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Research Article

Evolution of Renal Function in Patient with Covid-19 Associated Acute Kidney Injury

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Abstract

Introduction: Acute Kidney Injury (AKI) is a common complication among patients hospitalized with COVID-19. The incidence of AKI is estimated to be around 5-80%, according to the series, but data on renal function evolution is limited. Our main objective was to describe the incidence of AKI in patients with SARS-CoV2 infection; secondarily, we analyzed the severity of AKI and medium-term renal function evolution in these patients.

Material and Method: Retrospective observational study that included patients hospitalized a single hospital diagnosed with SARS-CoV-2 infection, who developed AKI (March-May 2020). We register clinical and demographic characteristics, creatinine upon admission, and prior to discharge; as well as creatinine and CKD-EPI glomerular filtration rate (eGFR) after at least 3 months after discharge. Chronic Kidney Disease (CKD) was defined according to KDIGO stages based on the eGFR (G3-G5). The KDIGO classification was used to define and classify AKI. Recovery of kidney function was defined as difference in at discharge or posthospitalization creatinine < 0.3 mg/dl with respect basal creatinine. The clinical follow-up ranged from admission to death or end of study.

Results: Of 258 patients hospitalized with SARS-CoV2 infection, AKI occurred in 73 (28.3%): 35 (48%) KDIGO-1, 15 (21%) KDIGO-2 and 23 (31%) KDIGO-3. The mean stay was related with the severity of AKI: 7 days (3-11) for KDIGO-1 versus 12 days (8-35) for KDIGO-3 ($p=0.02$). The stage of CKD established differences in the severity of AKI: 66.6% (n=6) of the patients with CKD G4-5 presented AKI-KDIGO 3 versus only 25.0% (n=4) in the CKD G3 patients ($p=0.02$).Admission to intensive care unit (ICU) was more frequent in KDIGO 2-3 vs KDIGO-1 (39% (n=15) vs 9% (n=3)) ($p <0.01$). Of the 48 patients discharged, 30 (62,5%) had recovered their baseline renal function upon discharge. Only 2 are still on Renal Replacement Therapy (RRT) (2.7% of all patients); 25 (34%) patients died, with a median time of 3 days from DRA diagnosis (1-8). Renal function of 35 patients were monitored, without differences between renal function pre and post-hospitalization in related test. A 77% (n=37) of discharged patients recovered their baseline renal function in the post-hospitalization control.

Conclusions: The incidence of AKI in the context of COVID-19 in our series was 28.3%, with an associated mortality of 34.2%. Most of the patients presented AKI KDIGO 1. The severity of AKI is associated with a longer hospital stay, admission to the ICU and the requirement for RRT. The advanced stages CKD pre-admission showed more severity of AKI. The maintenance in RRT in our series was low. Patients who were discharged for recovery/improvement of COVID-19 had normalized kidney function during subsequent follow-up, regardless of the severity of the developed AKI.

Keywords: Acute kidney injury; Chronic kidney disease; COVID19; SARS-CoV2

Introduction

Acute Kidney Injury (AKI) and kidney abnormalities seem to be associated with Coronavirus Disease 2019 (COVID-19) severity and, consequently, worse short-term outcomes. First series of Chinese patients reported that the incidence of AKI in COVID-19 patients ranges from 0.5 to 5.1% [1,2]. Later, a greater association between COVID-19 and kidney injury, manifested as proteinuria, haematuria, and acute kidney damage has been repeatedly published. Current literature reports that the incidence of AKI ranges widely, reaching 46% of patients hospitalized for COVID-19 [3] and 80% of those requiring admission to Intensive Care Units (ICU) [4]. AKI is associated with a poor vital prognosis, with a mortality that ranges between 33% and 57% [2,5]; in critically ill patients, mortality can reach 83% [6]. Chronic Kidney Disease (CKD) has not only been postulated as a risk factor for developing AKI in patients with COVID-19, but it has also been related to severe infection and a worse prognosis [2,3,7,8]. The requirement of Renal Replacement Therapy (RRT) in patients with Sars-Cov2 infection who develop AKI ranges between 15-19%. A substantial percentage of these patients remained on the technique at the time of publication [3-4,9].

The published literature on the medium-long-term renal function evolution of patients with AKI and SARS-CoV2 infection is limited, and the risk of progression to CKD remains to be established. Our main objective was to describe the incidence of AKI in patients hospitalized for SARS-CoV2 infection; secondarily, we analysed the severity of AKI and medium-term renal evolution in these patients.

Methods

Study Population and Design

This retrospective cohort study was conducted on hospitalized patients with the diagnosis of COVID-19 and AKI at Virgen Macarena Hospital between March 1 and May 15, 2020. A confirmed case of COVID-19 was defined by a positive RT-PCR assay of a specimen collected via nasopharyngeal swab. The study population was 73 patients. The dataset was obtained from electronic medical records; all data were anonymized and subsequently analysed. The search was carried out in the Hospital's Clinical Laboratory computer system, including in selection criteria: maximum creatinine in the year prior to hospital admission, creatinine at hospital admission, and maximum creatinine during admission.

Clinical Follow-Up

According to the hospital stay, we classified the patients according to two possible alternatives: hospital discharge with recovery of renal function and hospital discharge without recovery of kidney function. Clinical follow-up was carried out from hospital admission for SARS-CoV2 until death, hospital discharge, or post-hospitalization control 3 months after discharge.

Data Sources

Variables related to patient comorbidities, SARS-Cov-2 infection, AKI, and clinical outcome were recorded.

Patient Comorbidities: Hypertension (HT), diabetes mellitus, CKD, cardiovascular disease (including ischemic heart disease, cerebrovascular accident and/or peripheral arterial disease), Chronic Obstructive Pulmonary Disease (COPD), asthma, oncohematological pathology and obesity (defined as body mass index > 30 kg/m^2). CKD was defined as an estimated glomerular filtration rate of <60 mL/min/1.73m^2, using the Chronic Kidney Disease Epidemiology Collaboration corresponding to CKD Stage 3 or more according to the KDIGO classification.

Variables Related to SARS-Cov2 Infection: days of hospital stay, radiological diagnosis of pneumonia, need for Mechanical Ventilation (MV) and / or admission to the ICU. The outcome of COVID-19 was also recorded as death or hospital discharge.

Variables Related to AKI: creatinine and eGFR 6 months prior to admission, upon admission, discharge, and 3 months after hospitalization. The maximum creatinine reached during admission was also collected. To analyse the impact of AKI on the individual's renal function, the difference between creatinine and eGFR (pre-admission/discharge, pre-admission/post-hospitalization) were calculated and used in the subsequent analyses. AKI stages were defined using the classification established by the KDIGO Clinical Practice Guideline for Acute Kidney Injury [10]. The need to start RRT, the modality of RRT used, and the need to stay in RRT at discharge of the patient and 3 months after hospitalization were collected.

Acute Kidney Injury

AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dl over a 48-hour period or 50% increase in baseline creatinine [10]. AKI stages were defined using the KDIGO AKI stage creatinine definitions: stage 1 as an increase in serum creatinine of ≥0.3 mg/dl or increase of ≥1.5-1.9 times baseline serum creatinine, stage 2 as an increase to ≥2-2.9 times from baseline serum creatinine, and stage 3 as an increase to more than three times baseline serum creatinine or a peak serum creatinine 4.0 mg/dl or the requirement of RRT during hospital stay [10]. Urine study was not considered due to lack of data. Recovery of kidney function was defined as difference in at discharge or posthospitalization creatinine < 0.3 mg/dl with respect basal creatinine [3].

Renal Replacement Treatment

Following clinical criteria, RRT was started in those AKI with oliguria (diuresis <0.3 ml/kg/h during 24 hours), refractory fluid overload, severe hyperkalemia (K > 6.5 mEq/L) or severe metabolic acidosis (pH <7.1).

Statistical analysis

Statistical analyses were performed using SPSS version 26. Continuous variables were expressed as mean and 95% Confidence Interval (CI) or median and Interquartile Range (IQR), as appropriate. They were compared using Student t test or the Wilcoxon test according to their distribution. Normal distribution of the data was examined by the Shapiro-Wilk-test. Categorical variables were summarized as counts and percentages and were evaluated using Chi-squared or Fishers exact test.

For comparison of subgroups according to AKI stage, ANOVA was used for independent samples. The comparison of previous and post-hospitalization parameters was performed using Student's t test for related data after validating the principles of randomness, normality, and equality of variances. For survival analyses, we generated Kaplan-Meier curves; comparison was done using the log-rank test. Significance level was set at 0.05.

Results

Clinical Characteristics and AKI incidence

From March to May 2020, 258 COVID-19-positive patients were hospitalized at our hospital. AKI occurred in 73 patients (28.3%). The median time from hospital admission until AKI diagnoses was 2 (IQR, 0-5) day, and the median time from onset of symptoms to AKI diagnosis was 7 (IQR, 4-10) days.

Most AKI patients were male (n = 46, 63%) with a median age of 69 years (IQR 57-76). Patient demographics and pre-existing conditions are displayed in Table 1. HT was present in 56.2% (n = 41) of the cases, diabetes mellitus in 37.0% (n = 27) and cardiovascular disease in approximately 23.3% (n = 17); 19% (n = 4) of the patients were obese. CKD was present in 34.2% (n = 25) of the patients who developed AKI, being the most frequent comorbidity after HT and diabetes mellitus. Regarding the treatment used for the management of COVID19 infection in these patients: 61 (83.5%) received Lopinavir/Ritonavir, 60 (82.1%) Hydroxychloroquine, 20(27.3%) pulse intravenous steroids, 7 (9.5%) Tocilizumab and 4 (5.4%) Interferon beta.

CHARACTERISTICS	Study population (n=73)	KDIGO (n=35)	1 KDIGO 2 (n=15)	KDIGO 3 (n=23)	P value
Age, years, median (IQR)	69.0 (57- 76)	70 (52-79)	66.5 (62-71)	69.5 (57-77)	0.65
Sex, n (%) Male	46 (63.0)	20 (57.1)	13 (80.0)	14 (60.9)	0.22
Comorbidities, n (%)					
Hypertension	41 (56.2)	19 (54.3)	8 (53.3)	15 (65.2)	0.67
Diabetes mellitus	27 (37.0)	12 (34.3)	3 (20.0)	12 (52.2)	0.26
CV disease	17 (23.3)	7 (20.0)	3 (20.0)	7 (30.4)	0.52
COPD	11 (15.1)	4 (11.4)	1 (6.7)	6 (26.1)	0.07
Asthma	3 (4.1)	1 (2.9)	0	2 (8.7)	0.21
Oncohematological	16 (24.6)	6 (17.1)	1 (6.7)	1 (4.3)	0.42
pathology	9 (13.8)				
Obesity	14 (19.2)	5 (14.3)	7 (46.7)	2 (8.7)	0.33
CKD, n (%)					
eFG > 60 ml/min/m^2	40 (61.5)	18 (60.0)	13 (80.0)	9 (50.0)	0.92
G3		9 (30.0)	3 (20.0)	4 (20.0)	
G4-5		3 (10.0)	0	6 (30.0)	
IQR: Interquartile Range; **CV:** Cardiovascular; **COPD:** Chronic Obstructive Pulmonary Disease; **CKD:** Chronic Kidney Disease					

Table 1: Clinical and demographic characteristics of the patients included in the study, with stratification according to the severity of acute kidney injury.

Acute Kidney Injury Severity

According to the KDIGO classification, we found that 48% (n=35) of the patients had AKI stage KDIGO 1, 21% KDIGO 2 (n=15) and 31% (n=23) KDIGO 3 (Figure 1). Although we did not find significant differences, the group of KDIGO3 patients presented greater comorbidity (Table 1). The stage of CKD prior to admission was the only differential factor regarding the severity of AKI. We obtained significant differences when adding in subgroups (eGFR>60 ml/min + CKD G3 versus CKD G4-5): patients with eGFR>60 ml/min/1.73m^2 and CKD G3 more frequently presented AKI KDIGO 1-2 (77 % (n=43) versus 21% (n=12) of DRA KDIGO 3); 67% (n=6) of patients with CKD G4-5 were KDIGO 3 (p = 0.02).

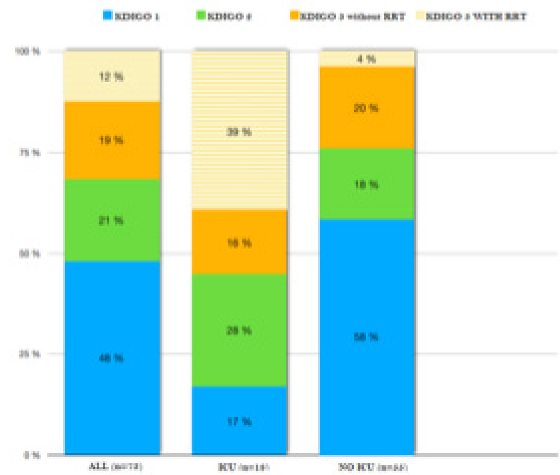

Figure 1: Distribution of the patients included in the study according to the KDIGO classification. Shows the distribution of the patients included in the study according to the severity of AKI. In total: 35 KDIGO 1, 15 KDIGO 2, 23 KDIGO 3. In ICU: 3 KDIGO 1, 5 KDIGO 2, 10 KDIGO 3. Among patients without admission to ICU: 32 KDIGO 1, 10 KDIGO 2, 13 KDIGO 3. 70% (n=7) of AKI KDIGO 3 in the ICU group required RRT versus 15% (n = 2) in those who did not require intensive care.

An 88% (n=64) of the patients developed pneumonia. The percentage of patients with pneumonia was similar in the three AKI subgroups (Table 2). 43.5% (n = 10) of the patients with AKI KDIGO 3 required MV, compared to about 5.7% (n = 2) and 26.7% (n = 4) in groups 1 and 2 respectively (p = 0.003). The 43.5% (n = 10) of AKI KDIGO 3 required admission to an ICU versus approximately 8.6% (n = 3) of DRA KDIGO 1 and 33.3% (n = 5) in AKI KDIGO 2 (p = 0.07) (Table 2). In our population (n=73), 18 patients required admission to the ICU (about 25% of all patients with AKI). Figure 1 graphically summarizes the relationship between the severity of AKI and the need for ICU admission. Among the patients admitted to the ICU, there was there was a majority of AKI KDIGO 3 (3 (17%) DRA KDIGO 1, 5 (28%) KDIGO 2 and 10 (55%) KDIGO 3) compared to the group of patients who did not require it, with an inverse distribution (32 (58%) KDIGO 1, 10 (18%) KDIGO 2 and 13 (24%) KDIGO 3) (p <0.01). The percentage of patients with AKI KDIGO 3 who required RRT was higher among seriously ill patients admitted to the ICU: 70% (n=7) of AKI KDIGO 3 in the ICU group required RRT versus 15% (n = 2) in those they did not require intensive care.

CHARACTERISTICS	Study population (n=73)	KDIGO (n=35)	1 KDIGO 2 (n=15)	KDIGO 3 (n=23)	P value
Pneumonia, n (%)	64 (87.7)	30 (85.7)	13 (86.7)	21 (91.3)	0.86
Mechanical ventilation, n (%)	16 (21.9)	2 (5.7)	4 (26.7)	10 (43.5)	0.003
ICU, n (%)	18 (24.7)	3 (8.6)	5 (33.3)	10 (43.5)	0.007
Death, n (%)	25 (34.2)	9 (25.7)	3 (20.0)	13 (56.5)	0.02
ICU: Intensive Care Unit					

Table 2: Characteristics related to the severity of the SARS-CoV2 infection, with stratification according to the severity of acute kidney injury.

Renal Replacement Therapy

Nine of the AKI patients required RRT during stay, representing an incidence of 12.3%. Patients with RRT were younger [60 years (IQR, 55-66) versus 70 years (IQR 60-78) in patients without RRT], they had HT in an 66.7% (n=6) of cases, diabetes mellitus in 33.3% (n=3) and obesity in 11.1% (n=1) (Table 3). There were significant differences between the need for RRT and admission to the ICU and MV (p=0.001) (Table 3). Death rate was no different between the patients in both subgroups (p= 1.0). Intermittent hemodialysis (IHD) was required in 7 (78%) patients, for a median of 7 days (IQR 3-12). The continuous depurative technique with venovenous hemodialysis (VVHD) was used in 4 patients (44%), in two of whom it was alternated with IHD. The mean time of VVHD was 5 days (IQR 2-8). Low permeability polyamide membrane dialyzers were employed.

CHARACTERISTICS	Study population (n=73)	RRT (n=9)	NO RRT (n=64)	P value
Age, years, median (IQR)	69 (57-76)	60 (55-66)	70 (60-78)	0.03
Sex, n (%) Male	46 (63.0)	6 (66.7)	40 (62.5)	1
Comorbidities, n (%)				
Hypertension	41 (56.2)	6 (66.7)	35 (54.7)	0.74
Diabetes mellitus	27 (37.0)	3 (33.3)	24 (37.5)	1
CV disease	17 (23.3)	0	17 (26.6)	0.17
COPD	11 (15.1)	0	11 (17.2)	0.39
Asthma	3 (4.1)	1 (11.1)	2 (3.1)	0.33
Oncohematological	8 (11.0)	0	8 (12.5)	0.57
pathology				
Obesity	14 (19.2)	1 (11.1)	13 (20.3)	0.48
CKD, n (%)				
eFG > 60 ml/min/m^2	40 (61.5)	5 (62.5)	35 (61.4)	0.66
G3	16 (24.6)	1 (12.5)	15 (26.3)	
G4-5	9 (13.8)	2 (25.0)	7 (12.3)	
Pneumonia, n (%)	64 (87.7)	8 (88.9)	56 (87.5)	1
Mechanical ventilation, n (%)	16 (21.9)	7 (77.8)	11 (17.2)	0.001
ICU, n (%)	18 (24.7)	7 (77.8)	9 (14.1)	0.001
Death, n (%)	25 (34.2)	3 (33.3)	22 (34.4)	1

IQR: Interquartile Range; CV: Cardiovascular; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; ICU: Intensive Care Unit

Table 3: Clinical and demographic characteristics of the patients included in the study according to the need for renal replacement therapy.

Short-Term Clinical Course

In the total population with AKI (n=73), 48 were discharged due to cure or improvement of the SARS-CoV-2 infection (26 patients with AKI KDIGO 1, 12 AKI KDIGO 2, 10 AKI KDIGO 3). The mean hospital stay was associated with the severity of AKI: 7 days (IQR 3, 11) for AKI KDIGO 1, 11 days for KDIGO 2 (IQR 5, 22) and 12 days (IQR 8-35) for AKI KDIGO 3 patients (p=0.02). According to the end hospital stay; two possible alternatives were considered: hospital discharge with recovery of renal function and discharge without recovery of renal function. Of the 48 patients discharged, 30 (41.0% of all AKI patients; 62.5% of hospital discharges) had already recovered their baseline renal function (16 patients KDIGO 1, 11 KDIGO 2 and 3 KDIGO 3) (Figure 2). The remaining 18 (37.5%) patients had not recovered renal function at that time (10 KDIGO 1, 1 KDIGO 2 and 7 KDIGO 3). At hospital discharge, only 2 of the 9 patients who required RRT remained dependent on the technique (another 5 recovered kidney function and 2 died). This represents 2.7% of the patients who developed AKI and 0.77% of the total number of patients admitted for COVID-19. A total of 25 patients died during stary from COVID-19, which represents 34.2%. Table 4 shows the comorbidity and clinical characteristics of the patients according to the outcome. No significant differences were observed except for the presence of COPD, which was more frequent among deceased patients.

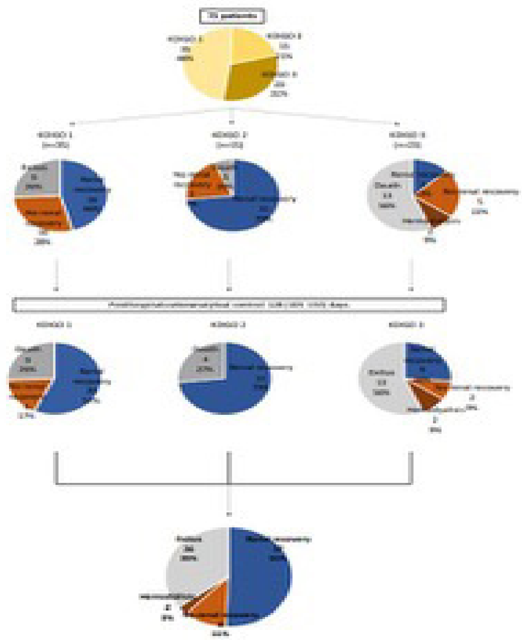

Figure 2: Short-medium-term clinical evolution of the patients included in the study. Shows the evolution of the patients included in the study: death versus hospital discharge (with or without recovery of renal function) at the end of admission due to SARS-CoV2 infection and after 128 days of clinical follow-up. At hospital discharge: KDIGO 1: 9 (26%) death; 16 (46%) renal recovery; 10 (28%) no recovery; KDIGO 2: 3 (20%) death, 11 (73%) renal recovery, 1 (7%) no recovery; KDIGO 3: 13 (56%) death, 3 (13%) renal recovery, 7 (31%) no recovery. Post-hospitalization analytical control: KDIGO 1: 9 (26%) death, 20 (57%) kidney recovery, 6 (17%) no recovery; KDIGO 2: 4 (27%) death; 11 (73%) renal recovery; KDIGO 3: 13 (56%) death; 6 (26%) renal recovery, 4 (18%) no renal recovery. Overall, from the third month after hospitalization: 26 (35%) death; 37 (51%) renal recovery; 10 (14%) no recovery.

CHARACTERISTICS	Study population (n=73)	Surviving patients (n=48, 65%)	Dead patients (n=25, 35%)	P value
Age, years, median (IQR)	69 (57-76)	67 (52-73)	73 (64-81)	0.02
Sex, n (%) Male	46 (63.0)	32 (66.7)	14 (56.0)	0.52
Comorbidities, n (%)				
Hypertension	41 (56.2)	26 (54.2)	15 (60.0)	0.82
Diabetes mellitus	27 (37.0)	15 (31.3)	12 (48.0)	0.25
CV disease	17 (23.3)	9 (18.8)	8 (32.0)	0.32
COPD	11 (15.1)	3 (6.3)	8 (32.0)	0.01

Asthma	3 (4.1)	3 (6.3)	0	0.54
Oncohematological	8 (11.0)	4 (8.3)	4 (16.0)	0.54
pathology				
Obesity	14 (19.2)	12 (25)	2 (8.0)	0.64
CKD, n (%)				
eFG > 60 ml/min/m2	40 (61.5)	27 (62.8)	13 (59.1)	0.54
G3	16 (24.6)	9 (20.9)	7 (31.8)	
G4-5	9 (13.8)	7 (16.3)	7 (31.8)	
Pneumonia, n (%)	64 (87,7)	40 (83.3)	24 (96.0)	0.23
Mechanical ventilation, n (%)	16 (21,9)	7 (14.6)	11 (44.0)	0.01
ICU, n (%)	18 (24,7)	6 (12.5)	10 (40.0)	0.02
RRT, n (%)	25 (34.2)	6 (12.5)	3 (12.0)	3 (12.0)

IQR: Interquartile Range; CV: Cardiovascular; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; ICU: Intensive Care Unit; RRT: Renal Replacement Therapy

Table 4: Clinical and demographic characteristics of AKI patients according to mortality.

From the point of view of the severity of the SARS-CoV2 infection, practically all the deceased patients had presented pneumonia (n=24; 96.0%), finding a statistically significant association between mortality and the need for admission to the ICU (p=0.01) and MV (p=0.02). Death occurred in a median time of 11 days (IQR, 8-14) from the onset of symptoms, 8 days (IQR, 5-10 days) from admission and 3 days (IQR, 1-8) from the diagnosis of AKI. The Kaplan-Meier survival analysis identifies significantly lower survival in AKI KDIGO 3 patients compared to AKI KDIGO 1 and 2 (log-rank 0.009) (Figure 3).

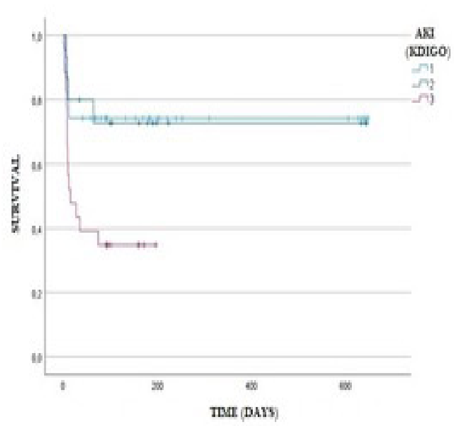

Figure 3: Kaplan-Meier survival curves for patients according to KDIGO classification. The blue line indicates patients with AKI KDIGO 1, the green line indicates patients with AKI KDIGO 2, and the red line is for those with AKI KDIGO 3. Figure 3 describes the Kaplan-Meier survival curve according to the KDIGO classification, representing the days until loss of follow-up, death, or last post-hospitalization analytical control. Patients with AKI KDIGO 3 had a significantly lower survival compared to DRA KDIGO 1 and 2 (log-rank 0.009).

Medium-Term Clinical Evolution

The creatinine and eGFR values of the included patients are summarized in Table 5. Before admission, these patients presented a mean eGFR of 69 ml/min (SD 29; 95%CI 61-76), with no differences between the different AKI stages (p=0.54). Creatinine levels during admission increased by a mean value of 0.53 (SD 0.28; 95%CI 0.42-0.63) mg/dl in the group of patients who developed AKD KDIGO 1, 1,13 (SD 0.60; 95%CI 0.79-1.46) mg/dl in the DRA KDIGO2 group and 3.30 (SD 2.05; 95%CI 1.37-4.25) mg/dl in the DRA KDIGO 3 group (p <0.001), reaching maximum creatinine of 1.64 (SD 0.63; 95%CI 1.42-1.85), 2.10 (SD 0.67; 95%CI 1.71-2.47) and 5.16 (SD 2.78; 95% CI 3.96-6.36) respectively (p <0.001) (Table 5). At the end of the stay (discharge or death of the patient), the mean creatinine was 1.89 (SD 1.60; 95% CI 1.52-2.27) with a mean creatinine differential of 0.66 mg/dl with respect to the value prior to the admission (SD 1.19; 95%CI 0.37-0.96) (Table 5). The data varied according to the severity of the AKI.

Analytical parameters	Total	KDIGO 1	KDIGO 2	KDIGO 3	P value
Previous creatinine, mg/dl, (SD, 95%CI)	**1.28 (0.91, 0.94-1.35)**	**1.14 (0.55, 0.93-1.37)**	0.97 (0.32, 0.78-1.14)	1.71 (1.41, 1.05-2.37)	0.31
Previous eFG, ml/min/1,73m², (SD, 95%CI)	69 (29, 61-76)	68 (25, 59-78)	82 (27, 67-97)	59 (33, 43-74)	0.54
Admission creatinine, mg/dl, (SD, 95%CI)	1.70 (1.48, 1.35-2.05)	1.40 (0.64, 1.16-1.62)	1.32 (0.62, 0.98-1.66)	2.42 (2.35, 1.40- 3.43)	0.01
Admission eFG, ml/min/1,73m², (SD, 95%CI)	55 (26, 49- 61)	55 (22, 48-63)	62 (25, 49- 76)	48 (32, 34-62)	0.27
Maximum creatinine, mg/dl, (SD, 95%CI)	2.84 (2.28, 2.31-3.37)	1.64 (0.63, 1.42-1.85)	2.10 (0.67, 1.72-2.47)	5.16 (2.78, 3.96- 6.36)	<0.001
Previous/maximum creatinine difference, mg/dl, (SD, 95%CI)	1.52 (1.68, 1.10-2.94)	0.53 (0.28, 0.42-0.63)	1.13 (0.60, 0.79-1.46)	3.30 (2.05, 2.33- 4.25)	<0.001
Discharge/death creatinine, mg/dl, (SD, 95%CI)	1.89 (1.60, 1.52-2.27)	1.30 (0.50, 1.13-1.47)	1.11 (0.56, 0.80-1.42)	3.30 (2.16, 2.37- 4.24)	<0.001
Previous/ discharge or death creatinine difference, mg/dl, (SD, 95%CI)	0.66 (1.19, 0.37-0.96)	0.15 (0.44, - 0.02-0.31)	0.15 (0.67, - 0.22-0.52)	1.83 (1.45, 1.14- 2.51)	<0.001
Posthospitalization creatinine, mg/dl, (SD, 95%CI)	1.68 (2.04, 0.98-2.38)	1.18 (0.53, 0.91-1.43)	1.02 (0.24, 0.82-1.22)	3.54 (3.79, 0.37- 6.71)	0.009
Posthospitalization eFG, ml/min/1,73m², (SD, 95%CI)	66 (30, 56- 76)	66 (30, 56- 76)	72 (27, 59-85)	83 (22, 65- 102)	0.001

Table 5: Analytical evolution of the patients included in the study. ANOVA test for independent samples.

Post-hospitalization renal function was monitored in 35 of the 48 patients who were discharged (19 (54%) KDIGO 1, 8 (23%) KDIGO 2, 8 (23%) KDIGO 3). The median time to analytical control after hospital discharge was 128 days (IQR, 103-153). In the post-hospitalization control, 7 more patients had recovered baseline renal function (Figure 2). Therefore, a total of 37 patients had recovered baseline renal function at that time. This represented 50.6% of all AKI patients and 77.0% of patients who did not die during admission due to COVID-19. Table 6 shows the pre/post-hospitalization creatinine and eGFR of the patients monitored according to the severity of AKI. The mean posthospitalization creatinine was 1.68 mg / dl (SD 2.04; 95%CI 0.98-2.38) and the mean eGFR was 66 ml/min/1.73m^2 (SD 30; 95%CI 56-76). The paired comparative analysis did not show significant pre-post-hospitalization differences in creatinine or eGFR (p=0.33 and p=0.69, respectively).

KDIGO	Previous creatinine, mg/dl, (SD, 95%CI)	Posthospitalization creatinine, mg/dl, (SD, 95%CI)	P value	Previous eFG, ml/min/1,73m2, (SD, 95%CI)	Posthospitalization eFG, ml/min/1,73m2, (SD, 95%CI)	P value
Total (n=35)	**1.48 (1.17, 1.07-1.90)**	**1.68 (2.04, 0.98-2.38)**	0.33	66 (30, 56-77)	66 (30, 56-76)	0.69
KDIGO 1 (n=19)	1.09 (0.50, 0.84-1.33)	1.18 (0.53, 0.92-1.43)	0.06	74 (25, 61-86)	72 (27, 59, 85)	0.24
KDIGO 2 (n=8)	1.07 (0.40, 0.73-1.39)	1.02 (0.24, 0.82-1.22)	0.69	76 (27, 53-98)	83 (22, 65-102)	0.39
KDIGO 3 (n=8)	2.98 (1.76, 1.35-4.61)	3.54 (3.79, 0.37-6.71)	0.96	36 (30, 8-64)	35 (22, 17-53)	0.41

Table 6: Analytical evolution of patients with monitoring of post-hospitalization renal function parameters. Analysis for pre-posthospitalization paired data.

Discussion

Acute Kidney Injury Incidence

AKI has been described as the second most frequent complication after severe Acute Respiratory Distress Syndrome (ARDS) in patients with COVID-19 [11]. However, its incidence may have been underestimated due to the retrospective design and the lack of homogeneity in the definition of AKI in published studies. The reported incidence of AKI ranges between 0.5%-5% in Chinese series and 11-46% in Western patients [1-3,12], reaching values of up to 76-80% in patients admitted to the ICU [3,4]. Fu et al., in a meta-analysis with 49,048 patients from 142 studies, reported a incidence of 28.6% in the United States and Europe8. These data are consistent with our study. However, Spanish series indicated a lower incidence, between 11-15% [10-12]. Perhaps this could respond to the fact that our hospital has an electronic alarm system designed to identify small significant increases in creatinine, identifying all cases of AKI with greater sensitivity.

Our AKI patients were mostly men, elderly, hypertensive and diabetic. Age, male sex, HT, diabetes mellitus and history of cardiovascular disease have been previously identified in the literature as predisposing factors for AKI in SARS-CoV-2 infection [6,8-9,13]. CKD is the most frequent comorbidity after HT and diabetes in our group. Portolés et al [12] reported a similar prevalence of CKD, associating it with a higher incidence of AKI, severity of SARS-CoV-2 infection and mortality. Other studies also associated CKD with longer hospital stay and ICU requirements [3,14]. The Egfr prior to admission was the only identified risk factor to develop AKI in our series; in fact, eGFR less than 30ml/min/1.73m^2 was associated with greater severity of the AKI. However, similarly to previous studies3,9, most of our patients had AKI KDIGO 1. The Spanish group of the Infanta Leonor Hospital identified AKI KDIGO 1 of prerenal cause as the most frequent in their series, representing 70% of cases [15].

Patients with the most severe AKI had a significantly lower survival compared to KDIGO 1 and 2 AKIs (log-rank 0.009). This close relationship between the severity of AKI and in-hospital mortality was reported in most of the published series, identifying it as a determining prognostic factor in SARS-CoV-2 infection [5,6,9,11].

Need for Renal Replacement Therapy

The main published studies reported an incidence of RRT in patients admitted for Sars-CoV-2 of 14-19%3,9, although important variations according to different series were evident [8,15,16]. Differences in the incidence of AKI, clinical management of the patient in each hospital, as well as the saturation of the Health Systems and the availability of technical and human resources to respond to this need, have been determining factors that have been able to influence these oscillations. In our study, RRT was required in 12% of all patients who developed AKI during admission, reaching 39% in the group of patients with AKI KDIGO [3].

Dialyzed patients were younger compared to the group of non-dialyzed patients. We do not have a clear justification for this fact. Although there could be a negative selection bias in older patients with a lower expectation of cure, it is also true that the patients who developed severe AKI, in most cases, were patients admitted to the ICU, with severe pneumonia and subjected to aggressive manoeuvres of ventilation. Therefore, they were more inflamed patients, with more hypoxemia, and with a higher overall probability of developing AKI in any context other than COVID-19.

Short-Term Clinical Evolution

More than half of the patients in our series were discharged home due to cure-improvement of the clinical picture of SARS-Cov2 infection. As previously reported in other series [14], the severity of AKI was related to the mean hospital stay. Only two patients remained on RRT, which represented 2.7% of all patients who developed AKI and 0.77% of all patients admitted for COVID-19. This result is frankly lower than the 11-37% found in the literature [3,4,9]. However, the permanence in RRT in previous series was referred to the moment of publication or to a specific moment in the course of the disease. For example, Rubin on al [4] reported the need for RRT on the seventh day after AKI. It is likely that the final percentage of dialysis-dependent patients would have been lower.

The proportion of patients who died in our series was high (34.2%), and consistent with mortality rates reported in the literature [2,9,15]. All publications have identified the development of AKI during hospitalization for COVID19 as an independent predictor of mortality, conditioning higher mortality in those patients with more severe kidney involvement [5,6]. In the study of Williamson et al. [13], eGFR < 60 ml/min /1.73m^2 was associated with a higher risk of death, with a Hazard ratio of 1.33 (1.28-1.40) for eGFR between 30-60 ml/min /1, 73m^2 and 2.52 (3.33-2.72) for eGFR less than 30 ml/min/1.73m^2. Contrary to these data, the presence of previous CKD did not decisively influence the mortality of our patients. However, our analysed population is small to extract conclusive results.

Medium-Term Clinical Evolution

There are limited data on the medium-long-term renal evolution of patients admitted for SARS- CoV-2 infection with AKI. Chan, et al. [3] reported that 65% of the patients who survived admission for COVID-19 recovered their kidney function at the time of hospital discharge; this percentage were over 69% after a mean follow-up of 21 days. These data are consistent with our study: 62.5% of patients had recovered their baseline renal function at the time of discharge. However, at 128 days of follow-up, renal recovery reached 77.0% of the survivors. Our study should be interpreted considering the following limitations. It is a retrospective study, therefore, with possible information biases. Furthermore, the small sample size, limited to a single centre, could make it difficult to extrapolate the results. We do not have a urine study in most patients, parameters that could guide us on the underlying pathogenic mechanisms of AKI. However, and even though the follow-up time is limited, it provides information on the short- medium-term evolution of kidney function in patients who developed AKI during hospitalization for COVID-19.

Conclusion

The incidence of AKI during hospitalization for SARS-CoV-2 during the first wave of the pandemic in our hospital area was very high, reaching 28.3%, with an associated mortality of 34.2%. The presence of CKD prior to admission was the only variable that was associated with the severity of AKI. In most of the patients who were discharged from hospital, renal function was recovered ad integrum after 3 months. The implications of AKI associated with SARS-CoV-2 infection in the development and progression of CKD are not yet clear. However, our data allow to be optimistic, and suggest that most patients affected by COVID-19 could recover renal function in the short-medium term.

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