

Discharge Creatinine Level Predicts Long-term Clinical Outcomes in Patients with Infective Endocarditis

Enfektif Endokarditli Hastalarda Taburcu Kreatinin Değerinin Uzun Dönem Klinik Sonuçlardaki Öngördürücülüğü

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ABSTRACT

Background: The impact of admission creatinine levels on long-term mortality in infective endocarditis (IE) is well known. The relationship between discharge creatinine levels and long-term clinical outcomes of IE has not been studied yet. The goal of the present study was to evaluate the association between discharge creatinine values and long-term unfavorable outcomes of IE.

Materials and Methods: A total of 118 IE patients were retrospectively obtained. Patients were classified into two tertiles, based on discharge creatinine levels. The high discharge creatinine group (n=39) was identified as having a creatinine level in the third tertile (>0.93 mg/dL) and the low group (n=79) was identified as having a level in the lower two tertiles (≤0.93 mg/dL) to evaluate long-term follow-up.

Results: Long-term mortality was more frequent in the high group (33.3% vs. 11.3%, p=0.03). Although high discharge creatinine level (>0.93 mg/dL) was found as an independent parameter of long-term mortality (odds ratio: 2.21, 95% confidence interval: 1.34-3.65 p=0.002), estimated glomerular filtration rate did not predict long-term mortality. All-cause and heart failure-associated rehospitalization patients had higher discharge creatinine values (1.2±0.8 vs. 0.9±0.3, p=0.002 and 1.2±0.8 vs. 0.9±0.3, p=0.001, respectively).

Conclusion: High discharge creatinine level are related to long-term mortality and rehospitalization in IE.

Keywords: Endocarditis, creatinine, mortality

ÖZ

Amaç: Enfektif endokarditli (EE) hastalarda taburcu kreatinin değerlerinin uzun dönem mortaliteye etkisi bilinmektedir. EE hastalarında taburcu kreatinin değerinin uzun dönem klinik sonuçlar ile ilişkisi değerlendirilmemiştir. Bu çalışmada EE hastalarında taburcu kreatinin değerinin uzun dönem istenmeyen klinik sonuçlarla ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Toplam 118 EE hastası retrospektif olarak elde edildi. Hastalar taburcu kreatinin değerlerine göre iki gruba ayrıldı. Taburcu kreatinin değeri >0,93 mg/dL olan hastalar yüksek taburcu kreatinin grubu (n=39), taburcu kreatinin değeri ≤0,93 mg/dL olan hastalar düşük taburcu kreatinin grubu (n=79) olarak tanımlandı.

Bulgular: Yüksek taburcu kreatinin grubundaki hastalarda uzun dönem mortalite artmış olarak saptandı (%33,3 vs. %11,3, p=0,03). Yüksek taburcu kreatinin değeri (>0,93 mg/dL) uzun dönem mortalitenin bağımsız belirleyicisi (olasılık oranı: 2,21, %95 güven aralığı: 1,34-3,65 p=0,002) olmasına rağmen tahmini glomerüler filtrasyon hızı uzun dönem mortalite ile ilişkili olarak değerlendirilmedi. Tüm nedenli ve kalp yetersizliği ile ilişkili hastaneye tekrar yatış oranları yüksek taburcu kreatinin grubundaki hastalarda daha sık izlendi (1,16±0,78 vs. 0,85±0,3, p=0,002 ve 1,15±0,81 vs. 0,87±0,34, p=0,001).

Sonuç: EE hastalarında yüksek taburcu kreatinin değeri artmış uzun dönem mortalite ve tekrar hastaneye yatış ile ilişkilidir.

Anahtar Kelimeler: Endokardit, kreatinin, ölüm



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Introduction

Infective endocarditis (IE) is a condition characterized by severe morbidity and mortality. Although there have been improvements in diagnosis and medical and surgical therapy, the complications and mortality rates of the disease have remained high. Mortality rates range from 9-26% in-hospital and 10-40% for long-term period (1,2,3,4). Previous studies have reported association with admission creatinine levels and mortality from IE (5,6,7). The impact of discharge creatinine levels on long-term mortality and outcomes of IE has not yet been studied. The aim of this study was to evaluate the impact of discharge creatinine levels and long-term unfavourable outcomes of IE.

Material and Methods

A total of 171 IE patients were obtained in a retrospective study between January 2008-December 2020 at the University of Health Sciences Türkiye, Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Training and Research Hospital and January 2013-January 2021 Private Medikar Hospital. The modified Duke criteria (8) used for a definitive diagnosis of IE. Forty-eight patients died in-hospital, and five patients who treated with hemodialysis were excluded. Therefore, 118 patients were evaluated. The study population was divided into tertiles, according to discharge creatinine values. The high discharge creatinine group (n=39) was classified as having a creatinine level in the third tertile (>0.93 mg/dL) and the low group (n=79) was classified as having a level in the lower two tertiles (≤0.93 mg/dL) to evaluate long-term follow-up. Estimated glomerular filtration (eGFR) was calculated by modification of diet in renal disease formula (9).

The study population was analyzed according to clinical, laboratory, and echocardiographic parameters. Blood samples were obtained three separate venipuncture sites for blood cultures. On admission and during in-hospital stay, hematologic and biochemical measurements were noted by daily. Within 72 hours of admission, each patient

was evaluated through a comprehensive echocardiographic examination. Serum creatinine concentrations were calculated with the Jaffe method.

Mortality was determined as a death during follow-up. Hypertension (HT) was determined as use of antihypertensive agent, a systolic pressure >140 mm Hg, or a diastolic pressure >90 mm Hg. Diabetes mellitus was defined as the usage of insulin or antidiabetic drugs. Acute kidney injury was determined serum creatinine level rised more than 0.3 mg/dL (10). Paravalvular abscess, dehiscence of the prosthetic valve, fistula, and indication of surgical treatment were defined according to previous guidelines (2). Heart failure was defined as the having of pulmonary edema or cardiogenic shock occurring with valvular perforation, intracardiac abscess, fistula, or valvular obstruction.

Follow-up data were noted from hospital documents. The primary endpoint was all-cause mortality. All of rehospitalizations were noted.

Statistical Analysis

Quantitative variables were shown as mean value ± standard deviation, and qualitative variables were expressed as percentages. Comparisons of parametric values assessed by means of a two-tailed Student's t-test. χ^2 or Fisher's Exact test used to compare with categorical variables. A backward stepwise multivariate logistic regression analysis was used to determinate predictors of mortality. Age greater than 65 years, admission creatinine level, HT, surgical therapy, and peak and discharge creatinine levels were evaluated. The cumulative survival curves for mortality were established using the Kaplan-Meier method, with differences evaluated using the log-rank test. All statistical analyses were noted by using SPSS version 15.0 (SPSS Inc., Chicago, IL).

Results

The clinical and demographic parameters of the patients are summarized in Table 1. Mean age was 45.9±18.3. Prosthetic valve endocarditis was seen in 35 patients, and admission creatinine level was 1.0±0.7. Surgical treatment

Table 1. Clinical and demographic findings of the study patients

Age (years)	45.9±18.3	Dehiscence	11 (34.3)
Male gender	71 (60.1)	Abscess	21 (17.7)
Diabetes mellitus	9 (7.6)	Fistula	13 (11)
Hypertension	34 (28.8)	WBC (10 ⁹ g/dL)	10.2±4.7
Mitral native	24 (20.3)	Hemoglobin (g/dL)	11.1±2.1
Aort native	22 (18.6)	Admission creatinine (mg/dL)	1.0±0.7
Mitral and aortic involvement	11 (9.3)	LVEF (%)	55±10.8
Lead endocarditis	15 (12.7)	Surgical treatment	71 (60.1)
Prosthetic valve	32 (27.1)		

Mean (SD) and n (%) are reported for continuous and categorical variables, respectively.
 LVEF: Left ventricular ejection fraction, WBC: White blood cell, SD: Standard deviation

was performed on 71 patients. A comparison of the clinical and demographic findings of patients with survival and non-survival is listed in Table 2. C-reactive protein levels were parallel in survival and non-survival patients (105.1±85.3 vs. 110.1±79.7, p=0.8, respectively). The causative microorganisms were *Viridans streptococci* (30 patient, 25.4%), *Staphylococcus aureus* (14 patient, 11.8%), coagulase negative *Staphylococcus* (29 patient, 24.5%) *Enterococcus* spp. (6 patient, 5.0%), culture-negative (25 patient, 21.1%) and other microorganisms (14 patient, 11.8%).

The values of admission, peak, and discharge creatinine and eGFR levels in survival and non-survival subjects are listed in Table 3. Admission, peak, discharge creatinine and eGFR levels were higher in the mortality group. Table 4 and Table 5 present admission, peak, discharge creatinine and eGFR levels with all-cause and heart failure-associated rehospitalization. Patients with rehospitalization had higher discharge creatinine and eGFR values. Multivariate logistic regression analysis indicate that age and discharge creatinine level were independent parameters of long-term mortality (Table 6).

Table 2. Comparison of the clinical and demographic findings of patients with survival and non-survival

	Survival (n=96)	Non-survival (n=22)	p
Age (years)	42.4±17.3	61.0±14.5	<0.001
Male gender	61 (63.5)	10 (45.4)	0.11
Diabetes mellitus	6 (6.2)	3 (13.6)	0.23
Hypertension	21 (21.8)	13 (59)	0.001
Dehiscence	8 (8.3)	3 (13.6)	0.44
Abscess	18 (18.7)	3 (13.6)	0.57
Fistula	10 (9.6)	3 (13.6)	0.66
WBC (10 ⁹ g/dL)	10.3±4.0	10.1±7.1	0.85
Hemoglobin (g/dL)	11.2±2.2	10.5±1.8	0.14
LVEF (%)	55.3±11.0	53.9±10.6	0.58
Surgical treatment	62 (64.5)	9 (40.9)	0.04
AKI	35 (36.4)	15 (68.1)	0.007

Mean (SD) and n (%) are reported for continuous and categorical variables, respectively.
LVEF: Left ventricular ejection fraction, WBC: White blood cell, AKI: Acute kidney injury, SD: Standard deviation

Table 3. Admission, peak and discharge levels of the survival and non-survival patients

	Survival group (n=96)	Non-survival group (n=22)	p
Admission creatinine (mg/dL)	0.9±0.4	1.4±1.3	0.009
Peak creatinine (mg/dL)	1.4±0.8	2.2±1.7	0.002
Discharge creatinine (mg/dL)	0.8±0.3	1.4±0.9	< 0.001
Admission eGFR (mL/min)	95.5±35.0	69.7±28.4	< 0.001
Peak eGFR (mL/min)	70.9±36.0	41.5±21.1	< 0.001
Discharge eGFR (mL/min)	103.8±33.4	67.0±35.7	< 0.001

eGFR: Estimated glomerular filtration rate

Table 4. Admission, peak and discharge creatinine levels of the all-cause rehospitalization and non-rehospitalization patients

	Non-rehospitalization (n=85)	Rehospitalization (n=33)	p
Admission creatinine (mg/dL)	1.0±0.4	1.19±1.1	0.1
Peak creatinine (mg/dL)	1.4±0.8	1.9±1.5	0.04
Discharge creatinine (mg/dL)	0.9±0.3	1.2±0.8	0.002
Admission eGFR (mL/min)	94.6±35.4	80.6±33.2	0.052
Peak eGFR (mL/min)	69.7±36.8	54.3±30.1	0.03
Discharge eGFR (mL/min)	101.7±34.5	82.7±37.3	0.01

eGFR: Estimated glomerular filtration rate

Discharge creatinine level 0.93 mg/dL was determined as an efficacious cut-off value for long-term mortality (area under curve=0.71; 95% confidence interval 0.58-0.84, p=0.003), the sensitivity was 59.1%, and the specificity was 72.9%. Long-term mortality was more frequent in the high-discharge creatinine group (Figure 1). The median follow-up time was 40 months and long-term mortality increased in the high discharge creatinine group. (11.3% vs. 33.3%, p=0.03).

Discussion

This is the initial study to investigate the impact of discharge creatinine levels on long-term mortality and clinical outcomes in IE. In the present study, we found that discharge creatinine level was an independent parameter of long-term mortality and rehospitalization. Although eGFR level was related to rehospitalization it was not predictor of long-term mortality.

IE is a life-threatening condition. The mortality rate of the disease was 15% in a 1980s cohort, mortality rates have remained high despite improvements in diagnosis and medical and surgical therapy (1,2,3,4,9). Many studies have shown the relationship between renal dysfunction and cardiovascular diseases (10,11,12,13,14,15,16). Shlipak

et al. (10) evaluated 130.099 elderly patients hospitalized with myocardial infarction, and they found that mild and moderate renal failure (creatinine level >1.5 mg/dL) were related to increased long-term mortality. Furthermore, Santopinto et al. (12) reported that the creatinine clearance

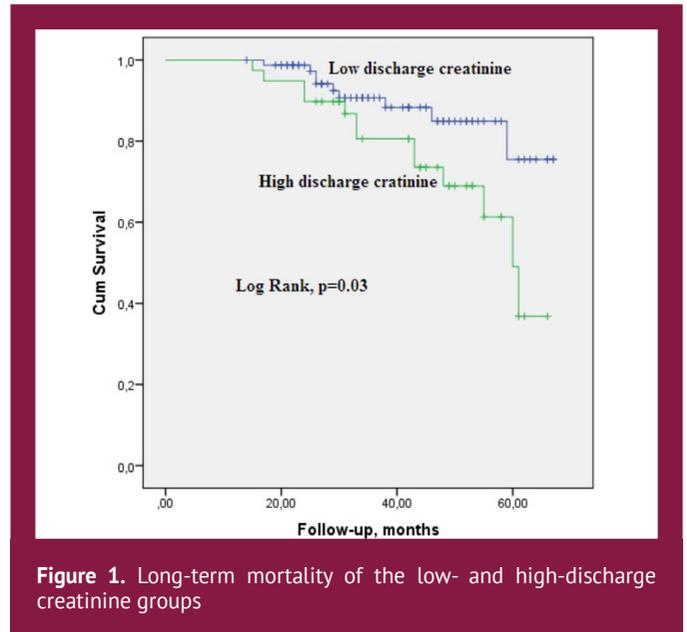


Figure 1. Long-term mortality of the low- and high-discharge creatinine groups

Table 5. Admission, peak and discharge creatinine levels of the heart failure related rehospitalization and non-rehospitalization patients

	Non-rehospitalization (n=91)	Rehospitalization (n=27)	p
Admission creatinine (mg/dL)	1.0±0.4	1.2±1.3	0.05
Peak creatinine (mg/dL)	1.4±0.8	2.0±1.6	0.002
Discharge creatinine (mg/dL)	0.9±0.3	1.2±0.8	0.001
Admission eGFR (mL/min)	93.6±35.3	81.0±33.7	0.1
Peak eGFR (mL/min)	68.7±36.0	54.4±32.1	0.06
Discharge eGFR (mL/min)	100.4±35.8	82.9±36.3	0.03

eGFR: Estimated glomerular filtration rate

Table 6. Effects of multiple variables on long-term mortality in univariate and multivariate Cox regression analysis

	Univariate OR	95% CI	p	Multivariate OR	95% CI	p
Age	1.057	1.023-1.093	0.001	1.055	1.025-1.087	<0.001
Admission creatinine	1.624	1.136-2.32	0.008			
HT	2.47	0.9-6.83	0.08			
Surgical treatment	0.24	0.08-0.73	0.01			
Peak creatinine	1.6	1.2-2.13	0.001			
Discharge creatinine	2.6	1.7-4.01	<0.001	2.29	1.339-3.647	0.002
Admission eGFR	0.98	0.966-0.995	0.007			
Peak eGFR	0.972	0.955-0.990	0.002			
Discharge eGFR	0.975	0.961-0.988	<0.001			

HT: Hypertension, eGFR: Estimated glomerular filtration rate, OR: Odds ratio, CI: Confidence interval

rate was related to mortality and major bleeding in acute coronary syndrome (ACS). Marenzi et al. (14) examined 2756 patients with ACS, and they showed that during treatment in the intensive cardiac care unit, creatinine level increases of more than 0.3 mg/dl were an important predictor of mortality. Cystatin C (CysC) is a useful parameter to evaluate renal function. Akgul et al. (15) showed that high CysC levels were related to the higher increased both in-hospital and one-month mortality of patients with ST-elevation myocardial infarction.

IE is associated with renal dysfunction, and previous studies have shown the impact of in-hospital creatinine levels and long-term mortality (5,6,7). There are several reasons for renal dysfunction in IE. Focal and diffuse glomerulonephritis characterized by immune complex deposition, vasculitic glomerulonephritis, acute interstitial nephritis, renal infarcts due to septic embolism or haemodynamic disturbance, and nephrotoxic antibiotics such as aminoglycosides are associated with renal failure in IE. Immune complexes have been shown in up to 90 percent of patients, and their levels were successfully lowered as a result of antibiotic therapy (17). Both focal and diffuse glomerulonephritis may occur in the same patients, and it may be present despite the absence of clinical signs of renal failure. Furthermore, vasculitic and immune complex glomerulonephritis may be associated with cell-mediated immunity (18,19). Hypotensive episodes because of heart failure, renal emboli, or severe septicaemia may even cause acute tubular damage and renal cortical necrosis (20). Microscopic hematuria, pyuria, or proteinuria occurs, and gross hematuria may be related to renal infarction. Majumdar et al. (21) investigated renal pathological findings in IE and evaluated 62 patients' renal tissue obtained by necropsy or biopsy. They found that localized infarction was the most frequent renal lesion. Acute glomerulonephritis, which was mainly vasculitic glomerulonephritis, was seen in 26% of samples.

Moreover, Erbay et al. (7) showed that a creatinine level ≥ 2 mg/dL was an important risk factor for mortality from IE. Hsu et al. (22) examined 315 patients and reported that renal dysfunction (creatinine level ≥ 1.5) was an independent predictor of in-hospital mortality of IE. In a related study, Wallace et al. (5) investigated 208 IE patients retrospectively within the first 48 hours after admission for clinical markers, and they showed that serum creatinine levels >133 $\mu\text{mol/dL}$ were related to in-hospital and long-term mortality. In addition, Koeda et al. (23) found that the admission creatinine and eGFR values were associated with in-hospital mortality from IE. Buchholtz et al. (24) prospectively investigated 231 IE patients, and they divided patients into four groups according to their

admission-estimated endogenous creatinine clearance (ECC). In this study, in which the mean follow-up was 453 days, they showed that patients in group IV (ECC <30 mL/min) were strongly related to both in-hospital and long-term mortality. In contrast, we did not find association between eGFR level and long-term mortality. Bjurman et al. (25) evaluated 125 IE patients, and they noted CysC levels at admission and after two weeks of treatment. They showed that CysC levels were important predictors of mortality.

The association between discharge creatinine levels and long-term unfavourable outcomes in IE has not yet been reported. Many studies have shown the impact of admission creatinine, ECC, eGFR, and CysC levels and long-term mortality (5,24,25). Wallace et al. (5) noted that a cut-off creatinine level was 133 $\mu\text{mol/dL}$ (1.5 mg/dL) was an important parameter for in-hospital and six-month mortality. In this study, we found that discharge creatinine cut-off value of 0.93 mg/dL was an important parameter of long-term mortality from IE. In addition, eGFR value was not a factor of long-term mortality in IE. Notably, we reported that discharge creatinine level may be associated with long-term mortality in IE.

The precise mechanism for this relationship is not known. Although successful antibiotic therapy normalizes urinary parameters in most patients, microscopic hematuria or proteinuria may continue for a long time. In these patients, extensive residual glomerular changes, such as proliferation or sclerosis of glomeruli, have been shown on postmortem examination (17). This condition may, in fact, be related to a genetic mechanism.

Study Limitations

Our study is a retrospective, non-randomized, single-centre study and may be related to selection bias. In addition, we did not look at other laboratory markers such as CysC, and we did not calculate ECC, and the effects of diet modification on renal disease.

Conclusion

Our study showed that discharge creatinine level is an important parameter of long-term mortality and rehospitalization in IE. Creatinine is a easily available, inexpensive marker for predicting long-term mortality and clinical outcomes of IE.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Ethics Committee of the Karabük University with the decision numbered 2023/1227 on 17/01/2023.

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., M.E., Concept: M.E., Design: M.E., Data Collection or Processing: M.B., Analysis or Interpretation: M.B., M.E., Literature Search: M.B., Writing: M.B., M.E.

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