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# CHARACTERISTICS OF ACUTE KIDNEY INJURY IN ADULT PATIENTS WITH SEVERE COVID-19

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**Abstract** We conducted a retrospective cohort study to report the clinical characteristics, incidence and outcomes of patients with severe COVID-19 with acute kidney injury (AKI). One-hundred and sixtytwo intensive care unit (ICU) admitted patients in a tertiary level hospital in the city of Buenos Aires with COVID-19 diagnosis were included. We hypothesized that COVID-19 related AKI would develop in the period of more severe hypoxemia as an early event and late AKI would be more probably related to intensive care unit complications. For this purpose, we divided subjects into two groups: those with early AKI and late AKI, before and after day 14 from symptom onset, respectively. A stepwise multivariate analysis was conducted to find possible AKI predictors. AKI incidence was 43.2% (n = 70) of the total patients admitted into ICU with severe COVID-19, 11.1% (n = 18) required renal replacement therapy. In-hospital mortality was higher (58.6%) for the AKI group. AKI occurred on a median time of 10 (IQR 5.5-17.5) days from symptom onset. A history of hypertension or heart failure, age and invasive mechanical ventilation (IMV) requirement were identified as risk factors. Late AKI (n = 25, 35.7%) was associated with sepsis and nephrotoxic exposure, whereas early AKI occurred closer to the timing of IMV initiation and was more likely to have an unknown origin. In conclusion, AKI is frequent among critically ill patients with severe COVID-19 and it is associated with higher in-hospital mortality.

**Key words**: acute kidney injury, renal failure, COVID-19, renal replacement therapy, intensive care, sepsis

**Resumen** ***Características de la injuria renal aguda en pacientes adultos con COVID-19 grave.*** Llevamos a cabo un estudio retrospectivo con el objetivo de describir las características clínicas, incidencia y desenlaces de los pacientes con injuria renal aguda (IRA) asociada a la COVID-19. Se incluyeron 162 pacientes con diagnóstico de COVID-19 admitidos en una unidad de cuidados intensivos en un hospital de tercer nivel en la Ciudad de Buenos Aires. Nuestra hipótesis consistió en que la IRA asociada a COVID-19 sería un evento temprano asociado a la gravedad de la hipoxemia y la IRA tardía se relacionaría con complicaciones propias de la UCI. Por ello se clasificó la IRA en temprana y tardía, según sucediera antes o después de los 14 días desde el inicio de síntomas. Se realizó un análisis multivariado mediante regresión logística escalonada para evaluar posibles factores de riesgo. La incidencia de IRA fue de 43.2% (n = 70), 11.1% (n = 18) requirieron terapia de reemplazo renal. La mortalidad intrahospitalaria fue mayor (58.6%) en el grupo con IRA. El diagnóstico de IRA se realizó en una mediana de 10 (IQR = 5.5-17.5) días desde el inicio de los síntomas. El antecedente de hipertensión e insuficiencia cardíaca, la edad y el requerimiento de ventilación mecánica invasiva (VMI) fueron identificados como factores de riesgo para IRA. La IRA tardía (n = 25, 35.7%) estuvo asociada a sepsis y exposición a nefrotóxicos, mientras que la IRA temprana (n = 45, 64.2%) estuvo temporalmente asociada al inicio de la VMI y en muchos casos no se pudo filiar una etiología. En conclusión, la IRA es una complicación frecuente en pacientes con COVID-19 grave y está asociada a una alta mortalidad intrahospitalaria.

**Palabras clave**: injuria renal aguda, falla renal, COVID-19, terapia de reemplazo renal, terapia intensiva, sepsis.

## Abbreviations

| | | | |
|---|---|---|---|
| AKI | Acute kidney injury | HF | Heart failure |
| ACE 2 | Angiotensin converting enzyme 2 | ICU | Intensive care unit |
| ACEI | Angiotensin I converting enzyme inhibitor | IMV | Invasive mechanical ventilation |
| ARB | Angiotensin II receptor blocker | KDIGO | Kidney Disease Improving Global Outcomes |
| CKD | Chronic kidney disease | NSAID | Non-steroidal anti-inflammatory drugs |
| COVID-19 | Coronavirus disease 19 | PCR | Polymerase chain reaction |
| COPD | Chronic obstructive pulmonary disease | PEEP | Positive end expiratory pressure |
| eGFR | Estimated glomerular filtration rate | RRT | Renal replacement therapy |

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**KEY POINTS**

- Acute Kidney Injury (AKI) is a frequent complication of severe COVID-19 patients that is associated with higher morbidity and mortality.
- We found different risk factors for AKI: age, a history of hypertension and heart failure, and Invasive mechanical ventilation requirement.
- Late episodes are frequently persistent. They are associated with sepsis and nephrotoxic exposure.
- Early AKI is temporally related with the period of more severe manifestations of COVID-19 and mechanical ventilation initiation, with risk factors still not elucidated. It is also persistent and has a similar mortality and RRT requirement than late AKI.

Acute kidney injury (AKI) is a condition in critically ill patients frequently associated with sepsis[1]. Moreover, it is a frequent complication of SARS-CoV-2 infection and it is often related to the severity of illness and mortality particularly in patients admitted into the intensive care unit (ICU)[2, 3]. Underlying mechanisms are poorly understood, but they could involve tropism of SARS-CoV-2 for the kidney via angiotensin converting enzyme 2 (ACE 2), systemic inflammation and microvascular thrombosis[4]. In addition, the occurrence of sepsis, cardio-renal syndrome, hypoxemia, the use of nephrotoxic drugs and high positive end expiratory pressure (PEEP) levels have been proposed as alternative causal pathways[5]. The reported timing of AKI occurrence in Coronavirus disease 19 (COVID-19) is variable across different studies, but it is on average between 5 to 9 days from symptom onset. However, it has also been described as a late complication[6]. Therefore, additional studies are needed to further characterize the incidence, timing and risk factors for AKI among patients with severe COVID-19.

The present single center, retrospective cohort study was conducted to both estimate cumulative incidence and to identify factors associated with AKI, mortality and intensive care unit (ICU) related complications among adult patients with severe COVID-19, focusing on identifying different AKI phenotypes as recommended by the consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup[7]. The objective is to further improve the knowledge on this subject and to help critical care physicians in identifying patients at higher risk of poor clinical outcomes.

## Materials and methods

The present is a single center, retrospective cohort study including adult patients with severe COVID-19 admitted to ICU from March 17th to September 13th of 2020, at the Hospital Italiano de Buenos Aires, a tertiary teaching hospital located in Buenos Aires, Argentina. Patients were eligible if they were 18 years or older, had a confirmed COVID-19 diagnosis by means of real-time-polymerase-chain-reaction (Bosphore 2019 Novel Coronavirus Detection Kit v2 from Anatolia GeneWorks, Turkey) testing from throat swab or tracheal aspirate samples, and were admitted to the ICU during hospital stay. Patients with a history of end stage kidney disease requiring renal replacement therapy (RRT) and renal transplant recipients were excluded. Patients included in the presented study were followed from COVID-19 diagnosis until hospital discharge or death.

This study was approved by the local ethics review board (protocol number 1636) and was conducted according to the amended Declaration of Helsinki. Informed consent was waived because of the observational nature of the study.

Demographic, history of comorbidities, severity of COVID-19 illness, scoring systems used to predict mortality (APACHE II, SOFA and Charlson score) were systematically calculated at ICU admission and laboratory data from electronic medical charts were retrieved. The comorbidities considered were diabetes mellitus, hypertension, obesity, chronic obstructive pulmonary disease (COPD), heart failure (HF), chronic kidney disease (CKD), stroke, asthma, tobacco use and active malignancies. Laboratory assessment consisted of a complete blood count, coagulation testing, assessment of renal function, and measure of electrolytes, C-reactive protein (CRP), procalcitonin, pro b-type natriuretic peptide (pro-BNP), lactate dehydrogenase, high-sensitivity cardiac troponin, d-dimer and ferritin.

Data regarding invasive mechanical ventilation (IMV) requirement and ventilation parameters on the first day (i.e. PEEP, $PaO_2/FiO_2$) were also captured. $PaO_2/FiO_2$ was calculated as the relation between the first partial pressure of oxygen measured after intubation and the fraction of inspired oxygen set on the ventilator. Data concerning prescribed drugs during hospital stay was extracted from medical records. Specifically, we documented the prescription of nephrotoxic drugs such as polymyxins and aminoglycosides during hospital stay. In addition, drugs from the ambulatory setting were also recorded [e.g. immunosuppressants, corticosteroids, ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB)]. Finally, the length of hospital stay, length of period under IMV, days from symptom onset until ICU admission and IMV were calculated for each patient. A nephrologist and a critical care specialist (CFV and NCR) reviewed electronic medical charts in order to assess the cause of AKI.

AKI was defined following the 2012 Kidney Disease Improving Global Outcomes (KDIGO) definitions[8]. Baseline creatinine was defined as the last creatinine obtained on the ambulatory setting within the last year prior to hospital admission. Glomerular filtration rate was estimated (eGFR) using CKD-EPI[9] formula.

Transient AKI was defined as an episode lasting 48 hours from symptom onset with sustained reversal for at least 48 hours; and persistent AKI as an episode lasting more than 48 hours[10]. Sepsis-associated acute kidney injury was defined as an episode occurring in the context of sepsis or septic shock following the sepsis-3 consensus[10,11]. Renal replacement therapy (RRT) requirement during hospital stay was also recorded.

As an exploratory analysis, episodes of AKI were classified occurring within the first 14 days (early AKI) and after day 14 from symptom onset (late AKI), describing epidemiologic characteristics, identifying causes of AKI, severity of disease and RRT requirements for each group. We collected PEEP and $PaO_2/FiO_2$ values on the day of the episode. Norepinephrine dose was calculated as the average dose administered on the full day on which AKI occurred in micrograms/kg of body weight/minute. The main hypothesis was that early AKI would develop in the period of more severe hypoxemia[12] and late AKI would be more probably related to intensive care unit complications such as hospital-acquired infections and nephrotoxic drug exposure.

Data conforming to a normal distribution was presented as mean ± SD, and median and quartiles were used for non-normal distribution. Rate comparisons were performed by chi-squared test. Student's, Wilcoxon rank-sum, Wilcoxon signed-rank, and Kruskal-Wallis tests were used to compare means across groups according to the number of groups and distribution of variables.

A bivariate and multivariate logistic regression analysis was performed to identify risk factors associated with AKI. Variables were entered into the model when the p-value was lower than 0.15 in the bivariate analysis (Supplementary appendix, table s1). The final model after a stepwise approach included age, a history of hypertension or HF and IMV requirement. $PaO_2/FiO_2$ was not included because of the high correlation with IMV (only patients with this feature had $PaO_2/FiO_2$ values available)

STATA v.14.2 (StataCorp LLC, College Station, Tx) was used for analysis. All reported p values are two-sided and p value < 0.05 was used as threshold for statistical significance.

## Results

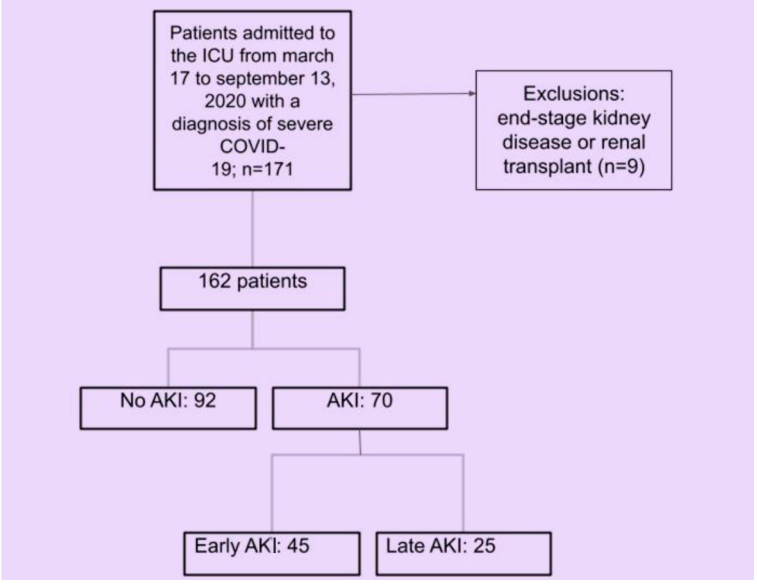
A total of 171 patients with COVID-19 diagnosis admitted to ICU were initially evaluated. Nine subjects were excluded because they were kidney transplant recipients or presented end stage kidney disease (Figure 1). Overall, 162 were included in the final analysis. Some patients of the cohort were already described by Carboni Bisso et al[13] and Simonovich et al[14]. Baseline clinical, demographic and laboratory data is presented in Table 1. The cohort was composed of older adults (mean age 66 ± 13.2 years) and 109 (67.3 %) were male. It is worth mentioning that hypertension, diabetes mellitus and coronary artery disease were the most prevalent comorbidities and 88.3 % (n = 143) of patients presented with at least one comorbidity.

Overall, 70/162 (43.2%) patients developed AKI during hospital stay. Differences between groups were recognizable. Patients with AKI were older, more prone to present a history of hypertension, heart failure and ARB/ACEI treatment. Baseline eGFR was lower for patients that subsequently developed AKI during hospital stay. In particular, non AKI patients had baseline KDIGO 1 or 2, whereas AKI patients had mostly KDIGO 2, 3a and 3b (Table 1). In addition, creatinine and urea values on ICU admission were significantly higher on patients with AKI with a median of 1.08 (IQR 0.85-1.47) vs. 0.76 (IQR 0.7-1.15) mg/dL, and 48 (IQR 37.0-74.0) vs. 37.0 (IQR 27.0-46.0) mg/ml, respectively. Regarding inflammatory parameters, no differences were found between groups on D-dimer, C-reactive protein, ferritin, lactate dehydrogenase and procalcitonin levels. Troponin and pro-BNP levels were higher among patients with AKI. The KDIGO AKI stage during hospital stay was distributed as follows (Table 2): 26 (37.1 %) subjects in stage 1, 16 (23.2%) in stage 2, 28 (40.6%, second events are included) in stage 3 and 18 (25.7 %) developed AKI-RRT (11.1 % of the total ICU cohort).

In-hospital mortality was higher in the AKI group (58.6% vs. 13%, p <0.001). It varied widely according to the previous eGFR rate, occurring in 20.5, 32.5, 47.1, 75.0 and 50.0 % of patients in stages I, II, III, IV and V of CKD disease, respectively. In-hospital mortality in AKI patients who required RRT was 77.7% and 51.9 % in those who did not (p = 0.06).

Overall, individuals with AKI during hospital stay presented more severe disease, with higher APACHE II and SOFA scores at ICU admission. Additionally,

Fig. 1.– Study population




*Early AKI: AKI occurring before day-14 from symptom onset*
*Late AKI: AKI occurring after day-14 from symptom onset*

TABLE 1.– *Baseline characteristics of patients in the study*

| | Entire cohort (n = 162) | No AKI (n = 92) | AKI (n = 70) | p-value[a] |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age, mean ± SD years | 66.4 (13.2) | 62.8 (14.3) | 71.1 (9.7) | < 0.001 |
| Male sex, n (%) | 109 (67.3) | 63 (68.5) | 46 (65.7) | 0.73 |
| BMI, median (IQR) kg/m$^2$ | 28.7 (25.8-32.5) | 28.7 (25.9-32.0) | 28.8 (25.4-33.3) | 0.44 |
| Baseline comorbidities – n (%) | | | | |
| Cerebrovascular disease | 2 (1.2) | 1 (1.0) | 1 (1.4) | 1.0 |
| Diabetes mellitus | 31 (19.1) | 16 (17.4) | 15 (21.4) | 0.55 |
| Coronary artery disease | 25 (15.4) | 11 (11.5) | 14 (20.0) | 0.19 |
| COPD | 10 (6.2) | 2 (2.2) | 8 (11.4) | 0.02 |
| Asthma | 10 (6.2) | 7 (7.6) | 3 (4.3) | 0.51 |
| Active or past smoker | 14 (8.6) | 7 (7.6) | 7 (10.0) | 0.78 |
| Hypertension | 87 (53.7) | 39 (42.4) | 48 (68.6) | 0.001 |
| Heart failure | 9 (5.6) | 2 (2.2) | 7 (10.0) | 0.04 |
| Chronic kidney disease | 28 (17.3) | 9 (9.8) | 19 (27.1) | 0.003 |
| Malignancy | 22 (13.6) | 10 (10.9) | 12 (17.1) | 0.26 |
| Coexisting conditions | 143 (88.3) | 76 (82.6) | 67 (95.7) | 0.01 |
| Charlson severity index | 4.0 (3.0-5.0) | 3.0 (1.0-5.0) | 5.0 (4.0-6.0) | < 0.001 |
| Baseline eGFR in ml/min/1.73 m$^2$, n (%) | | | | |
| > 90 | 44 (27.2) | 38 (41.3) | 6 (8.5) | < 0.001 |
| 60-89 | 84 (51.9) | 42 (45.6) | 42 (60) | |
| 45-59 | 18 (11.1) | 6 (6.5) | 12 (17.1) | |
| 30-44 | 8 (4.9) | 2 (2.1) | 6 (8.6) | |
| 15-29 | 2 (1.2) | 1 (1) | 1 (1.4) | |
| < 15 | 0 (0.0) | 0 | 0 | |
| Regular medications in the ambulatory setting, n (%) | | | | |
| ACEI/ARB | 55 (34.0) | 25 (27.2) | 30 (42.8) | 0.04 |
| Immunosuppressants | 20 (12.3) | 7 (7.6) | 13 (18.6) | 0.052 |
| Corticosteroids | 7 (4.3) | 3 (3.3) | 4 (5.7) | 0.47 |
| Blood biochemical parameters on ICU admission, median (IQR) | | | | |
| WBC count per ml | 7937 (5781-12302) | 7984 (6070-11395) | 7700 (5300-12690) | 0.94 |
| Lymphocyte, % | 8.9 (5.0-14.8) | 9.23 (5.9-14.7) | 7.7 (4.2-15.7) | 0.38 |
| Neutrophil, % | 85.0 (77.3-90.0) | 84.7 ( 77.4-89.1) | 85.0 (76.9-90.5) | 0.62 |
| Hematocrit, % | 39.0 (35-42.1) | 39.8 (36.0-42.4) | 38.5 (34.0-41.0) | 0.17 |
| Platelet count, per ml | 201.4 (153.2-257.0) | 205.0 (164.8-267.8) | 195.8 (145.2-246.8) | 0.22 |
| D-dimer levels, mg/ml | 1002.5 (677.0-1563.5) | 905.0 (621.0-1321.0) | 1139.0 (730.0-1635.0) | 0.19 |
| C-reactive protein, mg/l | 99.6 (54.9-169.0 | 101.0 (58.5-176.0) | 99.0 (48.7-163.5) | 0.80 |
| Serum ferritin levels, ng/ml | 740.5 (397.3-1329.7) | 794.4 (351.0-1436.0) | 564.7 (411.0-1153.0) | 0.48 |
| Serum lactate dehydrogenase levels, IU/m | 297.0 (256.0-349.0) | 292.0 (256.0-340.5) | 312.0 (259.0-386.0) | 0.24 |
| Prothrombin time, % | 86 (73-95) | 88 (76-97) | 80 (62-92) | 0.003 |
| Troponin levels, pg/ml | 13.05 (7.9-29.8) | 9.6 (6.8-14.0) | 27.3 (14.6-75.0) | 0.06 |
| pro-BNP levels, pg/ml | 407 (138-983) | 244 (82.0-548.0) | 657 (352.0-2092.5) | 0.003 |
| Procalcitonin levels, ng/ml | 0.2 (0.09-0.57) | 0.19 (0.09- 0.46) | 0.30 (0.12-1.21) | 0.58 |
| Creatinine level, mg/dL | 0.87 (0.7-1.15) | 0.76 (0.64-0.96) | 1.08 (0.85-1.47) | < 0.001 |
| Urea levels, mg/ml | 42.0 (32.0-56.0) | 37.0 (27.0-46.0) | 48.0 (37.0-74.0) | < 0.001 |

*ICU: intensive care unit; BMI: body mass index; eGFR: estimated glomerular filtration rate; ACEI: angiotensin-converting enzyme inhibitors; ARA: angiotensin II receptor antagonists; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; BNP: brain natriuretic peptide*

[a]*p-value results from comparing patients with acute kidney injury and without acute kidney injury*

TABLE 2.– *Severity of disease and outcomes*

| | Entire cohort (n = 162) | No AKI (n = 92) | AKI (n = 70) | p-value[a] |
|---|---|---|---|---|
| Severity of disease | | | | |
| APACHE score, median (IQR) | 10.0 (7.0-14.0) | 9.0 (5.0-13.0) | 12 (9.0-15.0) | < 0.001 |
| SOFA score, median (IQR) | 2.0 (1.0-4.0) | 2.0 (1.0-3.0) | 3.0 (2.0-5.0) | < 0.001 |
| Invasive mechanical ventilation, n % | 104.0 (64.2) | 45.0 (48.9) | 59.0 (84.3) | < 0.001 |
| PEEP in cm of water, median (IQR) | 10.0 (8.0-12.0) | 10.0 (8.0-12.0) | 9.0 (8.0-12.0) | 0.32 |
| $PaO_2/FiO_2$ ratio, median (IQR) | 200.0 (146.2-267.5) | 205.0 (152.0-300.0) | 190.5 (127.5-237.0) | 0.06 |
| Neuromuscular blockade requirement, n % | 66 (44.9) | 25 (30.5) | 41 (63.1) | < 0.001 |
| Prone positioning requirement, n (%) | 37 (22.8) | 17 (20.5) | 20 (31.3) | 0.14 |
| Length of IMV in days, median (IQR) | 18.0 (8.0-36) | 13.0 (6.0-31.0) | 19.5 (10.0-40.5) | 0.13 |
| Stage of KDIGO AKI, n % | | | | |
| Stage 1 | - | - | 26 (37.1) | - |
| Stage 2 | - | - | 16 (23.2) | |
| Stage 3 | - | - | 28 (40.6) | |
| RRT, n (%) | 18.0 (11.1) | - | 18.0 (25.7) | - |
| Outcomes | | | | |
| Length of in hospital stay in days, median (IQR) | 19.5 (10.0-34.0) | 15.0 (9.0-28.0) | 26.0 (12.0-38.0) | 0.02 |
| Length of ICU stay in days, median (IQR) | 12.0 (5.0-26.0) | 8.0 (4.0-20.0) | 18.0 (10.0-29.0) | < 0.001 |
| In-hospital mortality, n (%) | 53 (32.7) | 12 (13) | 41 (58.6) | < 0.001 |

*PEEP: positive end-expiratory pressure; IMV: invasive mechanical ventilation; RRT: renal replacement therapy*

[a]*p-value results from comparing patients with acute kidney injury and without acute kidney injury*

they were more prone to undergo IMV during ICU stay. Regarding ventilatory parameters, no differences were found between groups on $PaO_2/FiO_2$ ratio and PEEP levels on day-1 of IMV. Higher neuromuscular blockade was required in the AKI group. Length of ICU and hospital stay was higher in AKI patients. Finally, it was observed a roughly four-fold increase in the incidence of death during hospital stay among patients developing AKI.

In a prespecified bivariate analysis, older age, history of hypertension and COPD, and ARB/ACEI use were associated with AKI development in patients with COVID-19 admitted to the ICU (Supplementary appendix, Table s1). Results of multivariate analysis are reported in the supplementary appendix (Table s2). Independent risk factors for AKI development included age, hypertension, IMV requirement during hospitalization and a history of heart failure.

Among the 70 patients developing AKI during ICU stay, 45 and 25 (64.28 and 35.71 %) patients developed early and late AKI as a first episode, respectively. No differences between groups were found in demographic characteristics (age, sex, BMI), comorbidities (Diabetes, hypertension, cerebrovascular disease, coronary artery disease, COPD, Asthma, tobacco use, a history of heart failure, chronic kidney disease and malignancies) and severity scores (APACHE, SOFA). Median time from symptom onset to first AKI diagnosis was 10 days (IQR 5.5 to 17.5). Late AKI episodes were more frequently persistent and had a higher KDIGO stage. They were also more frequently associated with sepsis and with nephrotoxic drug exposure (Table 3). Regarding vasopressor therapy and serum lactate, there were no differences between groups. Median time from IMV initiation to early AKI development was 1 (IQR: 0 - 2) day, while this time on late AKI patients was 11 (IQR 1 - 25) days ($p < 0.001$). Higher PEEP levels were seen in this group on the day of AKI onset, too. Finally, RRT rates and mortality were similar for both groups.

## Discussion

In this retrospective cohort study conducted in a tertiary teaching hospital in Buenos Aires, a high cumulative incidence of AKI was found among patients with severe COVID-19. Further, patients developing AKI presented higher mortality. Comprehensive data regarding baseline characteristics of patient's risk factors for AKI during hospital stay was gathered. Additionally, characteristics of AKI were captured in order to shed light on the underlying physiopathology of kidney injury in patients

TABLE 3.– *Clinical characteristics and outcomes of patients presenting with early and late acute kidney injury during hospitalization*

| | Entire cohort (n = 70) | No AKI (n = 45) | AKI (n = 25) | p-value[a] |
|---|---|---|---|---|
| AKI characteristics | | | | |
| Time of AKI presentation since symptoms onset in days, median (IQR) | 10 (5.5-17.5) | 7 (4-10) | 22 (17-30) | < 0.001 |
| Time from symptom onset to IMV in days, median (IQR) | 7 (4.5-9) | 6 (4-8) | 9 (6-13) | < 0.001 |
| Days from IMV initiation to AKI in days, median (IQR) | 2 (0-9) | 1 (0-2) | 11 (1-25) | < 0.001 |
| Stage of AKI | | | | |
| Stage 1 | 37 (52.9) | 25 (55.6) | 12 (48.0) | 0.49 |
| Stage 2 | 12 (17.1) | 9 (20.0) | 3 (12.0) | |
| Stage 3 | 20 (28.6) | 11 (15.7) | 9 (36.0) | |
| Transient AKI | 19 (27.1) | 16 (35.6) | 3 (12.0) | 0.07 |
| Persistent AKI | 51 (72.9) | 29 (64.4) | 22 (88.0) | 0.03 |
| RRT requirement, no. (%) | 18 (25.7) | 13 (28.89) | 5 (20.0) | 0.41 |
| IMV at AKI onset, no. (%) | 50 (71.4) | 29 (64.4) | 21 (84.0) | 0.05 |
| 24 hours urine output volume in liters, mean ± SD | 1.3 ± 0.79 | 1.08 (0.60) | 1.63 (0.93) | 0.006 |
| Serum lactate levels at AKI onset in mmol/l, mean (SD) | 2.43 (1.86) | 2.47 (2.01) | 2.35 (1.38) | 0.81 |
| PEEP in cm of water on day of AKI onset, mean (SD) | 9.80 (2.59) | 10.77 (2.29) | 8.39 (2.40) | 0.002 |
| $PaO_2/FiO_2$ ratio on day of AKI onset, mean (SD) | 209.0 (115.0) | 207.5 (134.3) | 210.0 (84.3) | 0.95 |
| Norepinephrine dose in µg per kg per body weight per minute on day of AKI onset, mean (SD) | 0.14 (0.18) | 0.11 (0.14) | 0.19 (0.24) | 0.21 |
| Sepsis, n (%) | 26 (37.1) | 13 (28.9) | 13 (52.0) | 0.03 |
| Nephrotoxic exposure, n (%)[b] | 15 (21.4) | 4 (8.9) | 11 (44.0) | < 0.001 |
| Outcomes | | | | |
| Length of IMV, median (IQR) | 19.5 (10-40.5) | 15 (9-30) | 30 (17-46) | 0.004 |
| In-hospital Mortality, n (%) | 41 (58.6) | 26 (57.8) | 15 (60.0) | 0.47 |

*AKI: acute kidney injury; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor antagonists; IMV: invasive mechanical ventilation; PEEP: positive end expiratory pressure; RRT: renal replacement therapy.*
*These are the characteristics of the first episodes of AKI. A group of patients had second episodes which are included when analyzing KDIGO stage associated mortality and RRT requirements*

[a]*p-value results from comparing patients with AKI and without AKI*
[b]*polymyxins and aminoglycosides are included*

with COVID-19. To our knowledge, this is the first report describing the timing and precipitating factors for AKI among severely ill patients with COVID-19 in Argentina.

According to previous studies involving adult patients with severe COVID-19, study subjects with AKI presented multiple comorbidities[15], including a history of hypertension, higher Charlson score, CKD, COPD and a history of HF. It is worth mentioning that other critical care conditions leading to AKI present a similar set of risk factors[16]. Regarding laboratory measures, no association between inflammatory parameters and the occurrence of AKI was found. Of note, troponin and pro-BNP levels on ICU admission were higher in AKI patients. This could be a manifestation of multiorgan involvement or right ventricular overload due to secondary pulmonary hypertension[17-18]. However, reverse causation cannot be ruled out, since AKI often leads to fluid overload.

The incidence of AKI in our cohort is comparable to that reported elsewhere[3, 19-22]. Nevertheless, we found a low incidence of AKI-RRT compared with those reports. This disparity could be explained by differences in comorbidities and in the severity of the disease between the cohorts or by differences on RRT initiation criteria.

Noteworthy, in-hospital mortality was higher in patients presenting with AKI and significantly higher in those requiring RRT. This may reflect a higher burden of comorbidities

rather than a deleterious effect of RRT, specifically age, severity of disease marked by higher APACHE II and SOFA scores, and higher IMV requirement. In line with these findings, a retrospective cohort study of patients with COVID-19 published by Fisher et al.[23] compared COVID-19 associated AKI with a historical cohort. They reported that COVID-19 associated AKI had a higher rate of severe AKI and worsening clinical outcomes when compared to a historical cohort, i.e. RRT, IMV, ICU admission and in-hospital mortality. This suggests a more severe course of AKI among patients with COVID-19 when compared to other conditions requiring critical care.

Timing on which AKI occurred was particularly considered as an important clinical feature to elucidate the effect of COVID-19 on kidney function. For this purpose, a period of time in the course of the disease in which the most severe manifestations (particularly hypoxemia) occur was identified, e.g., before day 14 from symptom onset[12]. AKI onset coincided with this period of time in our study (median of 10 days from symptom onset; IQR 5-17), and was strongly related with the moment of IMV initiation, mainly on early episodes (Table 3). IMV and neuromuscular blockade requirements were significantly higher in the AKI group (Table 2). Nevertheless, no direct association with hypoxemia or PEEP was found. Other mechanisms for AKI not measured in this study such as inflammation mediated by IL-6, direct effect of SARS CoV-2, renin-angiotensin-aldosterone system disbalance or microvascular thrombosis may have been playing a role[7]. In this setting, AKI could be another target of multiorgan dysfunction due to COVID-19, occurring in the period of more severe respiratory manifestations. In keeping with our findings, recently Hirsh et al. found that 52.2% of subjects with severe COVID-19 presenting AKI during hospitalization developed it within 24 hours of intubation[24].

When considering the underlying causes of AKI in the cohort, the majority of late AKI episodes were associated with sepsis and nephrotoxic drug use. We could not filiate any risk factor to early AKI but it seems that it is a severe event, showing high in hospital mortality and RRT requirement.

Numerous limitations must be weighted when considering our findings. Since the present study was retrospective, data was already registered in secondary databases. The previous must be considered especially when correlating AKI causes. Missing data (specifically on CPK levels, abdominal hypertension, obstructive AKI and diuretic use) could potentially threaten the validity of our findings. In this line, data regarding urinalysis and inflammatory parameters such as IL-6 could not be captured because it is not routinely obtained for all patients in our institution. Finally, since patients were followed up until hospital discharge, information regarding renal recovery in the ambulatory setting was not retrieved.

However, some strengths must also be noted. Comprehensive data was gathered from baseline characteristics and relevant clinical outcomes for all study patients. Major associated factors such as sepsis, nephrotoxic drug exposure and vasopressor therapy were recorded. In addition, the transient nature of AKI episodes was thoroughly assessed by an expert nephrologist.

In conclusion, AKI is a frequent condition in patients with severe COVID-19, associated with higher in hospital mortality. Several risk factors are associated with AKI development in this setting, including increasing age, a history of hypertension or HF and IMV requirement. AKI is an early complication of severe COVID-19 adding significant morbidity and mortality, with a still unknown physiopathology. Late AKI is a condition associated with ICU complications such as sepsis and nephrotoxic exposure. In this setting, prevention and treatment of infections adequately could play a relevant role. Further studies should confirm our findings and shed light on the underpinnings of these associations.

**Conflict of interest:** None to declare

## References

1. Peerapornratana S, Manrique-Caballero CL, Gómez H, et al. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019; 96: 1083-99.
2. Wen C, Yali Q, Zirui G, et al. Prevalence of acute kidney injury in severe and critical COVID-19 patients in Wuhan, China. *SSRN Electronic Journal*. https://dx.doi.org/10.2139/ssrn.3555223
3. 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; 9: 989-98.
4. Bonaventura A, Vecchié A, Dagna L, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 2021; 21: 319-29.
5. Gabarre P, Dumas G, Dupont T, et al. Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med* 2020; 46: 1339-48.
6. 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.
7. 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.
8. Section 2: AKI Definition. *Kidney Int Suppl* 2012; 2: 19-36.
9. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604-12.
10. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; 13: 241-57.

11. Bellomo R, Kellum JA, Ronco C, et al. Acute kidney injury in sepsis. *Intensive Care Med* 2017; 43: 816-28.
12. 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.
13. Carboni Bisso I, Huespe I, Lockhart C, et al. COVID-19 in the intensive care unit. Analysis of the experience during the first month of pandemic. *Medicina (B Aires)* 2020; 80 Suppl 3: 25-30.
14. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A Randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med* 2021; 384: 619-629.
15. 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.
16. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; 14: 607-25.
17. Li D-K, Mao J-Y, Long Y, et al. Pulmonary hypertension with adult respiratory distress syndrome: prevalence, clinical impact, and association with central venous pressure. *Pulm Circ* 2020; 10: 2045894020933087.
18. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; 5: 802-10.
19. Gupta S, Coca SG, Chan L, et al. AKI Treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol* 2021; 32: 161-76.
20. Lowe R, Ferrari M, Nasim-Mohi M, et al. Clinical characteristics and outcome of critically ill COVID-19 patients with acute kidney injury: a single centre cohort study. *BMC Nephrol* 2021; 22: 92.
21. Sang L, Chen S, Zheng X, et al. The incidence, risk factors and prognosis of acute kidney injury in severe and critically ill patients with COVID-19 in mainland China: a retrospective study. *BMC Pulm Med* 2020; 20: 290.
22. Doher MP, Torres de Carvalho FR, Scherer PF, et al. Acute kidney injury and renal replacement therapy in critically ill COVID-19 patients: Risk Factors and Outcomes: A Single-Center Experience in Brazil. *Blood Purif* 2020; 50: 520-30.
23. 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.
24. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* 2020; 98: 209-18.

## Supplementary appendix

TABLE s1. *Bivariate exploratory analysis for AKI. Potential predictors of AKI among patients with severe COVID-19 infection*

| Covariate | Crude Odds Ratio (95% CI) | p-value |
|---|---|---|
| Age in years | 1.05 (1.03 to 1.09) | < 0.001 |
| Male sex | 0.90 (0.47 to 1.74 ) | 0.76 |
| Obesity | 1.04 (0.56 to 1.97) | 0.88 |
| Hypertension | 2.85 (1.48 to 5.50) | 0.002 |
| COPD | 5.46 (1.12 to 26.60) | 0.04 |
| Immunosuppression | 2.27 (0.92 to 5.63) | 0.07 |
| ACEI/ARA 2 therapy | 1.77 (0.91 to 3.41) | 0.09 |
| Heart failure history | 4.81 (0.96 to 23.93) | 0.05 |
| Coronary artery disease | 1.71 (0.74 to 3.95) | 0.20 |
| CKD | 3.44 (1.44 to 8.22) | 0.005 |
| Diabetes mellitus | 1.22 (0.55 to 2.68) | 0.62 |
| IMV requirement | 6.10 (2.78 to 13.35) | < 0.001 |
| $PAO_2/FiO_2$[a] | 0.99 (0.99 to 1.00) | 0.05 |

*COPD: chronic obstructive pulmonary disease; ACEI: angiotensin-converting enzyme inhibitors; ARA2: angiotensin II type 1 receptor antagonists; CKD: chronic kidney disease; and IMV: invasive mechanical ventilation.*

[a]*The first day of IMV.*

TABLE s2.– *Multivariate analysis. AKI predictors*

| Covariable | Odds Ratio (95% CI) | p-value |
|---|---|---|
| Age in years | 1.04 (1.01 to 1.08) | 0.02 |
| Chronic hypertension | 3.01 (1.31 to 6.90) | 0.008 |
| IMV | 11.41 (4.19 to 31.05) | < 0.001 |
| Heart failure history | 15.89 (2.17 to 116.44) | 0.006 |

*IMV: Invasive mechanical ventilation*

*Variables were entered into the model when p-value was less than 0.15 in the bivariate analysis (Supplementary appendix, table s1). A history of hypertension or heart failure, age and IMV requirement were independent predictors for AKI. Multivariate logistic regression was used to adjust for the different variables.*