

THE INCIDENCE, RISK FACTORS AND IMPACT OF ACUTE KIDNEY INJURY IN HOSPITALIZED PATIENTS DUE TO COVID-19

PEHUÉN FERNÁNDEZ^{1, 2}, EMANUEL J. SAAD^{2, 3}, AUGUSTO DOUTHAT BARRIONUEVO³, FEDERICO A. MARUCCO^{2, 3}, MARÍA CELESTE HEREDIA^{2, 3}, AYLÉN TARDITI BARRA³, SILVINA T. RODRIGUEZ BONAZZI³, MELANI ZLOTOGORA³, MARÍA ANTONELLA CORREA BAROVERO³, SOFÍA M. VILLADA⁴, JUAN PABLO MALDONADO¹, MARÍA LUJÁN ALAYE¹, JUAN PABLO CAEIRO^{2, 4}, RICARDO A. ALBERTINI^{2, 3}, JORGE DE LA FUENTE^{1, 2}, WALTER G. DOUTHAT^{1, 2}

¹Servicio de Nefrología, Hospital Privado Universitario de Córdoba, ²Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), ³Servicio de Clínica Médica, Hospital Privado Universitario de Córdoba, ⁴Servicio de Enfermedades Infecciosas, Hospital Privado Universitario de Córdoba, Córdoba, Argentina

Abstract The incidence of acute kidney injury (AKI) in hospitalized patients with COVID-19 is variable, being associated with worse outcomes. The objectives of the study were to evaluate the incidence, risk factors (considering demographic characteristics, comorbidities, initial clinical presentation and associated complications) and impact of AKI in subjects hospitalized for COVID-19 in two third-level hospitals in Córdoba, Argentina. A retrospective cohort study was conducted. We included 448 adults who were consecutively hospitalized for COVID-19 between March 3 and October 31, 2020 and were followed throughout the hospitalization. The incidence of AKI was 19% (n = 85; stage I = 43, stage II = 17, and stage III = 25, 18 required renal replacement therapy). In the multivariate analysis, the variables that were independently associated with AKI were: age (for every 10 years, adjusted odd ratio [95%CI] = 1.30 [1.04-1.63], p = 0.022), history of chronic kidney disease –CKD– (9.92 [4.52-21.77], p < 0.001), blood neutrophil count at admission –BNCA– (for every increase of 1000 BNCA, 1.09 [1.01-1.18], p = 0.037) and requirement for mechanical ventilation –MV– (6.69 [2.24-19.90], p = 0.001). AKI was associated with longer hospitalization, higher admission (63.5 vs. 29.7%; p < 0.001) and longer stay in the intensive care unit, a positive association with respiratory bacterial superinfection, sepsis, respiratory distress syndrome, MV requirement and mortality (mortality without AKI = 12.4% vs with AKI = 47.1%; stage I = 26%, stage II = 41% and stage III = 88%; p < 0.001). AKI was independently associated with higher mortality (3.32 [1.6-6.9], p = 0.001). In conclusion, the incidence of AKI in adults hospitalized for COVID-19 was 19% and had a clear impact on morbidity and mortality. The independent risk factors for AKI were: Age, CKD, BNCA and MV.

Key words: acute kidney injury, COVID-19, SARS-CoV-2, epidemiology, risk factors, mortality

Resumen *Incidencia, factores de riesgo e impacto de la lesión renal aguda en pacientes hospitalizados por COVID-19.* Los objetivos del estudio fueron evaluar la incidencia, los factores de riesgo (considerando características demográficas, comorbilidades, presentación clínica inicial y complicaciones asociadas) y el impacto de la lesión renal aguda –LRA– en sujetos hospitalizados por COVID-19 en dos instituciones de alta complejidad de Córdoba, Argentina. Se realizó un estudio de cohorte retrospectivo. Se incluyeron 448 adultos que fueron hospitalizados por COVID-19 entre el 3 de marzo y el 31 de octubre del 2020 con seguimiento durante toda la hospitalización. La incidencia de LRA fue 19% (estadio I = 43, estadio II = 17 y estadio III = 25, 18 requirieron diálisis). Las variables que se asociaron de manera independiente con el LRA fueron: edad (por cada 10 años, *odd ratio* ajustado [IC95%] = 1.30 [1.04-1.63], p = 0.022), enfermedad renal crónica –ERC– (9.92 [4.52-21.77], p < 0.001), recuento de neutrófilos sanguíneos al ingreso –NSI– (por cada incremento de 1000 NSI, 1.09 [1.01-1.18], p = 0.037) y asistencia respiratoria mecánica –ARM– (6.69 [2.24-19.90], p = 0.001). Los sujetos con LRA presentaron una internación más prolongada, mayor requerimiento (63.5 vs. 29.7%; p < 0.001) y estadía más prolongada en unidad de cuidados intensivos, una asociación positiva con sobreinfección respiratoria bacteriana, sepsis, síndrome de distrés respiratorio, requerimiento de ARM y mortalidad (mortalidad sin LRA 12.4% vs. con LRA 47.1%; estadio I = 26%, estadio II = 41% y estadio III = 88%; p < 0.001). LRA se asoció de manera independiente a mayor mortalidad (3.3 [1.6-6.9], p = 0.001). En conclusión, la incidencia de LRA en adultos hospitalizados por COVID-19 fue del 19% y tuvo un claro impacto en la morbi-mortalidad. Los factores de riesgo independientes de LRA fueron: edad, ERC, NSI y ARM.

Palabras clave: lesión renal aguda, infecciones por coronavirus, epidemiología, estudios de cohortes, factores de riesgo, mortalidad

Received: 10-V-2021

Accepted: 20-VIII-2021

Postal address: Pehuén Fernández, Hospital Privado Universitario de Córdoba, Naciones Unidas 346, Barrio Parque Vélez Sarsfield, 5016 Córdoba, Argentina

e-mail: pehuenfernandez@hotmail.com

KEY POINTS

Current knowledge

- The incidence of acute kidney injury (AKI) in adults hospitalized for SARS-CoV-2, the risk factors for AKI and the impact on morbidity and mortality, varies widely according to reports in different parts of the world.

Contribution of the article to current knowledge

- The incidence of AKI in adults hospitalized for SARS-CoV-2 was 19%.
- The independent risk factors for AKI were age, chronic kidney disease, mechanical ventilation and neutrophil count at admission (the latter not described in previous studies).
- Mortality in subjects with AKI was 47.1% and was also associated with other adverse outcomes.

The outbreak of severe acute respiratory syndrome (COVID-19) due to SARS-CoV-2 has quickly turned into a global pandemic with devastating consequences^{1,2}. The first case reported in Córdoba, Argentina was on March 3, 2020³. As of May 8, 2021, more than 230 000 infected people had been reported, and more than 3.1 million in Argentina⁴.

Patients with COVID-19 present an eminently respiratory affection that can trigger in its most severe forms an acute respiratory distress syndrome (ARDS), although cardiac, hematological, digestive, neurological and renal affection has also been described⁵⁻⁷. The incidence of acute kidney injury (AKI) in patients hospitalized for COVID-19 varies between 0.5% and 80.3% according to the different series⁵⁻¹². Direct viral cytotoxicity in kidney cells and kidney damage secondary to hypoperfusion and hypoxia due to hemodynamic instability, heart and lung damage, damage mediated by pro-inflammatory cytokines such as thrombotic microangiopathy and rhabdomyolysis, among others, have been described as possible etiologies of AKI¹³⁻¹⁵. As in AKI due to other causes, AKI secondary to COVID-19 has been associated with adverse outcomes, including worsening of other comorbidities, greater use of health care resources, and higher mortality¹⁶. Current reports of mortality among subjects hospitalized for COVID-19 with AKI vary widely across different cohorts, ranging from 7 to 100%^{12, 17-19}. Factors associated with AKI and its impact on patients hospitalized for COVID-19 have not yet been evaluated in our country. Local studies are needed to better understand the AKI associated with COVID-19 and thus optimize the management of this disease and its complications.

The objectives of the study were to evaluate the incidence, risk factors, and impact of acute renal failure in hospitalized subjects due to active SARS-CoV-2 infection in two third level hospitals in Córdoba, Argentina.

Material and methods

A retrospective cohort study was conducted. Adults who were hospitalized due to active SARS-CoV-2 infection between March 3, 2020 and October 31, 2020 in the Hospital Privado Universitario de Córdoba and Hospital Raúl Angel Ferreyra in Córdoba city were consecutively included.

Patients hospitalized for reasons other than COVID-19 and those who were referred to another institution within the first 48 hours of admission were excluded.

An active SARS-CoV-2 infection was defined as confirmed diagnosis by any of the available methods (RT-PCR, antigen or serology for SARS-CoV-2) and admission to hospital within the first 21 days from the onset of symptoms or confirmation of the diagnosis (whichever occurred first).

Demographic data, comorbidities, clinical characteristics, and complementary studies carried out at hospital admission, as well as those related to the treatment and evolution of each patient, were obtained from the electronic medical record. Each case was followed up throughout the hospitalization.

AKI and AKI stages were defined according to The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for acute kidney injury²⁰. The presence of comorbidities was defined according to the record in the clinical history that the patient had this pathology and / or presented its diagnostic characteristics, according to current definitions. Based on this, arterial hypertension was defined according to American College of Cardiology/American Heart Association (ACC/AHA)²¹, obesity as the presence of a body mass index ≥ 30 Kg/m²²² and diabetes mellitus according to the criteria of American Diabetes Association²³. Chronic kidney disease was defined as a structural or functional abnormality of the kidney present for more than 3 months and determined by the reduction of the glomerular filtration rate below 60 ml/min/1.73 m²²⁴, ischemic heart disease as the inadequate supply of blood to the myocardium due to obstruction of the epicardial coronary arteries and chronic heart failure as the presence of compatible clinical symptoms, with objective evidence of heart failure and that specific treatment was indicated for it²⁵. Regarding complications, pneumonia was defined according to current diagnostic criteria, based on symptoms and the presence of compatible pulmonary infiltrates in diagnostic imaging methods²⁶, acute respiratory distress syndrome according to the Berlin criteria²⁷ and bacterial superinfection was defined as respiratory co-infection during the course of the disease or hospital stay²⁸. Any patient with a SOFA score ≥ 2 who also have a vasopressor requirement and an elevated lactate > 2 mmol/l (>18 mg/dl) was considered that underwent a septic shock²⁹.

The determination of creatinine was performed by using the kinetic Jaffé method (Roche Diagnostics, Sussex, United Kingdom) traceable to the IDMS reference method in a Modular P autoanalyzer (normal value-NV: 0.6-1.2 mg/dl). The calibration of the test was performed with a commercial lyophilized calibrator for automated systems. Leukocytes (NV: 4.5-9.4 k/ μ l), neutrophils (NV: 35-70%), lymphocytes (NV: 20-43%) and platelets (NV: 150-350 k/ μ l) were measured by flow cytometry (XN-3000 autoanalyzer, SYSMEX, Japan); C-reactive protein (NV < 0.6 mg/dl) and ferritin (NV: 15-250 ng/ml in men and 10-150 in women) by immunoturbidimetry (COBAS 8000- c702 autoanalyzer, ROCHE, Germany); procalcitonin (NV < 0.5 ng/ml) and ultrasensitive troponin T (NV < 14 pg/ml) by electrochemiluminescence (COBAS 8000- e801 autoanalyzer, ROCHE, Germany); and D-dimer (NV < 0.5 μ g/ml) by enzyme linked fluorescent assay (Mini VIDAS autoanalyzer, BIOMÉRIEUX, France). All the determinations used participated in internal and external quality control programs (RIQAS, United Kingdom) and surpassed the recommended analytical quality specifications (acceptable total error).

According to the institutional action protocol and taking into account the clinical criteria, the availability of drugs and the scientific evidence at each moment, the therapeutic options were: prophylactic heparin with enoxaparin 40 mg/day during the entire hospitalization, dexamethasone 8 mg/day for 10 days (or its equivalent in hydrocortisone), convalescent plasma 1 dose/day of 200 ml for 2 days, hydroxychloroquine sulfate 200 mg/12 h for 10 days, Lopinavir 400 mg + Ritonavir 100 mg/12 h for 10-14 days, nebulized ibuprofen 50 mg/8 h until the moment of clinical improvement or up to 28 days from the beginning of its administration, ruxolitinib 15 mg/day for 14 days, tocilizumab 4-8 mg/kg/day one dose and methylprednisolone 250 mg/day for 3 days. To receive off-label prescription drugs, all patients signed an informed consent. When there was suspicion or confirmation of respiratory bacterial superinfection ceftriaxone 2 g/day combined with azithromycin 500 mg/day for at least 5 days were the first option. Other antibiotics were used according to the infectious focus and medical criteria.

For statistical analysis, continuous variables were expressed as mean and standard deviation or median (M) and 25-75 percentile interquartile range (IQR) and their comparison was made with Student's t-test or Mann-Whitney according to the variable distribution. Categorical variables were expressed as absolute frequency (n) and relative frequency (%) and were compared with chi-square test or Fisher's exact test, according to the expected frequencies. To assess the risk factors for AKI (dependent variable 1) and if it was independently associated with death (dependent variable 2), logistic regression was used. In the first place, univariate analyzes were performed considering as independent variables all demographic characteristics, comorbidities, initial clinical presentation and associated complications during follow-up, and then all the variables that reached statistical significance were included in multivariate models (independent variables), except those that presented more than 20% of missing data. Then the best models were chosen according to the adjusted R^2 value and the Akaike information criterion. Goodness of fit was checked using the Hosmer Lemeshow test. To assess whether AKI was independently associated with mortality, we adjusted for the rest of the complications that were associated with mortality

in the univariate analysis. Adjusted odd ratio (aOR) with its 95% confidence interval (95% CI) was used as association measures. All the tests were two-tailed and a p value less than 0.05 was considered statistically significant. Statistical analysis was performed with Stata 14 statistical program (Stata-Corp. LP., College Station, TX, USA).

The study was reviewed and approved by the research committee of the Hospital Privado Universitario de Córdoba who decided that informed consent was not necessary due to the observational and retrospective design of the study, the anonymity of the data and that it did not represent any risk for the participants.

Results

During the study period, 450 adults were hospitalized due to active SARS-CoV-2 infection. Two patients were referred to another institution during the first 48 hours and were excluded from the analysis (Fig. 1). A total of 448 patients were included, with a median age of 63 (IQR 53-75) years, 63.6% were men. Seventeen % had criteria for admission to the intensive care unit (ICU) at hospital admission. The most frequent comorbidities were hypertension (55.1%), obesity (31.7%) and diabetes (28.1%) and the most frequent clinical manifestations were fever (74.8%) and respiratory symptoms such as cough and dyspnea (Table 1). Pneumonia was evidenced in 95.8% of the patients. The incidence of AKI was 19% (85/448). Of these, 36 (42.3%) presented AKI upon admission and 49 (57.7%) developed it during hospitalization. Stage 1 AKI was observed in 50.6%, stage 2 in 20% and stage 3 in 29.4%. In this last group, 18 subjects required renal replacement therapy (RRT). The incidence of AKI among patients who remained only in general ward throughout their hospitalization was 10.8% (31/286) and among

Fig. 1.– Flow chart of the inclusion of the subjects in the study and the assignment of groups

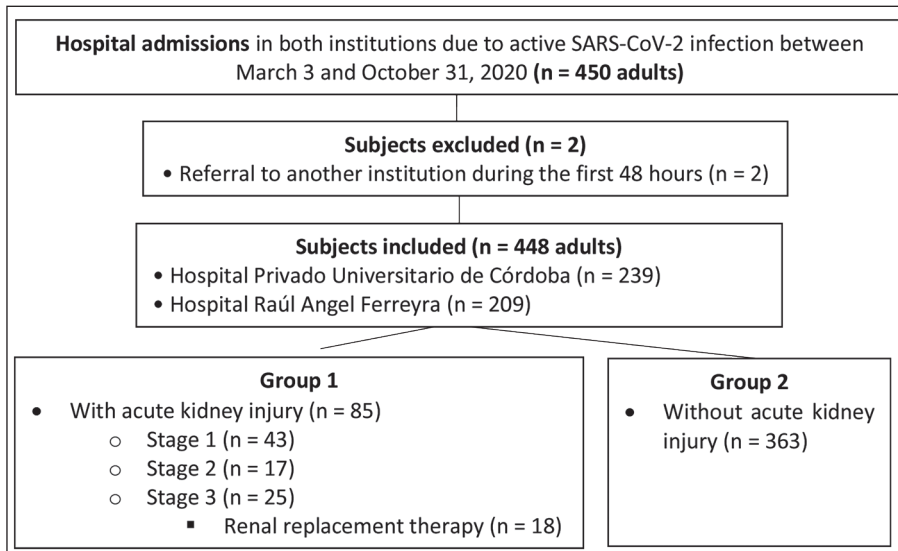


TABLE 1.— *Baseline characteristics and clinical presentation at the time of hospital admission of the studied population*

Baseline clinical characteristics	Todos (n 448)
Meets admission criteria in	
General ward, n (%)	372 (83)
Intensive care unit, n (%)	76 (17)
Comorbidities	
Arterial hypertension, n (%)	247 (55.1)
Obesity, n (%)	142 (31.7)
Diabetes mellitus, n (%)	126 (28.1)
Chronic kidney disease, n (%)	46 (10.3)
Immunocompromised, n (%)	43 (9.6)
Ischemic heart disease, n (%)	35 (7.8)
Chronic heart failure, n (%)	31 (6.9)
Clinical manifestations at hospital admission	
Fever, n (%)	335 (74.8)
Cough, n (%)	298 (66.5)
Dyspnea, n (%)	272 (60.7)
Asthenia, n (%)	231 (51.6)
Myalgia, n (%)	131 (29.2)
Diarrhea, n (%)	106 (23.7)
Laboratory analysis at hospital admission	
Leukocytes/ μ l, Median (IQR)	7000 (5200-9675)
Neutrophils/ μ l, Median (IQR)	5176 (3593-7480)
Lymphocytes/ μ l, Median (IQR)	1029 (710-1452)
Platelets less than 110 000/mm ³ , n (%)	37(8.3)
Creatinine in mg/dl, Median (IQR)	0.99 (0.79-1.22)
Urea in mg/dl, Median (IQR)	35 (27-48)
C-reactive protein in mg/dl, Median (IQR)	7.01 (3.67-12.10)
Procalcitonin in ng/ml, Median (IQR)	0.13 (0.08-0.25)
(Only performed in 204 patients)	
Ultrasensitive troponin T in ng/l, Median (IQR)	10.4 (6.4-21.9)
(253 studies were conducted)	
Ferritin in ng/dl, Median (IQR) (Only performed in 431 patients)	1033 (510-1893)
D-dimer in μ g/ml, Median (IQR) (Only performed in 418 patients)	0.55 (0.27-1.11)

IQR= interquartile range

subjects who required ICU at some point during their hospitalization was 33.3% (54/162).

Regarding patients with AKI, a higher percentage had criteria for admission in ICU, were predominantly males and were older, compared to those who did not present AKI (control group). As for comorbidities, the AKI group had a higher percentage of chronic kidney disease (CKD), immunocompromise, and ischemic heart disease compared to the control group. In the admission laboratory tests, subjects with AKI had higher values of total leukocytes, neutrophils, higher percentage of thrombocytopenia, and higher levels of procalcitonin, troponin T and dimer D. All these characteristics were considered risk factors and variables significantly associated with AKI

in the univariate analysis. There was also a clear trend for patients with AKI to have a higher percentage of arterial hypertension and chronic heart failure as comorbidities, lower lymphocyte count at admission, and higher levels of C-reactive protein and ferritin, but these differences were not statistically significant (Table 2). There were no differences in the presence of symptoms/signs upon admission and/or pneumonia between with and without AKI groups (94.1 vs. 96.1%; $p = 0.378$).

During hospitalization, 96.9% received prophylactic heparin, 85% dexamethasone or hydrocortisone, 57.6% antibiotics (47.1% azithromycin, 42.2% ceftriaxone), and 37.5% convalescent plasma. A smaller percentage of patients received: hydroxychloroquine (0.7%), ritonavir/

TABLE 2.— Differences between baseline characteristics and clinical presentation at hospital admission between patients with and without acute kidney injury (AKI)

Baseline clinical characteristics	AKI + (n = 85)	AKI - (n = 363)	p
Institution			
Hospital Privado, n (%)	49 (57.6)	190 (52.3)	0.377
Hospital Raúl Angel Ferreyra, n (%)	36 (42.3)	173 (47.7)	
Meets admission criteria in			
General ward, n (%)	58 (68.2)	314 (86.5)	< 0.001
Intensive care unit, n (%)	27 (31.8)	49 (13.5)	
Demographic characteristics			
Male gender, n (%)	62 (72.9)	223 (61.4)	0.047
Age, M (IQR)	69 (62-77)	62 (52-74)	0.001
Comorbidities			
Arterial hypertension, n (%)	53 (62.3)	194 (53.4)	0.137
Obesity, n (%)	27 (31.8)	115 (31.7)	0.988
Diabetes mellitus, n (%)	26 (30.6)	100 (27.6)	0.575
Chronic kidney disease, n (%)	25 (29.4)	21 (5.8)	< 0.001
Immunocompromised, n (%)	13 (15.3)	30 (8.3)	0.048
Ischemic heart disease, n (%)	14 (16.5)	21 (5.8)	0.001
Chronic heart failure, n (%)	9 (10.6)	22 (6.1)	0.139
Laboratory analysis at hospital admission			
Leukocytes/ μ l, M (IQR)	8400 (5500-10800)	6900 (5100-9000)	0.009
Neutrophils/ μ l, M (IQR)	6003 (3900-8827)	5103 (3534-7227)	0.028
Lymphocytes/ μ l, M (IQR)	882 (621-1407)	1075 (736-1464)	0.064
Platelets less than 110 000/ mm^3 , n (%)	16 (18.8)	21 (5.8)	< 0.001
Creatinine in mg/dl, M (IQR)	1.35 (1.06-1.83)	0.93 (0.74-1.11)	< 0.001
Urea in mg/dl, M (IQR)	53 (40-78)	33 (25-44)	< 0.001
C-reactive protein in mg/dl, M (IQR)	7.97 (4.10-13.85)	6.68 (3.54-11.60)	0.109
Procalcitonin in ng/ml, M (IQR)	0.22 (0.12-0.48)	0.13 (0.07-0.20)	< 0.001
U-TT in ng/l, M (IQR)	19.8 (10.4-37.2)	8.9 (5.9-19.3)	< 0.001
Ferritin in ng/dl, M (IQR)	1280 (652-1922)	995 (470-1882)	0.159
D-dimer in μ g/ml, M (IQR)	0.70 (0.45-1.36)	0.52 (0.24-1.00)	< 0.001

M= Median; IQR= interquartile range; LDH= lactate dehydrogenase; U-TT= ultrasensitive troponin T

lopinavir (0.9%), nebulized ibuprofen (2.2%), and immunomodulatory drugs (ruxolitinib/tocilizumab, 1.1%). A higher percentage of subjects in the AKI group received piperacillin-tazobactam, Imipenem or meropenem, and convalescent plasma compared to the control group. The median length of hospital stay was 17 (IQR = 13-22) days. During follow-up, complications were bacterial superinfection (12.3%), septic shock (8.8%), ARDS (27.9%), ICU admission (36.2%), and mechanical ventilation (MV) requirement (14.7%). Overall mortality was 19%. Patients with AKI presented a longer hospitalization, greater requirement and time of stay in the ICU, a significant positive association with bacterial superinfection, sepsis,

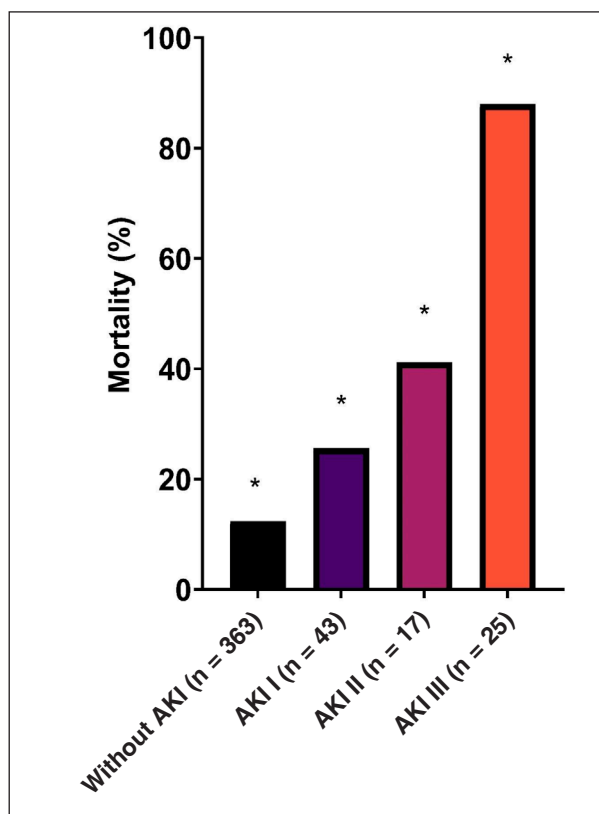
ARDS, MV and also presented ~4-fold higher mortality compared to the control group (table 3). Mortality incidence varied according to the stage of AKI (Fig. 2). In subjects who required RRT, all were on MV and mortality was in 16 out of 18. The 2 survivors in this subgroup recovered their kidney function at the time of hospital discharge. The final multivariate model chosen to evaluate the risk factors for AKI included the variables sex, age, history of CKD, immunocompromised, neutrophil and platelet count, MV, septic shock and bacterial superinfection. The variables that were independently associated with AKI in this adjusted analysis were age (for every 10 years, aOR = 1.30, 95%CI = 1.04-1.63, p = 0.022), history of

TABLE 3.– Medications received and associated complications in subjects with and without acute kidney injury (AKI)

Events during follow-up	All (n = 448)	AKI + (n = 85)	AKI - (n = 363)	p
Medications received				
Convalescent plasma, n (%)	168 (37.5)	43 (50.6)	125 (34.4)	0.006
Corticosteroids, n (%)	381 (85)	71 (83.5)	310 (85.4)	0.663
Antibiotics, n (%)	258 (57.6)	59 (67.4)	199 (54.8)	0.014
Ceftriaxone	189 (42.2)	35 (41.2)	154 (42.4)	0.834
Azithromycin	211 (47.1)	38 (44.7)	173 (47.7)	0.624
Piperacillin-tazobactam	64 (14.3)	30 (35.3)	34 (9.4)	< 0.001
Imipenem or meropenem	11 (2.5)	7 (8.2)	4 (1.1)	0.001
Low molecular weight/ unfractionated heparin, n (%)	434 (96.9)	82 (96.5)	352 (97)	0.735
Complications and events				
Days of hospitalization, M (IQR)	17 (13.2-22)	21 (16-26)	16 (13-22)	< 0.001
ICU requirement, n (%)	162(36.2)	54 (63.5)	108 (29.7)	< 0.001
Days in ICU, M (IQR)	8 (4-15)	12 (8-19)	6 (3-11)	< 0.001
Mechanical ventilation, n (%)	66 (14.7)	42 (49.4)	24 (6.6)	< 0.001
ARDS, n (%)	125 (27.9)	54 (63.5)	71 (19.6)	< 0.001
Septic shock, n (%)	39 (8.8)	23 (27.4)	16 (4.4)	< 0.001
Patients with bacterial superinfection, n (%)	55 (12.3)	32 (37.6)	33 (9.1)	< 0.001
Death, n (%)	85 (19)	40 (47.1)	45 (12.4)	< 0.001

M= Median; IQR= interquartile range; ICU= Intensive care unit; ARDS= Acute respiratory distress syndrome

Fig. 2.– Mortality in patients without acute kidney injury (AKI) and with AKI stages I, II and III



* Pearson chi-square test (3) = 94.37; p<0.001

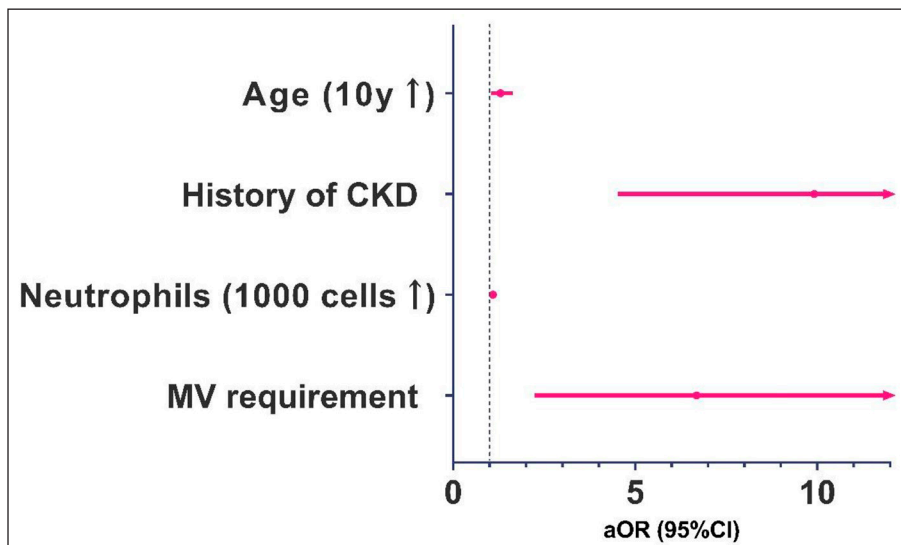
CKD (aOR= 9.92, 95%CI = 4.52-21.77, p < 0.001), blood neutrophil count (per 1000 cells increase, aOR = 1.09, 95%CI = 1.01-1.18, p = 0.037) and MV requirement (aOR = 6.69, 95%CI = 2.24-19.9, p = 0.001), (Figure 3). Among the complications found during follow-up, the only ones that were independently associated with mortality in the adjusted multivariate analysis were: AKI (aOR = 3.3, 95%CI = 1.6-6.9, p = 0.001), ARDS (aOR = 8.8, 95%CI = 3.8-20.5, p < 0.001) and MV requirements (aOR = 3.6, 95%CI = 1.2-10.4, p = 0.020).

Discussion

In the present study, the incidence, risk factors, and complications associated with AKI were evaluated in subjects hospitalized in two high complexity third-level hospitals in Córdoba, Argentina.

In a meta-analysis that included more than 13000 patients in China, the United States and different European countries, most of them hospitalized, the incidence of AKI was 17% and approximately 5% required RRT³⁰. These percentages were very similar to those found in our study (AKI 19%, RRT 4%) and the criteria to define AKI were exactly the same. In Argentina, a single study carried out in a public tertiary hospital in Buenos Aires used the same AKI criteria³¹. In that prospective cohort they included 417 COVID-19 patients admitted to the general ward. AKI occurred in 4.8% of the patients, and 0.7% required RRT (only 3 patients, another 6 already required RRT prior to

Fig. 3.— Independent risk factors for acute kidney injury found in multivariate analysis



Multivariate logistic regression analysis: age (for every 10 years, aOR = 1.30, 95%CI = 1.04-1.63, $p = 0.022$), history of CKD (aOR = 9.92, 95%CI = 4.52-21.77, $p < 0.001$), blood neutrophil count (per 1000 cells increase, aOR = 1.09, 95%CI = 1.01-1.18, $p = 0.037$) and MV requirement (aOR = 6.69, 95%CI = 2.24-19.9, $p = 0.001$). Other variables included in the final model but without statistical significance were: sex, immunocompromised, platelet count, septic shock and bacterial superinfection.

CKD = chronic kidney disease; MV = mechanical ventilation; aOR = adjusted odd ratio; 95%CI = 95% confidence interval

hospitalization). These percentages are much lower than those reported in our cohort and this may be mainly due to the fact that the subjects included were two decades younger, had fewer comorbidities such as hypertension (16.7 vs. 55.1%), diabetes (15.3 vs. 28.1%) and CKD (3.1 vs. 10.3%), the majority presented with a mild disease (86.8%) and a lower percentage of pneumonia (51.9% vs. 95.8%). In addition, patients with critical illness at admission were excluded in this study. Another series in Argentina reports an incidence of kidney injury of 7% but does not specify the criteria used to define AKI and both the baseline characteristics and the severity of the disease differ from that of the patients included in our cohort³². In a multicenter prospective cohort study in Argentina, which included 1909 adults with COVID-19 admitted to the ICU with invasive mechanical ventilation, the incidence of AKI (using the same definition as in our study) was 52.2%, RRT 19.5% and the presence of AKI was also one of the independent predictors of mortality³³. In our series, the incidence of AKI among subjects who required ICU at some point during their hospitalization was lower (33.3%), but not all of these patients required invasive mechanical ventilation, and this was an independent risk factor for AKI demonstrated in our study. This wide range of incidence of AKI in subjects hospitalized for COVID-19 described in the literature (between 0.5 and 80.3%)⁵⁻¹² could be explained by the following reasons: use of different definitions of AKI, hospitalizations in isolation centers only for

epidemiological precaution, use of different hospitalization criteria, presence of different demographic, clinical and severity characteristics in the subjects included in each study, use of different protocols for monitoring renal function and treatments to avoid renal hypoperfusion and the use of drugs nephrotoxic and different follow-up periods.

Currently described independent predictors of AKI in subjects with COVID-19 include age, male gender, history of obesity, diabetes, hypertension, cardiovascular disease, CKD, elevated IL-6 levels, baseline angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers use, exposure vancomycin and non-steroidal anti-inflammatory drugs, septic shock, hypoxia, and MV^{8-10, 34, 35}. In Argentina, to our knowledge there are no publications on the risk factors for AKI in patients with COVID-19. In our study, in addition to age, history of CKD and MV, blood neutrophil count at admission was also identified as an independent predictor of AKI, a variable that had not been identified in previous studies that could be from great value to consider in the initial evaluation. Furthermore, in the univariate analysis male sex, immunocompromise, coronary heart disease, thrombocytopenia, and higher inflammatory markers such as procalcitonin, troponin, and dimer-D were also associated with AKI, although later in the multivariate adjustment lost statistical significance. And other comorbidities such as hypertension and heart failure, a lower count of blood lymphocytes, and other inflammatory markers such as C-reactive protein and ferritin, presented

a clear trend of association with AKI, but without statistical significance. This may be due to the number of subjects included and statistical power.

On the other hand, patients with AKI were more frequently treated with convalescent plasma and piperacillin tazobactam, imipenem or meropenem; these differences are probably explained by the more severe condition in this group of patients and antibiotic staging due to poor response to the initial antibiotic or established microbial resistance.

In the same meta-analysis mentioned previously, the mortality rate of patients with AKI was 52%³⁰, a percentage similar to that found in our study (47.1%). In our cohort, as in others, AKI has been identified as an independent predictor of mortality^{9, 33, 34, 36, 37}, and the higher the AKI stage, the greater the risk⁹. In addition, AKI in our series was associated with other complications such as long-term hospitalization, admission to ICU and prolonged stay in intensive care, among others.

The limitations of our study are mainly based on its retrospective nature, although in both institutions there was a protocol for action against COVID-19 which would tend to unify management. The restriction of follow-up during hospitalization could have partially underestimated the true incidence of AKI if there were patients with a short hospital stay who presented this complication after hospital discharge.

In conclusion, the determination of AKI risk factors allows the early identification of the susceptible subjects. The analysis of incidence, complications and the impact associated with AKI, such as mortality and prolongation of hospital stay, reflect the importance of early diagnosis and adequate treatment. This epidemiological analysis can be useful for planning and allocating resources in the event of a possible new outbreak.

Acknowledgments: To the Fundación Nefrológica de Córdoba and Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC) for the support to cover publication costs.

Disclosure: The preliminary manuscript was posted on the preprint server for health sciences MedRxiv on June 1, 2021 (doi: <https://doi.org/10.1101/2021.05.31.21257656>).

Conflict of interest: None to declare

References

- Callaway E. Time to use the p-word? Coronavirus enters dangerous new phase. *Nature* 2020; 579: 12.
- Van Staden C. COVID-19 and the crisis of national development. *Nat Hum Behav* 2020; 4: 443-4.
- Milanesio M, Escudero D, Caeiro JP. Covid-19 disease. Report of the first confirmed case in Córdoba (Argentina) and literatura review. *Rev Fac Cien Med Univ Nac Cordoba* 2020; 77: 110-2.
- Ministerio de salud de Argentina. Información epidemiológica, 2020. In: <https://www.argentina.gob.ar/salud/coronavirus-COVID-19/sala-situacion>. Accessed May 2021.
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061-9.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382: 1708-20.
- Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; 98: 209-18.
- Bowe B, Cai M, Xie Y, Gibson AK, Maddukuri G, Al-Aly Z. Acute kidney injury in a national cohort of hospitalized US veterans with COVID-19. *Clin J Am Soc Nephrol* 2020; 16: 14-25.
- Xia P, Wen Y, Duan Y, et al. Clinicopathological features and outcomes of acute kidney injury in critically ill COVID-19 with prolonged disease course: A retrospective cohort. *J Am Soc Nephrol* 2020; 31: 2205-21.
- Fisher M, Neugarten J, Bellin E, et al. AKI in Hospitalized Patients with and without COVID-19: A Comparison Study. *J Am Soc Nephrol* 2020; 31: 2145-57.
- Rubin S, Orieux A, Prevel R, et al. Characterization of acute kidney injury in critically ill patients with severe coronavirus disease 2019. *Clin Kidney J* 2020; 13: 354-61.
- Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; 98: 219-27.
- Battle D, Soler MJ, Sparks MA, et al. Acute kidney injury in COVID-19: Emerging evidence of a distinct pathophysiology. *J Am Soc Nephrol* 2020; 31: 1380-3.
- Hassanein M, Radhakrishnan Y, Sedor J, et al. COVID-19 and the kidney. *Cleve Clin J Med* 2020; 87: 619-31.
- Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 2020; 16: 747-64.
- Wang D, Yin Y, Hu C, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. *Crit Care* 2020; 24: 1-9.
- Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect* 2020; 26: 767-72.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-62.
- Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2020; 120: c179-84.
- Whelton PK, Carey RM, Aronow WS. Detection, evaluation, and management of high blood pressure in adults a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* 2018; 71: 1269-324.
- Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--The evidence report. National Institutes of Health. *Obes Res* 1998; 6: 51S-209S.
- American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; 44: S15-S33.
- Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US com-

- mentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; 61: 649-72
25. Radford MJ, Arnold JM, Bennett SJ, Cinquegrani MP, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: A report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (Writing Committee to Develop Heart Failure Clinical Data Standards): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation* 2005; 112: 1888-916
 26. Lopardo G, Basombrio A, Clara L, et al. Neumonía adquirida de la comunidad en adultos. Recomendaciones sobre su atención. *Medicina (B Aires)* 2015; 75: 245-57
 27. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38: 1573-82
 28. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: A living rapid review and meta-analysis. *Clin Microbiol Infect* 2020; 26: 1622-9.
 29. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315: 801-10.
 30. Robbins-Juarez SY, Qian L, King KL, et al. Outcomes for patients with COVID-19 and acute kidney injury: A systematic review and meta-analysis. *Kidney Int Rep* 2020; 5: 1149-60.
 31. Melendi SE, Pérez MM, Salas CE, et al. COVID-19 with and without pneumonia: Clinical outcomes in the internal medicine ward. *Medicina (B Aires)* 2020; 80: 56-64.
 32. Ludueña MG, Labato M, Chiaradia V, Yamuni J, Finocchietto P, Pisarevsky A. Análisis de los primeros 100 pacientes internados por COVID-19 en el Hospital de Clínicas José de San Martín, Universidad de Buenos Aires. *Medicina (B Aires)* 2020; 80: 48-55.
 33. Estenssoro E, Loudet CI, Ríos FG, et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATICOVID): A prospective, multicentre cohort study. *Lancet Respir Med* 2021; S2213-2600(21)00229-0.
 34. Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 2021; 32: 151-60.
 35. See YP, Young BE, Ang LW, et al. Risk Factors for development of acute kidney injury in COVID-19 patients: A retrospective observational cohort study. *Nephron* 2021; 145: 256-64.
 36. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020; 97: 829-38.
 37. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol* 2020; 31: 1157-65.