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Are we aware of COVID-19-related acute kidney injury in intensive care units?

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Abstract. – OBJECTIVE: Coronavirus disease-19 (COVID-19) primarily affects the respiratory system. In some cases, the heart, kidney, liver, circulatory system, and nervous system are also affected. COVID-19-related acute kidney injury (AKI) occurs in more than 20% of hospitalized patients and more than 50% of patients in the intensive care unit (ICU). In this study, we aimed to review the prevalence of COVID-19-related acute kidney injury, risk factors, hospital and ICU length of stay, the need for renal replacement therapy. We also examined the effect of AKI on mortality in patients in the ICU that we treated during a 1-year period.

PATIENTS AND METHODS: The files of patients with COVID-19 (n=220) who were treated in our ICU between March 21st, 2020, and June 1st, 2021, were analyzed retrospectively. Demographic data of the patients, laboratory data, and treatments were examined. Patients were divided into two groups, group I patients without AKI and, group II patients with AKI. The patients with AKI were evaluated according to the theKidney Disease Improving Global Outcomes (KDIGO) classification and were graded.

RESULTS: Of the 220 patients included in the study, 89 were female and 131 were male. The mean age of patients with AKI (70.92±11.28 years) was statistically significantly higher than among those without AKI (58.87±13.63 years) (p<0.001). In patients with AKI, ICU length of stay, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, initial lactate levels, need for mechanical ventilation, duration of mechanical ventilation, and secondary infection rates were found to be statistically significantly higher. Discharge rates from the ICU in patients without AKI were statistically higher (75.3% *vs.* 26.6%), and mortality rates were significantly higher in patients with AKI (67.8% *vs.* 14.3%).

CONCLUSIONS: Various studies conducted have shown that patients with COVID-19 are at risk for AKI, and this is closely related to age, sex, and disease severity. The presence of AKI in patients with COVID-19 increases mortality, and this is more evident in patients hospitalized in the ICU. In our study, the prevalence of AKI was higher in older patients with high APACHE II scores and initial lactate levels. Comorbidities such as hypertension, chronic kidney disease, and coronary artery disease in patients with AKI were higher than in those without AKI.

Key Words:
COVID-19, Intensive care unit, Acute kidney injury.

Introduction

Unexplained acute respiratory disease was first detected in the Chinese province of Wuhan in December 2019. Then, on February 12th, the International Committee on Virus Taxonomy declared that the cause of this disease was a new coronavirus, and named this virus Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). The World Health Organization (WHO) named the disease caused by this virus corona virus disease 2019 (COVID-19)[1]. The disease quickly spread all over the world, causing a pandemic and becoming a serious threat to human health. As of the end of October 2021, more than 249 million cases and more than 5 million deaths have been detected worldwide.

SARS-CoV-2 is transmitted through droplets or direct contact[2,3]. The virus primarily attacks respiratory tracts cells, which is why dyspnea is the main clinical finding in most patients. In some cases, the heart, kidney, liver, circulatory system, and nervous system are also affected[4,5]. Renal failure in patients with COVID-19 may be caused by rhabdomyolysis, hypoxemia, dehydration, underlying diseases, or non-steroidal anti-inflammatory drugs (NSAIDs) intake[6]. Initial reports of COVID-19-related acute kidney injury (AKI) were negligibly insignificant[7,8]. However, with increasing evidence, it has been observed that AKI is more common in patients with

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COVID-19 hospitalized in clinics and intensive care units (ICUs). Although reported rates of AKI are highly variable, available evidence indicates that more than 20% of hospitalized patients and more than 50% of patients in ICU_s are affected by this disease[9-11].

In this study, we aimed to review the prevalence of COVID-19-related AKI, risk factors, hospital and ICU length of stay, and the need for renal replacement therapy. The effect of AKI on mortality in patients we treated during a 1-year period in our ICU was also examined.

Patients and Methods

The study was initiated after obtaining the approval of the Ministry of Health and the Local Ethics Committee. Patients with COVID-19 whose diagnosis was confirmed in Polymerase Chain Reaction (PCR) test, were included in the study. A retrospective analysis was performed of the files of patients who were followed up and treated in the anesthesia ICU for more than 7 days between March 21st, 2020, and June 1st, 2021. Demographic data of the patients, laboratory data (hemogram, inflammatory markers, blood urea nitrogen, creatinine, glomerular filtration rate values) during the treatment process in the ICU,and the treatments given were examined. Patients who did not develop AKI were defined as group I, and patients who developed AKI were defined as group II.The laboratory data of the patients in group II were evaluated according to the Kidney Disease Improving Global Outcomes (KDIGO) classification and graded. Patients with a creatinine increase of 1.5-1.9 times the basal value were categorized as grade I AKI, patients with a creatinine increase 2-2.9 times their baseline values were considered grade II AKI, and patients with a creatinine increase more than 3 times the basal value or Cre>4 mg/dL were categorized as grade III AKI. Patients with COVID-19 PCR (-), patients discharged from the ICU in less than 72 hours, and those with missing data were excluded from the study.

Study Group

All patients who were treated in the COVID-19 ICU (n=222) between the dates specified in the study plan were included in the study. Only two patients who died within the first 72 hours of admission to the ICU were excluded from the study.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, and categorical data are presented as numbers and percentages. In the intergroup analysis of continuous variables, normality analyses were performed using the Kolmogorov-Smirnov goodness of fit test. The independent samples *t*-test was used in the analysis of data that had normal distribution, and the Mann-Whitney U test was used in the analysis of data that were not distributed normally. Comparisons of categorical data were made using the Chi-square test (Fisher's exact test when necessary). Analyses were performed using the IBM SPSS version 22.0 statistical software (IBM Corporation, Armonk, NY, USA). The level of statistical significance was accepted as $p<0.05$.

Results

Of the 220 patients included in the study, 89 were female and 131 were male. The mean age of the patients was 66.70±13.42 years.The mean age of patients with AKI (70.92±11.28 years) was statistically significantly higher than among those without AKI (58.87±13.63 years) ($p<0.001$). There was no statistically significant difference between the groups in terms of average body mass index (BMI) values and sex ratios ($p=0.470$, $p=0.740$, respectively). The nutricscore value was 3 and above was 80.2% in the AKI group, and 59.7% in the non-AKI group ($p<0.001$). It was observed that the probability of developing AKI was higher in patients with hypertension (HT), coronary artery disease (CAD), and chronic kidney disease (CKD) ($p=0.024$, $p=0.003$ and $p=0.029$, respectively) (Table I).

In patients with AKI, ICU length of stay, APACHE II scores, initial lactate levels, need for mechanical ventilation, duration of mechanical ventilation, and secondary infection rates were found to be statistically significantly higher (Table II). The rate of patients with procalcitonin levels ≥2 in patients with AKI (66.2%) was significantly higher (18.2%) than in patients without AKI ($p<0.001$). Discharge rates from the ICU were statistically higher in the group without AKI (75.3% *vs.* 26.6%), and mortality rates were significantly higher in group with AKI (67.8%) *vs.*14.3%) ($p<0.001$) (Table II).

Lymphopenia, C-reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), and procalcitonin (PCT) levels in patients with AKI [320(30-1770), 275 (60.45-563), 1628 (84-

Table I. Comparison of groups in terms of socio-demographic and clinical characteristics.

	Group I (without AKI)	Group II (with AKI)	Total	p
Number, %	77 (35%)	143 (65%)	220 (100%)	
Age (years) (mean ± SD)	58.87 ± 13.63	70.92 ± 11.28	66.70 ± 13.42	< 0.001*
BMI(kg/m^2) (mean ± SD)	29.85 ± 5.80	29.27 ± 5.50	29.47 ± 5.60	0.470*
Sex (n, %)				0.740**
Female	30 (39.0%)	59 (41.3%)	89 (40.5%)	
Male	47 (61.0%)	84 (58.7%)	131 (59.5%)	
Nutricscore (n, %)				< 0.001**
0	24 (31.2%)	17 (12.0%)	41 (18.7%)	
1	6 (7.8%)	11 (7.7%)	17 (7.8%)	
2	1 (1.3%)	0 (0.0%)	1 (0.5%)	
3	39 (50.6%)	56 (39.4%)	95 (43.4%)	
4	7 (9.1%)	58 (40.8%)	65 (29.7%)	
COPD (n, %)	6 (7.8%)	23 (16.1%)	29 (13.2%)	0.097**[a]
Asthma (n, %)	11 (14.3%)	13 (9.1%)	24 (10.9%)	0.261**[a]
HT (n, %)	33 (42,9%)	84 (58,7%)	117 (53,2%)	0.024**
DM (n, %)	24 (31.2%)	61 (42.7%)	85 (38.6%)	0.095**
CAD (n, %)	9 (11.7%)	42 (29.4%)	51 (23.2%)	0.003**[a]
CVD (n, %)	0 (0.0%)	6 (4.2%)	6 (2.7%)	0.093**[a]
CKD (n, %)	0 (0.0%)	9 (6.3%)	9 (4.1%)	0.029**[a]
Immunosuppression (n, %)	5 (6.5%)	5 (3.5%)	10 (4.5%)	0.325**[a]

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CVD: Cerebro vascular diseases, CKD: Chronic kidney disease.

18792), 5830 (780-115400), 712 (290-14280), and 7.5 (0.03-190)], were found to be statistically significantly higher compared with those without AKI[440 (100-2370), 218 (26-487), 914 (35-4687), 3800 (440-59630), 564 (233-1326) and 0.24 (0-51)] respectively (p<0.001).There was no statistically significant difference between the groups in terms of hemoglobin, platelet,and lymphocyte values (Table III).

Mortality rates were significantly higher in patients with COVID-19 related AKI (67.8% *vs.*14.3%), and this elevation increased in parallel with AKI grade (grade I 59.5%, grade II 80.6%, grade III 100%) (Table IV).

Discussion

The first reports of COVID-19 focused on acute respiratory distress syndrome (ARDS) in patients. Later, it was understood that various kidney problems, primarily AKI, could be seen in many patients with COVID-19. Different mechanisms have been proposed for the formation of COVID-19-related AKI. The presence of high fever, shock, dehydration, hypoxemia and the use of NSAIDs, antiviral drugs, antibiotics and various drugs with the potential for nephrotoxicity in patients with COVID-19 can cause AKI. One of these mechanisms is through direct damage to the intrinsic renal cells by SARS-CoV-2[12,13]. Advanced age, and some comorbidities, such as diabetes mellitus and hypertension, may induce or aggravate the occurrence and progression of AKI[14]. In our observational case-control study, patients in the group developing AKI had advanced age. The frequency of HT, CAD, and CKD was also higher in these patients. These findings support the literature.

Other proposed mechanisms for SARS-CoV-2-mediated renal damage are prothrombotic coagulopathy, nephrotoxic mediators released during cytokine storm, and disturbances in the angiotensin aldosteronesystem[15]. In our study, the statistically significant increase in inflammatory markers in all patients with AKI suggested that the predominant cause of AKI in our patients was the hyperinflammatory process. The presence of HT in 84% of patients indicate that HT may have provoked the development of AKI in these patients.

The prevalence of AKI in several published studies about hospitalized patients with COVID-19 and AKI varies widely due to differences in hospital admission criteria, differences in the definition of AKI, ethnic differences, and other variables. Studies also have large heterogeneity in terms of demographic

Table II. Comparison of the groups in terms of clinical parameters related to hospitalization and intensive care unit stay.

	Group I (without AKI) (n = 77)	Group II (with AKI) (n = 143)	p
Hospital LOS (days) (mean ± SD)	22.48 ± 14.14	22.92 ± 12.94	0.818*
ICU LOS (days) [median (min-max)]	11 (1-84)	15 (1-65)	**0.007****
Ward LOS (days) [median (min-max)]	1 (0-20)	2 (0-16)	0.471**
APACHE II score [median (min-max)]	16 (4-38)	19 (8-54)	**< 0.001****
P/F ratio[median (min-max)]	88 (11-400)	82 (42-352)	0.131**
Initial lactate level [median (min-max)]	1.31 (0.35-5.86)	1.66 (0.08-12.2)	0.003**
Mechanical ventilation duration (days) [median (min-max)]	0 (0-84)	10 (0-65)	**< 0.001****
Need for mechanical ventilation (n, %)	28(36.4%)	107 (74.8%)	**< 0.001*****
Discharge rate from ICU	58 (75.3%)	38 (26.6%)	**< 0.001*****
Secondary infections (n, %)	15 (19.5%)	56 (39.2%)	**0.004***[a]
Type of infection (n, %)			0.305***
Ventilator-associated pneumonia	9 (60,0%)	44 (80,0%)	
Urinary tract infections	1 (6,7%)	1 (1,8%)	
Catheter-associated infections	2 (13,3%)	6 (10,9%)	
Circulatory system infections	3 (20,0%)	3 (5,5%)	
Surgery-associated infections	0 (0,0%)	1 (1,8%)	
Causative microorganisms (n, %)			0.430***
No microorganisms	1 (7.1%)	1 (1.8%)	
K. Pneumoniae	0 (0.0%)	3 (5.5%)	
P. Aeruginosa	0 (0.0%)	1 (1.8%)	
S. Aureus	1 (7.1%)	1 (1.8%)	
Fungal infection	1 (7.1%)	1 (1,8%)	
Gram + microorganisms	1 (7.1%)	0 (0.0%)	
A. Baumannii	11 (78.6%)	48 (87.3%)	
Procalcitonin ≥ 2 (n, %)	14 (18.2%)	94 (66.2%)	**< 0.001*****
D-dimer > 1000 (n, %)	70 (90.0%)	136 (95.1%)	0.253***[a]
Chronic kidney disease (n, %)	0 (0.0%)	19 (13.3%)	**< 0.001***[a]
Diuretic usage (n, %)	31 (40.3%)	91 (63.6%)	**0.001***[a]
IV contrast agents (n, %)	8 (10.4%)	19 (13.3%)	0.668***[a]
NSAIDs (n, %)	5 (6.5%)	3 (2.1%)	0.132***[a]
Exitus (n, %)	11 (14.3%)	97 (67.8%)	**< 0.001*****

*Independent samples *t*-test. ** Mann Whitney U test. ***Chi-square test (aFisher's exact test). Hospital LOS: Length of stay in hospital, ICU LOS: Length of stay in the intensive care unit, Ward LOS: Length of stay in the ward (pre ICU), APACHE II score: Acute physiology and chronic health evaluation II score, P/F ratio: PaO_2/FiO_2 at admission to ICU, IV: Intravenous, NSAIDs: Non- steroidal anti-inflammatory drugs.

data, disease severity, risk factors, morbidities, and mortality[16].

When the five studies conducted in the United States of America (USA), [Hirsh et al[17] (n=5499), Chan et al[18] (n=3235), Mohamed et al[19] (n=575), Süleyman et al[20] (n=355) and Zahit et al[21] (n=469)],

Table III. Comparison of groups in terms of inflammatory markers.

	Group I (without AKI) (n = 77)	Group II (with AKI) (n = 143)	p
Platelet	203 (57-663)	204 (32-605)	0.823*
Lymphocite	440 (100-2370)	320 (30-1770)	< 0.001*
Ferritin	914 (35-4687)	1628 (84-18792)	< 0.001*
D-dimer	3800 (440-59630)	5830 (780-115400)	< 0.001*
CRP	218 (26-487)	275 (60.45-563)	< 0.001*
LDH	564 (233-1326)	712 (290-14280)	< 0.001*
PCT	0.24 (0-51)	7.5 (0.03-190)	< 0.001*

*Mann Whitney U Test. Hemoglobin (gr/dL), Platelet ($10^3/\mu L$), Lymphocite ($10^3/\mu L$), Ferritin (ng/ml), D-dimer (ng/ml). CRP: C reactive protein (mg/L), LDH: Lactate dehydrogenase (IU/L), PCT: Procalcitonin (ng/ml).

Table IV. Mortality rates of patients with COVID-19.

	Group I (without AKI)	Group II (with AKI)			
	Total	Grade I	Grade II	Grade III	Total
Patient (n,%)	77 (35%)	98 (44.5%)	41 (18.6%)	4 (1.8%)	143 (65%)
Exitus (n,%)	**11 (14.3%)**	**58 (59.7%)**	**35 (85.36%)**	**4 (100%)**	**97 (67.8%)**

were examined together, some important results emerged. Some of the results of these studies are summerized in the Table V (Table V).

In these studies, the prevalence of AKI in hospitalized patients with COVID-19 varies between 27% and 45%. The prevalence was higher in patients in the ICU (61-76%). Mortality rates in hospitalized patients with COVID-19 without AKI are quite low in most cases, around 6%. The mortality rate in patients with COVID-19-related AKI varies between 35-71%. Mortality in patients in stage III is higher than in patients in stage I and stage II (52-88%)[16], regardless of whether they have renal replacement therapies.In our study, 65% of the patients with COVID-19 who were treated in our ICU had AKI. The mortality rate of our patients with AKI was significantly higher than in patients without AKI (67.8% *vs.* 14.3%). The increase of mortality rates wasin parallel with AKIgrade (grade I 59.5%, grade II 80.6%, grade III 100%). Our observation is consistent with the data of the studies mentioned above.

After the importance of the relationship between COVID-19 and AKI was understood, studies on COVID-19 AKI increased and various meta-analyses were published. The first meta-analysis by Lin et al[22] was published in the British Medical Journal in November 2020. In this meta-analysis, the data of 79 articles and 49692 patients (30974 Asian, 3213 European and 15480 North American patients) were examined, and it was observed that the prevalence of AKI increased with the increase in the severity of the COVID-19 infections, and the European and North American patients were older than Chinese patients (>60 years: 62.3% *vs.* 46.5%) and mortality rates were higher than in Chinese patients (13.3% *vs.* 12.4% $p<0.05$). The patients with AKI in our study were older like the European and North American patients (70.92±11.28 years)[22].

Morbidity and mortality significantly increase in older patients infected with SARS-CoV-2, which may be due to weakened immune system functions and sensitization of aged tissues to viral replication[23,24]. The above-mentioned meta-analysis and another study[25] showed that advanced age was an independent risk factor for the development of AKI. Various publications are showing that sex is important in the severity of COVID-19 disease, mortality, and complication rates[26,27]. The significantly lower viral clearance in male patients SARS-CoV-2 infection than in female patients may explain the increased incidence of complications or severity of symptoms in male patients[28]. High rates of alcohol and cigarette consumption, as well as biologic differences between the sexes (androgen-sensitive elements of the transmembrane protease serine 2) may also predispose men to AKI in SARS-CoV-2 infections[45]. Similar to the patients mentioned in the studies earlier, 60% of patients with COVID-19 who we treated in our ICU were male.However, no difference was found between male and female patients in terms of the development of AKI and mortality.

Conclusions

Various studies have shown that patients with COVID-19 are at risk for AKI, and this is closely related to age, sex, and disease severity. The presence of AKI in patients with COVID-19 increases mortality, and this is more evident in patients hospitalized in ICU. Accordingly, kidney functions should be monitored closely, and AKI diagnoses should be made early. Controllable factors should be prevented with effective treatment strategies from the moment patients are admitted to ICUs. Adequate fluid replacement should be performed, hypotension and hypoxemia should be prevented, and nephrotoxic drugs should be avoided especially in older male patients with comorbidities and severe COVID-19.

Table V. AKI studies in COVID-19 patients in the USA.

	Total number of patients	AKI prevalence %	Patients with AKI in intensive care			Mortality rates		
			Total AKI %	Stage III %	RRT in MV %	Mortality in AKI %	Mortality without AKI %	Stage III, mortality in RRT %
Hirsh et al[17]	5499	36%	76%	46.7%	23.2%	34%	5.6%	54%
Chan et al[18]	3235	43.5%	68%	63%	34%	45%	7%	52% (ICU)
Mohamed et al[19]	575	28%	61%	73%		50%		72%

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

NeclaDereli: Design of the study, drafting the article. MunireBabayigit: acquisition of data, analysis of data. Oral Menteş: making critical revisions. FilizKoç: interpretation of data. Ozlem Ari: interpretation of data. EsraDoğan: acquisition of data. EsraOnhan: acquisition of data.

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