Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1202444

J Med Palliat Care 2022; 3(4): 335-340

The C-reactive protein-to-albumin ratio predicts one-year mortality in living donor kidney transplantation

C-reaktif protein albumin oranı canlıdan böbrek naklinde ilk yıl mortaliteyi öngörmektedir

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Cite this article as: Merhametsiz Ö, Çat A. The C-reactive protein-to-albumin ratio predicts one-year mortality in living donor kidney transplantation. J Med Palliat Care 2022; 3(4): 335-340.

ABSTRACT

Aim: The aim of this study was is to evaluate the effectiveness of the preoperative C-reactive protein (CRP)/albumin ratio on first year mortality after living donor kidney transplantation.

Material and Method: This retrospective single-center study includes a total of living kidney transplant recipients' data who were transplanted between 2011-2020 years. Thirty-six patients who died within the first year after kidney transplantation among 2143 living kidney transplant recipients were included in the study group. Patients who have similar comobordities like mortality group patients who survives than one year after living donor kidney transplantation were enrolled as control group.

Results: First year mortality was 1.67% (36/2143) in ten years. Patients in the mortality group were older than the control group (53±13 vs 43±12, p=0.002). The median time spent on dialysis in the mortality group was longer than in the control group (13 months vs 1 month, p=0.029). The median CRP/albumin ratio was higher in the mortality group (2.77 vs 0.85, p=0.001). CRP and CRP/albumin ratio were determined as independent factors affecting mortality in the first year after living donor kidney transplantation as a result of multivariate Cox regression analysis (HR=1.040;95% CI, 1.011-1.069; p=0.004 vs HR=1.148 95% CI, 1.044-1.262; p=0.007, respectively). ROC analysis showed that the CRP/albumin ratio had the power to predict one-year mortality (AUC 0.650 95% CI 0.513-0.787, p=0.041). Kaplan-Meier survival analysis showed a statistically significant difference between the two groups in terms of the cut-off value for CRP/albumin ratio (1.52).

Conclusion: This study shows that the CRP/albumin ratio can be used to predict mortality in the first year after living donor kidney transplantation.

Keywords: Living donor kidney transplantation, mortality, C-reactive protein, albumin

Our research's data was presented in 13th Istanbul University Capa Medical School, Capa Nephrology Congress as 'Oral Presentation' on Jan 2021.

ÖZ

Amaç: Bu çalışmanın amacı, preoperatif C-reaktif protein (CRP)/albumin oranının canlıdan böbrek nakli sonrası ilk yıl mortalite üzerinde etkinliğini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 2011-2020 yılları arasında canlıdan böbrek nakli yapılmış 2143 hastadan ilk yılda ölen 36 hasta mortalite grubu olarak alındı. Kontrol grubu olarak benzer kronik hastalıklara sahip bir yıldan daha uzun süredir takipli olan canlıdan böbrek nakli yapılmış benzer sayıda hasta kontrol grubu olarak alındı.

Bulgular: On yıl için ilk yıl mortalitesi %1,67 (36/2143)'dir. Mortalite grubunda hastalar kontrol grubuna göre daha yaşlıdır (53±13 karşılık 43±12, p=0,002). Mortalite grubundaki hastaların diyalizde geçirdiği ortanca süre kontrol grubuna göre uzundur (13 aya karşılık 1 ay, p=0,029). Ortanca CRP/albumin oranı mortalite grubunda daha yüksekti (2,77 karşılık 0,85, p=0,001). CRP ve CRP/albumin oranı, çok değişkenli Cox regresyon analizi sonucunda, canlıdan böbrek nakli sonrası ilk yıl mortaliteye etki eden bağımsız faktörler olarak saptandı (HR=1,040 %95 CI 1,011-1,069; p=0,004 karşılık HR=1,148 %95 CI, 1,044-1,262; p=0,007 sırasıyla). ROC analizi CRP/albumin oranının bir yıllık mortaliteyi tahmin etme gücüne sahip olduğunu gösterirken (AUC 0,650 %95 GA 0,513-0,787, p=0,041). CRP/albumin oranı eşik değerine (1,52) göre yapılan Kaplan-Meier sağkalım analizi iki grup arasında fark olduğunu göstermiştir.

Sonuç: Bu çalışma, CRP/albumin oranının canlıdan böbrek nakli sonrasında ilk yıl içerisinde gelişen mortaliteyi öngörmede kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Canlı donörden böbrek nakli, mortalite, C-reaktif protein, albumin

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Received/Geliş: 10.11.2022 **Accepted/Kabul:** 30.11.2022

INTRODUCTION

All acute-phase reactants respond to inflammatory events to varying degrees. Among these markers, C-reactive protein (CRP) is a positive acute phase protein, and the prognostic value of CRP levels in many diseases has been demonstrated in studies since there may be a relationship between the increase in CRP level and the severity of the infection (1-3). Albumin is a negative acute phase protein whose level decreases in response to infection and has been proposed as a clinical tool for estimating the severity of inflammation and malnutrition in patients with chronic diseases such as chronic kidney disease (4-6). The CRP/albumin ratio, a combined index of CRP and albumin levels, has been investigated in many clinical studies as an indicator of inflammatory status. These studies stated that the CRP/albumin ratio could be used as a prognostic indicator of morbidity and mortality to evaluate clinical outcomes (7-11). Chronic inflammation, common in patients with end-stage renal disease (ESRD), is a critical factor in the pathogenesis of atherosclerosis and affects the development of cardiovascular disease in renal transplant recipients (12-14). Thus, renal transplant recipients have a higher risk of cardiovascular system-related mortality compared to the general population (15-17). Despite major advances in organ transplantation, there are no reliable pre-transplant tests that can consistently identify patients who may be at high risk for mortality after kidney transplantation and that can be used to guide treatment decisions.

The present study aimed to determine the value of the preoperative CRP/albumin ratio as an independent prognostic indicator to predict the mortality of kidney transplant recipients (KTRs) in the first year following living donor kidney transplantation (LDKT).

MATERIAL AND METHOD

The study was retrospective, single-center, and approved by Istanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 17.11.2020, Decision No: 11-533). All procedures involving human participants were approved in accordance with the ethical standards of the Institutional and/or National Research Committee, including the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards.

In this study, KTRs who developed mortality within the first year (n=36, mortality group) among patients (total 2143 patients) who had a living donor kidney transplant at our center from 2011 to end of 2020 were included. As the control group, we selected patients with similar comorbidities, followed for more than one year. Control group patients were manually selected from patients who survived for more than one year, by matching them with the chronic diseases of mortality group patients. The two groups regarding donor and recipient characteristics and CRP/albumin ratio were compared.

Demographic characteristics, chronic diseases and laboratory information of the patients at their first hospitalization for kidney transplantation were reviewed and recorded in the hospital information management system. Serum CRP (mg/L) levels were studied in the Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) autoanalyzer using the immunoturbidimetric method, and albumin (g/dL) in the Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) autoanalyzer using the colorimetric BCG method. CRP/albumin ratio was calculated by dividing the patients' pre-transplant CRP levels by their albumin levels.

Statistical Analysis

Nominal and ordinal parameters were described by frequency analysis. Means and standard deviations were used for the description of scale parameters. Kolmogorov Smirnov Test was used for the normality distribution test of scale parameters. Mann-Whitney U test was used for non-normally distributed parameter differences, whereas the independent samples t-test was used for normally distributed parameters. Chi-square test and chi-square likelihood ratio were used for categorical parameter differences. ROC (receiver operating curve) analysis was used for diagnostic values of research parameters. Multivariate Cox regression analysis was used to determine the factors affecting first-year mortality after LDKT. All variables were subjected to univariable multivariate regression analysis to reveal the factors affecting first-year mortality. Multivariable Cox regression analysis was performed, in which the variables observed to be statistically significant as a result were included in the univariable multivariate regression analysis. Kaplan-Meier analysis was used for survival estimation. SPSS 22.0 for Windows version was used for analysis at 95% Confidence Interval with 0.05 alpha levels.

RESULTS

The causes of mortality in patients who died in the first year were infection (n=20, 55.6%, three of these patients died due to SARS-COV-2), cardiovascular events (n=11, 30.6%), cerebrovascular events (n=3, 8.3%), and unknown causes (n=2, 5.5%), respectively.

A comparison between the characteristics of the patients who developed mortality in the first year and the control group is presented in **Table 1**. The first-year mortality rate (36/2143) was 1.67% which means first

year survival was 98.33%. A statistically significant difference was determined between the groups in terms of gender, body mass index (BMI), and age (p=0.007, p=0.044, p=0.002, respectively). While most patients (83.3%) who died in the first year were receiving renal replacement therapy (RRT, mostly hemodialysis), this rate was 50% in the control group, and this difference was statistically significant (p=0.004). It showed KTRs who undergone preemptive kidney transplantation have less mortality. The spending time on dialysis in the mortality group was significantly longer than the control group (median, 13 months vs 1 month, p=0.029). There was no difference between the groups regarding primary disease causing ESRD and cardiovascular disease. In terms of immunological evaluation, the number of HLA mismatches was higher in the mortality group compared to the control group (median, 4 vs 3, p=0.022). While there was no difference between the groups in terms of albumin, CRP was statistically significantly higher in the mortality group (median, 10.1 vs 3.7, p=0.002). Also, the CRP/albumin ratio was also statistically significantly higher in the mortality group (median, 2.77 vs 0.85, p=0.001).

Multivariate Cox regression analysis revealed that (Forward: LR), female gender, BMI, recipient age, receiving RRT, number of HLA mismatches, CRP, and CRP/albumin ratio had an impact on mortality. Since the CRP/albumin ratio is affected by the CRP value, the CRP/albumin ratio and CRP were subjected to multivariable Cox regression analysis in 2 separate models. CRP/albumin ratio in model 1 and CRP in model 2 were effective variables on mortality in the first year after LDKT (p=0.004, p=0.007, respectively). In Model 1, CRP/albumin ratio was found to increase first year mortality by 1.148 times, while in model 2, CRP increased by 1.040 times. The Cox regression analysis of the factors affecting mortality in the first year after LDKT is presented in **Table 2**.

ROC analysis (**Figure 1**) indicated that the CRP/albumin ratio had the power to predict one-year mortality (AUC 0.650 95% CI 0.513-0.787, p=0.041 cut-off CRP/Albumin ratio 1.52), whereas CRP had no power to predict one-year mortality (AUC 0.635 95% CI 0.497- 0.773, p=0.065, cut-off CRP 5.5). ROC analysis determined that the cut off value for the CRP/albumin ratio >1.52 (61.3% sensitivity, 68.8% specificity) was statistically significant for one-year mortality. A statistically significant difference was observed between the two groups (log-rank p= 0.034) according to the one-year Kaplan-Meier survival analysis, according to the cut-off value of CRP/albumin ratio of 1.52 (**Figure 2**).

Table 1. Characteristics of the first year recipient mortality and control group

	Mortality at One Year		p
	Yes (n=36)	No (n=32)	
Donor age, years	45±14	49±14	0.272
Donor sex, f/m (m%)	23/13 (36.1%)	10/22 (68.8%)	**0.007**
Donor BMI, (kg/m²)	28 (20-42)	25 (20-34)	**0.044**
Recipient age, years	53±13	43±12	**0.002**
Recipient sex, f/m (m%)	21/15 (58.3%)	15/17 (46.9%)	0.345
Recipient BMI, (kg/m²)	26±6	27±4	0.730
Relative,(yes %)	16/20 (55.6%)	14/18 (56.3%)	0.954
RRT/Preemptive, (RRT%)	6/30 (83.3%)	16/16 (50%)	**0.004**
RRT duration, months	13 (0-228)	1 (0-156)	0.029
Primary disease			
DM	12 (34.3%)	7 (24.1%)	
HT	6 (17.1%)	3 (10.3%)	0.589
Chr.Gn	5 (14.3%)	6 (20.7%)	
Other	12 (34.3%)	13 (44.8%)	
CVD, (yes%)	18/18 (50%)	22/10 (31.3%)	0.117
HLA mismatch	4 (2-6)	3 (1-6)	**0.022**
Class I PRA	27/8 (22.9%)	24/7 (22.6%)	0.979
Class II PRA	23/12 (34.3%)	24/7 (22.6%)	0.295
Immunologic risk			
Low	18 (50%)	21 (65.6%)	
Moderate	12 (33.3%)	7 (21.9%)	0.424
High	6 (16.7%)	4 (12.5%)	
Induction			
Bsx	0 (0%)	1 (3.1%)	0.547
ATG	31 (86.1%)	26 (81.3%)	
ATG+PF	5 (13.9%)	5 (15.6%)	
ATG total dose	950 (0-2200)	600 (0-2000)	0.067
BPAR			
No	27 (75%)	21 (65.6%)	0.632
ATCMR	5 (13.9%)	5 (15.6%)	
AAMR	4 (11.1%)	6 (18.8%)	
CRP (mg/L)	10.1 (0.8-46.8)	3.7 (0.1-15.8)	**0.002**
Albumin (g/L)	4.1 (2.5-5)	4.2 (2.2-4.8)	0.060
CRP/Alb ratio	2.77 (0.20-15.20)	0.85 (0.02-3.81)	**0.001**

Numbers which are normally distributed are given as mean and standart deviation. Numbers which are not normally distributed are given as median and minimum, maximum, and percentages by row. BMI: Body mass index RRT: Renal replacement therapy DM: Diabetes mellitus HT: Hypertension Chr Gn: Chronic glomerulonephritis CVD: Cardiovascular disease HLA: Human lokocyte antigen PRA: panel reactive antibody Bsx: Basiliximab ATG: Anti-thymoycyte globulin PF: Plasmapheresis BPAR: Biopsy proven acute rejection ATCMR: Acute T-cell mediated rejection AAMR: Acute antibody mediated rejection CRP: C-reactive protein

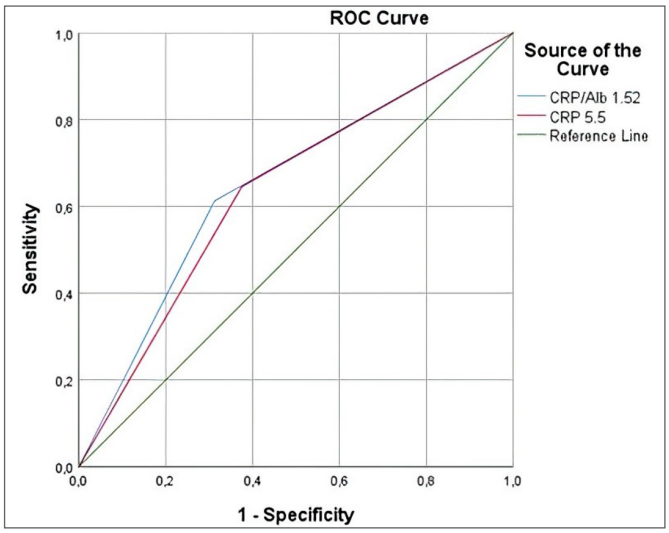

Figure 1. Receiver operating curve for CRP and CRP/Albumin ratio

Table 2. Factors affecting recipient mortality in the first year after living donor kidney transplantation

Mortality at 1st year (Cox regression)	Univariable		Multivariable (model 1)		Multivariable (model 2)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Donor age, years	0.989 (0.966-1.013)	0.354				
Donor sex, female	2.297 (1.161-4.546)	0.017	2.253 (0.972-5.222)	0.058	2.206 (0.956-5.089)	0.064
Donor BMI, (kg/m²)	1.068 (1.006-1.134)	0.031	1.059 (0.984-1.140)	0.125	1.061 (0.985-1.142)	0.117
Recipient age, years	1.044 (1.014-1.073)	0.003	1.016 (0.986-1.048)	0.302	1.015 (0.984-1.047)	0.337
Recipient sex, female	0.700 (0.360-1.358)	0.291				
Recipient BMI, (kg/m²)	0.996 (0.928-1.069)	0.909				
Relative,yes	1.012 (0.831-2.789)	0.972				
RRT/Preemptive	3.041 (1.261-7.333)	0.013	2.479 (0.973-6.317)	0.057	2.211 (0.872-5.607)	0.095
RRT duration, (months)	1.004 (0.998-1.009)	0.174				
DM	1.448 (0.733-2.860)	0.286				
HT	1.589 (0.663-3.820)	0.301				
CVD	1.543 (0.802-2.970)	0.194				
HLA mismatch	1.298 (1.035-1.629)	0.024	1.203 (0.899-1.609)	0.214	1.192 (0.890-1.598)	0.238
Class I PRA	0.909 (0.414-1.997)	0.812				
Class II PRA	1.274 (0.635-2.556)	0.495				
Immunologic risk						
Low	Reference category					
Moderate	1.332 (0.640-2.770)	0.443				
High	1.250 (0.495-3.156)	0.637				
Induction						
ATG	Reference category					
ATG+PF	0.845 (0.328-2.176)	0.727				
ATG total dose	1.270 (0.388-4.155)	0.692				
BPAR						
No	Reference category					
ATCMR	0.869 (0.334-2.257)	0.772				
AAMR	0.595 (0.208-1.701)	0.332				
CRP/Albumin ratio	1.127 (1.045-1.216)	0.002	1.148 (1.044-1.262)	**0.004**		
CRP	1.043 (1.018-1.069)	0.001			1.040 (1.011-1.069)	**0.007**

Numbers are given as median and minimum, maximum, and percentages by row; BMI: Body mass index RRT: Renal replacement therapy DM: Diabetes mellitus HT: Hypertension CVD: Cardiovascular disease HLA: Human lokocyte antigen PRA: panel reactive antibody ATG: Anti-thymocyte globulin PF: Plasmapheresis BPAR: Biopsy proven acute rejection ATCMR: Acute T-cell mediated rejection AAM: Acute antibody mediated rejection CRP: C-reactive protein

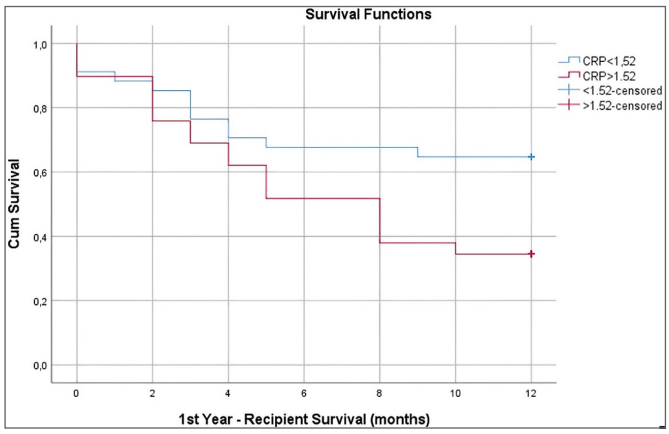

Figure 2. First year recipient survival according to CRP/Albumin cut-off value Kaplan-Meier survival analyses demonstrating the probability of first year survival based on CRP/Albumin ratio cut-off value (1.52) in the kidney recipient patients.

DISCUSSION

Early mortality after LDKT is one of the most undesirable outcomes of kidney transplantation. The first-year mortality in LDKT is mostly associated with infections and cardiovascular events (26,27). However, there is no current useful predictor tool for posttransplantation early mortality. Therefore, our study aimed to determine the value of the preoperative CRP/albumin ratio as an independent prognostic indicator to predict mortality in the first year following LDKT.

The present study revealed that the patients in the mortality group were older, had a longer median time on dialysis, had a higher HLA mismatch, and had lower preemptive transplant rates than the survivors. Since the establishment of the control group was based on the similarity of comorbid diseases that may affect mortality, differences of comorbidities did not found between the groups. The present study determined the CRP and CRP/albumin ratio as an effective independent risk factor for one-year mortality. We demonstrated that CRP levels and CRP/albumin ratios were significantly higher in the mortality group before LDKT. Van Ree et al. (18) reported that kidney transplant recipients who had a functioning graft one year after kidney transplantation

with higher CRP and lower albumin levels have high mortality risk. Although there was no difference between the groups in terms of albumin in our study, the fact that it was close to statistical significance gives the opinion that a significant difference may occur in larger case numbers.

Many studies have revealed that systemic inflammation is common in ESRD patients due to elevated serum proinflammatory cytokines and chemokines, and this inflammatory state can lead to severe complications and death (2,18-21). Acute phase reactants respond to inflammatory events in varying degrees and directions. Of these, CRP is a positive acute phase protein synthesized in the liver by inducing proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF), especially interleukin (IL)-6, whose level increases in response to infection, ischemia, and trauma (7,8,22,23). On the other hand, the albumin level decreases inversely with the degree of the inflammatory response due to the hypercatabolic state occurring in inflammatory processes and increased serum cytokines reducing albumin synthesis in the liver (6,24). In the present study, we think that high CRP levels and high CRP/albumin ratios in the mortality group may be associated with the high level of an inflammatory situation in ESRD patients.

Inflammation indicators are objective markers that show inflammation noninvasively and are used to evaluate disease activity. The CRP/albumin ratio, determined by the level of CRP and albumin parameters to each other, is a newly used prognostic biomarker based on inflammation (7-11). It was indicated in many studies that the CRP/albumin ratio could be used as a prognostic indicator of morbidity and mortality in patients with sepsis, cancer, and chronic inflammatory diseases (7-11). Park et al. (9) reported that the CRP/albumin ratio was significantly associated with early allograft dysfunction and poor patient survival in patients undergoing living donor liver transplantation. Kim et al. (10) stated that the CRP/albumin ratio of patients at admission can be used as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock and that the optimal cut-off value for CRP/albumin ratio as a predictor of mortality, being 5.09. Our study revealed that the CRP/albumin ratio is a crucial independent predictor of mortality in living donor kidney transplant recipients as 1.52. Although our study showed that both CRP/albumin and CRP were the only independent risk factors affecting one-year mortality in living donor kidney transplant recipients, the ROC curve analysis showed that CRP did not have the power to predict mortality in the first year after LDKT in our study group. In the ROC curve analysis, we demonstrated that when the cut-off value of 1.52 was chosen for the CRP/Albumin ratio, it had the power to predict one-year mortality with a sensitivity of 61.3% and a specificity of 68.8%. Therefore, this suggests that the CRP/albumin ratio may be more effective in predicting one-year mortality in LDKT recipients than CRP alone. Also, in the present study, it was found patients with values higher than the optimal cut-off value of the CRP/albumin ratio had a significantly higher probability of developing mortality.

Krüger et al. (14) reported that high pretransplantation serum CRP levels were associated with all-cause and cardiovascular mortality after kidney transplantation. Varagunam et al. (21) revealed that high CRP level before renal transplant is independently associated with all-cause and cardiovascular mortality in renal transplant recipients and can be used as a useful predictive marker in the follow-up of patients after transplantation. In their study, Molnar et al. (25) associated low pre-transplant serum albumin concentration with increased all-cause and cardiovascular mortality, a higher risk of delayed graft function, and higher graft loss in renal transplant recipients. Hsiung et al. (5) showed that the presence of hypoalbuminemia in the pre-ESRD-predialysis phase was associated with increased cardiac mortality, hospitalization, infection-related mortality, and mortality in the first year after dialysis. However, our study indicated that although CRP and albumin parameters are good predictors of mortality in renal transplant patients, the CRP/albumin ratio, which is the combined index of CRP and albumin, is better at predicting mortality because it has a higher AUC value than CRP.

Our study has some limitations. First, not all factors that could be confusing could be excluded due to its retrospective design, and some factors may not have been included in the study. Secondly, there is no repeated measurement of CRP and albumin values and, thus CRP/albumin ratios. So it was not possible for the present study shows reflecting the inflammatory process after kidney transplantation. Third, although the control group was selected as patients with similar characteristics in comorbid diseases, a possible selection bias cannot be excluded. Fourth, the preference for first-year mortality limited the number of cases, which did not allow for subgroup analysis according to causes of mortality. As a result, although all variables that may affect first-year mortality were tried to be included in the multivariate analysis, selection bias cannot be excluded entirely, so the results should be interpreted with caution. For the CRP/albumin ratio to accurately predict mortality, prospective studies involving a larger number of cases involving multiple centers are required.

CONCLUSION

We demonstrated that the CRP/albumin ratio, which can be easily calculated from simple, inexpensive, and routinely used clinical tests, has predictive power in predicting mortality in the first year after LDKT. We think that the evaluation of the CRP/albumin ratio reflecting systemic inflammation would be more useful in predicting the clinical course of the patients, as opposed to separately analyzing CRP and albumin in renal transplant patients where inflammation plays an important role.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 17.11.2020, Decision No: 11-533).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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