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Prognostic and Risk Factors in Renal Transplant Recipients During the COVID-19 Pandemic

Author(s) [1]Kadir Gökhan Atılgan, [2]Büşra Erinç Altıntaş, [1]Gülay Ulusal Okyay, [1]Fatma Ayerden Ebinç, [1]Ebru Gök Oğuz, [3]İrfan Şencan, [1]Mehmet Deniz Aylı

Affiliation(s)
[1]University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Nephrology, Ankara, Turkey
[2]University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Internal Medicine, Ankara, Turkey
[3]University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey

Corresponding Author Kadir Gökhan Atılgan, Etlik City Hospital, Department of Nephrology, Ankara, Turkey.
E-mail: drgokhanatilgan@gmail.com

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Abstract

Background: We aim to compare potential factors that may affect the prognosis of kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) with the diagnosis of COVID-19.

Method: This single-center retrospective study was conducted at the University of Health Science Diskapi Yildirim Beyazit Training and Research Hospital hospital. From March 1, 2021, to September 30, 2021, 110 individuals diagnosed with COVID-19 and ≥18 years old were included in our study. The study population comprised 29 kidney transplant recipients (KTRs) and 81 hemodialysis patients (HDPs). Data were collected from the hospital's software and included patient descriptive features, laboratory test results, medication records, demographic information, comorbidities, and clinical outcomes of COVID-19 diagnosis, such as mortality and discharge rates.

Results: A total of 110 patients (29 KTRs, 81 HDPs) were evaluated. There was no significant difference in mortality rates observed between the groups (p=0.117). Coronary artery disease (CAD) was found to be associated with mortality in both KTRs and HDPs (p=0.001 and p=0.021, respectively). A logistic regression analysis model identified age above 55 years as a significant mortality-related factor in HDPs (p=0.039). Pro-brain natriuretic peptide (pro-BNP) and procalcitonin levels at admission, and increase in serum creatinine, neutrophil count, lactate dehydrogenase (LDH), d-dimer, procalcitonin and urea urea during hospitalization were associated with death in KTRs (p<0.05).

Conclusion: This study highlights comparable mortality rates in KTRs and HDPs hospitalized due to COVID-19. Kidney injury (increase in creatinine, urea), presence of CAD, proBNP, D-dimer, LDH), and inflammation (increase in neutrophil count, procalcitonin) could be a predictor of mortality in KTRS with COVID-19. Despite ongoing debates on immunosuppressive medications, our findings suggest a potential role in mitigating COVID-19 severity. Additionally, age > 55 years is a strong indicator of in HDPs with COVID-19.

Keywords: COVID-19, CoronaVac, Pfizer-BioNTech, vaccine side effects, allergies

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is associated with an increased risk of morbidity and mortality among individuals with comorbidities such as chronic kidney disease (CKD) (1). Kidney transplant recipients (KTRs) pose significantly poorer prognoses in COVID-19 when compared to the general population. This increased vulnerability is associated with the presence of comorbidities and the impact of immunosuppressive therapy (2).

The preliminary data highlighted the disproportional higher COVID-19 fatality rates in the kidney transplanted population compared with the general population (3). Besides studies indicate that kidney transplantation provides a more favorable survival rate

during the COVID-19 pandemic compared to other renal replacement therapies, despite a few opposite claims (4-6). Hence, the specific impact of COVID-19 on KTRs remains uncertain.

Immunization stands as the most robust defense against diseases, however, studies including KTRs reveal a diminished antibody response, even after the second dose of an mRNA vaccine, when compared to the general population (7). It is a fact that KTRs are at risk since most of the available data are based on mRNA vaccination results of patients who have undergone solid organ transplants and considering that vaccination with mRNA is the most common method (8).

Adverse outcomes in individuals with COVID-19 were found to be correlated with various factors, including gender, age, lifestyle, and cardio-metabolic symptoms (9). The identification of prognostic factors holds pivotal importance in both the prevention and management of disease development in kidney transplant recipients (KTRs), a high-risk group susceptible to COVID-19. (10).

In this study, we aimed to investigate potential prognostic factors in KTRs and hemodialysis patients (HDPs), who were diagnosed with COVID-19 and required hospitalization.

METHODS

Study Design

This is a retrospective single-center case-control study. The standard treatments for COVID-19 patients aligned with the guidelines outlined by the Ministry of Health of the Republic of Turkey. The study ethics approval was obtained from the local clinical research ethics committee of our hospital (IRB no: 114/06). This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects

Patients and Protocols

The study encompassed adult individuals (≥18 years old) who were kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) without a history of kidney transplantation. These participants sought medical attention at our hospital between March 01, 2021, and September 30, 2021, and were subsequently admitted to COVID-19 services or the intensive care unit. Inclusion criteria were based on positive COVID-19 PCR test results and the presence of ground glass opacities and/or mixed consolidation areas in lung computed tomography. HDPs were confirmed whether they had received an adequate previous hemodialysis treatment by inquiring about their records (patients with KT/V> 1.2 were included).

The immunosuppressive therapy consisted of prednisolone, mycophenolic acid, calcineurin inhibitors, or mammalian target of rapamycin (mTOR) inhibitors. Mycophenolic acid doses were reduced by half and prednisolone doses were doubled following the diagnosis of COVID-19. Based on lymphocyte counts and clinical course, mycophenolic acid therapy was interrupted when mandatory. One patient received anakinra (3x200mg intravenously) and three patients received tocilizumab (8 mg/kg, at a maximum dose of 800 mg). A patient treated with tocilizumab also received a cytokine filter therapy (Ultraflux EMiC2 Fresenius Medical Care Turkey).

After admission, laboratory and imaging tests were conducted as clinically indicated, encompassing complete blood counts, serum biochemistry, ferritin, procalcitonin, D-dimer, fibrinogen, N-terminal pro-brain natriuretic peptide (proBNP), C-reactive protein (CRP), and lactate dehydrogenase (LDH). Additionally, chest X-ray and computed tomography were performed. Symptoms, medical history, comorbidities, physical examination findings, age, gender, length of hospital stay, and the outcomes (death or discharge) were recorded from the hospital's software. ProBNP levels were specifically assessed on the initial day of admission. The changes in the study parameters were demonstrated by calculating a Δ (the difference between the baseline levels at admission [parameter-1] and the peak levels after admission [parameter-2] for the following tests: urea, creatinine, LDH, neutrophils, lymphocytes, ferritin, fibrinogen, D-dimer, procalcitonin, and CRP).

STATISTICAL ANALYSIS

Simple arithmetic means and percentages were employed to synthesize demographic and clinical data. The distribution characteristics of continuous variables were examined using the Shapiro-Wilk test and histograms. Continuous variables were summarized as the arithmetic mean ± standard deviation (SD) or median (minimum-maximum), depending on the type and distribution. Intergroup comparisons of parametric and nonparametric variables were carried out using the independent samples t-test and the Mann-Whitney U test, respectively. Categorical variables were compared using the chi-square test. Logistic regression was utilized to assess the effects of continuous variables on mortality and survival in both the kidney transplant recipients (KTRs) and hemodialysis patients (HDPs) groups. The analysis was conducted using Statistical Package for Social Sciences version 23 software. $P<0.05$ was assumed as significant.

RESULTS

The study encompassed a total of 110 patients, consisting of 29 KTRs and 81 HDPs. 43 individuals (39.1%) were women. **Table 1** presents the descriptive statistics

Table 1. Distribution of demographic characteristics, comorbidities and symptoms in KTRs and HDPs

		KTRs, N(%)		HDPs, N(%)		P value
Age (year)	≤55	16	55.2	32	39.5	0.144
	>55	13	44.8	49	60.5	
Sex	Female	10	34.5	33	40.7	0.553
	Male	19	65.5	48	59,3	
Prognosis	Discharge	25	86.2	58	71.6	0.117
	Death	4	13.8	23	28.4	
DM	Yes	20	69.0	46	56.8	0.251
	No	9	31.0	35	43.2	
HT	Yes	18	62.1	40	49.4	0.240
	No	11	37.9	41	50.6	
CAD	Yes	26	89.7	63	77.8	0.163
	No	3	10.3	18	22.2	
Cough	Yes	10	43.5	33	50.8	0.548
	No	13	56.5	32	49,2	
Dispnea	Yes	13	56.5	29	44.6	0.326
	No	10	43.5	36	55.4	
Diarrhea	Yes	20	87.0	59	90.8	0.604
	No	3	13.0	6	9.2	
Nausea Vomiting	Yes	20	87.0	63	96.9	0.076
	No	3	13.0	2	3.1	
Myalgia	Yes	13	56.5	51	78.5[a]	**0.042**
	No	10	43.5[b]	14	21.5	
Fever	Yes	18	78.3	38	58.5	0.090
	No	5	21.7	27	41.5	
Headache	Yes	21	91.3	61	93.8	0.678
	No	2	8.7	4	6.2	

KTRs; kidney transplant recipients, HDPs; hemodialysis patients, DM; diabetes mellitus, HT; hypertension, CAD: coronary artery disease

of categorical patient characteristics. The groups demonstrated similarity in terms of gender distribution, comorbidity rates, and age groups (divided into two groups as >55 and ≤55 years of age). The duration of hospital stay averaged 11.6±9.4 days for KTRs and 14.3±13.8 days for HDPs. 27 individuals died, constituting a mortality rate of 24.5%. The mortality rate was relatively higher in HDPs, however, no statistically significant difference was observed between the two groups (p=0.117). The frequency of myalgia as a presenting complaint was significantly higher in KTRs compared to HDPs (56.5% vs 21.5%, p= 0.042).

The mean age was 50.66±11.73 years and 58.89±14.22 years in KTRs and HDPs, respectively (p=0.006). In the HDPs group, the mean levels of urea-1, urea-2, creatinine-1, creatinine-2, ferritin-1, CRP-2, and ΔCRP, and the neutrophil-2/lymphocyte-2 ratio were significantly higher, and in the KTRs group, the mean levels of LDH-2, ΔLDH, and lymphocyte-2 were significantly higher (p<0.05) (Table 2).

The presence of coronary artery disease (CAD) was associated with mortality in the KTRs group (p=0.001), however, this association was found in individuals aged >55 years (p=0.039) and those with CAD in the HDPs group (p=0.021) (Table 3).

In the KTRs group, the levels of creatinine-2,

Table 2. Descriptive values of numerical characteristics of KTRs and HDPs groups

	Group	N	Mean	SD±	P value
Age (Year)	KTRs	29	50.66	11.73	**0.006**
	HDPs	81	58.89	14.22	
CCI	KTRs	29	2.93	1.49	0.655
	HDPs	81	2.79	2.05	
Urea1 (mg/dl)	KTRs	29	53.08	31.33	**0.001**
	HDPs	78	106.58	50.20	
Urea2 (mg/dl)	KTRs	29	62.90	37.23	**0.001**
	HDPs	72	130.36	57.23	
ΔUrea	KTRs	29	-9.82	22.55	0.080
	HDPs	72	-23.83	56.92	
Creatinine1 (mg/dl)	KTRs	29	1.66	1.16	**0.031**
	HDPs	78	9.93	21.04	
Creatinine2 (mg/dl)	KTRs	29	1.72	1.43	**0.001**
	HDPs	71	6.52	2.90	
ΔCreatinine	KTRs	29	-0.06	0.71	0.573
	HDPs	71	0.10	0.17	
Neutrophile1	KTRs	29	4572.93	1916.52	0.918
	HDPs	79	5929.49	5409.88	
Neutrophile2	KTRs	29	4712.00	3159.56	0.924
	HDPs	73	5753,01	4894,84	
Lenfocyte1	KTRs	29	1066.14	630.73	0.072
	HDPs	76	987,30	783,11	
Lenfocyte2	KTRs	29	1188.97	780.37	**0.001**
	HDPs	70	965.59	968.53	
LDH1 (mg/dl)	KTRs	27	268.37	163.85	0.101
	HDPs	69	322.75	149.97	
LDH2 (mg/dl)	KTRs	27	377.07	477.52	**0.020**
	HDPs	57	352,49	191,90	
ΔLDH	KTRs	27	-108.70	455.35	**0.024**
	HDPs	57	-20.61	186.46	
Ferritin1 (µg/L)	KTRs	22	663.60	894.19	**0.031**
	HDPs	67	2425.71	2612.37	
Ferritin2 (µg/L)	KTRs	23	963.87	1387.85	0.112
	HDPs	39	1900.67	1706.83	
Fibrinogen1 (g/L)	KTRs	22	470	164.43	0.820
	HDPs	75	477.84	134.05	
Fibrinogen2 (g/L)	KTRs	22	454.68	154.37	0.864
	HDPs	48	461.15	141.92	
ΔFibrinogen	KTRs	22	15.32	158.54	0.461
	HDPs	51	50.08	193.71	
D-dimer1 (µg/ml)	KTRs	24	1.71	4.40	0.187
	HDPs	75	3.70	4.09	
D-dimer2 (µg/ml)	KTRs	23	2.37	6.97	0.239
	HDPs	59	3.71	3.50	
ΔD-dimer	KTRs	23	-0.60	8.54	0.793
	HDPs	58	0.43	4.06	
Procalsitonin1 (µg/L)	KTRs	25	1.31	5.09	0.154
	HDPs	76	71.07	417.79	
Procalsitonin2 (µg/L)	KTRs	24	8.91	28.10	0.067
	HDPs	51	17.74	74.84	
ΔProcalsitonin	KTRs	24	-7.56	24.82	0.143
	HDPs	52	24,94	190,71	
Probnp (ng/L)	KTRs	24	1904.27	3711.01	0.122
	HDPs	73	17079.1	13052.15	
AST (mg/dl)	KTRs	29	38.36	55.94	0.617
	HDPs	77	27.89	26.07	
ALT (mg/dl)	KTRs	29	33.66	29.57	0.134
	HDPs	77	22.73	32.55	
CRP1 (mg/L)	KTRs	28	65.93	74.14	0.507
	HDPs	75	121.12	118.90	
CRP2 (mg/L)	KTRs	27	52.38	82.95	**0.017**
	HDPs	57	90.83	82.12	
ΔCRP	KTRs	27	15.94	77.85	**0.026**
	HDPs	57	36.94	127.04	
Neutrophile1/Lenfocyte1	KTRs	29	7.70	12.00	0.405
	HDPs	76	8.48	10.18	
Neutrophile2/Lenfocyte2	KTRs	29	8.26	14.69	**0.025**
	HDPs	68	9.41	12.17	

CCI; Charlson co-morbidity index, LDH; lactate dehydrogenase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; c-reactive protein

neutrophil-1, neutrophil-2, LDH-2, D-dimer-2, procalcitonin-1, procalcitonin-2, proBNP, Δurea, ΔLDH, Δferritin, and Δprocalcitonin were significantly

Table 3. Evaluation of the relationship between mortality and categorical features in KTRs and HDPs

n %			Discharge		Death		
			n	%	n	%	p value
KTRs	Age (Year)	<=55	14	87.5	2	12.5	0.823
		>55	11	84.6	2	15.4	
	Sex	Female	8	80.0	2	20.0	0.482
		Male	17	89.5	2	10.5	
	DM	No	17	90.0	3	10.0	0.779
		Yes	8	77.8	1	22.2	
	HT	No	16	94.4	2	5.6	0.592
		Yes	9	72.7	2	27.3	
	CAD	No	25	84.6	1	15.4	0.001
		Yes	0	100.0	3	0.0	
HDPs	Age (Year)	<=55	27	84.4	5	15.6	0.039
		>55	31	63.3	18	36.7	
	Sex	Female	27	81.8	6	18.2	0.091
		Male	31	64.6	17	35.4	
	DM	No	36	78.3	10	21.7	0.128
		Yes	22	62.9	13	37.1	
	HT	No	31	77.5	9	22.5	0.245
		Yes	27	65.9	14	34.1	
	CAD	No	49	77.8	14	22.2	0.021
		Yes	9	50.0	9	50.0	

DM; diabetes mellitus, HT; hypertension, CAD; coronary artery disease

higher in non-survivors (p<0.05) (**Table 4**). In HDPs, Δneutrophil and ΔLDH were significantly higher and lymphocyte-2 was significantly lower in non-survivors. The values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported as indicators of poor prognosis in COVID-19 within the general population, did not demonstrate a significant association with mortality in the comparative analysis of the two groups (p=0.924 vs p=0.218 and p=0.217 vs p=0.845, KTRs vs HDPs respectively).

We performed a univariate binary logistic regression analysis to evaluate the risk ratios of mortality-related factors. **Table 5** demonstrates the results from the logistic regression analysis. Only HDPs above 55 years of age had a significantly higher risk of death (OR: 3.135 (1.026-9.582) (p=0.045). The risk of death was significantly higher in patients with CAD in both groups (OR: 3.500 (1.167-10.498) (p=0.025).

DISCUSSION

It is controversial whether the course of COVID-19 is different in KTRs compared to HDPs. Identification of prognostic factors in KTRs is crucial to lower worse outcomes. In this study, mortality rates in KTRs and HDPs requiring hospitalization due to COVID-19 were similar and CAD was associated with mortality in both of the KTRs and HDPs groups.

The relationship between COVID-19 and mortality remains unclear in KTRs (4-6,11). Mortality rates in KTRs were reported as 28% by a study conducted at Columbia University, 25% in Spain, and 25% in Italy

Table 4. Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

	Group	Prognosis	N	Mean	SD±	P value
Age (Year)	KTRs	Discharge	25	50.16	11.71	0.579
		Death	4	53.75	13.15	
	HDPs	Discharge	58	57.88	15.15	0.257
		Death	23	61.43	11.42	
CCI	KTRs	Discharge	25	2.76	1.51	0.065
		Death	4	4.00	0.82	
	HDPs	Discharge	58	2.53	2.07	0.060
		Death	23	3.43	1.88	
Urea1 (mg/dl)	KTRs	Discharge	25	54.66	32.79	0.508
		Death	4	43.23	20.29	
	HDPs	Discharge	55	107.06	51.94	0.897
		Death	23	105.43	46.84	
Urea2 (mg/dl)	KTRs	Discharge	25	58.01	36.20	.076
		Death	4	93.48	31.82	
	HDPs	Discharge	49	128.54	58.86	0.697
		Death	23	134.23	54.67	
ΔUrea	KTRs	Discharge	25	-3.35	12.89	**0.049**
		Death	4	-50.25	29.79	
	HDPs	Discharge	49	-21.49	54.33	0.615
		Death	23	-28.80	63.08	
Creatinine1 (mg/dl)	KTRs	Discharge	25	1.65	1.21	0.926
		Death	4	1.71	0.90	
	HDPs	Discharge	56	11.37	24.69	0.339
		Death	22	6.27	2.51	
Creatinine2 (mg/dl)	KTRs	Discharge	25	1.52	1.26	**0.050**
		Death	4	2.98	1.94	
	HDPs	Discharge	49	6.74	3.23	0.265
		Death	22	6.04	1.96	
ΔCreatinine	KTRs	Discharge	25	0.13	0.28	0.126
		Death	4	-1.27	1.33	
	HDPs	Discharge	49	0.05	2.26	0.748
		Death	22	0.23	2.01	
Neutrophile1	KTRs	Discharge	25	4143	1473.56	**0.014**
		Death	4	7260	2396.50	
	HDPs	Discharge	56	6249.29	6017.74	0.627
		Death	23	5150.87	3512.42	
Neutrophile2	KTRs	Discharge	25	4086	2365.96	**0.050**
		Death	4	8625	4970.83	
	HDPs	Discharge	51	5427.06	4223.99	0.833
		Death	22	6508.64	6229.71	
ΔNeutrophile	KTRs	Discharge	25	57.08	2265.67	0.255
		Death	4	-1365	4879.87	
	HDPs	Discharge	51	129.22	5466.74	**0.050**
		Death	22	-1517.73	4053.07	
Lenfocyte1	KTRs	Discharge	25	1047.92	622.17	0.569
		Death	4	1180	772.14	
	HDPs	Discharge	53	1040.85	841.54	0.384
		Death	23	863.91	627.64	
Lenfocyte2	KTRs	Discharge	25	1256	772.56	0.154
		Death	4	770	798.42	
	HDPs	Discharge	47	1113	1135.29	**0.007**
		Death	23	664.35	325.39	

continues...

(12-14). According to the data provided by the European Kidney Association COVID-19 Database (ERACODA), the mortality prediction rate within 28 days was 21.3% in KTRs and 25.0% in HDPs (15). A multicenter study conducted in Turkey revealed a mortality rate of 12.5%

Table 4 (continues). Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

ΔLenfocyte	KTRs	Discharge	25	-208.08	651.67	0.486
		Death	4	410	1192	
	HDPs	Discharge	47	-79.70	1282.86	0.368
		Death	23	199.57	561.28	
Neutrophile1/ Lenfocyte1	KTRs	Discharge	25	6.40	9.81	0.411
		Death	4	15.80	21.75	
	HDPs	Discharge	53	9.16	11.73	0.919
		Death	23	6.94	4.93	
Neutrophile2/ Lenfocyte2	KTRs	Discharge	25	4.91	5.97	0.067
		Death	4	29.16	32.43	
	HDPs	Discharge	46	7.45	8.02	0.100
		Death	22	13.50	17.58	
LDH1 (mg/dl)	KTRs	Discharge	24	275.13	171.17	0.419
		Death	3	214.33	84.63	
	HDPs	Discharge	46	320.67	156.35	0.809
		Death	23	326.91	139.60	
LDH2 (mg/dl)	KTRs	Discharge	24	258.21	189.74	**0.041**
		Death	3	1328	1012.11	
	HDPs	Discharge	35	316.20	136.44	0.380
		Death	22	410.23	249.76	
ΔLDH	KTRs	Discharge	24	16.92	99.30	**0.007**
		Death	3	-1113.67	936.91	
	HDPs	Discharge	35	21.46	145.55	**0.050**
		Death	22	-87.55	225.32	
Ferritin1 (µg/L)	KTRs	Discharge	20	527.35	523.34	0.568
		Death	2	2026.10	2739.19	
	HDPs	Discharge	46	2103.18	2065.93	0.380
		Death	21	3132.19	3486.30	
Ferritin2 (µg/L)	KTRs	Discharge	21	708.71	703.21	0.126
		Death	2	3643	4094.15	
	HDPs	Discharge	25	1621.56	1131.40	0.650
		Death	14	2399.07	2394.83	
ΔFerritin	KTRs	Discharge	20	-144.45	332.20	**0.030**
		Death	2	-1616.90	1354.96	
	HDPs	Discharge	24	94.13	1760.72	0.694
		Death	14	-145.50	2162.14	
Fibrinogen1 (g/L)	KTRs	Discharge	19	480.95	169.29	0.445
		Death	3	400.67	132.67	
	HDPs	Discharge	53	484.13	139.22	0.532
		Death	22	462.68	122.40	
Fibrinogen2 (g/L)	KTRs	Discharge	19	473.11	147.72	0.164
		Death	3	338	173.67	
	HDPs	Discharge	33	451.24	141.50	0.479
		Death	15	482.93	145.29	
ΔFibrinogen	KTRs	Discharge	19	7.84	141.17	0.590
		Death	3	62.67	284	
	HDPs	Discharge	36	76.03	206.42	0.140
		Death	15	-12.20	147	
D-dimer1 (µgml)	KTRs	Discharge	21	1.66	4.69	0.060
		Death	3	2.04	1.44	
	HDPs	Discharge	52	3.68	4.04	0.735
		Death	23	3.76	4.30	

continues...

among KTRs, while another independent multicenter study from the same region reported mortality rates of 21% in KTRs and 25.4% in HDPs (4,16). In our study, mortality rates were found similar; 13.8% in KTRs and 28.4% in HDPs. This study demonstrates similar

Table 4 (continues). Comparison of survivors (discharge) and died (death) in the KTRs and HDPs groups.

D-dimer2 (µg/ml)	KTRs	Discharge	20	2.33	7.48	**0.028**
		Death	3	2.65	1.73	
	HDPs	Discharge	39	3.67	3.18	0.898
		Death	20	3.80	4.15	
ΔD-dimer	KTRs	Discharge	20	-0.60	9.13	0.523
		Death	3	-0.61	2.99	
	HDPs	Discharge	38	0.56	4.39	0.695
		Death	20	0.19	3.43	
Procalsitonin1 (µg/L)	KTRs	Discharge	21	0.30	0.50	**0.041**
		Death	4	6.61	12.70	
	HDPs	Discharge	54	40.51	257.44	0.986
		Death	22	146.07	669.19	
Procalsitonin2 (µg/L)	KTRs	Discharge	21	0.62	1.76	**0.010**
		Death	3	66.96	57.22	
	HDPs	Discharge	35	20.66	89.05	0.707
		Death	16	11.35	25.19	
ΔProcalsitonin	KTRs	Discharge	21	-0.32	1.43	**0.010**
		Death	3	-58.24	51.60	
	HDPs	Discharge	36	39.25	228.01	0.372
		Death	16	-7.28	27.62	
Probnp (ng/L)	KTRs	Discharge	20	994.62	2569.51	**0.004**
		Death	4	6452.50	5537.94	
	HDPs	Discharge	53	16736.87	12935.89	0.769
		Death	20	17985.85	13652.92	
AST(mg/dl)	KTRs	Discharge	25	27.65	17.18	0.217
		Death	4	105.28	141.15	
	HDPs	Discharge	54	29.27	28.62	0.845
		Death	23	24.67	18.97	
ALT (mg/dl)	KTRs	Discharge	25	33.46	30.22	0.924
		Death	4	34.92	29.19	
	HDPs	Discharge	54	25.95	37.50	0.218
		Death	23	15.17	13.70	
CRP1 (mg/L)	KTRs	Discharge	25	63.63	72.73	0.683
		Death	3	85.09	100.57	
	HDPs	Discharge	53	126.12	121.51	0.557
		Death	22	109.08	114.22	
CRP2 (mg/L)	KTRs	Discharge	24	42.70	72.56	0.123
		Death	3	129.79	137.05	
	HDPs	Discharge	39	74.23	63.43	0.074
		Death	18	126.82	105.92	
ΔCRP	KTRs	Discharge	24	23.52	62.12	0.589
		Death	3	-44.70	167.96	
	HDPs	Discharge	39	57.72	131.43	**0.012**
		Death	18	-8.07	106.82	

CCI; Charlson Comorbidity Index, LDH; lactate dehydrogenase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, CRP; c-reactive protein

mortality rates in KTRs and HDPs to the previous reports from Turkey, in contrast to lower mortality rates reported from other countries. We believe that the relatively younger ages of KTRs in this study may have contributed to these results. There is a debate regarding the potential augmentation of COVID-19 severity risk associated with the use of immunosuppressive medications. This debate originates from the fact that medications used in transplant patients act on T cells, but not on memory T and B cells (17). In contrast, a recent study has indicated that therapeutic doses of tacrolimus potently

Table 5. Effects of demographic and biochemical parameters on mortality in KTRs and HDPs groups

	KTRs 95% C.I.for OR				HDPs 95% C.I.for OR			
		Lower	Upper	P value		Lower	Upper	P value
Age Group (>55 *vs* <=55)	1.273	0.154	10.530	0.823	3.135	1.026	9.582	**0.045**
Sex (Female *vs* Male)	2.125	0.252	17.927	0.488	0.405	0.140	1.174	0.096
CCI	1.729	0.830	3.602	0.144	1.244	0.975	1.587	0.079
HT	1.778	0.213	14.860	0.595	1.786	0.668	4.776	0.248
DM	0.708	0.063	7.919	0.780	2.127	0.798	5.670	0.131
CAD	72.000	3.512	1476.122	**0.006**	3.500	1.167	10.498	**0.025**
ΔUrea	0.890	0.796	0.995	**0.041**	0.998	0.989	1.007	0.610
ΔCreatinine	0.011	0.000	5.036	0.149	1.039	0.824	1.311	0.744
ΔNeutrophile	1.000	0.999	1.000	0.324	1.000	1.000	1.000	0.218
ΔLenfocyte	1.001	1.000	1.001	0.138	1.000	1.000	1.001	0.329
ΔLDH	0.984	0.958	1.011	0.235	0.996	0.993	1.000	**0.050**
ΔFerritin	0.997	0.994	1.000	0.092	1.000	1.000	1.000	0.704
ΔFibrinogen	1.002	0.994	1.002	0.573	0.997	0.994	1.001	0.145
ΔD-dimer	1.000	0.865	1.000	0.999	0.977	0.854	1.118	0.737
ΔProcalsitonin	0.881	0.522	1.488	0.636	0.975	0.939	1.013	0.191
ΔCRP	0.990	0.975	1.005	0.175	0.995	0.990	1.001	0.078
Neutrophile1/Lenfocyte1	1.045	0.979	1.116	0.190	0.971	0.909	1.038	0.393
Neutrophile2/Lenfocyte2	1.097	0.998	1.206	**0.050**	1.042	0.994	1.092	0.085

OR; Odds Ratio; CI; confidence interval for OR, CCI; Carlson-Comorbidity Index, LDH; lactate dehydrogenase, CRP; C-reactive protein, DM; diabetes mellitus, HT; hypertension, CAD; coronary artery disease

can suppress the proliferation of human coronaviruses in cell culture media (18). This data has given rise to a hypothesis suggesting that standard immunosuppressive therapy in KTRs may potentially inhibit cytokine release, thereby mitigating disease severity and reducing the associated risk of mortality. Moreover, numerous studies in the literature have indicated that various vaccines administered for prophylaxis against diverse infections might confer protection against COVID-19 (19,20). A study by Gürsel et al. has reported that different vaccines can protect against various pathogens, as shown in COVID-19 (21). Some attenuated vaccines, such as Bacillus Calmette-Guerin (BCG), which is listed on the vaccination schedule in our country, can protect against different pathogens of acute respiratory tract infections. The mechanism underlying the nonspecific immunization by the BCG vaccine is suggested to be through the induction of innate immunity (21). Genetic and racial differences are also considered to play an important role in COVID-19 (22).

In this study, there is no impact of age on mortality in KTRs. However, in the HDPs group, being older than 55 years was associated with mortality. Previous studies reported that hypertension (HT), diabetes mellitus (DM), and CAD are the most common comorbidities in non-survivor COVID-19 patients. CAD was the only factor associated with mortality in both KTRs and HDPs in the current study. Similarly, a recent study reported CAD first as the most common cause of mortality due to COVID-19 (23).

Previous studies reported a significant association between acute kidney injury with multi-organ failure and mortality in COVID-19 patients (24,25). In this study, increased urea and creatinine levels suggest an acute kidney injury associated with mortality in KTRs. Additionally, we assessed the influence of neutrophil and lymphocyte counts, the neutrophil/lymphocyte ratio, and levels of procalcitonin, ferritin, and CRP as inflammation parameters on the outcomes of COVID-19. In the KTRs group, inflammatory parameters linked with mortality included neutrophils, procalcitonin, and ferritin. Exacerbation of the inflammatory status in COVID-19 has been associated with an unfavorable prognosis in the general population (10). In this study, we revealed an increased inflammatory status in the KTRs who died. Although we noted lymphocytopenia in the KTRs group, aligning with recent research findings, this observation did not achieve statistical significance. The small number of KTRs and the lack of immunization results associated with vaccinations during the study period are the limitations of our study. During the study period, the patients completed the three-dose schedule of the vaccine. The patients in the KTRs group received attenuated vaccines as the standard first two doses. The patients received either attenuated or mRNA vaccines as the third dose depending on patient preferences. Because of the lack of results to evaluate the immune response, the effect of vaccination on mortality and prognosis could not be evaluated in the study. A recent study involving 30 transplant recipients revealed that, following the administration of the standard two doses of an mRNA vaccine, 6 individuals exhibited a poor immune response, while 24 showed no immune response at all. The study has subsequently reported the outcomes of immunization in this patient cohort with a third dose of the vaccine

(26). In the nonresponder group, the antibody titers on the 14th day following vaccination revealed a strong positive antibody response in 6/24 (25%) recipients and a negative response in 16/24 (67%) recipients. In their later report, the same team reported the results of vaccination of 18 KTRs with the fourth dose. In 3 out of 6 patients (3/18) (16.6%) with a negative antibody response after the third dose of an mRNA vaccine, the antibody response remained negative after the fourth dose (27).

As stated in the limited number of recent studies, the immune responses of KTRs receiving vaccines against COVID-19 do not appear as precise as those obtained in the general population. Our study may add value by identifying the factors affecting the prognosis and reporting the risk ratios during the era when the efficacy of vaccines in transplant recipients is still being discussed. To the best of our knowledge, this is the first study investigating the prognostic factors of COVID-19 in KTRs in Turkey.

CONCLUSION

This study highlights the comparable mortality rates in KTRs and HDPs hospitalized due to COVID-19. The association of CAD with mortality underscores the importance of recognizing specific risk factors in these populations. Despite the unresolved debate on the impact of immunosuppressive medications, our findings suggest a potential role of immunosuppressive regimens in inhibiting cytokine release, offering a novel perspective on managing COVID-19 severity in KTRs. The study's limitations, such as a small KTR sample size and a lack of immunization results, are acknowledged. Nevertheless, this research contributes valuable insights into the unique challenges faced by KTRs during the COVID-19 era.

ETHICAL DECLARATIONS

Conflict of Interest Statement: The author declares no conflicts of interest related to this research.

Informed consent: NA (This is retrospective study)
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Ethical Issues: This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects. The study ethics approval was obtained from the local clinical research ethics committee of our hospital (IRB no: 114/06).

Author Contributions: The authors declared that they all participated in the design, execution, and analysis of the study and that they approved the final version of the paper.

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