Acute kidney injury (AKI) subphenotypes and acute kidney disease (AKD) in patients with severe and critical COVID-19.

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Purpose of the study

The emergence of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus in December 2019 rapidly evolved into a global pandemic. Uruguay was not immune to this pandemic, presenting peak infection rates between September 2020 and June 2021.
Although the main primary presentation of this virus has been pulmonary dysfunction (in the form of pneumonitis and acute respiratory distress syndrome [ARDS]), an increasing number of reports have identified other dysfunctions, such as renal dysfunction, with prognostic implications in terms of morbidity and mortality.
The objective of this study was to analyze the prognostic impact of renal compromise in COVID-19, particularly AKI and AKD.
The following were the specific objectives of the study:

(1) Determine the incidence of proteinuria, haematuria, AKI, with their different subphenotypes, and AKD associated with COVID-19.
(2) Determine the association of indirect factors with the development of AKI.
(3) Determine the prognostic implications of renal involvement on morbidity and mortality and the different degrees of organ support.

Materials and methods

This was a prospective, observational and analytical study of a cohort of patients with severe and critical COVID-19 admitted to the ICU at Hospital Español, ASSE, Montevideo, Uruguay. The COVID-19 was confirmed via RT-PCR for the SARS-CoV-2 virus.
Inclusion criteria: patients older than 18 years with severe and critical COVID-19 treated in the ICU.
Exclusion criteria : patients under 18 years of age and patients without a confirmed diagnosis of COVID-19.
Definitions:
-World Health Organization (WHO) severity COVID-19 definitions:
1-Critical COVID-19: ARDS, sepsis, septic shock, provision of life-sustaining therapies.
2-Severe COVID-19: oxygen saturation < 90% on room air; accessory muscle use, respiratory rate > 30 breaths per minute.
-Definitions for AKI and different subphenotypes:
1-AKI: KDIGO criteria based on delta creatinine and urinary output in a period of up to 7 days, including stages of severity (1-3).
2-Transient AKI: duration up to 48 hours.
3-Persistent AKI: duration between 48 hours and seven days.
4-Community AKI: diagnosed within the first 24 hours of stay in the ICU.
5-Nosocomial AKI: diagnosed after the first 24 hours of stay in the ICU.
6-Recovery of renal function: return of the renal function to baseline level.
7-AKI recurrence: new episode of AKI after recovery of renal function.
-Definitions for AKD and chronic kidney disease (CKD):
1-Acute kidney disease (AKD): renal dysfunction of more than seven days and up to 90 days of duration.
2-Chronic kidney disease (CKD): renal dysfunction lasting longer than 90 days.

Statistical analysis: Descriptive variables are expressed as n (%), mean (± SD), or median (IQR [interquartile range] Q1-Q3). Univariate and multivariate analyses were performed. Survival analysis was performed using the Kaplan-Meier test and log-rank test. Statistical differences were considered significant when the p-value was less than 0.05.

Results

n= 233 patients with severe and critical COVID-19 admitted to the ICU at Hospital Español between September 2020 and May 2021.
General characteristics of the population studied are presented in Table 1.
Figure 1 shows the comorbidities of the population studied, predominated arterial hypertension (41%), diabetes (22%), obesity (15%) and chronic obstructive pulmonary disease (COPD) (13%).
Table 2 shows the frequencies of renal involvement (haematuria, proteinuria, AKD, and AKI, with their different subphenotypes).
AKI associated with COVID-19 occurred in 47.9% of the population studied (107/233), severe AKI (KDIGO stages 2 and 3) in 79.4% (85/107), and nosocomial AKI in 47.7% (52/107). AKD in 41.1% of those with AKI (44/107), with 29.9% (32/107) requiring KRT.
Table 3 provides the characteristics of the patients who presented AKI associated with COVID-19 and those who did not show AKI.
The mortality at ICU discharge for patients with AKI was 78/107 (72.9%), and that for patients without AKI was 61/126 (48.4%) (p = .000).
Mortality of patients with AKI and KRT was 28/32 (87.5%), the four survivors who required KRT had normal renal function at ICU discharge.
Figure 2 shows the mortality status at discharge for patients with AKI based on KDIGO stage: stage 1, 36.4% (8/22); stage 2, 68.4% (13/19); and stage 3, 86.4% (57/64); p. = .000.
Table 4 provides the different characteristics of patients who survived and those who died during their ICU stay.
The multivariate analysis indicated that plasma ferritin concentration predicted the risk of developing AKI (OR 1.00, 95% CI: 1.000-1.001, p = .043).
The multivariate analysis indicated that normal renal function at discharge (OR .055, 95% CI: .014-.213, p = .000), age (OR 1.040, 95% CI: 1.008-1.073, p = .015) and the use of vasopressors (OR 43.62, 95% CI: 4.905-387.924, p = .001) were predictors of risk of death at discharge from ICU.
Figure 3 shows the mortality status at discharge of the patients based on the degree of organic support used: IMV, 38.7% (12/31); IMV + vasopressors, 78.9% (86/109); and IMV + vasopressors + KRT, 96.3% (26/31) (p = .000).
ICU stay (days [median, IQR $_{25\text{-}75}$]) based on degree of organ support was as follows: IMV, 25 (12.5-36.3); IMV + vasopressors, 18 (6-27.5); and IMV + vasopressors + KRT, 15 (6-31) (p = .063).

Discussion

In this study, we analyzed the data of 233 patients admitted to the ICU of Hospital Español for severe and critical COVID-19, there was a predominance of AKI in patients with more severe disease and was associated with significantly higher mortality. The normalization of renal function was a predictive and protective factor of the risk of death. AKI severity and the degree of multiorgan support were associated with a progressive increase in mortality.
When analyzing mortality at ICU based on the degree of organ support, significantly higher and increased mortality was observed.
Identification of AKI subphenotypes can facilitate research and clinical management. Several approaches have been utilized for subphenotyping patients. These approaches are: clinical characteristics (oligoanuric AKI, community AKI, nosocomial AKI), AKI evolution over time (transient AKI, persistent AKI, AKI recurrence), AKI severity (AKI stages 1, 2, and 3, severe AKI), and AKI biomarkers. AKI subphenotypes are associated with different outcomes and can be used to define certain therapeutic strategies.
AKI was observed in 47.9% of patients, and more than half of them presented oligoanuria. Among the different AKI subphenotypes analyzed, the predominance of AKI of community origin (52.3%), severe AKI (stages 2 and 3) (79.4%), and AKD (41.1%) was notable. One-third of patients with AKI required KRT in the form of IHD.
A total of 13% and 23.4% of patients with AKI had recurrent episodes of AKI and normal renal function upon discharge from the ICU.
In different reported series of critically ill patients with COVID-19, the incidence of AKI based on KDIGO criteria ranged from 30.6% to 86.5%. Mortality at discharge reported for critically ill patients with AKI associated with COVID-19 ranged from 35% to 60.5%. The percentage of patients requiring KRT ranged from 8.6% to 20.6%. Among the patients who survived, one-third remained dependent on KRT at hospital discharge. Renal function did not recover in a high percentage of patients with AKI (between 45.73% and 47%).
In this study, patients who developed AKI were older, had more CKD, higher APACHE II and SOFA scores and higher mortality at discharge from the ICU (72.9% vs. 48.4%). Patients with AKI had significantly lower lymphocyte counts and higher LDH and ferritin values. Patients with AKI had significantly lower pH and SBE levels as well as higher potassium concentrations.
The presence of proteinuria and haematuria in patients who developed AKI was significantly higher than those who did not develop AKI.
The pathogenesis of AKI in patients with COVID-19 is multifactorial, involving both the direct effects of the SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection, in addition to mechanisms relating to the critical care management of COVID-19 (fluid balance, mechanical ventilation, hypovolemia, vasopressors, nephrotoxins, sepsis).
If we consider the indirect factors involved in the development of AKI, there was a significantly greater presence of IMV, vasopressor use, positive fluid balance, and nephrotoxic agents in patients with AKI.
When comparing non-survivor patients with survivors, the former were significantly older, had higher APACHE II and SOFA scores and CRP, LDH, and ferritin concentrations, and more significant lymphopenia. A significantly higher percentage of non-survivors required NIV, IMV, vasopressors, and KRT.
Non-survivor patients had a significantly higher proportion of AKI, severe AKI, oligoanuria, nosocomial AKI, AKD, and AKI recurrence. A significantly higher percentage of survivor than non-survivor patients had a normal renal function at discharge (69% vs. 6.4%).
In the multivariate analysis of this series of patients, AKI was not an independent risk factor for mortality, but normal renal function at discharge (OR .055), age (OR 1.04), and the use of vasopressors (OR 43.62) were.
In this study, the only predictive risk factor for the development of AKI was plasma ferritin level.

References

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Figure 1-Comorbidities of the population studied.

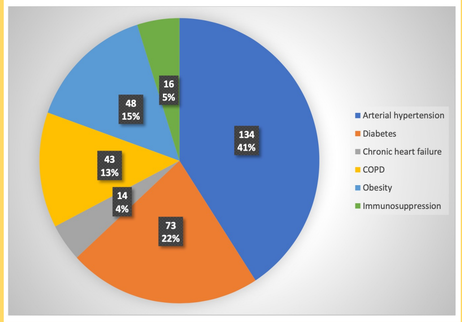

Figure 2- Mortality status at discharge for patients with AKI based on KDIGO stage.

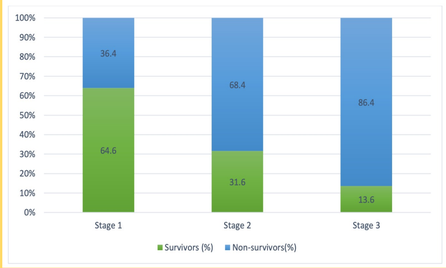

Figure 3- Mortality status at the discharge of the patients based on the degree of organ support.

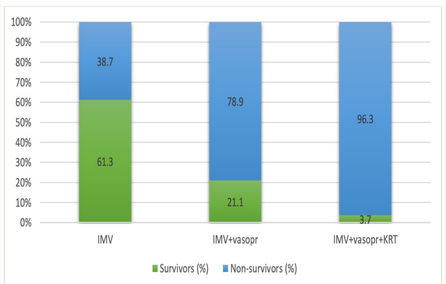

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Table 1-General characteristics of the studied population.

Age (years, [mean, SD])	62.7 ± 14.7
Male gender (n [%])	133 (57.1%)
Length of stay ICU(days,[median, IQR$_{25\text{-}75}$])	14 (6-26)
APACHE II score (mean, SD)	17.2 ± 9.1
SOFA global score (mean, SD)	5.43 ± 3.3
CRP (mg/L [mean, SD])	189.6 ± 109.7
Lymphocyte count (n/mm^3 [median, IQR$_{25\text{-}75}$])	500 (300-800)
LDH (U/L [median, IQR$_{25\text{-}75}$])	657 (444.5-891)
Ferritin (ng/mL [median, IQR$_{25\text{-}75}$])	1599 (816-2625.5)
D dimer (µg UEF/ml [median, IQR$_{25\text{-}75}$])	2.46 (0.71-6.4)
CKD (n [%])	25 (10.7%)
O2 (n [%])	98 (42.1%)
HFNO (n [%])	89 (38.2%)
NIV (n [%])	99 (42.5%)
IMV (n [%])	168 (72.1%)
IMV length (days [median, IQR$_{25\text{-}75}$])	14 (5-26)
Vasopressors (n [%])	146 (62.7%)
KRT (n [%])	38 (16.3%)
IMV + vasopressors (n [%])	109 (46.8%)
IMV + vasopressors + KRT (n [%])	29 (12.4%)
Positive fluid balance (n [%])	53 (22.7%)
Nephrotoxics (n [%])	91 (39.1%)
Nosocomial superinfection (n [%])	154 (66.1%)
ICU Mortality (n [%])	139 (59.7%)

HFNO: high flux nasal oxigen
NIV: non invasive ventilation
IMV: invasive mechanical ventilation
KRT: kidney replacement therapy
CRP: C-reactive protein
IHD: intermitent hemodialysis

Table 2-Renal involvement characteristics.

Proteinuria (n [%])	110/233 (47.2%)
Haematuria (n [%])	100/233 (42.9%)
AKI (n [%])	107/233 (47.9%)
Maximum creatinine concentration (mg/dL [median, IQR$_{25\text{-}75}$])	2.83 (1.85-4.37)
Oligoanuria (n [%])	60/107 (56.1%)
Community AKI (n [%])	56/107 (52.3%)
Nosocomial AKI (n [%])	52/107 (47.7%)
AKI stage 1 (n [%])	22/107 (20.5%)
AKI stage 2 (n [%])	19/107 (17.8%)
AKI stage 3 (n,[%])	66/107 (61.7%)
Severe AKI (stages 2 and 3) (n [%])	85/107 (79.4%)
Transient AKI (n [%])	20/107 (18.7%)
Persistent AKI (n [%])	43/107 (40.2%)
AKD(n [%])	44/107 (41.1%)
AKI recurrence (n [%])	14/107 (13%)
KRT (n [%])	32/107 (29.9%)
Normal renal function at ICU discharge (n [%])	25/107 (23.4%)

Table 3-Characteristics of patients with AKI versus patients without AKI.

	AKI	No AKI	p
Age (years [mean, SD])	66.84 ± 13.26	59.12 ± 15.02	,000
Male gender (n [%])	64/107 (59.8%)	69/126 (54.8%)	,438
CKD (n [%])	17/107 (15.9%)	8/126 (6.3%)	,019
APACHE II score(mean, SD)	19.49 ± 9.18	15.26 ± 8.65	,000
SOFA score (mean, SD)	6.32 ± 3.31	4.68 ± 3.17	,000
Length of stay ICU(days,[median, IQR$_{25\text{-}75}$])	12 (6-21.5)	16 (7-29.5)	,045
Died at ICU discharge (n [%])	78/107 (72.9%)	61/126 (48.4%)	,000
CRP (mg/L [mean, SD])	198.13 ± 114.2	182.34 ± 105.6	,278
Lymphocyte count (n/mm^3 [median, IQR$_{25\text{-}75}$])	400 (200-600)	500 (400-900)	,000
LDH (U/L [median, IQR$_{25\text{-}75}$])	678 (509-990)	645 (378-851)	,034
Ferritin (ng/mL [median, IQR$_{25\text{-}75}$])	2041 (1164-3156)	1429 (702-2348)	,001
D dímer (µg UEF/ml [median, IQR$_{25\text{-}75}$])	2.57 (0.60-7.4)	2.44 (0.74-5.92)	,973
Serum albumin (gr/dL [mean, SD])	2.92 ± 0.7	3.04 ± 0.6	,168
Serum sodium (mEq/L [mean, SD])	138.2 ± 9.6	138.6 ± 8	,771
Serum potassium (mEq/L [mean, SD])	4.8 ± 1.11	4.3 ± 0.98	,001
pH (mean, SD)	7.28 ± 0.16	7.38 ± 0.12	,000
PaCO2 (mm Hg [mean, SD])	48.32 ± 21	48.11 ± 17	,934
SBE (mmol/L [mean, SD])	-4.6 ± 7.2	2.3 ± 8.2	,000
O2 (n [%])	45/107 (42.1%)	53/126 (42.1%)	,999
HFNO (n [%])	38/107 (35.5%)	51/126 (40.5%)	,437
NIV (n [%])	40/107 (37.4%)	59/126 (46.8%)	,146
IMV (n [%])	84/107 (78.5%)	84/126 (66.7%)	,045
Vasopressors (n [%])	77/107 (72%)	69/126 (54.8%)	,007
Proteinuria (n [%])	63/79 (79.7%)	47/94 (50%)	,000
Haematuria (n [%])	59/81 (72.8%)	41/101 (40.6%)	,000
Positive fluid balance (n [%])	38/107 (35.5%)	15/126 (11.9%)	,000
Nephrotoxics (n [%])	52/107 (48.6%)	39/126 (31%)	,006
Nosocomial superinfection (n [%])	74/107 (69.2%)	80/126 (63.5%)	,363
Vaccines (n [%])	3/107 (2.8%)	8/126 (6.3%)	,204

Table 4-Characteristics of survivors and non-survivors during ICU stay.

	Survivors	Non-survivors	p
Age (years [mean, SD])	58.88 ± 15.04	65.22 ± 13.99	,001
Male gender (n [%])	47/94 (50%)	86/139 (61.9%)	,073
CKD (n [%])	6/94 (6.4%)	19/139 (13.7%)	,078
APACHE II score (mean, SD)	13.82 ± 7.26	19.49 ± 9.56	,000
SOFA score (mean, SD)	4.12 ± 2.85	6.32 ± 3.35	,000
CRP (mg/L [mean, SD])	166 ± 104	205 ± 110	,006
Lymphocyte count (n/mm^3 [median, IQR$_{25\text{-}75}$])	500 (400-950)	400 (215-700)	,000
LDH (U/L [median, IQR$_{25\text{-}75}$])	595 (386-767)	699 (479-1020)	,004
Ferritin (ng/mL [median, IQR$_{25\text{-}75}$])	1252 (727-2309)	1981 (1065-3191)	,001
D dimer (µg UEF/ml [median, IQR$_{25\text{-}75}$])	2.43 (0.62-5.3)	2.5 (0.83-7.64)	,143
O2 (n [%])	58/94 (61.7%)	40/139 (28.8%)	,000
HFNO (n [%])	45/94 (47.9%)	44/139 (31.7%)	,012
NIV (n [%])	32/94 (34%)	67/139 (48.2%)	,032
IMV (n [%])	42/94 (44.7%)	126/139 (90.6%)	,000
Vasopressors (n [%])	26/94 (27.7%)	120/139 (86.3%)	,000
KRT (n [%])	5/94 (5.3%)	33/139 (23.7%)	,000
KRT in AKI (n [%])	4/94 (4.3%)	28/139 (20.1%)	,001
IMV alone (n [%])	19/94 (20.2%)	14/139 (10.1%)	,029
IMV + vasopressors (n [%])	23/94 (24.5%)	84/139 (60.4%)	,000
IMV + vasopressors + KRT (n [%])	1/94 (1.1%)	28/139 (20.1%)	,000
Proteinuria (n [%])	44/75 (58.7%)	66/98 (67.3%)	,240
Haematuria (n [%])	40/77 (51.9%)	60/105 (57.1%)	,487
AKI (n [%])	29/94 (30.9%)	78/139 (56.1%)	,000
Oligoanuria (n [%])	4/94 (4.3%)	63/139 (45.3%)	,000
AKI stage 1 (n [%])	14/94 (14.9%)	8/139 (5.8%)	,019
AKI stage 2 (n [%])	6/94 (6.4%)	13/139 (9.4%)	,416
AKI stage 3 (n [%])	9/94 (9.6%)	57/139 (41%)	,000
Severe AKI (stages 2 and 3) (n [%])	15/94 (16%)	70/139 (50.4%)	,000
Community AKI (n [%])	21/94 (22.3%)	35/139 (25.2%)	,619
Nosocomial AKI (n [%])	10/94 (10.6%)	42/139 (30.2%)	,000
Transient AKI (n [%])	9/94 (9.6%)	11/139 (7.9%)	,657
Persistent AKI (n [%])	13/94 (13.8%)	30/139 (21.6%)	,134
AKD (n [%])	8/94 (8.5%)	37/139 (26.6%)	,001
AKI recurrence (n [%])	1/94 (1.1%)	13/139 (9.4%)	,009
Normal renal function at ICU discharge (n [%])	20/29 (69%)	5/78 (6.4%)	,000
Positive fluid balance (n [%])	17/94 (18.1%)	36/139 (25.9%)	,163
Nephrotoxics (n [%])	33/94 (35.1%)	58/139 (41.7%)	,310
Nosocomial superinfection (n [%])	48/94 (51.1%)	106/139 (76.3%)	,000
Vaccines (n [%])	5/94 (5.3%)	6/139 (4.3%)	,723
Length of stay ICU(days,[median, IQR$_{25\text{-}75}$])	12 (7-30.5)	15 (5.5-25.5)	,385

Conclusions

Renal involvement, such as AKI and AKD, has been shown to be frequent in patients with severe and critical COVID-19. There was a predominance of more severe AKI stages, and AKI was associated with significantly higher mortality. The normalization of the renal function served as a predictive and protective factor of the risk of death. AKI severity and degree of multiorgan support were associated with a progressive increase in mortality. The early detection of AKI and the control of indirect aetiological factors could prevent its progression to more severe stages and a worse prognosis.