JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2025; 9: 258-266
https://doi.org/10.30621/jbachs.1451540
RESEARCH ARTICLE

IMPACT OF HEMOGLOBIN–ALBUMIN–LYMPHOCYTE–PLATELET (HALP) SCORE ON MORTALITY IN ABOVE-ANKLE AMPUTATION OF DIABETIC FOOT INFECTION

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Received: 12.03.2024; **Accepted:** 05.03.2025; **Available Online Date:** 31.05.2025

Cite this article as: Yağar H, Vural A, Dolanbay T. Impact of Hemoglobin–Albumin–Lymphocyte–Platelet (HALP) Score on Mortality in Above-Ankle Amputation of Diabetic Foot Infection. J Basic Clin Health Sci 2025; 9: 258-266.

ABSTRACT

Purpose: Diabetic foot ulcers are one of the important reasons for amputations. The hemoglobin–albumin–lymphocyte–platelet (HALP) score is a marker of the inflammatory and nutritional status of the individual. Aim of this study is to investigate the relationship between the HALP score and mortality in patients undergoing above-ankle amputation due to diabetic foot infection.
Material and Methods: The demographic data (age, sex), deaths during hospitalization, laboratory values and mortality through 3-6-9-12 months were recorded. Chi square and t test were used for categorical comparison and logistic regression tests were used for mortality risk estimation.
Results: The mortality rates in hospital and in the 3rd, 6th, 9th, and 12th months were 13.1%, 37.7%, 48.5%, 53.8%, and 56.2% respectively. HALP score below 21.55 was associated with a 2.975 times higher risk for 1-year mortality (odds ratio: 2.975; 95% CI: 1.252–7.069; $p = 0.014$). Female gender, HALP score below 21.55, and age over 65 predict 20.2% overall 1-year mortality risk (Nagelkerke $R^2 = 0.202$).
Conclusion: The HALP score is a novel risk factor for mortality in patients undergoing amputation for diabetic foot ulcers. Also; older age and female gender are independent risk factors for 1-year mortality.

Keywords: Diabetic foot, risk factor scores, prognosis, amputation, mortality

INTRODUCTION

Amputations due to diabetes mellitus (DM) not just represent a medical concern but are public health issues at large, posing a substantial economic burden to nations (1). A study conducted in the United Kingdom revealed that 8.6% of adults had DM, with the risk of lower-extremity amputation increased by 23-fold (2). Alarmingly, approximately half of non-traumatic amputations are caused by diabetes-related complications (3). Studies have shown that the 5-year mortality rate for diabetes-related amputations can be up to 55% (4,5). The lifetime risk of the development of diabetes-related foot ulcers in patients with diabetes is 25% (6). Diabetic foot ulcers are one of the important reasons for amputations (7). Foot ulceration and amputation are closely related in patients with DM. In addition, 85% of amputations in patients with diabetes develop after an active foot ulcer (8).

The underlying factors for diabetic foot ulcers are neuropathic, neuroischemic, ischemic, or nonischemic–nonneuropathic (9). A multicenter study found that more than 63% of patients had the triad of trauma, neuropathy, and deformity, with edema,

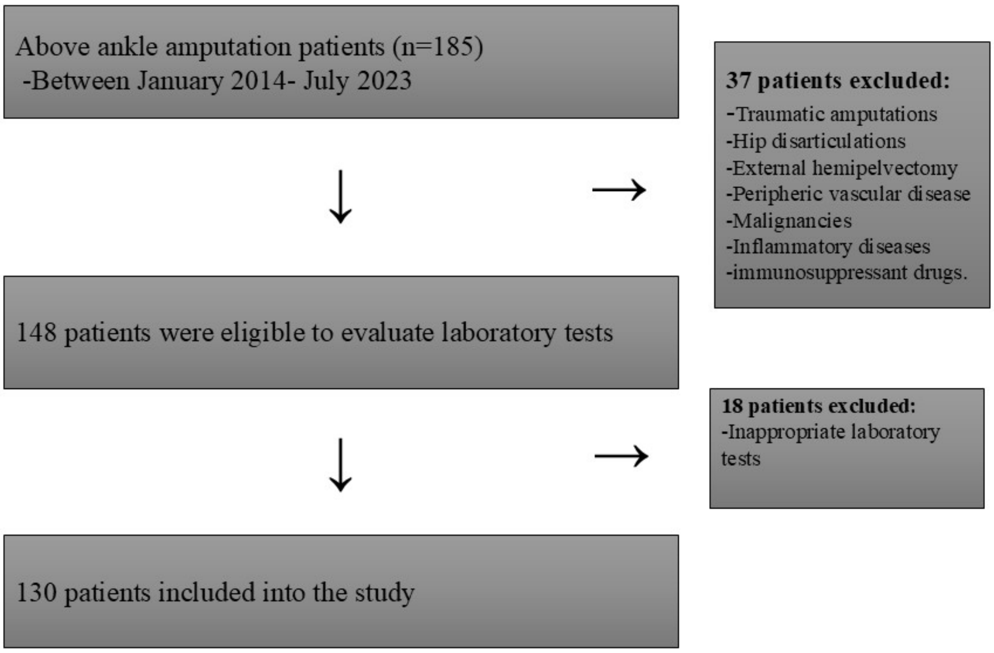

Figure 1. Flowchart of patient's selection criterias

ischemia, and callus formation involved in the etiology (10).

Wagner's classification for diabetic foot ulcers is still widely used (11). These ulcers are evaluated between grades 0 and 5. Grade 0 ulcer indicates the presence of deformity or cellulitis without an open lesion. Grade 1 ulcer indicates a superficial ulcer; grade 2 indicates those that have reached the tendon ligament, joint capsule, or deep fascia without abscess or osteomyelitis. Grade 3 ulcer indicates an ulcer that reaches deep tissues, including abscess, osteomyelitis, and joint sepsis besides grade 2. Grade 4 describes a localized gangrenous condition of the forefoot or heel, whereas a grade 5 ulcer describes a diffuse gangrenous condition of the entire foot (11). Wagner type 0-1-2 ulcers usually necessitate debridement and antibiotic treatments, whereas Wagner type 3-4-5 ulcers may require debridement and amputation at various levels (12). Most of these patients visit emergency departments prior to amputation, leading to their hospitalization for subsequent follow-up and surgical interventions (13).

The hemoglobin–albumin–lymphocyte–platelet (HALP) score is a marker of the inflammatory and nutritional status of the individual and is used to assess prognosis across many malignancies and diseases (14,15). The HALP score is calculated using the following formula: hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L)/platelet count (/L) (14,15,16). However, despite its significance, no study to date has investigated the relationship between the HALP score, which indicates the nutritional and inflammatory status of the patient, and above-ankle amputations due to diabetic foot ulcers.

Hence, this study aimed to investigate the relationship between the HALP score and mortality in patients undergoing above-ankle amputation due to diabetic foot infection.

MATERIAL AND METHODS

This retrospective study was conducted at the Department of Orthopedics and Traumatology and Emergency Medicine, Niğde Ömer Halisdemir University Medical School, between January 1, 2014, and July 1, 2023. The study protocol was approved by the Non-Invasive Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (Date: 29.08.2023, Decision No: 401670, Protocol No: 2023/51). The study was conducted following the criteria of the Declaration of Helsinki.

This retrospective study included patients who underwent above-ankle amputation due to diabetic foot infection. The inclusion criteria were as follows:

Table 1. Comparison of age and gender with patients'mortality status

Variables	n (total=130)	Deceased at 1-year	Survival at 1-year	p
Age, years mean (SD)	67.3 (15.6)	72.44 (13.3)	64.75 (15.1)	0.01*
Gender, n (%)				
female (expected count)	37	25 (18.1)	10 (16.9)	0.004**
male (expected count)	93	36 (42.9)	47 (40.1)	

* t test; ** Chi-Square test (continuity correction) SD, standart deviation

(a) a diagnosis of DM type 1 or 2, (b) above-ankle amputation(knee disarticulations,below knee and above knee amputations) due to Wagner type 3-4-5 diabetic ulcer, (c) appropriate laboratory tests 1 week before above-ankle amputation. The exclusion criteria were as follows: amputation levels other than above the ankle, also hip disarticulation and external hemipelvectomy, individuals without available laboratory data within 1 week prior to surgery, individuals with acute traumatic amputations, amputations due to peripheral vascular diseases without diagnosis of diabetes, malignancies, active and chronic inflammatory diseases, and individuals using immunosuppressant drugs.

The study was conducted with 185 patients who underwent above-ankle amputation due to diabetic foot infection between January 1, 2014, and July 1, 2023. All patients admitted from the emergency department or orthopedic outpatient clinics were included. Of these, 55 patients who did not meet the inclusion criteria were excluded. The study was completed with 130 patients. Flowchart of the patients selection criterias is shown in Figure 1.

The demographic data (age, sex), deaths during hospitalization, and laboratory values were recorded. The laboratory values, including hemoglobin and albumin levels, lymphocyte and platelet counts, and C-reactive protein (CRP) level, were obtained within 1 week before amputation. The following formula was used to determine the HALP score: Albumin (g/L) × Hemoglobin (g/L) × Platelet count (/L)/lymphocyte count (/L)(14,15,16). The dates of patient deaths were obtained through the national death notification system, and their mortality status was determined in the 3rd, 6th, 9th, and 12th months. Patients were divided into two main groups: deceased and living patients. Comparisons of categorical and noncategorical variables were made between the groups.

To calculate the 1-year mortality risk, regression analysis using both univariable and multivariable methods were done. Prior to creating a model for multivariable regression analysis, variables deemed statistically significant in categorical comparisons underwent univariable regression analysis. Patients were divided into two groups based on the age variable in the 1-year mortality risk estimation: those under 65 and those above 65.

Statistical Analysis

A retrospective design was used to collect data, and statistical analyses were performed using SPSS software (IBM SPSS Statistics Version 22, SPSS Inc., IL, USA. In the realm of descriptive statistics, the categorical data were expressed as frequencies and percentages, and the continuous data were expressed as mean ± standard deviation or median (minimum-maximum). Independent sample t test and chi-square analysis were used to compare categorical and non-categorical variables such as HALP scores, age and gender. The Kolmogorov–Smirnov test was used to evaluate whether noncategorical data showed normal distribution. The analysis results indicated that the continuous variables had a normal distribution. Therefore, the Pearson correlation test was conducted to examine the relationship between continuous data. The optimum threshold value of the HALP score for 1 year mortality prediction was determined by receiver operating characteristic (ROC) analysis and Youden index maximization (sensitivity+specificity-1). As the study had a retrospective design, it included all data that met the inclusion criteria; however, *a priori* power analysis was not performed. Youden index maximization (sensitivity+specificity-1) and receiver operating characteristic (ROC) analysis were used to find the optimal threshold value of the HALP score for mortality prediction. One-year mortality risk was estimated using binary logistic regression analysis with 95% confidence interval. To calculate the 1-year mortality risk, regression analysis using both univariable and multivariable methods were done.

Table 2. Univariable analysis for 1 year mortality risk prediction

Variables	Exp(B)	95%CI for Exp(B) Lower-Upper	Sig
HALP score <21.55	2,975	1,252-7.069	0.014
Gender (female)	3.264	1.392-7.653	0.007
Age >65	2.913	1.347-6.300	0.007

Table 3. Multivariable analysis for 1 year mortality risk prediction

Variables	Exp(B)	95%CI for Exp(B) Lower-Upper	Sig
HALP score <21.55	3,156	1,236-8.059	0.016
Gender (female)	2,977	1.215-7.297	0.017
Age >65	2,441	1.074-5.551	0.033

Model summary for Block 0: Begining Model, -2 Log likelihood:163.447; Block 1: Method = Enter, -2 Log likelihood 144.049. Hosmer and Lemeshow test sig.: 0.984; Nagelkerke R square: 0.202

Prior to creating a model for multivariable regression analysis, variables deemed statistically significant in categorical comparisons underwent univariable regression analysis. Patients were divided into two groups based on the age variable in the 1-year mortality risk estimation: those under 65 and those above 65. *P* value <0.05 indicating the significance level were used in all statistical analyses. In this study, a post-hoc power analysis was conducted between two independent groups to determine the prognostic value of the HALP score on 1-year mortality (Group 1: n = 57, Group 2: n = 61).The test's statistical power was determined to be 85.4% based on a medium effect size (Cohen's d = 0.5) and a significance threshold of 5% (α = 0.05).

RESULTS

The study included 130 patients who met the inclusion criteria. The mean age of these patients was 67.3 ± 15.6 years (range = 20–97 years). Of these patients, 37 (28.5%) were female and 93 (71.5%) were male. Patients (n=130) were compared by gender for 1 year mortality, statistically significant difference was found between male and female gender (p=0.01). Chi-squared analysis showed that the mortality rate was higher for female gender than male gender. Also, it was shown that the mean age of patients who deceased at 1 year was higher than the patients survived at 1 year and this difference was statistically significant(p=0.004). These associations are shown in Table 1.

The optimal cut-off point for the HALP score was determined to be 21.55. As a result, in the univariable analysis, patients with a HALP score below 21.55 had a 1-year mortality risk that was 2.975 times than that of patients with a score above 21.55. (odds ratio=2.975, 95% CI [1.252-7.069]; p=0.014). Female gender had a 3.264 times 1-year mortality risk than male gender (odds ratio=3.264, 95% CI [1.392-7.653]; p=0.007). The 1-year mortality risk for individuals over 65 is 2,913 times than for those under 65. (95% Confidence Interval [1.347-6.300] = 2.913; p = 0.007). Table 2 displays these findings. The constructed multivariable model is shown Table 3. The model with being a female gender and a HALP score of less than 21.55 and older than 65 age estimates a 20.2% overall 1-year mortality risk (Nagelkerke R square: 0.202).

The mean survival time was 331.7 ± 525.18 days (range = 1–2304 days). The mortality rates of the patients in hospital and in the 3rd, 6th, 9th, and 12th months were 13.1%, 37.7%, 48.5%, 53.8%, and 56.2%, respectively. These mortality rates are shown in Table 4.

Table 4. Patients' mortality rates in various periods

	n (130)	%
In-hospital mortality	17	13.1
3rd-month mortality	49	37.7
6th-month mortality	55	48.5
9th-month mortality	60	53.8
12th-month mortality	61	56.2

Table 5. Correlation between 3rd-, 6th-, 9th-, and 12th-month mortality and the HALP score

HALP score			Mean	SD	p*
3rd-month mortality	Yes	49	15.0698	9.3784	0.087
	No	81	19.0227	16.76499	
6th-month mortality	Yes	55	14.3147	9.12868	0.02
	No	67	20.2236	17.80826	
9th-month mortality	Yes	60	14.3678	8.9635	0.015
	No	60	20.9895	18.56099	
12th-month mortality	Yes	61	14.3052	8.90192	0.01
	No	57	21.5951	18.85299	

SD, Standard deviation, * t test

The HALP scores showed no statistically significant difference between those who died and those who did not die during the 3-month mortality (p = 0.087). Although the 3-month mortality in patients with low HALP scores was higher, it was not statistically significant. However, statistically significant differences were found in 6-month mortality (p = 0.02), 9-month mortality (p = 0.015), and 12-month mortality (p = 0.01). Hence, patients with low HALP scores had higher 6-, 9-, and 12-month mortality. The relationship between the 3-, 6-, 9-, and 12-month mortality of the patients and the HALP score is depicted in Table 5.

The study found a weak negative correlation between the age of the patients and the HALP scores (p = 0.029, r = –0.192). A weak negative correlation was also observed between the CRP levels of the patients and their HALP scores (p = 0.012, r = –0.223). The relationship between the HALP score and age, and the CRP level is presented in Table 6.

Table 6. Correlation between HALP score with age and CRP level

Variable		HALP score
Age	r	–.192*
	p	.029
	n	130
CRP	r	–.223*
	p	.012
	n	127

Correlation is significant at the 0.05 level (two-tailed), CRP: C-reactive protein, HALP: hemoglobin–albumin–lymphocyte–platelet

DISCUSSION

Laboratory findings are the independent factors for investigating the prognosis of diseases (17). To the best of our knowledge, this study was novel in examining the correlation between HALP scores and above-ankle amputation prognosis after diabetic foot infections. The main finding of this study was that patients who underwent above-ankle amputation due to diabetic foot ulcers and patients with a low HALP score had higher mortality rates in the 6th, 9th, and 12th months.

A meta-analysis conducted by Zhang et al. showed that diabetic foot ulcers occurred more frequently in the male population (18). Nather et al. investigated limb loss in diabetic feet and reported that it occurred almost equally in male and female patients, the mean age of the patients was 60 years, and most were in their fifth and sixth decades (19). An epidemiological study conducted by Hicks et al. reported that the mean age of patients with diabetic foot ulcers was 62.9 ± 0.1 years and 59% of the patients were male (20). The mean age of the patients in our study was 67.3 ± 15.6 years and male sex was predominant, consistent with previous studies.

In a prospective cohort study, advanced age was shown to be an independent risk factor (21). In a meta-analysis, it was shown that older age is a higher risk for mortality (22). In the study conducted by Seghieri et al. on 165,650 patients, it was shown that mortality was higher in female (23). A study conducted in California showed that the mortality rate was 37.7 in female and 29.7 in male per 1000 amputations (24). In our study, we showed that older age and female gender are independent risk factors for 1-year mortality, similar to the literature.

In a study conducted in Nigeria involving 336 patients, the in-hospital mortality rate of patients followed up due to diabetic foot ulcers was found to be 21.4% (25). A study conducted in Turkey involving 401 patients found the in-hospital mortality rate of patients hospitalized due to diabetic foot infections to be 3%. While selecting these patients, all diabetic foot infections were evaluated regardless of whether they required amputation (17). A study conducted in the United Kingdom reported an in-hospital mortality rate of 8.4% in patients with diabetic foot infection who did not undergo amputation and 7.2% in the group in which amputation was performed due to diabetic foot infection (26). Malyar et al. found the in-hospital mortality rate to be 2.8% in patients who had isolated diabetic foot syndrome (27). A study conducted in Brazil involving 654 patients found the in-hospital mortality rate of patients with diabetic foot lesions to be 12% (28). In the present study, the in-hospital mortality after above-ankle amputation was 13.1%. The demographic characteristics, socioeconomic characteristics, glycemic monitoring, and so forth, might affect the results regarding in-hospital mortality rates of diabetic foot infections.

Vuorlaakso et al. found 1-year overall survival to be 41.7% in patients undergoing major amputation due to diabetic foot infection (29). In a 430-patient prospective cohort study, the 1-year mortality from hospital admission after diabetic foot infection was 8.9% (21). Another study reported that the presence of diabetic neuropathic ulcers or related amputations had a higher 5-year mortality than many malignant diseases (30). A prospective study including 347 patients in a multidisciplinary foot center reported a 1-year death rate of 9% in patients with a diabetic foot infection (31). Consistent with previous studies, the present study also found that patients who underwent major amputation for diabetic foot ulcers had high mortality rates at follow-up up to 1 year.

Many reliable biomarkers have been investigated to evaluate the prognosis of diabetic foot ulcers; some of these are neutrophil-to-lymphocyte ratio (32,33), platelet-to-lymphocyte ratio (34), and matrix metalloproteinase-1/ tissue inhibitors of matrix metalloproteinase-1 ratio (35). However, the nutritional status of patients is not evaluated using these biomarkers. Nutritional status is an essential predictor in determining the prognosis of diabetic foot ulcers and should be given importance because it affects diabetic foot ulcer outcomes (36,37,38). The HALP score is used to evaluate prognosis in many diseases and malignancies because it shows nutritional status (39,40,41). A retrospective study showed that the Geriatric Nutritional Risk Index and the HALP score, which are used to evaluate geriatric malnutrition, had similar nutritional results (42). No study to date has explored the correlation between the HALP score and prognosis in diabetic foot ulcers. This study showed that the 6th-, 9th-, and 12th-month mortality rates were higher in patients with low HALP scores. Furthermore, we showed that 2,975 times increased risk is found for 1 year mortality for those with HALP scores lower than 21.55.

Forster et al. found that poor nutritional status was associated with advancing age (43). Agarwalla et al. reported that malnutrition was common in older age groups (44). The present study found a negative correlation between the HALP score and advancing age. Thus, a negative correlation existed between age and nutritional status, consistent with previous studies. In addition, high serum CRP levels have also been shown to be associated with low nutritional status (45). A prospective cohort study conducted with 237 patients showed a statistically significant correlation between inflammatory markers, including CRP, and malnutrition (46). Similarly, the present study found a negative correlation between CRP and HALP scores.

Limitations

This retrospective study was conducted in a single center with a limited number of patients, which represents an inherent limitation. Furthermore, The differing metabolic impacts of various amputation levels on the body constitute one of the most critical limitations of this study which focuses on evaluating mortality. Additionally, the lack of evaluation of the vascular status of the extremity and the treatments administered accordingly constitutes another major limitation of this study.

CONCLUSION

The HALP score is a novel risk factor in patients undergoing amputation for diabetic foot ulcers. Also, older age and female gender are independent risk factors for 1-year mortality. Prospective studies including long-term follow-up are needed for a better understanding of the predictive capabilities of the HALP score.

Acknowledgement: None.

Author contribution: Concept and Design: HY, AV. Data Collection or Processing: HY, AV, TD. Analysis or Interpretation: AV, TD, Literature Search: HY, AV. Writing: HY Critical review: AV, TD.

Conflict of interests: No conflict of interest was declared by the authors.
Ethical approval: The study protocol was approved by the Non-Invasive Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (Date: 29.08.2023, Decision No: 401670, Protocol No: 2023/51). The study was conducted following the criteria of the Declaration of Helsinki.
Funding The authors declared that this study received no financial support.
Peer-review: Externally peer-reviewed.

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