Original Article

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Comprehensive Analysis of Prognostic Factors Affecting Postoperative Mortality in Adult Patients Undergoing Lower Extremity Amputation due to Diabetic Foot Ulcer

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Abstract

Aim: Mortality is significantly increased in patients undergoing amputation for diabetic foot ulcers (DFUs). The new biomarkers prognostic nutritional index (PNI), C-reactive protein (CRP)/albumin ratio, and comorbidities may help predict prognosis. This study aimed to determine the factors affecting mortality in DFU patients undergoing amputation.

Methods: This study is a retrospective case series of patients who underwent lower extremity amputation due to DFU between 2016 and 2018. Data on demographics, clinical information, laboratory test results, comorbidities, hospital stays, re-amputations, and complications were recorded. PNI was calculated using serum albumin concentration and lymphocyte count.

Results: A total of 97 patients (21 females and 76 males) were analyzed in the study, with 18 patients having bilateral lower extremity amputations (foot amputation, below-knee amputation, and above-knee amputation). The mean age was 64.48 years, and the mean follow-up period was 34.27 months. The mean length of hospital stay was 19.09 days, with a mean of 1.34 days spent in the intensive care unit. Preoperative laboratory test results showed a mean creatinine level of 1.4 mg/dL, a urea level of 55.22 mg/dL, an albumin level of 2.8 g/L, and a fasting blood glucose level of 168.8 mg/dL. The mean preoperative PNI was 39.31, and the mean CRP/albumin ratio was 42.51. Intensive care unit admission, CRP/albumin ratio, and CRP levels significantly affect 1-year postoperative mortality. The cut-off value for CRP as determined by receiver operating characteristic analysis was 89.9 mg/L. No significant association was found between comorbidities and mortality.

Conclusion: We demonstrated that comorbidities and the new biomarker PNI did not affect mortality. CRP levels, intensive care unit admission, and the new predictor CRP/albumin ratio significantly affected 1-year mortality.

Keywords: Diabetic foot ulcer, amputation, prognostic nutritional index, C-reactive protein, C-reactive protein/albumin ratio

Introduction

Diabetic foot ulcer (DFU) is one of the most difficult diseases to manage among emergency department admissions. DFU is a serious complication of diabetes mellitus that affects millions of individuals worldwide (1). It is characterized by the formation of chronic wounds on the feet, often leading to severe infections and tissue damage. In some cases, amputation becomes necessary to prevent the spread of infection and improve the patient's quality of life (2). However, amputation is associated with significant postoperative mortality rates, making it crucial to identify prognostic factors that influence patient outcomes (3).

It has been claimed that comorbidities affect postoperative mortality in patients with DFU (4). Conditions such as cardiovascular disease, chronic kidney disease, peripheral arterial disease, and chronic obstructive pulmonary disease contribute to increased surgical risk, delayed wound healing, and higher rates of infection, ultimately leading to a higher mortality risk (4). Managing and optimizing the control of these comorbidities before and after amputation is essential for improving patient outcomes.

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Infection is a major complication of DFUs and strongly influences postoperative mortality. The presence of infection at the time of amputation, particularly deep-seated or systemic infections, is associated with poorer outcomes and increased mortality rates (5). Furthermore, elevated levels of inflammatory markers, such as C-reactive protein (CRP), have been linked to a higher mortality risk in patients with DFU undergoing amputation (6,7). Early detection and management of infections, along with monitoring of inflammatory markers, are crucial for reducing postoperative mortality rates. We believe that promising new biochemical values [such as prognostic nutritional index (PNI) and CRP/albumin ratio], which are also used to predict other complications of diabetes, may provide guidance in predicting survival after amputation (8).

The aims of this study were (1) to investigate the relationship between biomarkers, comorbidities, length of intensive care unit (ICU) stay, and mortality, and (2) to examine the factors affecting the need for re-amputation in a single tertiary referral center. This study provides a comprehensive analysis of the prognostic factors affecting postoperative mortality in patients undergoing amputation due to DFUs.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2022/89, date: May 11, 2022) and conducted in accordance with the principles of the Helsinki Declaration. The participants were informed that the data would only be used for scientific purposes.

Study Design

The medical records of 109 patients who underwent lower extremity amputation due to DFUs between 2016 and 2018 at our institution were retrospectively identified. The inclusion criteria for the study were: (1) patients with DFUs (2) patients undergoing lower extremity amputation (foot amputation, below-knee amputation, and above-knee amputation), and (3) complete clinical and radiographic data. The exclusion criteria were: (1) patients who underwent surgery for reasons other than diabetes foot ulcers; (2) lost to follow-up; and (3) inadequate medical records.

Based on the above eligibility criteria, after excluding 12 patients, the remaining 97 patients were included in the study (Figure 1). Demographic and clinical data were collected from the hospital's electronic database and medical records, including gender and follow-up duration. The study was designed in two parts. In the first part, the relationship between laboratory test results, comorbidities, ICU length of stay, and 1- and 5-year survival was investigated. The PNI was calculated using serum albumin concentrations and lymphocyte counts in the peripheral blood. In the second part, the factors affecting re-amputation were reviewed.

Intra- and postoperative complications were recorded. Patients who underwent revision surgery are noted.

Statistical Analysis

Statistical analysis was performed using the SPSS (IBM, Armonk, New York, USA) version 24.0 statistical software. Descriptive statistical methods were used to evaluate the study data. A Kaplan-Meier survival analysis was performed. Furthermore, potential prognostic factors were identified by univariate Cox regression analysis. Elements with p values (two-sided) of 0.05 were included in the multivariate Cox proportional hazard model to identify independent variables in a stepwise fashion. Receiver operating characteristic curves were generated to determine the accuracy of the data. Differences with $p \leq 0.05$ were considered statistically significant.

Results

The demographic data of the patients is presented in Table 1. According to the Kaplan-Meier analysis, the 1-year and 5-year survival rates of patients were 70% (68/97) and 43% (42/97), respectively (Figure 2).

In part 1, preoperative mean creatine was 1.4±1.5 mg/dL and urea was 55.22±38.16 mg/dL. The mean

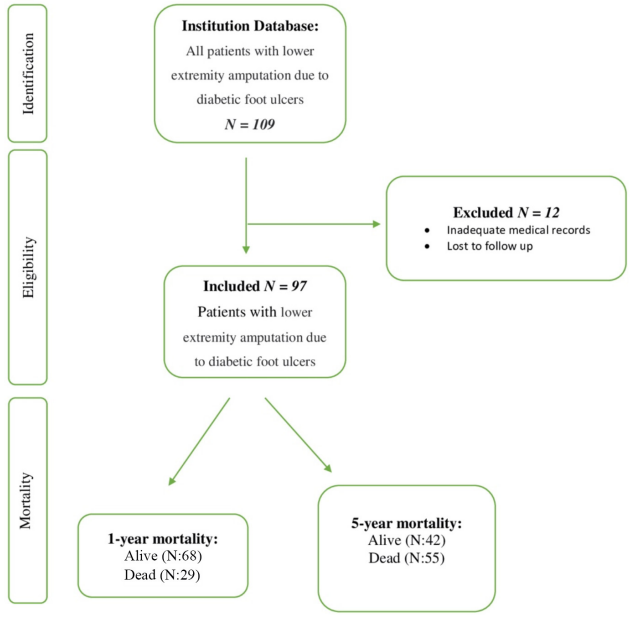

Figure 1. Flow chart of the study

preoperative albumin level was 2.8 2.8±0.6 g/L. The mean preoperative fasting blood glucose of the patients was measured 168.8±78.1 mg/dL. The mean preoperative PNI and CRP/albumin ratios of the patients were 39.31±16.1 and 42.51±42.89 respectively. In the statistical analysis, it was found that the CRP/albumin ratio (p=0.045) and CRP levels (p=0.032) significantly affected the 1-year mortality of the patients in the postoperative period. Receiver operating characteristic analysis was performed, and the cut-off value for CRP was found to be 89.9 mg/L (Figure 3). The mean length of hospital stay was 19.09±15.94 days, and the mean length of stay in ICU was 1.34±3.37 days (range, 0-14). We observed that the length of stay in the intensive care unit (p=0.002) was an independent risk factor for 1-year mortality. When comorbidities were examined, no correlation was found between hypertension, cerebrovascular disease, chronic obstructive pulmonary disease, peripheral artery disease, coronary artery disease, renal disease, dementia, and mortality. When the relationship between comorbidities, laboratory test results, and 5-year survival was analyzed, we observed that the factors examined had no effect on mortality.

In part 2, when the relationship between the aforementioned parameters and re-amputation was examined, we found that ICU length of stay (p=0.014), preoperative platelet/lymphocyte ratio (PLR) (p=0.014), and preoperative fasting blood glucose (p=0.032) were independent risk factors.

Discussion

Diabetes mellitus is a systemic disease that simultaneously affects many systems in the body and is associated with an increased incidence of morbidity and mortality. DFU is one of the most difficult and serious complications of diabetes mellitus and has a direct impact on survival. The current literature focuses mainly on the progression of diabetic wounds, but we have chosen to focus on the factors that influence mortality after lower extremity amputation. The findings highlight the importance of identifying and addressing these factors in clinical practice, revealing several key factors that significantly influence patient outcomes.

While there are many studies examining mortality after DFU in the literature, there are very few studies examining mortality after amputation. In our study, our mortality rates after amputation were found to be compatible with those reported in the literature (9). Elderly patients often present with reduced physiological reserves and a higher burden of comorbidities, which may impair their ability to tolerate and recover from surgery. Contrary to previous studies, advanced age does not have a significant effect on increasing postoperative mortality in patients with DFU undergoing amputation (10).

Table 1. The demographic data of the patients	
Number of patients	**97**
Age (years)	64.48±11.41 (range, 38-90)
Gender (Female/Male)	21/76
Bilateral/unilateral amputation	18/79
Follow up period (months)	34.27±24.05 (range, 0.03-99.8)

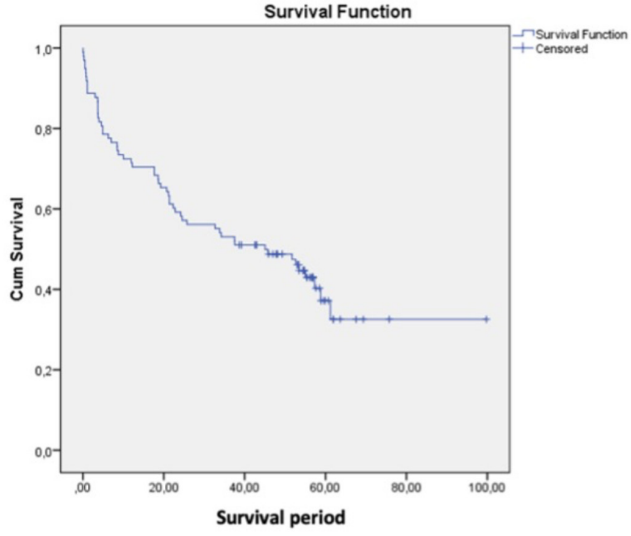

Figure 2. The Kaplan-Meier curves illustrating the survival

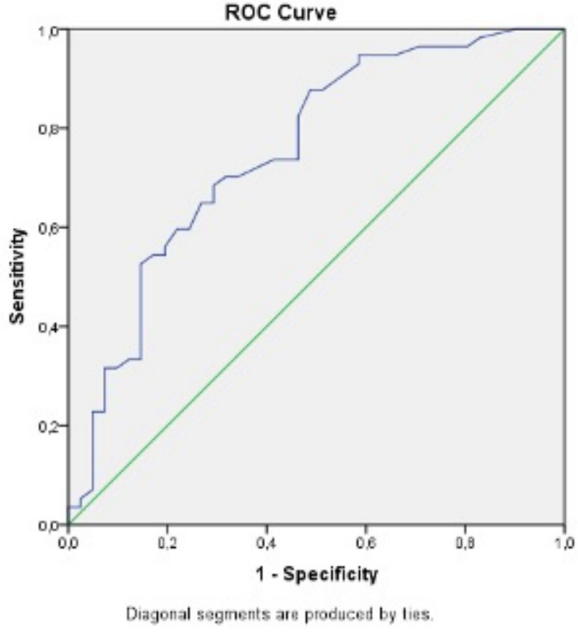

Figure 3. ROC curve for CRP levels (cut off-89,9, sensitivity: 0.702 specificity: 0.683)
ROC: Receiver operating characteristic, CRP: C-reactive protein

Table 2. Laboratory test results at the time of admission to the emergency department	
	Mean ± SD
CRP (C-reactive protein) (mg/L)	104.96±87.84
Hemoglobin (g/dL)	10.41±1.83
HbA1c (%)	9.39±2.29
WBC (White blood cells)	12.13±5.97
Neutrophil	9.97±8.25
Lymphocyte	2.25±3.05
NLR (Neutrophil to lymphocyte ratio)	6.21±4.78
RDW (Red blood cell distribution width)	34.09±184.01
PLT (Platelet count)	351.22±150.04
PLR (Platelet/lymphocyte ratio)	220.38±130.93
Urea (mg/dL)	55.27±37.97
Creatine (mg/dL)	1.42±1.52
Fasting blood glucose (mg/dL)	167.24±78.18
Albumin (g/L)	2.80±0.57
PNI (Prognostic nutritional index)	39.31±16.10
CRP/albumin	42.51±42.89
CRP/PNI	3.07±3.04
SD: Standard deviation	

It has been claimed many times in the literature that the presence of comorbidities such as cardiovascular disease, chronic kidney disease, peripheral artery disease, and chronic obstructive pulmonary disease increases postoperative mortality rates (4). These comorbidities create additional risks for the surgical procedure, delay wound healing, and increase susceptibility to infections. Unlike the literature, we did not find a relationship between these comorbidities and mortality. However, it is imperative that healthcare providers comprehensively evaluate and manage these conditions preoperatively to optimize patient outcomes.

Infection remains a major complication in patients with DFU and has a significant impact on postoperative mortality. Worse outcomes and higher mortality rates were observed in patients with deeply located or systemic infections (5). High levels of inflammatory markers, including CRP, have been found to predict increased mortality risk (6,11-14). In our study, we also revealed that CRP has a clear effect on survival. Timely detection, rapid management of infections, and careful monitoring of inflammatory markers are critical for reducing postoperative mortality rates.

The PNI, which is evaluated by peripheral blood lymphocyte count and serum albumin, is a new biomarker that shows the patient's immune status and adaptation to infection and diseases. We did not observe a relationship between PNI and mortality in our study. However, both CRP and the CRP/albumin ratio are biomarkers that have started to be used in the follow-up of diabetic complications. Receiver operating characteristic analysis revealed that the cut-off value for CRP was 89.9, and mortality increased for CRP values ≥90. In our study, we also revealed that these markers are significant predictive factors of survival in DFU follow-up (15).

The relationship between length of hospital stay and diabetes-related amputation has been studied, but to our knowledge, no study has investigated the relationship between length of stay in the ICU and amputation due to diabetes (16). The length of stay in the ICU is an independent risk factor affecting mortality after amputation due to DFU.

Although studies have shown a relationship between cerebrovascular disease, sex, chronic renal failure, and 5-year mortality, we could not find a relationship between 5-year mortality and any of the parameters examined in our study (17).

Studies have been conducted to investigate the causes of re-amputation in patients with diabetes (18). In our study, we found a relationship between re-amputation and the length of intensive care unit stay, preoperative PLR, and pre-operative fasting blood glucose.

Study Limitations

The findings of this study should be interpreted in light of its potential limitations. The most important limitation of the study was that it was retrospective, had a limited sample size, and lacked a case series for comparison. In addition, many surgeons participated in the surgeries. Despite these limitations, the current investigation has several strengths. To the best of my knowledge, this is the first study in the literature showing that the CRP/albumin ratio is effective in predicting mortality after amputation due to DFU, whereas PNI is not effective. In addition, this is one of the rare studies that determined a cut-off value for CRP. All surgeries were performed at a single tertiary referral center. Prospective randomized comparative studies are required in the future.

Conclusion

This comprehensive analysis highlights the importance of considering multiple prognostic factors in evaluating postoperative mortality in patients undergoing amputation due to DFUs. CRP levels, ICU length of stay, and CRP/albumin ratio are independent risk factors for 1-year mortality. Understanding and addressing these prognostic factors is crucial for healthcare professionals to optimize patient care, accelerate wound healing, reduce complications, and ultimately reduce mortality in this vulnerable patient population.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2022/89, date: May 11, 2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.E., M.Ek., M.Y., Design: M.E., M.Ek., M.Y., Data Collection and/or Processing: M.E., M.Ek., E.G., K.A.C., Analysis and/or Interpretation: M.E., M.Ek., Literature Research: M.E., M.Ek., Writing: M.E., M.Ek.

Conflict of Interest: No conflicts of interest were declared by the authors.

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