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Evaluation of mortality of COVID-19 patients with acute kidney injury (AKI) in comparison to the non-AKI patients

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ABSTRACT

Introduction: Acute kidney injury (AKI) is prevalent in the coronavirus disease-2019 (COVID-19). There are little data on the relationship between renal dysfunction and COVID-19 prognosis.

Objectives: The aim of this research was to investigate the effects of AKI in COVID-19 patients hospitalized to the Golestan and Razi hospitals in Ahvaz, Iran.

Patients and Methods: In this retrospective cohort study, a total of 194 COVID-19 patients were included, consisting of 79 patients with AKI and 115 patients without AKI. Primary and secondary outcomes were compared between the two groups.

Results: According to the findings, mortality was significantly different between the two groups, and mortality was higher in the AKI group ($P < 0.001$). The mean length of hospital stay was statistically significantly higher in the AKI group ($P = 0.024$). Moreover, there was a significant correlation between intensive care unit (ICU) admission and the study group ($P < 0.001$). Staging of AKI group were seen as; stage I (49.37%), stage II (36.71%), and stage III (13.92%). No significant correlation was observed between outcome and the stages of AKI ($P = 0.496$). Furthermore, 14 patients (17.72%) needed renal replacement therapy (RRT) in the AKI group.

Conclusion: Although AKI is a common finding in COVID-19 patients, most patients were in stage I disease, which returned to normal after COVID-19 treatment. According to our research, COVID-19 rarely leads to serious and persistent kidney injury. However, the risk of death is increased in COVID-19 patients with AKI. Therefore, it is necessary to evaluate the renal function tests during the course of disease.

Implication for health policy/practice/research/medical education:

Some studies reported that the incidence of acute kidney injury (AKI) in COVID-19 patients was higher than the incidence of AKI in non-COVID-19 patients. The study was conducted on 194 COVID-19 patients admitted to Golestan and Razi hospitals in Ahvaz, Iran. According to our results, COVID-19 does not cause serious and permanent kidney injury. Since the rate of mortality of COVID-19 patient is higher in the AKI group, it is recommended that patients with COVID-19 should be assessed for AKI.

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, Hubei province, China, in December 2019 and quickly spread to other countries throughout the world (1,2). While respiratory infections are the most prevalent cause of COVID-19, it may affect any organ system (3). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had the greatest impact on the lungs, followed by the kidneys (4). Although initial findings

from China suggested that only 3%-5% of COVID-19 patients suffered from acute kidney injury (AKI) (4,5), European and American findings depicted a rate of up to 34% (6,7).

Current knowledge suggests nonspecific mechanisms for COVID-19-related AKI. However, particular mechanisms, such as direct viral infection through angiotensin-converting enzyme 2 (ACE2) receptor, which is extremely expressed in the kidney, renin-angiotensin-

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aldosterone system (RAAS) disorder, and increased pro-inflammatory cytokines in terms of the viral infection and microvascular thrombosis have been proposed (8).

SARS-CoV-2 starts the infection process by attaching to receptors on the host cell membrane that are functional. The post-mortem examination of COVID-19 patients showed varying degrees of acute tubular necrosis, lymphocyte infiltration, and viral RNA, suggesting a direct invasion to the renal tubules (3). AKI is known to cause fluid overload, metabolic disorders, fluid-electrolyte imbalance, impaired neutrophil function and immune system dysfunction, all of which might additionally make contributions to worsening outcomes in COVID-19 individuals (9).

In brief, AKI affects the prognosis of patients with COVID-19, expanded mortality and morbidity and, the need for renal replacement therapy (RRT), and imposes a greater burden on the hospitals and patients (10).

The link between renal dysfunction and COVID-19 prognosis is in general poorly understood. As well as, it is unclear how much the AKI condition predisposes COVID-19 individuals to severe illness and negative outcomes (11). In this regard, a rapid and primary diagnosis of AKI, leads physicians to help manage patients with COVID-19.

Objectives

This study aimed to determine the consequences of AKI in COVID-19 patients admitted to Golestan and Razi hospitals in Ahvaz, Iran.

Patients and Methods

Study design

This is a retrospective cohort study of AKI prevalence in admitted COVID-19 patients at Razi and Golestan hospitals from 20 December 2021 to 20 March 2022. COVID-19 infection was defined based on positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 nucleic acid. The medical documents of 194 individuals with laboratory-confirmed COVID-19, more than 18 years old, were analyzed. Children, those with established end-stage renal disease, and people who had a kidney transplant were all excluded. Two groups of patients were formed. The control group was COVID-19 patients who have normal kidney function and the case group was characterized by the COVID-19 patients who showed AKI during their hospitalization.

Acute kidney injury was determined based on KDIGO guidelines; including 1) increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, 2) increase in creatinine by >1.5 times the base in the last 7 days, and 3) urine output <0.5 mL/kg/h for > 6 hours. AKI stage was determined using the peak serum creatinine level from baseline

after diagnosis of AKI, therefore the increase in serum creatinine by 1.5-1.9 mg/dL, 2-2.9 mg/dL, and 3 times the baseline values were determined as stages 1, 2, and 3 of AKI, respectively (12).

The severity of lung involvement was defined as mild ground glass opacity (GGO) (less than 25%), moderate (25%-50%), and severe (more than 50%) (13). The daily values of urea and creatinine were recorded. For each patient, we collected baseline patient features such as primary laboratory tests, consisting lung computed tomography (CT) scan information, demographic data, medications usage, clinical characteristics, treatment (respiratory supports), RRT and clinical outcomes in the designed questionnaire. Laboratory data included serum electrolytes, complete blood count, admission time serum creatinine, discharge time serum creatinine, blood gas analysis, and serum albumin and also urine analysis tests. Finally, primary outcomes such as death were recorded, as well as secondary outcomes such as duration of admission, intensive care unit (ICU) admission, degree of pulmonary involvement, use of mechanical ventilation in the ICU and its duration, requirement for RRT, and renal function status at discharge.

Statistical analysis

Statistical analysis was performed by SPSS software version 22 (IBM, Chicago, USA). The quantitative and qualitative variables were indicated as mean \pm SD and number (percentage), respectively. Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to test for the distribution. Differences were compared by using the *t* test or Mann-Whitney U test as appropriate. For the test of significances, chi-square/Fisher's exact test was calculated to compare the frequencies among groups. *P* value less than 0.05 was considered statistically significant.

Results

A total of 194 patients were included in this study, with 115 having normal creatinine levels and being referred to the non-AKI group, since 79 having abnormal serum creatinine levels (rising tendency) and being referred to the AKI group. There was no significant association between gender and the groups ($P=0.053$). Moreover, the clinical symptoms were not different among the groups; however, vital signs, blood pressure, and temperature were different. Furthermore, the history of the pre-existing disease has shown 49 (25.2%) with diabetes mellitus, 50 (27.75%) with hypertension, 17 (8.76%) with ischemic heart disease, and 10 (5.15%) with heart failure, and also nine patients (4.63%) with malignancies. Further, 18 (22.78%) and 13 (16.45%) in the AKI group had used non-steroidal anti-inflammatory drugs and ACE inhibitors and angiotensin II receptor blockers (ARBs),

respectively. Patients with AKI were more likely to have ICU admission ($P<0.001$) and thereby had a higher death rate than the normal group ($P<0.001$; Table 1). Moreover, patients with AKI stayed at the hospital longer than the non-AKI group (9.34 ± 5.5 versus 7.51 ± 5.45 , $P=0.024$).

According to AKI stages, 39 patients (49.37%) were classified as stage 1, 29 patients (36.71%) as stage 2 and 11 patients (13.92%) as stage 3. For 17.72% of AKI patients, RRT was conducted. Our study showed serum creatinine levels at baseline and before discharge differed considerably across stages. There was no statistically significant correlation between AKI severity and outcome ($P=0.49$; Table 2). The prevalence of leukopenia and anemia in COVID-19 patients with AKI was significantly higher, although the lymphopenia between two groups was not significant (Table 3). Besides, in AKI group, the value of erythrocyte sedimentation rate (ESR), and serum concentrations of lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood sugar, ferritin and potassium was significantly higher, which represents the relation between disease severity and kidney involvement.

As well, the rate of metabolic acidosis was considerably higher in this group (Table 4).

Discussion

The aim of this study was to detect how AKI affected COVID-19 patients at Ahvaz's Golestan and Razi hospitals. According to our findings, the lungs are the most damaged organ, causing symptoms such as cough and shortness of breath. The ACE2 is considered a cell receptor in COVID-19. Interestingly, ACE2 expression in renal tissue is approximately 100-fold higher than in respiratory organs, which illustrates that renal cells may be the target of SARS-CoV and SARS-CoV-2 infection. There are limited clinical information on AKI during SARS-CoV-2 infection (14). AKI is a common complication among hospitalized COVID-19 patients for an extensive variety of diagnoses. The reason for AKI in COVID-19 cases is not completely perceived (15).

The incidence of hyperglycemia, hyperkalemia, hyperphosphatemia, elevated lactate dehydrogenase, CPK, ESR, and ferritin were higher in AKI patients. In addition, the AKI group had a greater incidence of

Table 1. Baseline and clinical features of patients

Variables	Groups		P value	
	Non-AKI (n=115)	AKI (n=79)		
Gender	Male	46 (40%)	21 (26.58%)	0.053
	Female	69 (60%)	58 (73.41%)	
Age (year)	18-65 years	74 (64.34%)	37 (46.83%)	0.015
	≥ 65 years	41 (35.35%)	42 (53.16%)	
BMI (kg/m ²)	19	2 (1.73%)	2 (2.53%)	0.002
	19-25	37 (32.17%)	7 (8.86%)	
	25-30	52 (45.21%)	51 (64.55%)	
	≥ 30	24 (20.86%)	19 (24.05%)	
Clinical symptoms	Edema	24 (20.86%)	20 (25.31%)	0.46
	Myalgia	100 (86.95%)	62 (78.48%)	0.43
	Gastrointestinal symptoms	61 (53.04%)	31 (39.24%)	0.059
	Respiratory distress	73 (63.47%)	52 (65.82%)	0.73
Vital signs	Low BP	19 (16.52%)	27 (34.17%)	0.017
	High BP	8 (6.95%)	5 (6.32%)	
	Normal BP	88 (76.52%)	47 (59.49%)	0.026
	Low fever	43 (37.39%)	45 (56.96%)	
	High fever	56 (48.69%)	27 (34.17%)	
	Normal temperature	16 (13.91%)	7 (8.86%)	
	O ₂ saturation <93%	62 (53.91%)	46 (58.22%)	0.552
	O ₂ saturation ≥93%	53 (46.08%)	33 (41.77%)	
Normal respiratory rate	52 (45.21%)	26 (32.91%)	0.086	
	Increasing respiratory rate	63 (54.78%)		53 (67.08%)
Pulmonary CT scan	Mild GGO	14 (12.17%)	7 (8.86%)	0.748
	Moderate GGO	48 (41.73%)	33 (41.77%)	
	Sever GGO	53 (46.08%)	39 (49.36%)	
Outcome	Death	17 (14.78%)	33 (41.77%)	< 0.001
	Discharge	98 (85.21%)	46 (58.22%)	
Admission	ICU	28 (24.34%)	41 (51.89%)	< 0.001
	General	87 (75.65%)	38 (48.10%)	

BP: Blood pressure, GGO: Ground-glass opacification, ICU: Intensive care unit

Table 2. Evaluations based on AKI stages

Variables		Stage I (n=39)	Stage II (n=29)	Stage III (n=11)	P value
Serum creatinine (mg/dL)	On admission	1.59 ± 0.21	2.45 ± 0.49	5.02 ± 0.84	<0.001
	Pre discharge	1.31 ± 1.05	1.97 ± 1.72	2.60 ± 1.64	0.019
Pulmonary CT scan	Mild GGO	4 (13.79%)	3 (7.69%)	0 (0%)	0.148
	Moderate GGO	21 (72.41%)	9 (23.07%)	3 (27.27%)	
	Sever GGO	14 (48.27%)	17 (43.58%)	8 (72.72%)	
Outcome	Death	14 (48.27%)	13 (33.33%)	6 (54.54%)	0.49
	Discharge	25 (86.20%)	16 (41.02%)	5 (45.45%)	

GGO: Ground-glass opacification.

Table 3. Laboratory findings in patients

Laboratory findings	Range	Groups		P value
		Non- AKI (n=115)	With AKI (n=79)	
White blood cell (×10 ⁹ /L)	Normal	112 (97.39%)	71 (89.87%)	0.026
	Abnormal	3 (2.60%)	8 (10.12%)	
Lymphocyte (%)	Normal	65 (56.52%)	37 (46.83%)	0.18
	Abnormal	50 (43.47%)	42 (53.16%)	
Platelet (×10 ⁹ /L)	Normal	98 (85.21%)	61 (77.21%)	0.154
	Abnormal	17 (14.78%)	18 (22.78%)	
Hemoglobin (g/dL)	Normal	30 (26.08%)	11 (13.92%)	0.041
	Abnormal	85 (73.91%)	68 (86.07%)	
AST/ALT (U/L)	Normal	62 (53.91%)	40 (50.63%)	0.65
	Abnormal	53 (46.08%)	39 (49.36%)	
PTT/PT (s)	Normal	105 (91.30%)	69 (87.34%)	0.37
	Abnormal	10 (8.69%)	10 (12.65%)	
	Abnormal	53 (46.08%)	39 (49.36%)	

AST: Aspartate transaminase, ALT: Alanine transaminase, PTT: Partial thromboplastin time, PT: Prothrombin time, ALP: Alkaline phosphatase.

metabolic acidosis. However, there were no significant differences in the serum levels of sodium, calcium, C-reactive protein, albumin, D-dimer, and liver enzymes between the two groups. The mortality in the AKI group was 41.7%, and in the non-AKI group was about 14.7%. The current study findings demonstrated a significant correlation between outcome and the study group ($P < 0.001$; Table 1).

The study by Robbins-Juarez et al showed that AKI was related to the increased risk of mortality among COVID-19 patients, which was similar to our findings (16). The death rate in AKI cases was 63.9% in the study by Dai et al, which was substantially higher than in patients without AKI (17). Patients with AKI also had a higher death rate in the study by Xiao et al (14). The results of these studies are the same as our study. Regarding urinary findings, in AKI group, the incidence of hematuria was significantly higher than the non-AKI group, whereas the incidence of proteinuria and leukocyturia were not different between the two groups. Our study showed most of the patients were in stage I of AKI (43.36%). Furthermore, 29 out

of 79 patients (36.70%) and 11 patients (13.92%) were stages 2 and 3, respectively. In a study by Fominskiy et al in Italy, out of 99 patients, 72 (75%) developed AKI. Most patients had stage I of AKI (45.8%), while 15 patients (20.8%) and 24 patients (33.4%) had stage II and III of AKI, respectively (2). In another cohort study by Hirsch et al, evaluated the manifestations, risk factors, and consequences of AKI in hospitalized COVID-19 patients. Their results showed that out of 5499 patients with COVID-19, AKI was detected in 993 (36.6%) of cases. The prevalence of stages I, II and III of AKI were 46.5%, 22.4%, and 31.1%, respectively (18).

In these studies, similar to our findings, most of AKI patients were in stage I, indicating that renal involvement in COVID-19 patients is more reversible and mild. Of note, the occurrence of stage I of AKI is high in critically ill patients; since most patients of this category seems having favorable outcomes. However, progression to stage III of AKI is associated with an extremely high mortality rate. In this regard, evaluation of renal function and prevention of AKI play a significant role in the clinical

Table 4. Biochemical laboratory tests

Laboratory tests	Non- AKI (n=115)	With-AKI (n=79)	P value
BS (mg/dL)	165.07 ± 86.63	214.86 ± 114.13	0.001
BUN1 (mg/dL)	18.47 ± 7.26	53.00 ± 31.03	<0.001
Sodium (mEq/L)	139.42 ± 6.06	139.09 ± 15.82	0.84
Kalium (mg/dL)	4.21 ± 0.75	4.71 ± 0.92	<0.001
Calcium (mg/dL)	8.47 ± 0.87	8.43 ± 2.09	0.87
Phosphorus s(mg/dL)	3.81 ± 1.55	4.35 ± 1.95	0.043
Albumin (g/dL)	3.63 ± 0.85	3.40 ± 0.67	0.05
LDH (IU/L)	951.31 ± 351.11	1235.38 ± 618.55	<0.05
CPK (IU/L)	164.00 ± 158.66	309.72 ± 344.19	0.001
ESR (mm/h)	41.40 ± 20.09	48.71 ± 22.49	0.019
CRP (mg/L)	1.93 ± 0.92	1.86 ± 0.85	0.59
D-dimer (ng/mL)	1713.66 ± 1360.19	5837.38 ± 23445.86	0.273
Ferritin (ng/mL)	1023.52 ± 507.65	1288.33 ± 492.39	0.01
pH	7.38 ± 0.07	7.32 ± 0.12	<0.001
PCO2 (mm Hg)	41.44 ± 11.34	36.56 ± 11.66	0.004
HCO3 (mEq/L)	36.56 ± 11.66	24.52 ± 8.97	<0.001

BS: Blood Sugar, LDH: Lactate dehydrogenase, CPK: Creatine Phosphokinase, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

management of COVID-19 (14). According to our findings, a notable association between the age of patients and the study group ($P = 0.015$) was detected. Our study showed a greater proportion of patients with AKI were 65 years or older than patients without AKI. In accordance with our findings, Xiao et al found that patients with AKI were older than those without AKI (14). Similarly to the study by Hirsch et al, older age was a risk factor for AKI(18). In the study of Dai et al, AKI patients with COVID-19 had significantly higher rates of C-reactive protein than patients without AKI (17), indicating a secondary bacterial infection in these patients. While in our study, no significant difference was observed between the mean of CRP in the two groups ($P = 0.596$).

The mechanical ventilation usage was significantly different between the two groups. In the group of patients with AKI, using the mechanical ventilation was higher ($P < 0.001$). While in the study of Trifi et al, the mechanical ventilation usage between the two groups was not significantly different ($P = 0.12$) (19).

There was no significant difference in the mean length of ICU admission between the two groups ($P = 0.211$). Similar to our findings, Trifi et al found no statistically significant difference in ICU hospitalization duration among the groups. Other variables, such as underlying conditions such as heart failure, diabetes, and cancer, may also be implicated. Our findings are consistent with reports of the intensive care national audit and research center, which illustrated AKI patients generally had more severe disease and required persistent lymphopenia, invasive mechanical ventilation, and vasopressor support(20).

Based on our results, no significant difference was reported between lung CT-scan and the study groups ($P = 0.748$). Similar to our results, in the study of Trifi et al, lung CT-scan in the group with and without AKI was not significantly different ($P = 0.999$) (19). In addition, in the current investigation, no correlation between the stages of AKI and the severity of lung CT-scan results was seen, indicating that variables other than the degree of pulmonary involvement contributed to the development of AKI. No significant correlation between stages and the patients' outcome ($P = 0.496$) was detected in our study. Probably because most patients were in stage I and accordingly other factors beyond the AKI were involved in mortality. In our study, 14 patients (17.72%) received RRT. In the study of Fominskiy et al and Hirsch et al, 17.7% and 14.3% of patients required RRT (2, 18). However, there was a lot of variations across researches throughout the world. According to our findings and previous studies, the occurrence of AKI during COVID-19 exacerbated the complications of disease and increased the mortality (21). The study by Cheng et al showed that patients with primary renal abnormalities (increased serum creatinine, proteinuria, hematuria, and AKI) had higher mortality rates (1). Additionally, according to the study by Azeem et al, the overall hospital mortality rate for patients with and without AKI were 6.7% and 1%, respectively. This study also showed that the probability of survival was lower in patients with AKI (15). In brief, it seems that that AKI is associated with negative clinical consequences, including increased hospital expenditures, death, and long-term hospitalization (21).

Conclusion

In conclusion, AKI is linked to a noticeably higher mortality rate among hospitalized COVID-19 patients as compared to non-AKI patients. The kidneys are the target organ of SARS-CoV-2 and the outbreak of AKI in admitted COVID-19 patients is high. Accordingly, the deterioration of kidney function exacerbates damage to other organs. Additionally, COVID-19 cases have a higher mortality rate when it is associated with AKI. In our study, AKI is a common finding in COVID-19 patients. Our study showed most patients were in stage I, which returned to normal kidney function after COVID-19 treatment. According to our study, COVID-19 leads to less severe and permanent kidney damage. We recommend that kidney function should be evaluated in COVID-19 patients and renal function monitoring should be continued after discharge to control for progression to CKD. We recommend that larger, multicenter studies to be conducted in the future to learn more about the impact of AKI on prognosis and disease outcomes.

Limitations of the study

There were various limitations in this study. Since non-hospitalized patients were not included in the present investigation, we were unable to extrapolate our findings to outpatient AKI settings. Second, we received no follow-up information after discharge. Third, the causality interpretation of the association between effects and exposures was not attainable owing to the observational character of the research.

Authors' contribution

Conceptualization: LSN. Methodology: HSH, MT and LSN. Validation: AGH. Formal Analysis: FJM. Investigation: LSN and AGH. Resources: SHA. Data Curation: MT. Writing—Original Draft Preparation: MT. Writing—Review and Editing: MT and AGH. Visualization: HSH, LSN. Supervision: AGH, SHA. Project Administration: HSH, MT and LSN. Funding Acquisition: HSH.

Ethical issues

The study protocol conforms to the ethical guidelines of Declaration of Helsinki (1975). The study was approved by the Ethics Committee of Ahvaz Jundishapur university of medical sciences, Ahvaz, Iran (Ethics number: IR.AJUMS.REC.1400.023). Written informed consent was obtained from all patients. The present research was extracted from the nephrology fellowship dissertation of Mina Tafazoli at this university (registration no: 4386). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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