Original Paper

Acute Kidney Injury Outcome in COVID-19 Patients

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Introduction. Despite the high incidence of AKI in patients with COVID-19, the characteristics and consequences of this condition have not been well studied.
Methods. This retrospective cohort study investigated the clinical characteristics, treatment methods, and outcome of COVID-19 patients aged 18 years and older who were hospitalized in Imam Hossein Hospital, Tehran, from February 20th, 2020 to June 20th, 2020.
Results. Out of the total 367 patients with COVID-19, 104 (28%) patients were diagnosed with AKI at the time of admission or during hospitalization, 86 (23%) and 18 (5%) patients were diagnosed with the AKI on admission (early AKI) and after the first 24 h (late AKI), respectively. Concerning the AKI stages, 20 (19%) and 18 (17%) patients were in stages 2 and 3, and the cause of AKI in 52 (50%) patients was renal. Moreover, out of all patients with AKI, 25 (24%) and 29 (28%) patients had transient (Kidney function improvement within 48 h) and persistent AKI (kidney function improvement between 48 h to 7 days). Furthermore, 32 (31%) patients developed acute kidney damage (AKD) (no improvement in AKI after 7 days). The survival rate of AKI patients was lower in higher stages of AKI, and in cases that the reason for kidney dysfunction was renal or unknown. However, there was no difference in the mortality rate between the early and late AKI.
Conclusion. Since about one-third of the patients with AKI eventually develop AKD, it is of great importance to closely monitor all COVID-19 patients, especially the high-risk ones, for the appropriate diagnosis and treatment of AKI.

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INTRODUCTION

In December 2019, a new coronavirus was detected in Wuhan, China, causing severe acute respiratory syndrome called COVID-19 in February 2020.[1] In March 2020, the World Health Organization introduced it as a global pandemic given, the unprecedented spread of the virus and its high rate of morbidity and mortality[2]. Although infection is mild in most cases, about 20% of the patients will require hospitalization or admission to the ICU wards for severe shortness of breathing and pneumonia.[3]

Severe cases of COVID-19 disease were initially identified as an acute respiratory distress syndrome characterized by interstitial and alveolar pneumonia. It was initially reported that COVID-19 disease did not cause acute kidney injury (AKI).[4-8] Later, it became clear that other organs, such as kidneys could also be involved. Subsequent studies, however, have shown that renal impairment is a common complication in patients with COVID-19.[9, 10] According to a review study by Kolhe *et al.*, the reported incidence of AKI was about 22-36% in the United States and 5.1-10.5% in China.[9, 11-14] In a review study by Fu *et al.*, the mean incidence of AKI was 28.6% in 20 studies conducted in the United States and Europe and 5.5% in 62 studies conducted in China.[15] Iran is one of the countries with a high prevalence of COVID-19 and a reported AKI incidence of 24% (CI:17-31%) in these patients. [16]

It is worth mentioning that, the mortality rate has been higher in COVID-19 patients with AKI, and AKI has been more prevalent among patients with severe cases of the disease[17]. Most studies have assessed the effect of AKI on the prognosis of COVID-19 disease. However, few studies have evaluated the characteristics and consequences of AKI in these patients. It has been reported that kidney function may not improve fully in most patients who recover from the disease.[18-21] This study was designed to investigate the characteristics and consequences of AKI in patients with COVID-19.

MATERIALS AND METHODS

This retrospective cohort study was conducted on patients aged over 18 with COVID-19, confirmed by polymerase chain reaction (PCR) test, in Imam Hossein Hospital, Tehran, from February 20th to June 20th, 2020. Patients with a history of chronic kidney disease were excluded from the study. We collected data related to the demographics, previous medical history, vital signs, symptoms, oxygen saturation, laboratory results, length of hospital stay, patients' outcomes (i.e., discharge or death), and the requirements for mechanical ventilation, dialysis or ICU admission. Moreover, severe illness was defined by mechanical ventilation requirement, ICU admission, or death.

The diagnosis of AKI was made based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. We recorded the first time of AKI diagnosis for each participant considering early AKI for patients with AKI at the time of admission and late AKI for those who develop AKI on the second day or later. The stages and causes of AKI (prerenal, renal, and post renal) were also recorded. Ultrasonography was used to detect postrenal AKI.[22] The AKI outcome was assessed within the first seven days after the diagnosis of AKI for each patient. The kidney function recovery was defined by the return of serum creatinine to its baseline level or by improvement in urinary output. The AKI was considered transient AKI when the condition improved within 48 h, while in a persistent AKI, the improvement occurred within 48 h to 7 days. Acute kidney damage (AKD) was defined when there was no recovery of kidney function after seven days.[23] The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1399.116).

The study data were analyzed using the SPSS software (Version 25). Qualitative variables were expressed by frequency and percentage, and the quantitative variables were presented by mean and standard deviation. The Chi-square test and the independent-sample t-test were used to compare the two groups. A P value less than .05 was considered statistically significant.

RESULTS

During the study, 367 patients with COVID-19 were admitted to the hospital. A total of 104 (28%) patients were diagnosed with AKI. 86 patients (23%) in the first 24 h (early AKI) and 18 patients (5%) on the second day or later (late AKI). Patients with and without AKI were compared in terms of the demographic characteristics of patients and medical history (Table 1). The mean age of AKI was higher in patients with AKI ($P < .001$), and the majority of the patients were male ($P < .05$). In addition, the frequency of hypertension and cardiovascular diseases were significantly higher in patients with AKI ($P < .05$).

Table 2 presents the baseline vital signs and other clinical symptoms of the participants, showing no significant differences in the vital signs between the two study groups. ($P > .05$) The most prevalent symptoms among patients with AKI included shortness of breathing, cough, fever, fatigue, and chills. There was no significant difference between the two groups in the frequency of different symptoms except for cough and fatigue, which were significantly more prevalent among patients without AKI ($P < .05$).

Table 3 shows initial laboratory results, and Table 4 compares the severity of the disease and outcomes in participants of the two groups. Compared to the patients without AKI, the needs for hemodialysis and mechanical ventilation were

Table 1. Comparison of Demographic Characteristics and History of Diseases Between the Two Groups With and Without AKI

	Total (n = 367)	No AKI (n = 263)	AKI (n = 104)	*P*
Age, year	62 ± 18	57 ± 17	72 ± 15	< .001*
Gender				
Male	212 (58%)	140 (53%)	72 (69%)	< .05**
Female	155 (42%)	123 (47%)	32 (31%)	
Medical History				
Diabetes	91 (25%)	64 (24%)	27 (26%)	> 0.05**
Hypertension	106 (29%)	65 (25%)	41 (39%)	< .05**
Hypercholesterolemia	23 (6%)	15 (6%)	8 (8%)	> .05**
Hypertriglyceridemia	15 (4%)	11 (4%)	4 (4%)	> .05**
Lung Disease	34 (9%)	20 (8%)	14 (13%)	> .05**
Cardiovascular Disease	56 (15%)	31 (12%)	25 (24%)	< .05**
Gastrointestinal Disease	5 (1%)	3 (1%)	2 (2%)	> .05**
Liver Disease	5 (1%)	2 (1%)	3 (3%)	> .05**
Cancer	30 (8%)	22 (8%)	8 (8%)	> .05**
Cigarette Smoking	38 (10%)	25 (10%)	13 (13%)	> .05**
Drug Abuse	22 (6%)	16 (6%)	6 (6%)	> .05**

*Independent t test, **Chi-square test

Table 2. Comparison of Vital Signs and Other Symptoms at Baseline Between the Two Groups With and Without AKI

	Total (n = 367)	No AKI (n = 263)	AKI (n = 104)	*P*
Vital Signs				
Number of Breaths per minute	19 ± 10	19 ± 10	18 ± 8	> .05
Temperature, Degrees Celsius	37.4 ± 0.8	37.3 ± 0.7	37.4 ± 0.8	> .05
Heart Rate per minute	88 ± 15	88 ± 13	89 ± 17	> .05
Systolic Blood Pressure, mmHg	118 ± 16	117 ± 13	117 ± 20	> .05
Diastolic Blood Pressure, mmHg	74 ± 9	74 ± 8	74 ± 9	> .05
Arterial Oxygen Saturation,%	90 ± 8	90 ± 7	87 ± 8	< .05
Symptoms				
Dyspnea	266 (72%)	196 (75%)	70 (67%)	> .05
Cough	243 (66%)	186 (71%)	57 (55%)	< .05
Sputum	64 (17%)	46 (17%)	18 (17%)	> .05
Fever	209 (57%)	149 (57%)	60 (58%)	> .05
Shaking	106 (29%)	77 (29%)	29 (28%)	> .05
Headache	25 (7%)	18 (7%)	7 (7%)	> .05
Fatigue	143 (39%)	113 (43%)	30 (29%)	< .05
Myalgia	56 (15%)	39 (15%)	17 (16%)	> .05
Anosmia	8 (2%)	8 (3%)	0 (0%)	> .05
Epigastric Pain	24 (7%)	14 (5%)	10 (10%)	> .05
Diarrhea	51 (14%)	36 (14%)	15 (14%)	> .05
Constipation	5 (1%)	2 (1%)	3 (3%)	> .05
Nausea	78 (21%)	55 (21%)	23 (22%)	> .05
Vomit	66 (18%)	46 (17%)	20 (19%)	> .05
Melena	4 (1%)	1 (0%)	3 (3%)	> .05
Hematemesis	2 (1%)	0 (0%)	2 (2%)	> .05
Rectorragia	2 (1%)	0 (0%)	2 (2%)	> .05

*Independent t test, **Chi-square test

significantly higher in the patients with AKI ($P < .001$). There was no significant difference between the two groups in terms of ICU admission ($P > .05$) or the duration of hospital stay ($P < .05$). However, the number of deaths and the presence of severe illness (defined by the occurrence of death, the requirement of dialysis, intubation, mechanical ventilation or ICU admission) were

Table 3. Comparison of Laboratory Test Results Between Two Groups With and Without AKI

	Total (n=367)	No AKI (n = 263)	AKI (n = 104)	*P**
FBS, mg/dL	151 ± 79	151 ± 77	151 ± 86	> .05
ESR, mm/hour	46 ± 26	45 ± 26	48 ± 25	> .05
CRP, mg/L	59 ± 62	55 ± 63	70 ± 57	< .05
Urea, mg/dL	46 ± 35	33 ± 13	77 ± 50	< .001
Cr, mg/dL	1.4 ± 1	1.1 ± 0.4	2.2 ± 1.5	< .001
Na, mmol/L	137 ± 5	137 ± 4	137 ± 7	> .05
K, mmol/L	4.2 ± 0.6	4.1 ± 0.5	4.4 ± 0.7	< .001
Mg, mEq/L	2 ± 0.5	1.9 ± 0.5	2 ± 0.4	> .05
Ca, mg/dL	8.4 ± 1.1	8.5 ± 1.1	8.4 ± 1.2	> .05
P, mmol/L	3.4 ± 1.2	3.2 ± 0.9	3.9 ± 1.5	< .001
PT, sec	13 ± 6	12 ± 6	14 ± 5	< .05
PTT, sec	27 ± 8	25 ± 7	29 ± 10	< .05
INR	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	< .001
Lactate, U/L	22 ± 14	19 ± 10	27 ± 20	< .05
LDH, U/L	610 ± 328	584 ± 277	671 ± 417	> .05
CK, U/L	281 ± 516	250 ± 481	360 ± 589	> .05
CK MB, ng/mL	40 ± 195	49 ± 230	20 ± 41	> .05
Hb, g/dL	12.6 ± 2.2	12.8 ± 2	12.1 ± 2.4	< .05
WBC, 10^9/L	8 ± 6	8 ± 5	10 ± 7	< .05
PMN, %	73 ± 12	71 ± 12	77 ± 12	< .001
LYM, %	20 ± 11	22 ± 12	15 ± 10	< .001
Platelets, 10^9/L	202 ± 96	206 ± 99	190 ± 88	> .05
AST, U/L	50 ± 51	45 ± 41	65 ± 70	< .05
ALT, U/L	40 ± 44	38 ± 40	45 ± 53	> .05
ALK, U/L	243 ± 608	201 ± 168	351 ± 1113	> .05
Bilirubin, μmol/L	1.3 ± 1.6	1.1 ± 1.5	1.5 ± 1.7	> .05
Albumin, g/L	3.7 ± 0.6	3.8 ± 0.7	3.6 ± 0.6	> .05
Uric Acid, mg/dL	7.7 ± 15	4.5 ± 1.7	12.1 ± 22.7	< .05

*Independent sample t test

Table 4. Comparison of Treatment Characteristics, Hospital Stay, and Outcome Between the Two Groups With and Without AK

	Total (n = 367)	No AKI (n = 263)	AKI (n = 104)	*P*
Need dialysis during treatment	11 (3%)	0 (0%)	11 (11%)	< .001*
Requires intubation and mechanical ventilation	47 (13%)	17 (7%)	30 (29%)	< .001*
Admission in the ICU	25 (7%)	15 (6%)	10 (10%)	> .05*
Death	74 (22%)	25 (10%)	49 (47%)	< .001*
Existence of severe disease ***	91 (25%)	38 (14%)	53 (51%)	< .001*
Duration of hospital stay, days	5 (3 to 8)	5 (3 to 8)	6 (3 to 10)	> .05**

*Chi-square test, **Mann-Whitney U test
*** Existence of any of the following condition including need for dialysis, intubation and mechanical ventilation, admission in ICU, and death were considered as severe diseases.

significantly more prevalent among patients with AKI (*P* < .001). Moreover, half of the patients with AKI were severely ill and died subsequently.

Regarding the AKI stages, 66 (64%), 20 (19%), and 18 (17%) patients were categorized as in stage 1, stage 2, and stage 3, respectively. The cause of AKI in 52 (50%) and 45 (43%) patients was renal and pre-renal, respectively. The reasons for AKI development in 7 (7%) patients were unknown due to the death of patients on the first day of admission or the impossibility of assessment. Moreover, of all the AKI patients with renal causes, 56% (29 patients) were in stages 2 and 3. The frequency of AKI with these stages was 13% (6 patients) in patients with pre-renal cause, and the difference was significant (*P* < .001). In terms of recovery status, 25 (24%) and 29 (28%) patients had transient (recovered in less than 48 h) and persistent AKI (improved within 48 h to 7 days). Moreover, 32 (31%) patients did not recover within seven 7 days after the diagnosis of AKI and developed AKD. It was impossible to determine the recovery status of 18 (17%) patients who died.

There was no significant difference between the two groups of patients with early AKI (n = 38, 44%) and late AKI (n = 11, 61%) in terms of mortality ($P > .05$). However, the survival of the patients with stage 3 of the disease was significantly lower than those with stage 1 and 2 ($P = .016$). Figure 1 presents the mortality rate of patients without AKI and in different stages of AKI. As indicated in Figure 2, patients with pre-renal causes of AKI had a lower mortality rate (11 patients, 24%) as compared with AKI patients with renal causes (34 patients, 65%) and unknown causes (4 patients, 57%)($P < .001$).

DISCUSSION

In our study, the frequency of AKI in the hospitalized patients with COVID-19 was 28%, 23% on admission and 5% during hospitalization. The mortality rates and the frequency of severe illness (leading to the need for dialysis, intubation, mechanical ventilation, ICU admission, and death) were significantly higher in patients with AKI. About two-thirds of AKI patients were in stage

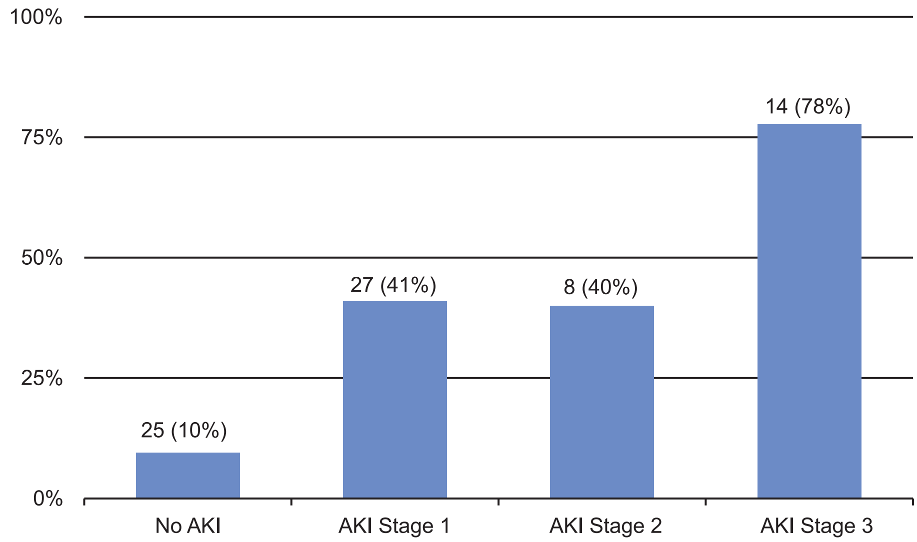

Figure 1. The Mortality Rate in Patients Without AKI and Different Stages of AKI

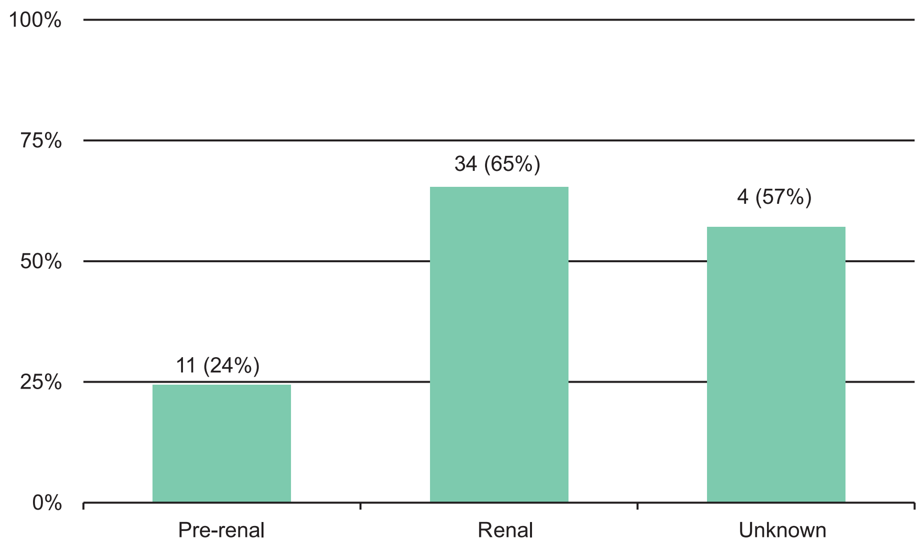

Figure 2. Mortality Rate Based on the Cause of AKI

1, and the cause of AKI was renal in 50% of the patients. No patient was diagnosed with post-renal causes for AKI by ultrasound. Overall, about half of the patients recovered, and a third developed AKD. The mortality rate of AKI patients was higher in patients with advanced stages of AKI. Moreover, patients with renal or unknown reasons for the development of AKI had a higher mortality rate compared to others. However, there was no difference in the survival rate between the patients with early and late AKI.

In early studies, the reported prevalence of AKI in COVID-19 patients was 3-9%;[4-6] however, more recent studies, especially those conducted in western countries, have reported a higher prevalence of this disorder.[14,18, 24]

Renal impairment is a common complication in patients with COVID-19. However, meta-analyses conducted in this field have revealed different results.

According to the study conducted by Fu *et al.*, the mean incidence of AKI in 20 studies performed in the United States and Europe and 62 studies from China was reported to be 28.6% and 5.5%, respectively.[15] In a study carried out on 73 patients in Bahrain, AKI was detected in 29 patients (39.7%), of whom seven 7 patients (9.6%) had received hemodialysis.[25] We have already reported an incidence of 22.8% for AKI in 254 patients with COVID-19 (127 diabetic patients and 127 non-diabetic patients). In a meta-analysis performed in Iran, the incidence of AKI was reported to be 24% (17-31%). Our study result seems similar to those reported in Iran and many western countries. The discrepancies observed in the incidence of AKI in patients with COVID-19 in different countries and regions can be attributed to differences in admission criteria (such as hospitalization or ICU admission), demographic characteristics, and comorbidities.[11]

The obtained results in the present study showed that AKI was associated with higher mortality in patients with COVID-19. Similarly, most other studies have reported that the occurrence of AKI in this group of patients can be associated with higher morbidity mortality.[13, 17, 27, 28] Patients with COVID-19 are prone to the conditions leading to ICU admission, mechanical ventilation, kidney replacement therapy, and death. Overall, the mortality rate of COVID-19 patients with AKI compared with those without AKI was reported to be 52.4% vs. 26.3%.[29-31] The reported risk of death in patients with AKI has been 4.6 times higher than those without AKI.[15]

The results of this study showed that both renal and pre-renal causes were associated with AKI in COVID-19 patients. However, patients with renal causes were more prone to develop higher stages of the disease and suffered from a higher mortality rate. Based on previous studies, various mechanisms leading to kidney damage in patients with COVID-19 included; dehydration, cytokine storm syndrome, direct viral invasion to tubular, interstitial, and glomerular cells via ACE2 receptor, changes in microvasculature structure, damage to tubules due to severe immunological reactions; and infiltration of inflammatory cells into the interstitial kidney tubules.[8,32-35]

In this study, nearly about two-thirds of AKI patients were in stage 1 of the disease, about half of patients recovered, and a third developed AKD. As with the incidence of AKI, the stage of AKI and its recovery rate have been reported differently.

In a study conducted by Rubin *et al.*, the prevalence of AKI in 71 patients admitted to four ICUs in France was 11% on admission and 80% during hospitalization, with one-third of patients at each stage. In that study, transient and persistent AKI were detected in 7% and 93% of patients. Only 28% of these patients recovered within the seven days after the admission.[20]

In a study by Chan *et al.* in New York, of 3,235 patients 35%, 20%, and 52% of patients were diagnosed with stage 1, 2, and 3 of AKI, respectively. Only 33% of these patients had recovered, 70% had AKD at the time of hospital discharge. In survivors of this study, 57% improved, and 43% were discharged with AKD. In another study conducted by Charytan *et al.* on 4,732 patients in New York, the incidence of AKI was reported to be 29.3%, with half of the patients in stage 1 and more than a third in stage 3. The creatinine level returned to baseline at discharge in 77.1% of survived patients[19]. Based on another New York report, in the study performed by Ng *et al.* on 9,657 patients, 51.7% of patients with AKI in stages 1-3 survived, of whom 74.1% had improved renal function at discharge. However, only 16.9% of patients in stage 3D survived, of whom 66.7% had improved kidney condition[36]. According to Soheili *et al.*, the prevalence of AKI has been 45.9%

in 946 patients with COVID-19, of whom 44.3%, 0.7%, and 0.8% were in stage 1, stage 2, and stage 3, respectively.[37]

This difference between the characteristics of patients with AKI and their rate of recovery is mainly due to the various studied populations. It can be said that in higher stages of the disease, the mortality rate of patients during hospitalization increases, while the rate of recovery at discharge decreases.

To the best of the authors' knowledge, the present study is one of the few studies conducted on the characteristics and outcomes of AKI patients in Iran. Regarding the limitations of the present study, one can refer to the fact that it was conducted as a retrospective study in one medical center. Therefore, it was not possible to determine the exact cause of AKI (especially renal type). Moreover, in some cases, the report of laboratory tests, such as d-dimer, ferritin, and urine analysis was not possible due to the lack of data in a large number of patients. Therefore, it is necessary to conduct more comprehensive studies in this field. In summary, according to a high incidence of AKI patients with COVID-19 and regarding the fact that about one-third of patients with AKI eventually develop AKD, it is important that all COVID-19 patients, especially high-risk patients, be closely monitored for the appropriate diagnosis and treatment of AKI.

CONCLUSION

The findings of the present study indicated that about 28% of all the hospitalized patients with COVID-19 were diagnosed with AKI, and some underlying factors, such as old age, hypertension, and cardiovascular disease were more common among these patients. In addition, the need for dialysis, intubation, mechanical ventilation, and mortality were higher in them. About two-thirds of AKI patients were in stage 1 of AKI, and the cause of AKI was renal in half of the patients. Overall, about half of the patients recovered, and about a third developed AKD.

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