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A Retrospective Study on Kidney Transplant Recipients Diagnosed with COVID-19

Böbrek Nakli Alıcılarında COVİD-19 Deneyimi Retrospektif Çalışma

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Abstract

Objective: Solid organ transplantation may cause a predisposition to coronavirus disease-2019 (COVID-19) infections. In the present study, it was aimed to investigate the outcomes of kidney transplant recipients diagnosed with COVID-19.

Materials and Methods: In this retrospective cohort study, files of 1034 kidney transplant recipients from one center were reviewed. 95 of these patients had contracted COVID-19 between March 1, 2020, and March 31, 2021. In this context, patients were divided as survivors and non survivors. Statistical analysis was performed with a student-t test and p<0.05 was accepted as the threshold of significance.

Results: Related 95 patients with COVID-19, were males (58 (61%)). The mean age of all patients was 48.6 ± 11.2 years, and 31 of these patients had received cadaveric transplants (32.6%). Most symptoms were seen in similar frequency in the two groups, with fever in 31%, cough in 39%, myalgias in 59%, and diarrhea in 20%. On the other hand, while only 24% of the survivor group experienced dyspnea, all of the non-survivor group had dyspnea (p<0.05).

Mortality was 12.6% (12 patients). Non-survivors were older (55.89 ± 6.99 vs 47.56±11.33 years; p<0.05), in terms of a higher body mass index (28.8 ± 5.5 vs 25.5 ± 5.0 kg/m2; p< 0.05), more frequently having diabetes (50% vs. 30%; p< 0.05), with longer hospitalization durations (8.5 ± 10.6 vs 3.05 ± 5.93 days; p<0.01) than survivors. Besides, leukocytosis (15.24 ± 8.80 vs 7.13 ± 3.39 /mm3), increased liver function tests (ALT and AST (632 ± 1041 and 2722 ± 4662 vs 22.8 ± 16.8 and 23.3 ± 12.6 (U/L) p<0.001), increased ferritin (2301.3 ± 1349.1 ng/ml vs 898.4 ± 1007.6 ng/ml, p< 0.05), increased lactate dehydrogenase (554±305 vs 252±130 mg/dl, p<0.001), increased procalcitonin (1.310±1.285 vs 0.108±0.105 ng/ml, p<0.001) were more frequent in non-survivors. Estimated glomerular filtration rate levels were lower (11.12 ± 1.89 vs 50.75 ± 21.99 ml/min, p<0.05). Hemodialysis was required for all non-survivors and 2% of survivors. Survival was significantly lower in patients with cadaveric transplants (Kaplan Meier analysis; p<0.05).

Conclusion: Renal transplant recipients with COVID-19 experienced had an increase in terms of acute kidney injury and mortality in the present study. Furthermore, mortality was higher in cadaveric patients.

Keywords: Acute Kidney Injury, Coronavirus Disease 2019, Renal Transplant Recipients.

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Öz

Amaç: Solid organ nakli olanlar, Koronavirüs Hastalığı-2019 (COVİD-19) enfeksiyonlarına yatkın olabilir. Bu çalışmada COVİD-19 tanısı alan böbrek nakli alıcılarının sonuçlarının sunulması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmada, 1 Mart 2020 ile 31 Mart 2021 tarihleri arasında bir merkezden 95 böbrek nakli alıcısının dosyaları kullanıldı, 95'ine COVİD-19 tanısı konuldu. Hastalar hayatta kalanlar ve hayatta kalmayanlar olarak ayrıldı. İstatistiksel olarak student t testi yapıldı ve p<0.05 düzeyi anlamlı kabul edildi.

Bulgular: 95 hastanın 58'i (%61) erkek olup, yaş ortalaması 48,6±11,2 yıl, kadavra nakli yapılan 31 hasta (%32,6) vardır. Belirtiler olan ateş %31, öksürük %39, miyalji %59, ishal %20, genel olarak benzerdi; nefes darlığı hayatta kalanların %24'ünden olduğu halde hayatını kaybedenlerin tümünde mevcuttu (p<0,05). Mortalite 12 (%12,6) idi. Ölenler daha yaşlıydı 55,89±6,99 ve 47,56±11,33 (p<0,05), vücut kitle indeksi daha yüksekti 28,8 ± 5,5 ve 25,5 ± 5,0 kg/m2 (p< 0,05), diyabet %50 ila 30 (p< 0.05) daha belirgindi. Ölenlerde hastanede kalış süresi 8.5±10.6 güne karşılık 3,05 ± 5,93 gün (p< 0,01) daha uzundu.

Ölenlerde lökositoz 15,24 ± 8,80 ve 7,13 ± 3,39 /mm3, karaciğer fonksiyon testleri ALT ve AST 632 ± 1041 ve 2722 ± 4662 ila 22,8 ±16,8 ve 23,3 ± 12,6 U/L, (p<0,001), ferritin 2301,3 ± 1349,1 ve 898,4 ± 1007,6 ng/ml (p<0,05), laktat dehidrojenaz 554 ± 305 ve 252 ± 130 (mg/dl) (p<0,001), prokalsitonin 1,310 ± 1,285 ve 0,108 ± 0,105 ng/ml (p<0,001) artmıştır. Tahmini glomerüler filtrasyon hızı düzeyleri 11,12 ± 1,89'a karşılık 50,75±21,99 ml/dk (p<0,05) azalmıştır. Hayatta kalmayanların tümü ve hayatta kalanların %2'sinin hemodiyaliz ihtiyacı vardı. Kaplan Meier analizinde kadavra hastalarında sağkalım anlamlı olarak daha düşüktü (p<0,05).

Sonuç: COVİD-19'lu böbrek nakli alıcılarında akut böbrek hasarı ve mortalite oranı artmıştır, kadavradan nakilli hastaların sağkalımı daha düşük olmuştur.

Anahtar Kelimeler: Akut Böbrek Hasarı, Coronavirüs-19 Hastalığı, Böbrek Nakli Alıcıları.

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported from Wuhan. Most clinical symptoms are similar to influenza, which include fever, cough, myalgia, dyspnea, diarrhea, anosmia, and taste problems. Co-morbidities may affect the defense against viral disease. Sepsis, pneumonia, acute respiratory distress syndrome, multi-organ failure, and eventually death may be seen in this disadvantaged group.

The first report on COVID-19 infections in renal transplant recipients is also from Wuhan, China, which documented 10% mortality (1 in 10 patients) (2). Solid organ transplant recipients may be more likely to experience severe COVID-19 infection, as they are on immunosuppressive treatment. It is well known that transplant recipients are more likely to contract COVID-19 infection and to experience a more severe disease. Knowledge of COVID-19 infections in kidney transplant recipients continues to increase. Those with a high mortality risk are the elderly and those with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus (3).

As the disease is still prevalent worldwide, it is important to report all relevant COVID-19 data. We aimed to present the demographics and clinical features with outcomes of COVID-19 infection among a large number of renal transplant recipients at one center.

Materials and Methods

This study was designed as a retrospective cohort review of 1034 kidney transplant recipients in Acibadem Bursa Hospital registry, among whom 95 were found to have COVID-19 in between March 1, 2020 and March 31, 2021. The study was approved by the Acıbadem Mehmet Ali Aydınlar Üniversitesi Tıbbı Araştırmalar Değerlendirme Kurulu (date: 22.04.2022 and approval number: 2022-07/10). Patient demographics, clinical presentations, laboratory data, immunosuppressive medications, and treatment modalities, along with age, sex, weight, type of transplantation, primary kidney disease, presence of comorbid conditions, clinical outcomes and duration of hospitalization were determined.

Biochemical tests including kidney function tests, liver function tests, lactate dehydrogenase (LDH), D-dimer, ferritin, C-reactive protein (CRP), complete blood count, procalcitonin.

Statistical analysis was performed with SPSS-22 for Windows (SPSS Inc. Chicago IL, USA). The continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of distribution. The Mann–Whitney test was used to compare the variables that weren't normally distributed. Student's t-test was used to compare the variables with normal distribution. To compare the qualitative data, the chi-square test or Fisher's exact test (when chi-square test assumptions did not hold due to low expected cell counts) was used. Kaplan Meier analysis was used as a survival test. Survivor patients and non survivors were compared and $p<0.05$ level was used for statistical significance.

Results

The 95 renal transplant recipients who had COVID-19 had a mean age of 48.6±11.2 years, 58 (61%) males, 31 (32.6%) had received cadaveric transplants, 10 (10.5%) had primary renal disease with diabetes, 10 (10.5%) had glomerulonephritis, 6 (6.3%) had autosomal dominant polycystic kidney disease, 4 (4.2%) had amyloidosis, 5 (5.2%) had vesicoureteral reflux. Most symptoms were seen in similar frequency in the two groups, with fever in 31%, cough in 39%, myalgias in 59%, and diarrhea in 20%. On the other hand, while only 24% of the survivor group experienced dyspnea, all of the non-survivor group had dyspnea ($p<0.01$).

The mortality rate was 12.6% (12 patients). Non-survivors were older (55.89±6.99 vs 47.56±11.33 years; $p=0.015$) in terms of a higher body mass index (28.8 ± 5.5 vs 25.5 ± 5.0 kg/m2; $p=0.047$), more frequently having diabetes (50% vs. 30%; $p=0.005$), with longer hospitalization durations (8.5 ± 10.6 vs 3.05 ± 5.93 days; $p=0.009$) than survivors (Table 1).

Leukocytosis (15.24 ± 8.80 vs 7.13 ± 3.39/mm3), increased liver function tests (ALT and AST) (632 ± 1041 and 2722 ± 4662 vs 22.8 ± 16.8 and 23.3 ± 12.6 (U/L) $p=0.001$), increased ferritin (2301.3 ± 1349.1ng/ml vs 898.4 ± 1007.6ng/ml, $p=0.029$), increased lactate dehydrogenase (554 ± 305 vs 252 ± 130 (mg/dl), $p<0.001$), increased procalcitonin (1.310 ± 1.285 vs 0.108 ± 0.105 (ng/ml), $p<0.001$) were more frequent in non-survivors. Estimated

glomerular filtration rate levels were lower (11.12 ± 1.89 vs 50.75 ± 21.99 ml/min, p=0.004) (Table 2). Hemodialysis was required for all non-survivors and 2% of survivors. Survival duration was shorter in cadaveric transplant recipients, according to Kaplan Meier analysis (Figure 1).

Table 1
Baseline Demographics, Symptoms, And Comorbidities of Kidney Transplant Recipients With COVID-19

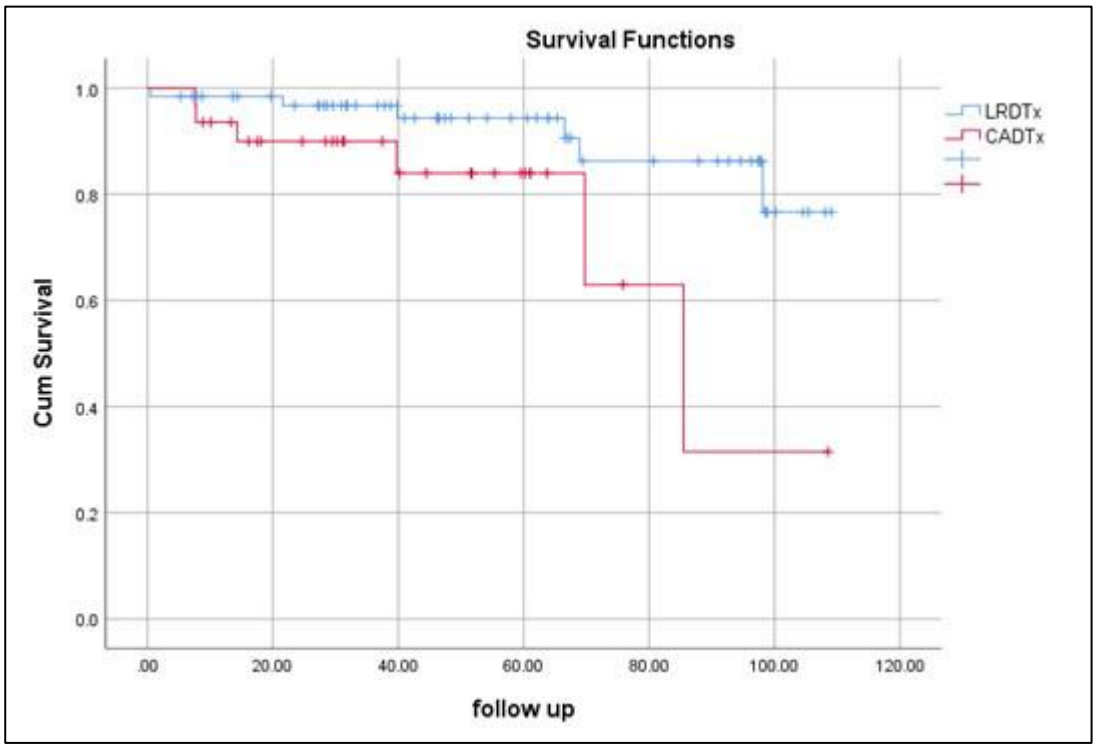
	Total (n:95)	**Survivors (n:83)**	**Non-Survivors (n:12)**	***p***
Age (years)	48.61±11.20	47.56 ± 11.33	55.89 ± 6.99	**0.015**
Height (cm)	166.4±10.30	165.9 ± 10.40	169.6 ± 9.38	0.262
Weight (kg)	72.11±16.08	70.26 ± 15.09	84.28 ± 17.78	**0.004**
BMI (kg/m2)	25.9±5.2	25.5 ± 5.0	28.8 ± 5.5	**0.047**
Male (%)	61	58	83	0.634
Cadaveric tx (%)	33	30	50	0.173
DM (%)	33	30	50	**0.005**
Heart disease (%)	23	22	33	0.377
HT (%)	37	35	50	0.317
Smoking (%)	28	29	25	0.781
Fever (%)	31	29	42	0.375
Cough (%)	39	42	17	0.244
Dyspnea (%)	34	24	100	**0.000**
Myalgias (%)	59	58	67	0.693
Diarrhea (%)	20	18	29	0.548
Chest radiographic findings consistent with viral pneumonia (%)	85	83	100	0.283
Favipravir (%)	95	94	100	0.550
Hospitalization (%)	40	36	75	**0.034**
Hospitalization days	3.74±6.87	3.05 ± 5.93	8.50 ± 10.7	**0.009**

BMI: Body mass index, **DM**: Diabetes mellitus, **HT**: Hypertension.

Table 2
Laboratory Data of Kidney Transplant Recipients With COVID-19

	Total (n:95)	**Survivors (n:83)**	**Non-Survivors(n:12)**	***p***
White-cell count (/mm3)	7.62±4.21	7.13 ± 3.39	15.2 ± 8.80	**0.001**
Lymphocyte count(/mm3)	15.4±11.1	16 ± 11.2	7.30 ± 7.11	0.193
Platelet count (/mm3)	231.4±82.7	236.7 ± 80.5	150.3 ± 89.2	0.080
ALT (U/L)	69.7±290.4	22.8 ± 16.8	632 ± 1041	**<0.001**
AST (U/L)	211.6±1232.5	23.33 ±12.6	2722 ±4662	**<0.001**
BUN (mmol/L)	34.43±24.50	31.02 ± 19.71	86.67 ± 36.07	**<0.001**
eGFR (ml/min)	47.70±23.67	50.75 ± 21.99	11.12 ± 1.89	**0.004**
Creatinine (mg/dl)	4.05±10.56	4.00 ± 10.92	4.71 ± 0.88	0.912
Ferritin (ng/ml)	1006.3±1083.7	898.4 ± 1007.6	2301.3 ±1349.1	**0.029**
D-dimer (µg/L)	86.2±295.1	93.6± 307.5	4.65 ± 4.03	0.624
C-reactive protein (mg/L)	15.43±39.07	15.32 ± 40.40	16.92 ± 4.34	0.946
Procalcitonin (ng/ml)	0.279±0.600	0.108 ± 0.105	1.310 ± 1.285	**<0.001**
Lactate dehydrogenase (mg/dl)	277±166	252 ± 130	554 ± 305	**0.001**
Creatine kinase (U/L)	156.9±357.4	46.40 ± 40.86	451.7 ± 673.4	0.094

ALT: Alanine aminotransferase, **AST**: Aspartate aminotransferase, **BUN**: Blood urea nitrogen, **eGFR**: Estimated glomerular filtration rate.



LRDTx: Living related donor transplantation, **CADTx**: Cadaveric donor transplantation.

Figure 1. Survival Functions

Discussion

The present study includes a relatively large number of patients. The mortality rate of COVID-19 in renal transplant recipients is high and essentially connected with old age, obesity, diabetes mellitus, presence of dyspnea, high inflammatory biochemical markers, and cadaveric transplant recipients.

In this study, patients were predominantly male and were in the 5th decade, having mostly primary renal diseases, diabetes, glomerulonephritis, autosomal dominant polycystic kidney disease, amyloidosis, and vesicoureteral reflux. In a report from USA Montefiore Medical Center in New York, Akalin et al. reports 26 renal transplant recipients with COVID-19, of which 72% were males, with a median age of 60 years, 94% with hypertension, 69% with diabetes, and 75% had received a deceased donor kidney (4). In the international TANGO consortium of 144 patients, including renal transplant recipients presenting with COVID-19 in twelve centers, 66% were males, aged 62 years and causes of original kidney disease included diabetes mellitus in 30%, glomerulonephritis in 17%, hypertension in 14%, and polycystic kidney disease in 9%. Most patients (78%) had a cadaveric kidney transplantation (5).

In the present study which included 95 patients, 61% male and a mean age of 49 years, cadaveric transplantation 32.6%, primary renal disease with diabetes 10.5%, glomerulonephritis 10.5%, autosomal dominant polycystic kidney disease 6.3%, amyloidosis 4.2%, vesicoureteral reflux 5.2%. Symptoms were similar overall; fever 31%, cough 39%, myalgia 59%, and diarrhea 20%, but all non-survivor group had dyspnea than 24% of the survivor group significantly.

Generally, clinical findings of COVID-19 included cough and dyspnea as respiratory symptoms and at least 2 of new deficiencies of taste or smell, sore throat, headache, myalgia, chills, fever and diarrhea. Diarrhea was especially more frequent in renal transplantation patients (6). More than 80% of patients showed only mild symptoms or no symptoms at all. In hospitalized patients 50% need oxygen supplementation and 20-25% experience conditions like respiratory failure, and intubation, systemic shock, multi-organ failure (7). Incubation periods may range from 2 to 14 days. Most of the complications occur within 12 days (8).

Mortality rates may be higher at the beginning of the pandemic due to insufficient number of tests, initial results of Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu/map.html) were 8-15% to nowadays 3% in the United States and would be much lower (9).

In the general population of COVID-19 patients' autopsies from lungs unique microvascular findings revealing significant injury of endothelium were found. Microangiopathy and thrombosis were seen in respiratory tract pathology, and microthrombus formation in the kidney, heart, brain and limbs was also described (10). Macrophage activation and cytokine storm lead to release of tissue factor and coagulation factors activation, and finally a multisystem inflammatory syndrome may be seen (11).

In the present study, COVID-19 symptoms at admission were myalgia, cough, dyspnea, fever, and diarrhea. There were no significant differences in the frequency of symptoms among survivor and non-survivor groups, except dyspnea which was present in all patients in the non-survivor group. Akalin et al found initial symptoms as fever in 58%, and diarrhea in 22% of patients. Stable patients without respiratory system symptoms (22%) were followed in outpatient clinic (4). The predominant constitutional symptoms on admission were high fever, dyspnea (67%), followed by myalgia (53%) and diarrhea (5). The classical symptoms of viral disease may seem less severe in renal transplant recipients due to immunosuppressive medications.

We found that all non-survivors had dyspnea. Hypoxia and dyspneic condition in COVID-19 was found to be a mortality risk factor in various studies (6, 12, 13). In the present study, 12 of 95 patients have died, with a mortality rate of 12.6%. Some transplant centers in New York reported mortality and hospitalization rates as 13%–30% and 32%–100%, respectively. Italy, Spain, and France mortality rates were between 19% to 50% (12-18).

A review conducted with 10926 COVID-19 patients pointed out solid organ transplantation as a mortality risk factor with an odd ratio of 6 (20), while another study compared transplant patients (38 kidneys and 9 non-kidney organs) with 100 hospitalized non-transplant controls and did not find a correlation between transplantation and death (21). Supporting this, in a multicenter cohort study including over 4000 adults and investigating admission to intensive care units with COVID-19, Molnar et al found that mortality within 4 weeks of ICU hospitalization was similar in transplant and non-transplant patients (22).

In the present study, non-survivors were older, higher body mass index scores, with diabetes, and had a longer hospitalization time. Factors associated with higher mortality in the literature include advanced age, diabetes, obesity, weakness, chronic heart, kidney and lung disease, and longer duration of dialysis (19). Mortality predictors were reported as lymphopenia, increased d-dimer, IL-6, procalcitonin, C-reactive protein, ferritin, and lactate dehydrogenase (18).

In the present study, significant increases in leukocyte counts, liver function tests (ALT and AST), ferritin, lactate dehydrogenase and procalcitonin values were found in the non-survivors group, in comparison with the survivors.

Although the mortality rate is higher in males, female patients during SARS-CoV-2 infection can achieve a significantly stronger T-cell activation than male patients (23) In our study mortality rates were the same among male and female gender.

Development of acute kidney injury in coronavirus patients my occur via several mechanisms. The infection may directly harm kidney cells. SARS-CoV-2 uses ACE-2 as a cell passage receptor (24), and in humans, ACE-2 is expressed in renal proximal-tubular cells and podocytes (25, 26). COVID micro-particles were detected in proximal tubular cells and podocytes in a post-mortem kidney pathology study in 26 coronavirus patients from China; those micro-particles were consistent with diffuse intense renal-proximal tubular injury and periodic vacuolation of podocytes (27). SARS-CoV-2 viral micro-particles additionally are recognized in persistent blood, with a normal time of a few weeks between infection identification in the blood and AKI. It can be suggested that just renal contamination may be a key cycle forcing the occurrence of this high-risk condition (28, 29). One study discovered that SARS-CoV-2 may also enter target cells that deplete CD 147, which is extraordinarily delivered in the kidneys, as a cell surface receptor (30, 31). Sepsis likely is one of the main etiological conditions of AKI in those sick patients (32) and is normal in perished Coronavirus patients. To be sure, about 20% of seriously hospitalized Coronavirus patients had viral sepsis and deep respiratory

distress syndrome (ARDS) (33). Advancement of AKI could be seen in severe sepsis and hypoxia associated with acute tubular necrosis and various hyperinflammation conditions (34). This hyperinflammation is directly related to cytokine release syndrome (CRS), which leads to intra-renal aggravation and expanded vascular porousness (35). CRS was detected in Coronavirus patients, with especially increased levels of IL-6 (36). Organ crosstalk may likewise oversee AKI pathogenesis. To be sure, ARDS and related hypoxemia, irritation, and intubation could lead to the debasement of renal hemodynamics and usefulness (37). Annat et al (38) tracked down filtration that continuous positive pressure ventilation was enough to diminish pee yield, glomerular filtration rate, and renal blood flow, possibly causing AKI. Medication or hyperventilation-related rhabdomyolysis can likewise bring about rounded poisonousness. Investigations of Coronavirus diagnosed patient kidney pathology have proposed that rhabdomyolysis might be an infectious condition as confirmed by the pigmented projects filled tubules and expanded degrees of creatine phosphokinase (27). At last, various pathogenic elements are probably going to add to the frequency and seriousness of AKI in patients experiencing Coronavirus. In the present study, renal transplant recipients with COVID-19 were found to have an increased rate of acute kidney injury and that survival was lower in cadaveric transplant patients. AKI, as indicated by estimated glomerular filtration rate levels, was lower in non-survivors and all non-survivors needed hemodialysis.

Although there was no data about difference between deceased and alive related kidney transplantation for survival from COVID-19; in the present study pointed out that survival was lower in cadaveric patients. This may be due to our relatively large series of patient.

Limitations of this study was a retrospective study design, and absence of advanced biochemical tests like IL-6, and postmortem pathologic examinations.

Conclusion

Factors associated with increased mortality in renal transplant recipients experiencing COVID-19 infection include cadaveric transplantation, advanced age, higher body mass index, presence of co-morbidities like diabetes, presence of dyspnea, a longer hospitalization duration, and acute kidney injury.

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Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar Üniversitesi Tıbbı Araştırmalar Değerlendirme Kurulu (date: 22.04.2022 and approval number: 2022-07/10).

Informed Consent: Consent was not obtained as it was a retrospective study.

Conflict of Interest: Authors declared no conflict of interest.

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Author Contributions: Idea/Concept: SD; Design: HÇ; Supervision: MŞ, MED; Funding: HÇ, ABO; Materials: -; Data Collection/Processing: HÇ; Analysis/Interpretation: SD; Literature Review: EH; Drafting/Writing: EH; Critical Review: HÇ, MED, EH, MŞ, ABO, SD. The authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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