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Outcomes, Risk Factors, and Incidence of Acute Kidney Injury in Hospitalized COVID-19 Patients

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Abstract

Background: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2) is the virus causing Coronavirus Disease 2019 (COVID-19). Apart from respiratory disease, this virus can affect different organs.

Objectives: Therefore, multiple mechanisms have been hypothesized for Acute Kidney Injury (AKI) in COVID-19. In this study, we evaluate the incidence and prognosis of AKI in COVID-19 patients.

Methods: This retrospective cohort study assessed 397 COVID-19 patients hospitalized between April 1, 2020, and September 30, 2021. Patients with a sudden rise of serum creatinine level, more than 0.3 mg/dl in two days or more than 50% of the initial level in one week, were diagnosed with AKI. Demographic, laboratory, and clinical features were compared in AKI patients with patients without AKI.

Results: A total of 397 patients with a mean age ± standard deviation of 55.42 ± 15.26 years were included in the study. According to diagnostic criteria, 48 (12.1%) patients developed AKI. Old age, a history of hypertension, and chronic renal failure were suggested as risk factors for AKI. High levels of C-Reactive Protein, Erythrocyte Sedimentation Rate, Lactate Dehydrogenase, D-dimer, and serum phosphorus upon arrival were also associated with an increased risk of AKI. In addition, the incidence of hypernatremia and hyperkalemia increased mortality in patients with AKI.

Conclusion: The incidence of AKI in admitted COVID-19 patients affects the duration of hospitalization, the chance of ICU admission, and mortality. It is important to limit the use of nephrotoxic drugs and to maintain water-electrolyte balance to prevent the incidence of AKI and improve the outcome.

Keywords: Acute kidney injury, COVID-19, Renal replacement therapy, Water-electrolyte imbalance

1. Background

In December 2019, physicians in Wuhan, China, reported first cases of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2 infection) (1-3). On February 11, 2020, the World Health Organization (WHO) formally selected the name Coronavirus Disease 2019 (COVID-19) for the disease caused by this virus, and a month later, on March 11, declared it a global pandemic. The spread of this virus was so rapid that despite all the global efforts focusing on the pandemic, it infected more than 670 million people in about two years and killed about 6.8 million (4).

The COVID-19 has a vast range of clinical symptoms and can vary from asymptomatic infection to a mild upper airway disease or severe viral pneumonia and, ultimately, respiratory failure and death (5, 6). Reports indicate that the most common symptoms include fever (88%), dry cough (67.7%), and rhinorrhea (4.8%) (7).

To date, several studies have been performed on this disease, which reported the effect of this virus on various organs (8). Although diffuse alveolar injury and acute respiratory failure have been the most critical aspects of COVID-19 (5), the multiorgan manifestations of this virus need to be assessed.

Acute Respiratory Syndrome Coronavirus-2 has four types of structural proteins, one of which is spike proteins. Spike proteins, a type of glycoprotein, are made up of two chains, S1 and S2. Coronavirus infection begins by binding the S1 chain of the spike protein to the ACE2 receptor and thus binding the virion to the cell (9, 10). Based on previous studies and analyses, the ACE2 receptor is abundant in renal tubular cells, Leydig cells, and seminiferous tubule cells (11). Therefore, with the identification of the method of SARS-CoV2 infection, concerns were raised about the renal involvement of this infection.

Due to the kidneys' prominent physiological role and vulnerability, many systemic problems will adversely affect their function. As a result, in addition to direct viral injury, systemic mechanisms, including acute pulmonary injury (12), myocarditis (13), sepsis (14), coagulopathy (15), cytokine storm (16, 17), and rhabdomyolysis (18) have been suggested for Acute Kidney Injury (AKI) in COVID-19 patients.

In a study conducted in 2020, Sargiacomo et al. reported that older age, chronic kidney disease (CKD), and the presence of other chronic diseases

(such as hypertension, diabetes mellitus, obesity, heart failure, and chronic obstructive pulmonary disease) are associated with the severity of COVID-19 and represent risk factors for the incidence of AKI in hospitalized COVID-19 patients (19). Lin et al., in an article published in 2020, suggested that COVID-19 patients who develop AKI have a higher risk of in-hospital death with an odds ratio of 11.05 (20).

2. Objectives

Therefore, the present study aimed to evaluate the outcomes, risk factors, and incidence of Acute Kidney Injury in patients hospitalized with COVID-19.

3. Methods

This retrospective cohort study included adult COVID-19 patients (above 18 years old) admitted to Karaj, Iran's University hospitals for infectious and internal diseases (Shahid Rajaei and Imam Ali Hospitals) from April 1, 2020, to September 30, 2021. Additionally, multiple admissions for one patient and known cases of heart failure and End-Stage Renal Disease (ESRD) were excluded from the study. Finally, 397 patients were selected as study samples via single-stage cluster sampling.

A definitive diagnosis of COVID-19 was made based on a positive SARS-CoV2 PCR test or a lung CT-Scan in favor of COVID-19 in patients with symptoms of this disease. Hospitals' radiologists reported the lung CT-Scans, and infectious disease or internal medicine specialists assessed patients' symptoms. Based on COVID-19 treatment guidelines of the Ministry of Health and Medical Education of Iran, only patients with severe dyspnea (Dyspnea at rest with a respiratory rate above 30 per minute), oxygen saturation below 90%, or altered mental status were admitted to the hospitals.

3.1. Inclusion Criteria

1. Patients with definitive symptoms of COVID-19
2. Admitted to Shahid Rajaei or Imam Ali Hospitals (both located in Karaj, Iran) from April 1, 2020, to September 30, 2021
3. Older than 18 years old

3.2. Exclusion Criteria

1. Multiple admissions for one patient
2. Past medical history of heart failure or ESRD

After the approval of the Research Ethics Committee of Alborz University of Medical Sciences and the issuance of the Ethics Code (IR.ABZUMS.REC.1399.199), patients' information retrospectively were collected from the files and recorded in the relevant checklists. The collected information included patients' ID, chief complaint, history of chronic diseases, height, weight, duration of hospitalization, duration of Intensive Care Unit (ICU) admission, treatments, and outcome. In addition, we recorded patients' lab results using checklists through the Hospital Information System (HIS).

The incidence of AKI was the primary endpoint of this research. At the time of admission, serum creatinine, BUN (blood urea nitrogen), sodium, and potassium levels were measured in all patients according to initial COVID-19 guidelines. These tests were repeated in case of clinical suspicion of AKI or prolongation of the hospitalization.

Based on the AKIN classification (21), patients whose serum creatinine level increased by more than 0.3 mg/dL during two days or more than 50% of the initial level within one week were diagnosed with AKI. The patients were divided into two groups based on the incidence or absence of AKI, and the collected data, including patients' characteristics, lab data, treatments, and outcomes, were compared in these two groups.

All patients received standard of care for COVID-19 based on the Ministry of Health and WHO's treatment guidelines. In addition, we collected and analyzed medications used to treat patients to assess their role as risk factors for AKI and minimize their bias.

Descriptive statistics were reported as a median and interquartile range for continuous and proportions for categorical variables. In addition, baseline patient characteristics and outcomes were compared between the two groups using the Chi-squared test, Fischer exact test, and t-test, and a *P*-value of less than 0.05 was considered statistically significant. Multivariate linear regression was used to investigate the relationship between baseline characteristic features and AKI incidence. All statistical analyses were performed using SPSS (version 16).

4. Results

We included 397 COVID-19 patients in the study, 333 (83.9%) patients from Imam Ali and the rest from Shahid Rajaei Hospital. Patients' age range was from 18 to 98 years with a mean age of 55.42 ± 15.26. A total of 199 (50.1%) patients were male. Acute Kidney Injury occurred in 48 (12.1%) patients, labeled as AKI patients. Furthermore, 31 (7.8%) patients had serum creatinine higher than the normal range (1.3 mg/dl) at admission; however, with fluid therapy and hydration, the creatinine level decreased to normal; these patients were not included in the AKI patients' group.

Patients' characteristics are summarized in Table 1. The mean age of AKI patients was significantly higher than no-AKI patients; however, the sex distribution in the two groups showed no statistically significant difference. All patients' hospitalization duration was in the range of 1 to 37 days, with a

Table 1. Comparison of demographic characteristics and outcomes in patients with and without acute kidney injury

Characteristics	All patients (n=397)	AKI patients (n=48)	No-AKI patients (n=349)	P-value
Age—yr. (mean ± SD)	55.42 ± 15.26	61.96 ± 16.58	54.52 ± 14.87	0.001*
Male sex—no. (%)	199 (50.1)	25 (52.1)	174 (49.9)	0.722**
Days admitted in hospital	8.5 ± 4.52	8.75 ± 6.10	6.66 ± 4.20	0.003*
BMI (kg/m2)	27.75 ± 4.92	27.75 ± 4.29	27.88 ± 4.86	0.877*
History of diabetes mellitus	92 (22.9)	25 (12)	79 (22.6)	0.715**
History of hypertension	120 (30.2)	24 (50)	96 (27.5)	0.001**
History of chronic kidney disease	10 (2.5)	6 (12.5)	4 (1.1)	<0.001**
ICU admission	104 (26.2)	35 (72.9)	69 (19.8)	<0.001**
In-hospital death	60 (15.1)	27 (56.3)	33 (9.5)	<0.001**
Days admitted in ICU	5.95 ± 5.09	6.09 ± 5.75	5.88 ± 4.76	0.850*

*T-test, **Pearson Chi-square, AKI: Acute Kidney Injury

mean of 8.50 ± 4.52, which was significantly longer in AKI-patients (P=0.003).

A total of 120 (30.2%) patients had a history of hypertension, which was significantly higher in AKI patients [50%; P=0.001]. Moreover, 10 (2.5%) patients had a history of CKD, and AKI was more common in these patients (P<0.001). We used logistic regression to investigate the risk factors for AKI incidence. Age, history of diabetes mellitus, hypertension, and CKD entered the model as independent variables, and the model was significant [P<0.001, df=4, Chi-squared=26.756; Table 2]. Based on this analysis, old age, a history of hypertension, and CKD are risk factors for AKI incidence in hospitalized COVID-19 patients.

A total of 60 (15.1%) patients died during hospitalization. This number was 27 (56.3%) in patients with AKI and higher than no-AKI patients [33 (9.5%); P<0.001]. Also, 104 (26.2%) patients were admitted to the ICU. This number was 35 (72.9%) in patients with AKI and higher than no-AKI patients [69 (19.8%); P<0.001].

Comparing the results of the tests performed upon arrival, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Lactate Dehydrogenase (LDH), D-dimer, and serum phosphor concentration was significantly higher in patients with AKI than no-AKI patients (P<0.05 in all five parameters). However, among the factors reported in the Arterial Blood Gas test, only the level of HCO_3 was significantly different between the two groups; it was lower in patients with AKI [P=0.034; Table 3].

We analyzed the drugs prescribes in both groups of patients. The results showed that the administration of Meropenem, Vancomycin, Imipenem, and Actemra was significantly higher in patients with AKI during hospitalization (P<0.05 in all four parameters).

The Pearson correlation coefficient was used to investigate the relationship between creatinine increase and the duration of hospitalization and ICU admission. This analysis showed a significant and direct relationship between the amount of creatinine increase and the hospitalization duration (P=0.016 and r=0.345); however, no significant correlation was observed between the amount of creatinine increase and the number of ICU admission days (P=0.147 and r=0.220). In addition, the amount of increase in serum creatinine level did not significantly differ in patients who died (1.49±1.40 mg/dl) and those who were discharged [1.41±1.24 mg/dl; P=0.838].

Around 10 (2.5%) patients underwent Renal Replacement Therapy (RRT) during hospitalization, of which five patients underwent hemodialysis only once and the other five underwent 3 to 12 times. Of the five patients who underwent hemodialysis once, in 4 patients, the plan for dialysis was not entirely performed due to the patient's death and only in 1 patient the RRT plan was completed with one dialysis session. On the other hand, only one of the 5 patients who underwent dialysis three times or more died. Out of 10 patients who underwent hemodialysis, 5 (50%) died; this was not statistically different from all AKI patients [27 (56.3%); P=0.65].

Serum sodium levels were normal (135 to 145 mEq/L) in 283 (71.3%) patients during hospitalization. However, 99 (24.9%) patients developed hyponatremia, and 15 (3.8%) patients developed hypernatremia while hospitalized. Hypernatremia was significantly higher in patients with AKI than in no-AKI patients.

We compared AKI Patients' outcomes based on their serum sodium level condition (Table 4). All 9 (100%) AKI patients who developed hypernatremia died. The mortality of AKI patients with normal sodium concentration (41.1%) and hyponatremia (60%) was significantly lower (P=0.006).

Serum potassium levels in 318 (80.1%) patients were normal (3.5 to 5 mEq/L) during hospitalization (Table 4). However, 52 (13.1%) patients developed

Table 2. Result of logistic regression on Acute Kidney Injury incidence (Dependent variable: AKI incidence)

Independent variables	Odds ratio	95% Confidence Interval for odds ratio	P-value*
Age—yr.	1.028	1.005, 1.052	0.017
History of diabetes mellitus	0.593	0.269, 1.307	0.195
History of hypertension	2.107	1.047, 4.239	0.037
History of chronic kidney disease	8.447	2.183, 32.681	0.002

*Logistic regression

Table 3. Comparison of laboratory findings upon arrival in the two groups, with and without acute kidney injury (CRP: mg/L, ESR: MM/hr, LDH: U/L, CPK, ferritin: micrograms/L, D-dimer: ng/mL, Serum Ca, P, Mg: mg/dL, CO2, HCO3: mEq/L)

Test	All patients (n=397)	AKI patients (n=48)	No-AKI patients (n=349)	P-value*
CRP	85.04 ± 60.03	123.76 ± 54.29	79.87 ± 58.98	<0.001
ESR	47.27 ± 28.5	57.86 ± 32.98	48.90 ± 27.60	0.015
LDH	712.07 ± 372.0	989.97 ± 688.05	675.21 ± 289.52	<0.001
CPK	514.3 ± 271.57	460.97 ± 308.09	522.85 ± 265.68	0.613
D-dimer	1.96 ± 1.53	2.33 ± 2.26	1.88 ± 1.33	0.021
Ferritin	666.4 ± 406.4	1033 ± 692.58	588.3 ± 365.89	0.064
Serum Ca	8.32 ± 0.46	8.1 ± 1.26	8.37 ± 0.76	0.311
Serum P	3.73 ± 1.29	9.4 ± 2.26	3.51 ± 0.85	0.005
Serum Mg	2.32 ± 1.19	2.24 ± 0.45	2.34 ± 1.27	0.364
PH	7.44 ± 0.08	7.42 ± 0.08	7.44 ± 0.07	0.205
PCO2	38.54 ± 10.4	38.04 ± 10.24	38.63 ± 10.44	0.732
HCO3	26.04 ± 5.27	24.56 ± 4.83	26.43 ± 5.32	0.034

*T-test

Table 4. Comparison of incidence of hyponatremia, hypernatremia, hypokalemia, or hyperkalemia in the two groups, with and without acute kidney injury

Electrolyte condition	All patients (n=397)	AKI patients (n=48)	No-AKI patients (n=349)	P-value*
Hyponatremia	99 (24.9)	10 (20.8)	89 (25.5)	
Normal sodium	283 (71.3)	29 (60.4)	254 (72.8)	<0.001
Hypernatremia	15 (3.8)	9 (18.8)	6 (1.7)	
Hypokalemia	52 (13.1)	5 (10.4)	47 (13.5)	
Normal potassium	318 (80.1)	26 (54.2)	292 (83.7)	<0.001
Hyperkalemia	27 (6.8)	17 (35.4)	10 (2.9)	

*Pearson Chi-square

Table 5. Comparison of ICU admission, in-hospital death, and days admitted in ICU in the patients with AKI, based on their sodium and potassium level condition

Outcome	All AKI patients (n=48)	Hyponatremia (n=10)	Normal (n=29)	Hypernatremia (n=9)	P-value*
ICU admission	35 (72.9)	8 (80)	18 (62.1)	9 (100)	0.065
In-hospital death	27 (56.3)	6 (60)	12 (41.4)	9 (100)	0.006
Days admitted in ICU	6.09 ± 5.76	6.63 ± 1.46	5.33 ± 2.97	7.11 ± 4.88	0.730
		Hypokalemia (n=5)	Normal (n=26)	Hyperkalemia (n=17)	
ICU admission	35 (72.9)	3(60)	15 (57.7)	17 (100)	0.002
In-hospital death	27 (56.3)	1 (20)	11 (42.3)	15(88.2)	0.001
Days admitted in ICU	6.09 ± 5.76	5.33 ± 2.51	5.27 ± 4.35	9.46 ± 7.18	0.707

*Pearson Chi-square

hypokalemia and 27 (6.8%) hyperkalemia. The incidence of hyperkalemia in AKI patients (35.4%) was significantly higher than in no-AKI patients [2.9%; P<0.001].

Table 5 displays the assessment of the ICU admission, mortality, and duration of ICU admission in AKI patients based on their serum potassium condition. There was a statistically significant difference between the three groups in terms of mortality and ICU admission (P<0.05 in both cases); however, the duration of ICU admission showed no statistically significant difference between the three groups (P=0.707).

5. Discussion

In this retrospective cohort study, the incidence of AKI was 12.1% and associated with older age, history of hypertension, and CKD. The mortality rate in AKI patients was much higher than in no-AKI patients. The present study revealed that in admitted COVID-19 patients, the duration of hospitalization and the likelihood of admission to the ICU were directly related to AKI incidence. Additionally, sodium and potassium imbalances were more common among AKI patients and was significantly associated with patients' worse outcome.

In three different studies carried out by Cheng, Li, and Ng on AKI in COVID-19 patients, the incidence of AKI was reported to be between 5.4% and 39.9%, and mortality in these patients was 30% to 40% (22-24). Moreover, Silva et al., in a systematic review, reported an incidence rate of 31% for AKI, and the mortality of 39.2% in these patients (25). Although the AKI incidence rate in our study was compatible with their findings, the mortality rate was higher. This difference is mainly because these studies were conducted on admitted patients. Due to the COVID-19 pandemic, in low-resource countries, only patients with severe diseases were admitted, consequently, the higher rate of complications is accepted in these patients (26).

In a study on AKI and COVID-19, Fabrizi et al. reported a correlation coefficient of 0.913 (P<0.001) between hypertension and the incidence of AKI (27). This is compatible with our finding that a history of hypertension was significantly found more in AKI patients.

In a study on COVID-19 patients hospitalized in New York City area, Richardson et al. reported that 3.2% of all patients were treated with RRT. However, their study failed to report the outcomes of patients who received RRT (28). Khalili et al. reported a nearly same rate of RRT in an Iranian population (29). Our data confirms both of these studies findings on the rate of RRT. Our study further adds that most patients who died despite receiving RRT, only received one session; which can be resulted from delayed initiation of hemodialysis.

As shown in Zarbock et al. study, early RRT can reduce mortality more than delayed initiation of RRT among critically ill AKI patients (30). Furthermore, an in-vitro study by Harm et al. on Cytokine removal in extracorporeal blood purification showed that by cytokine adsorption, RRT can treat patients with cytokine storm (31); treating cytokine storm can prevent AKI.

Amin et al. reported that hyperkalemia in hospitalized COVID-19 patients, was associated with higher incidence rate of AKI (70.1% vs. 25.9%, P<0.001), ICU admission (OR: 1.05, 95% CI: 1.01-1.09), and in-hospital mortality (42% vs. 11%, P<0.001) (32). In addition, Shrestha et al. investigated the effects of hypernatremia on hospitalized COVID-19 patients. They noted that hypernatremia was also associated with ICU admission and mortality in these patients (33). Our study confirms both of these findings, reporting a significant association between incidence of AKI and these electrolyte imbalances, hypernatremia, and hyperkalemia. We further assessed their effects on AKI patients, specifically, which was compatible with Amin et al. and Shrestha et al. findings on all COVID-19 patients.

Considering that the leading cause of hypernatremia is water imbalance, dehydration may have been a factor in electrolyte imbalance and further exacerbating the disease in these patients. Therefore, special attention should be paid to fluid intake in patients hospitalized with COVID-19 who develop AKI. Because of the alveolar damage in COVID-19 patients, they are more susceptible to developing acute respiratory distress syndrome (ARDS) with excessive fluid therapy. A study conducted by Matthay et al. on ARDS in 2019, suggests a conservative approach for fluid therapy in patients with acute lung injury. This study recommends reducing the overall fluid balance 500-1000 ml per day by reducing intravenous fluid and using diuretics (34); since these guidelines for ARDS management were commonly used in COVID-19 treatment, one can make the case that overly conservative fluid management could be the leading cause of dehydration, hypernatremia, and AKI in hospitalized COVID-19 patients.

6.1. Limitations

- The urinary output was not recorded in most patients; therefore, we only relied on serum and creatinine to diagnose AKI.
- Urine casts, 24-h urine analysis, and kidney biopsy can be used to determine the cause and the site of kidney injury. Unfortunately, none of the above was available in our study.

6. Conclusion

Since the incidence of AKI could result in worse outcome of hospitalized COVID-19 patients, it is necessary to limit nephrotoxic drugs in patients with the risk or in the early stages of AKI. In addition, appropriate fluid therapy is essential to prevent AKI and the electrolyte imbalances related to it. An early initiation of RRT in AKI patients, could probably improve the outcome in these patients.

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Footnotes

Conflicts of Interest: None.
Funding: A total of 200$ was granted for data collection by Alborz University of Medical Sciences.
Ethics Declaration: This research was conducted following the Declaration of Helsinki's Ethical Principles for Medical Research. Before beginning the data collection, the study's methods were approved by the Alborz University of Medical Sciences' Research Ethics Committee (Ethics Code: IR.ABZUMS.REC.1399.199). Also, this committee waived informed consent. All patients received standard of care and no change in their treatment was made. The patients' personal information remained confidential and the data was collected based on their file numbers.

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