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ORIGINAL ARTICLE – OPEN ACCESS

Dialysis Requirements of Kidney Transplant Recipients During COVID-19

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ABSTRACT

Objective: The complications of Coronavirus Disease 2019 (COVID-19) have increased among kidney transplant recipients (KTR) due to chronic immunosuppression and comorbidities. Additionally, acute kidney injury (AKI) is frequently observed during COVID-19. This study aimed to investigate the impact of COVID-19 on kidney allograft survival.

Materials and Methods: The retrospective, single-center investigation study included 88 patients who had a functioning kidney allograft prior to COVID-19 diagnosis. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection was confirmed with a polymerase chain reaction (PCR) test and thoracic computerized tomography. AKI and dialysis requirements were analyzed using laboratory, demographic, and clinical parameters.

Results: The median age of the patients was 44.5 (34.3-53.8) years, and the median allograft survival was 59.0 (20.8-116.5) months. The mean baseline estimated glomerular filtration rate (eGFR) was 58.2 (21.2-92.8) ml/min/1.73 m^2 before the COVID-19 diagnosis. The frequency of AKI was 70.4% (62 patients), and dialysis therapy was required in nine patients (10.2%). The clinical features of COVID-19 and inflammatory markers had no statistical significance in predicting dialysis requirements. However, logistic regression analysis indicated that serum protein level (p=0.034), serum albumin level (p=0.048), hemoglobin (p=0.028), baseline eGFR (p=0.033), and age (p=0.041) were significantly predictive for dialysis requirements.

Conclusion: Age, anemia, and decreased baseline eGFR are related to severe AKI and dialysis therapy in KTR during COVID-19.

Keywords: Acute kidney injury, COVID-19, dialysis, kidney transplantation, mortality

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was initially identified in Wuhan, China in December 2019, and is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection (1). The virus soon spread worldwide, and the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern on January 30, 2020 (2). It is unclear whether solid organ transplant recipients (SOTR) are at a higher risk for acquiring SARS-CoV-2 infection than the general population. However, chronic immunosuppression may decrease the infectious dose required to cause infection and disrupt sufficient immune response once an infection is established. The mortality rate of SOTR was higher than the general population, reaching 20–25% in the early stages of the pandemic (3).

COVID-19 has variable clinical features, ranging from asymptomatic to respiratory failure (4). The disease can cause complications in almost all systems of the body, and secondary infections related to COVID-19 can further exacerbate health problems.

Impaired kidney function has been detected at high rates in COVID-19. The kidneys are listed as significantly affected organs in severe illness (5). The incidence of acute kidney injury (AKI) ranges from 28% to 46% among hospitalized patients with COVID-19 diagnosis in the United States of America. AKI is associated with a poor prognosis and leads to a high mortality rate during COVID-19 (6). Many potential factors induce AKI, such as direct viral infection, cytokine-mediated injury, and hypoxic injury. However, the kidney injury mechanism is still unclear in COVID-19. The new onset of hematuria and proteinuria can be considered the initial findings of the affected kidney by SARS-CoV-2 infection. Proteinuria could be caused by the cytotropic effects of the virus on the podocytes (7).

COVID-19 has influenced all subgroups of chronic kidney disease (CKD) patients, such as kidney transplant recipients (KTR) and dialysis patients. KTR tend to have infections and malignancies because of lifelong immunosuppressive therapy.

Comorbidities such as senility, hypertension, diabetes mellitus (DM), and cardiovascular disease have contributed to poor prognosis (8), increasing the frequency of COVID-19 complications among KTR. Immunosuppression management during COVID-19 should be considered based on the individual clinical status, and expert consensus recommends attenuation of therapy according to illness severity (9). In this study, we aim to evaluate the renal complications of COVID-19 in KTR and kidney allograft survival during the pandemic.

MATERIALS and METHODS

Study Design

This single-center, retrospective, cross-sectional study was conducted at Erciyes University Hospital. Kidney transplant recipients who were diagnosed with COVID-19 between May 2020 and February 2021 were included in this study. This time period was prior to the utilization of vaccination for COVID-19 in Türkiye. Both inpatients and outpatients were enrolled in this study. Inpatients were screened from nephrology clinics, pandemic clinics, and intensive care units. Outpatients were screened from ambulatory patient clinics in the nephrology department. Key inclusion criteria were age ≥18 years and having a functioning kidney allograft without dialysis requirements prior to COVID-19 diagnosis. SARS-CoV-2 infection was confirmed by two methods: Real-Time (RT) polymerase chain reaction (PCR) in nasopharyngeal swabs and/or typical lung involvement/lesion for COVID-19 in thoracic computerized tomography (CT). Patients with a failed kidney allograft before the COVID-19 diagnosis were excluded. Patients who had negative PCR tests and radiological findings inconsistent with COVID-19 were excluded. All consecutive serum creatinine measurements were screened for renal complications during COVID-19. However, only the first assessment of laboratory parameters concurrent with the COVID-19 diagnosis was utilized for the other analyses. We obtained patient data from an electronically available hospital data system.

Definitions

The COVID-19 Reporting and Data System (CO-RADS) classification was utilized for the radiological definition and diagnosis of COVID-19 (10). CO-RADS category 4, 5 and 6 were accepted for the radiological diagnosis of COVID-19. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines criteria were used for the definition of acute kidney injury AKI. AKI is defined as any of the following: an increase in serum creatinine (SCr) by ≥0.3 mg/dL within 48 hours; or an increase in SCr to ≥1.5 times baseline, known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 hours.

Ethical Considerations

The trial protocol was approved by the Ethics Committee of Erciyes University with the decision numbered 2022/72 on 19/01/2022. The Ministry of Health of the Republic of Türkiye, with the 2021-11-16T17_37_35 document numbered, approved the trial permission. This clinical investigation was carried out in accordance with the Helsinki Declaration.

Statistical Analysis

The normality of data was tested with the Shapiro-Wilk test, q-q plots, and histogram plots. Mann-Whitney U was used to compare the medians of quantitative variables for the dialysis-required and nondialysis-required groups. The chi-square test in the dialysis-required group tested relationships between categorical variables. Univariate and multivariate [Backward Stepwise (Wald)] binary logistic regression analysis was performed to determine the factors affecting the probability of dialysis requirements. The data analysis was conducted using TURCOSA (Turcosa Analytics Ltd Co, Türkiye, www.turcosa.com.tr) statistical software. The significance level was considered as $p<0.05$.

Table 1. Demographic features and laboratory results of the patients

Quantitative variables	Median (Q1–Q3)
Age (years)	44.5 (34.3–53.8)
BMI (kg/m^2)	24.8 (22.8–27.6)
BSA (m^2)	1.8 (1.7–2.0)
Graft survival (months)	59.0 (20.8–116.5)
Baseline eGFR (ml/min/1.73 m^2)	58.2 (21.2–92.8)
BUN first (mg/dL)	24.0 (17.5–44.8)
BUN last (mg/dL)	24.0 (13.0–46.0)
Creatinine first (mg/dL)	2.2 (1.5–4.0)
Creatinine last (mg/dL)	1.6 (1.2–2.8)
Sodium (mEq/L)	136.5 (133.5–139.0)
Potassium (mEq/L)	4.4 (4.0–4.7)
Calcium (mg/dL)	8.8 (8.5–9.3)
Phosphate (mg/dL)	3.1 (2.6–4.5)
Calcium-phosphate product (mg^2/dL^2)	26.0 (23.0–37.3)
Protein (g/dL)	6.5 (5.8–7.0)
Albumin (g/dL)	3.8 (3.7–4.2)
Leukocytes (per microliter)	6270.0 (4562.5–7680.0)
Hemoglobin (g/dL)	11.8 (9.9–13.1)
Lymphocyte (per microliter)	695.0 (427.5–1360.0)
Platelet (10^9/L)	195.0 (170.5–287.8)
CRP (mg/L)	43.0 (7.0–57.8)
D-dimer (ng/mL)	930.0 (300.0–2680.0)
Ferritin (ng/mL)	733.0 (343.0–1597.0)

eGFR: Estimated glomerular filtration rate; BUN: Blood urea nitrogen; BMI: Body mass index; BSA: Body surface area; CRP: C-reactive protein; Q: Quartile; Creatinine first: Measured at the onset of disease; Creatinine last: Measured at the recovery of disease or the last assesment

RESULTS

A total of 88 KTR diagnosed with COVID-19 were screened, including 17 outpatients (19.3%) and 71 inpatients (80.7%). Of the cohort, 41 (46.5%) patients were female and 47 (53.5%) patients were male. The median age of patients was 44.5 years (Q1 34.3 years, Q3 53.8 years), and the median duration of allograft survival was 59.0 months (Q1 20.8, Q3 116.5). The mean baseline estimated glomerular filtration rate (eGFR) was 58.2 (21.2–92.8) ml/min/1.73 m^2 before COVID-19 diagnosis. The mortality rate during the screening period was 6.8% (6 patients). Demographic and laboratory information of patients is summarized in Table 1.

Table 2. Regression analysis of factors affecting dialysis requirements

Variables	Dialysis required Median (Q1–Q3)	Dialysis non-required Median (Q1–Q3)	p*	Single LR OR (95% CI)
Age (years)	60.0 (43.5–60.0)	40.0 (33.0–49.0)	**0.027**	**1.146 (1.005–1.307) p=0.041**
BMI (kg/m^2)	25.0 (19.3–26.6)	24.7 (22.8–27.7)	0.569	0.857(0.652–1.126) p=0.268
BSA (m^2)	1.9 (1.6–2.0)	1.8 (1.7–1.9)	0.522	0.214 (0.001–52.670) p=0.583
Baseline eGFR (ml/min/1.73 m^2)	31 (18.5–37.5)	64 (53.0–72.0)	**0.002**	**0.236 (0.007–0.919) p=0.033**
Graft survival (months)	117.0 (61.0–290.0)	51.0 (12.0–94.0)	0.051	1.019 (0.998–1.040) p=0.070
Sodium (mEq/L)	135.0 (124.0–136.5)	137.0 (135.0–139.0)	0.093	0.826 (0.651–1.047) p=0.113
Potassium (mEq/L)	4.6 (4.1–4.8)	4.2 (4.0–4.7)	0.351	4.054 (0.264–62.222) p=0.315
Calcium (mg/dL)	8.5 (8.0–8.7)	8.9 (8.6–9.4)	**0.030**	0.194 (0.026–1.449) p=0.110
Phosphate (mg/dL)	4.8 (3.3–7.8)	3.0 (2.6–3.5)	0.088	2.309 (0.961–5.550) p=0.061
Ca x P (mg^2/dL^2)	41.0 (27.0–65.5)	25.0 (23.0–31.0)	0.101	1.089 (0.990–1.198) p=0.081
Protein (g/dL)	5.8 (5.5–6.1)	6.7 (6.3–7.1)	**0.020**	**0.088 (0.009–0.830) p=0.034**
Albumin (g/dL)	3.7 (3.1–3.7)	3.9 (3.7–4.3)	**0.018**	**0.027 (0.001–0.963) p=0.048**
Leukocyte (per microliter)	7110.0 (6420.0–11180.0)	5110.0 (4280.0–6880.0)	0.051	1.000 (1.000–1.001) p=0.142
Hemoglobin (g/dL)	9.1 (7.1–10.4)	12.2 (10.7–14.3)	**0.006**	**0.366 (0.149–0.898) p=0.028**
Lymphocyte (per microliter)	790.0 (370.0–1240.0)	670.0 (420.0–1370.0)	0.696	1.000 (0.999–1.001) p=0.669
Platelet (×10^9/L)	199.0 (179.5–273.0)	190.0 (167.0–290.0)	0.804	0.999 (0.983–1.015) p=0.892
CRP (mg/dL)	80.0 (5.5–150.0)	41.0 (6.0–51.0)	0.374	1.017 (0.996–1.038) p=0.108
D-dimer (ng/dL)	2680.0 (1740.0–6750.0)	580.0 (215.0–1187.5)	**0.016**	1.000 (1.000–1.000) p=0.786
Ferritin (ng/dL)	1135.0 (646.0–4097.7)	427.0 (272.0–1388.5)	0.213	1.000 (1.000–1.001) p=0.249

LR: Logistic regression; OR: Odd ratio; CI: Confidence interval; BMI: Body mass index; BSA: Body surface area; Ca x P: Calcium phosphate product; CRP: C-reactive protein; p*: Mann-Whitney U test; p: Logistic regression analysis

Initially, all patients were analyzed for AKI during the course of COVID-19, and the frequency of AKI was determined to be 70.4% (62 patients). AKI accompanied by dialysis requirements was detected in 9 patients (10.2%). The distribution of emergency dialysis indications was as follows: volume overload 66.6% (6 patients), uremic status 22.2% (2 patients), and hyperkalemia 11.1% (1 patient). Peritoneal dialysis (PD) was not administered in this cohort; hence, hemodialysis (HD) was the only dialysis modality used in all patients.

Table 3. Analysis of immunosuppression regimen, diagnostic method, and gender

Variables	Dialysis		χ^2	p*	Single LR, OR (%95 CI)
	Required (%)	Non-required (%)			
Sex					
Female	4 (44.4)	37 (46.8)	0.007	0.932	1.091 (0.147-8.123)
Male	5 (55.6)	42 (53.2)			p=0.932
PCR					
Positive	7 (77.7)	62 (78.5)	4.126	**0.042**	8.000 (0.911-70.275)
Negative	2 (22.3)	17 (21.5)			p=0.061
Lung CT					
Positive	6 (66.7)	52 (65.9)	0.505	0.477	0.429 (0.040-4.637)
Negative	3 (33.3)	27 (34.1)			p=0.486
Immunosuppression			0.960	0.811	NS
CNIs+MMF	7 (77.8)	65 (82.3)			
CNIs+mTORi	1 (11.1)	9 (11.4)			
MMF+mTORi	1 (11.1)	3 (3.8)			
CNIs+Steroid	0 (0.0)	1 (2.5)			

MMF: Mycophenolate mofetil; CNIs: Calcineurin inhibitors; mTORi: Mammalian target of rapamycin inhibitors; LR: Logistic regression; CI: Confidential interval; OR: Odds ratio; NS: Non-significant; CT: Computed tomography; PCR: Polymerase chain reaction; p*: Mann-Whitney U test; p: Logistic regression analysis

Two patients' dialysis requirements were temporary, and seven patients maintained chronic dialysis therapy. The renal outcomes of patients with AKI during COVID-19 are summarized in Figure 1.

The urinary findings were analyzed in this cohort during COVID-19. An increase in proteinuria was the most frequent alteration, observed in 40.9% (36 patients) in urinalysis. Furthermore, new-onset hematuria was seen in 11.3% (10 patients), new-onset pyuria was observed in 7.9% (7 patients), and 47.7% (42 patients) showed no significant alteration in urine. The protein-to-creatinine ratio (milligrams per milligrams) was used to determine proteinuria in a urine sample.

The laboratory parameters were analyzed between the dialysis-required and dialysis-not-required groups. Univariate binary logistic regression analysis was performed to determine factors affecting dialysis requirements. There was a statistically significant difference in serum protein level (p=0.034), serum albumin level (p=0.048), hemoglobin (p=0.028), and baseline eGFR (p=0.033) between the two groups. According to multiple binary logistic regression [Backward Stepwise (Wald)] analysis, hemoglobin was found to be the most significant factor (OR=0.370 CI (0.150–0.914) p=0.031). The demographic features were also analyzed between the dialysis-required and dialysis-not-required groups. There was a statistically significant difference in age (p=0.041) between the two groups. However, there was no statistically significant difference in gender (p=0.932) between the two groups. These results are summarized in Table 2.

The COVID-19 diagnostic methods were analyzed between the dialysis-required and dialysis-not-required groups. The results of lung involvement (p=0.486) and PCR (p=0.061) had no statistically significant relationship with dialysis requirements in the univariate binary logistic regression analysis.

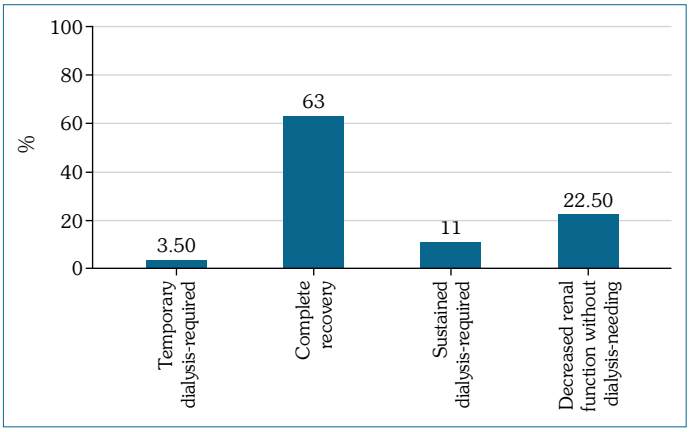

Figure 1. Renal outcomes in 62 patients who developed AKI during COVID-19

The immunosuppression regimens were analyzed in relation to dialysis requirements. The triple regimen consisting of calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and glucocorticoids was the most frequently used (66.7%) treatment protocol. There was no statistically significant difference between the immunosuppression regimens used prior to COVID-19 diagnosis, and the results are summarized in Table 3.

DISCUSSION

The retrospective analysis conducted in this study found that dialysis-required AKI in kidney transplant recipients (KTRs) during COVID-19 was related to age, albumin, baseline eGFR, and hemoglobin. The prevalence of AKI was found to be high (70.4%) in KTRs compared to the general population during COVID-19. Aging, hypoalbuminemia, and anemia are related to poor progno-

sis in many diseases and have various clinical courses. Additionally, decreased baseline renal function is a worse prognostic factor in the recovery of all types of AKI (11). Age has been determined as a significant risk factor for COVID-19 both severity and fatality (12). Decreased albumin and hemoglobin levels might reflect the severity of the inflammatory process in COVID-19. However, inflammatory markers in COVID-19, including C-reactive protein (CRP), ferritin, and D-dimer, had no statistical significance in predicting dialysis requirements in this study.

An increased mortality rate (6.8%) was observed due to COVID-19 in the KTR compared to the general population. The proper fatality rate of SARS-CoV-2 infection has been estimated between 0.15% and 1% since most infections are asymptomatic and many mild infections have not been diagnosed (13). SARS-CoV-2 infection leads to a significantly increased mortality rate in CKD patients than in patients with normal kidney functions. CKD was classified as a risk factor comorbidity for severe COVID-19 by the Centers for Disease Control and Prevention (CDC) in 2021 (14). Likewise, immunosuppression has been considered a potential risk factor for severe COVID-19 (15).

Reported case series have shown that the mortality rate increased in all SOTR above 60 years old. In the European Renal Association COVID-19 Database (ERACODA) study, which enrolled 1,073 patients, the COVID-19 survey has been evaluated in dialysis and KTR groups. The number of KTR was 305 (28%), and the dialysis group was 768 (72%). COVID-19-related 28-day mortality was 21.3% in KTR and 25.0% in dialysis patients. The mortality rate increased in both groups compared to the general population (16). The Turkish Society of Nephrology (TSN) 2021 registry has reported an increased mortality rate in KTR (7.9%) during COVID-19. Various studies emphasized age as the significant variable related to mortality (16, 17).

The COVID-19 pandemic also affected organ transplantation activities. As a result, patients were deprived of transplantation benefits, and waiting list numbers increased during the pandemic (18). Moreover, the transmission of the virus to healthcare professionals disturbed medical facilities' performance (19).

In a meta-analysis of approximately 13,000 cases, the majority of which were hospitalized, the incidence of AKI was determined as 17%. However, the range of AKI incidence in the included studies was broad (range 0.5% to 80%). Dialysis was required in approximately 5% of AKI patients (20). Cravedi et al. (21) reported an AKI prevalence of 51% in 144 KTR with a COVID-19 diagnosis cohort.

The hospitalization rate was quite frequent (80.7%) in our cohort. This high rate is associated with an accepted health policy during the early period of the pandemic in Türkiye, as patients in the high-risk group were still hospitalized and followed up even if they did not need it during the COVID-19 period. Additionally, six patients were admitted to the intensive care unit due to unstable clinical status.

Ten hospitalized COVID-19 patients with AKI diagnosis were investigated for histopathologic findings and clinical features of kidney injury. Proteinuria was detected in all patients, and dialysis was required in eight patients. All biopsy materials observed various degrees of acute tubular necrosis. Viral particles were not detected at ultrastructural evaluation (22).

The combination of CNIs, MMF, and glucocorticoids was the most frequent regimen in this cohort. However, this treatment protocol was not associated with AKI occurrence. The consensus of experts recommended interrupting anti-metabolite drugs, even in cases of mild severity of the disease, and this practice was almost global (23). We managed the immunosuppression therapy consistent with this recommendation during the pandemic. Lymphopenia is a common sign of viral infections, including coronavirus. Therefore, anti-metabolite drug such as MMF and azathioprine can be interrupted during COVID-19. In addition, researchers demonstrated weak proof for MMF cessation and increased rejection rate or graft loss (24). CNIs inhibit the proliferation of SARS-CoV-2 in vitro via cyclophilin and immunophilin pathways (25). Hypothetically, maintenance immunosuppression can prevent cytokine storm, despite the lack of sufficient supportive data (23). However, these agents can also contribute to secondary bacterial infections. Entirely interrupting immunosuppressive therapy may be reasonable in only critical care patients (16).

This study had some limitations, such as the number of individuals and the lack of uniformity in COVID-19 treatment. Nevertheless, the treatment of all patients contained only favipiravir as antiviral therapy. Also, we used only one assessment of the laboratory variables. The pathological process of kidney dysfunction was not elucidated clearly in this cohort due to not performing an allograft biopsy. Therefore, acute rejection attacks or glomerular disease were not defined as the etiology of AKI. Radiological kidney examination was performed in patients with refractory AKI to parenteral hydration to exclude post-renal causes. However, hydronephrosis was not detected in the allograft kidneys of any patients.

CONCLUSION

Lastly, these results reflect the period before the administration of approved vaccines in Türkiye. These single-center research results reveal an increased risk of AKI and mortality rate, consistent with different literature series. We hope that this presented study can contribute to the practice of clinicians. Increased mortality and kidney injury rates may be relevant to CKD, immunosuppression, or comorbidities. Large meta-analyses with increased patient numbers will probably elucidate the kidney injury mechanism in COVID-19. In conclusion, physicians should be alert regarding kidney injury in KTR during COVID-19.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 19.01.2022, number: 2022/72).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – CU, İK; Design – CU, İK; Supervision – CU, İK; Resource – TY, SK; Materials – TY, SK; Data Collection and/or Processing – CU, TY; Analysis and/or Interpretation – TY, SK; Literature Search – CU, SK; Writing – CU, İK; Critical Reviews – İK.

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