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ORIGINAL ARTICLE

Severe acute kidney injury in critically ill COVID-19 patients

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Abstract

Background Acute kidney injury (AKI) is frequent in Coronavirus Infection Disease 2019 (COVID-19) patients. Factors associated with AKI in COVID-19 intensive care unit (ICU) patients and their outcomes have not been previously explored.

Methods Prospective observational study of COVID-19 patients admitted to the ICUs of the Hospital Clínic of Barcelona (Spain), from March 25th to April 21st, 2020, who developed AKI stage 2 or higher (AKIN classification). The primary goal was to describe the characteristics of moderate-severe AKI of COVID-19 patients in an ICU context. As a secondary goal, we aimed to find independent predictors of AKI progression, Renal Replacement Therapy (RRT) requirement and mortality among these patients.

Results During the study period, 52 out of 237 ICU patients, developed AKIN stage 2 or higher and were included in the study. A Sequential Organ Failure Assessment (SOFA) score at AKI diagnosis of 8 or higher was associated with RRT, OR 5.2, p 0.032. At the time of AKI diagnosis, patients had a worse liver profile and higher inflammation markers than at admission. Fifty per cent of the patients presented AKI progression from AKIN 2 to 3 and 28.85% required RRT. The use of corticosteroids in 69.2% of patients was associated with a reduced requirement of RRT, OR 0.13 (CI 95% 0.02–0.89), p 0.037. AKI was associated with high mortality (50%) and a longer hospital stay, median 35 vs 18 days (p 0.024).

Conclusions The prevalence of moderate/severe AKI in COVID-19 patients admitted to the ICU is high and has a strong correlation with mortality and length of hospital stay.

Keywords COVID-19 · Acute kidney injury · Intensive care · Renal replacement therapy

Introduction

The outbreak of the new Coronavirus Infection Disease 2019 (COVID-19) has rapidly evolved into a global pandemic with devastating consequences [1, 2]. On May 20th, 2020, Spain had 232,555 patients affected by COVID-19 and ranked 5th in the world for most positive cases [3]. At the Hospital Clínic of Barcelona, the first case was detected on February 25th, and from then until May 21st, 2,418 patients were admitted to the institution, of whom, 444 (18.36%) required intensive care unit (ICU) admission.

COVID-19 patients predominantly develop respiratory symptoms, and in some patients, it evolves to acute respiratory distress syndrome (ARDS) or multi-organ failure, including kidney injury [3]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infects the host using the angiotensin-converting enzyme 2 receptor (ACE2) that is expressed in several organs, including the kidney [4–7]. Acute kidney injury (AKI) is frequent in COVID-19; reports from China, Italy, and the USA found a rate of AKI that ranges widely from 0.5 to 36.6% in hospitalized patients,

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and it portends poor prognosis [8–16]. As for critically ill patients, the described incidence was 19–23% [17, 18].

Several contributors have been proposed in the pathogenesis of AKI in patients with COVID-19: immunologic injury associated with inflammatory response, direct cytotoxicity over endothelial and tubuloepithelial cells and podocytes, microthrombi and thrombotic microangiopathy, or cardiorenal syndrome due to right ventricular failure may be present [19, 20].

Factors associated with AKI in COVID-19 ICU patients and their outcomes have not been previously explored. The objective of our study is to describe the characteristics of moderate-severe AKI in the ICU context. As a secondary objective, we attempted to find independent predictors of AKI progression to renal replacement therapy (RRT) requirement and mortality.

Methods

This is a prospective observational study. SARS-CoV-2 infection was diagnosed by reverse transcription-quantitative PCR (RT-PCR) assay of nasopharyngeal swab specimens. We included all the patients with COVID-19 who developed AKI ≥ 2 according to AKIN classification [21], and who were admitted to the ICUs of the Hospital Clínic of Barcelona (Spain) from March 25th to April 21st, 2020. The exclusion criteria were: chronic dialysis treatment, kidney transplant, or chronic kidney disease (CKD) KDIGO stage 4 (estimated glomerular filtrate rate (eGFR) less than 30 ml/min) [22]. The patients were followed-up until discharge from hospital, death, or the last follow-up day (July 15th, 2020).

Demographic variables, including Body Mass Index (BMI), date of illness onset and symptoms, vital signs, blood test studies and Sequential Organ Failure Assessment (SOFA) score (at hospital admission, at AKI stage 2 diagnosis, and at RRT start), use of vasoactive drugs, pharmacological treatments received, use of mechanical ventilation, RRT characteristics, urinary output at AKI stage 2, date of RRT start, date of ICU/hospital discharge and mortality were recorded. Comorbidities, which included cardiovascular disease, current or previous history of smoking, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV) infection, and presence of active neoplasm, were also assessed, as were angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) treatment at baseline. The suspected cause of AKI was evaluated; COVID-19-related AKI was considered if no other explanation was evident or suspected after diagnostic workup. RRT indication, modality and dose were based on clinical judgment.

In general, patients with hemodynamic stability and use of vasopressors at a dose lower than 0.1 mcg/kg/min received intermittent hemodialysis, according to our protocol. The choice between continuous hemodialysis with medium cutoff or continuous hemodiafiltration was based on logistic criteria and the experience of each intensive care unit within the hospital.

AKI recovery was defined if last creatinine level was less than twice that at baseline.

Overall mortality and length of stay (LOS) among patients with COVID-19 diagnosis admitted to the ICU during the study period, and without exclusion criteria, were collected and compared with the cohort of patients with AKI.

Statistical analysis

Data were described as mean ± standard deviation (SD) if normally distributed, or median and interquartile range otherwise. Categorical variables were expressed as absolute and relative (%) frequencies. Group comparisons were made by Student's *t* test, Logistic regression, Fisher's exact *t* test or Mann–Whitney *U* test for independent groups when appropriate. Statistical associations were explored univariately, and all p values < 0.05 were included in the multivariate analysis. Statistical analyses were performed using IBM SPSS statistics V25.0 software (IBM Corp, Armonk, NY, USA). A two-sided p value ≤ 0.05 was used to indicate statistical significance.

Results

General characteristics

Two-hundred and thirty-seven patients with COVID-19 and without exclusion criteria required ICU admission. Fifty-two (21.4%) patients presented AKI ≥ 2 of the AKIN classification and were included in the study. The median follow-up was 35.5 (IQR 36.75) days. Table 1 summarizes the demographic and clinical characteristics of the patients at hospital admission.

Patients were mostly male (76.9%), with a median age of 71.5 (61–74.75) years. Regarding comorbidities, 73.08% of the patients presented at least one, with hypertension, diabetes and COPD being the most frequent (59.6%, 21.2% and 21.2%, respectively). Overweight was present in 17% of the patients, and 13.5% presented CKD stage 3. Twenty-one per cent of the patients (n = 11) were on treatment with ACEI, and 15.4% with ARBs at admission. Both antihypertensive drugs were discontinued in all patients at admission.

The median time from symptom onset to hospital and ICU admission were 7 (IQR 5) and 10 (IQR 4) days,

Table 1 Baseline characteristics of patients at hospital admission

	All patients (n = 52)
Age (years), median (IQR)	71.5 (13.75)
Sex (male)	40 (76.9%)
Comorbidities	
None	14 (26.9%)
Hypertension	31 (59.6%)
Diabetes	11 (21.2%)
Cardiac failure	2 (3.8%)
Ischemic heart disease	3 (5.8%)
BMI ≥ 30 kg/m^2	9 (17.3%)
COPD	11 (21.2%)
Active smoker	3 (5.8%)
Active cancer	3 (5.8%)
HIV infection	1 (1.9%)
CKD III	7 (13.5%)
Clinical characteristics at admission	
Fever	44 (84.6%)
Pneumonia	49 (94.25%)
Dyspnea	39 (75.5%)
FiO_2 (%), median (IQR)	35 (39)
$SatO_2$ (%), median (IQR)	95 (6)
PaO_2/FIO_2, mean ± SD	243 ± 155
SOFA, mean ± SD	5.78 ± 3.26
Days from onset to hospital admission, median (IQR)	7 (5)
Days from onset to ICU, median (IQR)	10 (4)
ACEIs	11 (21.2%)
ARBs	8 (15.4%)
Mean baseline creatinine (mg/dL), median (IQR)	0.96(0.43)
Median baseline eGFR CKD-EPI (ml/min), mean ± SD	76.52 ± 20

Median (IQR)/n(%)/mean ± SD

BMI Body Mass Index, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *CKD* chronic kidney disease, *ACEIs* angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *$PaFiO_2$* arterial blood oxygen pressure, *FiO_2* fraction of inspired oxygen, *MV* mechanical ventilation, *SOFA* Sequential Organ Failure Assessment score, *eGFR* Estimated Glomerular Filtration Rate

respectively. Pneumonia was present in 94.2% of cases, with a mean PaO_2/FiO_2 of 243 ± 155 mmHg, and a mean SOFA at admission of 5.78 ± 3.26.

Table 2 summarizes the laboratory findings. At the time of AKI diagnosis, patients had a worse liver profile, higher levels of D-dimer, procalcitonin, leukocytes, and platelets than at admission. C-Reactive Protein (CRP) levels were lower at AKI diagnosis compared to admission values. SOFA scores also showed a significant increase between admission and AKI diagnosis (5.79 ± 3.26 and 8.38 ± 2.43, respectively, $p < 0.01$).

Thrombotic events occurred in ten patients (19.23%): eight pulmonary thromboembolisms and two peripheral arterial occlusions. On the other hand, hemorrhagic complications occurred in 11 patients (21.15%): four gastrointestinal bleeds, three retroperitoneal bleeds, three muscle and one central nervous system bleeds.

Treatment

Most of the patients received therapy with the combination of hydroxychloroquine, azithromycin (96.2%), and lopinavir/ritonavir (94.2%). Steroids were administered to 69.2% of the patients with a mean cumulative dose of 544 ± 496.38 mg of prednisone. Tocilizumab was used in 48.1% of cases; the median time between admission and tocilizumab administration was two days (1–4), mean dose 561 ± 276.24. Five (9.6%) patients with refractory inflammatory response were treated with Anakinra.

Regarding antithrombotic treatment, 5 (9.6%) patients were anticoagulated, 38 (73%) received antithrombotic prophylaxis, and 9 (17.3%) did not receive antithrombotic therapy at hospital admission. At diagnosis of AKI, 10 (19.2%) patients were on anticoagulant treatment, 38 (73%) with prophylaxis and 4 (7.7%) without antithrombotic

Table 2 Laboratory findings

	At admission	At AKI	p
Creatinine (mg/dL) [0.3—1.3]	1.11 (1.12)	2.23 (1)	0.001
Hemoglobin (g/dL) [12–15]	13.8 (32.5)	11.9 (3.9)	0.001
WC count ($\times 10^6$/L) [1–4, 4–11]	7255 (8687)	12,500 (11,212.5)	0.001
Lymphocytes ($\times 10^6$/L) [100–1000]	700 (400)	700 (700)	0.56
Platelets ($\times 10^9$/L) [130–400]	184.5 (119)	226.5 (174.25)	0.002
Prothrombin time (%) [80–100]	68.45 (119)	73.1 (20.52)	0.43
Sodium (mmol/L) [135–145]	138 (5)	138.5 (6)	0.016
Potassium (mmol/L) [3.5–5.5]	3.8 (0.8)	4.1 (1.07)	0.021
D-Dimer (ng/ml) [< 500]	1100 (4450)	2800 (5750)	0.026
Lactate dehydrogenase (U/L) [< 234]	429 (235)	461 (496)	0.63
C-reactive protein (mg/L) [< 1]	13.58 (42.25)	8 (18.18)	0.02
Procalcitonin (ng/mL) [< 0.5]	0.23 (1.56)	0.92 (3.13)	0.005
Bilirubin (mg/dL) [0.2–1.2]	0.5 (0.5)	1 (1.4)	0.001
AST (U/L) [5–40]	56.5 (42.25)	51.5 (57.75)	0.99
ALT (U/L) [5–40]	43 (38)	53.5 (61.75)	0.027
Ferritin (µg/L) [15–200]	N/D	1215 (1817)	

Median (IQR)/n (%)/mean ± SD

[] Normal values, *WC* white cells, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *N/D* no data

therapy. Low molecular weight heparin was used in 40 (76.9%) and 43 (82.69%) patients at admission and at AKI diagnosis, respectively. Moreover, three and five patients received unfractionated heparin at hospital admission and AKI diagnosis, respectively. One patient received fondaparinux at AKI time because of heparin-induced thrombocytopenia.

AKI characteristics

AKI characteristics and evolution are described in Table 3. Most of the patients (84.6%) developed AKI during the ICU stay, within a median of 5 and 12 days from admission and the onset of symptoms, respectively. Twenty-six (50%) of the cases progressed to more severe AKI.

Patients were mostly non-oliguric at AKI diagnosis, but those who started RRT developed it more frequently (in the 24 h before RRT onset). Hyperkalemia was not a frequent finding at the time of AKI diagnosis.

At AKI diagnosis, 73% of the patients were on treatment with vasoactive drugs, with a median noradrenaline dose of 0.19 mcg/kg/min (IQR 0.46).

Suspected intrinsic AKI related to severe COVID-19, which accounted for 71.15% (n 37) of cases, was the most common form of kidney dysfunction. The other probable causes of AKI that were identified included: hemorrhagic shock related to anticoagulation treatment (4); contrast nephropathy (3); drug nephrotoxicity (2); cardiac arrest (2); liver failure (2); heart failure (1) and pancreatitis (1).

Fifteen patients (28.85%) required RRT, including 13 with continuous renal replacement therapy (CRRT). Median time from admission to RRT was 12 (IQR 10) days. RRT mean time was 10.87 ± 9.28 days. CRRT was the only modality in eight patients, while five patients received CRRT followed by intermittent modality, and two patients were treated with intermittent modalities alone. When CRRT was used, the modalities included continuous hemodialysis with medium cut-off dialyzers (MCO) (n = 5) and continuous hemodiafiltration with high-flux hemofilter (n = 8). Anticoagulation consisted of citrate in six patients and heparin in six patients.

At the end of follow-up, 31 (59.6%) patients recovered from the AKI episode.

Outcomes

Variables associated with RRT or mortality are described in Tables 4 and 5 and 6 (Supplementary material).

Baseline and admission creatinine was higher in patients who died, p 0.011 and 0.02, respectively (Table 6 supplementary materials). In univariate analysis, the variables associated with higher mortality in AKI patients were age > 60 years (p 0.017), and presence of one or more comorbidities (p 0.03). On the contrary, recovery from AKI was associated with less probability of death, p < 0.001. In the multivariate analysis, only AKI recovery retains significance (p 0.005).

Overall mortality among patients with COVID-19 diagnosis admitted to the ICUs during the study period, and

Table 3 AKI characteristics and evolution of the patients

	All patients (n = 52)
AKI present at hospital admission	8 (15.4%)
AKI occurrence during hospital stay	44 (84.6%)
Days from hospital admission to AKI, median (IQR)	5 (9.25)
Days from symptom onset to AKI, median (IQR)	12 (8–18)
Pa/FIO_2 at AKI, mean ± SD	209.51 ± 94.71
Mechanical ventilation (MV)	44 (84.6%)
Days hospital admission MV, median (IQR)	1 (3)
SOFA at AKI, mean ± SD	8.38 ± 2.43
Vasoactive drugs at AKI	38 (73.1%)
Noradrenaline dose mcg/kg/min, median (IQR)	0.19 (0.459)
Diuresis 24 h prior to AKI diagnosis (mL), median (IQR)	1500 (1352)
Diuresis 24 h before first RRT diagnosis (mL), median (IQR)	330 (665)
AKI stage at diagnosis	
Stage 2	43 (82.7%)
Stage 3	9 (17.3%)
Renal replacement therapy (RRT)	15 (28.85%)
Days from hospital admission to first RRT, median (IQR)	12 (11)
RRT days, median (IQR)	7 (17)
RRT at death	5 (9.6%)
Continuous renal replacement therapy (CRRT)	13 (25%)
CRRT days, mean ± SD	6.77 ± 3.56
Intermittent RRT sessions, median (IQR)	6 (3–9)
AKI progression from AKIN2 to AKIN3/RRT	26 (60.46%)
AKI recovery	31 (59.6%)
Total death	27 (51.92%)
Death with AKI stage 2	1 (1.92%)
Death with AKI stage 3	20 (38.5%)
Discharged	25 (48.08%)

Median (IQR)/n (%)/mean ± SD

AKI acute kidney injury, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *IQR* interquartile range, *SD* standard deviation, *GFR* glomerular filtration rate, *SOFA* Sequential Organ Failure Assessment score, $PaFiO_2$ arterial blood oxygen pressure, *MV* mechanical ventilation

without exclusion criteria, n = 237, was 16.87% (n = 40). In the non-AKI patients, mortality was 7.3% (n = 13), while in AKI patients it was 51.92% (n = 27), p < 0.001, OR 10.67 (95% CI 5.1–22.33). The median time to death after AKI diagnosis was eight days (IQR 13). AKI was also associated with longer hospital LOS, 35 (IQR 36.75) vs 18 (IQR 20) days in AKI vs non-AKI patients, respectively (p 0.018)).

Regarding RRT, in the univariate analysis, a SOFA score of 8 or more at AKI diagnosis was associated with the need for RRT, p 0.032, OR 4.52, with sensitivity and specificity of 73% and 62%, respectively. However, the non-renal SOFA score at AKI was not associated with RRT. Also the use of vasoactive drugs at AKI diagnosis was not associated with RRT requirement, p 0.06. On the contrary, the use of corticosteroids was associated with less requirement of RRT, p 0.03, OR 0.24.

In the multivariate analysis, a SOFA score of 8 or more and corticosteroid use at AKI diagnosis were associated with RRT, OR 6.15, p 0.015, and OR 0.16, p = 0.017 respectively.

Discussion

Kidney involvement is frequent in COVID-19. Cheng et al. described kidney abnormalities in more than 40% of COVID-19 patients in Wuhan (China), including proteinuria, hematuria and elevated serum creatinine [14]. Also, any degree of AKI has been associated with mortality in COVID-19 hospitalized patients [9–11, 13–15, 17, 23]. In this prospective observational single-center study, moderate-severe AKI was associated with high mortality (50 vs 7.3%) and hospital length of stay (35 vs 18 days).

Table 4 Univariate and multivariate analysis of clinical characteristics and treatment related to RRT

	Univariate		Multivariate	
	OR (CI 95%)	p	OR (CI 95%)	p
Male (yes)	0.76 (0.19–3.03)	0.7	–	–
Age > 60 years	5.18 (0.6–44.72)	0.13	–	–
Hypertension history	0.7 (0.21–2.34)	0.56	–	–
Diabetes	0.91 (0.2–4.01)	0.89	–	–
COPD	0.19 (0.02–1.66)	0.13	–	–
CKD III	0.98 (0.17–5.73)	0.99	–	–
BMI > 30	0.6 (0.1–3.51)	0.57	–	–
Presence of one or more comorbidities	1.56 (042–5.77)	0.51	–	–
ARB history	0.31 (0.03–2.73)	0.29	–	–
ACEI history	0.48 (0.09–2.54)	0.39	–	–
SOFA ≥ 8 at AKI	4.52 (1.2–16.97)	0.03	6.5 (1.43–29.82)	0.015
Non-renal SOFA ≥ 7 at AKI	2.07 (0.58–7.44)	0.26	–	–
Mechanical ventilation	3.27 (0.37–29.16)	0.29	–	–
PA/FIO2 admission < 200 mmHg	0.58 (0.16–2.13)	0.41	–	–
PA/FIO2 at AKI < 200 mmHg	2.04 (0.59–7.05)	0.26	–	–
AKIN 3 at diagnosis time	4.12 (0.93–18.36)	0.05	–	–
Vasoactive drugs at AKIN	7.58 (0.89–64.33)	0.06	–	–
Corticosteroids	0.24 (0.07–0.87)	0.03	0.16 (0.04–0.73)	0.017
Tocilizumab	1.21 (0.36–4)	0.76	–	–
Lopinavir/Ritonavir	0.91 (0.83–0.35)	0.26	–	–
Thrombotic event	1.07 (0.24–4.85)	0.93		

AKI acute kidney injury, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *IQR* interquartile range, *SD* standard deviation, *GFR* glomerular filtration rate, *SOFA* Sequential Organ Failure Assessment score, $PaFiO_2$ arterial blood oxygen pressure, *MV* mechanical ventilation, *BMI* Body Mass Index, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *CKD* chronic kidney disease, *ACEIs* angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, $PaFiO_2$ arterial blood oxygen pressure, FiO_2 fraction of inspired oxygen

Several mechanisms of kidney damage have been described, but many facts point to direct damage. Low counts of SARS-CoV-2 virus have been detected in kidney cells [20]; furthermore, SARS-CoV-2 infects the host using the ACE2 receptor, transmembrane serine protease 2, and cathepsin L, all are enriched in kidney tissue [24]. Even more endothelial cells express ACE2 receptors, and direct infection of SARS-CoV-2 on engineered human blood vessel organoids has been described [25]. Kidney histology in patients with COVID-19 has shown the presence of acute tubular necrosis, and moderate-to-severe lymphocytic infiltration and collapsing glomerulopathy [12, 20, 26]. The virus could also initiate CD68 + macrophage infiltration together with complement C5b-9 deposition to mediate tubular damage [12].

In our cohort, AKI episodes occurred together with worsening respiratory symptoms (median time from admission to AKI of 5 days), which supports either a direct mechanism of damage to the kidney or an immune-mediated one. In this sense, patients had higher bilirubin, D-dimer, and platelets at AKI diagnosis compared to the admission levels, supporting the hypothesis that severe AKI is part of multiorgan failure that occurs in the context of the cytokine storm that has been described in these patients. In accordance with this, a SOFA score of 8 or more at the time of AKI diagnosis was associated with higher RRT requirement. Also, procalcitonin was higher at the time of AKI diagnosis, which could be related to an inadvertent bacterial co-infection. Bacterial over infection cannot be ruled out as a worsening factor in AKI patients. However, it was not possible to confirm this overlap beyond a suspected diagnosis in most patients.

The treatment protocol for COVID-19 in our center included antiviral therapy with lopinavir/ritonavir, hydroxychloroquine and azithromycin. If patients showed clinical deterioration then biological therapy, which in the majority of cases included an anti-IL-6 (tocilizumab), an anti-IL-1 (anakinra) and/or corticosteroids, was recommended. In our cohort, the inflammatory response was treated with corticosteroids and tocilizumab in 69.2% and 48.1% of cases, respectively, at a median time of two days after admission. The use of corticoids was associated with a 13% reduction in RRT requirement.

In our cohort, 19.23% of patients presented a thrombotic event, confirming the high incidence reported in the

Table 5 Univariate and multivariate analysis of clinical characteristics and treatment related to in-hospital mortality

	Univariate		Multivariate	
	OR (CI 95%)	p	OR (CI 95%)	p
Male (yes)	1.1 (0.3–4.02)	0.88	–	–
Age > 60 years	7.03 (1.34–36.82)	0.017	4.16 (0.65–26.6)	0.13
Hypertension history	1.85 (0.6–5.66)	0.28	–	–
Diabetes	3.09 (0.72–13.32)	0. 17	–	–
COPD	3.08 (0.72–13.3)	0.182	–	–
CKD III	6.86 (0.76–61.67)	0.1	–	–
BMI > 30	0.5 (0.1–2.41)	0.46	–	–
Presence of one or more comorbidities	4.52 (1.2–16.97)	0.03	3.29 (0.69–15.46)	0.13
ARB history	1.67 (0.35–7.84)	1	–	–
ACEI history	1.84 (0.47–7.25)	0.38	–	–
SOFA ≥ 8 at AKI	2.58(0.8435–7.93)	0.09	–	–
Non-renal SOFA ≥ 7 at AKI	1.1 (0.3–4.02)	0.88	–	–
Mechanical ventilation	0.6 (0.13–2.82)	0.7	–	–
PA/FIO2 admission < 200 mmHg	0.42 (0.12–1.47)	0.17	–	–
PA/FIO2 at AKI < 200 mmHg	0. 85 (0.27–2.63)	0.77	–	–
AKIN 3 at diagnosis time	0.4 (0.09–1.79)	0.28	–	–
RRT (yes)	1.08 (0.32–3.6)	0.89	–	–
RRT more than 7 days	1.25 (0.16–9.92)	1	–	–
AKI recovery	0.11 (0.03–0.42)	0.001	0.13 (0.03–0.54)	0.005
Vasoactive drugs at AKIN	0.75 (0.22–2.58)	065	–	–
Corticosteroids	1.12 (0.34–3.63)	0.85	–	–
Tocilizumab	0.63 (0.21–1.88)	0.4	–	–
Lopinavir/Ritonavir	0.52 (0.04–6.13)	1	–	–
Thrombotic event	0.55 (0.13–2.24)	0.49	–	–

AKI acute kidney injury, *RRT* renal replacement therapy, *CRRT* continuous renal replacement therapy, *IQR* interquartile range, *SD* standard deviation, *GFR* glomerular filtration rate, *SOFA* Sequential Organ Failure Assessment score, $PaFiO_2$ arterial blood oxygen pressure, *MV* mechanical ventilation, *BMI* Body Mass Index, *COPD* chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *CKD* chronic kidney disease, *ACEIs* angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, $PaFiO_2$ arterial blood oxygen pressure, FiO_2 fraction of inspired oxygen

literature [15, 27, 28]. Antithrombotic prophylaxis or anticoagulation was initiated in most of the patients. It is possible that microthrombi and thrombotic microangiopathy can contribute to the pathogenesis of AKI in patients with COVID-19 [15], but given the low number of cases that did not receive these treatments in our study, associations with AKI outcome could not be established. Nevertheless, we want to emphasize the relatively high incidence of major bleeding complications (21.15%). Patients with impaired kidney function have an increased risk of bleeding, and therefore, the risk/benefit of thromboprophylaxis must be balanced.

The treatments used in our cohort may have altered the course of AKI as the number of patients who required RRT in the present study is relatively low (15/237, 6%) compared to other recent cohorts with an incidence of RRT in ICU patients between 17 and 51% [12, 13, 16, 17, 23, 29, 30].

The present study has some limitations. First, given the observational nature of the study, bias cannot be ruled out in the beneficial effect of the corticosteroids. Second, the limited number of patients with RRT makes it challenging to come to conclusions about the best strategy for dialyzing patients. Also, the usefulness of MCO in the COVID-19 cytokine release syndrome needs further investigation in randomized studies [12].

An important point to consider is that all the patients with CKD KDIGO stage 4 were excluded from the present study to more clearly demonstrate the impact and evolution of AKI in the context of severe COVID-19. Therefore, these results cannot be extrapolated for patients with severe chronic kidney disease.

Given the observational nature of the study, there are no details on proteinuria and hematuria since they were not generally evaluated in our center during the pandemic. There is also no histological material, which would be very useful to describe the type of injury in AKI associated with COVID-19.

In conclusion, in our study the prevalence of moderate/severe AKI in COVID-19 in the ICUs is associated with high mortality and hospital length of stay. Present data suggest that corticosteroid treatment may be related to less RRT, but further research is needed to confirm these data.

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