days from nephrology to RRT	–	–	–	0.0 (0.0–0.0)	–	–
CVVHDF modality, n (%)	–	–	–	33 (97.0)	–	–
Change of modality during treatment, n (%)	–	–	–	14 (53.8)	–	–
Days in the ICU using RRT	–	–	–	15.0 (10.0–24.0)	–	–
Days in the hospital using RRT	–	–	–	22.0 (10.0–29.0)	–	–

Data are presented as median (quartile 25%–quartile 75%) or n (%). Percentages may not total 100 because of rounding. AKI, acute kidney injury; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy; IMV, invasive mechanical ventilation; CVVHDF, continuous venovenous hemodiafiltration.

Table 4. Multivariable model after multiple imputation for AKI

	Odds ratio (95% CI)	p value
Baseline and severity of illness		
Age	0.88 (0.43–1.81)	0.734
SAPS3	1.67 (0.71–3.92)	0.237
Comorbidities		
Charlson Comorbidity Index	1.24 (0.76–2.00)	0.387
Hypertension	1.57 (0.66–3.70)	0.303
Drugs and support at ICU admission		
Use of lopinavir-ritonavir	1.99 (0.55–7.21)	0.290
Use of invasive ventilation	7.60 (1.37–42.05)	0.020
Use of vasopressor	0.58 (0.12–2.73)	0.490
Use of steroids	1.41 (0.61–3.23)	0.420
Use of diuretic	4.14 (1.27–13.49)	0.019
Laboratory tests at ICU admission		
Lymphopenia	1.20 (0.51–2.82)	0.667
Baseline Cr	2.50 (1.33–4.69)	0.005
D-dimer	1.22 (0.70–2.14)	0.471
CRP	0.78 (0.49–1.23)	0.280

CI, confidence interval; AKI, acute kidney injury; SAPS, Simplified Acute Physiology Score; ICU, intensive care unit; CRP, C-reactive protein.

AKI Characteristics

AKI was diagnosed in 50.2% (n = 101) of all patients, and the median age was 73 years (IQR, 56.0–84.0). Forty-three (42.6%) patients were stratified as stage 1; 19 (18.8%), stage 2; and 39 (38.6%), stage 3 AKI. Their processes of care are shown in Table 3.

After adjustment in a multivariable analysis, the development of AKI was independently associated with diuretic use, IMV, and higher baseline Cr (Table 4; online suppl. Tables 1–3; for all online suppl. material, see www.karger.com/doi/10.1159/000513425). AKI was developed in 80% (70/87) of the patients who required IMV. The median time between the beginning of IMV and the diagnosis of AKI was 1 day (IQR, 0–1). Seventy-two percent of patients were diagnosed with AKI during the first day of IMV.

Among survivors, patients with AKI remained on IMV longer (10.5 [6.5–16.8] vs. 6 [6–9] days; p < 0.001). The clinical outcomes according to the development of AKI are shown in Table 5. In online suppl. Figures 1 and 2, time until hospital and ICU discharge are presented as Kaplan-Meier curves, respectively.

Dialysis Characteristics

Thirty-four percent of the 101 AKI patients received RRT. After adjustment on multivariable analysis, higher C-reactive protein (CRP) and baseline Cr were associated with RRT requirement (Table 6; online suppl. Tables

was lower in patients with AKI than in those without (78.71 [57.98–98.33] vs. 96.75 [83.82–116.31], p < 0.001). Incidence of proteinuria was higher in AKI patients (69.8 vs. 28.6%, p = 0.002) The results are presented in Table 2.

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Table 5. Clinical outcomes according to the development of AKI or the need for RRT

	AKI (n = 101)	Non-AKI (n = 100)	Unadjusted effect estimate (95% CI)	p value	Adjusted effect estimate (95% CI)*	p value
Renal outcomes						
Cr at discharge, mg/dL	1.00 (0.87–1.46)	0.90 (0.72–1.00)	0.15 (−0.05 to 0.34)[a]	0.139	0.73 (0.22–1.24)[a]	0.037
Clinical outcomes						
ICU mortality, n (%)	21 (20.8)	5 (5.0)	5.00 (1.93–15.50)[b]	0.002	2.81 (0.93–9.97)[b]	0.081
Hospital mortality, n (%)	22 (21.8)	5 (5.0)	5.29 (2.06–16.37)[b]	0.001	3.06 (1.01–10.94)[b]	0.059
28-day mortality, n (%)	18 (17.8)	5 (5.0)	3.72 (1.38–10.04)[c]	0.009	1.72 (0.62–4.78)[c]	0.301
60-day mortality, n (%)	24 (23.8)	5 (5.0)	5.11 (1.95–13.40)[c]	<0.001	2.79 (1.04–7.49)[c]	0.04
Duration of ventilation in survivors, days	10.5 (6.5–16.8)	6.0 (3.0–9.0)	5.22 (2.18–8.26)[a]	<0.001	6.52 (1.60–11.44)[a]	0.009
ICU length of stay, days	13.5 (5.2–25.0)	5.0 (3.0–8.0)	0.36 (0.26–0.51)[d]	<0.001	0.44 (0.31–0.62)[d]	<0.001
Hospital length of stay, days	18.0 (12.8–32.2)	10.0 (6.5–14.0)	0.31 (0.22–0.44)[d]	<0.001	0.38 (0.27–0.55)[d]	<0.001

	RRT (n = 34)	Non-RRT (n = 166)	Unadjusted effect estimate (95% CI)	p value	Adjusted effect estimate (95% CI)*	p value
Renal outcomes						
Cr at discharge, mg/dL	3.50 (2.00–4.34)	0.90 (0.77–1.06)	2.53 (0.94–4.11)[a]	0.002	2.53 (1.02–4.05)[a]	0.001
RRT at hospital discharge	1/9 (11.1)	–	–	–	–	–
Clinical outcomes						
ICU mortality, n (%)	12 (35.3)	14 (8.4)	5.92 (2.41–14.54)[b]	<0.001	4.39 (1.56–12.49)[b]	0.005
Hospital mortality, n (%)	12 (35.3)	15 (9.0)	5.49 (2.25–13.32)[b]	<0.001	3.98 (1.42–11.15)[b]	0.008
28-day mortality, n (%)	7 (20.6)	16 (9.6)	2.27 (0.93–5.51)[c]	0.071	1.11 (0.41–2.96)[c]	0.836
60-day mortality, n (%)	12 (35.3)	17 (10.2)	3.75 (1.79–7.85)[c]	<0.001	2.21 (1.01–4.85)[c]	0.047
Duration of ventilation in survivors, days	17.0 (11.8–36.8)	6.0 (4.5–11.0)	12.78 (2.72–22.83)[a]	0.012	12.91 (6.67–19.15)[a]	<0.001
ICU length of stay, days	29.0 (19.5–37.0)	6.0 (3.0–11.0)	0.23 (0.15–0.35)[d]	<0.001	0.26 (0.17–0.40)[d]	<0.001
Hospital length of stay, days	33.0 (30.0–40.0)	12.0 (8.0–17.0)	0.20 (0.12–0.35)[d]	<0.001	0.20 (0.12–0.35)[d]	<0.001

Data are presented as median (quartile 25%–quartile 75%) or n (%). Percentages may not total 100 because of rounding. CI, confidence interval; AKI, acute kidney injury; ICU, intensive care unit; RRT, renal replacement therapy. * All models are adjusted by SAPS3 and Charlson Comorbidity Index. [a] Effect estimate is median difference from a quantile regression with $T = 0.50$ and results estimated with bootstrap with 1,000 resamples. [b] Effect estimate is odds ratio from a generalized linear model with a binomial distribution. [c] Effect estimate is hazard ratio from a Cox proportional hazard model. [d] Effect estimate is subdistribution hazard ratio from a Fine-Gray competing risk model.

4–6). CVVHDF was the initial modality used in 97% of patients, who remained on RRT for a median of 15 days (IQR 10–24) during ICU stay (Table 3). The delivered dialysis dose of CVVHDF and the filtration fraction during the first 7 days of therapy were 36.7 mL/kg/h (32.2–37.9) and 21.7% (18.8–23.1), respectively. A simple analysis showed no significant difference in the delivered dialysis dose between the survivors and those who died: 36.8 (32.1–38.0) and 35.0 (33.7–37.7) mL/kg/h, respectively, $p = 0.710$. The median of water balance in the first 7 days of CRRT showed no significant difference between those who died and the survivors, 1.99 and 2.28 L,

respectively, $p = 0.488$. The filter life span was 80.0 h (47.6–94.0). 161 filters were used. The main reasons for stopping the filter circuit were as follows: scheduled change ($n = 78$, 48.4%), early filter coagulation ($n = 36$, 22.4%), change of dialysis modality or recovery of kidney function ($n = 25$, 15.5%), technical problems ($n = 7$, 4.3%), for tests or procedures, ($n = 5$, 3.1%), and death or palliative care ($n = 10$, 6.2%).

All patients receiving RRT were on IMV. Additional clinical outcomes according to the use of RRT are shown in Table 5. Figure 1 shows the time from onset of symptoms to AKI and RRT.
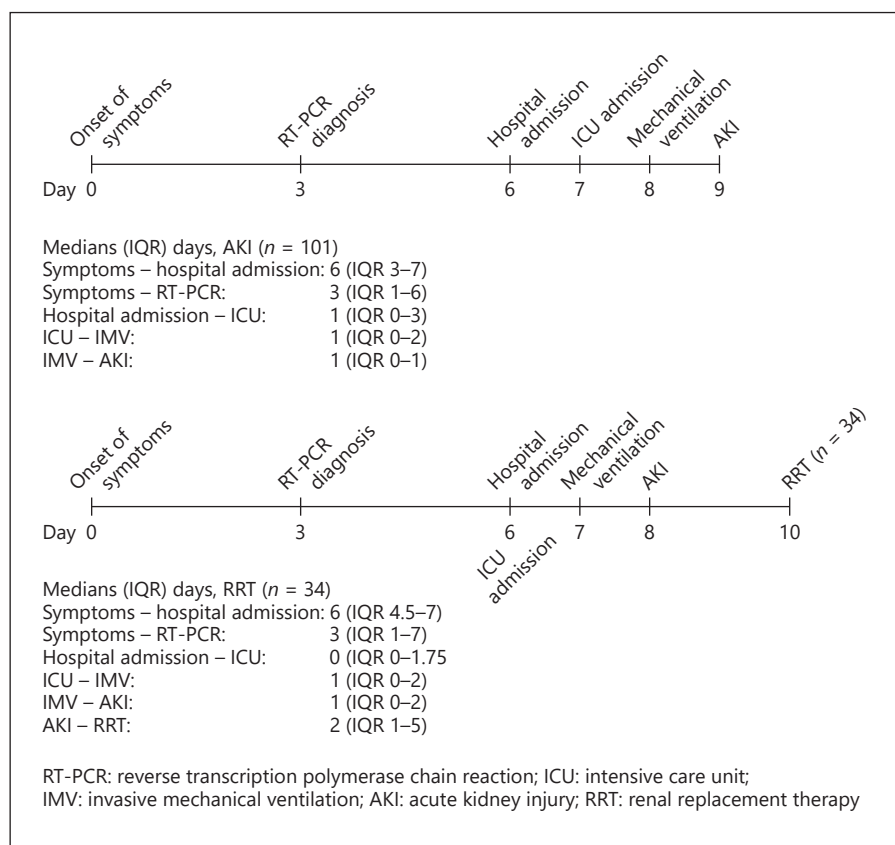
Fig. 1. AKI and RRT timelines: the time from onset of symptoms to AKI or RRT.

Table 6. Multivariable model after multiple imputation for RRT

	Odds ratio (95% CI)	p value
Baseline and severity of illness		
SAPS3	1.13 (0.57–2.23)	0.730
Comorbidities		
Charlson Comorbidity Index	1.17 (0.67–2.04)	0.574
Drugs and support at ICU admission		
Use of lopinavir-ritonavir	1.87 (0.49–7.09)	0.357
Use of vasopressor	55.20 (4.52–674.59)	0.002
Use of diuretics	1.88 (0.25–14.00)	0.536
Laboratory tests at ICU admission		
Cr	2.90 (1.56–5.38)	0.001
D-dimer	1.42 (0.94–2.14)	0.099
CRP	1.96 (1.04–3.70)	0.037

RRT, renal replacement therapy; CI, confidence interval; SAPS, Simplified Acute Physiology Score; ICU, intensive care unit; CRP, C-reactive protein.

Mortality

Overall 60-day mortality rate was 14.4% ($n = 29$). For AKI patients, the rate was 23.8% ($n = 24$) versus 5% ($n = 5$) for the non-AKI group (HR 2.79 [1.04–7.49], $p = 0.040$). The 60-day mortality rate in the RRT group was 35.3% ($n = 12$) versus 10.2% ($n = 17$) in the non-RRT group (HR 2.21 [1.01–4.85], $p = 0.047$). Survival curves are shown in Figure 2 and online suppl. Figure 3. The main causes of death were respiratory failure 51.7% ($n = 15$), shock 17.2% ($n = 5$), cardiovascular disease 17.2% ($n = 5$), and sepsis 13.8% ($n = 4$).

Discussion

Key Findings

In ICU patients with COVID-19, AKI occurred in half of cases and was associated with baseline serum Cr level, use of IMV, and use of diuretics. In patients with more severe AKI (stage 3D), baseline serum Cr levels and higher blood levels of CRP at ICU admission were associated with requiring RRT. In the AKI group, the duration of
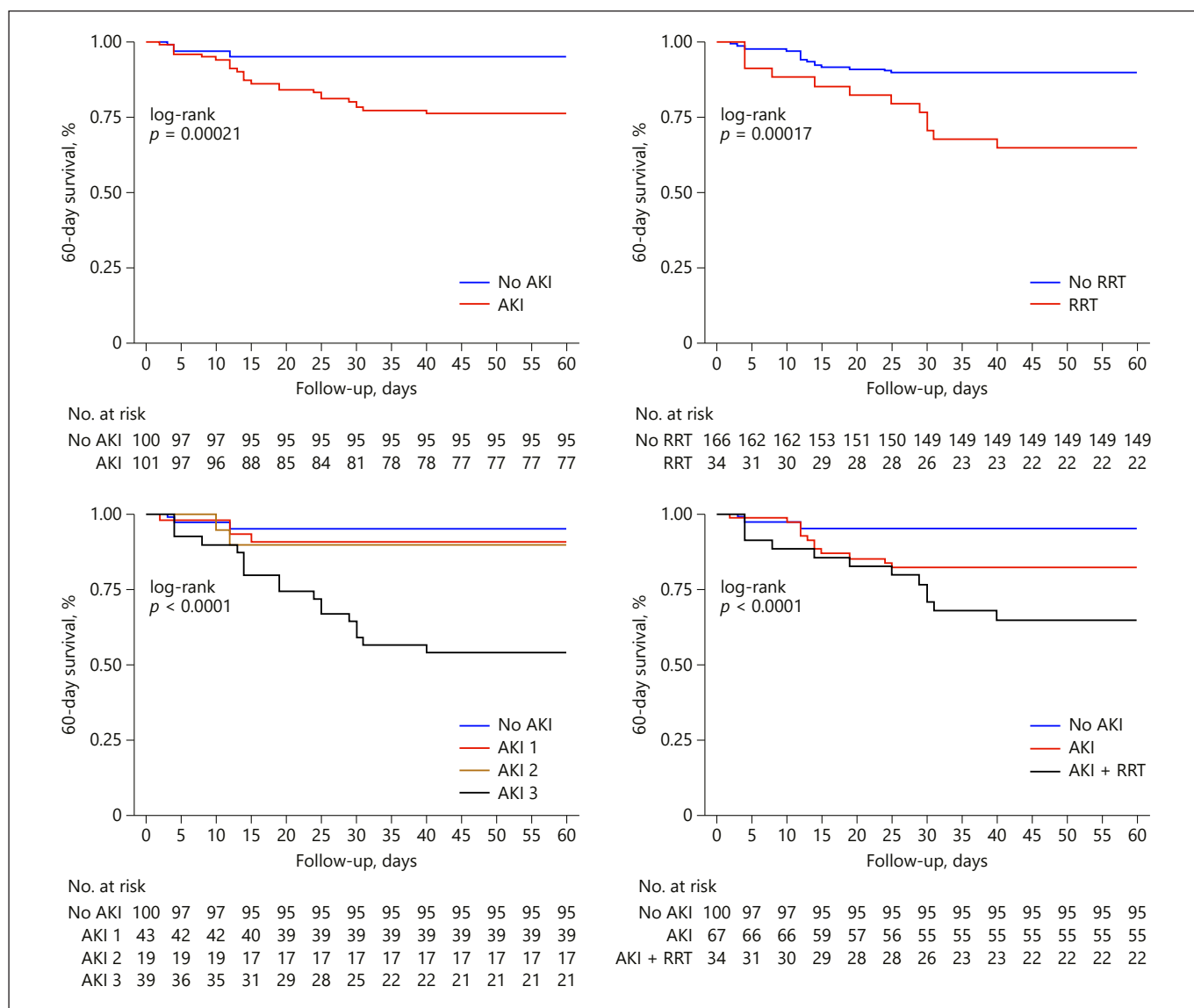
Fig. 2. Kaplan-Meier curve showing 60-day survival. AKI, acute kidney injury; RRT, renal replacement therapy.

IMV was prolonged, and the length of stay in ICU and in hospital was longer. AKI and RRT were independent risk factors for 60-day mortality.

Relationship to Previous Findings

AKI in the context of COVID-19 has been subject to several previous studies. Cheng et al. [9] found an AKI rate of 5.1%. Lim et al. [18] reported an AKI incidence of 18.3% in hospitalized patients; among these, 37.5% were classified as stage 1. Hirsch et al. [3] showed that the incidence was even higher (36.6%), and the majority was in stage 1 (46.5%). Our study exclusively enrolled patients in

the ICU, and the incidence of AKI was 50%. About 40% of these developed the mildest form (stage 1 AKI). Another initial small report of only 21 ICU patients demonstrated that 19% had AKI [11]. Recently, Gupta et al. [19] observed an incidence rate of 42.8% (restricted to stage 2 and 3) in 2,215 patients with COVID-19 admitted to ICU.

COVID-19 patients may also present with hematuria and proteinuria, suggesting inflammation and glomerular endothelial damage as an additional event in the genesis of AKI [12, 20, 21]. Our study shows that patients who have AKI also had a higher incidence of proteinuria. However, few patients had urinalysis available at the ICU

admission and many had conditions associated with proteinuria (diabetes, hypertension, and obesity).

In the current study, 72% of patients were diagnosed with AKI in the first 24 h of mechanical ventilation and IMV increased the risk of having AKI by almost 8-fold. This link has also been observed elsewhere [3]. In a cohort that evaluated only patients on mechanical ventilation, AKI occurred in 75% of patients [22]. In our study, AKI developed in 80% of mechanically ventilated patients. In a systematic review and meta-analysis, van den Akker et al. [23] showed that IMV increased the odds for AKI by 3 times. Despite the difficulty of dissociating the effects of the lung infectious/inflammatory disease on kidney function, several studies suggest that IMV may induce or worsen AKI [7, 24] and several mechanisms have been proposed to explain this association [25, 26].

In our study, the use of a loop diuretic was associated with AKI. Studies using diuretics, especially furosemide, in patients at risk for or with overt AKI have presented mixed results [27, 28]. In the current study, we could not ascertain the cause and effect relationship between the use of diuretic and AKI.

Higher baseline Cr was associated with AKI in this analysis. Multiple mechanisms present in CKD make critically ill patients more prone to AKI, including inflammation, oxidative stress, and changes in microcirculation [29]. A postmortem histopathology study showed mild to severe arterionephrosclerosis, diabetic nephropathy, and features suggestive of acute tubular injury in a case series of fatal COVID-19 infections. Furthermore, some of these patients had AKI during hospital admission [30]. These findings suggest that acute injury-on-CKD may also be connected in patients with COVID-19.

Seventeen percent of overall patients required RRT. RRT was applied in 34% of patients with AKI and in 39% of those on IMV. According to Hirsch et al. [3], 5.2% of hospitalized patients with COVID-19 received RRT. Among patients with AKI, 14.6% underwent dialysis and, of those on dialysis, 96.8% were on ventilators [4]. Cummings et al. [31] analyzed 257 critically ill patients with COVID-19 and reported 31% on RRT. In the study by Gupta et al. [19], the need for dialysis was 20.1%. Fominskiy et al. [22] evaluated patients with COVID-19 on mechanical ventilation and showed that 17.7% of patients required dialysis. Thus, AKI stage 3D seems to be common in patients with COVID-19, especially in those on ventilatory support.

AKI could be a consequence of uncontrolled inflammation in COVID-19 patients [18, 22]. CRP blood level at ICU admission was an independent risk factor for dialysis-requiring AKI in our cohort. Thus, high CRP levels could identify patients more prone to organ dysfunction, including kidney failure. High CRP level was associated with AKI in other diseases as well [32–34].

AKI and RRT mortality rates in our analysis were lower compared to other studies [19, 25, 35]. Differences in admission policies, length of follow-up, learnings from the experience of the first centers to suffer from COVID-19 outbreaks, and differences in population or in the prevalence of comorbidities make these comparisons difficult. In our cohort of patients, AKI and RRT were independent risk for 60-day mortality. Two meta-analysis also showed AKI was associated with increased risk of mortality in COVID-19 patients [35, 36]. On the other hand, other studies have not shown AKI as a risk factor for death in COVID-19 [31, 37]. Like other diseases, AKI in COVID-19 patients seems to be associated with adverse outcomes and its awareness must be highlighted.

Study Implications

Our data confirm that AKI is a concern in patients with COVID-19 admitted to the ICU. Moreover, AKI develops temporally after the onset of IMV and its most severe stage is associated with baseline kidney dysfunction and signs associated with inflammation such as increased level of CRP. Finally, our findings provide important prognostic information regarding survival, time in ICU, time in hospital, and recovery of renal function in these patients.

Strengths and Limitations

To the best of our knowledge, this is the first report on AKI in critically ill patients from Brazil, currently one of the epicenters of the COVID-19 pandemic. It was possible to track the clinical course of the COVID-19 from the beginning of the first symptoms to the onset of RRT. During the follow-up and after the mortality analysis, we were able to verify a definitive primary outcome, 60-day mortality, in 100% of the events of our cohort and report on renal recovery.

Limitations exist as this is a single-center study and could include selection bias and limited external validity. However, it brings some useful information for professionals committed to the treatment of patients with COVID-19. ICU admission and discharge policies may differ between centers. However, the ICU multidisciplinary team developed a protocol comprising well-defined criteria for ICU admission. In 48% of the cases, we did not have a baseline Cr value and using the lowest value during hospitalization may have overestimated the incidence of

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AKI [13]. There is some controversy in using baseline Cr (independent variable) as a risk factor for AKI (dependent variable) since the definition of AKI requires this variable. However, multiple previous studies have assessed the role of pre-illness Cr as a predictor of AKI [38–42]. Finally, because this is an observational study, no cause and effect relationship can be inferred.

In conclusion, we found that in ICU-admitted COVID-19 patients, the occurrence of AKI was common and temporally associated with IMV. Patients with high levels of CRP, perhaps presenting a greater inflammatory state, presented with the most severe form of AKI. AKI and RRT were independent risk factors for 60-day mortality.

Appendix

COVID-19 ICU Treatment Protocol
Briefly, the criteria for admission to the ICU included at least one of the following: supplemental oxygen (nasal oxygen catheter >3.0 L/min) to keep pulsed oximetry oxygen saturation (SpO_2) levels >94% or the respiratory rate ≤24 bpm; noninvasive ventilation to keep SpO_2 >94% or respiratory rate ≤24 bpm; acute respiratory failure treated with IMV; hemodynamic instability or shock, defined as arterial hypotension (systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg), or signs of poor organ or peripheral perfusion (altered consciousness, oliguria, lactate ≥2 mmol/L, among others), with or without the use of vasopressors; sepsis with arterial hypotension, need for vasopressor or lactate ≥4 mmol/L; or septic shock according to Sepsis-3 criteria.

In patients who required endotracheal intubation, the initial ventilatory parameters were the following: mode (pressure-controlled ventilation), tidal volume (6 mL/kg of predicted body weight), positive end-expiratory pressure (PEEP) of 15 cm H_2O, respiratory rate of 20–24 per minute to keep the minute volume between 7 and 10 L per minute, driving pressure (plateau pressure [PEEP]) of 15 cm H_2O, initial target of SpO_2 between 92 and 96%, and end-tidal carbon dioxide ($EtCO_2$) between 30 and 45 mm Hg. An arterial blood gas analysis was collected 1 hour after endotracheal intubation for adjustments of the initial mechanical ventilation parameters. If partial arterial pressure of oxygen to fractional inspired oxygen ratio (PaO_2/FiO_2) was <200, a recruitment maneuver was performed (with PEEP of 25 cm H_2O and driving pressure of 15 cm H_2O for 5 min) and PEEP was adjusted to 18 cm H_2O. If necessary, PEEP was adjusted to a maximum of 20 cm H_2O. If PaO_2/FiO_2 remained <200, then the patient was placed in a prone position.

Hemodynamic management (fluids, vasopressors, and inotropes) aimed to maintain an average blood pressure of 65 mm Hg and proper tissue perfusion parameters. If at least 2 of the following markers were present (lactate >18 mg/dL, GapCO$_2$ >6 mm Hg, and capillary refill time >3 s), cardiac output was monitored. Invasive blood pressure monitoring by arterial cannulation and a central venous catheter placement were used in patients receiving noradrenaline at a dose >0.1 mcg/kg/min. If noradrenaline dose is >0.5 mcg/kg/min, adrenaline 0.01 mcg/kg/min was started. Hydrocortisone continuous infusion of 200 mg was used if norepinephrine was >0.2 mcg/kg/min at the end of 6 h of resuscitation.

After 48 h of IMV, maintenance of null or negative fluid balance was suggested using furosemide, if necessary. If there was an increase in the need for vasopressors or changes in tissue perfusion markers, clinical and laboratory signs suggestive of hypovolemia, null or positive fluid balance was advised.

At that time, the use of hydroxychloroquine at a dose of 400 mg every 12 days and azithromycin 500 mg once daily for 10 days, was recommended. Pantoprazole 40 mg once daily and unfractionated heparin 5,000 IU subcutaneously 3 times daily were used as prophylaxis for stress ulcers and venous thromboembolism, respectively. Ceftriaxone or ceftaroline were used as first-line antibiotic therapy when a bacterial infection was suspect.

Statement of Ethics

A local Ethics Committee reviewed and approved this study (CAAE 30525320.0.0000.0071). All procedures were performed in accordance with the World Medical Association's Declaration of Helsinki. Informed consent was obtained from all patients using the appropriate emergency consent mechanisms.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

M.S.D. designed and coordinated the study. M.P.D., F.R.T.C., and B.G.B. collected data. A.S.N. did statistical analysis. M.P.D., F.R.T.C., P.F.S., R.B., A.S.N., and M.S.D. did analysis and interpretation of data. M.P.D., F.R.T.C., P.F.S., and M.S.D. drafted the manuscript. P.F.S., T.N.M., A.L.A., B.C.S., F.D.C., T.D.C., L.J.R.F., B.F.C.S., V.G.P., M.C.B., J.C.M.M., O.F.P.S., R.B., and M.S.D. made contributions to literature search and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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