Acute kidney injury in hospitalized patients with COVID-19

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Abstract

Introduction: The incidence of AKI in coronavirus disease 2019 (COVID-19) patients ranges from 0.5 to 35% and has been associated with worse prognosis. The purpose of this study was to evaluate the incidence, severity, duration, risk factors and prognosis of AKI in hospitalized patients with COVID-19.

Methods: We conducted a retrospective single-center analysis of 192 hospitalized COVID-19 patients from March to May of 2020. AKI was diagnosed using the Kidney Disease Improving Global Outcome (KDIGO) classification based on serum creatinine (SCr) criteria. Persistent and Transient AKI were defined according to the Acute Disease Quality Initiative (ADQI) workgroup definitions.

Results: In this cohort of COVID-19 patients, 55.2% developed AKI (n=106). The majority of AKI patients had persistent AKI (n=64, 60.4%). Overall, in-hospital mortality was 18.2% (n=35) and was higher in AKI patients (28.3% vs 5.9%, p<0.001, unadjusted OR 6.03 (2.22-16.37), p<0.001). On a multivariate analysis, older age (adjusted OR 1.08 (95% CI 1.02-1.13), p=0.004), lower Hb level (adjusted OR 0.69 (95% CI 0.53-0.91), p=0.007) and acidemia at presentation (adjusted OR 5.53 (95% CI 1.70-18.63), p=0.005), duration of AKI (adjusted OR 7.91 for persistent AKI (95% CI 2.39-26.21), p=0.001) and severity of AKI (adjusted OR 2.30 per increase in KDIGO stage (95% CI 1.10-4.82), p=0.027) were independent predictors of mortality.

Conclusion: AKI was frequent in hospitalized patients with COVID-19. Persistent AKI and higher severity of AKI were independent predictors of in-hospital mortality.

Introduction

Since late 2019, the coronavirus disease 2019 (COVID-19) outbreak has resulted in over 4.5 million cases worldwide as of May 2020.[1,2] The World Health Organization (WHO) classified COVID-19 as a pandemic which has been associated with significant morbidity and caused over 300.000 deaths. [3]

The majority of patients present with mild symptoms including fever, dyspnea, cough, headache and diarrhea or are even asymptomatic. [4,5] More severe cases of pneumonia can lead to acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure and death. [6,7]

Current literature reports that the incidence of acute kidney injury (AKI) in COVID-19 patients ranges widely from 0.5 to 35% and has been associated with worse prognosis. The disparities in incidence reports may result from different definitions to classify AKI and different populations studied. [7–13]

AKI is characterized by a rapid decrease in renal function defined as an increase in serum creatinine (SCr) and/or a decline in urine output (UO). [14] AKI is a common in hospitalized patients, with an incidence which can reach 60% in critically ill patients and is associated with increased in-hospital mortality. [15] AKI is a frequent complication in ARDS patients, namely in older patients and patients with significant comorbidities. [16]

In COVID-19 patients, kidney impairment appears to be multifactorial resulting from systemic inflammatory response to sepsis, local disruption in renin angiotensin aldosterone system (RAAS) homeostasis and direct cytopathic effect of the virus. [17]

The present study retrospectively analyzed data to study the incidence, severity, duration, risk factors and prognosis of AKI in hospitalized patients with COVID-19.

Materials And Methods

This study is a retrospective analysis of hospitalized patients admitted to a Dedicated Unit for COVID-19 patients (UICIVE) at the Department of Medicine of the Centro Hospitalar Universitário Lisboa Norte (CHULN), in Lisbon, Portugal, between March 2020 and May 2020. The Ethical Committee approved of this study, in agreement with institutional guidelines and informed consent was waived, given its retrospective and non-interventional nature.

We selected as eligible all adult patients (≥18 years of age) who tested positive by polymerase chain reaction testing of a nasopharyngeal sample for COVID-19 and were admitted at the UICIVE from March 1st to May 31st of 2020. For patients who had multiple qualifying hospital admissions, we included only the first hospitalization. Exclusion criteria comprised (a) chronic kidney disease (CKD) patients on renal replacement therapy, (b) patients who underwent renal replacement therapy one week prior to admission, (c) patients who had less than 2 determinations of SCr and (d) patients who were discharged or died less than two days after admission.

Data was collected from individual electronic clinical records. The following variables were analyzed: patient demographic characteristics (age, gender, ethnicity, body weight and height); comorbidities [diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), cirrhosis, CKD and/or active malignancy]; current treatment with RAAS inhibitors; disease severity according to the Sequential Organ Failure Assessment (SOFA) [18] score and Brescia-COVID Respiratory Severity Scale (BCRSS) at admission; laboratory values at admission [serum hemoglobin, hematocrit, neutrophil, lymphocyte count and platelet count, serum albumin, serum ferritin, SCr, procalcitonin (PCT) and C-reactive protein (CRP), arterial blood gas and pH analysis, lactic acid dehydrogenase (LDH)]; exposure to nephrotoxins during the first week of admission [non-steroidal anti-inflammatory drugs (NSAIDS), radiocontrast, vancomycin, aminoglycosides]; need for intensive care unit (ICU) admission; need for mechanical ventilation; vasopressor use; treatment options used for COVID-19 (hydroxychloroquine, lopinavir/ritonavir, corticosteroids, tocilizumab).

Diagnosis of COVID-19 was based on the WHO interim guidelines. [19]

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification, using the serum creatinine (SCr) criteria, as follows: Stage 1: increase in SCr by 0.3 mg/dL within 48 hours or a 1.5-1.9 times increase in SCr from baseline within 7 days; Stage 2: 2.9 times increase in SCr within 7 days; Stage 3: 3 times or more increase in SCr within 7 days or initiation of renal replacement therapy (RRT). [20] Patients were stratified according to the highest AKI stage attained during their hospital stay. Persistent AKI was defined as continuance of AKI according to KDIGO criteria beyond 48 h according to the consensus report of the ADQI 16 Workgroup. [22] Transient AKI was defined as AKI of less than 48 h duration. [22]

Pre-admission SCr (SCr within the previous three months) was considered as baseline value. The estimated glomerular filtration rate (eGFR) for patients with previous baseline SCr was calculated using the Chronic

Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. [21] When unavailable, baseline SCr was estimated from the MDRD equation, accepting the lower limit of a normal baseline GFR of 75 mL/min/1.73m2, as previously proposed. [20]

Diabetes mellitus was diagnosed according to the American Diabetes Association criteria. [23] Hypertension diagnosed according to the 2018 European Society of Cardiology (ESC) and European Society of Hypertension Guidelines. [24] COPD comprised emphysema and chronic bronchitis. CVD was considered whenever a history of cerebrovascular disease, chronic heart failure of any cause, cardiac ischemic disease and/or peripheral arterial disease was documented. N/L ratio at admission was calculated as: Neutrophil count / Lymphocyte count.

The analyzed outcomes were the development of AKI and in-hospital mortality.

Categorical variables were described as the total number and percentage for each category, whereas continuous variables were described as the mean ± standard deviation. Continuous variables were compared with the Student's t-test and categorical variables were compared with the Chi-square test. All variables underwent univariate analysis to determine statistically significant factors which may have contributed to AKI development and in-hospital mortality. Subsequently, variables with a significant statistical difference were included in the multivariate analysis using the Cox logistic regression method. Data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a P-value <0.05. Statistical analysis was performed with the statistical software package SPSS for windows (version 21.0).

Results

Participants

From March 1st to May 31st, 236 patients were admitted to UICIVE with a diagnosis of COVID-19 on admission. We focused on 192 patients after excluding 44 patients as depicted in Figure 1.

A majority of Caucasian (n=174, 90.6%) males (n=100, 52.1%) were hospitalized with a mean age of 72.2±16.4 years. There was a large prevalence of hypertensive (n=131, 68.2%), CVD (n=68, 35.4%), diabetic (n=54, 28.1%) and CKD (n=38, 19.8%) patients. Forty-two percent of patients were medicated with RAAS inhibitors. Almost 20% of hospitalized patients (n=38) required admission to an intensive care unit (ICU) mostly due to respiratory failure, 15.1% of patients fulfilled ARDS criteria and 16.7% of patients required mechanical ventilation. Most patients had a SOFA score of at least 2 (57.8%), and 12.5% of patients had a SOFA score of at least 4. Almost 30% of patients had a BCRSS score of at least 2.

At admission, mean SCr was 1.33±1.82mg/dL, mean hemoglobin was 13.0±2.1 and almost 40% of patients were anemic, mean NL ratio was 6.49±5.71, mean serum albumin was 3.37±0.59 g/dL and more than 70% of patients had hypoalbuminemia, mean serum ferritin was 1100.6±1298.3 ug/L, mean CRP was 9.71±8.72mg/dL, mean lactate level was 15.65±10.60 mg/dL and 27% of patients were acidemic.

During the first week of admission, 20.8% of patients were exposed to nephrotoxins, namely NSAIDS, radiocontrast, vancomycin or aminoglycosides. Concerning treatment, a vast majority of patients were medicated with hydroxycloroquine (n=140, 72.9%) and lopinavir/ritonavir (n=128, 66.7%). Only 3 patients were

treated with tocilizumab and 10.9% of patients required corticosteroids. Mean time to ICU admission was 3.2±1.8 days.

Mean length of hospital stay was 22.3±23.9 days. Baseline characteristics of this cohort are described in Table 1.

AKI

In this cohort of COVID-19 patients, 55.2% developed AKI (n=106). Of these, 64.2% of patients (n=68) presented AKI at admission and the remaining developed AKI within the first week of hospitalization. Mean time to AKI development was 2.2±0.9 days. Patient characteristics according to AKI development are described in Table 1.

Patients with AKI were older (75.6±14.6 vs 67.6±17.4, p=0.001; unadjusted OR 1.03 (95% CI 1.01-1.05), p=0.001), were more likely to have pre-existing hypertension (78.3% vs 56.5%, p=0.001; unadjusted OR 2.78 (95% CI 1.48-5.22), p=0.001), CKD (28.3% vs 9.4%, p=0.001; unadjusted OR 3.96 (95% CI 1.70-9.19), p=0.001) and COPD (19.8% vs 7.1%, p=0.012; unadjusted OR 3.25 (95% CI 1.25-8.48). p=0.016), and to be medicated with RAAS inhibitors (51.9% vs 30.6%, p=0.002; unadjusted OR 2.60 (95% CI 1.42-4.75), p=0.002). Mean baseline SCr was higher in AKI patients (1.02±0.47 vs 0.84±0.26, p=0.002; unadjusted OR 4.40 (95% CI 1.64-11.83), p=0.003).

At admission, these patients had higher SCr (1.72±2.37 vs 0.84±0.25, p=0.001; unadjusted OR 35.81 (95% CI 10.48-122.38). p<0.001), higher NL ratio (7.8±6.5 vs 4.9±4.0, p<0.001; unadjusted OR 1.13 (95% CI 1.05-1.21), p=0.001) and were more likely acidemic (34.0% vs 20%, p=0.032; unadjusted OR 2.06 (95% CI 1.06-4.01)).

During the first week of hospitalization, patients more exposed to nephrotoxins were more likely to develop AKI (27.4% vs 12.9%, p=0.015; unadjusted OR 2.53 (95% CI 1.18-5.44), p=0.017).

AKI patients required more ICU admission (30.2% vs 7.1%, p<0.001), mechanical ventilation (26.4% vs 4.7%, p<0.001) and vasopressor use (7.5% vs 0%, p=0.008) and fulfilled more ARDS criteria (22.6% vs 5.9%, p=0.001). More AKI patients were treated with hydroxycloroquine (78.3% vs 67.1%, p=0.047) and corticosteroids (16.2% vs 4.7%, p=0.009).

The majority of AKI patients had persistent AKI (n=64, 60.4%). According to AKI severity, most patients were KDIGO stage 1 (n=66, 60.0%), followed by KDIGO stage 3 (n=24, 21.8%) and KDIGO stage 2 (n=20, 18.2%). Ten percent of AKI patients required renal replacement therapy (RRT), five patients required continuous RRT and the remaining intermittent RRT.

On a multivariate analysis, admission SCr (adjusted OR 48.01 (95% CI 10.46-220.45), p<0.001) and exposure to nephrotoxins (adjusted OR 3.60 (95% CI 1.30-9.94), p=0.014) were independent predictors of AKI.

Transient versus Persistent AKI

There were no statistically significant differences between transient versus persistent AKI concerning demographic and clinical characteristics, nor laboratory values at admission.

Compared with transient AKI, patients with persistent AKI had a higher proportion of patients with more severe AKI (KDIGO stage 3 31.3% vs 7.1%, KDIGO stage 2 21.9% vs 14.3%, KDIGO stage 1 45.3% vs 78.6%, p=0.002), required more often ICU admission (37.5% vs 19.0, p=0.045), and RRT (14.1% vs 2.4%, p=0.044). These patients had higher mortality rate than transient AKI patients (37.5% vs 11.9%, p=0.004).

AKI and outcomes

Overall, in-hospital mortality was 18.2% (n=35). Mortality was associated with older age (83.6±12.6 vs 69.6±16.1, p<0.001; unadjusted OR 1.08 (95% CI 1.04-1.12), p<0.001), pre-existing CVD (60% vs 29.9%, p=0.001, unadjusted OR 3.51 (95% CI 1.65-7.49), p=0.001) and CKD (42.9% vs 14.6%, p<0.001, unadjusted OR 5.14 (95% CI 2.26-11.71), p<0.001); lower Hb (11.8±2.4 vs 13.2±1.9, p<0.001, unadjusted OR 0.73 (0.61-0.88), p=0.001), higher SCr (2.49±4.00 vs 1.08±0.54, p<0.001, unadjusted OR 2.42 (95% CI 1.44-4.06), p=0.001), lower albumin (3.14±0.56 vs 3.42±0.58, p=0.014, unadjusted OR 0.45 (95% CI 0.23-0.87), p=0.018) and acidemia (45.7% vs 23.6%, p=0.008, unadjusted OR 2.73 (95% CI 1.28-5.84), p=0.001) at admission. (Table 2)

Mortality was also associated with AKI (28.3% vs 5.9%, p<0.001, unadjusted OR 6.03 (2.22-16.37), p<0.001). AKI patients also had a more prolonged length of hospital stay (26.5±26.2 days vs 17.1±19.6 days, p=0.007).

On a multivariate analysis, AKI was not an independent predictor of mortality (adjusted OR 3.00 (95% CI 0.86-10.52), p=0.086). Thus, we performed a sensitivity analysis to include only patients with persistent AKI. On a multivariate analysis, older age (adjusted OR 1.08 (95% CI 1.02-1.13), p=0.004), lower Hb level (adjusted OR 0.69 (95% CI 0.53-0.91), p=0.007), acidemia (adjusted OR 5.53 (95% CI 1.70-18.63), p=0.005), duration of AKI (adjusted OR 7.91 for persistent AKI (95% CI 2.39-26.21), p=0.001) and severity of AKI (adjusted OR 2.30 per increase in KDIGO stage (95% CI 1.10-4.82), p=0.027) were independent predictors of mortality. (Table 3)

Discussion

In this retrospective cohort we report a high incidence of AKI associated with COVID-19. More than 50% of infected patients developed AKI and the majority of these were transient and had lower severity changes in renal function. Remarkably, only persistent AKI and higher severity AKI were associated with mortality in these patients.

AKI is a frequent diagnosis in hospitalized patients. [14] Recent studies have suggested the association of AKI and COVID-19, despite an initial report by Wang et al which described there was no AKI in 116 patients in Wuhan.[25] This study included a majority of mild pneumonia patients had no patients had previous CKD which may explain the absence of AKI. In fact, in our cohort previous CKD and baseline SCr were important risk predictors of AKI development.

One of the studies which reports the lower rate of AKI is a retrospective study of 1099 hospitalized patients and outpatients in China, in which AKI was only present in 6 patients (0.5%). [5] In a retrospective cohort of 52 critically ill COVID-19 patients, Yang et al reported a 29% incidence of AKI and a mortality of 61.5% which was associated with the severity of the pneumonia. [11] In another study, the incidence of AKI ranged from 3.5% in moderate disease patients to 42.9% in critically ill patients. [26] Furthermore, AKI patients had a higher mortality rate. [27] Indeed, AKI was most often present in more severe cases of COVID-19. [28]

In our cohort of hospitalized COVID-19 patients, AKI was present in 55%. The more frequent use of hydroxycloroquine and corticosteroids in AKI patients in our cohort reflects the presence of moderate to severe disease in these patients. This severity of COVID-19 in our cohort explains the large incidence of AKI. The fact that 30% of AKI patients required ICU admission within the first week of admission, also points out the contribution of AKI to disease severity.

The largest multicenter cohort included 5449 hospitalized COVID-19 patients in which 36.6% developed AKI. Hirsch et al reported a majority of patients with lower severity of AKI, in this study 46.5% of patients were KDIGO stage 1, and also reported that most AKI cases developed early in the course of COVID-19. [29] This is in accordance with our results as we reported a prevalence of 60% of KDIGO stage 1, and most patients presented with AKI at admission or within the first two days.

The etiology of AKI in patients with COVID-19 appears to be multifactorial, including ischemic injury, cytokine storm, and direct cytopathic effects on the kidney.[30] Despite the considerable focus on the use of RAAS inhibitors and severity of COVID-19, as it is theorized that the intake of these drugs might enable virus entry and replication, in both Hirsch's study and in our cohort the use of RAAS inhibitors was not associated with AKI development or mortality.[31–33]

AKI has been associated with an increased risk of in-hospital mortality in multiple settings. [15,34] The mortality rate of COVID-19 is estimated to be around 6% worldwide, still 81% of COVID-19 cases are mild. [1] The rate of mortality in hospitalized patients ranges from 10-30% and is much higher in critically ill patients. [9,12,35–37]

Cheng et al demonstrated that renal dysfunction defined as either elevated baseline SCr, hematuria, proteinuria and AKI, was associated with mortality in a prospective cohort of 701 hospitalized patients with COVID-19. [38] Despite reporting an incidence of AKI of only 5.1%, this study reported a higher risk of mortality according to AKI severity. [39] Lim et al studied 164 hospitalized patients with an AKI incidence of 18% and demonstrated that AKI KDIGO stage 3 was independently associated with mortality. [40] This is also consistent with the results of our cohort, as we reported an increased risk of mortality with the severity of AKI (adjusted OR 2.30 per increase in KDIGO stage (95% CI 1.10-4.82), p=0.027). Consistent with previous data we reported an increased risk of mortality associated with older age, lower hemoglobin and acidemia.

Our cohort is the first to study the impact of AKI duration in COVID-19 patients and its association with outcomes. Indeed, the association of rapid kidney function recovery and better short-term survival has been previously reported in other settings. [22,41–43] The impact of AKI duration on prognosis led to the development of a standardized definition of transient and persistent AKI, based on recovery of kidney function within 48 hours, by the ADQI Workgroup. [22]

Rubin et al analyzed AKI in 77 critically ill patients with COVID-19 and demonstrated that persistent AKI was present in the majority of patients (93%). [44] In their study, clinical and laboratory characteristics were similar between patients with persistent and transient AKI. [44] These findings were also present in our cohort.

We demonstrated that persistent AKI was present in 60% of patients and was associated with a significant increase in mortality risk (adjusted OR 7.91 (95% CI 2.39-26.21), p=0.001). In our study, transient AKI did not

carry an increased risk for in-hospital mortality.

Our study has some important virtues. Firstly, we defined AKI according to the KDIGO classification using SCr criteria. Additionally, we applied the standardized definitions of transient and persistent AKI as defined by the ADQI workgroup to evaluate its impact on prognosis. Also, despite its retrospective design, the studied variables were routinely recorded in daily practice which allowed for the analysis of important covariates with impact on AKI development and outcome.

This study has important virtues to be noted. This is the first study demonstrating an association between duration of AKI and mortality in patients with COVID-19. This is the largest single center cohort of AKI patients with COVID-19. Also, we used the current KDIGO definition of AKI and the AKIN definitions of transient and persistent AKI.

Nevertheless, this study has certain limitations. Firstly, the single-center and retrospective nature of our study limits generalizability. Secondly, 15.6% of patients did not have baseline SCr and baseline renal function had to be estimated with the MDRD equation, which might have led to overestimation of AKI. Finally, we could not determine the exact mechanisms contributing to AKI and mortality in these patients.

To conclude, we demonstrated that AKI was frequent in hospitalized patients with COVID-19 and that persistent and higher severity of AKI were predictors of in-hospital mortality. Although we could not find predictors of persistent AKI in this modest cohort size, further studies should focus on this matter to allow for the early recognition of high-risk patients.

Declarations

Ethics approval and consent to participate

The Ethical Committee of Centro Hospitalar Universitário Lisboa Norte approved of this study, in agreement with institutional guidelines and informed consent was waived, given its retrospective and non-interventional nature.

Consent for publication

Not applicable

Competing interests

There is no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Authors' contributions

JG and JAF made substantial contributions to the study concept and design, analysis and interpretation of data, and were involved in drafting the manuscript and revising it critically for important intellectual content. JAF, JO, FM, JB, CC, CC, SB participated in the acquisition of data. LA and JAL were involved in the critical revision of the manuscript.

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References

1. Organization WH. Coronavirus disease 2019 (COVID-19) Situation Report – 119. ttps://www.who.int/docs/default-source/coronaviruse/situation-reports/20200518-covid-19-sitrep-119.pdf?sfvrsn=4bd9de25_4.
2. Saúde DG de. Relatório de Situação – 78. https://covid19.min-saude.pt/wp-content/uploads/2020/05/78_DGS_boletim_20200519.pdf.
3. Ren YR, Golding A, Sorbello A, et al. A Comprehensive Updated Review on SARS-CoV-2 and COVID-19. *J Clin Pharmacol*. May 2020:jcph.1673. doi:10.1002/jcph.1673
4. Kakodkar P, Kaka N, Baig M. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus*. April 2020. doi:10.7759/cureus.7560
5. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032
6. Kakodkar P, Kaka N, Baig M. A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19). *Cureus*. April 2020. doi:10.7759/cureus.7560
7. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032
8. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. March 2020:m1091. doi:10.1136/bmj.m1091
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
10. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*. 2020;323(16):1612. doi:10.1001/jama.2020.4326
11. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. doi:10.1016/S2213-2600(20)30079-5
12. 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(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

13. 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(11):1061. doi:10.1001/jama.2020.1585
14. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet (London, England)*. 2019;394(10212):1949-1964. doi:10.1016/S0140-6736(19)32563-2
15. Gameiro J, Agapito Fonseca J, Jorge S, Lopes J. Acute Kidney Injury Definition and Diagnosis: A Narrative Review. *J Clin Med*. 2018;7(10):307. doi:10.3390/jcm7100307
16. Panitchote A, Mehkri O, Hastings A, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):74. doi:10.1186/s13613-019-0552-5
17. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol*. 2020;16(6):308-310. doi:10.1038/s41581-020-0284-7
18. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017;43(3):304-377. doi:10.1007/s00134-017-4683-6
19. Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. https://www.who.int/publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected.
20. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Nephron*. 2012;120(4):c179-c184. doi:10.1159/000339789
21. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009;150(9):604. doi:10.7326/0003-4819-150-9-200905050-00006
22. 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(4):241-257. doi:10.1038/nrneph.2017.2
23. Standards of Medical Care in Diabetes–2009. *Diabetes Care*. 2009;32(Supplement_1):S13-S61. doi:10.2337/dc09-S013
24. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104. doi:10.1093/eurheartj/ehy339
25. Wang L, Li X, Chen H, et al. Coronavirus Disease 19 Infection Does Not Result in Acute Kidney Injury: An Analysis of 116 Hospitalized Patients from Wuhan, China. *Am J Nephrol*. 2020;51(5):343-348. doi:10.1159/000507471
26. 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(6):1157-1165. doi:10.1681/ASN.2020030276
27. 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(6):1157-1165. doi:10.1681/ASN.2020030276
28. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Virol*. 2020;127:104371. doi:10.1016/j.jcv.2020.104371
29. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. May 2020. doi:10.1016/j.kint.2020.05.006

30. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2. *J Am Soc Nephrol*. May 2020:ASN.2020040432. doi:10.1681/ASN.2020040432
31. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *J Hypertens*. 2020;38(5):781-782. doi:10.1097/HJH.0000000000002450
32. Sommerstein R, Kochen MM, Messerli FH, Gräni C. Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect? *J Am Heart Assoc*. 2020;9(7). doi:10.1161/JAHA.120.016509
33. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. May 2020. doi:10.1016/j.kint.2020.05.006
34. Brown JR, Rezaee ME, Marshall EJ, Matheny ME. Hospital Mortality in the United States following Acute Kidney Injury. *Biomed Res Int*. 2016;2016:1-6. doi:10.1155/2016/4278579
35. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7
36. Lim J-H, Park S-H, Jeon Y, et al. Fatal Outcomes of COVID-19 in Patients with Severe Acute Kidney Injury. *J Clin Med*. 2020;9(6):1718. doi:10.3390/jcm9061718
37. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Virol*. 2020;127:104371. doi:10.1016/j.jcv.2020.104371
38. 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(5):829-838. doi:10.1016/j.kint.2020.03.005
39. 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(5):829-838. doi:10.1016/j.kint.2020.03.005
40. Lim J-H, Park S-H, Jeon Y, et al. Fatal Outcomes of COVID-19 in Patients with Severe Acute Kidney Injury. *J Clin Med*. 2020;9(6):1718. doi:10.3390/jcm9061718
41. Sood MM, Shafer LA, Ho J, et al. Early reversible acute kidney injury is associated with improved survival in septic shock. *J Crit Care*. 2014;29(5):711-717. doi:10.1016/j.jcrc.2014.04.003
42. Perinel S, Vincent F, Lautrette A, et al. Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients. *Crit Care Med*. 2015;43(8):e269-e275. doi:10.1097/CCM.0000000000001077
43. Fidalgo P, Ahmed M, Meyer SR, et al. Association between transient acute kidney injury and morbidity and mortality after lung transplantation: A retrospective cohort study. *J Crit Care*. 2014;29(6):1028-1034. doi:10.1016/j.jcrc.2014.07.024
44. 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*. June 2020. doi:10.1093/ckj/sfaa099

Tables

Table 1 – Patients' baseline characteristics and according to AKI development

Characteristic	Total (n=192)	No-AKI (n=85)	AKI (n=106)	p- value
Age (year)	72.2±16.4	67.6±17.4	75.6±14.6	0.001
Gender (Male) – n (%)	100 (52.1)	41 (48.2)	59 (55.7)	0.307
Race (Caucasian) – n (%)	174 (90.6)	74 (87.1)	99 (93.4)	0.136
Co-morbidities – n (%)				
Hypertension	131 (68.2)	48 (56.5)	83 (78.3)	0.001
Diabetes	54 (28.1)	18 (21.2)	36 (34.0)	0.051
CVD	68 (35.4)	25 (29.4)	42 (39.6)	0.142
CKD	38 (19.8)	8 (9.4)	30 (28.3)	0.001
COPD	27 (14.1)	6 (7.1)	21 (19.8)	0.012
Cirrhosis	3 (1.6)	2 (2.4)	1 (0.9)	0.436
Neoplasia	31 (16.1)	16 (18.8)	15 (14.2)	0.384
RAAS inhibitors – n (%)	81 (42.2)	26 (30.6)	55 (51.9)	0.002
Baseline SCr (mg/dl)	0.94±0.40	0.84±0.26	1.02±0.47	0.002
Baseline eTFG (mL/min/1.73m2)	77.02±23.97	84.5±22.2	71.3±23.7	0.000
SOFA Score ≥ 4	24 (12.5)	6 (7.1)	18 (17.0)	0.040
Brescia Score ≥ 2	52 (27.0)	16 (18.8)	36 (34.0)	0.019
Laboratory				
Admission SCr (mg/dl)	1.33±1.82	0.84±0.25	1.72±2.37	0.001
Hemoglobin (g/dl)	13.0±2.1	13.1±1.9	12.9±2.2	0.556
Anemia – n (%)	76 (39.6)	33 (38.8)	43 (40.6)	0.807
NL ratio	6.49±5.71	4.9±4.0	7.8±6.5	<0.001
Serum albumin (g/dl)	3.37±0.59	3.41±0.66	3.34±0.53	0.438
Hypoalbuminemia – n (%)	142 (74)	58 (68.2)	84 (79.2)	0.083
Serum ferritin (ug/dL)	1100.6±1298.3	802.3±548.4	1293.9±1582.3	0.045
CRP (mg/dL)	9.71±8.72	8.49±8.07	30.75±5.11	0.082
Acidemia	53 (27.6)	17 (20)	36 (34.0)	0.032
Lactate level (mg/dL)	15.65±10.60	14.9±11.8	16.2±9.4	0.401
Nephrotoxins – n (%)	40 (20.8)	11 (12.9)	29 (27.4)	0.015
ICU admission – n (%)	38 (19.8)	6 (7.1)	32 (30.2)	<0.001
Mechanical ventilation – n (%)	32 (16.7)	4 (4.7)	28 (26.4)	<0.001
Vasopressor use – n (%)	8 (4.2)	0 (0)	8 (7.5)	0.008
ARDS – n (%)	29 (15.1%)	5 (5.9)	24 (22.6)	0.001
COVID-19 treatment				
Hydroxycloroquine – n (%)	140 (72.9)	57 (67.1)	83 (78.3)	0.047
Lopinavir/ritonavir – n (%)	128 (66.7)	52 (61.2)	76 (71.7)	0.101
Tocilizumab – n (%)	3 (1.6)	1 (1.2)	2 (1.9)	0.683
Corticosteroids – n (%)	21 (10.9)	4 (4.7)	17 (16.2)	0.009
AKI – n (%)	106 (55.2)			
Persistent AKI – n (%)	64 (33.3)		64 (60.4)	

KDIGO stage 1 – n (%)	66 (34.4)		66 (60.0)	
KDIGO stage 2 – n (%)	20 (10.4)		20 (18.2)	
KDIGO stage 3 – n (%)	24 (12.5)		24 (21.8)	
RRT requirement – n (%)	11 (5.7)		11 (10.3)	
LOS in hospital (days)	22.3±23.9	17.1±19.6	26.5±26.2	0.007
Discharge SCr (mg/dl)	1.00±0.72	0.75±0.24	1.21±0.94	0.000
AKD – n (%)	39 (20.3)			
In-hospital mortality – n (%)	35 (18.2)	5 (5.9)	30 (28.3)	<0.001

Table 2 - Characteristics of patients according to in-hospital mortality

Characteristic	Mortality (n=35)	Survival (n=157)	p- value
Age (year)	83.6±12.6	69.6±16.1	<0.001
Gender (Male) – n (%)	19 (54.3)	81 (51.6)	0.773
Race (Caucasian) – n (%)	34 (97.1)	140 (89.2)	0.143
Co-morbidities – n (%)			
Hypertension	27 (77.1)	104 (66.2)	0.210
Diabetes	12 (34.3)	42 (26.8)	0.370
CVD	21 (60)	47 (29.9)	0.001
CKD	15 (42.9)	23 (14.6)	<0.001
COPD	8 (22.9)	19 (12.1)	0.098
Cirrhosis	1 (2.9)	2 (1.3)	0.495
Neoplasia	8 (22.9)	23 (14.6)	0.233
RAAS inhibitors – n (%)	15 (42.9)	66 (42.0)	0.740
Baseline SCr (mg/dl)	1.16±0.63	0.89±0.31	<0.001
Baseline eTFG (mL/min/1.73m2)	60.9±25.1	80.6±22.2	<0.001
SOFA Score > 4	10 (38.6)	14 (8.9)	0.001
Brescia Score > 2	14 (40.0)	38 (24.2)	0.057
Laboratory			
Admission SCr (mg/dl)	2.49±4.00	1.08±0.54	<0.001
Hemoglobin (g/dl)	11.8±2.4	13.2±1.9	<0.001
Anemia – n (%)	21 (60)	55 (35.0)	0.006
NL ratio	8.50±7.87	6.05±5.05	0.023
Serum albumin (g/dl)	3.14±0.56	3.42±0.58	0.014
Hypoalbuminemia – n (%)	29 (82.9)	113 (72.0)	0.185
Serum ferritin	1805.0±2346.0	918.8±765.9	0.003
CRP (mg/dL)	10.3±8.9	9.6±8.7	0.646
Acidemia	16 (45.7)	37 (23.6)	0.008
Lactate level	21.7±18.2	14.3±7.4	<0.001
Nephrotoxins – n (%)	8 (22.9)	32 (20.4)	0.744
ICU admission – n (%)	5 (14.3)	33 (21.0)	0.394
Mechanical ventilation – n (%)	4 (11.4)	28 (17.8)	0.383
Vasopressor use – n (%)	2 (5.7)	6 (3.8)	0.609
ARDS – n (%)	3 (8.6)	26 (16.6)	0.244
COVID-19 treatment			
Hydroxycloroquine – n (%)	22 (62.9)	118 (75.2)	0.189
Lopinavir/ritonavir – n (%)	18 (51.4)	110 (70.1)	0.054
Tocilizumab – n (%)	0 (0)	3 (1.9)	0.415
Corticosteroids – n (%)	5 (14.3)	16 (10.2)	0.410
AKI – n (%)	29 (82.9)	77 (49.0)	<0.001
Persistent AKI – n (%)	24 (68.6)	40 (25.5)	<0.001

KDIGO stage 1 – n (%)	13 (37.1)	53 (33.8)	0.081
KDIGO stage 2 – n (%)	7 (20)	13 (8.3)	
KDIGO stage 3 – n (%)	10 (28.6)	14 (8.9)	
RRT requirement – n (%)	5 (14.3)	6 (3.8)	0.175
LOS in hospital (days)	15.2±15.4	23.9±25.1	0.053
LOS in ICU (days)	3.9±8.9	10.6±16.4	0.179

Table 3 - Univariate and multivariate analysis of factors predictive of AKI and mortality in COVID-19 patients

	AKI				Mortality			
	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	1.03 (1.01-1.05)	0.001	1.02 (1.00-1.05)	0.084	1.08 (1.04-1.12)	<0.001	1.08 (1.02-1.13)	0.004
	1.35 (0.76-2.34)	0.308			1.14 (0.53-2.32)	0.773		
)	2.10 (0.78-5.68)	0.143			4.13 (0.53-32.11)	0.175		
	2.78 (1.48-5.22)	0.001	1.69 (0.65-4.42)	0.283	1.72 (0.73-4.05)	0.214		
	1.91 (0.99-3.70)	0.053			1.43 (0.65-3.12)	0.372		
	1.58 (0.86-2.89)	0.143			3.51 (1.65-7.49)	0.001	1.28 (0.43-3.78)	0.659
	3.96 (1.70-9.19)	0.001	0.43 (0.13-1.45)	0.172	5.14 (2.26-11.71)	<0.001	1.21 (0.33-4.37)	0.775
	3.25 (1.25-8.48)	0.016	1.26 (0.37-4.30)	0.430	2.15 (0.86-5.42)	0.104		
	0.40 (0.04-4.43)	0.452			2.28 (0.20-25.87)	0.506		
	0.71 (0.33-1.54)	0.385			1.73 (0.70-4.27)	0.237		
	2.60 (1.42-4.75)	0.002	1.41 (0.60-3.29)	0.793	1.14 (0.53-2.42)	0.740		
	4.40 (1.64-11.83)	0.003			4.23 (1.66-10.81)	0.003		
	35.81 (10.48-122.38)	<0.001	48.01 (10.46-220.45)	<0.001	2.42 (1.44-4.06)	0.001	1.33 (0.80-2.21)	0.277
	0.96 (0.84-1.10)	0.554			0.73 (0.61-0.88)	0.001	0.69 (0.53-0.91)	0.007
	1.08 (0.60-1.93)	0.807			2.78 (1.31-5.90)	0.008		
	1.13 (1.05-1.21)	0.001	1.05 (0.96-1.14)	0.296	1.06 (1.01-1.13)	0.031	0.96 (0.88-1.06)	0.439
	0.81 (0.47-1.39)	0.437			0.45 (0.23-0.87)	0.018	0.76 (0.28-2.11)	0.600
a	1.78 (0.92-3.42)	0.085			1.88 (0.73-4.85)	0.190		
	1.00 (1.00-1.01)	0.063			1.00 (1.00-1.01)	0.010		
	1.03 (1.00-1.07)	0.084			1.01 (0.97-1.05)	0.644		
	2.06 (1.06-4.01)	0.034	1.13 (0.46-2.79)	0.793	2.73 (1.28-5.84)	0.001	5.53 (1.70-18.63)	0.005
	1.01 (0.98-1.04)	0.404			1.06 (1.02-1.10)	0.002		
	2.53 (1.18-5.44)	0.017	3.60 (1.30-9.94)	0.014	1.16 (0.48-2.79)	0.745		
					0.64 (0.23-1.79)	0.397		
					0.61 (0.20-1.87)	0.387		

					0.48 (0.14-1.69)	0.253		
					6.03 (2.22-16.37)	<0.001	3.00 (0.86-10.52)	0.086
					7.02 (3.09-15.95)	<0.001	7.91 (2.39-26.21)	0.001
					1.74 (1.05-2.851)	0.030	2.30 (1.10-4.82)	0.027
					2.37 (0.66-8.44)	0.184		
	1.02 (1.00-1.04)	0.010			0.98 (0.95-1.00)	0.061		

Figures

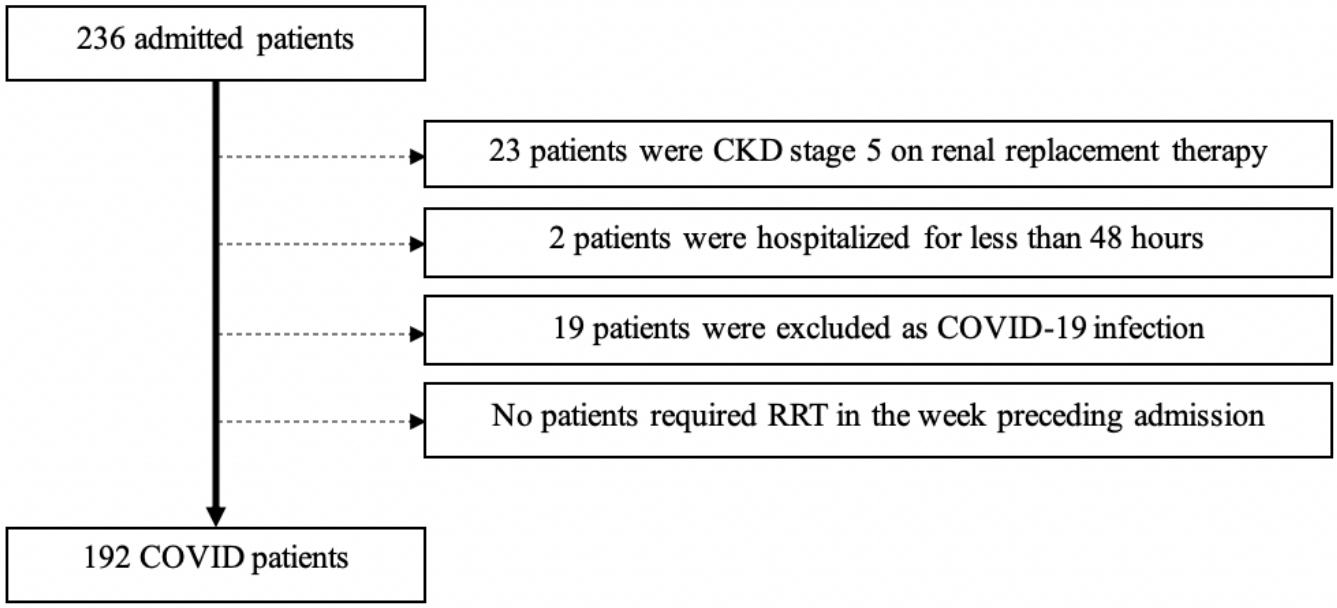

Figure 1

Flow-chart of patient selection