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Outcomes Among Hospitalized Acute Kidney Injury - related COVID-19 Patients

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Abstract

Introduction. Although diffuse alveolar damage and respiratory failure are the key features of coronavirus disease 2019 (COVID-19), the involvement of other organs such as the kidney has also been reported. The reports of the incidence of acute kidney injury (AKI) in COVID-19 patients vary widely. In this study, we report our experience with AKI in COVID-19 patients and provide its incidence, risk factors, and prognosis to expand the current understanding of this complication.
Methods. In this single-center, retrospective observational study, we analyzed the data of 269 COVID-19 patients admitted to the Clinic for nephrology in Sarajevo, BH, from March 2020 through April 2021. Information regarding demographics, comorbidities, medications, clinical and laboratory data, and outcomes was collected from the electronic medical records. We excluded COVID-19 patients from our study if they were on maintenance dialysis or were kidney transplant recipients. The earliest day of the serum creatinine change that met the KDIGO criteria for AKI was selected as day 1 of AKI. Statistical analyzes were performed using SPSS 21 Windows (version 21.0).
Results. The median age of the patients was 64.2 years, and 59.85% of them were male. Most of these patients presented with dyspnea (96.65%), cough (92.19%), and fever (87.73%). Of all the patients studied, 69.88% were discharged, 16.73% died during hospitalization, and 13.38% were transferred to another institution. The incidence of AKI during hospitalization was 28.99% (n=78) and was significantly higher in patients who presented with eGFR <60 mL/min/1.73 m^2 (65.38 vs. 34.61%). The in-hospital mortality was significantly higher in patients with an eGFR <60 mL/min/1.73 m^2 (26 pts.) then in patients with an eGFR ≥60 mL/min/1.73m^2 (19 pts.) at presentation. Compared with patients without AKI, patients with AKI had higher levels of white blood cells (WBC), inflammatory markers, and had low pulse oxygen saturation at admission. The number of patients requiring renal replacement therapy (RRT) during hospitalization was 23. In the multivariable model, AKI (stage 3) is associated with a higher risk of hospital mortality during the follow-up period.
Conclusion. AKI in our hospitalized COVID-19 patients was common and carried high mortality, especially in patients with AKI stage 3. RRT did not improve survival.

Keywords: Coronavirus disease 19, Acute kidney injury, Renal replacement therapy, Hospital mortality

Introduction

Coronavirus disease 2019 (COVID-19) is associated with high morbidity and mortality [1]. Two other coronavirus infections, SARS 2002-03 and Middle East Respiratory Syndrome (MERS) in 2012 caused severe respiratory syndrome in humans. All three of these emerging infectious diseases are caused by coronaviruses. While COVID-19 is primarily an infection that can cause pneumonia and hypoxemia, other organs are involved, including the kidney, gastrointestinal tract, and heart. Reports are numerous, but the incidence of acute renal injury (AKI) secondary to COVID-19 (COV-AKI) is high, with a prevalence level of as much as 68% in critically ill patients in New York City, USA [2].
Most AKI cases are mild to moderate. However, dialysis rates may be as high as 30% and survival may be reduced when AKI occurs. Kidney failure appears to occur late in the course of the disease, so there may be a window for treatment. Treatment currently consists primarily of preventive measures as no directed treatment for AKI is available. This makes AKI in general, and in the current COVID-19 pandemic in particular, an essential condition to be addressed [3].
In this study, we report our experience with AKI in COVID-19 patients. The study's primary objective was to determine the incidence of in-hospital AKI in COVID-19 patients and to study baseline characteristics and la-

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boratory data associated with its development. The study's secondary objective was to identify risk factors and prognosis of AKI and thus provide a broader understanding of these complications in a hospitalized group of COVID patients at the Nephrology Clinic in the past year.

Material and methods

All adult patients >18 years of age admitted to the Clinic for nephrology with COVID-19 infection from March 2020 through April 2021 were studied in this retrospective analysis. COVID-19 infection was diagnosed based on clinical presentation, radiographic lung abnormalities, and a positive SARS CoV-2 of real-time PCR. We excluded COVID-19 patients from our study who were on maintenance dialysis or were kidney transplant recipients. We collected the demographics, prior medical history, including outpatient medications and prior level of kidney function, comorbidities, the presenting clinical symptoms when available, and in-hospital laboratory data from the electronic medical record. Laboratory data consisted of complete blood count, kidney and liver function, pulse oximetry, hemostasis parameters, creatinine kinase, lactate dehydrogenase, procalcitonin, and inflammatory markers: - C-reactive protein (CRP), ferritin, interleukine-6, and D-dimer. Our laboratory provided the normal range of these measures. The Kidney Disease Improving Global Outcome (KDIGO) (4) definition was used to identify AKI. The estimated glomerular filtration rate (eGFR) on admission was taken as baseline eGFR and was divided into <60 and ≥60 mL/min/1.73m^2. eGFR was estimated using the Modification of Diet in Renal Disease Study (MDRD) equation. The earliest day of the serum creatinine change that met the KDIGO criteria for AKI was selected as day 1 of AKI. The peak serum creatinine value was used to determine the stage of AKI, with an increase in the serum creatinine of 1.5-1.9, 2.0-2.9, and >3 times the baseline serum creatinine defined as AKI stages 1, 2, and 3, respectively.

Statistical Analysis

The distribution of baseline characteristics was summarized according to AKI status using mean ± standard deviation for normally distributed data or median and interquartile range (IQR) values for non-normal distribution. Categorical variables were presented as frequency and percentage. The mean of continuous variables was compared by using independent t-tests and the Kruskal-Wallis test (across the stages of AKI). We used the Cox proportional hazard (PH) regression to determine the association of kidney disease indicators and in-hospital mortality. Statistical analyses were performed using SPSS 21 Windows (version 21.0, SPSS Inc, Chicago, Illinois, USA). All tests were two-sided, and P values <0.05 or at a confidence level of 95% were considered significant.

Results

We pooled 269 in-hospital patients between March 2020 and April 2021. Five patients were excluded, three cases with chronic kidney disease (one case receiving regular maintenance dialysis, one with membranous glomerulonephritis, one with nephrotic syndrome), one case diagnosed with pericardial effusion after admission, one case missing the core medical record. Baseline characteristics of these patients are shown in Table 1.
The median age of the patients was 64.2 years, and 59.85% of them were male. Most of these patients presented with dyspnea (96.65%), cough (92.19%), and fever (87.73%). Of all the patients studied, were discharged 69.88%, 16.73% died during hospitalization, and 13.38% were transferred to another institution. On admission, eGFR was <60 mL/min/1.73 m^2 in 44.1% (n=107) of the patients. Patients with an eGFR <60 mL/min/1.73 m^2 at presentation were significantly older (mean age 68.03 vs. 61.22 years; p<0.0001), more likely to be males (54.03 vs. 45.96%), and have hypertension, diabetes, hyperlipidemia, and were higher smoker among other preexisting comorbidities. The incidence of AKI during hospitalization was 28.99% (n=78) and was significantly higher in patients who presented with eGFR <60 mL/min/1.73 m^2 (65.38 vs.34.61%). Twenty four, 4, and 29 of these patients had AKI stages 1, 2 and 3, respectively. Eleven out of 32 patients with documented chronic kidney disease (CKD) before admission developed AKI during the hospitalization. Overall, the in-hospital mortality was 16.73% in COVID-19 patients. The in-hospital mortality was significantly higher in patients with an eGFR <60 mL/min/1.73 m^2 (26 pts.) than in patients with an eGFR ≥60 mL/min/1.73m^2 (19 pts.) at presentation.
Table 2 shows the results of clinical and laboratory tests of the patients performed on admission. Compared with the patients without AKI, the patients with AKI had higher white blood cells (WBC) and neutrophil counts, higher levels of D-dimer, C-reactive proteins (CRP), procalcitonin, interleukine-6 (IL-6), creatine kinase, and had low pulse oxygen saturation at admission, also they appeared to have mild symptoms of dyspnea, possibly as a result of gradual deterioration of the condition to allow for adaption and compensation.
The number of patients requiring renal replacement therapy (RRT) during the hospitalization was 23 (Table 3). This represented 8.5% of all patients and 29.48% of those with AKI. All the patients who required RRT by definition had stage 3 AKI. The modalities of RRT were continuous RRT in 3 patients (13.04% of all those who required RRT) and intermittent hemodialysis in 20 patients (86.9%). One patient required both modalities of RRT.

Table 1. Characteristics of COVID-19 patients admitted in the hospital stratified by baseline eGFR

Characteristic	All patients *n* = 269	eGFR ≥60 mL/min/1.73 m^2 *n* = 162 (55.9%)	eGFR <60 mL/min/1.73 m^2 *n* = 107 (44.1%)	*p* value
Age, mean (SD)	64.2(±15.5)	61.22(±16.6)	68.03(±13.2)	<0.0001
Gender, male *n* (%)	161(59.85)	74(45.96)	87(54.03)	<0.001
BMI, median (IQR)	29(25.6-34.2)	29.2(25.7-34.3)	28.2(25.6-33.8)	0.2
Preexisting comorbidities, n (%)				
Hypertension	193(71.75)	67(34.72)	126(65.28)	<0.001
Diabetes	99(36.8)	27(27.27)	72(72.73)	0.002
COPD	24(8.92)	17(40.8)	7(29.16)	0.05
Cancer	11(4.09)	7(63.63)	4(36.36)	0.16
Smoker	121(44.98)	45(37.19)	76(62.8)	0.07
Hyperlipidemia	147(54.64)	70(47.61)	77(52.38)	0.02
Drugs, n (%)				
ACEi	138(51.3)	43(31.16)	95(68.84)	0.007
ARB	42(15.61)	24(57.14)	18(42.86)	0.2
Statin	171(63.57)	79(46.2)	92(53.8)	0.001
NSAID	48(17.84)	36(75)	12(25)	0.80
Aspirin	178(66.17)	56(31.46)	72(40.45)	0.001
Hemodynamic instability at presentation, *n* (%)	70(14.93)	31(11.89)	39(18.84)	0.03
Signs and symptoms, n (%)				
Fever	236(87.73)	143(53.16)	93(39.4)	0.04
Myalgia	118(43.86)	66(55.9)	52(44.06)	0.96
Nausea/vomiting	45(16.73)	25(55.5)	20(44.4)	0.96
Cough	248(92.19)	156(62.9)	92(37.09)	0.001
Dyspnea	260(96.65)	153(58.85)	107(41.15)	0.09
Diarrhea	52(19.54)	29(55.77)	23(44.23)	0.98
Chest pain	25(9.29)	19(76)	6(24)	0.04
AKI during hospitalization	78(28.99)	27(34.6)	51(65.4)	<0.001
Stage 1	33(12.3)	9(27.3)	24(72.7)	<0.001
Stage 2	7(2.6)	3(42.9)	4(57.14)	0.05
Stage 3	38(14.1)	9(23.7)	29(76.3)	<0.05
Disposition on discharge, n (%)				
Home	188(69.88)	114(60.63)	74(39.36)	<0.001
Transferred to other departments	36(13.38)	23(63.88)	13(36.11)	0.001
In hospital death	45(16.73)	19(42.22)	26(57.7)	0.04

Abbreviations: COPD - Chronic obstructive pulmonary disease; ACEi - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin II receptor blocker; NSAID - Non-steroidal anti-inflammatory drugs

Table 2. Clinical and laboratory findings of the hospitalized patients positive for COVID-19

Characteristic	All patients	COVID-19 with AKI	COVID-19 and no AKI	p value
Initial vital signs, mean				
Temperature, °C	37.3±1.3	37.4±1.4	37.3±1.2	0.6
Respiratory rate, breaths/min	21.6±6.3	22.3±6.8	20.6±5.4	0.001
Pulse oximetry %	92.8	91.7	94.3	0.001
Pulse rate, beats/min	98.3±20	99.1±21.3	97.2±19.3	0.01
Initial laboratory dana				
WBC (10^9/L)	8.7±7.0	9.3±6.9	7.8± 7.1	0.001
Neutrophils (x10^9/L)	6.7±4.0	7.3±4.2	5.8±3.5	0.05
Lymphocyte (x10^9/L)	0.76(0.47-1.25)	0.68(0.47, 1.05)	0.91 0.63, 1.25)	0.03
PLT (x10^9/L)	138(118-190)	142(118-190)	171 130-190)	0.08
Creatinine (µmol/L)	113±65	184±342	93±73	<0.05
Procalcitonin(ng/mL)	0.06(0.03-0.15)	1.08(0.08-1.78)	0.05(0.03-0.12)	<0.05
CRP (mg/L)	78.8(4.8-19.1)	138.5±108	73.2(6.1-22.4)	0.001
D-dimer (mg/L)	1.7(0.9-3.8)	2.2(1.1-6.2)	1.1(0.7-2.3)	0.001
IL-6 (pg/ml)	15.57(3.07-39.62)	32.85(20.15-401.9)	11.61(2.71-37.82)	0.017
LDH (U/L)	403(300-546)	458(336-637)	350(270-451)	0.04
CK (U/L)	100(58-172)	118(69-223)	99(52-154)	0.03
Ferritin (ng/ml)	762.5(384-1420)	911(490.5-1667.5)	609.5(296-1086.5)	0.001

Abbreviations: WBC-white blood cells; PLT-Platelet count; CRP-C-reactive protein; IL-6-interleukin-6; LDH-Lactate dehydrogenase; CK-Creatine kinase

Table 3. SARS CoV-2 patients stratified by stages of AKI and demand for dialysis

Characteristic	Acute Kidney Injury					P value no RRT vs. RRT	P value stages AKI
	Stage 1 (33)	Stage 2 (7)	Stage 3 all pts. (34)	Stage 3 - no RRT (11)	Stage 3 – RRT (23)		
Age, median (IQR)	71(58-80)	65.5(54-74.5)	67(54-74)	71(60-77)	62(50–66)	0.19	0.005
Gender, male *n* (%)	19(57.57)	4(57.14)	26(76.47)	14(14.17)	12(35.29)	0.011	0.98
BMI, median (IQR)	27.9(25.8-32.5)	29.2(27.4-32.6)	31.5(27.5-35.5)	29.4(26.8-33.8)	34.4(27.7-40.3)	0.041	0.11
Preexisting comorbidities, n (%)							
Hypertension	26(78.78)	4(57.14)	30(88.23)	18(52.94)	12(35.29)	0.052	0.017
Diabetes	11(33.33)	4(57.14)	29(85.29)	9(26.47)	20(58.82)	0.42	0.53
COPD	4(12.12)	0	6(17.64)	5(14.70)	1(2.94)	0.56	0.65
Cancer	0	2(28.57)	4(11.76)	4(11.76)	0(0.00)	0.82	0.29
Smoker	28(84.84)	2(28.57)	17(50.0)	8(23.52)	9(26.47)	0.71	0.26
Hyperlipidemia	10(30.3)	7(100.0)	24(70.58)	12(35.29)	12(35.29)	0.46	0.04
Drugs, *n* (%)							
ACEi	23(69.69)	3(42.85)	26(76.47)	14(41.17)	12(35.29)	0.17	0.37
ARB	2(6.06)	0	2(5.88)	0	0	0.41	0.71
Statin	10(30.3)	7(100.0)	27(79.41)	17(50)	10(29.41)	0.85	0.035
NSAID	5(15.15)	5(71.42)	10(29.41)	7(20.58)	3(8.82)	0.04	0.71
Aspirin	23(69.69)	6(85.71)	29(85.29)	12(35.29)	17(50)	0.53	0.58
Hemodynamic instability at presentation, *n* (%)	7(21.21)	6(85.71)	20(58.82)	15(44.11)	5(14.7)	<0.001	0.52
Disposition on discharge, n (%)							
Discharged	18(54.54)	4(57.14)	13(38.23)	4(11.76)	9(26.47)	0.45	<0.001
Transferred to other departments	8(24.24)	1(14.28)	10(29.41)	3(8.82)	7(20.58)		
In hospital death	7(21.21)	2(28.57)	11(32.35)	4(11.76)	7(20.58)	<0.001	0.82
Recovery of kidney functions during hospitalization							
Full recovery	16(48.48)	2(28.57)	12(35.29)	9(26.47)	3(8.82)		<0.01
Partial recovery	10(30.3)	4(57.14)	11(32.35)	6(9.30)	5(14.7)		0.58

Abbreviations: COPD-Chronic obstructive pulmonary disease; ACEi-Angiotensin-converting enzyme inhibitors; ARB-Angiotensin II receptor blocker; NSAID-Non-steroidal anti-inflammatory drugs

Table 4. Association of kidney disease with in-hospital mortality in COVID-19 patients

Variables	95% CI	*p* value	HR
eGFR <60 mL/min/1.73m^2	1.31–1.91	0.01	1.58
Acute kidney injury	1.12–2.55	0.04	1.58
Stage 1	0.60-3.28	0.43	1.4
Stage 2	0.79-1.91	0.37	1.22
Stage 3	1.2–2.96	0.01	2.04

Abbreviations: eGF-estimated glomerular filtration rate; CI-onfidence interval, HR-hazard ration

Unfortunately, 30.43% of the patients who were treated with RRT (7 out of 23 patients) died during the hospitalization. Of those with stage 3 AKI who were not dialyzed, 36.4% (4 out of 11) died. Kidney function recovered sufficiently in 9 patients treated with RRT and no longer required dialysis upon discharge.

In the multivariable model, adapted to age, gender, and comorbidities, eGFR <60 ml/min, and AKI (stage 3) are associated with a higher risk of hospital mortality during the follow-up period (Table 4.)

Discussion

Acute kidney injury is common in critically ill patients with COVID-19, affecting approximately 20-40% of patients admitted to hospital and is considered as a marker of disease severity and an adverse prognostic factor for survival. AKI appears to result from the interaction of multiple variables via various basic pathophysiological mechanisms [5].

In this observational, retrospective study of COVID-19 patients, we found significant rates of patients who developed in-hospital AKI. Current evidence suggests that in COVID-19 patients, there is a higher prevalence of AKI in patients with more severe forms of COVID-19. AKI develops early during hospitalization and results from an interplay of virus-mediated injury and a dysregulated inflammatory response [6]. The need for dialysis is considered to be a negative survival prognostic factor. Knowledge of AKI can lead to better optimization and prognostication of patients with COVID-19.

Compared to studies of AKI in COVID-19 patients from other countries, we found our incidence to be is similar to that in an Italian study (27.8%) [7]. As compared with the above-cited study, the incidence of stage 3 AKI was highest in our cohort. It is not possible to determine with certainty the causes of this variation. However, we did remark a higher prevalence of comorbid conditions in our group.

We found that among the 269 patients included in this study, the incidence of AKI was substantially higher than the overall incidence of 0.5%-7% reported in previous studies [1] and was comparable to that in critically ill patients hospitalized with other illnesses [8]. The high incidence of AKI observed in this study was presumably attributed to several reasons. First, most of the COVID-19 patients included in this study had severe disease. Although many patients had low pulse oxygen saturation at admission, they appeared to have mild symptoms of dyspnea, possibly as a result of gradual deterioration of the condition to allow for adaption and compensation. The rapid deterioration after admission in many patients also suggests the severe condition of these patients. Second, the methods that we used to diagnose and stage AKI might cause overestimation of the incidence and severity. In the early stage of the COVID-19 outbreak, the medical resources were overwhelmed and many patients did not have a baseline serum creatinine test before admission or in the previous year so that we could only estimate the baseline serum creatinine according to the patients' sex, weight, medical history, and other related parameters. The incidence of AKI was determined based on baseline values and serum creatinine levels within seven days of admission. In order to reduce the bias of the estimation, we used the eGFR method for AKI diagnosis in these patients [9], by which the incidence of AKI was 28.6%, respectively. The estimated baseline serum creatinine levels by the eGFR method differed significantly from the test results of some of the patients whose baseline serum creatinine results were available. The inaccuracies in the estimated baseline serum creatinine level might have caused an overestimation of AKI incidence in our study.

However, even the overestimated incidence of AKI does not directly affect our investigation of the risk factors of AKI. We found that older age, multiple preexisting comorbidities, increased white blood cell count, and low lymphocyte count were all risk factors for AKI in patients with COVID-19. Markers of acute inflammation (ferritin and CRP), muscle injury (creatinine kinase), increased levels of PCT, and D-dimer levels were significantly higher in patients with a low eGFR at presentation and in those with AKI, suggesting causality by a dysregulated immune/inflammatory response, the so-called "cytokine" storm.

The prevalence of several preexisting comorbidities, including chronic lung diseases and dyslipidemia, did not differ significantly due to the relatively small number of cases of AKI in this study. Lymphopenia indicates that decreased immunity might occur in patients with COVID-19, and increased levels of PCT and CRP suggest that some patients may have secondary bacterial infections that caused excessive inflammatory responses. Previous studies [1,9] have shown that patients with COVID-19 have significantly increased D-dimer levels, multiple organ damage, and electrolyte disturbances. Our study showed that these abnormalities were more pronounced in patients with AKI. The occurrence and development of AKI often lead to the imbalance of blood volume and electrolytes, accumulation of metabolites, and aggravation of multiple organ dysfunction, thus creating a vicious cycle. The majority of patients with stage 1 AKI recovered and were discharged, but those who progressed into stage 2/3 AKI had a high mortality rate, possibly due to the untimely treatment. Early intervention of AKI is crucial in these patients, and continuous renal replacement should prevent AKI progression.

In our cohort, 23 of the 78 patients with AKI required RRT. Among those who received RRT, 7(20.58%) died versus 4(11.76%) in the stage 3 AKI group who did not undergo RRT ($p<0.001$). Thus, there was no significant improvement in survival, and the average mortality remained relatively high in both the RRT and non-RRT groups. These findings should prompt the early involvement of a palliative care team to define goals of care in patients with COVID-19 disease and stage 3 AKI. In our experience, ultrafiltration was not well tolerated. It often increased pressor requirements and did little to improve the ventilatory status. We observed a high incidence of hypercoagulability and frequent clotting of the dialysis filters, lines, and catheters. Thus, the patients required higher than the usual doses of heparin.

This study has several limitations. First, a small number of patients had a documented history of CKD, and we did not exclude them from this study. Data were collected retrospectively from medical records and often did not have information regarding prior renal function. Patients also may have had elevated creatinine on admission secondary to AKI suffered before hospitallization. If so, we may have underestimated the true overall incidence of COVID-19-associated AKI. It is not possible to rectify this problem, given the data at our disposal. This limits our study's general applicability but provides a unique insight into this population and broadens our understanding of COVID-19 disease. Data were missing on many patients at different stages of the hospitalization since they were collected retrospectively. Second, we did not explore the impact of treatment on AKI because our treatments were based on WHO's and (ADQI) standardized protocols [10,11], in which the antiviral drugs, antibacterial drugs, and hormones have little effect on renal function. Third, the urgency in data collection and the short follow-up

time of the patients (the shortest hospital stay of the patients was only 14 days) may affect the final prognostic evaluation of the patients to cause bias in survival time analysis. We especially emphasize that little data were available regarding urine output, a defining characteristic of AKI.

Nevertheless, even with the above limitations of our study, the high incidence of AKI and its negative impact upon survival is abundantly clear.

Conclusion

The kidney is a primary target organ of SARS-CoV-2 and the incidence of AKI is high in hospitalized patients with COVID-19. Deterioration of kidney function aggravates other organ damage. Preexisting cardiovascular and renal diseases are potential risk factors for AKI in patients with COVID-19.

Although the incidence of stage 1 AKI is high in critically ill patients, most of the patients can have favorable outcomes. However, progression into stage 2/3 AKI is associated with a very high mortality rate, and the prevention of AKI and monitoring of kidney function is thus vital in the clinical management of COVID-19. Our patients experienced a high incidence of AKI and high mortality, especially in AKI stage 3. Unfortunately, RRT provided little survival benefit. Larger, multicentered studies are needed to better understand AKI for its management in COVID-19 patients.

Conflict of interest statement: None declared

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