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Original Article

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Renal Involvement in Hospitalized COVID-19 Patients: Epidemiology, Risk Factors, and Correlation with Outcomes

Manouchehr Amini[1], Fatemeh Yaghoubi[1]*, Marjan Akhavan[1], Samira Abbasloo[1], Farnaz Tavakoli[1], Azarakhsh Baghdadi[2] and Monir Sadat Hakemi[1]

1. Nephrology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

*** Corresponding author**

Fatemeh Yaghoubi, MD
Nephrology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 8490 2469
Email: yaghoobifatemeh@yahoo.com
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Abstract

Background: While respiratory tract symptoms are the most frequent reasons for hospital admission in COVID-19 patients, renal involvement is common and is associated with worse outcomes. The aim of this study was to determine the incidence, risk factors and outcome of Acute Kidney Injury (AKI) in hospitalized COVID-19 patients in a referral center.

Methods: In a retrospective review, patients hospitalized for COVID-19 from February 2020 through April 2020 in a referral COVID center were studied. Demographic data, pre-existing comorbidities and drug history, along with laboratory data at presentation and during admission were recorded. AKI was diagnosed based on Kidney Disease Improving Global Outcomes (KDIGO) criteria. Data were analyzed to determine the incidence, risk factors and mortality of AKI.

Results: Finally, 200 patients were included, with a mean age of 60.5 years. Of these, 126 (63%) developed AKI and this number was 73.5% among the ICU-admitted patients. Patients who developed AKI were 4.29 times more likely to die. Pre-existing CKD, treatment with immunosuppressant, ICU admission, and the need for hemodialysis, were significantly associated with mortality. Among the eleven renal transplant recipients in this study, we found that a prior renal transplant was not associated with a higher rate of AKI but was significantly associated with increased mortality after correcting for age and gender.

Conclusion: Our findings showed a high incidence of AKI in patients admitted due to COVID-19, with a higher risk in ICU patients and it was a significant predictor of mortality. Further research is encouraged to understand the etiology of AKI, along with the long-term outcomes in the patients.

Keywords: Acute kidney injury, COVID-19, ICU admission, Mortality, ICU admission, Proteinuria, SARS-CoV-2

Background

Coronavirus disease 19 (COVID-19), caused by the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) has been a worldwide burden from the beginning of 2020, affecting close to 30 million individuals and claiming nearly one million lives as of September 14, 2020 (1). The respiratory tract is the most common site of symptoms, both in the outpatient setting and admitted patients. While Acute Respiratory Distress Syndrome (ARDS) is the most frequent reason for admission, renal involvement was also reported with varying frequency from the earliest reports. However, with the continued care and better understanding of the disease course and complications, several authors noticed and reported a growing rate of Acute Kidney Injury (AKI) in COVID-19 patients, especially in those who were hospitalized in ICU (2-6). The mechanism by which COVID-19 induces renal injury is still not well comprehended. Kidney biopsy results have shown that COVID-19 affects the kidneys in the vascular, tubular, and glomerular compartments (7). Acute Tubular Necrosis (ATN) has been the most common biopsy finding.

AKI has also been found to correlate with complications and clinical outcomes. In a systematic review, Lim *et al* found that AKI is associated with increased mortality (relative risk: 13.38), severe disease (RR: 4.43), and the need for ICU care (RR: 5.90) (4). However, the initial reports did not focus on kidney injury, and most did not report creatinine levels. In a more recent report, Braun *et al* evaluated kidney biopsies from 63 patients with COVID-19 (8). They found SARS-CoV-2 RNA in 60% of the cases, which was also associated with older age and an increased number of coexisting conditions. They not only found a renal tropism in COVID-19, but also found renal involvement to be highly correlated with disease severity and increased risk of premature death within the first 3 weeks of the disease.

Iran was among the first countries to be hit by the COVID-19 pandemic. Shariati hospital has been one of the first sites to treat COVID patients and is a nationally designated hospital for managing the disease.

From the beginning of the pandemic, we have witnessed a high rate of AKI and related complications in COVID-19 patients. Therefore, the purpose of this study was to focus on the epidemiology of AKI in COVID-19 and the predictors of kidney involvement, and its association with complications and clinical outcomes in Shariati hospital, Tehran, IRAN. We also sought to assess the prevalence and outcomes of AKI in COVID-19 patients who were renal transplant recipients.

Materials and Methods

In an IRB-approved retrospective chart review, the electronic health records system of a tertiary referral center, Shariati hospital, Tehran, Iran, was queried for all patients admitted between February 20, 2020 and April 19, 2020. This timeframe coincides with the height of the COVID pandemic worldwide, and the peak caseload in Iran (9). From this database, patients with COVID-19 were selected in case the patient satisfied one of the criteria of: 1) A positive RT-PCR for SARS-CoV-2, 2) Highly-suggestive findings on chest CT-scan. Chest CT-scan has been shown to have a high sensitivity and specificity in the diagnosis of COVID-19 in multiple studies (10-12). Due to the overwhelming load on our center's laboratory during the peak infection period, we did not repeat negative Polymerase Chain Reaction (PCR) tests in patients with highly-suggestive findings on CT-scans. This was in accordance with the guidelines published by the Ministry of Health and the Iranian Society of Radiology (13,14). Highly-suggestive findings included ground glass/consolidation opacities, and bilateral/multi lobar involvement with a peripheral distribution.

Demographic data and underlying comorbidities of the selected patients including hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLP), rheumatologic disorders, and underlying renal disease, along with a complete drug history were recorded. Symptoms at presentation, laboratory data during the hospital stay and ICU admission, mortality rate and the COVID-specific treatments were extracted from the charts and reviewed. To evaluate acute renal involvement in COVID-19, we systematically reviewed all charts to extract urinalysis findings and serum creatinine (SCr) values in these patients. Kidney Disease Improving Global Outcomes (KDIGO) guidelines were used to define acute kidney injury (15). All of the 200 patients

having the above conditions for COVID-19 infection and admitted between February 20, 2020 and April 19, 2020 in Shariati Hospital entered our study, and only 15 patients with Covid-19 who underwent chronic dialysis were excluded from the study.

Statistical analysis

Descriptive statistics were used to evaluate frequencies and means. Student's t-tests were used to measure differences in means when the data were normally distributed, the Mann-Whitney U test was used to measure differences in means when the data were non-normally distributed, and chi-square tests were utilized for the categorical variables. Multiple logistic regression analysis was used to determine the association of independent variables with AKI and mortality. We included statistically significant findings in the regression model for each outcome. All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY, IBM Corp.). p-values of less than 0.05 were considered statistically significant.

Results

Two hundred patients satisfied the inclusion criteria and were included in the final analysis. Of these, 113 (56.5%) were male. The mean age was 60.5 years (SD=16.4, range, 20-96 years). In total, 189 patients had an RT-PCR for SARS-CoV-2 result on charts, of which 137 were positive (72.5%). All patients underwent chest CT-scan during the admission, with 130 (65%) having highly-suggestive findings for COVID-19.

The most common presenting symptom at the time

Table 1. Characteristics of the patients who developed AKI and its comparison with the patients who did not develop AKI).

Variable	No AKI	AKI	p-value
Medical history	**Number (%)**	**Number (%)**	
Hypertension	19 (25.6)	52 (41.2)	0.026
Hyperlipidemia	14 (18.9)	30 (23.8)	0.42
Diabetes mellitus	14 (18.9)	33 (26.1)	0.24
Renal transplant	4 (5.4)	7 (5.5)	0.96
CHF*	2 (2.7)	3 (2.3)	0.88
IHD*	5 (6.7)	18 (14.2)	0.10
AF*	2 (2.7)	6 (4.7)	0.48
Asthma	6 (8.1)	11 (8.7)	0.87
CKD*	0 (0)	8 (6.3)	0.027
Rheumatologic disorders	2 (2.7)	4 (3.1)	0.85
Hematologic disorders	5 (6.7)	15 (11.9)	0.24
Acute phase reactants			
CRP*	51.7 (40.1)	59.6 (38.2)	0.17
Procalcitonin	0.29 (0.24)	1.62 (3.43)	0.037
Albumin	4.1 (0.78)	3.2 (0.85)	0.001
Ferritin	378.7 (277.6)	1040.7 (1551.5)	0.12
Platelets count	176.6*103 (83*103)	199.8*103 (199.8*103)	0.10
Renal function			
Admission SCr*	1.12 (0.55)	1.19 (0.63)	0.43
Peak SCr*	0.93 (0.2)	2.71 (1.46)	<0.001

Significant comparisons are indicated in bold. Values are presented as number (%) for medical history and mean (standard deviation) for other variables. CHF*: congestive heart failure, IHD*: ischemic heart disease, AF*: atrial fibrillation, CKD*: chronic kidney disease, CRP*: C-reactive protein, SCr*: Serum creatinine.

Table 2. Mortality in the current study, and comparison made with patients who recovered regarding clinical characteristics

Variable	Mortality	Recovery	p-value
Male gender	33 (58.9)	80 (55.5)	0.66
Hypertension	24 (42.8)	47 (32.6)	0.17
Hyperlipidemia	15 (26.7)	29 (20.1)	0.30
Diabetes mellitus	14 (25)	33 (22.9)	0.75
Renal transplant	6 (10.7)	5 (3.4)	0.044
CHF *	3 (5.3)	2 (1.3)	0.10
IHD*	8 (14.2)	15 (10.4)	0.44
AF*	3 (5.3)	5 (3.4)	0.54
Asthma	7 (12.5)	10 (6.9)	0.20
Rheumatologic disorders	0 (0)	6 (4.1)	0.12
Hematologic disorders	10 (17.8)	10 (6.9)	0.021
CKD*	5 (8.9)	3 (2)	0.027
AKI*	47 (83.9)	79 (54.8)	<0.001
Hemodialysis	17 (30.3)	1 (0.7)	<0.001
ICU admission	26 (46.4)	42 (29.1)	0.021
Drug history			
ACE inhibitors	24 (42.8)	56 (38.8)	0.60
Immunosuppressant	18 (32.1)	18 (12.5)	0.001
Statins	19 (33.9)	45 (31.2)	0.71
Acute phase reactants			
CRP*	70.5 (17.7)	59.1 (15.8)	<0.001
Procalcitonin	2.68 (3.3)	0.8 (2.7)	0.07
Albumin	2.99 (0.8)	3.88 (0.79)	<0.001
Ferritin	1409 (2001)	1759 (910)	0.14
Platelets count	$175*10^3$ ($122*10^3$)	$197*10^3$ ($197*10^3$)	0.19

Significant comparisons are indicated in bold. Values are presented as number (%) for clinical characteristics and drug history, and mean (standard deviation) for the rest. CHF: congestive heart failure, IHD: ischemic heart disease, AF: atrial fibrillation, CKD: chronic kidney disease, AKI: acute kidney injury, ACE inhibitors: Angiotensin-converting enzyme inhibitors, CRP: C-reactive protein

of admission was dyspnea (in 122 patients, 61%), followed by fever (106 patients, 53%), cough (104, 52%), myalgia (63, 31.5%), nausea (26, 13%), diarrhea (9, 4.5%), chest pain (6, 3%), headache (5, 2.5%), and hemoptysis (2, 1%). Vital signs and lab data at the time of admission are available in the Appendices 1 and 2. During the admission, 57 (28.5%) had proteinuria, 25 (12.5%) leukocyturia, and 24 patients (12%) hematuria in their urinalysis. Also, serum troponin levels were assessed in 86 patients during the admission, of which 27 (31.4%) had abnormally high levels.

The mean serum creatinine (SCr) at the time of admission was 1.16 *mg/dl* (SD=0.6, range, 0.4-4.3 *mg/dl*). The mean peak SCr during admission was 2.05 *mg/dl* (SD=1.44, range, 0.5-8.2 *mg/dl*).

Based on the definitions of KDIGO, 126 patients (63%) developed AKI, of which 18 patients (9%) underwent hemodialysis during the study period. Among the 68 patients in need of ICU care, 73.5% (50 patients) had AKI. The mean age in patients who developed AKI was 4.3 years higher than patients who did not, but this comparison did not reach statistical

significance (p-value = 0.072). Other comparisons between patients who developed AKI and those who did not (no AKI) are summarized in table 1. Although patients who died were older than the recovered, it was not statistically significant (64 *vs.* 59.1, p-value = 0.17). Significant predictors of mortality included underlying hematologic disorders, underlying Chronic Kidney Disease (CKD), developing AKI during admission, undergoing dialysis, and ICU admission (Table 2).

AKI was a significant predictor of mortality, which increased the risk of mortality by 4.29 times (95% CI: 1.96-9.42). Moreover, on binary logistic regression analysis, patients with KDIGO stage 3 AKI, were 18.33 times more likely to die (p-value < 0.001, 95% CI: 7.1-47.2).

On multivariate logistic regression analysis, hemodialysis was a significant predictor of mortality, with an odds ratio of 8.9, as was lower albumin levels. Table 3 summarizes the results of a univariate and multivariate logistic regression analysis of the risk factors of mortality among the patients.

The most common comorbidities among patients were HTN (in 71 patients, 35.5%), DM (47, 23.5%), HLP (44 patients, 22%), ischemic heart disease (23, 11.5%), asthma (17, 8.5%), rheumatologic disorders (6, 3%), and congestive heart failure (5, 2.5%). 80 patients (40%) were being treated with ACE inhibitors, 36 (18%) with immunosuppressive drugs, and 64 (32%) with statins at the time of admission. Eight patients

Table 3. Risk factors of mortality according to univariate and multivariate logistic regression analysis

Variables	Univariate Model		Multivariate Model	
	OR	95% CI	OR	95% CI
Renal transplant	3.33	0.97 - 11.41	3.27	0.18 – 59.47
Hematologic disorders	2.91	1.13 - 7.44	1.25	0.19 – 8.21
CKD	4.60	1.06 - 19.97	3.02	0.02 – 3.98
AKI	4.29	1.95 - 9.42	2.73	0.43 – 17.05
Hemodialysis	17.71	5.67 - 55.26	8.93	1.35 – 59.10
ICU admission	2.10	1.11 - 3.97	0.58	0.15 – 2.16
Immunosuppressant	3.31	1.57 - 7.00	0.55	0.09 – 3.16
CRP	1.01	1.004 - 1.02	1.00	0.98 - 1.02
Albumin	0.25	0.12 - 0.52	0.28	0.11 - 0.66

Significant findings are indicated in bold. OR: odds ratio, 95% CI: 95% confidence interval, CKD: chronic kidney disease, AKI: acute kidney injury, ICU: intensive care unit, CRP: C-reactive protein

Table 4. The results of VIF and tolerance statistics

	Collinearity Statistics	
	Tolerance	VIF
Kidney transplant	0.581	1.722
Hematologic disease	0.717	1.394
CKD	0.777	1.286
AKI	0.496	2.018
Hemodialysis	0.554	1.805
ICU	0.960	1.042
Immunosuppressive	0.507	1.971
CRP	0.861	1.161
Albumin	0.704	1.420

(4%) were undergoing treatment for CKD, and 11 other patients (5.5%) had undergone a previous renal transplant.

National guidelines were followed for treating all the patients, which underwent several updates and iterations during the study period (14). As a result, all patients received hydroxychloroquine during admission, 171 (85.5%) received oseltamivir, 53 (26.5%) underwent treatment with Kaletra (lopinavir/ritonavir). Also, intravenous corticosteroids were added to the therapeutic regimen in 60 patients (30%) during their hospital stay, most commonly in ICU-admitted patients. 68 patients (34%) were admitted to the ICU due to a deteriorating clinical course. Overall, we recorded a 28% mortality rate (56 patients), with 144 patients (72%) being discharged either during the study period or afterward. At 48%, the mortality rate was higher in patients who required ICU admission. Table 4 showed that the results of VIF and tolerance statistics showed that the independent variables entered in the multiple logistic regression models do not correlate with each other.

Discussion

In the present study, we reported the COVID-19 patients admitted at Shariati referral Hospital and evaluated evidence of renal involvement and its association with outcomes and morbidity. We found a shockingly-high incidence of AKI (63%) in patients admitted for COVID-19. This alarming finding could be due to high number of critically ill patients admitted in the ICU of our center. Generally, we found a 28% mortality rate, and the development of AKI was actually a significant predictor of mortality in COVID-19. We also found that while patients with a previous renal transplant were not at a higher risk for AKI, they had a higher mortality rate overall.

Preliminary reports from China estimated AKI to occur in 0.5-7% of cases, and 2.9-23% of ICU patients (16-18). However, it was soon discovered that renal involvement in COVID-19 is more common and consists of a range of symptoms from mild proteinuria and hematuria to collapsing glomerulopathy, outright kidney failure, and the need for renal replacement therapies (4,6,7,19). The discrepancy observed in different studies might stem from the earlier reports focusing on the respiratory manifestations of an emerging pandemic and simply overlooking renal involvement in COVID. It could also be the result of a high mortality rate, which might have occurred earlier in the disease course, precluding any attention given to kidney function. With the expanding knowledge of the disease, patient care evolved significantly, the prognosis improved, and the consequences of kidney injury garnered attention. More recent studies (May 2020 onwards) have reported AKI in 17-43% of the hospitalized patients, and 61-76% of ICU patients, and a predilection for African-American patients (2,20-22). Along the same lines, we found a 63% rate of AKI in all-comers, and a 73.5% rate of AKI in patients admitted to the ICU. Our results also show that pre-existing hypertension and CKD are significantly associated with the development of AKI in hospitalized COVID patients. A recent study in 2021 reported that the most presented comorbidity with AKI was cardiovascular disease (58.2%) followed by diabetes (31.4%) (23). Another study conducted in 2021 in Turkey also showed that the most frequent comorbid conditions in patients with Covid-19 and AKI were hypertension (70.5%) and diabetes mellitus (43.8%) (24).

Perhaps more interestingly, patients with a prior renal transplant were not at a higher risk of developing AKI. Additionally, serum creatinine at the time of admission was not associated with an increased risk of developing AKI during admission.

AKI and renal involvement, in general, has been found to correlate with adverse clinical outcomes and mortality in COVID-19 and it was confirmed by our study. In a large series from New York, Hirsch *et al* found that among the 1993 patients who developed AKI during the hospitalization, 35% died (2). In another large study conducted in New York hospitals, patients who developed AKI were more likely to require ICU admission, mechanical ventilation, and vasopressor administration (20). Furthermore, ICU-admitted patients were far more likely to die when they had AKI (OR: 20.9), a trend that was also observed in all hospitalized patients (OR: 9.6). We also found that patients with AKI were 4.29 times more likely to die during their

hospital admission. This association was amplified in severe AKI, with patients having a KDIGO stage 3 AKI being 18.33 times more likely to die. Also, the study carried out by Arikan *et al* in Turkey showed that renal outcomes were worse in patients with AKI stage 3 and a high mortality in the advanced stage of AKI (24). In addition to AKI, we found that underlying hematologic disorders, CKD, receiving immunosuppressive drugs prior to admission, and requiring ICU admission or dialysis were significantly associated with in-hospital mortality among COVID patients. It has been proved that immunocompromised patients and the patients presented by multi-organ failure have more severe diseases with high mortality.

A unique aspect of this study was the presence of 11 renal transplant patients. We found that a prior renal transplant was not significantly associated with the development of AKI during admission. However, renal transplant patients had a higher risk of in-hospital mortality (p-value=0.44).

We acknowledge several limitations to this study. As a retrospective review of the patients, we were limited to the data in the charts. Therefore, while we could evaluate patient outcomes during their admission, we could not identify patients who have possibly had complications after discharge. However, it should be noted that the patient population in this study were from the first wave of the infection, and were generally only discharged after a full recovery, which might decrease the chances of us missing an adverse outcome. Also, renal biopsies were not performed in any patient, as it was not part of our diagnostic approach. However, renal autopsies are conducted to discern the renal implications of COVID-19, which will be reported later. Additionally, patients in this study received heterogeneous drug regimens, mainly due to the evolving knowledge during the first months of the pandemic and the changes in national guidelines. Finally, we did not evaluate the long-term consequences of AKI in COVID-19, which need to be further investigated in future studies. In this study, the results of VIF and Tolerance statistics showed that the independent variables entered in the multiple logistic regression models do not correlate with each other.

Conclusion

In conclusion, by investigating a cohort of hospitalized patients with COVID-19, we found a high incidence of AKI, which was even more among the ICU-admitted patients. Also, several risk factors of AKI were identified in the admitted patients. Furthermore, we found that hemodialysis was a significant risk factor for in-hospital mortality. Also, while being a renal transplant recipient failed to increase one's risk for developing AKI, it was significantly associated with in-hospital mortality. The results of this study might be useful in treating COVID-19 patients, especially those with pre-existing CKD or renal transplant. We encourage clinicians and researchers to further investigate the risk factors and pathophysiology of AKI in COVID-19 patients, and optimizing treatment strategies in patients who develop AKI to prevent adverse outcomes. Also, the chronic sequelae of COVID-19 patients recovered from AKI are yet to be shown, and we should anticipate a large population of patients with post-COVID CKD in the near future.

Ethics approval and consent to participate

The research followed the tenets of the Declaration of Helsinki. The research was approved by the ethics committee of Tehran University of Medical Sciences (Ethical code # IR.TUMS. VCR.REC.1399.037), with a waiver of the written consent.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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None.

Conflict of Interest

The authors declare that they have no competing interests.

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