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Research

Nutritional and Inflammatory Markers as Predictors of Major Amputation in Patients with Diabetic Foot Infections

Diyabetik Ayak Enfeksiyonu Olan Hastalarda Majör Amputasyon Öngörücüsü Nutrisyonel ve Enflamatuvar Belirteçler

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ABSTRACT

Objective: Diabetic foot infections (DFIs) are serious complications of diabetes mellitus and a major cause of lower extremity amputations. Identifying predictive factors for major amputation can guide treatment and improve patient outcomes.

Methods: In this retrospective cross-sectional study, 77 patients with DFIs who were treated between December 2022 and July 2024 were evaluated. Clinical and laboratory data were collected, including inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocyte count], hematologic parameters, and nutritional indices [albumin, hemoglobin, prognostic nutritional index (PNI)]. Amputations were classified as major or minor based on anatomical level. Statistical analyses were conducted to identify predictors of major amputation.

Results: Major amputations were performed in 25.9% of patients. Compared with patients without major amputation, those who underwent major amputation had significantly higher leukocyte, neutrophil, and platelet counts, CRP, and ESR levels and lower hemoglobin, albumin, and PNI scores (all $p<0.05$). No significant differences were observed in neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, or systemic immune-inflammation index values between the groups. PNI was strongly associated with the need for major amputation.

Conclusion: Nutritional status, especially PNI and serum albumin, and inflammatory markers are valuable predictors of major amputation in patients with DFIs. Early assessments of nutritional and inflammatory status may reduce the risk of amputation and improve prognosis.

Keywords: Diabetic foot infection, major amputation, prognostic nutritional index, inflammation, albumin

ÖZ

Amaç: Diyabetik ayak enfeksiyonu (DAE), diabetes mellitusun ciddi komplikasyonlarından biridir ve alt ekstremite amputasyonlarının başlıca nedenleri arasında yer alır. Majör amputasyon gerekliliğini öngörecek belirteçlerin tanımlanması, tedavi planlamasını kolaylaştırabilir ve hasta sonuçlarını iyileştirebilir.

Gereç ve Yöntem: Bu retrospektif, kesitsel çalışmada, Aralık 2022 ile Temmuz 2024 tarihleri arasında DAE nedeniyle takip edilen 77 hasta değerlendirildi. Hastalara ait klinik ve laboratuvar verileri [C-reaktif protein (CRP), eritrosit sedimentasyon hızı, lökosit sayısı, hemoglobin, albümin, prognostik beslenme indeksi (PBİ) gibi] toplandı. Amputasyonlar anatomik düzeye göre majör ve majör olmayan olarak sınıflandırıldı. İstatistiksel analizlerle majör amputasyonu öngören parametreler incelendi.

Bulgular: Hastaların %25,9'unda majör amputasyon yapıldı. Majör amputasyon uygulanan grupta lökosit, nötrofil, trombosit, CRP ve sedimentasyon düzeyleri anlamlı şekilde yüksek; hemoglobin, albümin ve PBİ değerleri ise anlamlı şekilde düşüktü ($p<0,05$). Nötrofil/lenfosit oranı, trombosit/lenfosit oranı ve sistemik immün-enflamatuvar indeks değerlerinde anlamlı fark gözlenmedi. Düşük PBİ skoru majör amputasyonla güçlü şekilde ilişkiliydi.

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ÖZ

Sonuç: DAE olan hastalarda beslenme durumu (özellikle PBİ ve serum albümin) ve enflamatuvar belirteçler majör amputasyon riskini öngörmede değerli olabilir. Bu parametrelerin erken değerlendirilmesi, amputasyon riskini azaltabilir ve prognozu iyileştirebilir.

Anahtar Kelimeler: Diyabetik ayak enfeksiyonu, majör amputasyon, prognostik beslenme indeksi, enflamasyon, albümin

INTRODUCTION

Diabetes mellitus is a chronic illness that affects several organ systems and is increasing in prevalence worldwide. Diabetes-related complications can cause serious harm, especially to the cardiovascular, neurological, and microvascular systems, and increase morbidity and mortality among patients. Diabetic foot infections (DFIs) represent one of the most severe complications of diabetes and are among the leading causes of hospitalizations and lower extremity amputations (1).

Reports indicate that 40-60% of non-traumatic lower-extremity amputations are due to DFIs (2). In diabetic patients, the development of peripheral neuropathy, peripheral arterial disease, and a weakened immune system impairs wound healing and predisposes patients to infection. Amputation becomes inevitable in cases where infection cannot be controlled, tissue necrosis occurs, or systemic complications develop (3).

It is well established that the extent of amputation directly affects patients' clinical prognosis. When there is extensive tissue loss or systemic spread, major amputation is the preferred option. Minor amputations, on the other hand, aim to preserve the limb's function. It is essential to understand the factors that influence the level of amputation in order to plan surgery for each patient and to prevent potential complications. The goal of this study was to identify the clinical and laboratory factors that led to the need for major amputation in patients with DFI.

METHODS

This single-center, retrospective, cross-sectional study included patients aged 18 years or older who were hospitalized for DFIs and followed-up at our hospital's wound care clinic between December 2022 and July 2024. Only patients with complete medical records were included in the study.

Demographic data (age, sex), comorbidities (hypertension, coronary artery disease, chronic kidney disease, peripheral artery disease, etc.), and laboratory parameters [leukocyte count, hemoglobin (Hb), neutrophil count, lymphocyte count, platelet count, creatinine, HbA1c, etc.] were retrospectively collected from the electronic medical records system.

Amputations performed proximal to the ankle joint were classified as "major amputations," while those performed distal to the ankle joint were classified as "minor amputations."

Inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin], blood-cell ratio indices [platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII)=(platelet count×neutrophil count)/lymphocyte count], and nutritional indices such as the prognostic nutritional index (PNI)=serum albumin (g/L)+[0.005×total lymphocyte count (mm^3)] and controlling nutritional status scores were examined to determine whether significant differences between the two groups. Causative pathogens were identified through deep tissue culture samples obtained during the debridement process.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 29, SPSS Inc., Chicago, IL, USA). Normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. For non-parametric variables, the Mann-Whitney U test was used; for parametric variables, the Student's t-test was applied. The chi-square test or Fisher's exact test, as applicable, was used to analyze categorical variables. A statistically significant difference was defined as $p<0.05$.

Ethical Approval

This study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Scientific Research Ethics Committee (approval no: 2025-08-12; date: 24.04.2025). As the study was retrospective and personal data were anonymized, informed consent was not required.

RESULTS

Of the 77 patients included in the study, 87% (n=67) were male, with a mean age of 62.6±11.9 years. The most common comorbidities were hypertension (n=46, 59.7%), coronary artery disease (n=36, 46.7%), chronic kidney disease (n=25, 32.4%), and peripheral arterial disease (n=25, 32.4%).

Major amputations were performed in 20 patients (25.9%), and minor amputations were performed in 15 patients (19.4%). Patients who underwent major amputation had significantly higher leukocyte counts (13006±5193 vs. 10160±4763; p=0.032), neutrophil counts (10638±5443 vs. 7975±4669; p=0.034), platelet counts (368750±107035 vs. 309166±105900; p=0.041), CRP levels (109±69 vs. 76±73; p=0.027), and ESR levels (82±30 vs. 60±30; p=0.004). In contrast, Hb (9.8±1.1 vs. 10.8±1.9; p=0.010), albumin (28±4 vs. 34±5; p<0.001), and PNI scores (36.79±6.11 vs. 42.17±6.26; p=0.003) were significantly lower in the major amputation group (Table 1).

Although patients with severe diabetes (HbA1c>10%) had a higher rate of major amputations, this difference was not statistically significant (38.4% vs. 23.4%; p=0.266).

A pathogenic microorganism was identified in 51 patients (66.2%). Among these, 9 (17.6%) had Gram-positive organisms, 26 (50.9%) had Gram-negative organisms, and 16 (31.5%) had polymicrobial infections. A total of 67 isolates were obtained. The most common pathogens identified

Table 1. Comparison of diabetic foot infection patients with and without major amputation

Variables	Total (n=77) n (%)/mean±SD	Major amputation + (n=20) n (%)/mean±SD	Major amputation - (n=57) n (%)/mean±SD	p-value	OR
Age	62.6±11.9	64.9±10.7	61.8±12.2	0.323	
Gender					
Male Female	67 (87) 10 (13)	18 (90) 2 (10)	49 (86) 8 (14)	0.644	0.68
Hypertension	46 (59.7)	12 (60)	34 (59.6)	0.970	1.01
Coronary artery disease	36 (46.7)	10 (50)	26 (45.6)	0.735	1.19
Chronic kidney disease	25 (32.4)	7 (35)	18 (31.6)	0.784	1.16
Peripheral artery disease	25 (32.4)	7 (35)	27 (47.4)	0.338	0.91
Laboratory results					
HbA1c	8.1±1.7	8.4±1.7	8.0±1.7	0.368	
White blood cell count (cell/µL)	11899±5003	13006±5193	10160±4763	**0.032**	
Hemoglobin (g/dL)	10.6±1.8	9.8±1.1	10.8±1.93	**0.010**	
Neutrophil count (cell/µL)	8667±4985	10638±5443	7975±4669	**0.034**	
Lymphocyte count (cell/µL)	1551±636	1550±719	1551±612	0.70	
Platelet count (cell/µL)	324642±108716	368750±107035	309166±105900	**0.041**	
C-reactive protein (mg/dL)	85±73	109±69	76±73	**0.027**	
Procalcitonin (ng/mL)	0.34±1.17	0.30±0.35	0.35±1.30	0.076	
Glucose (mg/dL)	171±86	179±92	169±84	0.86	
Blood urea nitrogen (mg/dL)	55±30	60±33	53±29	0.291	
Creatinine (mg/dL)	1.24±1.06	1.18±0.82	1.44±1.58	0.306	
Alanine aminotransferase (U/L)	19±25	19±14	20±27	0.214	
Aspartate aminotransferase (U/L)	22±25	23±14	21±28	0.176	
Albumin (g/L)	33±5	28±4	34±5	**<0.001**	
Total cholesterol (mg/dL)	148±44	156±48	146±43	0.479	
Triglycerides (mg/dL)	166±94	173±70	163±102	0.06	
Erythrocyte sedimentation rate	65±31	82±30	60±30	**0.004**	
PLR	231±95	262±99	221±91	0.76	
NLR	6.8±6.0	9.0±7.3	6.0±5.4	0.119	
SII	79.4±59.0	79.1±67.4	79.5±56.9	0.76	
PNI	40.8±6.6	36.79±6.11	42.17±6.26	0.003	
CONUT score	4.1±2.6	3.5±2.7	4.3±2.6	0.235	

PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index=(platelet count×neutrophil count)/lymphocyte count, PNI: Prognostic nutritional index=serum albumin (g/L)+[0.005×total lymphocyte count (mm^3)], CONUT: Controlling nutritional status score, OR: Odds ratio, SD: Standard deviation, HbA1c: Hemoglobin A1c

were *Proteus mirabilis* (n=18, 26.8%), *Enterococcus* spp. (n=10, 14.9%), *Klebsiella pneumoniae* (n=7, 10.4%), *Pseudomonas aeruginosa* (n=7, 10.4%), and *Escherichia coli* (n=6, 8.9%).

DISCUSSION

In our study, the demographic and clinical characteristics were comparable between the two groups. While inflammation is known to be a poor prognostic indicator in DFIs, previous studies have reported associations of inflammatory markers such as NLR, PLR, and SII with amputation and osteomyelitis in DFI patients (4-6). However, we did not observe significant differences in NLR, PLR, or SII values in patients who underwent major amputation. In contrast, a lower PNI was associated with an increased risk of major amputation in DFIs in our study.

PNI has been utilized as a diagnostic and prognostic tool in various conditions in which inflammation plays a central role, including malignancies, infectious diseases, and cardiovascular disorders (7-9). The PNI reflects the relationship between immune function and nutritional status, as its components are serum albumin level and total lymphocyte count. In line with our results, previous studies have demonstrated that reduced albumin levels are strongly associated with major amputations and mortality (10). Our findings revealed that the mean serum albumin level was 28±4 g/L in the major amputation group, compared with 34±5 g/L in the minor/non-amputation group; this difference was statistically significant ($p<0.001$).

Albumin is widely recognized as an indicator of nutritional status; however, in patients with diabetic foot, it also reflects disease severity, prognosis, and malnutrition (11,12). PNI includes both nutritional and inflammatory indicators, such as albumin level and lymphocyte count. Lower serum albumin levels indicate both poor nutritional status and increased disease severity (13). Additionally, nutritional status significantly influences immune function, and protein-energy malnutrition has been associated with immunodeficiency (14). Lower lymphocyte counts may suggest immune suppression or dysfunction (15). As in other studies (16,17), our study found that lymphocyte counts did not differ significantly between groups with and without major amputations. The use of the PNI formula, compared with lymphocyte counts alone, allowed us to observe a significant prognostic effect in the major amputation group. This situation also highlights the importance of malnutrition in these patients.

Malnutrition is also a significant nutritional concern among patients with diabetes mellitus (18,19). Given the frequent coexistence of diabetes and hypertension, vascular impairments are almost inevitable in patients with diabetic foot (20). This contributes to the development of ischemia, poor wound healing, and increased susceptibility to infection (21). Vascular impairment is a known risk factor for amputation in individuals with diabetic DFIs (21). Malnutrition, in combination with vascular pathologies, contributes to an increased risk of major amputation (21). Inflammation is a major contributor to the development of diabetes-related complications (22).

Hb levels were significantly lower in the major amputation group (9.8±1.1 g/dL vs. 10.8±1.9 g/dL; $p=0.010$). Low Hb levels typically indicate reduced oxygen-carrying capacity and, therefore, an increased risk of tissue hypoxia. In DFIs, inadequate oxygenation can delay wound healing, leading to infection progression and necrosis. This condition can be considered a significant risk factor that increases the likelihood of amputation. Furthermore, anemia can often be an indicator of underlying systemic problems such as chronic inflammation, malnutrition, and renal dysfunction. The literature demonstrates a clear relationship between anemia severity and DFI severity (23). Studies have also reported that low Hb levels are associated with poor prognosis, increased amputation rates, and even mortality (23).

In our study, leukocyte, neutrophil, and platelet counts, as well as CRP and ESR, were significantly higher in the group undergoing major amputation. Elevated levels of these parameters indicate that the infection has progressed to a systemic level and a widespread inflammatory response has developed. In diabetic patients, immune system activation in response to infection typically manifests as increased total leukocyte and neutrophil counts. High CRP and ESR levels are indicators of an acute-phase response and ongoing tissue inflammation. An increase in platelet count may indicate reactive thrombocytosis, a condition that develops in response to the release of cytokines during infection and inflammation. These findings suggest that inflammation is more severe and its systemic effects are more pronounced in cases requiring major amputation. Similarly, previous studies have reported mean CRP, white blood cell, ESR, and PLT values were significantly higher in patients with major amputations than in other patient groups (24).

Our study adds a new perspective to clinical practice by highlighting not only inflammatory markers but also parameters such as the PNI, which reflects nutritional status, as predictors of the risk of major amputation in patients with DFIs. One novel aspects of this study is that although PNI has previously been used primarily in oncology and cardiovascular disease, this study clearly demonstrates,

for the first time, its significant association with major amputation in this patient group.

Furthermore, the combined evaluation of inflammatory markers (CRP, ESR, leukocyte count) with hematological and nutritional indicators offers a multidimensional approach to assessing amputation risk. Data obtained from Türkiye are crucial for filling a gap in the literature on this topic and for demonstrating that low-cost, accessible laboratory parameters (PNI, Hb, albumin) can be used effectively in risk assessment, particularly in developing countries.

Study Limitations

There are certain limitations to this study. First, the retrospective and single-center design may limit the generalizability of the findings. Second, the nutritional assessment might have been affected by the lack of information on the patients' body mass indices and dietary intake on admission. Third, the unequal distribution between major and minor amputations limited subgroup comparisons because major amputations were relatively few. In future studies with larger and more balanced cohorts, it may be possible to better evaluate whether PNI differs significantly between groups undergoing major versus minor amputations. Despite these limitations, one significant advantage of our research is that every patient was treated by the same clinical team, ensuring standardized treatment approaches and minimizing variation that might affect amputation outcomes.

CONCLUSION

Among patients with DFIs, both increased inflammatory markers and decreased albumin and PNI, reflecting poor nutritional status, may serve as significant predictors of major amputation. Therefore, in addition to monitoring inflammatory markers, nutritional support—particularly albumin supplementation—should not be neglected during patient follow-up.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Scientific Research Ethics Committee (approval no: 2025-08-12; date: 24.04.2025).

Informed Consent: Retrospective study.

FOOTNOTES

Authorship Contributions

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

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