The Risk Factors and Clinical Outcomes Associated with Acute Kidney Injury in Patients with COVID-19: Data from a Large Cohort in Iran

Hormat Rahimzadeh^a Sina Kazemian^b Maryam Rahbar^a
Hossein Farrokhpour^b Mahnaz Montazeri^c Samira Kafan^d
Ahmad Salimzadeh^e Mohammad Talebpour^f Fazeleh Majidi^g
Atefeh Jannatalipour^g Effat Razeghi^{a, h}

^aDepartment of Nephrology Diseases, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran;

^bStudents' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, Iran; ^cDepartment of Infectious Diseases, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; ^dDepartment of Pulmonary Diseases, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; ^eRheumatology Research Center, Sina Hospital, Tehran University of Medical Science, Tehran, Iran; ^fDepartment of Surgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; ^gResearch Development Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; ^hNephrology Research Center, Center of Excellence in Nephrology, Tehran University of Medical Sciences, Tehran, Iran

Keywords

Acute kidney injury · COVID-19 · Mortality · Risk factors · SARS-CoV-2

Abstract

Introduction: Kidney involvement, ranging from mild hematuria and proteinuria to acute kidney injury (AKI) in patients with coronavirus disease-2019 (COVID-19), is a recent finding with various incidence rates reported among hospitalized patients with COVID-19. Given the various AKI rates and their associated risk factors, lack of AKI recovery in the majority of patients hospitalized with COVID-19, and limited data regarding AKI in patients with COVID-19 in Iran, we aim to investigate the potential risk factors for AKI development and its incidence in patients hospitalized with COVID-19.

Methods: In this retrospective cohort study, we enrolled

adult patients referred to the Sina Hospital, Iran, from February 20 to May 14, 2020, with either a positive PCR test or a highly susceptible chest computed tomography features consistent with COVID-19 diagnosis. AKI was defined according to the kidney disease improving global outcomes criteria, and patients were stratified based on their AKI staging. We evaluated the risk indicators associated with AKI during hospitalization besides in-hospital outcomes and recovery rate at the time of discharge. **Results:** We evaluated 516 patients with a mean age of 57.6 ± 16.1 years and a male-to-female ratio of 1.69 who were admitted with the COVID-19 diagnosis. AKI development was observed among 194 (37.6%) patients, comprising 61.9% patients in stage 1, 18.0% in stage 2, and 20.1% in stage 3. Out of all patients, AKI occurred in 58 (11.2%) patients during the hospital course, and 136 (26.3%) patients arrived with AKI upon admission. AKI development was positively associated with all of the in-hos-

pital outcomes, including intensive care unit admissions, need for invasive ventilation, acute respiratory distress syndrome (ARDS), acute cardiac injury, acute liver injury, multi-organ damage, and mortality. Patients with stage 3 AKI showed a significantly higher mortality rate, ARDS, and need for invasive ventilation than other stages. After multivariable analysis, male sex (odds ratio [OR]: 11.27), chronic kidney disease (CKD) (OR: 6.89), history of hypertension (OR: 1.69), disease severity (OR: 2.27), and high urea levels (OR: 1.04) on admission were independent risk indicators of AKI development. Among 117 (28.1%) patients who experienced AKI and survived, only 33 (28.2%) patients made a recovery from the AKI, and 84 (71.8%) patients did not exhibit full recovery at the time of discharge. **Discussion/Conclusion:** We found that male sex, history of CKD, hypertension, disease severity, and high serum urea were independent risk factors associated with AKI in patients with COVID-19. Also, higher stages of AKI were associated with increased risk of mortality and in-hospital complications. Our results indicate a necessity for more precise care and monitoring for AKI during hospitalization in patients with COVID-19, and lack of AKI recovery at the time of discharge is a common complication in such patients.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

Coronavirus disease-2019 (COVID-19) was first identified as a series of pneumonia cases with unknown origin in China, Hubei Province, in December 2019 [1]. World Health Organization declared the novel disease as pandemic due to rapid spreading and high transmission rate on March 11, 2020. The disease is caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with clinical features ranging from mild self-limiting respiratory tract infection or mild respiratory symptoms to severe acute respiratory distress syndrome (ARDS) and multi-organ failure and finally death [1]. Kidney involvement, including acute kidney injury (AKI), proteinuria, and hematuria, has been a recent finding among patients hospitalized with COVID-19 [2–4]. AKI is one of the most severe types of kidney involvement reported at various rates from 0.5% to as high as 50% in multiple studies in different countries [1, 3–17], and is considered a prognostic factor impacting both severity and mortality [1, 15, 16]. Many pathophysiological pathways have been suggested for kidney abnormality in COVID-19 patients, including direct invasion and cytotoxic effect of the virus on kidneys leading to acute tubular necrosis supported by evi-

dence of SARS-CoV-2 in kidney biopsy and urinary detection. Other mechanisms that accounted for kidney injury are prothrombotic state, hemodynamic instability, and cytokine storm [18–22]. Differences in study populations and comorbidities of patients, besides different admission guidelines and criteria used for AKI definition, can partially explain the various AKI rates reported [11]. Accordingly, in this retrospective cohort study conducted at Sina Hospital, Iran, we aim to investigate the potential risk factors for AKI development and its incidence in patients hospitalized with COVID-19 to develop more appropriate preventive measures.

Material and Methods

Statement of Ethics

Our study's protocol is in line with the 2013 Helsinki declaration and approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.005). All participants or their legal guardians gave written informed consent before inclusion in the study.

Study Design

In this cohort study, we retrospectively enrolled 611 patients ≥18 years old who were admitted to Sina Hospital, a tertiary educational center designated for patients with COVID-19 by the government, affiliated with Tehran University of Medical Sciences from February 20 to May 14, 2020. Patients with a history of hemodialysis or end-stage renal disease prior to the hospitalization were excluded. We used electronic medical records from each individual to obtain personal data, including demographic characteristics, past medical history, admission vital signs, laboratory parameters, and in-hospital outcomes and complications. The treatment used for patients mainly included antiviral agents (oseltamivir, lopinavir + ritonavir, interferon beta 1a, favipiravir, and umifenovir) and corticosteroids (dexamethasone, methylprednisolone, prednisolone, and hydrocortisone), according to the attending physician's discretion, based on national guideline published for standard care in patients with COVID-19 [23]. Besides, anticoagulant (enoxaparin sodium, heparin) was also used in patients determined to be at high risk for thromboembolic events [23]. The further details of patient care for individuals presenting with respiratory symptoms to Sina Hospital emergency department have been published previously [24].

Since there were no prior records of baseline serum creatinine (SCr) available in most patients, baseline SCr for each individual was imputed based upon a modification of diet in renal disease (MDRD) estimated glomerular filtration fraction of 75 mL/min/1.73 m² as per the kidney disease: Improving global outcomes (KDIGO) AKI guidelines [25]. The formula used to determine baseline serum creatinine was adopted with regard to Závada et al. [26], with the formula displayed in online suppl. Table 1 (see www.karger.com/doi/10.1159/000517581 for all online suppl. material).

COVID-19 diagnosis was defined as any of the following: (1) Positive real-time reverse-transcriptase polymerase chain reaction (PCR) test of oropharyngeal, nasopharyngeal, or endotracheal

swab specimens or (2) patients with high susceptibility according to the World Health Organization's interim guidance and Iranian national committee of COVID-19, including patients with ground-glass opacity alone or ground-glass opacity accompanied with consolidation in chest computed tomography, not entirely explained by lobar collapse, volume overload, or nodules in company with the history compatible with COVID-19 [27–30]. We excluded 88 patients due to lack of key information regarding their medical records or lack of laboratory data. Also, 7 patients were excluded due to prior history of end-stage renal disease, and 516 patients entered the final analysis.

Definitions

AKI was defined according to the KDIGO criteria as any of the following: (1) Increase in serum creatinine (SCr) to ≥ 1.5 times to 1.9 times of baseline occurred within the previous 7 days or an increase in SCr by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 h as stage 1, 2–2.9 times increase in serum creatinine within 7 days as stage 2, and 3 times or more increase in serum creatinine within 7 days as stage 3 (criteria for urine volume <0.5 mL/kg/h for 6 h was excluded since there were no records of patients' urine volume in electronic health data) [25]. AKI recovery was determined as <0.3 mg/dL (<26.5 $\mu\text{mol/L}$) difference from the baseline serum creatinine and with less than 50% increase from the baseline creatinine at the time of discharge [6, 31].

Cardiac disease was described as a history of coronary artery disease ($\geq 50\%$ stenosis in coronary arteries) or heart failure, or previous treatment for conditions named. History of stroke or transient ischemic attack was defined as cerebrovascular disease. Patients with a history of interstitial lung disease, asthma, or chronic obstructive pulmonary disease were identified as chronic lung disease. Chronic kidney disease (CKD) was defined as a glomerular filtration rate below 60 mL/min or need for renal replacement therapy. Patients with a history of neoplasm are considered positive for malignancy. ARDS was defined according to the Berlin definition criteria [32]. Acute cardiac injury (ACI) was identified if the serum level of high-sensitive cardiac troponin I was above the 99th percentile upper reference limit (11 pg/mL for women and 26 pg/mL for men) [33]. An increase in serum levels of alanine aminotransferase or aspartate aminotransferase more than 3 units above upper limit normal or alkaline phosphatase or total bilirubin more than 2 times of upper limit normal was diagnosed as acute liver injury (ALI) [34]. The neutrophil-to-lymphocyte ratio (NLR) was computed by dividing the absolute neutrophil count by the lymphocyte count. The platelet-to-lymphocyte ratio was calculated by dividing the absolute platelet count by the lymphocyte count. The systemic immune-inflammation index was measured by (neutrophil count $\times$ platelets)/(lymphocyte count). Patients with any of the following conditions were considered to have a severe disease: Oxygen saturation $\leq 93\%$, or $>50\%$ of lung involvement in chest computed tomography scan, dyspnea, septic shock, respiratory failure, or multiple organ dysfunction/failure. The remaining patients were categorized as nonsevere COVID-19. These criteria were defined in line with Wu and colleague's study and were modified to compare patients with severe COVID-19 to nonsevere patients in our study [35]. Multiple organ damage was determined as patients with at least 2 complications, including ARDS, ACI, AKI, or ALI. Positive drug history was considered as taking medication for at least 1 month before admission.

Statistical Analysis

Categorical variables were expressed as numbers and percentages (%) and analyzed using Fisher's exact test and χ^2 test. Distribution in continuous variables was checked based on the Kolmogorov-Smirnov and Shapiro-Wilk normality tests, P-P plot, and histogram to test the population study's normality. Continuous variables with normal distribution were presented as mean $\pm$ standard deviation and analyzed using independent samples *t* test. On the other hand, variables without normal distribution were reported as median (interquartile range) and were analyzed using the Mann-Whitney U test. Binary logistic regression analysis was used to evaluate the independent indicators associated with AKI incidence during hospitalization. Variables with $p < 0.05$ in univariate regression were enrolled in multivariate regression analysis as possible risk indicators (including age, male sex, disease severity, history of hypertension, diabetes mellitus [DM], cardiac disease, CKD, taking angiotensin-converting enzyme inhibitor [ACEI] or angiotensin II receptor blocker [ARB] medications, NLR, urea, and C-reactive protein [CRP] levels on admission). For statistical analysis, we used the SPSS 22 software for Windows (Chicago, IL, USA).

Results

Baseline Characteristics of Patients

A total of 611 patients were admitted to the Sina Hospital from February 20 to May 14, 2020, with the impression of COVID-19, which were confirmed later based on positive PCR swab test or clinical criteria defined. After excluding 95 patients, 516 patients entered the final analysis. The mean age was 57.6 ± 16.1 years, 62.8% were male, 360 (69.8%) patients incurred severe COVID-19, and 79 (15.3%) patients were admitted to the ICU at some point during their hospitalization. The mortality rate for the whole cohort was 19.4% (100 out of 516).

During this study, 194 (37.6%) patients developed AKI either on admission or during the hospital course. AKI occurred in 58 (11.2%) patients during the hospital course. In addition, there were 136 (26.3%) patients with AKI diagnosis upon admission, of whom 47 (34%) patients also had increased creatinine values during hospitalization. AKI staging was determined following KDIGO criteria, and 120 (61.9%) patients were categorized in stage 1, 35 (18.0%) patients in stage 2, and 39 (20.1%) patients in stage 3.

Although all of the included patients were highly suspicious for COVID-19 based on the national and international guidelines [36, 37], 289 (56.0%) patients underwent swab PCR test, of whom 131 (45.3%) were positive for COVID-19. Out of all patients with AKI ($N = 194$), a swab PCR test was done in 122 (62.9%) patients, with 56 (45.9%) specimens reported positive. The AKI inci-

Table 1. Baseline characteristics and in-hospital outcomes of COVID-19 patients with and without AKI

Characteristic [†]	Total (N = 516)	AKI (N = 194)	Non-AKI (N = 322)	p*
Demographics				
Age, year	57.6±16.1	60.6±17.5	55.8±14.9	0.002
Sex				
Female	192 (37.2)	29 (14.9)	163 (50.6)	<0.001
Male	324 (62.8)	165 (85.1)	159 (49.4)	
BMI, kg/m ²	27.5±4.6	27.1±4.2	27.7±4.9	0.346
Comorbidities				
Hypertension	213 (41.3)	104 (53.6)	109 (33.9)	<0.001
DM	166 (32.2)	82 (42.3)	84 (26.1)	<0.001
Cardiac disease	114 (22.1)	57 (29.4)	57 (17.7)	0.002
Cerebrovascular disease	18 (3.5)	12 (6.2)	6 (1.9)	0.013
Chronic lung disease	38 (7.4)	16 (8.2)	22 (6.8)	0.603
Malignancy	18 (3.5)	11 (5.7)	7 (2.2)	0.047
CKD	20 (3.9)	17 (8.8)	3 (0.9)	<0.001
Kidney transplant history	5 (1.0)	5 (2.6)	0 (0.0)	0.007
Drug history				
ACEI or ARB	101 (19.6)	55 (28.4)	46 (14.3)	<0.001
Vital signs on admission				
Heart rate	88.2±16.5	88.9±18.9	87.1±14.6	0.099
SBP, mm Hg	123.7±20.0	122.9±19.6	124.2±20.4	0.545
DBP, mm Hg	75.6±11.6	75.1±10.8	76.0±12.1	0.435
Respiratory rate	20.7±8.8	22.6±12.5	19.5±5.2	0.010
Temperature, °C	37.2±0.9	37.2±0.9	37.2±0.9	0.897
Oxygen saturation,	90.4±7.6	89.4±8.6	91.0±6.9	0.028
Laboratory data on admission				
WBC, ×10 ⁹ /L	6.5 (5.1–9.3)	6.7 (5.3–10.4)	6.2 (5.0–8.6)	0.009
Neutrophil, ×10 ⁹ /L	4.6 (3.4–7.2)	5.1 (3.8–8.2)	4.5 (3.3–6.6)	0.001
Lymphocyte, ×10 ⁹ /L	1.2 (0.9–1.7)	1.1 (0.8–1.5)	1.3 (0.9–1.8)	<0.001
Platelets, ×10 ⁹ /L	189.0 (149.2–251.7)	178.0 (144.0–231.2)	196.5 (151.0–260.2)	0.010
Neutrophil-to-lymphocyte ratio	3.8 (2.5–6.3)	4.8 (2.9–9.0)	3.5 (2.2–5.2)	<0.001
Platelet-to-lymphocyte ratio	156.2 (115.0–213.0)	157.8 (115.2–238.6)	153.4 (114.3–204.2)	0.115
SII	752.8 (444.4–1,320.3)	880.0 (492.6–1,734.2)	734.9 (392.1–1,148.7)	0.001
RBC, ×10 ¹² /L	4.7 (4.2–5.1)	4.8 (4.0–5.2)	4.6 (4.3–5.0)	0.312
Hemoglobin, g/dL	13.7 (12.4–15.1)	13.9 (12.3–15.3)	13.6 (12.4–15.0)	0.351
Urea, mg/dL	30.5 (22.2–46.0)	44.0 (30.0–74.2)	26.0 (20.0–35.0)	<0.001
BUN/creatinine ratio	15.1 (11.2–25.8)	17.6 (12.0–43.1)	13.5 (9.8–21.9)	<0.001
Creatinine, mg/dL	1.05 (0.89–1.27)	1.34 (1.17–1.77)	0.94 (0.84–1.08)	<0.001
GFR, mL/min	66.65 (53.41–79.48)	53.48 (35.70–68.25)	72.18 (62.63–83.79)	<0.001
Baseline serum creatinine**	0.95 (0.89–1.21)	0.93 (0.88–0.98)	1.03 (0.90–1.24)	<0.001
Discharge creatinine	1.07 (0.90–1.35)	1.40 (1.16–2.11)	0.95 (0.85–1.08)	<0.001
Sodium, mmol/L	135.7 (132.4–138.8)	135.3 (132.1–139.0)	135.8 (132.7–138.7)	0.633
Potassium, mmol/L	4.2 (3.9–4.6)	4.3 (4.0–4.7)	4.1 (3.8–4.5)	<0.001
Calcium, mmol/L	8.6 (8.2–9.0)	8.6 (8.0–9.0)	8.7 (8.3–9.1)	0.017
Phosphorus, mmol/L	3.3 (2.9–3.9)	3.4 (2.9–4.1)	3.3 (2.9–3.8)	0.153
Magnesium, mmol/L	2.2 (2.0–2.5)	2.2 (2.0–2.5)	2.2 (2.0–2.5)	0.657
CRP, mg/L	57.1 (21.2–104.0)	69.4 (37.5–125.3)	47.4 (16.7–85.3)	<0.001
ESR, mm/h	44.0 (25.5–74.0)	46.0 (26.0–75.0)	41.0 (24.2–71.0)	0.400
LDH, U/L	532.0 (431.5–698.5)	572.0 (467.5–772.0)	523.5 (415.7–668.7)	0.005
hs-cTnI, pg/mL	6.0 (1.5–18.7)	10.3 (3.1–40.0)	4.3 (1.5–9.9)	<0.001
AST, U/L	50.0 (38.0–68.2)	60.0 (41.0–79.0)	46.0 (37.0–59.0)	<0.001
ALT, U/L	36.0 (27.0–51.0)	40.0 (32.0–58.0)	34.0 (25.0–48.0)	<0.001
ALP, U/L	166.0 (128.0–214.0)	166.0 (127.0–213.5)	167.0 (129.0–214.0)	0.760
In-hospital outcomes				
Hospital length of stay, day	4.0 (2.0–7.0)	5.0 (3.0–9.0)	4.0 (2.0–6.0)	<0.001
ICU admission	79 (15.3)	55 (28.4)	24 (7.5)	<0.001
Severity	360 (69.8)	151 (77.8)	209 (64.9)	0.002
Mortality	100 (19.4)	77 (39.7)	23 (7.1)	<0.001
ARDS	161 (31.3)	78 (40.4)	83 (25.8)	0.001
Invasive ventilation	68 (13.2)	54 (27.8)	14 (4.3)	<0.001
ACI	111 (21.5)	61 (31.4)	50 (15.5)	<0.001
ALI	54 (10.5)	29 (14.9)	25 (7.8)	0.010
Multiorgan damage	139 (26.9)	109 (55.2)	30 (9.3)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ACI, acute cardiac injury; AKI, acute kidney injury; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine transaminase; ARB, angiotensin II, receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; hs-cTnI, high-sensitive cardiac troponin I; LDH, lactate dehydrogenase; RBC, red blood cell; SBP, systolic blood pressure; SII, systemic immune-inflammation index; WBC, white blood cell. [†] Data are presented as mean±standard deviation, number (%), or median (interquartile range). * Statistically significant p values are bolded. ** Based on MDRD calculation formula (eGFR = 75 mL/min/1.73 m²).

Table 2. In-hospital outcomes according to different stages of AKI by the KDIGO in patients with COVID-19

In-hospital outcome [†]	AKI (N = 194)	Stage 1 (N = 120)	Stage 2 (N = 35)	Stage 3 (N = 39)	p value*
Mortality	77 (39.7)	27 (22.5)**	18 (51.4)	32 (82.1)**	<0.001
Severity	151 (77.8)	87 (72.5)	29 (82.9)	35 (89.7)	0.058
ARDS	78 (40.4)	39 (32.8)**	15 (42.9)	24 (61.5)**	0.006
Invasive ventilation	54 (27.8)	20 (16.7)**	12 (34.3)	22 (56.4)**	<0.001
ACI	61 (31.4)	30 (25.0)	15 (42.9)	16 (41.0)	0.048
ALI	29 (14.9)	11 (9.2)**	9 (25.7)	9 (23.1)	0.015
Multiorgan damage	109 (56.2)	54 (45.0)**	26 (74.3)	29 (74.4)	<0.001

ACI, acute cardiac injury; AKI, acute kidney injury; ALI, acute liver injury; ARDS, acute respiratory distress syndrome. [†] Data are presented as number (%). * Statistically significant *p* values are bolded. ** Statistically significant Bonferroni-adjusted *p* values (*p* < 0.0083).

dence rate in patients with a positive PCR test was 42.7% (56 out of 131 patients), similar to the whole cohort results.

Baseline characteristics of patients are presented in Table 1. Patients who developed AKI were more likely to be older, male, and with more underlying diseases except for chronic lung disease compared to patients without AKI. About 59.9% of patients were reported to have at least 1 comorbidity, and the most prevalent comorbidities were hypertension (41.3%), DM (32.2%), and cardiac disease (22.1%). Out of 194 patients with AKI, 151 (77.8%) patients had a severe form of COVID-19, and 54 (27.8%) patients needed invasive ventilation. The ICU admission and mortality rate were significantly higher in the AKI group than the non-AKI group (28.4% vs. 7.5%, *p* value <0.001, 39.7% vs. 7.1%, *p* value <0.001, respectively). We also stratified patients based on their AKI staging into 3 groups and performed subgroup analysis (online suppl. Table 1). Patients who reached higher AKI stages were more likely to be older and have DM, CKD, and malignancy as their past medical history and take ACEI or ARB medications before admission.

There was no significant difference in vital signs on admission between the 2 groups except for lower oxygen saturation and higher respiratory rate on admission in patients with AKI. In terms of laboratory data, white blood cells, neutrophil count, NLR, systemic immune-inflammation index, urea, potassium, calcium, CRP, LDH, high-sensitive cardiac troponin I, aspartate aminotransferase, and alanine aminotransferase were significantly higher in patients with the development of AKI.

During this study, 161 patients underwent urine analysis test comprising 84 (52.1%) patients with no proteinuria, and trace or mild (1+), moderate (2+), and severe (3+ and 4+) reported in 38 (23.6%), 20 (12.4%), and 19

(11.8%) patients, respectively. There was a significant difference in proteinuria incidence in patients who developed AKI compared to non-AKI patients (63.9% vs. 29.3%, *p* value: <0.001). Among patients with AKI, 86 (44.3%) patients had records of urine analysis tests available, with 29 (33.7%) of them reported as mild proteinuria, 13 (15.1%) with moderate, and 13 (15.1%) with severe proteinuria and 31 (36.1%) patients with no proteinuria exhibited in urine analysis.

Based on the final status of discharge or mortality, among 117 (28.1%) patients who experienced AKI and survived, 33 (28.2%) patients made a recovery from the AKI, and 84 (71.8%) patients did not fully recover at the time of discharge. Deceased patients exhibited similar recovery rates (15/77 [19.5%] patients were recovered from AKI), indicating no difference in recovery rate between the discharged and deceased groups (28.2% vs. 19.5%, respectively, *p* value = 0.168).

AKI Staging and In-Hospital Outcomes

AKI development was positively associated with all of the in-hospital outcomes, including ICU admissions, need for invasive ventilation, ARDS, ACI, ALI, multiorgan damage, and mortality. Moreover, we evaluated the in-hospital outcomes according to the patients' AKI staging (Table 2). All in-hospital outcomes increased in higher stages of AKI, with a statistically significant difference among the 3 stages except for disease severity (*p* value: 0.058). Patients with stage 1 AKI had a significantly lower mortality rate (22.5%), ARDS, need for invasive ventilation, ALI, and multiorgan damage compared to other groups. On the other hand, patients with stage 3 AKI had a significantly higher mortality rate (71.1%), ARDS (61.5%), and a need for invasive ventilation (56.4%) (Table 2).

Table 3. Logistic regression analysis for risk indicators of AKI development during hospitalization in patients with COVID-19

	Model 1 [†]			Model 2 [‡]		
	odds ratio	95% CI	<i>p</i> value*	odds ratio	95% CI	<i>p</i> value*
Age	1.02	1.01–1.03	0.001			
Male sex	5.83	3.71–9.16	<0.001	11.27	5.97–21.26	<0.001
Severity	1.90	1.26–2.86	0.002	2.27	1.35–3.83	0.002
Hypertension	2.26	1.57–3.25	<0.001	1.69	1.03–2.79	0.039
DM	2.07	1.42–3.03	<0.001			
Cardiac disease	2.04	1.27–3.27	0.003			
CKD	10.21	2.95–35.33	<0.001	6.89	1.57–30.18	0.010
ACEI/ARB	2.37	1.53–3.69	<0.001			
NLR	1.03	1.00–1.05	0.047			
Urea (mg/dL)	1.04	1.03–1.05	<0.001	1.04	1.03–1.05	<0.001
CRP (mg/L)	1.01	1.00–1.01	<0.001			

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II, receptor blocker; AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; DM, diabetes mellitus; NLR, neutrophil-to-lymphocyte ratio. * Statistically significant *p* values are bolded. [†] Univariate binary logistic regression. [‡] Multivariate binary logistic regression adjusted for age, sex, hypertension, DM, cardiac disease, CKD, history of ACEI/ARB, NLR, urea, and CRP.

Predictors of AKI Development

We used univariate logistic regression analysis to identify the potential risk indicators of AKI development during hospitalization, which revealed older age, male sex, disease severity, history of hypertension, DM, cardiac disease, CKD, history of treatment with ACEI/ARB medications, higher NLR, urea, and CRP as potential predictors of AKI (Table 3). However, after multivariate analysis, only male sex (odds ratio [OR]: 11.27, 95% confidence interval [CI]: 5.97–21.26, *p* value: <0.001), disease severity (OR: 2.27, 95% CI: 1.35–3.83, *p* value: 0.002), history of hypertension (OR: 1.69, 95% CI: 1.03–2.79, *p* value: 0.039), CKD (OR: 6.89, 95% CI: 1.57–30.18, *p* value: 0.010), and higher serum urea levels on admission (OR: 1.04, 95% CI: 1.03–1.05, *p* value <0.001) were independently associated with AKI development during hospitalization (Table 3). In the sensitivity analysis in patients with positive PCR test (*N* = 131), we found disease severity, male sex, DM, and urea levels on admission as independent risk indicators of AKI development during hospitalization (online suppl. Table 2).

Discussion

In this retrospective cohort study, 516 patients with COVID-19 were evaluated for AKI development. We detected an incidence rate of 37.6% for AKI among all pa-

tients and a similar rate of 42.7% in patients with a positive PCR test. In the multivariable model, male sex, disease severity, history of CKD, hypertension, and high serum urea levels on admission were identified as independent risk indicators of AKI development during hospitalization.

Renal involvement in SARS-CoV-2 and Middle Eastern respiratory syndrome coronavirus is a common complication with different presentations, including high rates of proteinuria and hematuria reported [2, 38]. In addition, patients with COVID-19 seem to have a significantly higher chance of developing AKI [6, 39]. Despite the limited number of urine analysis data available in this study, a substantial number of patients (48.8%) had proteinuria in urine analysis compatible with previous reports [2–4, 15, 40]. Besides, significantly higher proteinuria values were observed in patients who developed AKI than in patients who did not suffer from this complication (65.1% vs. 29.3%, *p* value: <0.001) [40, 41].

Many pathophysiologic pathways have been suggested for renal involvement in patients with COVID-19. It has been demonstrated that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2) receptor for cell entry [42–44]. ACE-2 receptors are mainly expressed in lung cells; however, they function in many other body organs, including the kidney and gastrointestinal tract, with a higher expression on the cell membranes [42, 45, 46]. The presence of SARS-CoV-2 RNA in glomerular cells shown by Puelles et al. [21] and SARS-CoV-2 detection in kid-

neys and urine of patients with COVID-19 demonstrated by Cheng et al. [47] could be supportive evidence for direct glomerular damage by the virus. Postmortem examinations of 6 patients with COVID-19 revealed severe acute tubular necrosis and lymphocyte infiltration accompanied by the detection of SARS-CoV-2 antigen in kidney tubules, suggesting not only direct cytotoxicity but also tubular injury mediated by complement deposition and macrophage activation [48]. In another study, Sue et al. [20] examined 26 postmortem patients with COVID-19 and observed endothelial damage by erythrocyte aggregation and diffused proximal tubule damage accompanied by loss of the brush border, corona virus-like particles in the tubular epithelium, and upregulation of ACE-2 in the kidney. Other potential factors contributing to the renal injury include the prothrombotic state induced by the virus, sepsis, systemic hemodynamic instability, hypoxemia, and possible drug interactions [4, 49, 50].

Here, we report a 37.6% AKI occurrence, consistent with 3 studies conducted in the USA and Brazil with 36.6%, 43%, and 50% AKI occurrence rates [6, 11, 17]. Nevertheless, this rate is higher than the largest meta-analysis performed to date by Fu et al. [15], with the pooled incidence rate of 28.6% for AKI, reported in hospitalized COVID-19 patients from the USA and Europe. On the other hand, in previously reported studies in China, there was a significantly lower incidence rate of AKI varying from 0.5% to 29.% [1, 4, 5, 7, 8, 10], and Fu et al. [15] reported an overall incidence rate of 5.5% for studies conducted in China. The difference between different ranges of AKI incidence may be explained by different population studies and underlying diseases of patients with COVID-19 in these studies. Our population's baseline features in this study were more similar to previous reports from Europe, the USA, and Brazil. Another explanation for varying ranges of AKI incidence could be different definitions of AKI used in different studies. In studies carried out in China, baseline SCr is mostly determined based on patients' first creatinine record after admission. However, in reports with higher rates of AKI, the baseline SCr is calculated according to previous creatinine records of patients before hospitalization available or imputation based on a glomerular filtration rate 75 mL/min/1.73 m² [6, 11]. Besides the inclusion criteria for admission, patients' ethnicity in different countries could potentially affect patient's baseline characteristics [16].

In previous studies, older age, male sex, history of CKD, hypertension, DM, and prior cardiovascular disease have been suggested as risk factors for AKI [5, 15]. In this study, after multivariable regression analysis, we found that male

sex, disease severity, history of CKD, hypertension, and high serum urea levels on admission were associated with a higher risk for AKI development during the hospitalization (Table 3). In our subgroups analysis, we found that patients with higher AKI stages were more likely to be older, with a positive history of hypertension, DM, CKD, malignancy, and take ACEI or ARB medications before the hospitalization (online suppl. Table 1). There were also significantly higher in-hospital complications such as ARDS, ACL, ALI, multiorgan damage, and a higher mortality rate, which indicates the close relationship between higher stages of AKI and poor clinical outcome in line with previous data reported (Table 2) [11, 16]. Furthermore, patients with stage 3 AKI showed substantially higher mortality rates than patients with lower AKI stages, in line with the study conducted by Zamoner et al. [17] that reported stage 3 AKI as an independent risk factor for mortality in ICU patients hospitalized with the COVID-19 diagnosis.

Recent studies demonstrated that risk factors associated with disease severity and COVID-19 mortality were also associated with increased risk of AKI development in these patients [1, 11]. In a study by Russo et al. [51], CKD was reported as a substantial risk factor for AKI, which is in line with our findings in the current study (OR: 6.89). Moreover, in keeping with previous findings, hypertension was identified as a risk indicator of AKI after adjustment [15, 16]. However, DM, previous cardiovascular disease, obesity, and ACEI/ARB medications which were previously considered to increase the risk of AKI in patients with COVID-19 were not identified as independent risk indicators in this study [15, 17, 52].

In this study, a considerable number of patients (71.8%) did not exhibit full recovery at the time of discharge. Lack of AKI recovery in the COVID-19 setting has been pointed out before [2, 6]. A study by Pei et al. [2] showed that only 45.7% of patients with COVID-19 made a complete recovery from AKI at the time of discharge. The discrepancy seen among recovery rates may be due to different hospital lengths of stay and follow-up in studies. This rate is significant and highly alerting that warrants further research to fully understand the processes of pathophysiology and appropriate interventions to prevent this complication in patients with COVID-19.

In conclusion, we demonstrated that male sex, disease severity, previous history of CKD, hypertension, and high serum urea level on admission are independent risk indicators of AKI development during hospitalization in COVID-19 patients. In addition, patients with higher stages of AKI are at higher risk of in-hospital mortality and complications. Hence, close monitoring for serum creatinine dur-

ing hospitalization and a long-term follow-up to further investigate CKD after COVID-19-associated AKI might be crucial in susceptible patients with COVID-19, and more supportive care must be considered in patients with AKI.

Limitations

Results reported in the present study should interpret in light of the following limitations. First, this is a retrospective cohort study, and specific inferences regarding the relationship between AKI and exposures cannot be made. Second, since our population study included patients hospitalized in a single tertiary center, the extracted data cannot represent all patients with COVID-19. Third, according to missing data on the patient's baseline creatinine, we used the estimated creatinine method, which is in line with several other studies done on this subject [6, 26, 53]. Fourth, it is a single-center study on the Iranian population, and future multicenter studies on different ethnicities are needed. Fifth, due to the high burden imposed by the disease, data regarding the patients who undergone dialysis, need for acute renal support, and further investigation of its risk factors could not be provided.

Acknowledgement

We acknowledge all the hardworking health-care workers involved in the diagnosis and treatment of patients in Sina Hospital, doing their best in the time of the pandemic. We are indebted to the Research Development Center of Sina Hospital for its help and support.

References

- 1 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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):1054–62.
- 2 Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol*. 2020;31(6):1157.
- 3 Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
- 4 Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829–38.
- 5 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–20.
- 6 Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Shan Z, et al. AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol*. 2020;32:15160.
- 7 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–9.
- 8 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
- 9 Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–13.
- 10 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, 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):475–81.
- 11 Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98:20918.
- 12 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA*. 2020;323(20):2052–9.
- 13 Taher A, Alalwan AA, Naser N, Alsegaï O, Alaradi A. Acute kidney injury in COVID-19 pneumonia: a single-center experience in Bahrain. *Cureus*. 2020;12(8):e9693.

Statement of Ethics

This study's protocol was in line with the 2013 Helsinki declaration and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.005). All participants or their legal guardians gave written informed consent before inclusion in the study.

Conflict of Interest Statement

The authors of this study declare that they have no conflict of interest.

Funding Sources

This study has been supported by the Tehran University of Medical Sciences (grant number: 99-1-101-47193). The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision of submission.

Author Contributions

E.R., H.R., and H.F. contributed to the conception or design of the work. S.K., H.F., H.R., F.M., and M.R. contributed to the acquisition, analysis, or interpretation of data for the work. H.F., S.K., and F.M. drafted the manuscript. E.R., H.R., M.M., and S.K. (2), A.S., M.T., and A.J. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

- 14 Husain SA. Early description of coronavirus 2019 disease in kidney transplant recipients in New York. *J Am Soc Nephrol*. 2020;31(6):1150–6.
- 15 Fu EL, Janse RJ, de Jong Y, van der Endt VHW, Milders J, van der Willik EM, et al. Acute kidney injury and kidney replacement therapy in COVID-19: a systematic review and meta-analysis. *Clin Kidney J*. 2020;13(4):550–63.
- 16 Zahid U, Ramachandran P, Spitalewitz S, Alasadi L, Chakraborti A, Azhar M, et al. Acute kidney injury in COVID-19 patients: an inner city hospital experience and policy implications. *Am J Nephrol*. 2020;51(10):786–96.
- 17 Zamoner W, Santos C, Magalhães LE, de Oliveira PGS, Balbi AL, et al. Acute kidney injury in COVID-19: 90 days of the pandemic in a Brazilian public hospital. *Front Med*. 2021;8:622577.
- 18 Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med*. 2020;8:73842.
- 19 Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417–8.
- 20 Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219–27.
- 21 Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med*. 2020;383(6):590–2.
- 22 Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. *J Am Soc Nephrol*. 2020;31(8):1683–7.
- 23 COVID-19 NCMo. National COVID-19 treatment flowcharts, sixth version 2020. Available from: corona.behdasht.gov.ir/files/site1/files/Covid-19_Treatment_Flowcharts_V6.pdf.
- 24 Mohammad T, Azar H, Alireza O, Haleh A. Rationale and design of a registry in a referral and educational medical center in Tehran, Iran: Sina Hospital COVID-19 registry (SHCo-19R). *Advan J Emerg Med*. 2020;4(2s).
- 25 Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17(1):204.
- 26 Závada J, Hoste E, Cartin-Ceba R, Calzavacca P, Gajic O, Clermont G, et al. A comparison of three methods to estimate baseline creatinine for RIFLE classification. *Nephrol Dial Transpl*. 2010;25(12):3911–8.
- 27 World Health Organization. *Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance*; 2020 March 2. Geneva, Switzerland: World Health Organization. Contract No: WHO/COVID-19/laboratory/2020.4.
- 28 Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*. 2020;295(1):210–7.
- 29 Salehi S, Abedi A, Balakrishnan S, Gholamreza-zadeh A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. *AJR Am J Roentgenol*. 2020;215(1):87–93.
- 30 Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. *Radiology*. 2020;295(3):200463.
- 31 Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol*. 2020;31(6):1157–65.
- 32 Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–33.
- 33 Adams JE3rd, Bodor GS, Dávila-Román VG, Delmez JA, Apple FS, Ladenson JH, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation*. 1993;88(1):101–6.
- 34 Dufour DR, Lott JA, Nolte FS, Gretch DR, Koff RS, Seeff LB. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clin Chem*. 2000;46(12):2027–49.
- 35 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020;323(13):1239–42.
- 36 World Health Organization. Clinical management of COVID-19. 2020 [updated may 27 2020. Available from: <https://www.who.int/publications/i/item/clinical-management-of-covid-19>.
- 37 COVID-19 Epidemiology Committee. COVID-19 epidemiology. [updated 23 september 2020. Available from: <https://behdasht.gov.ir/>.
- 38 Cha RH, Joh JS, Jeong I, Lee JY, Shin HS, et al. Renal complications and their prognosis in Korean patients with middle east respiratory syndrome-coronavirus from the central MERS-CoV designated hospital. *J Korean Med Sci*. 2015;30(12):1807–14.
- 39 Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int*. 2005;67(2):698–705.
- 40 Chaudhri I, Moffitt R, Taub E, Annadi RR, Hoai M, Bolotova O, et al. Association of proteinuria and hematuria with acute kidney injury and mortality in hospitalized patients with COVID-19. *Kidney Blood Press Res*. 2020;45(6):1–15.
- 41 Zhou H, Zhang Z, Fan H, Li J, Li M, Dong Y, et al. Urinalysis, but not blood biochemistry, detects the early renal impairment in patients with COVID-19. *medRxiv*. 2020. 2020.04.03.20051722.
- 42 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271–e8.
- 43 Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*. 2020;581(7807):215–20.
- 44 Verdecchia P, Cavallini C, Spanevello A, Anelli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med*. 2020;76:14–20.
- 45 Albini A, Noonan DM, Pelosi G, Di Guardo G, Lombardo M. The SARS-CoV-2 receptor, ACE-2, is expressed on many different cell types: implications for ACE-inhibitor- and angiotensin II receptor blocker-based antihypertensive therapies-reply. *Intern Emerg Med*. 2020;15(8):1583–4.
- 46 Du M, Cai G, Chen F, Christiani DC, Zhang Z, Wang M. Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. *Gastroenterology*. 2020;158(8):2298–301.e7.
- 47 Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97(5):829–38.
- 48 Diao B, Wang C, Wang R, Feng Z, Zang J, Yang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv*. 2020.
- 49 Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The novel coronavirus 2019 epidemic and kidneys. *Kidney Int*. 2020;97(5):824–8.
- 50 Coccheri S. COVID-19: the crucial role of blood coagulation and fibrinolysis. *Intern Emerg Med*. 2020;15(8):1369–73.
- 51 Russo E, Esposito P, Taramasso L, Magnasco L, Saio M, et al. Kidney disease and all-cause mortality in patients with COVID-19 hospitalized in Genoa, Northern Italy. *J Nephrol*. 2020;34:17383.
- 52 Soleimani A, Kazemian S, Karbalai Saleh S, Aminorroaya A, Shajari Z, et al. Effects of angiotensin receptor blockers (ARBs) on in-hospital outcomes of patients with hypertension and confirmed or clinically suspected COVID-19. *Am J Hypertens*. 2020;33:110211.
- 53 Bagshaw SM, Uchino S, Cruz D, Bellomo R, Morimatsu H, Morgera S, et al. A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury. *Nephrol Dial Transpl*. 2009;24(9):2739–44.