



Persistent or Exacerbated Lymphopenia Predicts Mortality in Kidney Transplant Recipients Hospitalized with COVID-19

COVID-19 Geçiren Böbrek Nakli Alıcılarında Persistan veya Kötüleşen Lenfopeni Mortaliteyi Öngörür

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ABSTRACT

Objective: Kidney transplant recipients are at increased risk for severe coronavirus disease-2019 (COVID-19) because of chronic immunosuppressive therapy and impaired cellular immunity. Lymphopenia is a well-established predictor of adverse outcomes in the general population; however, the prognostic significance of persistent lymphopenia during hospitalization in kidney transplant recipients remains poorly defined. This study aimed to evaluate the association between persistent or exacerbated lymphopenia and clinical outcomes, including mortality and renal function, in hospitalized kidney transplant recipients with COVID-19.

Methods: We conducted a retrospective cohort study including adult kidney transplant recipients hospitalized with laboratory-confirmed COVID-19 at a tertiary referral center between March 2020 and January 2022. Patients were classified based on the presence or absence of persistent or exacerbated lymphopenia during hospitalization. Demographic characteristics, comorbidities, laboratory findings, treatments, and clinical outcomes were compared between groups. The primary outcome was in-hospital mortality. Secondary outcomes included intensive care unit (ICU) admission, requirement for respiratory support, requirement for invasive mechanical ventilation, length of hospital stay, requirement for hemodialysis, and renal function at 90 days after discharge. Independent predictors of mortality were identified using multivariable logistic regression analysis.

Öz

Amaç: Böbrek nakli alıcıları, kronik immünoşüpresif tedavi ve bozulmuş hücrel immünite nedeniyle koronavirus hastalığı-2019 (COVID-19) açısından ağır seyir riski taşıyan hasta grubunu oluşturmaktadır. Lenfopeninin genel popülasyonda kötü klinik sonuçların önemli bir belirteci olduğu bilinmesine karşın, hastanede yatış süresince devam eden veya kötüleşen lenfopeninin böbrek nakli alıcılarındaki prognostik değeri yeterince aydınlatılamamıştır. Bu çalışmada, persistan veya kötüleşen lenfopeni ile mortalite ve böbrek fonksiyonları başta olmak üzere klinik sonuçlar arasındaki ilişkinin değerlendirilmesi amaçlandı.

Yöntemler: Bu retrospektif kohort çalışmasına, Mart 2020 ile Ocak 2022 tarihleri arasında üçüncü basamak bir merkezde laboratuvar olarak doğrulanmış COVID-19 tanısıyla hastaneye yatırılan erişkin böbrek nakli alıcıları dahil edildi. Hastalar hastanede yatış sürecinde persistan veya kötüleşen lenfopeni varlığına göre gruplandırıldı. Demografik özellikler, komorbiditeler, laboratuvar bulguları, uygulanan tedaviler ve klinik sonuçlar gruplar arasında karşılaştırıldı. Birincil sonlanım noktası hastane içi mortaliteydi. İkincil sonlanım noktaları yoğun bakım ünitesi yatışı, solunum desteği gereksinimi, invaziv mekanik ventilasyon ihtiyacı, hastanede yatış süresi, hemodiyaliz gereksinimi ve taburculuk sonrası 90. gündeki böbrek fonksiyonları olarak belirlendi. Mortalite ile ilişkili bağımsız belirleyiciler çok değişkenli lojistik regresyon analizi ile değerlendirildi.

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ABSTRACT

Results: A total of 181 kidney transplant recipients were included, 63% of whom developed persistent or exacerbated lymphopenia. Patients with persistent or exacerbated lymphopenia experienced significantly higher rates of ICU admission, respiratory support, invasive mechanical ventilation, prolonged hospitalization, and in-hospital mortality compared with other patients (all $p < 0.05$). They also had significantly higher levels of inflammatory markers, including ferritin and C-reactive protein. In multivariable analysis, persistent/exacerbated lymphopenia remained independently associated with in-hospital mortality after adjustment for age, inflammatory markers, and hemodialysis requirement [adjusted odds ratio 14.16 (95% confidence interval: 3.6-55.7), $p < 0.001$]. However, persistent lymphopenia was not associated with loss of renal function at 90 days.

Conclusion: Persistent or exacerbated lymphopenia during hospitalization is a strong independent predictor of in-hospital mortality among kidney transplant recipients with COVID-19 and is associated with greater disease severity and increased resource utilization. In contrast, it does not appear to predict 90-day renal function decline. Serial assessment of lymphocyte counts may provide a simple, inexpensive, and readily available tool for early risk stratification in hospitalized kidney transplant recipients with COVID-19.

Keywords: COVID-19, kidney transplantation, lymphopenia

Öz

Bulgular: Çalışmaya toplam 181 böbrek nakli alıcısı dahil edildi ve bunların %63'ünde hastanede yatış süresince persistan veya kötüleşen lenfopeni saptandı. Persistan lenfopenisi bulunan hastalarda yoğun bakım ünitesine yatış, solunum desteği gereksinimi, invaziv mekanik ventilasyon ihtiyacı, hastanede kalış süresi ve hastane içi mortalite oranları anlamlı olarak daha yüksekti (tüm karşılaştırmalar için $p < 0,01$). Ayrıca ferritin ve C-reaktif protein düzeyleri de bu grupta anlamlı olarak daha yüksekti. Çok değişkenli analizde persistan veya kötüleşen lenfopeni; yaş, enflamatuvar belirteçler ve hemodiyaliz gereksinimi için düzeltme yapıldıktan sonra da hastane içi mortalitenin bağımsız bir belirleyicisi olarak saptandı [düzeltilmiş olasılık oranı: 14,16 (%95 güven aralığı: 3,6-55,7), $p < 0,001$]. Buna karşın, persistan lenfopeni ile 90. gündeki böbrek fonksiyon kaybı arasında anlamlı ilişki saptanmadı.

Sonuç: Hastanede yatış süresince devam eden veya kötüleşen lenfopeni, COVID-19 nedeniyle hastaneye yatırılan böbrek nakli alıcılarında hastane içi mortalitenin güçlü ve bağımsız bir belirleyicisidir ve daha ağır hastalık seyri ile artmış sağlık hizmeti gereksinimiyle ilişkilidir. Buna karşın, orta dönem böbrek fonksiyon kaybını öngörmemektedir. Seri mutlak lenfosit sayısı değerlendirmesi, hastaneye yatırılan böbrek nakli alıcılarında erken risk sınıflandırmasında geleneksel enflamatuvar ve renal belirteçleri tamamlayıcı, kolay uygulanabilir ve düşük maliyetli bir yöntem olarak kullanılabilir.

Anahtar Sözcükler: COVID-19, böbrek nakli, lenfopeni

INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has caused substantial global morbidity and mortality since its emergence in late 2019. Although widespread vaccination, antiviral therapies, and advances in supportive care have improved clinical outcomes over the course of the pandemic, immunocompromised individuals remain at increased risk for severe disease, hospitalization, and death. Among these populations, kidney transplant recipients (KTRs) represent a particularly vulnerable group because of chronic immunosuppressive therapy, impaired cellular immunity, and the high prevalence of comorbid conditions such as hypertension, diabetes mellitus, and chronic kidney disease (CKD) (1,2).

COVID-19 frequently affects the kidneys through multiple mechanisms, including direct viral cytotoxicity, dysregulated immune activation, endothelial injury, thrombotic microangiopathy, and hemodynamic alterations. Consequently, acute kidney injury (AKI) is a common complication of COVID-19 and has consistently been associated with increased mortality and adverse long-term renal outcomes (3-6). In KTRs, the risk of graft dysfunction may be further exacerbated by baseline allograft vulnerability, nephrotoxic medications, and modifications to immunosuppressive therapy during acute infection (2,7). Although many patients recover from the acute phase of COVID-19, persistent deterioration of renal function has been reported after hospital discharge, which emphasizes the importance of identifying prognostic factors associated with subsequent graft outcomes (5).

Lymphopenia is one of the most consistent hematological abnormalities observed in patients with COVID-19 and is considered a hallmark of dysregulated host immune responses. Several studies have demonstrated that reduced peripheral lymphocyte counts are

associated with greater disease severity, respiratory failure, intensive care unit (ICU) admission, and mortality in the general population (1,8). The proposed mechanisms include direct virus-induced lymphocyte apoptosis, cytokine-mediated immune exhaustion, bone marrow suppression, and redistribution of activated lymphocytes to infected tissues (8). In KTRs, interpretation of lymphocyte counts is inherently more complex because chronic immunosuppressive therapy may induce baseline lymphopenia, impair adaptive immune responses, and delay immune reconstitution following viral infection (2).

Although numerous studies have described the clinical characteristics and outcomes of COVID-19 in KTRs, relatively few have specifically evaluated the prognostic significance of persistent lymphopenia or the trajectory of lymphocyte recovery during hospitalization in relation to both patient survival and renal allograft outcomes (2,7-10). Most previous studies have focused on lymphocyte counts at hospital admission, whereas the clinical significance of persistent or worsening lymphopenia throughout hospitalization remains poorly defined. We therefore hypothesized that failure of lymphocyte recovery reflects sustained immune dysfunction and may provide prognostic information beyond a single admission measurement.

Accordingly, the aim of this study was to evaluate whether persistent or worsening lymphopenia during hospitalization is associated with adverse clinical outcomes, in-hospital mortality, and 90-day renal function among KTRs hospitalized with COVID-19.

MATERIALS AND METHODS

Study Design and Population

This retrospective, observational cohort study included adult KTRs hospitalized with laboratory-confirmed COVID-19 at University

of Health Sciences Türkiye, Ankara Bilkent City Hospital Hospital between March 2020 and January 2022. A COVID-19 diagnosis was confirmed by positive reverse transcriptase-polymerase chain reaction testing for severe acute respiratory SARS-CoV-2.

A total of 211 consecutive COVID-19 KTRs were screened. Patients were excluded if they had active malignancy, pregnancy, severe chronic lung disease, congenital heart disease, and end-stage kidney disease requiring maintenance dialysis prior to admission. After applying the exclusion criteria, 181 patients were included in the final analysis.

The study protocol was approved by the University of Health Sciences Türkiye, Ankara City Hospital Clinical Research Ethics Committee no. 1 (approval no: E1-22-2292, date: 12.01.2022). The requirement for informed consent was waived because of the retrospective nature of the study.

Definitions

Admission lymphopenia was defined as either (1) an absolute lymphocyte count (ALC) $<1,000$ cells/ μ L at hospital admission or (2) an ALC accompanied by a decline of more than 50% compared with the patient's pre-infection baseline lymphocyte count. Transient lymphopenia was defined as recovery of the ALC to $>1,000$ cells/ μ L within 10 days after COVID-19 diagnosis.

Persistent lymphopenia was defined as failure of the ALC to recover above 1,000 cells/ μ L beyond 10 days after diagnosis or until death, if death occurred between 7 and 10 days.

Exacerbated lymphopenia was defined as the development of lymphopenia during hospitalization in patients who did not meet the admission lymphopenia criteria, with lymphopenia persisting for at least 7 consecutive days.

Patients who died within the first 7 days of admission were excluded from the lymphopenia groups. Baseline renal function was determined using the most recent outpatient serum creatinine measurement obtained before COVID-19 diagnosis. Renal function loss at 90 days were calculated using nearest serum creatinine measurement to 90th day (up to 30 days before and after the 90th day), if available. Estimated glomerular filtration rates (eGFR) were calculated using the CKD-Epidemiology Collaboration creatinine equation. A 25% or greater loss in eGFR was considered a loss of at 90 days.

Data Collection

Electronic medical records were reviewed to obtain demographic characteristics, transplant-related variables, comorbidities, maintenance immunosuppressive therapy, clinical presentation, laboratory findings at admission and during hospitalization, COVID-19-specific treatments, oxygen supplementation requirements, ICU admission, mechanical ventilation, duration of hospitalization, and in-hospital mortality.

Renal outcomes included the development of AKI, the requirement for renal replacement therapy, serum creatinine levels, and eGFR, assessed during hospitalization and follow-up. Changes in immunosuppressive treatment during hospitalization were also recorded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using histogram graphs and Kolmogorov-Smirnov test and presented as mean $\pm$ standard deviation. Categorical variables are presented as frequencies and percentages. Comparisons between groups were performed using the Independent Samples t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Factors associated with in-hospital mortality were evaluated using binary logistic regression. Variables considered clinically relevant and demonstrating an association with mortality in univariate analysis ($p < 0.10$) were selected as candidates for multivariable analysis. To minimize overfitting, the number of variables in the multivariable model was restricted according to the events-per-variable principle. Age was included in the multivariable model regardless of its significance in univariate analysis because of its established clinical relevance. Variables were checked for multicollinearity using variance inflation factors (VIF); VIF <2 was considered acceptable. Variable selection for the final model was performed using backward-stepwise likelihood-ratio elimination; adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

All statistical tests were two-sided, and a p -value <0.05 was considered statistically significant.

RESULTS

A total of 181 KTRs hospitalized with COVID-19 were included in the analysis. Five patients died before 7th day of their hospitalization, and were excluded from lymphopenia groups. Persistent or exacerbated lymphopenia was observed in 111 (63.1%) patients, whereas 65 (36.9%) patients had transient or no lymphopenia. Patients with persistent/exacerbated lymphopenia were significantly older than those without persistent lymphopenia (53.1 ± 12.1 vs. 48.6 ± 12.4 years, $p = 0.018$) and had a higher prevalence of hypertension (76.6% vs. 52.3%, $p < 0.001$). All patients were on maintenance immunosuppressive therapy. Baseline immunosuppressive regimens, years since transplantation, sex distribution, and the prevalence of diabetes mellitus and coronary artery disease were comparable between groups. Symptoms of COVID-19 were comparable between the lymphopenia groups. Corticosteroid treatment for COVID-19 was more prevalent among the persistent or exacerbated lymphopenia group (Table 1).

Baseline renal function was comparable between groups. Patients with persistent/exacerbated lymphopenia had significantly higher serum ferritin levels (866.1 ± 901.7 vs. 532.0 ± 633.3 ng/mL, $p = 0.009$), lower ALCs at admission (634.8 ± 424.1 vs. 920.5 ± 513.4 cells/ μ L, $p < 0.001$), and lower monocyte and eosinophil counts. No significant differences were observed in serum creatinine, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), or baseline lymphocyte counts (Table 2).

Persistent or exacerbated lymphopenia was associated with significantly worse clinical outcomes. Compared with patients with transient or no lymphopenia, these patients had higher rates of ICU

admission (51.4% vs. 18.5%, $p < 0.001$), invasive or non-invasive mechanical ventilation (29.7% vs. 9.2%, $p = 0.002$), intubation (22.5% vs. 6.2%, $p = 0.005$), and any respiratory support (84.7% vs. 61.5%, $p < 0.001$). Hospital length of stay was also significantly longer (19.1 ± 18.9 vs. 12.2 ± 10.2 days, $p < 0.001$). In-hospital mortality was markedly higher among patients with persistent or exacerbated lymphopenia (35.1% vs. 7.7%; $p < 0.001$). However, 90-day renal function loss was comparable between the groups (10.4% vs. 10.9%, $p = 1.000$) (Table 3).

In univariate logistic regression analysis, hemodialysis requirement, persistent or exacerbated lymphopenia, corticosteroid therapy for COVID-19, higher admission levels of CRP, ferritin, and urea, increased neutrophil count, and older age were significantly associated with in-hospital mortality. In the multivariable model, hemodialysis requirement (OR: 29.38, 95% CI: 6.61-130.64, $p < 0.001$); persistent/exacerbated lymphopenia (OR: 14.16, 95% CI: 3.60-55.69, $p < 0.001$); admission CRP (OR: 1.009 per mg/L increase,

95% CI: 1.003-1.015, $p = 0.005$); and age (OR: 1.044 per year, 95% CI: 1.00-1.083, $p = 0.023$) remained independent predictors of in-hospital mortality (Table 4).

Table 1. Comparison of demographics, comorbidities, baseline treatments, symptoms, and COVID-19 therapies between the groups.

	Persistent or exacerbated lymphopenia (n = 111)	Transient or no lymphopenia (n = 65)	p
Age (years)	53.1 $\pm$ 12.1	48.6 $\pm$ 12.4	0.018†
Male sex	78 (70.3%)	49 (75.4%)	0.465*
Diabetes mellitus	37 (33.3%)	20 (30.8%)	0.726*
Hypertension	85 (76.6%)	34 (52.3%)	<0.001*
Coronary artery disease	24 (21.6%)	13 (20.0%)	0.799*
Years since transplantation	7.2 $\pm$ 6.07	6.32 $\pm$ 4.97	0.42‡
Baseline immunosuppressive therapies			
Corticosteroids	103 (92.8%)	63 (96.9%)	0.327#
Tacrolimus	83 (74.8%)	56 (86.2%)	0.074*
Micofenilat mofetil	81 (73.0%)	54 (83.1%)	0.126*
Everolimus	11 (9.9%)	6 (9.2%)	0.883*
Cyclosporin	11 (9.9%)	3 (4.6%)	0.21*
Azathiopurine	8 (7.2%)	2 (3.1%)	0.327#
Sirolimus	4 (3.6%)	3 (4.6%)	0.71#
Admission symptoms			
Non-specific	59 (53.2%)	32 (49.2%)	0.615*
Fever	71 (64.0%)	32 (49.2%)	0.056*
Respiratory	79 (71.2%)	38 (58.5%)	0.085*
Gastrointestinal	23 (20.7%)	17 (26.2%)	0.406*
Treatments for COVID-19			
Corticosteroids	91 (82.0%)	35 (53.8%)	<0.001*
Colchicine	43 (38.7%)	19 (29.2%)	0.203*
Plasmapheresis	3 (2.7%)	0 (0.0%)	0.297#
IV-immunoglobulin	3 (2.7%)	0 (0.0%)	0.3#

†: Independent Samples t-test, *: Chi-squared test, ‡: Mann-Whitney U test, #: Fisher's exact test, COVID-19: Coronavirus disease-2019, IV: Intravenous.

Table 2. Comparison of laboratory variables between the groups.

	Persistent or exacerbated lymphopenia (n = 111)	Transient or no lymphopenia (n = 65)	p
Baseline eGFR (mL/dk/1.73 m ²)	58.7 $\pm$ 22.2	60.8 $\pm$ 18.6	0.558†
Admission eGFR (mL/dk/1.73 m ²)	49.3 $\pm$ 27.1	49.7 $\pm$ 20.2	0.9†
Urea (mg/dL)	79.9 $\pm$ 59.3	72.2 $\pm$ 50	0.871‡
Creatinine (mg/dL)	1.99 $\pm$ 1.34	1.77 $\pm$ 0.89	0.966‡
Albumin (g/L)	36.7 $\pm$ 6.29	38.3 $\pm$ 6.1	0.105†
Ferritin (mg/dL)	866.1 $\pm$ 901.7	532 $\pm$ 633.3	0.009‡
C-reactive protein (mg/dL)	84.6 $\pm$ 68.7	74.8 $\pm$ 76	0.12‡
White blood cells (/μL)	7195.7 $\pm$ 5111.5	7893.4 $\pm$ 4895.8	0.159‡
Neutrophils (/μL)	5916.1 $\pm$ 4946.3	6090.9 $\pm$ 4625.9	0.569‡
Monocytes (/μL)	411.4 $\pm$ 323	580 $\pm$ 987.9	0.032‡
Eosinophils (/μL)	29.5 $\pm$ 42.1	54.1 $\pm$ 76.2	0.033‡
Hemoglobin (g/dL)	11.8 $\pm$ 2.7	12.5 $\pm$ 2.07	0.061†
Platelets ($\times 10^9$ /L)	199.6 $\pm$ 79.6	223.3 $\pm$ 101.9	0.089†
Lymphocytes (/μL)	634.8 $\pm$ 424.1	920.5 $\pm$ 513.4	<0.001‡
Baseline lymphocytes (/μL)	1600.8 $\pm$ 817.3	1735.6 $\pm$ 821.1	0.212‡

†: Independent Samples t-test, ‡: Mann-Whitney U test, eGFR: Estimated glomerular filtration rate.

Table 3. Comparison of clinical outcomes between the groups.

	Persistent or exacerbated lymphopenia (n = 111)	Transient or no lymphopenia (n = 65)	p
Mortality	39 (35.1%)	5 (7.7%)	<0.001*
Mortality time (days)	21.5 $\pm$ 17.6	24.4 $\pm$ 14.5	0.591‡
Length-of-stay	19.1 $\pm$ 18.9	12.2 $\pm$ 10.2	<0.001‡
Length of ICU stay	17.1 $\pm$ 21.6	15 $\pm$ 11.8	0.975‡
ICU admission	57 (51.4%)	12 (18.5%)	<0.001*
Hemodialysis	13 (11.7%)	7 (10.8%)	0.849*
Renal function loss (at 90 days)	7 (10.4%)	5 (10.9%)	1#
Intubation	25 (22.5%)	4 (6.2%)	0.005*
Mechanical ventilation	33 (29.7%)	6 (9.2%)	0.002*
Any respiratory support	94 (84.7%)	40 (61.5%)	<0.001*

*: Chi-squared test, ‡: Mann-Whitney U test, #: Fisher's exact test, ICU: Intensive care unit.

Table 4. Logistic regression models predicting mortality.

	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	p	OR (95% CI)	p
Hemodialysis	13.49 (4.629-39.33)	<0.001	29.38 (6.608-130.64)	<0.001
P/E lymphopenia	7.333 (2.735-19.67)	<0.001	14.16 (3.598-55.69)	<0.001
Corticosteroid therapy for COVID-19	2.848 (1.68-4.829)	<0.001		
CRP at admission	1.009 (1.005-1.014)	<0.001	1.009 (1.003-1.015)	0.005
Ferritin at admission	1.001 (1-1.001)	<0.001		
Neutrophils at admission	1 (1-1)	<0.001		
Urea at admission	1.001 (1-1.002)	<0.001		
Age	1.048 (1.018-1.079)	0.002	1.044 (1.006-1.083)	0.023

P/E: Persistent or exacerbated, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence interval, COVID-19: Coronavirus disease-2019.

DISCUSSION

In this retrospective cohort of KTRs hospitalized with COVID-19, we demonstrated that persistent or exacerbated lymphopenia was strongly associated with adverse clinical outcomes, including ICU admission, need for respiratory support, invasive mechanical ventilation, prolonged hospitalization, and in-hospital mortality. More importantly, persistent or exacerbated lymphopenia remained an independent predictor of mortality after adjustment for age, inflammatory markers, and requirement for hemodialysis. In contrast, persistent lymphopenia was not associated with loss of renal function 90 days after infection. Collectively, these findings suggest that failure of lymphocyte recovery primarily reflects sustained immune dysfunction and disease severity, rather than subsequent deterioration of kidney allograft function.

KTRs remain among the most vulnerable populations to severe COVID-19 because of chronic immunosuppressive therapy, impaired T-cell-mediated immunity, and a high prevalence of cardiovascular and metabolic comorbidities. Early reports from international transplant registries consistently demonstrated markedly higher rates of hospitalization, ICU admission, and mortality among KTRs than those in the general population (11-14). Unlike previous studies that primarily evaluated lymphocyte counts at hospital admission, our study specifically focused on the longitudinal trajectory of lymphocyte recovery during hospitalization. This dynamic approach may better capture persistent immune dysfunction and may explain why serial lymphocyte assessment provided prognostic information beyond a single baseline measurement. Although widespread vaccination, antiviral therapies, and improvements in supportive care have substantially altered the clinical course of COVID-19, KTRs continue to experience disproportionately poor outcomes because vaccine-induced immune responses are frequently attenuated and protection against emerging viral variants remains incomplete. Recent evidence further suggests that mortality among KTRs has remained considerably higher than that of the general population even during the Delta and Omicron eras, underscoring the continued importance of accurate risk stratification in this vulnerable population (15).

Lymphopenia is hallmark laboratory abnormality observed in COVID-19 and has consistently been associated with severe

disease and death in the general population (1,16). Proposed mechanisms include direct viral injury to lymphocytes, cytokine-mediated apoptosis, immune exhaustion, impaired lymphopoiesis, and redistribution of activated lymphocytes into infected tissues (16,17). Among KTRs, these mechanisms are likely to be amplified by chronic immunosuppressive therapy, particularly antimetabolites and corticosteroids, leading to impaired lymphocyte proliferation and delayed adaptive immune recovery. Consequently, persistent lymphopenia may identify patients in whom immune recovery remains inadequate despite resolution of the initial viral insult.

Our findings extend previous observations by demonstrating that not only lymphopenia at hospital admission but also the persistence or worsening of lymphopenia throughout hospitalization identify patients at particularly high risk for death. While admission lymphocyte counts provide a static assessment of immune status, serial lymphocyte monitoring more accurately reflects the dynamic interaction between viral clearance, host immune recovery, systemic inflammation, and ongoing immunosuppression. Consistent with this concept, persistent or exacerbated lymphopenia remained independently associated with mortality after adjustment for age, CRP, and the requirement for hemodialysis. Moreover, recent evidence has shown that even early lymphopenia independently predicts adverse outcomes among hospitalized patients with COVID-19, supporting the hypothesis that persistent lymphocyte depletion represents an even stronger indicator of sustained immune dysfunction (18).

Our findings also suggest that persistent lymphopenia may represent an integrated biomarker reflecting both disease severity and inadequate recovery of adaptive immunity in KTRs. During severe COVID-19, antimetabolite therapy is frequently reduced or withdrawn temporarily to facilitate immune recovery, whereas calcineurin inhibitors and corticosteroids are generally individualized based on clinical status and graft function. Nevertheless, recovery of lymphocyte counts remains highly variable among transplant recipients, suggesting that persistent lymphopenia reflects ongoing immune dysregulation rather than immunosuppressive therapy alone. Contemporary reviews have similarly emphasized that balancing the restoration of antiviral immunity with minimizing the risk of acute rejection remains one of the principal therapeutic challenges in KTRs with COVID-19 (19).

Consistent with previous studies, markers of systemic inflammation were also associated with adverse outcomes in our cohort. Patients with persistent or exacerbated lymphopenia had significantly higher ferritin concentrations, whereas elevated CRP on admission independently predicted mortality. Hyperinflammation and immune dysregulation are well-recognized features of severe COVID-19 and contribute to endothelial injury, microvascular thrombosis, and multiorgan dysfunction (1,16,20). The coexistence of elevated inflammatory markers and persistent lymphopenia likely reflects a maladaptive immune response characterized by excessive innate immune activation together with impaired adaptive immunity, consistent with the cytokine storm paradigm proposed early during the pandemic (20).

The requirement for hemodialysis emerged as the strongest independent predictor of mortality in our cohort. AKI is a common complication of severe COVID-19 and has consistently been associated with increased mortality (2-6). The underlying mechanisms are multifactorial and include systemic inflammation, ischemic tubular injury, endothelial dysfunction, complement activation, and direct or indirect viral effects on the kidney (3,5,21). In KTRs, these mechanisms may be further aggravated by pre-existing allograft dysfunction, calcineurin inhibitor nephrotoxicity, volume depletion, and modifications of immunosuppressive therapy during acute illness. Our findings therefore reinforce previous observations that severe renal impairment requiring kidney replacement therapy is a robust marker of critical illness and poor prognosis among KTRs.

Study Limitations

This study has several limitations. First, its retrospective single-center design may have introduced selection bias and limited the generalizability of our findings to other transplant populations and healthcare settings. Second, although multivariable analyses were performed to adjust for clinically relevant covariates, the observational nature of the study precludes causal inference, and residual confounding from unmeasured variables cannot be excluded. Third, the limited number of mortality events may have reduced the statistical power of multivariable models and increased the risk of model overfitting, despite adherence to recommended model-building strategies. Furthermore, lymphocyte subset analysis was unavailable, preventing the evaluation of whether specific immune cell populations contributed differentially to the observed associations. Finally, the relatively small number of renal outcome events may have limited our ability to detect modest associations between persistent lymphopenia and subsequent allograft function.

CONCLUSION

Persistent or worsening lymphopenia during hospitalization strongly and independently predicts in-hospital mortality among KTRs with COVID-19 and is associated with greater disease severity, increased respiratory support requirements, and prolonged hospitalization. In contrast, persistent lymphopenia in our cohort was not associated with loss of renal function at 90 days, suggesting that sustained lymphocyte depletion primarily reflects acute immune dysregulation rather than subsequent allograft deterioration. Because ALCs are inexpensive, routinely available, and easily and serially monitored, they may serve as practical adjuncts to conventional inflammatory and renal biomarkers for early risk stratification in hospitalized KTRs.

Prospective studies with longer follow-up are warranted to validate these findings and to determine whether therapeutic strategies aimed at improving immune recovery can translate into better patient and allograft outcomes.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Ankara Bilkent City Hospital Clinical Research Ethics Committee no. 1 (approval no: E1-22-2292, date: 12.01.2022).

Informed Consent: The requirement for informed consent was waived because of the retrospective nature of the study.

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Footnotes

Authorship Contributions

Concept: A.C.K., M.Ö., A.B.B., E.C.Y., E.G., O.İ., E.S.Ş., O.Z., S.K., İ.A., F.D., Design: A.C.K., M.Ö., Data Collection or Processing: A.C.K., M.Ö., A.B.B., Analysis or Interpretation: A.C.K., E.C.Y., E.G., O.İ., E.S.Ş., O.Z., S.K., İ.A., F.D., Literature Search: A.C.K., M.Ö., Writing: A.C.K., M.Ö., A.B.B., E.C.Y., E.G., O.İ., E.S.Ş., O.Z., S.K., İ.A., F.D.

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