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Original Article

Risk factors and the level of laboratory biomarkers abnormalities amongst COVID-19 admitted patients with acute kidney injury: A retrospective cross-sectional study

Mahdi Zarei[1], Juan Carlos Cotrina-Aliaga[2], Samaneh Atbaeitabari[3], Mohammad Darvishi[4*], Sepideh KarkonShayan[5*], Reza Akhavan-Sigari[6,7]

[1]Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Facultad de Ingenieria, Universidad Peruana los Andes, Huancayo, Peru
[3]Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Infectious Diseases and Tropical Medicine Research Center (IDTMRC), Department of Aerospace and Subaquatic Medicine, AJA University of Medical Sciences, Tehran, Iran
[5]Student Research Committee, School of Medicine, Gonabad University of Medical Sciences, Gonabad, Iran
[6]Department of Health Care Management and Clinical Research, Collegium Humanum Warsaw Management University Warsaw, Poland
[7]Department of Neurosurgery, University Medical Center Tuebingen, Germany

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Abstract

Introduction: Infection with SARS-CoV-2 might lead to severe acute kidney injury (AKI) with high morbidity and mortality. Various incidence rates of AKI have been reported among hospitalized patients with COVID-19. Our study aimed to investigate the risk factors associated with AKI in hospitalized COVID-19 patients and the relevant changes in their blood biomarkers compared to COVID-19 patients without AKI.

Methods: In this retrospective cross-sectional study, 262 COVID-19-confirmed hospitalized patients were enrolled in the Department of Internal Medicine at Bohlool teaching hospital, Iran, from September 2019 to January 2020. Then, the information related to demographics, medical history, comorbid conditions, and clinical and laboratory findings was documented. Patients were categorized into two groups: Patients without AKI and patients with AKI.

Results: We detected 130 (49.6%) patients with AKI among the total number of 262 patients admitted with COVID-19. A total of 68 (25.9%) patients had severe disease, and fever (47.1%) was the most common presenting symptom. Older age, comorbid cardiovascular diseases (CVD), and severe COVID-19 were significantly associated with higher risk of AKI. Abnormal levels of white blood cells (WBC), neutrophil count, hemoglobin (Hb), prothrombin time (PT), international normalized ratio (INR), D-dimer, C-reactive protein (CRP), alkaline phosphatase (ALP), direct bilirubin, blood urea nitrogen (BUN), creatinine, potassium (K), ferritin (in female patients), albumin (Alb), pH, and oxygen saturation (SPO_2) was significantly associated with a higher risk of developing AKI in COVID-19 patients.

Conclusion: AKI was a common condition among COVID-19 patients in our sample. Our study confirms the effect of COVID-19 on the developing of AKI. The association between blood biomarkers, including hematologic and inflammatory markers indicate their potential role in the impairment of kidney function.

Introduction

Coronavirus disease 2019 (COVID-19) is a primarily respiratory infection, and occurs as a result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2). The common presentations include fever, cough, myalgia, dyspnea, headache, and urinary symptoms.[1,2] COVID-19 can also cause extrapulmonary manifestations, including cardiovascular, neurological, hepatic, and renal involvement.[3,4] Since the initial spread of SARS-CoV-2, many studies have been conducted on its probable complications. Previous studies have reported the incidence of acute kidney injury (AKI) as a result of COVID-19 infections with very high morbidity and mortality with various incidence rates in different

***Corresponding Authors:** Mohammad Darvishi, Email: darvishi1349@gmail.com; Sepideh KarkonShayan, Email: sepidehshayan76@gmail.com

studies. Chinese studies have reported the incidence of AKI varying from 0.5% to 29% in hospitalized patients.[5,6] Other studies conducted in the United States revealed an incidence of 28% to 46% and a mortality rate of 35% to 41%. The binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) might increase the binding of angiotensin receptor type II to angiotensin II type I receptor. Since this enzyme is abundantly expressed in proximal renal cells, the activation of renin-angiotensin-aldosterone system might lead to kidney damage as a result of the increased inflammation and fibrosis.[7-9] Studies have identified several risk factors associated with an increased risk of developing AKI, such as increased age, and lower socioeconomic level, and a history of chronic kidney disease (CKD).[10,11] Abnormal laboratory tests in AKI patients include changes in WBC count and LDH. Moreover, abnormal levels of inflammatory biomarkers in COVID-19 patients, such as C-reactive protein (CRP), liver function tests, and coagulation parameters such as D-dimer, are associated with an increased risk of multi-organ impairment and poor prognosis.[4,10]

Studies investigating AKI and its prognosis in COVID-19 patients are abundant. However, the results are heterogenous, and most of them have not comprehensively addressed the COVID-19-related renal impairments. Therefore, further studies are needed to evaluate the complications resulting from COVID-19-assocaited AKI.[12-14] Our study aimed to identify the risk factors associated with the development of AKI in COVID-19 patients and to report abnormalities in their blood biomarkers compared to patients with COVID-19 who did not develop AKI.

Materials and Methods

Study design

This study was a retrospective cross-sectional study conducted at the internal medicine department of Bohlool teaching hospital, Gonabad, northeast Iran (September 2019 - January 2020). This study was approved by the institutional ethics committee of Gonabad university of medical sciences (IRB number: IR.GMU.REC.1399.006). This study did not impose any cost on the patients' treatment process or the hospital's health system. All of the levels of the study were under the control of the experts.

Study population

In this study, all COVID-19-confirmed patients admitted to the department of internal medicine, Bohlool hospital, Gonabad, between September 2019 and January 2020 were included. Oral consent was obtained from all of the included patients. Confirmation of COVID-19 in the patients was conducted via nucleic acid detection of SARS-CoV-2 in throat swab samples of patients by reverse transcriptase polymerase chain reaction (RT-PCR) according to the predefined protocols.[15]

Data collection

History (signs, symptoms, comorbidities, and contact history), demographic data, clinical, laboratory, and imaging data, and the received treatments of the included patients were thoroughly documented. The diagnosis of AKI was made based on the Kidney Disease Improving Global Guidelines (KDIGO).[16-18] AKI in adults is defined as an increase in serum creatinine (Cr) $\geq$ 0.3 mg/dl, or an increase in serum Cr > 1.5 folds baseline (the minimum preadmission serum Cr value, and when not available, Serum Cr_{GFR-75}) in previous 7 days, urine volume < 0.5 mL/kg/h for more than 6h.[19] The severity of COVID-19 was evaluated in each patient using NCPERET criteria.[20] Dyspnea, blood oxygen saturation $\leq$ 93%, respiratory rate $\geq$ 30, arterial oxygen partial pressure/ fractional inspired oxygen (PaO_2/FiO_2) of 50% were utilized to define severe COVID-19 patients. The presence of cardiovascular diseases (CVDs) including coronary artery disease, cardiac disease, diabetes mellitus (DM), and liver diseases including hepatitis, fatty liver diseases, cirrhosis, liver malignancies, etc. was identified using the past medical history extracted from the documented history of patients.

Statistical analysis

All statistical analyses were conducted with SPSS (Version 26.0.0.1). Quantitative variables were described using the mean ± standard deviation (SD), median, and interquartile range (IQR), and qualitative variables were described as percentage and frequency. Independent T-test and Mann Whitney test were applied to compare the variables. A *P* value of < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

The total number of COVID-19-confirmed admitted patients between September 2019 and January 2020 consisted of 262 patients with the median age of 52 (IQR 32-75; age range 32-75 years), of which 134 (51.1 %) were male ($P < 0.001$). Among these patients, 7 (2.7%) presented with CVD, 1 (0.4%) presented with liver diseases, and none of them had DM (Table 1).

Incidence and severity of AKI in COVID-19 patients

130 (49.6%) patients developed AKI during their hospitalization among a total of 262 patients with confirmed COVID-19 ($P < 0.001$), of which 67 (50.8%) patients were male ($P = 0.899$). The median age of AKI patients was 70 (IQR 38.7-81) which was significantly higher than non-AKI patients with median age of 44 (IQR 28.5-58.7) ($P < 0.001$) (Table 1).

Comparison of comorbidities in COVID-19 patients

Regarding the associated comorbidities of AKI in COVID-19, we compared the prevalence of background medical conditions such as CVD, liver diseases, and DM in COVID-19 patients with and without AKI. None of

Table 1. Demographics and baseline characteristics of patients infected with SARS-CoV-2

	No. (%) Total (n = 262)	Non-AKI (n = 132)	AKI (n = 130)	*P* value	Test
Age (y), median (IQR)	52 (32-75)	44 (28.5-58.7)	70 (38.7-81)	< 0.001	Mann-Whitney
Gender					
Male	134 (51.1)	67 (50.8)	67 (51.5)	0.899	χ^2
Female	128 (48.9)	65 (49.2)	63 (48.5)		
Comorbidities					
CVD	7 (2.7)	0	7 (5.3)	0.007	χ^2
Liver disease	1 (0.4)	0	1 (0.8)	0.498	χ^2
DM	0	0	0	-	-
Signs and symptoms					
Fever	124 (47.1)	71 (53.8)	53 (40.5)	0.030	χ^2
Fatigue	79 (30)	40 (30.3)	39 (29.8)	0.925	χ^2
Chill	27 (10.3)	16 (12.1)	11 (8.4)	0.320	χ^2
Cough	99 (37.6)	63 (47.7)	36 (27.5)	0.001	χ^2
Pharyngalgia	9 (3.4)	7 (5.3)	2 (1.5)	0.092	χ^2
Sputum production	4 (1.5)	1 (0.8)	3 (2.3)	0.310	χ^2
Dizziness	14 (5.3)	4 (3)	10 (7.6)	0.096	χ^2
Headache	25 (9.5)	17 (12.9)	8 (6.1)	0.061	χ^2
Chest pain	10 (3.8)	4 (3)	6 (4.6)	0.511	χ^2
Shortness of breath	95 (36.1)	42 (31.8)	53 (40.5)	0.145	χ^2
Nausea & vomiting	36 (13.7)	18 (13.6)	18 (13.7)	0.980	χ^2
Duration of hospitalization	5 (3-7)	6 (3-7)	4 (2-7)	0.002	Mann-Whitney
Severe disease	68 (25.9)	24 (18.2)	44 (33.6)	0.002	χ^2

CVD: Cardiovascular disease; DM: Diabetes mellitus.
$P < 0.05$ is considered statistically significant.

the patients without AKI had the mentioned background medical conditions. Our results are demonstrated as follows (Table 1):

CVD (comorbid cardio-vascular disease)
As shown in Table 1, there were 7 patients (2.7%) with CVD, all of whom had AKI (5.3%). None of the COVID-19 patients without CVD had AKI. The incidence of CVD in AKI-positive COVID-19 patients was significantly higher than in those without AKI ($P = 0.007$). Hence, the presence of CVD might be a predictive factor of the incidence of AKI in COVID-19 patients.

Liver diseases
As shown in Table 1, there was 1 patient (0.4%) with liver disease with simultaneous AKI. None of the COVID-19 patients without liver diseases had AKI. The incidence of liver diseases in AKI-positive COVID-19 patients had no significant difference compared with non-AKI COVID-19 patients ($P = 0.498$). Hence, the presence of liver diseases is not associated with the incidence of AKI in COVID-19 patients.

Diabetes mellitus
According to our results, no patient with the history of DM was detected in our patients (Table 1).

Comparison of the clinical symptoms in COVID-19 patients
The most common symptoms in COVID-19 patients were fever (47.1%), cough (37.6%), shortness of breath (36.1%), fatigue (30%), nausea and vomiting (13.7%), chill (10.3%), headache (9.5%), dizziness (5.3%), chest pain (3.8%), pharyngalgia (3.4%), and sputum production (1.5%). The incidence of fever was significantly higher in non-AKI patients compared to AKI patients ($P = 0.030$). Moreover, coughing was more frequent in the non-AKI patients with COVID-19 compared to AKI patients ($P = 0.001$). Other symptoms did not reveal any significant difference between AKI and non-AKI patients ($P > 0.05$). The incidence of AKI was significantly higher in COVID-19 patients with severe disease ($P = 0.002$) (Table 1).

Clinical and laboratory data analysis
Hematological parameters
Hematological parameters were compared between COVID-19 patients with AKI and without AKI. Our results revealed that the levels of white blood cells (WBCs) ($P < 0.001$) and neutrophils ($P < 0.001$) were significantly higher in AKI patients. However, hemoglobin (Hb) level was significantly lower in AKI patients compared to non-AKI patients ($P = 0.002$). Hence, the levels of WBC, neutrophils, and Hb can be considered as predictive

factors of AKI in COVID-19 patients (Table 2).

Coagulation parameters

Coagulation parameters were compared between COVID-19 patients with AKI and without AKI. The values related to prothrombin time (PT) ($P<0.001$), international normalized ratio (INR) ($P<0.001$), and D-dimer ($P<0.001$) were significantly higher in AKI patients with COVID-19 patients compared to the patients without AKI. There was no statistically significant difference in the levels of partial thromboplastin time (PTT) and triosephosphate isomerase-1 (TPI-1) between AKI and non-AKI patients. Therefore, PT, INR, and D-dimer might be predictive of AKI in patients with COVID-19 (Table 2).

Inflammatory parameters

Inflammatory biomarkers were compared in COVID-19 patients with AKI and without AKI. Our results demonstrated a significant rise at the levels of C-reactive

Table 2. Comparison of clinical and laboratory parameters between AKI and non-AKI COVID-19 patients

		Normal range	Median (IQR)			
			Total (n=263)	Non-AKI (n=132)	AKI (n=131)	*P* value
CBC	WBC	4000-11000	7100 (4700-10800)	5900 (3955-8500)	8100 (5600-12075)	<0.001
	Hb	14-17.5	13.4 (11.9-14.5)	13.75 (12.6-14.7)	12.95 (11.6-14.1)	0.002
	Lymph	1500-5000	1200 (800-1800)	1200 (800-1675)	1200 (800-1850)	0.695
	Neut	1500-8000	4800 (3200-7400)	4025 (2687.5-6350)	5588 (3707.7-9475)	<0.001
	Plt	150000-450000	211000 (160000-278000)	202000(149000-262000)	221000 (175000-283000)	0.111
Coagulation biomarkers	PT	12-14	13.9 (13-15.3)	13.2 (12.8-14.5)	14.2 (13.2-15.8)	<0.001
	PTT	24-40	34 (30-40)	31.8 (29.7-38.1)	34.6 (30-40.3)	0.360
	INR	<1.1	1.1 (1.02-1.24)	1.05 (1-1.18)	1.16 (1.08-1.29)	<0.001
	TPI1	0–0.5	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.355
	D-dimer	<0.5	820 (510-1791)	622.2 (209.5-903.7)	1410 (805-3160)	<0.001
Inflammatory biomarkers	CRP	<1+	2 (0-3)	1 (0-2)	2 (1-3)	0.024
	ESR	<15	24 (11-40)	19 (9-37.5)	28 (13.5-47.25)	0.070
Biochemical tests	LDH	109-245	394 (337-557)	394 (349-515)	400 (325-573)	0.629
	ALT	<41	21 (13-36)	22 (13.5-33)	20 (12-36.5)	0.597
	AST	<37	30.5 (20-40)	29 (20-37.75)	31 (20-56.75)	0.133
	ALP	80-306	172 (136-231)	156 (131-196)	201 (158-297)	<0.001
	Alb	3.5-5.5	4.5 (3.9-4.9)	4.65 (4.45-4.97)	4.05 (3.55-4.61)	<0.001
	Bill total	<1.2	0.83 (0.56-1.27)	0.72 (0.53-1)	0.9 (0.6-1.4)	0.083
	Bill direct	0.1-0.3	0.28 (0.18-0.52)	0.22 (0.15-0.31)	0.31 (0.2-0.67)	0.011
	CPK	Male: 39-308	77.5 (54-107.5)	74 (54.75-124.75)	81.5 (50.5-105)	0.882
		Female: 26-192	61.5 (39.75-121.5)	62 (34-124)	61 (40.5-116)	0.897
	BUN	8-24	17 (13-24.7)	14 (11-16)	24 (18-37)	<0.001
	Cr	0.7-1.4	1.02 (0.84-1.27)	1 (0.83-1.1)	1.1 (0.89-1.5)	0.013
	Ferritin	Male: 24 to 336	142 (85-325.5)	180 (85-374)	139 (77.5-343.25)	0.522
		Female: 11 to 307	85 (60-148)	64 (37-128.25)	114 (66-176)	0.018
	Mg	1.5-2.8	2.1 (1.8-2.2)	2.1 (1.8-2.2)	2 (1.8-2.3)	0.387
	Na	135-145	136 (133-138)	136 (133.75- 138)	135 (132-138)	0.134
	K	3.5-5.5	3.83 (3.56-4.17)	3.78 (3.39- 4)	4 (3.65-4.3)	<0.001
VBG	pH	7.35-7.45	7.40 (7.36-7.43)	7.41 (7.38-7.43)	7.38 (7.33-7.42)	0.002
	PCO2	40-52	38.1 (33.7-43.2)	38.1 (34.4-41.8)	37.8 (33.5-44.4)	0.783
	HCO3	21.8-26.9	23.2 (20.8-25.9)	23.8 (21.1-25.8)	22.4 (20.3-25.9)	0.432
	SPO2	<90%	95 (92-96)	95 (93-96)	94 (91-96)	0.002
Blood Pressure	SBP	<120 mm	126.5 (115-143)	124 (115.25-139.75)	130 (113.25-145)	0.189
	DBP	<80 mm	80 (71-89)	80 (75-87)	79 (67-89)	0.589
	HR	60-100	98 (83-116)	98 (84-112)	99 (82-120)	0.927

VBG: Venous blood gas; SBP: Spontaneous bacterial peritonitis; DBP: diastolic blood pressure; HR: Heart rate.
$P<0.05$ is considered statistically significant.

protein (CRP) ($P=0.024$). However, erythrocyte sedimentation rate (ESR) level had no statistically significant difference between AKI and non-AKI patients. Hence, the level of CRP can be considered as predictive factor of AKI in COVID-19 patients (Table 2).

Biochemical tests

Biochemical blood tests including lactate dehydrogenase (LDH), alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin (Alb), total bilirubin (Bili total), direct bilirubin (Bili direct), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine (Cr), ferritin, magnesium (Mg), sodium (Na), and potassium (K) were compared between COVID-19 patients with AKI and without AKI. The values related to ALP ($P<0.001$), Bili direct ($P=0.011$), BUN ($P<0.001$), Cr ($P=0.013$), and K ($P<0.001$) were significantly higher in AKI patients with COVID-19 patients compared to the patients without AKI. The ferritin level showed a significant rise in female patients with AKI compared to non-AKI patients ($P=0.018$), However, there was no significant increase in the level of Ferritin in male patients with AKI compared to patients without AKI. Albumin level was significantly lower in AKI patients compared to non-AKI patients ($P<0.001$). Therefore, abnormalities in the levels of ALP, Bili direct, BUN, Cr, K, ferritin (in females), and Albumin might be predictors of AKI in patients with COVID-19 (Table 2).

Venous Blood Gas

Venous blood gas (VBG) analysis in COVID-19 patients revealed a significantly decreased blood pH ($P=0.002$) and blood oxygen saturation (SPO_2) ($P=0.002$) in AKI patients compared to patients without AKI. Hence, pH and SPO_2 might be useful biomarkers in the prediction of AKI in COVID-19 patients (Table 2).

Blood pressure

The blood pressure of COVID-19 patients with AKI was compared to those without AKI and the results revealed no significant difference between the mentioned groups. Hence, changes in blood pressure are not associated with the incidence of AKI in COVID-19 patients (Table 2).

Discussion

In this study, we analyzed the clinical findings of 262 patients with COVID-19 that were admitted to Bohlool teaching hospital, Gonabad, Iran to explore whether the disease can result in impaired renal function and AKI. SARS-CoV-2 infects renal tubular epithelial cells by binding of its spike proteins to their ACE2 receptors, which might result in AKI, especially in the presence of viremia.[21] A previous study reported impairments in kidney function of COVID-19 patients with the clinical findings such as proteinuria, elevated serum BUN and creatinine, and abnormal imaging studies of kidneys with computed tomography (CT) scan.[22] Another study reported higher prevalence of kidney impairments among COVID-19 hospitalized patients and its association with higher risk of in-hospital death.[23]

Our results revealed that 49.6% of patients developed AKI during their hospitalization. Higher age was associated with higher incidence of AKI in COVID-19 patients, but the gender had no association with AKI. Past medical history of CVD was detected as a risk factor for the incidence of AKI, as opposed to liver diseases and DM. Patients with severe COVID-19 had a higher risk of developing AKI and fever and coughing occurred more frequently among non-AKI patients. Consistent with our study, a meta-analysis evaluating the incidence of AKI among COVID-19 patients, reported the higher incidence of AKI in severe cases of the disease. The mortality rate was also significantly higher in COVID-19 patients with AKI.[24]

Further investigations of laboratory findings revealed the association of hematological parameters such as higher WBC and neutrophil counts and lower Hb with higher risk of AKI in COVID-19 patients. Increases in the levels of coagulation and inflammatory biomarkers such as PT, INR, D-dimer, and CRP were significantly associated with AKI. Biochemical blood tests that were highly abnormal in AKI patients compared with non-AKI patients included abnormalities in the levels of ALP, Bili Direct, BUN, Cr, K, Ferritin (in females), and Alb. In VBG analysis, lower pH and SPO_2 were among the probable predictive factors of AKI in COVID-19 patients.

Similar to our results, in a retrospective cohort study of AKI in COVID-19 patients among three hospital in united states, older age, male sex and elevated WBC, CRP, and D-dimer were found to be highly predictive of AKI in COVID-19 patients.[13] A study conducted to compare the incidence of AKI in COVID-19 cases and non-COVID-19 controls suggested that initial respiratory rate, WBC count, LDH, neutrophil to lymphocyte ratio were correlated with severe AKI.[25] In another study, age, DM, immunosuppression, high D-dimer levels, lymphopenia, invasive mechanical ventilation, and use of vasopressor or inotropic agents were associated with higher risk of AKI.[26]

The incidence of AKI in COVID-19 patients has been reported to be 0.5%-29% in different studies. These heterogenous reports have been caused by differences in the sample sizes, severity of the cases, and the presence of comorbidities in the studies samples with various prevalence.[10,27,28] In our sample which consisted of 262 patients with COVID-19, 130 (49.6%) developed AKI. The higher incidence of AKI in our study might be due to the higher prevalence of underlying medical conditions including CVD, higher severity of the disease due to selection of the sample among the hospitalized patients, and older age of the participants. Nevertheless, a meta-analysis by Lim et al found no significant association

between CVD and AKI.[27]

As mentioned, severe disease, D-dimer, and lymphopenia increase risk AKI, which is also an independent cause of nosocomial mortality. Patients with AKI, due to being more severe than non-AKI, need more hospitalization in intensive care, mechanical ventilation, corticosteroids and vasopressors. The use of immunosuppressive drugs also increases the risk of developing AKI. Besides that, the vasopressors increase the risk of septic shock and hypoperfusion following cytokine storm and exacerbate kidney damage.[26,29]

Study Limitation

Our study has several limitations. first, the sample size of this cross-sectional study of admitted patients with COVID-19 was small and may not be representative of all hospitalized COVID-19 patients. Second, we could not acquire the baseline serum creatinine in some of our patients, and this might have introduced bias. Third, we could not identify that AKI was a complication of infection with SARS-CoV or an adverse effect of prescribed drugs at the time of hospitalization. Finally, some of the urine biological tests specific for AKI were not tested for the patients. Hence, identifying the exact mechanism of kidney injury was not possible. More studies are needed to determine the cause of AKI and its prognosis in bigger sample sizes. However, we were able to investigate consequences other than mortality and the relevant changes in blood biomarkers and clinical findings.

Conclusion

According to our results, age, the presence of CVD, and severe COVID-19 were associated were higher risk of developing AKI among hospitalized COVID-19 patients. Moreover, significantly abnormal levels of WBC, neutrophil count, Hb, PT, INR, D-dimer, CRP, ALP, Bili Direct, BUN, Cr, K, Ferritin (in female patients), Alb, pH, and SPO_2 were associated with higher incidence of AKI. However, the evidence is limited in due to our small sample size. Further studies with larger samples are required to confirm our results.

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Authors' Contribution

Conceptualization: Mohammad Darvishi, Sepideh KarkonShayan, Reza Akhavan-Sigari.
Data curation: Sepideh KarkonShayan, Mahdi Zarei.
Formal analysis: Reza Akhavan-Sigari.
Investigation: Juan Carlos Cotrina-Aliaga, Samaneh Atbaeitabari.
Methodology: Mohammad Darvishi , Sepideh KarkonShayan.
Project administration: Reza Akhavan-Sigari.
Resources: Mahdi Zarei.
Software: Sepideh KarkonShayan, Mahdi Zarei.
Supervision: Mohammad Darvishi, Sepideh KarkonShayan.
Validation: Juan Carlos Cotrina-Aliaga, Samaneh Atbaeitabari.
Visualization: Juan Carlos Cotrina-Aliaga, Samaneh Atbaeitabari.

Study Highlights

What is current knowledge?

- Measurement of WBC, neutrophil count, Hb, PT, INR, D-dimer, CRP, ALP, Bili Direct, BUN, Cr, K, Ferritin, Alb factors in patients with risk factors (old age, underlying disease, severe symptoms) It is essential.
- None of the tests performed well enough to be introduced as a stand-alone diagnostic test for COVID-19 or to prioritize patients for treatment. Clinical and paraclinical symptoms are used to provide a general picture of the patient's health status.

What is new here?

Acute kidney injury (AKI) in COVID-19 disease has received less attention from the medical system. Occurrence of AKI following covid-19 has a bad prognosis and causes an increase in intensive care unit hospitalization, an increase in the need for renal replacement therapy (RRT), and an increase in mortality. Therefore, it is very important that the treatment system has sufficient awareness and knowledge about the effect of the coronavirus on the kidneys and the effect of AKI on mortality, and if necessary, prevent the disease from progressing with timely diagnosis and supportive treatment.

Competing Interests

None of the authors have conflicts of interest to disclose.

Ethical Approval

This study was approved by the institutional ethics committee of Gonabad university of medical sciences (IRB number: IR.GMU.REC.1399.006).

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