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Mortality Related to COVID-19 in Acute Renal Injury Patients: A Cohort Study

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Abstract

Introduction: The coronavirus, SARS-CoV-2, is the pathogen responsible for an acute respiratory distress syndrome that broke out in the Wuhan region and became a pandemic in early 2020. The clinical presentation of COVID-19 is polymorphic, dominated by respiratory symptoms and may be associated with cardiovascular, digestive and renal complications. The prognosis depends mainly on the patient's condition. Acute kidney injury (AKI) during severe SARS CoV-2 infection is frequent, multifactorial and associated with excess mortality. Its pathophysiology has not been fully elucidated, and seems to involve both direct and indirect mechanisms. The aim of our work is to describe the epidemiological, clinical, paraclinical and therapeutic profile of patients presenting with AKI and confirmed COVID-19 disease, and determine the prognostic factors associated with death. **Material and Methods:** This was a retrospective study conducted at IBN SINA Hospital, Rabat, between March 2020 and November 2021. We included patients with confirmed SARS-CoV-2 infection who developed AKI either on admission or during hospitalization. **Results:** We enrolled 95 patients with a mean age of 68 ± 13 years and a M/F sex ratio of 1.9. Diabetes was present in 33.7% of cases and hypertension in 32.6%. Most patients had influenza-like illness, lymphopenia and hyperferritinemia. Median creatinine on admission was 32 mg/l [17 - 64]. Temporary catheter hemodialysis was used in 21% of cases, with hyperkalemia for purification and ultrafiltration. There were 63 deaths, it was statically significantly related ($p < 0.05$) to medical management in intensive care and the need for intubation, to the extent of lung damage on chest CT ≥50%, to the presence of Stage 3 AKI, to the indication for an RRT session, and to initiation of methylprednisolone. Survival analysis was performed using the Kaplan-Meier curve, with median survival estimated at 12 days (95% confi-

dence interval 10 - 15 days). **Conclusion:** AKI in COVID-19 is multifactorial, and may be secondary to sepsis, hemodynamic failure or direct viral toxicity to the kidney. In our study, mortality was secondary to viral toxicity, clinical presentation, intensive care unit management and recourse to hemodialysis.

Keywords

Acute Kidney Injury, COVID-19, SARS-CoV-2, Hemodialysis

1. Introduction

The coronavirus disease (COVID-19) is a major public health crisis that broke out in December 2019 in the Wuhan region of China [1]. The coronavirus disease spread rapidly around the world, resulting in a global pandemic by early 2020 [2] [3].

Morocco recorded its first case of contamination on March 2, 2020 and the first recorded death was on March 11, 2020. From March 2, 2020 to November 30, 2021, Morocco recorded a total of 949,917 new cases and 14,776 deaths [4].

The clinical presentation of COVID-19 is variable, mainly characterized by respiratory symptoms that may progress to acute respiratory distress syndrome (ARDS), or may be associated with cardiovascular, digestive and renal complications [1] [5].

At the outbreak of the pandemic, kidney involvement was unknown, but it became a more common and dreaded complication in patients with COVID-19. Its incidence is estimated at 6%, but is highly variable from one study to another, ranging from 0.6% to 29% [6] [7].

This variability may be explained by differences in the clinical presentation of patients included in the studies, and in their therapeutic management [8] [9].

The pathophysiology of acute kidney injury (AKI) in COVID-19 is not entirely clarified, it involves direct mechanisms related to direct toxicity of the virus on tubular cells, and indirect mechanisms secondary to renal hypoperfusion caused by sepsis, cytokine storm and mechanical ventilation [10] [11]. This kidney damage can go from a slight increase in blood creatinine to advanced AKI, requiring renal replacement therapy (RRT) [12]. Several studies have highlighted the presence of urinary sediment anomalies and evidence of urinary excretion of SARS-CoV-2, suggesting the presence of a renal pool for the virus.

AKI is associated with an increased mortality rate, particularly in patients requiring RRT and those with multiple comorbidities [13] [14]. It represents a statistical risk factor for chronic kidney disease, with one-third of patients at risk of developing end-stage renal disease at hospital discharge [12] [15], thereby justifying the benefits of multi-disciplinary management, in particular when it comes to the challenging task of managing renal replacement therapy (RRT) and regular nephrological follow-up of these patients.

Although the international public health emergency linked to COVID-19 was declared over by the World Health Organization (WHO) on May 5, 2023, SARS-CoV-2 remains a major threat to public health worldwide.

The WHO has reported an 80% increase in the number of new cases from July 10 to August 6, 2023, compared with the previous 28 days, with 1.5 million additional infections. This represents a modest epidemic rebound, but one that calls for vigilance [16].

The risk of the emergence of new, more transmissible and/or more serious variants is also a real concern. Hence, the importance of taking advantage of the progress made since the emergence of COVID-19, and preserving and applying the lessons learned from the fight against this pandemic.

To this end, we have conducted a study to determine the prognostic and outcome factors of death in patients with AKI and SARS-CoV-2 disease at the Ibn Sina Hospital in Rabat.

2. Material and Methods

2.1. Study Type and Population

This is a 21-month retrospective cohort study, conducted between March 2020 and November 2021, at the IBN SINA Hospital in Rabat.

We included only patients admitted to hospital with confirmed COVID-19, regardless of the severity of the disease, who developed AKI either on admission or during hospitalization, and who required hemodialysis or not. We excluded dialysis and kidney transplant patients from the study.

The diagnosis of COVID-19 disease was confirmed by detection of the SARS-CoV-2 viral genome in the upper airways (nasopharynx) by RT-PCR technique or by the rapid antigen test (TRA) and/or a chest CT scan compatible with infection.

We took into consideration the highest serum creatinine during hospitalization to classify our patients.

We defined 3 stages of AKI according to the KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for Acute Kidney Injury : Stage 1 is defined by a serum creatinine ≥ 0.3 mg/dl or Stage 2 is defined as serum creatinine 2 to 2.9 times baseline plasma creatinine. Stage 3 is defined by serum creatinine 3 times baseline plasma creatinine or plasma creatinine ≥ 354 µmol/L, or requiring renal replacement therapy [14].

2.2. Studied Variables and Judgment Criteria

Patients' clinical data were collected from their medical records, hospitalized in the various COVID-19 units, and check-up data were taken from the CHU IBN SINA computer system (GREEN CUBE).

- We recorded demographic data: age, sex, medical history (arterial hypertension, diabetes, cancer, obesity, and smoking).
- We noted the various functional signs of COVID-19 reported by the patient

on admission: cough, dyspnoea, fever, headache, aches and pains, asthenia, and anosmia.

- We noted the need for intensive care and the clinical examination data on patient admission, namely disturbance of consciousness assessed by Glascow Score, blood pressure, temperature, heart rate, respiratory rate, oxygen saturation (SO_2) (determined at rest and in room air).

Biologically, we analyzed the results of the following tests performed at the time of admission:

- Cell blood count (CBC).
- CRP (mg/L), Sodium (mEq/L), Potassium(mEq/L), Alkaline reserve (mEq/L),
- D-dimer, Fibrinogen.

We studied the highest renal function (urea (g/l), creatinine (mg/l)) during hospitalization. Radiologically, we reported the level of suspicion of COVID-19 infection, classified according to the CO-RADS (COVID-19 Reporting and Data System) scale. The extent of these radiological lesions, based on the percentage of lung damaged, is assessed according to a scale ranging from 0 to 5:

Grade 1 defined by lung lesion extent <10%, Grade 2 defined by 10% - 25% involvement, Grade 3 defined by 25% - 50% involvement, Grade 4 defined by 50% - 75% involvement and Grade 5 defined by >75% involvement.

We noted the medical treatment received by patients: hydroxyhloroquine, antibiotics, and corticotherapy and the use of oxygen therapy by oxygen spectacles, high-concentration mask (HCM) and non-invasive ventilation (NIV), or invasive.

We noted the use or non-use of hemodialysis, specifying its indication, the number of sessions and the approach.

To identify the factors associated with mortality, we defined the patient's death as the main outcome. Favourable outcome was defined as the patient's recovery and discharge from hospital.

2.3. Statistical Analysis of Data

Qualitative variables were expressed as numbers and percentages, and compared using the chi2 test. Quantitative variables were expressed either as mean ± standard deviation if the distribution of the variable was normal, and compared using the "student" test, or as median with the interquartile range if the distribution of the variable was asymmetric, and compared using the Mann-Whitney test.

We studied the factors associated with death using univariate and multivariate logistic regression analyses. After a univariate study, all variables with a p less than 0.05 in the statistical test were introduced into the multivariable analysis model.

The significance level was set at 5% ($p < 0.05$).

Survival analysis was performed using the Kaplan-Meier curve, with comparison of survival curves using the Log-Rank test. The significance level was set at 5%.

Data were analyzed using Jamovi 2.3.9 software.

3. Results

Over a 21-month period, between March 2020 and November 2021, we identified 95 patients with COVID-19 disease with AKI. The average age of our patients was 68 ± 13 years, with a M/F sex ratio of 1.9.

As for comorbidities, diabetes was found in 33.7% of patients, followed by hypertension.

Of the 95 patients, 44% required intensive care.

The median hospital stay was 10 days [7 - 13].

Intubation on admission was indicated in 10.6% of patients, and corticosteroid therapy was administered in 85% of cases, including 81.5% with methylprednisolone (Table 1).

Renal replacement therapy was used in 20 patients for purification and ultrafiltration (Table 1).

Favourable outcome, defined as patient recovery, was noted in 33.7% of cases, and death in 66.3%.

Table 1. Patient profiles by stage of outcome.

	Total (n = 95)	Alive (n = 32)	Dead (n = 63)	p
Male[b]	63 (66.3%)	23 (72%)	40 (63.5%)	0.4
Average age (years)[a]	68 ± 13	67.2 ± 16	68.4 ± 11	0.67
Age ≥ 65 year old	16 (28.6%)	16 (50%)	40 (65.6%)	0.14
Intensive care management[b]	42 (44%)	1 (3%)	41 (65%)	<0.001
Comorbidities				
AH	31 (32.6%)	12 (37.5%)	19 (30.2%)	0.47
Diabetes[b]	32 (33.7%)	9 (28%)	23 (36.5%)	0.4
Obesity[b]	6 (6.3%)	0 (%)	6 (9.5%)	0.07
Cancer[b]	3 (3.2%)	0 (0%)	3 (4.8%)	0.2
Smoking[b]	7 (7.4%)	2 (6.3%)	5 (8%)	0.7
Symptoms				
Fever	69 (72.6%)	23 (72%)	46 (73%)	0.9
Headache[b]	83 (87.4%)	27 (84.4%)	56 (89%)	0.5
Dyspnea[b]	72 (75.8%)	18 (56.3%)	54 (85.7%)	0.002
Anosmia/Ageusia[b]	36 (38%)	18 (56.3%)	18 (28.6%)	0.009
Clinical examination				
GCS[a]	13 ± 3.7	15 ± 0.5	12 ± 4	0.004
Temperature[a]	37.4 ± 2	37.2 ± 2.6	38 ± 1.7	0.47
SBP[a] (cmhg)	12.3 ± 1.4	12.5 ± 1	12 ± 1.5	0.17

Continued

DBP[a] (cmhg)	7 ± 1	7 ± 1	6.6 ± 0.9	0.007
HR[a] (Beat/minute)	89 ± 17	86 ± 8.8	80 ± 1	0.76
RR[a] (Breath/minute)	25 ± 6	22 ± 5	26 ± 6	0.01
SpO_2[a] (%)	82.5 ± 10.7	86 ± 9	80.7 ± 11	0.02
Blood creatinine[c]	32 [17 - 64]	15 [14 - 25]	39 [24.5 - 65.5]	0.007
Stage AKI[b]				<0.001
Stage 1	20 (21%)	15 (47%)	5 (8%)	
Stage 2	11 (11.6%)	6 (18.8%)	5 (8%)	
Stage 3	64 (67.4%)	11 (34.4%)	53 (84%)	
Lymphocytes[c] (Element/mm³)	780 [548 - 1098]	927 [620 - 1320]	781 [495 - 1043]	0.08
White cells[c] (Element/mm³)	9175 [5785 - 13,578]	10,983 [5803 - 11,705]	11,080 [5740 - 13,904]	0.9
Hemoglobin[a] (g/dl)	12.2 ± 2.2	12 ± 2.2	12.7 ± 2.2	0.6
Platelets[c] (Element/mm³)	206,000 [146,000 - 303,000]	211,500 [146,750 - 263,500]	206,000 [143,000 - 309,000]	0.86
CRP[c] (mg/l)	159 [94.8 - 284]	152 [92 - 279]	183 [98 - 290]	0.4
D-Dimer[c] (ng/ml)	1700 [740 - 3800]	1320 [540 - 2200]	2010 [960 - 4733]	0.16
Fibrinogen[a] (g/l)	7 [5.5 - 8]	6.6 ± 1.7	7 ± 2.5	0.7
Ferritine[c] (ng/ml)	984 [568 - 1681]	979 [454 - 1312]	986 [613 - 1757]	0.3
Chest CT scan				<0.001
Extent of lesions ≥50%[b]	54 (67.5%)	7 (28%)	49 (89%)	
Oxygenotherapy[b]				<0.001
Oxygen goggles	14 (15%)	13 (40.6%)	1 (1.6%)	
High concentration mask	46 (49%)	13 (40.6%)	33 (53.2%)	
Non-invasive ventilation	17 (18%)	1 (3%)	16 (25.8%)	
Intubation	10 (10%)	0	10 (16.1%)	
≥2 antibiotiques[b]	40 (46.5%)	9 (32%)	31 (53.4%)	0.06
Corticotherapy[b]				<0.001
Prednisolone	7 (8.6%)	7 (30.4%)	0 (%)	
Dexamethasone	8 (10%)	0 (%)	8 (13.8)	
Methylprednisolone	66 (81.4%)	16 (69.6%)	50 (86.2%)	
Hemodialysis[b]	20 (21%)	1 (3%)	19 (30.2%)	0.002

[a]Expressed as mean ± standard deviation; [b]Expressed as headcount (percentage); [c]Expressed as median [interquartile range]. AH: Arterial hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; GCS: Glasgow Coma Scale; HR: Heart rate; RR: Respiratory rate; AKI: Acute kidney injury; CT scan: Computed tomography scan.

The percentage of deaths was statically significantly related ($p < 0.05$) to medical management in intensive care and the need for intubation, to the extent of lung damage on chest CT ≥50%, to the presence of Stage 3 of AKI, to the indication for an RRT session, and to initiation of methylprednisolone.

Mean Glasgow Coma Scale (GCS), diastolic blood pressure and SpO_2 were low and statistically significant in patients who died (Table 1).

In multivariable analysis, the variables statistically associated with death ($p < 0.05$) were diastolic blood pressure, percentage of lung involvement on chest CT and Stage 3 of AKI (Table 2).

Table 2. Logistic regression analyses of risk factors associated with death.

Variable	Univariable analysis			Multivariable analysis		
	OR	CI 95%	p	OR	CI 95%	p
Average age (years)	1	[0.9 - 1]	0.67	-	-	-
Male sex	0.68	[0.2 - 1.7]	0.4	-	-	-
Diabetes	1.47	[0.5 - 3.7]	0.4	-	-	-
AH	0.7	[0.3 - 1.7]	0.47	-	-	-
Smoking	1.3	[0.23 - 7]	0.7	-	-	-
Fever	1.06	[0.4 - 2.7]	0.9	-	-	-
Dyspnea	4.6	[1.7 - 12]	0.002	1.5	[0.2 - 9]	0.7
Disturbance of consciousness	1.3	[0.23 - 7]	0.7	-	-	-
SBP (cmhg)	0.8	[0.6 - 1]	0.17	-	-	-
DBP (cmhg)	0.5	[0.3 - 0.8]	0.01	0.4	[0.16 - 0.9]	0.04
SpO_2 (%)	0.9	[0.9 - 1]	0.028	-	-	-
RR (Breath/minute)	1.1	[1 - 1.2]	0.013	1.04	[0.9 - 1.2]	0.5
Lymphocytes (Element/mm^3)	0.9	[0.9 - 1]	0.09	-	-	-
CRP (mg/l)	1	[0.9 - 1]	0.3	-	-	-
Ferritine (ng/ml)	1	[0.9 - 1]	0.3	-	-	-
Chest CT scan						
Extent of lesions ≥50%	21	[6 - 70]	<0.001	12	[2.2 - 66]	0.004
Stage 3 of AKI	14.4	[4 - 48]	<0.001	31	[3 - 315]	0.003
Hydroxyhloroquine	1.3	[0.5 - 3]	0.5	-	-	-
Non-invasive ventilation	40	[3 - 539]	0.005	-	-	-
Hemodialysis	13	[2 - 105]	0.014	1.7	[0.13 - 23]	0.6

AH: Arterial hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein; RR: Respiratory rate; AKI: Acute kidney injury; CT scan: Computed tomography scan; OR: oddsratio.

Survival analysis was performed using the Kaplan-Meier curve, with median survival estimated at 12 days (95% confidence interval 10 - 15 days) (Figure 1).

The death rate was higher in patients with a percentage of lung lesions greater than 50%, and this was statistically significant ($p < 0.001$) (Figure 2).

It was also statistically higher in patients treated with dexamethasone (Figure 3). However, there was no statistically significant ($p = 0.077$) difference in the rate of death between patients who required hemodialysis and those who did not (Figure 4).

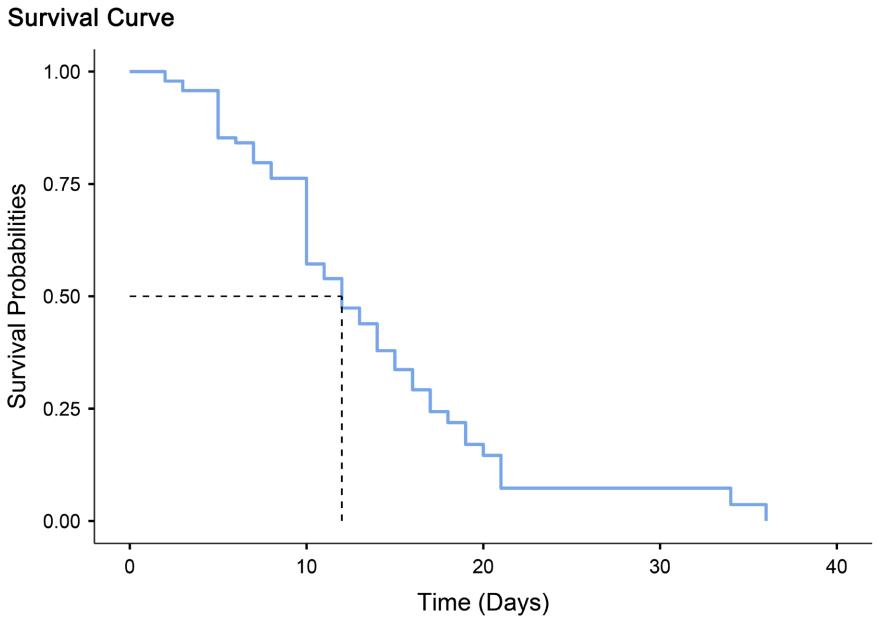

Figure 1. Kaplan-Meier survival curve for patients with AKI and COVID-19.

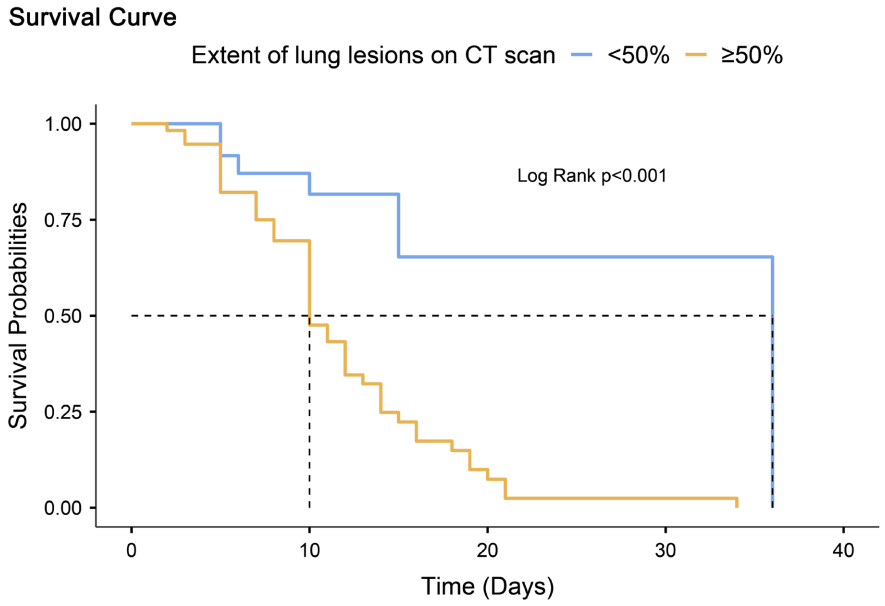

Figure 2. Kaplan-Meier survival curves for patients with AKI with COVID-19 according to percentage of lung involvement on chest CT.

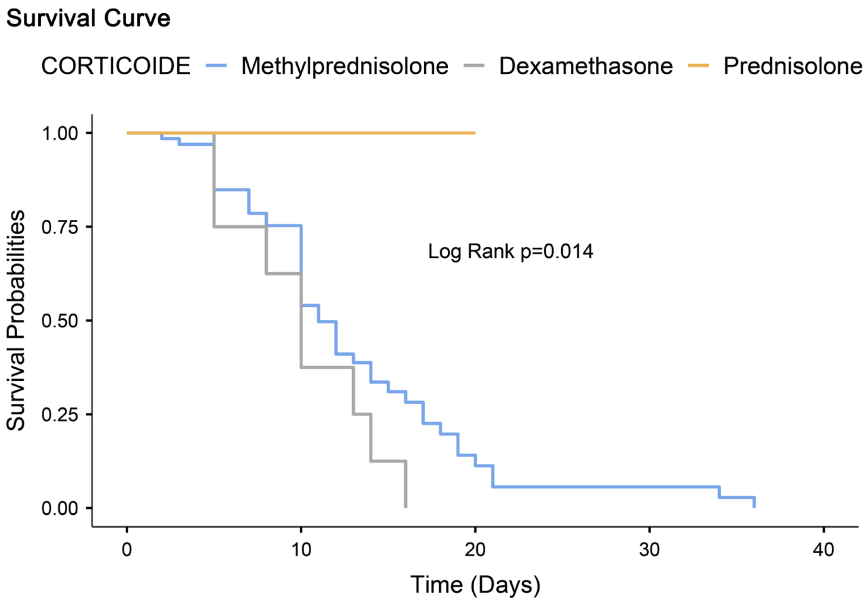

Figure 3. Kaplan-Meier survival curves for patients with AKI with COVID-19 according to corticosteroid therapy management.

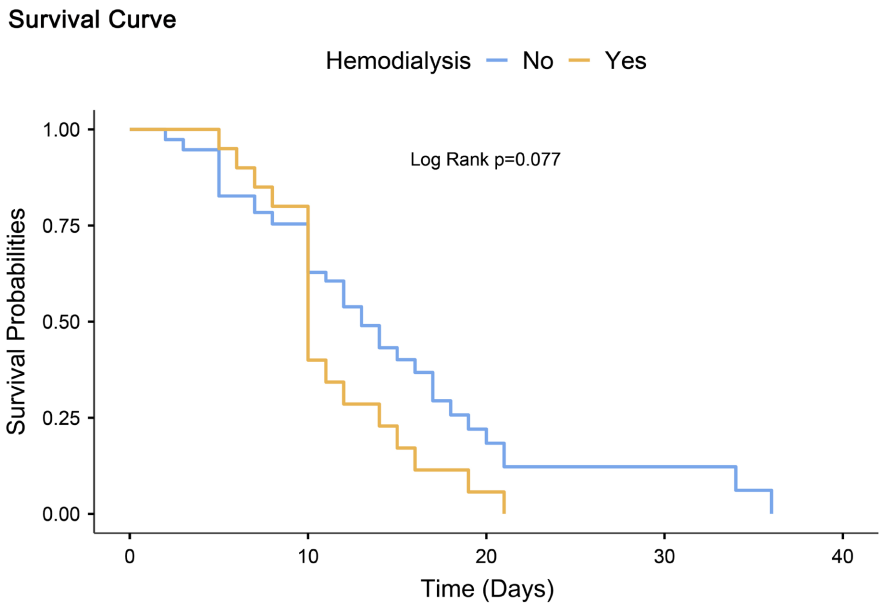

Figure 4. Kaplan-Meier survival curves for patients with AKI with COVID-19 according to indication for hemodialysis.

4. Discussion

In our study, death occurred in 66.3% of patients with COVID-19 who developed AKI during hospitalization. This increased intrahospital mortality has been confirmed by several studies, but with variations in mortality figures [13] [17].

This variability in numbers depends on the demographic profile in different countries and on the health authorities' response to the pandemic in its early stages [8] [9].

Thus, advanced age and male gender were identified in studies as risk factors associated with the occurrence of severe forms and excess mortality [1] [9] [18].

In our series, we did not find a significant increased risk of mortality in men, nor in elderly patients, perhaps due to our small sample size.

However, the rate of death was greater in patients with a percentage of lung damage greater than 50% ($p < 0.001$) and in patients receiving dexamethasone.

Several hypotheses have been put forward to explain the kidney damage caused by COVID-19, including direct toxicity of the virus on tubular cells, sepsis, cytokine storm and mechanical ventilation-related renal hypoperfusion [5].

Rhabdomyolysis, hypercoagulability with the development of microemboli and microthrombi, and macrophagic activation syndrome may also contribute to AKI [19].

The clinical presentation of COVID-19 is marked by prominent respiratory involvement, sometimes associated with acute respiratory distress syndrome, warranting prolonged intensive care hospitalization in its most severe form. It may also be associated with cardiovascular, digestive and renal complications [6] [10].

Functional signs suggestive of COVID-19 reported by our patients are variable and dominated by headache, dyspnea and fever, respectively in 87.4%, 75.8% and 72.6% of cases.

A meta-analysis involving 852 patients reported that the risk of mortality was higher in subjects showing dyspnoea on admission [20].

These results are compatible with the data reported in our series, where the presence of dyspnoea on admission was statically ($p = 0.002$) associated with an unfavorable outcome.

In Chan's study, a large proportion of patients with AKI had severe kidney damage (AKIN Stage 3: 40.6%), which is similar to the results of our study [18].

In the same way, in Ng's study, the incidence rate of death was higher in patients with Stage 3D AKI, and in patients requiring extrarenal dialysis [13].

These results are compatible with the data reported in our series, where the presence of Stage 3 AKI and recourse to hemodialysis were statically linked to death.

Therapeutically, no specific treatment can be proposed for all cases, and there is no evidence that the management of AKI in COVID-19 should be any different from other causes of AKI in hospitalized patients [21].

However, it has been recommended that a strategy be adopted that includes limitation of nephrotoxic drugs, medical treatment of hyperkalemia, and limitation of fluid intake in patients requiring hemodialysis [22].

However, the incidence of intensive care dialysis in patients with AKI and COVID-19 is high, in the range of 17% to 21%. The indications for initiating hemodialysis in these patients appear to be similar to those for patients developing ARF in the ICU [7] [23].

In the absence of an urgent indication, many trials have failed to demonstrate

an impact on mortality using early versus delayed initiation of ESRD. This implies personalizing the prescription of hemodialysis by taking into account the entire clinical context, and not just the degree of renal dysfunction measured by conventional means [24] [25].

The first clinical trial to demonstrate the benefit of corticosteroids in COVID-19 was the British RECOVERY trial. Mortality at day 28 in the dexamethasone group was significantly lower than in the standard of care group (22.9% vs. 25.7%—age-adjusted RR 0.83 [0.75 - 0.93]—$p < 0.001$) [26].

Thus, the use of methylprednisolone in a retrospective cohort study of 201 patients with COVID-19 could benefit patients who develop ARDS and reduce the risk of death [27].

In our series, the use of methylprednisolone was a risk factor associated with death, which may also be explained by the clinical severity of these patients.

Respiratory hypoxemia may be secondary to lung damage and impaired respiratory function caused by COVID-19. Effective oxygen supplementation is essential, and can help reduce complications [1] [27].

In our study, we found that the need for mechanical ventilation was associated with a higher mortality rate ($p < 0.001$). Thus all patients who required mechanical ventilation on admission passed away.

This confirms the results of the Richardson S study, in which the mortality rate in patients who were placed on mechanical ventilation was 88% [23]. This can be explained by the severity of the respiratory failure in our patients' respiratory conditions.

5. Conclusions

AKI is a serious complication in patients infected with coronavirus, particularly those hospitalized in intensive care units. It is associated with a major increase in the risk of mortality.

Kidney damage during COVID-19 was variable, with a risk of progression to end-stage renal failure and dialysis.

Long-term follow-up of these patients is required to understand the impact of AKI in COVID-19 on the subsequent development of chronic renal failure.

The international public health emergency may be over, but the pandemic is certainly not. The risk of emergence of new, more contagious and/or more severe variants is also very high, making it all the more crucial to integrate the battle against COVID-19 into larger prevention programs, and the need to continue devoting resources to ongoing surveillance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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