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Predictors of mortality in COVID-19 induced acute kidney injury

Enver Yüksel[1] | **Songül Arac**[2] | **Derya Deniz Altintaş**[3]

[1]Department of Nephrology, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

[2]Emergency Medicine, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

[3]Department of Radiology, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

Correspondence
Enver Yüksel, Department of nephrology: Gazi Yaşargil Training and Research Hospital, Fırat neighborhood 578 Street AZD Atlantis site blok no: 24 Kayapınar, Diyarbakır, Turkey.
Email: ferhat_enver@hotmail.com

Abstract

Background: We aimed to investigate the predictors of mortality in patients with COVID-19-induced acute kidney injury (COV-AKI).

Methods: We enrolled 803 patients who developed COV-AKI. The patients were divided into two groups: survivors and nonsurvivors.

Results: A multivariate logistic regression analysis showed that age ($p < 0.001$), increased admission C-reactive protein ($p = 0.016$), procalcitonin ($p = 0.019$), creatine kinase ($p = 0.04$), KDIGO stage 1 versus 2 AKI ($p < 0.001$), KDIGO stage 1 versus 3 ($p < 0.001$), the need for renal replacement therapy ($p = 0.002$) and highest creatinine ($p = 0.004$) were significantly associated with increased inhospital mortality. However, the mortality of patients with AKI on admission ($p = 0.002$) was found to be lower than those who developed AKI after hospitalization.

Conclusions: Among patients with COV-AKI, high-inflammatory response and severe AKI were associated with significantly higher mortality.

KEYWORDS

acute kidney injury, COVID-19, mortality, renal replacement therapy

1 | INTRODUCTION

Since the publication of the first reports of the SARS-CoV-2 infection in China, it has been reported that the SARS-CoV-2 infection is not limited to the respiratory system but also affects many other organs [1, 2]. Reports from various centers all over the world have pointed that COVID-19 patients suffer a high incidence of acute kidney injury (AKI) and there is a higher-than-expected need for renal replacement therapy in patients developing AKI [3–6]. In addition, mortality rates have been found to be higher among patients who develop AKI, especially those who receive renal replacement therapy (RRT) [3, 7].

According to our current knowledge, the virus uses angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 to enter human cells [8, 9]. This enzyme is known to exist in many tissues such as the brain, mouth mucosa, small intestine, and kidneys [8, 9]. A study that examined the autopsy samples of 26 patients who died from COVID-19 in China showed that SARS-CoV-2 invades kidney tissue, causing endothelial injury and acute tubular damage [10]. Although variable death rates have been reported in COVID-19-induced AKI (COV-AKI), a significant proportion of these patients died [11, 12]. Although a number of studies aimed to identify the risk factors of AKI and predictors of mortality in COVID-19 patients, the predictors of mortality in COV-AKI have not been sufficiently investigated [6, 11–13]. Thus we designed this study to determine the predictors for inhospital mortality among patients with COVID-19-induced AKI in the hospital course.

2 | MATERIALS AND METHOD

2.1 | Study design and participants

This is a single-center retrospective cohort study where patients who were hospitalized for COVID-19 and developed AKI were investigated. The study was initiated after it was approved by the Ministry of Health of the Republic of Turkey and approved by our hospital's local ethics committee (date and number of ethics committee: 15/01/2021, no: 640). All study data were obtained by means of our hospital's electronic health system (nucleus) and e-nabız, the national electronic health system (NEHS) of Turkey. Our study enrolled patients above the age of 18 with a positive reverse transcriptase-polymerase chain reaction (RT- PCR) test for COVID-19 in a nasopharyngeal swab sample and computerized tomography findings consistent with COVID-19, who needed hospitalization between 30/3/2020 and 30/10/2020. Our study enrolled patients above the age of 18 who developed AKI and had positive reverse transcriptase-polymerase chain reaction (RT-PCR) test for COVID-19 in nasopharyngeal swab sample and computed tomography findings compatible with COVID-19. Patients who were under the age of 18, who were transferred to another center, who had a history of dialysis or kidney transplantation, who had post-renal AKI or missing medical data, and who were discharged in less than 48 h were excluded. Patients with contrast-induced nephropathy (one patient), acute decompensated heart failure (two patients), or using active chemotherapeutic drugs (one patient) were excluded from the study. Also, the patients who had cardiac resuscitation in the emergency service and died within the first 24 h were excluded from the study (four patients).

2.2 | Data collection

The demographic properties, comorbidities, medical history, and current medications of the patients were recorded using their past medical history taken by the admitting physician and by reviewing the NEHS records. Patients with end-stage kidney disease and a history of renal transplantation were identified and excluded using their past medical history and the national electronic health system. Suspected cases were confirmed by calling transplant centers and dialysis centers to obtain information about their medical records. All patients diagnosed with COVID-19, whose creatinine values above were 0.9 for women and 1.25 for men, were screened for AKI.

The patients were divided into two groups according to nonsurvivors and survivors of inhospital mortality to determine the predictors for inhospital mortality. Additionally, we analyzed the patients to show the difference in the prognosis of patients who developed AKI after hospitalization compared to the onset day. The laboratory data used for analyses included full blood count, hepatic and renal function tests, coagulation tests, d-dimer, ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CK), procalcitonin, and electrolytes. Our study also provides data about the need for intubation, mechanical ventilation, and RRT. The admission laboratory values were taken on the day of patient admission. PCR test was performed from the nasopharyngeal swab samples of patients with the clinical presentation of COVID-19. Patients with respiratory symptoms were evaluated with a chest CT to detect pulmonary involvement before or after hospital admission. Hospital-acquired AKI was defined as the development of AKI any time after 48 h of hospitalization, on a patient who was admitted with normal renal function. This time of 48 h was used to allow subclinical community-acquired AKI to manifest [14]. RRT was performed on patients who had oliguria (urine output <0.3 ml/kg/h for 24 h) unresponsive to medical therapy, hypervolemia (fluid overload), severe hyperkalemia (K > 6.5 mEq/L), severe metabolic acidosis (pH <7.1), and rapidly deteriorated renal function and uremic symptoms.

2.3 | Definitions

AKI was defined as per Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dl over a 48-hour period or a 50% increase in baseline creatinine [15]. AKI stages were defined using the KDIGO AKI stage creatinine definitions: stage 1 as an increase in serum creatinine of ≥0.3 mg/dl or increase to ≥1.5–1.9 times baseline serum creatinine, stage 2 as an increase to >2–2.9 times from baseline serum creatinine, and stage 3 as an increase to more than three times baseline serum creatinine or a peak serum creatinine ≥4.0 mg/dl or if the patient received RRT during admission [16]. Baseline creatinine level was recorded from NEHS and defined as the mean creatinine level in the last 1 year (365 days) [6, 17, 18]. In patients with no past creatinine levels on NEHS were excluded from the study (ten patients). Since hourly urine output was incompletely recorded in our hospital's recording system, we did not use urine output, one of the KDIGO criteria, to diagnose AKI. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration's creatinine Equation [19]. KDIGO stage of the patients with AKI was determined in reference to the highest creatinine level. AKI recovery has

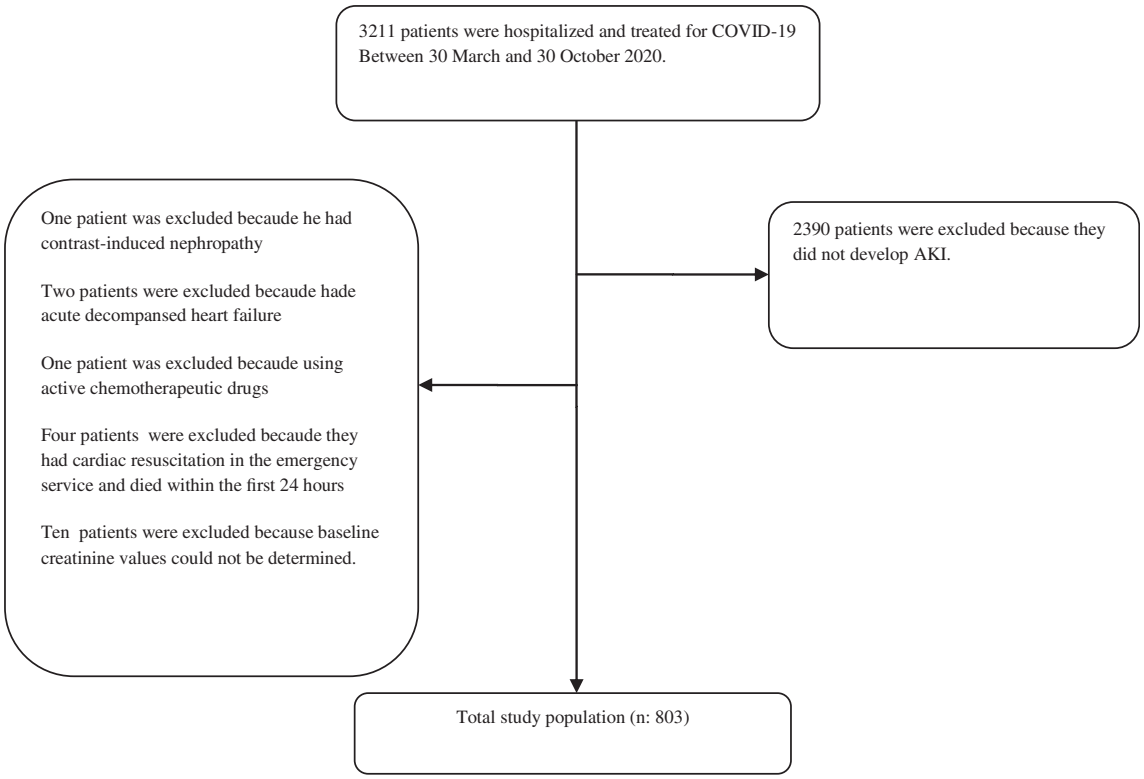

FIGURE 1 Flowchart of screened, excluded, and included patients.

been defined by the Acute Disease Quality Initiative 16 consensus group as the absence of AKI by both serum creatinine and urine output criteria within 7 days after AKI onset [17]. Chronic kidney disease (CKD) is defined as kidney disease persisting for 3 months or longer. Finally, Acute kidney disease (AKD) is considered to be structural and functional abnormalities of the kidney that are outside the definitions of AKI or CKD, have health effects, and have a duration of ≤3 months [20]. We compared the discharge creatinine level with the baseline creatinine level. When the discharge creatinine level was higher than the baseline creatinine level and that ratio was greater than a fourth of the baseline creatinine level, we diagnosed AKD. We came across some special circumstances. We excluded patients for whom we could not determine the baseline creatinine level. We also excluded patients who did not meet the KDIGO criteria but had creatinine levels that increased by at least 1.5 times in a period of more than 7 days because they could not meet the criteria. Our study was conducted in the early stages of the COVID-19 pandemic (30/3/2020 and 30/10/2020). At the time of study period, routine variant analysis was not performed in our region. Although, variant analysis was not performed in our study population, alpha-delta variants were the most common COVID-19 variants observed in our region during the study period.

2.4 | Statistical analysis

All statistical analyses were performed using the IBM SPSS software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The continuous variables were presented given as mean ± SD and median interquartile range 25%–75% (IQR) in case of nonnormally distribution. The categorical variables were expressed as percentages. Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. The continuous variables were compared with Student's *t*-test or Mann–Whitney U test according to data distribution. The categorical variables were compared using Chi-square or Fisher's exact tests if appropriate The cutoff value for AKI onset day for patients who developed AKI after hospitalization was determined using receiver operating characteristic (ROC) analysis. Univariate and multivariate logistic regression analyses were performed to evaluate the predictors for inhospital mortality. The clinically and biologically related variables with p value of <0.05 in ordinarily bivariate analysis were included in the

TABLE 1 Baseline characteristics and treatments of all study patients

Patient characteristics	All patients $n = 803$	Inhospital mortality		p value
		Survivors $n = 487$	Nonsurvivors $n = 316$	
Age in years (mean)	71 (61–79)	69 (59–76)	74 (66–82)	<0.001
Gender Male, % (n)	59 (474)	56.5 (275)	63 (199)	0.06
Hypertension, % (n)	61.8 (496)	63 (307)	59.3 (189)	0.35
Diabetes mellitus, % (n)	41.6 (334)	43.7 (213)	38.3 (121)	0.12
Congestive heart failure, % (n)	28.5 (229)	27.3 (133)	30.4 (96)	0.34
Chronic Lung Disease, % (n)	13.4 (108)	14.6 (71)	11.7 (37)	0.24
Chronic Kidney Disease, % (n)	18.7 (150)	15.8 (77)	23.1 (73)	0.01
Malignancy, % (n)	1.6 (13)	1.6 (5)	1.6 (8)	0.94
Cerebro-vascular disease, % (n)	7.3 (59)	5.7 (28)	9.8 (31)	0.03
ACEI, % (n)	20.3 (163)	20.7 (101)	19.6 (62)	0.70
ARB, % (n)	32.1 (258)	34.7 (169)	28.2 (89)	0.053
Antiaggragants, % (n)	37.4 (300)	37.6 (183)	37 (117)	0.87
Calcium channel blockers, % (n)	20.8 (167)	20.1 (98)	21.8 (69)	0.55
Oral anti-diabetic, % (n)	28 (225)	30.8 (150)	23.7 (75)	0.05
Insulin, % (n)	17.1 (137)	15.2 (74)	19.9 (63)	0.08
Beta- blockers, % (n)	25.5 (205)	26.9 (131)	23.4 (74)	0.26
Hydroxychloroquine sulfate, % (n)	29.9 (240)	36.1 (176)	20.3 (64)	<0.001
Antiviral drugs (favipiravir), % (n)	87.5 (703)	83.4 (406)	94 (297)	<0.001
Tocilizumab, % (n)	10.6 (85)	8.6 (42)	13.6 (43)	0.002
Corticosteroid, % (n)	58.2 (467)	59.9 (277)	60.1 (190)	0.36
Anticoagulant, % (n)	70 (562)	71.7 (349)	67.4 (213)	0.26
Convalescent plasma, % (n)	2.0 (16)	1 (5)	3.5 (11)	0.015
IVIG, % (n)	4.0 (32)	1.4 (7)	7.9 (25)	<0.001
Intubation, % (n)	40.0 (322)	4.1 (20)	95.4 (302)	<0.001
AKI, day of diagnosis (for all study patients) (n = day)	1 (1–4)	1 (1–2)	2 (1–6)	<0.001
RRT, % (n)	12.7 (102)	1.4 (7)	30.1 (95)	<0.001
AKI on admission	60.9 (489)	69.6 (339)	47.4 (150)	<0.001
AKI onset ≥3.5 days after hospitalization (194/314 patients) % (n)	24.2 (194)	40.7 (79/194)	59.3 (115/194)	0.005
Duration of hospitalization (n = day)	9 (5–13)	8 (6–12)	10 (7–16)	0.032

Note: Data are expressed as median interquartile range and count (percentage).
Abbreviations: AKI, acute kidney injury; ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; IVIG, intravenous immunoglobulin; RRT, Renal replacement therapy.

univariate logistic regression analysis. The variables with a p value of <0.05 in this analysis were also included in the multivariate logistic regression analysis. In stepwise multivariate regression analysis (Backward, Wald); effect size was adjusted with a univariate significance level of <0.05 for all variables. Adjusted odds ratios (OR) along with the confidence interval (CI) of 95% were presented. A 2-tailed p value<0.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Demographic and clinical characteristics

Among 3211 patients who were hospitalized for COVID-19 between 30 March and 30 October 2020, approximately 803 patients (25%) who developed AKI and met inclusion criteria were enrolled (Figure 1).

TABLE 2 Laboratory test results of surviving and nonsurviving patients

		Inhospital mortality		
	All patients, $n = 803$	**Survivors $n = 487$**	**Nonsurvivors $n = 316$**	***p* value**
White blood cell count, 10^3/ml	7.19 (5.85–11.35)	7.52 (5.82–10.4)	8.59 (6.07–13.3)	<0.001
Hemoglobin, g/dl	13.2 (11.7–14.6)	13.3 (11.7–14.7)	13.0 (11.8–14.5)	0.33
Neutrophil 10^3/ml	6.12 (4.22–9.50)	5.6 (4–8.4)	7.1 (4.6–11.5)	<0.001
Lymphocyte percentage, %	1.01 (0.71–1.42)	1.1 (0.82–1.56)	0.84 (0.59–1.24)	<0.001
Platelets, 10^3/L	210 (160–269)	215 (164–271)	201 (155–263)	0.13
Glucose mg/dl	136 (113–202)	132 (110–194)	143 (117–216)	0.02
BUN, mg/dl	58 (42–82)	55 (41–78)	61 (44–90)	0.01
Serum creatinine, mg/d (admission)	1.37 (1.1–1.66)	1.38 (1.16–1.65)	1.34 (1.0–1.7)	0.042
E GFR(CKD EPI) ml/dk/1,73m^2 (admission)	47 (34–60)	46 (34–59)	47 (35–63)	0.27
Sodium, mEq/L	136 (113–139)	136 (133–139)	137 (133–139)	0.45
Potassium, mEq/L	4.3 (3.9–6.74)	4.3 (3.9–4.74)	4.3 (3.9–4.77)	0.86
Calcium (albumin correction) mg/dl	8.8 (8.4–9.2)	8.8 (8.4–9.2)	8.8 (8.4–9.1)	0.20
Albumin, g/dl	3.1 (2.8–3.5)	3.3 (2.9–3.6)	2.9 (2.6–3.3)	<0.001
Lactate dehydrogenase U/L	339 (292–463)	317 (244–402)	417 (187–573)	<0.001
C-reactive Protein mg/L	101 (48–158)	82 (40–135)	127 (71–184)	<0.001
Procalcitonin, ng/ml	0.19 (0.09–0.63)	0.13 (0.06–0.28)	0.47 (0.19–1.7)	<0.001
Ferritin, µg/L	480 (229–897)	410 (196–796)	567 (304–1156)	<0.001
D-dimer, ng/ml	346 (215–704)	315 (183–558)	446 (278–933)	<0.001
Creatine kinase, IU/L	127 (63–279)	113 (61–230)	153 (67–361)	0.001
Highest serum creatinine	1.81 (1.45–2.82)	1.57 (1.36–1.96)	2.84 (1.94–4.34)	<0.001
Highest C-reactive Protein mg/L	156 (103–234)	126 (82–174)	218 (160–284)	<0.001
Highest procalcitonin, ng/mL	0.41 (0.14–2.6)	0.18 (0.08–0.4)	3.0 (1–12.1)	<0.001
Highest ferritin, µg/L	939 (388–2000)	597 (196–796)	567 (999–2000)	<0.001
Highest D-dimer,ng/ml	1171 (442–4432)	615 (295–1572)	2000 (2102–11 608)	0.001
Highest Creatine kinase, IU/L	260 (123–687)	174 (89–357)	676 (274–1550)	<0.001

Abbreviations: BUN, blood urea nitrogen; E GFR, estimated glomerular filtration rate; IVIG, intravenous immunoglobulin; RRT, renal replacement therapy.

Fifty-nine percent (474) of the patients were male, and the mean age of the patients was 71 (61–79) years. Hypertension was the most common coexisting disorder affecting 61.8% of patients, followed by diabetes mellitus (41.6%), Congestive heart failure (28.5%), Chronıc Kıdney Dısease (18.7%), Chronic Lung Disease (13.4%), Cerebrovascular disease (7.3%), Malignancy (1.6%). The demographic and clinical characteristics of the two groups as well as the treatments were summarized in Table 1.

3.2 | Clinical outcome

The patients were divided into two groups according to nonsurvivors and survivors of inhospital mortality in order to determine the predictors for mortality in patients with COV-AKI. The mean age of nonsurvivors was significantly higher than that of survivors ($p < 0.001$). In nonsurvivors, the rates of chronic kidney disease (CKD) and cerebrovascular disease were significantly higher than survivors ($p = 0.01$, $p = 0.03$, respectively). AKI developed significantly later during the hospital course in nonsurvivors compared to survivors, and the duration of hospitalization was significantly longer in nonsurvivors ($p < 0.001$, $p = 0.032$, respectively). In nonsurvivors, 30.1% (95) of patients underwent hemodialysis due to the need for RRT while only 1.4% (7) of patients in survivors underwent hemodialysis ($p < 0.001$). Similarly, the need for intubation was significantly higher in nonsurvivors ($p < 0.001$). The overall mortality rate of the study population was 39.3% while the mortality rates of patients admitted to intensive care unit and regular ward were 78.3% and 2.1%, respectively.

Laboratory results of the deceased patients, survivors, and the entire study population are shown in Table 2.

TABLE 3 Rates of KDIGO stages by all patients and the groups

AKI	All patients $n = 803$	Survivors $n = 487$	Nonsurvivors $n = 316$	p
Stage-1%, n	54.3 (436)	74.9 (365)	22.5 (71)	<0.001
Stage-2%, n	21.4 (172)	18.7 (91)	25.6 (81)	0.019
Stage-3%, n	24.3 (195)	6.4 (31)	51.9 (164)	<0.001

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes.

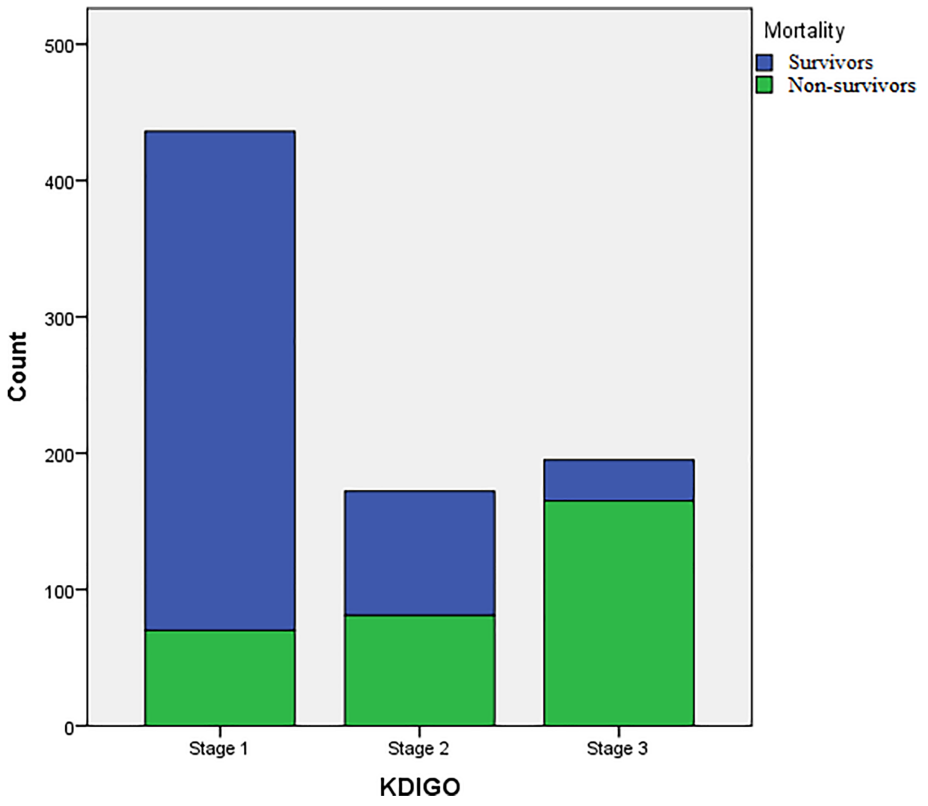

FIGURE 2 Comparison of inhospital mortality between KDIGO stages 1, 2, and 3.

Admission WBC, neutrophil, glucose, blood urea nitrogen (BUN), LDH, CRP, procalcitonin, ferritin, D-dimer, and CK levels were significantly higher in nonsurvivors ($p < 0.001$, $p < 0.001$, $p = 0.02$, $p = 0.01$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.001$, respectively). In contrast, admission lymphocyte, creatinine, and serum albumin were significantly lower in nonsurvivors ($p < 0.001$, $p = 0.042$, and $p < 0.001$, respectively). A high-admission CK level was statistically significant in multivariate analyses ($p = 0.04$). The highest levels of inflammatory markers during the course of the COVID-19 infection were compared between the two groups. The highest levels of serum creatinine, CRP, procalcitonin, ferritin, D-dimer, and CK were significantly higher in nonsurvivors ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.001$, respectively).

An AKI staging was performed in our population according to the KDIGO classification. 54.3% (436) of our patients were in stage 1; 21.4% (172) were in stage 2; and 24.3% (195) were in stage 3. In our study, we found that there was an increase in mortality in direct proportion with the increase in the KDIGO stage. The mortality rate was found to be the highest especially in KDIGO stage 3 (Table 3). Mortality rates according to each KDIGO group of all patients in stages 3, 2, and 1 were 84.1%, 47%, and 16.2%, respectively (Table 3, Figure 2).

The patients in stage 3 who needed RRT had a mortality rate of 93.1% (95/102), and the patients in stage 3 who did not need RRT had a mortality rate of 75.2% (70/93). 60.9% (489) of the patients had AKI on admission. Among patients who presented with AKI on admission, 59.1% (289/489) were in stage 1, 24.3% (119/489) in stage 2, and 16.5% (81/489) in stage 3. Patients who developed AKI during hospital stay had a higher mortality rate (52.9%, 166/314) compared to patients who had AKI on admission (30.7%, 150/489) (Table 1). The KDIGO stage-based mortality analysis according to AKI on admission showed a mortality rate of 74.0% (60/81) in stage 3, 37.8%

TABLE 4 Traditional univariate and multivariate logistic regression analysis for inhospital mortality

	Univariate			Multivariate		
	Unadjusted OR	**95% CI**	***p* value**	**Adjusted OR**	**95% CI**	***p* value**
Age	1.040	1.03–1.05	<0.001	1.07	1.02–1.12	0.001
Gender male	1.310	0.98–1.75	0.067			
Chronic Kidney Disease	2.16	1.11–2.87	0.01	0.68	0.23–1.97	0.484
Cerebro-vascular disease	1.78	1.04–3.03	0.03	1.20	0.54–2.51	0.064
Neutrophil 10^3/ml	1.002	1.001–1003	<0.001	1.00	0.98–1.06	0.179
Lymphocyte percentage	1.002	1.001–1.003	<0.001	1.00	0.97–1.05	0.582
Cretainine on admission	0.990	0.86–1.14	0.052			
Highest creatinine	2.560	2.16–3.02	<0.001	1.22	1.07–1.49	0.004
Albumin on admission	0.870	0.84–0.90	<0.001	0.93	0.84–1.04	0.237
LDH on admission	1.003	1.001–1.004	<0.001	1.00	0.99–1.03	0.179
CRP on admission	1.007	1.005–1.009	<0.001	1.04	1.01–1.07	0.016
Procalcitonin on admission	1.060	1.02–1.100	<0.001	1.03	1.01–1.06	0.019
Ferritin on admission	1.001	1.001–1.004	<0.001	1.01	0.98–1.03	0.085
D dimer on admission	1.001	1.001–1.003	<0.001	1.02	0.96–1.04	0.18
CK on admission	1.001	1.001–1.003	<0.001	1.03	1.01–1.05	0.04
AKI on admission	0.39	0.29–0.52	<0.001	0.45	0.27–0.75	0.002
AKI onset ≥3.5 days after hospitalization	1.94	1.21–3.10	0.006	2.31	0.99–5.37	0.52
KDIGO						
Stage 1 vs. 2	4.65	3.13–6.89	<0.001	3.25	2.01–5.62	<0.001
Stage 1 vs. 3	28.70	18.0–45.8	<0.001	6.62	3.13–14.1	<0.001
Stage 2 vs. 3	6.40	3.90–10.6	<0.001	6.32	3.81–10.9	0.13
RRT	29.40	13.4–64.5	<0.001	4.64	1.75–12.30	0.002

Abbreviations: AKI, acute kidney injury; CK, Creatine kinase; CRP, C-reactive Protein; KDIGO, Kidney Disease Improving Global Outcomes; LDH, lactate dehydrogenase; RRT, renal replacement therapy.

(45/119) in stage 2, and 15.5% (45/289) in stage 1. The KDIGO stage-based mortality rate of the group with AKI that developed during hospital stay was 92.5% (99/107) in stage 3, 70.6% (41/58) in stage 2, and 17.4% (26/149) in stage 1.

Patients who developed AKI after hospitalization were evaluated to show whether there was a difference in prognosis compared to the onset day. We had 314 patients who developed AKI in the hospital (Table 1). The ROC analysis of these patients revealed a cutoff of 3.5 days for mortality ($p = 0.005$) (Table 1). In other words, patients who developed AKI after ≥3.5 days had higher mortality than patients who developed AKI before this day. Logistic regression analysis was performed to show the difference in mortality in patients who developed AKI during the hospital stay compared to the onset day. While this result was found to be significant in the univariate analysis, it was not significant in the multivariate analysis ($p = 0.006$, $p = 0.52$, respectively) (Table 4).

The majority of the patients received favipiravir, anticoagulant, and glucocorticoids while a smaller subset of the patients received hydroxychloroquine, tocilizumab, intravenous immunoglobulin, and convalescent plasma. An analysis of COVID-19 treatments showed that the rate of hydroxychloroquine sulfate use was significantly higher in survivors whereas the rate of antiviral drug (favipiravir), tocilizumab, convalescent plasma, and IVIG (intravenous immunoglobulin) use was significantly greater in nonsurvivors ($p < 0.001$, $p < 0.001$, $p = 0.002$, $p = 0.015$ and $p < 0.001$, respectively).

3.3 | Predictors of mortality

In order to determine the independent predictors of inhospital death, we first conducted a univariate logistic regression analysis including the variables of age, sex, chronic kidney disease, cerebrovascular disease, admission neutrophil, lymphocyte, creatinine, albumin, LDH, CRP, procalcitonin, CK, ferritin, d-dimer, highest creatinine, AKI on admission, RRT, and KDIGO, which were

significantly different ($p < 0.05$) between the two groups and which were clinically and biologically correlated to mortality. A multivariate logistic regression analysis that included the significant variables in the univariate logistic regression analysis was performed to identify the independent predictors for inhospital mortality. As a result, age (OR 1.07, 95% CI 1.02–1.12, $p = 0.001$), admission CRP (OR 1.04, 95% CI 1.01–1.07, $p = 0.016$), procalcitonin (OR 1.03, 95% CI 1.00–1.06, $p = 0.019$), CK (OR 1.03, 95% CI 1.01–105, $p = 0.04$), KDIGO stage 1 versus 2 AKI (OR 3.25, 95% CI 2.01–5.62, $p < 0.001$), KDIGO stage 1 versus 3 AKI (OR 6.62, 95% CI 3.13–14.1, $p < 0.001$), RRT (OR 4.64, 95% CI 1.75–12.3, $p = 0.002$) and highest creatinine (OR 1.22, 95% CI 1.07–1.49, $p = 0.004$) were found to be significantly associated with increased inhospital mortality (Table 4). However, the mortality of patients with AKI on admission (OR 0.45, 95% CI 0.27–0.75, $p = 0.002$) was found to be lower than those who developed AKI after hospitalization. In addition, multivariate analysis found no significant difference in inhospital mortality in KDIGO grades 2 and 3 AKI (OR 6.32, 95% CI 3.81–10.9, $p = 0.13$).

4 | DISCUSSION

Several studies in the literature have examined the incidence and risk factors of AKI in COVID-19 patients [4, 19, 21]. However, factors correlated with mortality in COV-AKI have not been studied in detail. Thus, in the present study, we aimed to investigate the predictors of inhospital mortality in patients who developed COV-AKI. As far as we know, our study is one of the largest studies that examined predictors associated with mortality in patients who developed COV-AKI. Our study showed that age and higher levels of admission CRP, procalcitonin, and CK were significantly associated with inhospital mortality. In addition, KDIGO stage 2–3, highest creatinine, and RRT need were also significantly associated with inhospital mortality.

Cheng Y et al. showed that the prevalence of kidney disease is high in COVID-19 patients and that AKI is associated with inhospital mortality in these patients [3]. It has also been reported that COVID-19 patients with AKI on admission have higher inhospital mortality than those without AKI on admission [22]. In our study, the proportion of patients with AKI on admission was high (60.8%). This may be due to older age in patients with AKI, later hospital presentation, and more severe disease presentation. We found that the mortality ($p = 0.002$) of patients with AKI on admission was lower than those who developed AKI at the hospital. As evident in Table 1, while the rate of AKI was higher in the survivors at the time of admission (69.6%) compared to nonsurvivors (47.4%), the rate of hospital-acquired AKI was lower (30.4% and 52.6%, respectively). This result shows that the kidney functions of some of the survivors with AKI initially improved during their treatment. This suggests that the etiology of AKI in some of the survivors may be due to prerenal causes such as oral intake disorder, diarrhea, nausea, and vomiting and that this is improved with supportive treatment. The causes of AKI developing in the hospital are multifactorial. It mostly develops in patients who need intensive care, are hypotensive, dependent on a mechanical ventilator, and using multiple drugs. AKI is already known to be associated with increased inhospital mortality [3]. We know that AKI developing in these patients is associated with higher mortality [23]. We found that AKI developing during hospitalization was worse in predicting inhospital mortality in patients who developed COV-AKI.

Although the incidence of AKI has been reported between 0.5% and 36.6% in the initial reports on COVID-19, a review performed by Sreedhar found an AKI incidence of approximately 50% in patients treated at intensive care unit [2, 4, 6, 19, 24]. In our study, AKI incidence was 25.0%. It is not known exactly by which mechanisms AKI develops in patients with COVID-19. Renal injury may develop due to prerenal, renal, and postrenal causes but it may also be caused by small-vessel vasculitis, thrombi, cytokine storm, or viral particles that invade renal tissue and cause renal injury by cytopathic effects [25–29]. We already know that AKI is associated with increased inhospital mortality [3, 5]. While Hirsch et al. reported a mortality rate of 35% among patients who developed AKI, Chan et al. reported a mortality rate of 38.5% in a similar patient group [4, 6]. In our patient population, patients with AKI had a mortality rate of 39.3%. It has been previously reported that COVID-19 patients undergoing RRT have a poor prognosis [4, 6, 11]. According to our results, 12.7% (102/803) of patients with AKI needed RRT, and patients who received RRT had a mortality rate of 93.1%. RRT is mostly needed by patients with severe infection or multiple organ failure, those who are intubated, and those who are treated at the intensive care unit due to a need for cardiac support or respiratory failure [4, 6]. Consistent with previous reports, our study also revealed that higher mortality among patients who were in need of RRT.

It has been already reported that high levels of admission CK, CRP, and procalcitonin were associated with increased mortality in COVID-19 patients [3, 12, 13]. These biomarkers increase during the course of various diseases characterized by inflammation, infection, and tissue injury [12, 13]. A number of previous studies have suggested the use of increasing biomarkers in accordance

with the severity of the infection to predict disease severity and prognosis [30]. However, the relationship between these inflammatory biomarkers and mortality has not been adequately addressed in COV-AKI. Our study indicated that higher admission CK, CRP, and procalcitonin levels were correlated to mortality in patients who developed COV-AKI (Table 4). A high-AKI incidence had also been reported in the influenza A (H1N1) pandemic, which is the latest pandemic of recent history [31]. At that time, it was suggested that rhabdomyolysis may be a contributing factor to the etiology of AKI [31]. Our study revealed that high-admission CK levels were also associated with higher mortality.

We examined the relationship between the KDIGO stage and mortality. Similar to previous studies, our study demonstrated an increase in mortality in accordance with the KDIGO stage in patients with AKI [6, 13] (Table 3). The increase in mortality was significant in KDIGO stage 2 and stage 3. Especially in KDIGO stage 3, the mortality rate was found to be the highest and 50.4% of the patients who died were stage 3 patients (Table 3). Mortality was higher in KDIGO stage 3 irrespective of whether RRT was applied or AKI was present on admission.

A higher KDIGO stage is associated with increased severity of the renal injury. As the renal injury is worsened, electrolyte imbalance, metabolic acidosis, and hypervolemia may also be added to the clinical condition and these contribute to the worsening of the clinical condition of the patients. Additionally, as disease severity increases, and as respiratory and cardiac failure are worsened, renal injury is further worsened. Therefore, the mortality of advanced-stage AKI is high. It is important to closely monitor patients who present with AKI or have their renal function worsened during follow-up and to obtain a nephrology consultation at an early period. Early detection of worsening renal function and its effective treatment by providing adequate hemodynamic support and avoiding nephrotoxic agents may help the recovery of critically ill COVID-19 patients. Early diagnosis, follow-up, and effective treatment may lower mortality rates in these patients. Similar to previous reports, we found that 16% of our patients did not fully recover their renal function at discharge [5, 6, 32]. Creatinine levels that do not recover at discharge are the undesirable clinical condition in COVID-19 patients. Long-term follow-up of patients with renal dysfunction after discharge is important. These patients will contribute to a growing CKD population in the future.

In accordance with the health policy of the infection committee of our country and our hospital, favipiravir treatment was administered as an antiviral treatment in moderate, severe, and critical patients diagnosed with COVID-19. The reason for the higher rate of favipiravir treatment in nonsurvivors in our study was that the clinical presentation of these patients was more severe and the majority of them were administered favipiravir treatment. Therefore, the appearance of favipiravir treatment associated with mortality, as seen in Table 1, has caused confusion. In order to avoid this confusion, the treatments administered to the patients and shown in Table 1 were not included in the univariate and multivariate analysis.

Our study had some limitations. First, our study was a single-center study and this may affect the impact power of our study. Second, patients were unable to collect urine when diagnosing AKI and applying the criteria for AKI recovery. For this reason, the urine criterion, which is one of the KDIGO criteria, could not be applied. Third, because it is a retrospective study, some variables that may be associated with mortality may be missing.

In conclusion, although AKI was found to be predictive of an increased mortality rate among patients admitted with SARS-CoV-2 infection, various other predictors existed for mortality in COV-AKI. We determined that age, higher admission levels of CRP, procalcitonin, and CK, highest creatinine, KDIGO stage 2 and 3 AKI and RRT were significantly associated with increased inhospital mortality in COV-AKI. The mortality rate is substantially higher in patients who have KDIGO stage 2, 3 AKI, and who undergo RRT. However, we found that patients with AKI on admission had a lower mortality rate than patients who developed AKI during the hospital stay. Therefore, renal functions should be closely monitored in patients admitted and hospitalized due to COVID-19 infection. Early detection and treatment of renal dysfunction, especially after hospitalization, is of great importance. If these patients are closely monitored with the collaboration of the nephrology department, early and effective treatment may be provided.

AUTHORS CONTRIBUTIONS

Conception and design of the study (Enver Yüksel), data collection (All authors), statistical analysis (Enver Yüksel, Derya Deniz Altıntaş), interpretation of the data (Enver Yüksel, Derya Deniz Altıntaş), article writing (Enver Yüksel), manuscript review and modification (Enver Yüksel, Derya Deniz Altıntaş). All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study protocol is performed in accordance with the relevant guidelines in the manuscript. Informed consent from patients was waived due to the need for rapid data collection during the pandemic period by the institutional review board. The authors of this manuscript declare no ethical conflict. The research complied with the Declaration of Helsinki [33]. The study was approved by the Ethics Committee of our hospital after obtaining approval from the Ministry of Health (date and number of ethics committee: 15/01/2021, no: 640).

ORCID

Enver Yüksel https://orcid.org/0000-0003-0302-932X
Songül Arac https://orcid.org/0000-0001-6830-3639
Derya Deniz Altintaş https://orcid.org/0000-0002-2618-9177

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