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Investigation of acute kidney injury and related risk factors in patients with COVID-19

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ABSTRACT

Introduction: The 2019 recent coronavirus disease (COVID- 19) is a novel pandemic disease in the world. The main organ involved in this viral sepsis is the respiratory system.
Objectives: Regarding the expression of angiotensin-converting enzyme (ACE) receptors as entering route for virus' particles into cells, the kidney organ is another important target in this catastrophic sepsis. There is little data about renal complications and related risk factors in victims.
Patients and Methods: All patients with COVID-19 admitted to a referral and tertiary center (Shohada hospital, Khorramabad, Iran) were included in the study. The research was performed from February 20 to April 19, 2020. Diagnosis of patients was confirmed by COVID-19 upper respiratory sampling using real-time PCR. Patients' demographic data, clinical and laboratory variables were included in pre-designed questionnaires according to the considered factors; then all collected data was entered into SPSS-26 software and statistical analysis was performed.
Results: All COVID-19 patients included in the study were 232 cases. Out of them, 99 cases were female (42.7%) and 133 males (57.3%). Among patients, 19 cases had AKI (acute kidney injury); of these cases. Out of AKI patients, 12 (63.2%) were admitted to the ICU, whereas the mortality rate in patients with AKI was 63.2%. AKI was significantly associated with older age, ICU admission, and lower lymphocyte count. AKI occurrence was associated with the history of hypertension, or underlying kidney disease but hadn't a significant relationship with diabetes.
Conclusion: According to this study, age is an important risk factor for renal disease and poor outcomes in COVID-19 patients. Hence, old age patients should be given more attention. Concerning more prevalence of potassium disorders, further monitoring of hypokalemia or hyperkalemia is recommended. Considering, poor outcomes in patients with COVID-19 and AKI, nephrologist's consultation is necessary.

Implication for health policy/practice/research/medical education:
Coronavirus disease 2019 (COVID-19) is an ominous viral sepsis, resulting in multi-organ failure. Understanding of COVID-19 is evolving. Based on this study, AKI is a poor prognostic complication of hospitalized patients with COVID-19. Old age patients are more susceptible to AKI. Electrolyte monitoring included sodium and potassium disturbances should be more considered in patients.

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Introduction

The 2019 coronavirus disease (COVID- 19) is a recent ominous viral disease caused by the SARS-CoV-2 virus. COVID-19 has suddenly spread across the world. In March 2020 the World Health Organization (WHO), announced that the COVID-19 is a pandemic (1). The exact mechanism of action of the virus disease is still unknown. It is also discussed that the respiratory tract is the main system involved in disease. It is stated that COVID-19 binds to human angiotensin-converting enzyme 2 (ACE2) via its glycoprotein spike expressed on its envelope for entering the target cells. There is a great expression of ACE2 receptor on epithelia of the respiratory system, kidney, intestine and oral cavity (2-6). There are different studies about renal involvement in COVID-19 patients. For nephrologists, management of

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these patients is a challenging matter. A study showed that older age, severity of the disease, diabetes mellitus (DM), and positive fluid imbalance independently associated with acute kidney injury (AKI) (7-9).

In a review study, it was documented that AKI has several outcomes in subgroups of patients. In two subgroups of patients (severe type of COVID-19 and intensive care unit [ICU] patients), AKI was associated with higher mortality (10). Recent evidence suggests that the virus can directly invade the other organs aside from the respiratory system or cause an increase in inflammatory cytokines and lead to multi-organ failure such as AKI, acute liver injury, and coagulopathy (11).

The exact mechanism of action of COVID-19 and how it affects various systems in the body is not clear yet.

Objectives

Although it is theoretically suggested that COVID-19 has a significant effect on various organs of the body and kidneys, but from a laboratory point of view, this issue is still debatable. Studies also show that renal complications and AKI are more noticeable for critical and ICU patients, and the importance of this issue indicated the need for further research.

In this study, patients with COVID-19 disease were evaluated for renal outcomes and related risk factors. We assessed and analyzed the incidence of AKI, renal complications and other associated comorbidities according to the clinical and laboratory information of the patients.

Patients and Methods

Study design and data collection

All patients with COVID-19 admitted to a referral and tertiary hospital (Shohada hospital, Khorramabad, Iran), were included in the study. The study was performed from February 20 to April 19, 2020. During this period, demographic, clinical and laboratory information of patients were extracted from the recorded data. Diagnosis of patients was confirmed by COVID-19 upper respiratory sampling using real-time reverse transcription polymerase chain reaction (RT-PCR) methods.

Diagnostic methods

All admitted patients in ICU were critically ill subjects, which need to perform either mechanical ventilation or intensive care (because of an underlying problem and severe disease and hypoxia).

The diagnosis of AKI is based on the KDIGO guidelines (Kidney Disease: Improving Global Outcomes). AKI is identified as one of the following criteria: (1) serum creatinine concentration increase ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours, (2) serum creatinine concentration rise to ≥1.5 times baseline within the previous 7 days; or (3) a urine volume ≤0.5 mL/kg/h for 6 hours (12).

The history of kidney disease for patients was divided into some groups; no history of previous kidney disease, kidney transplant, chronic kidney disease (CKD) and history of some frequent risk factors for kidney disease including, DM, HTN (hypertension), renal calculi or history of previous urinary obstructive disease.

Oxygen saturation (O_2sat %) was measured at the beginning of the patient admission by pulse oximetry device and repeated frequently.

Statistical analysis

Patients' demographic data, clinical and laboratory variables were included in pre-designed questionnaires according to the considered factors; then all collected data was imported to SPSS 26 software and statistical analysis was performed.

Chi-square test was used to calculate *P* value for variables such as gender and t-test was performed for variables such as age. Odds ratio (OR) and confidence intervals (CIs) for some variables (such as age) were calculated by logistic regression. For other variables, crosstabs (Mantel–Haenszel test) was performed.

Results

Around 232 COVID-19 patients were included in the study. Out of all patients 99 cases were female (42.7%) and 133 (57.3%) were male. The mortality rate in all patients was 15.9% (37 cases) .Among patients 19 cases had AKI; of these cases, 11 (57.9%) were males and 8 (42.1%) females.

Out of AKI patients, 12 (63.2%) were admitted to the ICU, whereas the mortality rate in patients with AKI was 63.2%.

In this study, we evaluated age, gender, mortality rate, admitted ICU patients, hemoglobin (Hb) level, white blood cell (WBC) count, lymphocyte count, platelet count, serum creatinine, serum C-reactive protein (CRP), serum creatine phosphokinase (CPK), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), serum sodium level, serum potassium level, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP) and use of mechanical ventilation (Table 1).

We assessed the relationship between these factors and the incidence of AKI in hospitalized patients (Table 1). AKI was significantly associated with older age ($P<0.0001$), mortality ($P<0.0001$), ICU admission ($P<0.0001$), hemoglobin level ($P=0.001$), maximum WBC ($P<0.0001$), lower lymphocyte count ($P=0.002$), maximum ESR ($P=0.001$), maximum LDH ($P=0.002$), sodium disorder ($P=0.007$), potassium disorder ($P<0.0001$), mechanical ventilation ($P<0.0001$), duration of admission ($P=0.001$), history of hypertension ($P<0.0001$), history of ischemic heart disease ($P=0.004$), history of chronic obstructive lung disease (0.023),

Table 1. Suspected related factors to AKI in COVID-19 patients

Variables	AKI (n=19)	No AKI (n=213)	*P* value	Missing value	OR (95% CI)
Age	68.10 ± 16.2	51.42 ± 17.2	<0.0001[a]	0 (0)	
Gender					
Male	11 (57.9%)	122 (57.3%)	0.958[b]	0 (0)	
Female	8 (42.1%)	91 (42.7)%)			
Mortality					
Yes	12 (63.2%)	25 (11.7%)	<0.0001[b]	0 (0)	12.89 (4.63, 35.79)[c]
No	7 (36.8%)	188 (88.3%)			
ICU admission					
Yes	12 (63.2%)	30 (14.1%)	<0.0001[b]	0 (0)	10.45 (3.81, 28.68)[c]
No	7 (36.8)	183 (85.9%)			
Hemoglobin (g/dL)	12.04 ± 2.95	14.13 ± 2.06	<0.0001[a]	14 (6%)	
Maximum WBC (cells/µL)	8789.47 ± 7028.7	5772.27 ± 2713.4	<0.0001[a]	11 (4%)	
Lower lymphocyte count (cells/µL)	815.61 ± 326.29	1361.97 ± 720.23	0.002[a]	24 (10%)	
Platelet count (10^3/µL)	178.10 ± 95.73	204.14 ± 87.94	0.222[a]	15 (6%)	
Maximum creatinine (mg/dL)	2.15 ± 1.37	0.88 ± 0.31	<0.0001[a]	28 (12%)	
Maximum CRP			0.087[b]	37 (15.9%)	
Negative	10 (71%)	66 (36%)			
1+	2 (14%)	34 (18%)			
2+	2 (14%)	59 (32%)			
3+	0 (0%)	22 (12%)			
Maximum CPK (U/L)	258.48 ± 250.87	240.23 ± 731.34	0.919[a]	24 (10%)	
Maximum ESR (mm/h)	60.00 ± 31.88	33.15 ± 23.54	0.001[a]	92 (39%)	
Maximum LDH (U/L)	912.05 ± 303.53	682.36 ± 297.16	0.002[a]	17 (17%)	
Sodium disorders (meq/L)					
Low (<135)	2 (11.1%)	5 (2.9%)	0.007[b]	39 (16.8%)	
Normal	13 (72.2%)	164 (93.7%)			
High (>145)	3 (16.7%)	6 (3.4%)			
Potassium disorders (meq/L)					
Low (<3.5)	1 (5.6%)	23 (13.1%)	<0.0001[b]	39 (16.8%)	
Normal	13 (72.2%)	149 (85.1%)			
High (>5.5)	4 (22.2%)	3 (1.7%)			
Maximum AST (U/L)	24.75 ± 15.03	46.02 ± 77.24	0.34[a]	91 (39%)	
Maximum ALT (U/L)	24.91 ± 18.34	55.14 ± 69.34	0.13[a]	92 (39%)	
Maximum ALP (U/L)	187.10 ± 110.57	190.03 ± 108.23	0.93[a]	111 (47%)	
Duration of admission (days)	9.67 ± 6.96	5.75 ± 4.41	0.001[a]	0 (0)	
Mechanical ventilation					
Yes	11 (57.9)	16 (7.5%)	<0.0001[b]	0 (0)	16.93 (5.96, 48.06)[c]
No	8 (42.1)	197 (92.5%)			
History of DM					
Yes	5 (26.3%)	27 (12.7%)	0.099[b]	0 (0)	
No	14 (73.7%)	186 (87.3%)			
History of HTN					
Yes	11 (57.9%)	35 (16.4%)	<0.0001[b]	0 (0)	6.99 (2.62, 18.63)[c]
No	8 (42.1%)	178 (83.6%)			

Table 1. Continued

Variables	AKI (n=19)	No AKI (n=213)	*P* value	Missing value	OR (95% CI)
History of IHD					
Yes	7 (36.8%)	27 (12.7%)	0.004[b]	0 (0)	4.01 (1.45, 11.09)[c]
No	12 (63.2%)	186 (87.3%)			
History of COPD					
Yes	2 (10.5%)	4 (1.9%)	0.023[b]	0 (0)	6.14 (1.04, 36.01)[c]
No	17 (89.5%)	209 (98.1%)			
Underlying kidney disease					
No	16 (84.2%)	208 (97.7%)			
Transplant	1 (5.3%)	1 (0%)	0.001[b]	0 (0)	7.8 (1.7, 35.6)[c]
CKD	2 (10.5%)	4 (1.9%)			
Renal calculi	0 (0%)	1 (0.5%)			
First oxygen saturation	84.31 (%) ± 6.7	91.7 (%) ± 7.1	<0.0001[a]	0 (0)	

Abbreviation: AKI, acute kidney injury; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; WBC, white blood cell; CRP, C-reactive protein; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.
Hb; Hemoglobin (anemia was less than 14 for men and less than 12 for women).
[a] The *t* test was performed to calculate the *P* value (significant *P* value is <0.05).
[b] The chi-square was performed to calculate the *P* value (significant *P* value is <0.05).
[c] Crosstabs was used to calculate OR.

underlying kidney disease ($P=0.001$), and first oxygen saturation ($P<0.0001$). Confidence interval (CI) and odds ratio (OR) were calculated for some of the significant factors (Table 2).

Discussion

In our study, according to KDIGO criteria, 8.1% developed AKI while we had a total of 37 deaths (15.9%). In other studies frequency of AKI in COVID-19 patients was different, from 11% in the study by Wang et al (13), to 0.5% in the study by Guan et al (7). We supposed these different results may be due to, race of patients, comorbidity in COVID-19 patients, illness severity and diagnostic criteria for AKI diagnosis.

The majority of studies showed that kidney organ is a main target for coronavirus disease. Studies have mainly referred to three categories of injuries; damage caused by released inflammatory cytokines (such as IL-6), organ crosstalk (viral myocarditis, rhabdomyolysis, alveolar damage and renal medullary hypoxia) and systemic effects of viremia, (positive fluid balance and endotoxins) (14).

Table 2. Logistic regression analysis in some numerical data for odds ratios

Variables	*P* value	OR	95% CI for OR	
			Lower	Upper
Age	0.571	1.018	0.958	1.081
Hemoglobin	0.912	1.000	0.991	1.008
Maximum WBC	0.447	1.000	1.000	1.000
Lowest lymphocyte count	0.337	0.999	0.996	1.002
ESR	0.084	1.032	0.996	1.069
Maximum LDH	0.925	1.000	0.996	1.004
Duration of admission	0.840	1.020	0.842	1.236
First oxygen saturation	0.428	0.970	0.898	1.047

According to our results, most patients with AKI were critically ill patients and admitted to ICU, and AKI was also significantly associated with more ICU admissions. Correlation between AKI and mechanical ventilation requirement was significant. In our study, mortality rate in AKI patients compared to non-AKI patients was significantly more common. In a recent study, out of 116 COVID-19 patients, 21 (18.1%) developed AKI and compared to non-AKI patients they had more severe organ dysfunction, higher stage of disease status, higher level of respiratory support and also higher mortality rate (57.1% versus 12.6) (15). In the study by Murugan and Kellum, AKI is a well-recognized factor of poor prognosis (16).

In another study in China, in 138 COVID-19 patients, the incidence of AKI was 3.8 % and the ICU admission was 8.3% (17). This evidence may indicate a relationship between critical condition (ICU admission) and renal complications such as AKI.

Concerning poor prognosis role of AKI for all patients in hospitals and our results about AKI prevalence in COVID-19 patients, it necessitates paying attention to these groups of patients.

Another purpose of our study was determination of important risk factors for AKI in COVID-19 patients. Our study indicates that patients with higher mean age are more likely to develop AKI. We also found that the incidence of AKI was not higher in men. Similarly, a study in Wuhan which was included 701 patients, indicated that higher mean age is associated with higher creatinine baseline ($P<0.001$). In their study, men had higher baseline creatinine and by increasing duration of hospitalization, the incidence of AKI was higher (18). Likewise in our study, the relationship between duration of admission and AKI was significant.

In the US, the case fatality rate was highest among patients aged ≥85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%), 55 to 64 years (1% to 3%), 20 to 54 years (<1%), and ≤19 years (no deaths). Patients aged ≥65 years accounted for 80% of deaths (19). The occurrence of AKI has been reported in 25% of critical COVID-19 patients especially in patients with underlying disease (20).

Moreover a study in china indicated that male gender and higher mean age significantly associated with severe and critical types (21). Conversely, a multicenter study showed that male gender and higher mean age are not associated with higher risk for developing critical and severe type of COVID-19, though indicates that with increase duration of hospitalization the risk of AKI incidence was significantly higher (15). According to the results of available studies, the relationship between gender and mean age with occurrence of AKI is still unclear but it seems that duration of admission has an effect on AKI incidence in admitted patients.

Our study demonstrated that some laboratory factors had a significant relationship with AKI such as decreased level of Hb, maximum WBC count, lower lymphocyte count, ESR, LDH, and first oxygen saturation.

We also found some other factors had no significant correlation with AKI incidence such as AST, ALT, ALP, platelet, CPK and CRP. A study in china who diagnosed the AKI based on KDIGO criteria indicated that critically ill patients had higher risk for incidence of AKI; however there was no reliable correlation between AKI and WBC count, lymphocyte count, CRP and ESR (15). Furthermore, in a study in Wuhan, patients were divided into survivors and non-survivors. The results showed that decreased lymphocyte count, lower platelet count and higher creatinine value are associated with a higher incidence of mortality. Other laboratory factors included such as AST, ALT, Hb and WBC count had no correlation with patient's survival. In their study, AKI was the last pre-death complication and AKI was significantly related to mortality ($P<0.001$) (22).

Based on an evaluation of 333 patients in Tongji hospital, 35 (10.5%) of cases developed AKI, the mortality was generally higher in AKI patients (11.2 versus 1.2). Their study showed that decrease in oxygen saturation is related to critically and severity condition in COVID-19 patients ($P<0.001$). They also found that increase in CRP, ESR, AST, ALT, serum creatinine and decreased lymphocyte count was associated with critically and severe condition ($P<0.05$)(21).

Clearly, there is a variety of information about relationship between laboratory data and AKI in COVID-19 patients (23). However, decreased lymphocyte counts, increased LDH and increased basal creatinine are surrogate markers for AKI occurrence and severe poor outcome in covid patients.

Regarding mechanisms of viral infection, disturbances in immune systems are vital risk factors for higher probability of catastrophic sepsis syndrome. Hence, the history of chronic disease should be considered in management of subjects. Some studies documented that, patients with CKD are vulnerable to a more severe form of COVID-19 and experience a higher mortality rate than the general population (24).

Our review of hospitalized patients indicated that AKI occurrence is associated with history of hypertension, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD) and underlying kidney disease ($P<0.05$) but it has no significant relationship with diabetes. The study conducted by Cui et al indicated that AKI incidence had no correlation with respiratory disease, cardiac disease, hypertension, diabetes and CKD (15). Other study in China showed that critical ill patients had more chance for AKI occurrence ($P<0.05$) and also critical ill patients more than other patients had history of hypertension and diabetes (21). Therefore, whether common diseases such as hypertension, COPD, IHD and diabetes can influence patient prognosis and AKI occurrence, it still needs further studies.

For the nephrologist, the COVID-19 pandemic raises many questions about management of complications (25).

Proximal tubule in the kidney is a target site for virus involvement. There are some opinions about electrolytes imbalances or proteinuria in patients with COVID-19 with or without AKI (26).

Hypokalemia in some studies was reported. In a cohort of 175 patients infected with COVID-19, hypokalemia with increased kaliuresis, as a marker of renin–angiotensin–aldosterone system (RAAS) activation, was associated with the most severe forms of COVID-19 infections requiring ICU admission. Indeed, 93% of patients hospitalized in ICU had hypokalemia at admission (27).

In our study out of COVID-19 patients non-complicated with AKI, 13% had hypokalemia which was not significant. However, concerning life threatening complications of even mild electrolyte disorders in hospitalized patients, special attention should be considered to electrolytes imbalance in these patients. Finally, further studies with larger sample size are recommended.

Conclusion

We aimed to evaluate related factors to AKI in hospitalized COVID-19 patients and to recognize kidney complications. Most important result was higher incidence of AKI in critical ill and ICU admitted patients. AKI and other renal complications can be due to critical condition of patients or direct invasion of the virus or even both of these mechanisms (28).

In addition, according to the high rate of mortality in AKI patients perhaps it can be concluded that AKI is the last complication before death (22), even after liver and heart complications. The AKI incidence was significantly related to the older age and mortality, and this point can justify critically condition of patients with these complications. Regarding susceptibility of some chronic disease such as DM or CKD to AKI in COVID-19 patients, further attention should be considered in management of these groups.

Concerning, the correlation of AKI and mortality in COVID-19 patients and frequency of renal complication in these viral sepsis cases, group management and consultation with nephrologists in hospitalized patients is recommended especially in ICU admitted patients.

Limitations of the study

Our study has some limitations. This research was a retrospective study and, in some patients, complete and accurate laboratory information was not available. There was incomplete data about urinary finding in our research (hematuria or proteinuria). Because of the retrospective nature of the research, it was not possible to manage patients with AKI and investigate the effect of management and treatment of AKI on patient prognosis. Our recommendation for future study is monitoring patients during hospital treatment and also evaluation the effect of treatment and management of AKI on patient mortality and prognosis.

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Authors' contribution

BH contributed to conceptualization, methodology and also validation of the study. AZM participated in formal analysis, investigation and resources of study. MR participated in data curation, writing—original draft preparation and writing—review and editing. BH and MR contributed equally to visualization, supervision and project administration. AZM contributed to funding acquisition.

Conflicts of interest

The authors declared no competing interests.

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Lorestan University of Medical Sciences (ethical code# IR.LUMS.REC.1399.025) confirmed the study. The informed consent was taken from the patients. This study was extracted from M.D thesis of Mahdi Razani at this University (Thesis# 1397-1-99-1399). Moreover, ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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