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Acute kidney injury following COVID-19 and risk factors for progression to chronic kidney disease

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Abstract

Aim: Acute kidney injury (AKI) is one of the frequent complications of COVID-19 infection. The predictors of progressive kidney disease for patients with COVID-19- associated AKI (COV-AKI) are unclear. In our study, we aimed to demonstrate the risk factors of non-recovery of COV-AKI.

Materials and Methods: COV-AKI developed in 901 of 3,337 patients treated in our hospital for COVID-19 between April 1, 2020 and November 30, 2020. 331 of 901 patients with COV-AKI died at the hospital. Of these patients, 459 patients who met the inclusion criteria were included in the study, while 111 patients were excluded. At 3 months post-AKI, 399 of 459 cases (Group 1) recovered from AKI, and 60 (Group 2) did not.

Results: The median age of the patients included in the study was 68 (59-76), and 44.9% (206) of them were women. Thirty-five of 60 patients in Group 2 developed de novo chronic kidney disease while 25 patients had a history of chronic kidney disease (CKD) and experienced a disease progression. We found that patients with low serum albumin levels (hypoalbuminemia) at admission ($P<0.001$) were associated with non-recovery of AKI or occurrence of CKD progression, in COV-AKI.

Conclusion: Although the short-term outcomes of COV-AKI are relatively well-known, the long-term outcomes are needed to be clarified more. This study indicates hypoalbuminemia may be indicators of non-recovery in COV-AKI.

Introduction

SARS-CoV-2 disease, is a multisystemic acute inflammatory infectious disease affecting millions of people. In the course of COVID-19, acute kidney injury (AKI) is observed in 24-57% of hospitalized patients, while AKI is observed in 61-78% of critically ill patients [1-4]. In post-mortem studies, the most common renal pathology is acute tubular injury in patients with COVID-19-associated AKI (COV-AKI) [5, 6]. Acute kidney injury can arise via the direct effect (viral invasion) of SARS-CoV-2 and/or via systemic cytokine storm causing endothelial damage [6-8]. It is known that AKI is associated with the development of chronic kidney disease (CKD) and causes disease progression in patients with CKD [9]. It has also been reported to increase mortality in the short or long term [9]. It has been shown that in COV-AKI, the disease is more severe, the need for renal replacement is higher, and kidney functions recover more slowly [6]. These above-mentioned conditions may increase the risk of progression to CKD in COV-AKI.

Renal functions in patients who develop AKI usually result in complete recovery. However, some patients may develop severe renal dysfunction that may require a temporary or sustained renal replacement therapy (RRT) [9]. It has been shown that the frequency, duration, severity of AKI and the need for RRT are very important in the development of CKD [10].

The number of studies reporting the long-term results of COV-AKI is limited [10-12]. In our study, we aim to evaluate the predictors for the development of CKD and the mortality rates within the three months of discharge in COV-AKI.

Materials and Methods

Study design and participants

This cross-sectional study includes COVID-19 patients who were hospitalized in Gazi Yaşargil Training and Research Hospital between 4/1/2020-11/30/2020 due to the requirement of hospitalization for COVID-19 disease. All data of patients were achieved from patient files, the electronic health system (nucleus) of our hospital, and the

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Turkish National Electronic Health System (UESS). The discharged COVID-19 patients whose data was available were evaluated. COVID-19 diagnosis was established on positive polymerase chain reaction (PCR) for SARS-CoV-2 obtained from the nasopharyngeal swab. Patients above 18 years of age, patients transferred to another health center, dialysis patients, kidney transplant recipients, postrenal AKI cases, patients with missing data, unknown previous kidney function, patients discharged in less than 48 hours, and deaths in the hospital were excluded (Figure 1). The hospital local ethics committee approval was obtained (Gazi Yasargil Training and Research Hospital proof; 09/07/2021, no 852). Since the study was in a retrospective design an informed consent form was not available.

The patients were classified into two groups; Group 1 who recovered from AKI and Group 2 who did not recover, within 3 months of post-AKI.

Data collection

The demographic features and medical history of the patients and comorbidities were recorded by reviewing the NEHS records. The serum creatinine levels and estimated glomerular filtration rates (e-GFR) of the patients within three months after discharge were noted and calculated. E-GFR was calculated by an online calculation formula based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation [13].

Laboratory parameters of the patients at the time of admission to the hospital including complete blood count, liver and renal function tests, coagulation functions, d-dimer, ferritin, high-sensitivity C-reactive protein (hsCRP), lactate dehydrogenase, creatinine kinase, procalcitonin, and electrolytes were evaluated. Discharge serum creatinine is the last serum creatinine level of the patients just before discharge.

Definitions

Acute kidney injury was defined on the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria: a change in the serum creatinine of 0.3 mg/dl over a 48-hour period or a 50% increase in baseline creatinine known or presumed to have occurred in the past 7 days [14]. AKI was staged according to the KDIGO criteria (14). AKI staging was classified according to the highest serum creatinine levels by comparing with serum basal creatinine. The last 6 months (180 days) serum creatinine levels were considered to determine basal serum creatinine levels. AKI recovery was defined as the return of creatinine to <0.3mg/dl above baseline [15, 16].

The persistent decline in kidney function lasting >90 days was described as chronic kidney disease (CKD) based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline [17]. In this study, CKD was defined on the basis of serum creatinine levels (GFR <60 ml/min/1.73m2 for 3 or more months) indicated by K/DOQI. Chronic kidney disease is defined as structural and functional abnormalities of the kidney that have health effects and persist for more than 3 months. However, we could not evaluate the K/DOQI criteria for CKD other than serum creatinine-based kidney function due to the lack of sufficient studies of urinalysis and radiology in the pandemic era [17]. We defined hypoalbuminemia as serum albumin level less than 35 g/L [18].

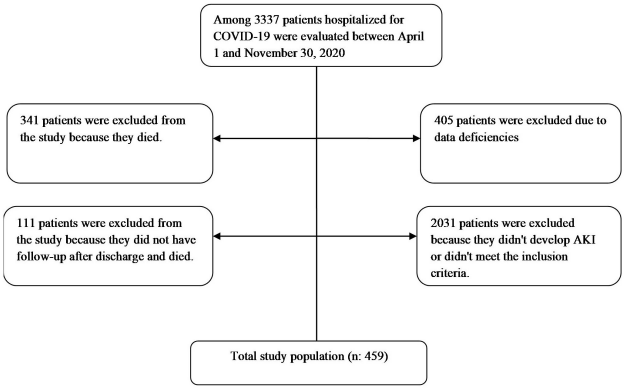

Figure 1. Flowchart of the enrollment process.

Statistical analysis

All statistical analyses were performed using IBM SPSS software 24.0 (Armonk, NY: IBM Corp.). The parametric and nonparametric continuous variables were presented as median interquartile range 25-75% (IQR). The Categorical variables were expressed aspercentages and numbers. Parametric and nonparametric continuous variables were analyzed using Student's t-test, Mann-Whitney U test, Chi-square or Fisher's exact tests as appropriate. A paired-group comparison was used to compare the parameters at discharge and 3 months post-AKI. Also, the impact of the factors on non-recovery AKI was analyzed by multivariate and univariate regression analyses. All statistical tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

Nine hundred and one COV-AKI cases (27%) that met the inclusion criteria were identified among the 3337 COVID-19 caused hospitalization between April 1 and November 30, 2020. While 36.7% (331) of the patients who developed COV-AKI died in the hospital, 63.3% (570) were discharged. Post-discharge, 10 patients died within 3 months, and 101 patients dropped out of follow-up. Those 111 COV-AKI cases (died or dropped out of follow-up) were excluded from the study and there were 459 remaining patients to assess (Figure 1). The median age of these patients was 68 (59-76) and 44.9% (206) were women. Hypertension was the most prevalent disease affecting 63.6% of COV-AKI and followed by diabetes mellitus (44.4%), coronary artery disease (CAD) (22.2%), chronic kidney disease (14.6 %). The demographic and clinical features of the two groups are given in Table 1.

Clinical outcome

At discharge, the kidney functions of 85.2% (391/459) of the study patients recovered, while 14.8% (68/459) did

Table 1. Basic characteristics and treatments of all study patients and patients with AKI whose kidney function recovered or not recovered at the third month.

Patient Characteristics	All patients, n=459	Patients recovering from AKI group 1 n=399	Patients whose AKI doesn't recovering group 2 n=60	P value
Age in years (median), % (n)	68 (59-76)	68 (59-75)	68.5 (60-78)	0.35
Gender female, % (n)	44.9 (206)	43.9 (175)	51.7 (31)	0.16
CKD, % (n)	14.6 (67)	10.5 (42)	41.7 (25)	<0.001
Hypertension, % (n)	63.6 (292)	62.4 (249)	71.7 (43)	0.19
Diabetes mellitus, % (n)	44.4 (204)	44.9 (179)	41.7 (25)	0.37
Congestive heart failure, % (n)	22.2 (102)	22.3 (89)	21.7 (13)	0.53
Lung disease, % (n)	66 (14.4)	57 (14.3)	9 (15)	0.56
Anticoagulant, % (n)	37.5 (172)	36.1 (144)	28 (46.7)	0.07
ACE, % (n)	20.9 (96)	20.6 (82)	23.3 (14)	0.36
ARB, % (n)	34.6 (159)	34.6 (138)	35.0 (21)	0.59
AKI on admission, % (n)	68.2 (313)	68.7 (274)	65.0 (39)	0.33
AKI developing in hospital, % (n)	31.8 (146)	31.3 (125)	35.0 (21)	0.17
Corticosteroid, % (n)	57. (264)	56.9 (227)	61.7 (37)	0.29
Intubation, % (n)	3.5 (16)	3.5 (14)	3.3 (2)	0.65
Treatment place in hospital intensive care, % (n)	15.5 (71)	15.0 (60)	18.3 (11)	0.31
Duration of hospitalization, %(n) (n=day)	10 (7-14)	10 (7-14)	11 (10-14)	0.001
KDIGO AKİ				
Stage 1, % (n)	74.9 (344)	78.3 (307)	59.2 (37)	0.038
Stage 2, %(n)	19 (87)	16.4 (70)	30.9 (17)	
Stage 3, %(n)	6.1 (28)	5.3 (22)	9.9 (6)	
RRT, % (n)	1.0 (5)	0.4 (2)	0.6 (3)	0.002

Data are expressed as median interquartile range and count (percentage): ACE: Angiotensin converting enzyme, AKI: acute kidney injury, ARB: Angiotensin II receptor blockers, CKD: Chronıc Kıdney Dısease, KDIGO :Kidney Disease Improvement Global Outcomes, RRT: Renal replacement therapy.

not. Median serum creatinine at discharge was found to be significantly higher in group 2 patients (1.54 mg/dL) than in group 1 patients (0.91 mg/dL) ($p<0.001$).

At 3 months post-COV-AKI, the kidney functions of 86.9% (399/459) of the study patients recovered (Group 1), while 13.1% (60/459) did not (Group 2). Renal functions of eight patients recovered within three months after discharge. Twenty-five patients (25/60, 41.7%) in Group 2 previously had CKD. Thirty-five patients (35/60) whose previous serum creatinine levels were normal were considered to have de novo CKD. A 77-year-old female patient with a previous stage 3 CKD became a chronic hemodialysis patient after COV-AKI. The sex and the median age of both groups were similar ($p=0.16$, $p=0.35$, respectively). The CKD prevalence and duration of hospitalization were found higher in Group 2 ($p<0.001$, $p=0.001$, respectively). Kidney functions did not recover at 3 months after discharge in 10.7% (37/344) of the patients in stage 1 AKI, 19.5% (17/87) in stage 2 AKI, and 21.3 % (6/28) in stage 3 AKI. Namely, as the AKI stage increased, the non-improved COV-AKI ratio at 3 months after AKI increased in relation to the AKI stages. Three patients in Group 2 and two patients in Group 1 required RRT. The demographic and clinical characteristics of the two groups at 3 months post-AKI are shown in Table 1.

At the time of hospitalization, lymphocyte, albumin, and e-GFR levels were significantly lower in Group 2 ($p=0.01$, $p<0.001$, $p=0.01$, respectively), compared to Group 1. In addition, baseline e-GFR levels of group 2 patients (66 ml/dk/1.73 m^2) were lower than group 1 (87 ml/dk/1.73 m^2) ($p<0.001$). The laboratory findings of the two groups at 3 months post-AKI are shown in Table 2. The total mortality rate in COV-AKI which includes all death both in hospital and within month 3 post-discharge, was 37.8% (341/901).

Predictors associated with non-recovery of renal functions

In order to evaluate the third-month follow-up results of patients who developed COV-AKI after discharge and to determine the predictors associated with non-recovery of renal functions, a paired-group comparison was performed. A univariate logistic regression analysis was performed on the variables found to be statistically significant ($p<0.05$) in the pairwise comparison. Variables such as CKD, serum albumin levels, baseline e-GFR, baseline serum creatinine, creatinine on admission and e-GFR at hospital admission, which were found to be associated with month 3 renal function improvement in univariate logistic regression analysis, were included in the multivariate regression analysis. As a result, hypoalbuminemia (OR 0.87, 95% CI 0.8-0.91, $p<0.001$) were found to be associated with non-recovery in COV-AKI (Table 3).

Table 2. Laboratory test results of all study patients and patients with AKI whose kidney function recovered or not recovered at the third month.

	All patients, n=459	Patients recovering from AKI n=378	Patients whose AKI doesn't recovering n=81	P value
WBC, 10^3/ml S	7.4 (5.7-10.3)	7.4(5.7-10.2)	8.0 (5.8-10.8)	0.44
Hemoglobin, g/dl	13.0 (11.7-14.3)	13.0 (11.8-14.3)	13.0 (10.8-14.2)	0.15
Lymphocyte, 10^3/ml	1.1(0.8-1.5)	1.1 (0.8-1.6)	0.93 (0.68-1.4)	0.01
Neutrophil 10^3/ml	5.5 (3.9-8.1)	5.4 (3.9-8.1)	6.1 (4.8-8.5)	0.17
Platelets 10^3/ml	216 (164-272)	219 (164-273)	214 (162-270)	0.66
Serum creatinine, mg/dL (application)	1.37 (1.15-1.64)	1.36 (1.14-1.60)	1.56 (1.2-2.0)	0.01
E GFR (CKD EPİ), ml/dk/1.73 m^2(application)	47 (35-60)	48 (35-63)	42 (28-52)	0.01
Baseline serum creatinine mg/dL	0.88 (0.78-1.0)	0.87 (0.72-0.97)	1.0 (0.89-1.2)	<0.001
Baseline e-GFR, ml/dk/1.73 m^2	85(70-96)	87(71-97)	66 (55-88)	<0.001
Discharge creatine, mg/dL	0.95 (0.80-1.1)	0.91 (0.8-1,0)	1.54 (1.21-1.79)	<0.001
Calcium (albumin correction) mg/dL	8.8 (8.4-9.2)	8.8 (8.4-9.2)	8.8 (8.2-9.1)	0.11
Albumin, g/L	33 (30-36)	33 (30-37)	29 (23-32)	<0.001
Lactate dehydrogenase U/L	317 (244-401)	317 (240-401)	314 (259-407)	0.35
C-reactive Protein mg/L	82 (40-135)	82 (39-133)	84 (40-147)	0.65
Procalcitonin, ng/mL	0.13 (0.06-0.24)	0.12 (0.06-0.22)	0.17 (0.08-0.35)	0.07
Ferritin, µg/L	412 (193-803)	418 (192-811)	381 (114-735)	0.74
D-dimer, ng/mL	309 (181-518)	302 (176-505)	347 (245-663)	0.03
Creatine kinase, IU/L	112 (61-230)	108 (60-220)	140 (75-295)	0.02

AKI: acute kidney injury, BUN: blood urea nitrogen, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, CRP: C-reactive Protein mg/L, e-GFR: estimated glomerular filtration rate, LDH: Lactate dehydrogenase, WBC: White blood cell count. Values are significant at $p < 0.05$.

Discussion

The determinants of non-recovery COV-AKI are needed to be clarified. To the best of our knowledge, our study will be one of the largest studies on the long-term outcome of patients with COV-AKI after discharge. Our aim in this study is to investigate the results of patients with COV-AKI at 3 months after discharge and the predictors of CKD development. Renal functions did not improve in 13.1% (60/459) of the patients in our study population at 3 months. Since 35 (35/459, 7.6%) of the patients whose kidney functions did not improve had previously normal kidney functions, these patients were diagnosed with de novo CKD. Of these, 25 had CKD previously and their renal functions progressed. In our study, hypoalbuminemia at hospital admission were the main determinant of kidney failure at 3 months.

Although many studies have shown that the risk of developing CKD increases after AKI, the pathogenesis of CKD development after AKI still remains unclear [19, 20]. Hypotheses such as the ischemia-reperfusion phenomenon, tubular injuries, renal arteriolar injuries, and endothelial dysfunction have been suggested to explain the development of CKD after AKI. Although AKI has been reported to be a risk factor for CKD, it is still unclear which patients are at high risk for CKD [21-23]. However, advanced age, severe AKI attack, prolonged AKI, need for RRT, recurrent AKI attacks, CKD, and hypoalbuminemia are considered as risk factors for long-term clinical outcomes of AKI [20]. In our study, the age and sex ratios of the two groups were similar. This result may be due to the increased in-hospital mortality of patients with advanced age who developed COV-AKI, and therefore the lower median age value of patients who were discharged from the hospital without improved kidney functions. Many studies have shown that chronic kidney disease is associated with non-recovery of kidney function in patients with AKI [18, 23]. In our study, the CKD rate in group 2 patients (41.7%) was higher than in group 1 patients (10.5%).

The most common pathological finding in patients with COV-AKI is acute tubular injury [25]. It has also been shown in kidney biopsies that SARS-CoV-2 infiltrates the kidney tissue and causes direct endothelial damage [26]. The etiology of AKI caused by COVID-19 disease is probably multifactorial due to factors such as hemodynamic instability, nephrotoxin exposure, cytokine storm, secondary infections, rhabdomyolysis, the cytopathic effect of the virus, acute respiratory distress, and associated hypoxia [5]. It is accepted that multifactorial AKIs have a higher risk of progression to CKD than AKIs due to a single cause [27]. The pathogenesis of continued renal dysfunction is unclear, despite the fact that patients in our cohort were treated and discharged for COVID-19. Similar to the pulmonary fibrosis that develops after pulmonary infections due to other coronavirus strains, the concern regarding that COV-AKI will cause progression to CKD by inducing tubulointerstitial fibrosis is increasing [10, 28, 29]. Nutget et al. reported that those with COV-AKI had a more severe AKI, a higher need for RRT and intensive care, and a greater reduction in e-GFR after discharge, compared with patients with AKI who didn't have COVID-19 [10]. These results may increase the risk of CKD in the long-term follow-up of patients who develop COV-AKI and the risk of progression in patients with CKD. Lumlertgul et al. reported that 16% of the patients had CKD at 3 months

Table 3. Traditional univariate and multivariate logistic regression analysis for patients with AKI whose kidney function recovered and not recovered at the third month.

	Univariate			Multivariate		
	Unadjusted	95 % CI	p value	Adjusted	95 % CI	p value
Creatinine on admission, mg/dL	1.61	1.18-2.20	0.003	1.22	0.80-1.87	0.34
E GFR(CKD EPİ), ml/dk/1.73 m^2(application)	0.97	0.96-0.99	0.003	1.00	0.98-1.03	0.54
Baseline serum creatinine mg/dL	22.6	6.97-73.2	<0.001	0.72	0.07-7.13	0.78
Baselin e-GFR, ml/dk/1.73 m^2	0.95	0.94-0.97	<0.001	0.97	0.94-1.01	0.17
Albumin on admission, g/L	0.85	0.81-0.90	<0.001	0.87	0.82-0.91	<0.001
Lymphocyte	1.00	0.99-1.01	0.97			
CK on admission, IU/L	1.00	0.99-1.02	0.64			
CKD	6.07	3.31-11.1	0.001	2.10	0.69-6.37	0.19
D-dimer, ng/mL	1.00	0.98-1.03	0.70			
Duration of hospitalization	1.02	0.99-.1.05	0.98			
Discharge creatine, mg/dL	1.01	0.96-1.05	0.60			
KDİGO						
Stage 1 vs 2	0.44	0.16.-1.16	0.97			
Stage 1 vs 3	0.89	0.31-2.53	0.82			
RRT	10.4	1.70-63.8	0.01	4.89	0.52-45.6	0.16

AKİ: Acute kidney injury, CK: Creatine kinase, CKD: chronic kidney disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, e-GFR: estimated glomerular filtration rate, KDIGO: Kidney Disease Improving Global Outcomes. Values are significant at $p < 0.05$.

after discharge in the study they conducted on critical patients with COV-AKI in the intensive care unit [12]. In our study, the rate of our patients with normal baseline kidney functions at 3 months' follow-up who were considered as CKD was 7.6% (35/459). This difference in the results at 3 months after discharge may be related to the intensive care needs, AKI severity, and RRT needs of the patients. The etiology of AKI and the factors responsible for the development of CKD after AKI are observed more frequently in patients in intensive care than in patients not in intensive care [19]. In particular, the need for RRT, which is considered to be a high risk for the development of CKD, is higher in patients intensive care [20]. In our study, the number of patients in need of intensive care (15.5%, 71/459) and receiving RRT (1.0%, 5/459) was lower compared to other studies. Most of our patients (74.9%) had AKI stage 1. At the beginning of the COVID-19 pandemic, there was a concern that COVID-19 might increase the risk of AKI and that the risk of CKD might increase in the long term in patients who developed COV-AKI [11]. Our study results show that this concern should be taken into consideration. Therefore, we recommend that centers and dialysis units where CKD patients are followed up should be prepared to meet this increasing patient load.

In previous studies, it was reported that 30% of patients who developed COV-AKI did not recover their kidney functions at discharge [4, 30]. In addition, it was shown that 36% of patients whose kidney functions did not recover to basal level during discharge did not recover in short-term follow-ups after discharge [4]. Recovery of kidney function after AKI is very important for patients, their families, and in terms of cost. With the prolongation of the pandemic, more effective treatments for COVID-19 were developed in randomized controlled studies over time [31, 32]. In addition, it was reported that there is a decrease in the progression of AKI with these newly developed treatments [12]. Other studies reported that dialysis dependency rates were between 8% and 56.5% [33-35]. In our study, the number of patients with CKD, who needed intensive care and had severe AKI (Stage 2.3 AKI and need for RRT) was lower. For these reasons, the number of patients who had a recent CKD diagnosis and were dialysis-dependent at 3 months may have been lower.

The serum albumin levels may decrease in cases such as urinary protein losses, lack of synthesis in the liver, systemic infection, and inflammation [36]. Hypoalbuminemia is common in moderate to severe COVID-19 infections [18]. In previous studies, the relationship between hypoalbuminemia and AKI in severe infections was shown [37,38]. Although the relationship between hypoalbuminemia and AKI was shown in some studies, the pathophysiological mechanism of this relationship has not been clearly demonstrated [39]. In the literature, some studies mention the renoprotective effect of albumin [39-40]. It is suggested that albumin achieves this effect by binding oxidative substances and reducing their toxic effects, maintaining intravascular oncotic pressure, maintaining renal perfusion, and also regulating medullary fluid reabsorption [40]. It has also been reported that hypoalbuminemia is a risk factor for the development of CKD in the long term. [19]. Shao et al. reported that hypoalbuminemia in critically ill patients increases the risk of AKI independently of other factors and is associated with progression from AKI to CKD [35]. Also in our study, hypoalbuminemia were found to be statistically significantly associated with renal failure at 3 months. In other words, hypoalbuminemia at admission increase the risk of developing CKD.

Our study had some limitations. Firstly, our study was a single-center study and this may affect the impact power

of our study. Secondly, all patients could not be included in the study because 17.7% (101/570) of the patients who developed COV-AKI and were discharged did not come to their follow-up examinations. Third, patients were unable to collect urine when diagnosing AKI and applying the criteria for AKI recovery.

Conclusion

AKI is a frequent complication in hospitalized patients with COVID-19. COV-AKI is an important predictor of CKD development. In our study, we found that patients with low admission serum albumin levels are at high risk with regard to developing CKD. It is very important to treat effectively the patient group developing COV-AKI and carrying risk factors in the early period and to follow closely in the long term.

Ethics approval

Approval was obtained from the ethics committee of Gazi Yasargil Training and Research Hospital (proof; 09/07/2021, no 852).

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