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

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Keywords
Acute kidney injury \cdot COVID-19 \cdot Mortality \cdot Risk factors \cdot 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-
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 evidence 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

**Introduction**

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**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.

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Risk Factors and Clinical Outcomes Associated with AKI in COVID-19 Patients

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 μmol/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 μmol/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 (≥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 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 × platelets)/(lymphocyte count). Patients with any of the following conditions were considered to have a severe disease: Oxygen saturation ≤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 χ² 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 ± 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 multivariable 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 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 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 × platelets)/(lymphocyte count). Patients with any of the following conditions were considered to have a severe disease: Oxygen saturation ≤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.

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

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>Total (N = 516)</th>
<th>AKI (N = 194)</th>
<th>Non-AKI (N = 322)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>57.6±16.1</td>
<td>60.6±17.5</td>
<td>55.8±14.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>192 (37.2)</td>
<td>29 (14.9)</td>
<td>163 (50.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>324 (62.8)</td>
<td>165 (85.1)</td>
<td>159 (49.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5±4.6</td>
<td>27±4.2</td>
<td>27.7±4.9</td>
<td>0.346</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>213 (41.3)</td>
<td>104 (53.6)</td>
<td>109 (33.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>166 (32.2)</td>
<td>82 (42.3)</td>
<td>84 (26.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>114 (22.1)</td>
<td>57 (29.4)</td>
<td>57 (17.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>18 (3.5)</td>
<td>12 (6.2)</td>
<td>6 (1.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>38 (7.4)</td>
<td>16 (8.2)</td>
<td>22 (6.8)</td>
<td>0.476</td>
</tr>
<tr>
<td>Malignancy</td>
<td>18 (3.5)</td>
<td>11 (5.7)</td>
<td>7 (2.2)</td>
<td>0.047</td>
</tr>
<tr>
<td>CKD</td>
<td>20 (3.9)</td>
<td>17 (8.8)</td>
<td>3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney transplant history</td>
<td>5 (1.0)</td>
<td>5 (2.6)</td>
<td>0 (0.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

### Drug history

- ACEI or ARB
- DOI: 10.1159/000517581

### Vital signs on admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N = 516)</th>
<th>AKI (N = 194)</th>
<th>Non-AKI (N = 322)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td>37.2±0.6</td>
<td>37.2±0.6</td>
<td>37.2±0.6</td>
<td>0.897</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>20.7±5.8</td>
<td>22.6±12.5</td>
<td>19.5±5.2</td>
<td>0.010</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75.6±11.6</td>
<td>75.1±10.8</td>
<td>76.0±12.5</td>
<td>0.437</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132.7±20.0</td>
<td>122.9±19.6</td>
<td>124.2±20.4</td>
<td>0.545</td>
</tr>
</tbody>
</table>

### Laboratory data on admission

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N = 516)</th>
<th>AKI (N = 194)</th>
<th>Non-AKI (N = 322)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dL</td>
<td>89.4±7.6</td>
<td>89.4±6.6</td>
<td>91.0±6.9</td>
<td>0.028</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.7 (12.4–15.1)</td>
<td>13.9 (12.3–15.3)</td>
<td>13.6 (14.1–20.4)</td>
<td>0.115</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>36.0 (27.0–51.0)</td>
<td>40.0 (32.0–58.0)</td>
<td>34.0 (25.0–48.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-cTnI, pg/mL</td>
<td>6.0 (1.5–18.7)</td>
<td>10.3 (3.1–40.0)</td>
<td>4.3 (1.5–9.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>114 (21.5)</td>
<td>61 (31.4)</td>
<td>50 (15.5)</td>
<td>0.657</td>
</tr>
</tbody>
</table>

### In-hospital outcomes

- 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; C/CUN, 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 (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

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

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).

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

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).
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 patients 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 kidney...

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

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1†</th>
<th>Model 2‡</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01–1.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>5.83</td>
<td>3.71–9.16</td>
</tr>
<tr>
<td>Severity</td>
<td>1.90</td>
<td>1.26–2.86</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.26</td>
<td>1.57–3.25</td>
</tr>
<tr>
<td>DM</td>
<td>2.07</td>
<td>1.42–3.03</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>2.04</td>
<td>1.27–3.27</td>
</tr>
<tr>
<td>CKD</td>
<td>10.21</td>
<td>2.95–35.33</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>2.37</td>
<td>1.53–3.69</td>
</tr>
<tr>
<td>NLR</td>
<td>1.03</td>
<td>1.00–1.05</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>1.04</td>
<td>1.03–1.05</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
</tbody>
</table>

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.
Risk Factors and Clinical Outcomes Associated with AKI in COVID-19 Patients

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...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, ACI, 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**

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**References**


**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.

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**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.
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