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RESEARCH

Prognostic role of HALP score, CRP/albumin ratio and CALLY index in diabetic foot ulcer-related major amputations

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Abstract

Purpose Diabetic foot ulcer (DFU) remains a major complication of diabetes mellitus and is a leading cause of non-traumatic lower extremity amputations. Biomarkers are used to predict disease prognosis and guide treatment decisions. This study aimed to evaluate the prognostic utility of three systemic inflammation and nutrition-based biomarkers HALP score, CRP/Albumin ratio, and CALLY index in predicting the major amputation risk among patients with DFU.

Methods A retrospective analysis was conducted on 252 DFU patients who underwent surgical debridement and/or amputation between January 2018 and December 2023. Demographic, clinical, and laboratory data were collected. Patients were grouped based on surgical intervention (minor vs. major amputation). The HALP score, CRP/Albumin ratio, and CALLY index were calculated from admission laboratory values. Cut-off values were determined using ROC analysis.

Results Major amputation was performed in 19% of the patients. The HALP score was significantly lower, while the CRP/Albumin ratio was higher, and the CALLY index was lower in the major amputation group ($p<0.001$ for all). The optimal cut-off values to predict major amputation were 19.96 for HALP (AUC = 0.750), 2.29 for CRP/Albumin (AUC = 0.853), and 0.71 for CALLY (AUC = 0.830). All three markers demonstrated significant correlations with markers of infection, inflammation, and ulcer severity.

Conclusion The HALP score, CRP/Albumin ratio, and CALLY index are easily accessible prognostic tools that may assist clinicians in identifying DFU patients at higher risk for major amputation. Integration of these biomarkers into routine patient monitoring can improve risk assessment and guide timely surgical decision-making.

Keywords Amputation · CALLY index · CRP/Albumin · Diabetic foot ulcer · HALP score

Introduction

Diabetic foot ulcer (DFU) is one of the most important complications of diabetes mellitus (DM), and its prevalence increases alongside with DM [1]. In addition to negatively impacting the quality of life for individuals, it leads to frequent hospital visits and an increase in healthcare costs. It is the most common cause of non-traumatic lower limb amputations [2]. The lifetime risk of developing DFU in DM patients has been reported to be between 19 and 34% [3]. In diabetic foot amputations, it has been reported that 85% of patients had previously been treated for DFU and later lost their limbs due to severe infections and gangrene [4].

Early risk assessment in DFU patients can reduce hospitalization, disability, and mortality rates. The biomarkers used for this purpose (objective measurements and evaluation features that indicate the effects of normal biological and pathogenic processes, as well as pharmacological agents

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on treatment) are significant for early clinical diagnosis, predicting the progression of the disease, and prevention.

Biomarkers that can be used for the monitoring and management of DFU patients include inflammatory biomarkers (procalcitonin, pentraxin-3, C-reactive protein [CRP], interleukin family, tumor necrosis factor alpha), genomic biomarkers, proteomic biomarkers, metabolic biomarkers, and microbial markers [4]. Among these biomarkers, inflammatory markers are obtained from laboratory tests frequently performed in routine patient follow-up. Biomarkers derived from combinations of inflammatory markers that are easy to use in daily practice can be used to predict the risk of major amputation associated with DFU.

Although serum albumin values are used as a parameter of nutritional status, they have found a role as an inflammatory marker of acute phase reactions. Inflammation and a heightened risk of malnutrition are both independently linked to hypoalbuminemia, whereas decreased serum albumin and elevated CRP levels serve as independent predictors of mortality [5]. CRP/Albumin ratio is a biomarker used to determine prognosis in cancer, critical illness, and infection by assessing inflammation and nutritional status. Higher CRP/Albumin ratio values have been associated with worse outcomes, such as increased severity of disease or risk of death [6]. When lymphocyte count, a well-established biomarker indicative of immune status, is incorporated into these parameters, the resulting C-reactive protein-albumin-lymphocyte (CALLY) index—originally proposed by Iida et al. [7] —emerges as a composite biomarker that continues to be investigated in contemporary research. The CALLY index has been accepted as a clinically applicable biomarker in the prognostic assessment of several types of cancer and has also been associated with chronic inflammatory diseases in recent studies [8–10]. The CALLY index has been shown to be a potential prognostic biomarker reflecting inflammation, nutritional status, and immune functions.

As a combined marker of inflammation and nutrition, the Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is utilized to assess the general physiological and nutritional condition of patients, particularly in settings where systemic stress or malnutrition is prevalent. The HALP score has been used in various malignancies, and a low HALP score is associated with poor prognosis [11]. As the HALP score reflects systemic inflammatory status and is easy to calculate, it is suggested as a useful tool in diseases with severe inflammation [12]. A substantial number of studies have also examined the prognostic relevance of the HALP score across a broad spectrum of benign disorders [13, 14]. Although the HALP score and CALLY index have been extensively validated as a prognostic indicator in various oncological settings, their applicability in non-malignant, chronic inflammatory conditions—such as diabetic foot ulcers—has not been adequately investigated. The HALP Score, CRP/Albumin Ratio, and CALLY Index including parameters reflecting both inflammatory and nutritional status, may serve as prognostic factors in diabetic foot ulcer patients whose condition is driven by the complex interaction of ischemia, infection and systemic catabolic responses. The present study aims to evaluate the relationship between the inflammatory biomarkers (HALP score, CRP/Albumin ratio and CALLY index) which may serve as predictors of disease prognosis, and the amputation in patients diagnosed with DFU.

Materials and methods

Patient selection

This retrospective study included patients who were diagnosed with DFU and underwent debridement and/or amputation between January 2018 and December 2023 at the Vascular Surgery Wound Care Unit of the General Surgery Department of Ankara University Faculty of Medicine. The study was approved by the Ankara University Human Research Ethics Committee with the approval number I11-809-23. Patients who were followed up with the diagnosis of DFU and hospitalized for surgical debridement and/or amputation are included. Exclusion criteria were patients who underwent superficial debridement in outpatient clinic conditions due to DFU, being under the age of 18, having a history of previous amputation, missing parameters used in the study, and having a diagnosis of cancer.

Data collection

The demographic characteristics (age and gender), risk factors, and comorbidities (peripheral artery disease [PAD], chronic kidney disease [CKD], coronary artery disease [CAD]), and laboratory findings (complete blood count, kidney function tests, albumin, CRP, HbA1c) of all patients were retrospectively examined. PAD was defined as an Ankle-Brachial Index below 0.9, or the presence of vascular circulation disorder detected by Doppler ultrasonography or CT angiography, or a history of open or endovascular peripheral artery revascularization. CKD was defined as patients with serum creatinine above 1.5 mg/dl. CAD was defined as a history of angina, myocardial infarction and coronary artery revascularization. The number, location, and area of DFU ulcers, as well as the presence of neuropathy (defined by the patient's symptoms and physical examination findings at the time of admission), ischemia, infection (confirmed by microbiological tests performed at the time of admission), and osteomyelitis (confirmed by radiological

imaging available at the time of admission), were evaluated, and the patients were classified according to the Wagner Classification [15]. The HALP score, CRP/Albumin ratio and CALLY index were calculated using the laboratory data obtained at the time of patient admission.

Study design

In this study, DFU was defined as a full-thickness skin lesion located below the ankle in patients with an established diagnosis of DM. This study aims to assess the prognostic utility of the HALP score, the CRP/Albumin ratio and CALLY index in predicting both the occurrence and extent of amputation in patients with DFU.

Patients were divided into two groups based on their amputation status: the first group included those who underwent debridement and minor amputations (toe and midfoot amputations), and the second group included those who underwent major amputations (transtibial and transfemoral). All patients who underwent major amputation had a history of debridement and/or minor amputation during the same hospitalization. In patients who underwent multiple amputations during hospitalization due to poor wound healing and infection, the final (most proximal) level of amputation was used for analysis, in accordance with similar studies in the literature [16, 17]. Optimal cut-off values for the HALP score, CRP/Albumin ratio and CALLY index were established to differentiate between amputation subgroups.

HALP score

The HALP score, defined by Chen et al. [18] in 2015, is an immuno-nutritional marker consisting of hemoglobin (g/L), albumin (g/L), lymphocyte (10^9/L), and platelet (10^9/L) counts. It is a scoring system used to assess immune status based on lymphocyte and platelet counts and nutritional status based on hemoglobin and albumin levels. The HALP score is calculated as:

HALP score = hemoglobin (g/L) x albumin (g/L) x lymphocyte (10^9/L)/platelet (10^9/L).

CALLY index

The CALLY index is a biomarker developed by Iida et al. [7] to predict prognosis in patients undergoing hepatectomy for hepatocellular carcinoma. It was established based on the observation that conditions commonly associated with malignancy—such as malnutrition, immunosuppression, and inflammation—are typically reflected by decreased albumin and lymphocyte levels and elevated CRP levels.

CALLY index = [albumin (g/L) × lymphocyte count (10^3/μL)]/CRP (mg/dL).

Statistical methods

The data were analyzed using the SPSS 11.5 software. Descriptive statistics for quantitative variables were expressed as mean ± standard deviation or median (minimum–maximum). For comparisons between two categories of a qualitative variable in terms of a quantitative variable, the Student's t-test was used when the assumption of normality was met, and the Mann-Whitney U test was applied otherwise. The chi-square test was employed to assess the relationship between two categorical variables. Since the assumption of normal distribution was not satisfied, the Spearman correlation test was used to evaluate the relationship between two continuous variables. Receiver Operating Characteristic (ROC) analysis was conducted to determine the optimal cut-off value for the quantitative variable. A p-value of <0.05 was considered statistically significant.

Results

A total of 252 patients who underwent debridement and/or amputation secondary to DFU are included in the study. The mean age of the patients was 66.3 (range 31–93) and 200 (79,4%) were male. Debridement and/or minor amputation were performed in 204 patients (81%) and major amputation in 48 patients (19%). Fifteen (31.25%) of the major amputations were transfemoral and 33 (68.75%) were transtibial. Among the patients who underwent major amputation, 42 had a history of minor amputation during the same hospitalization. Of these, 12 had a history of forefoot amputation, 11 had a history of toe amputation, and 19 initially underwent toe amputation followed by forefoot amputation. In the remaining 8 patients, debridement was performed at the time of admission, and they were followed accordingly; however, due to progression of wound size and infection during follow-up, major amputation ultimately became necessary. The Wagner grade for DFU patients was calculated as 2, 3, and 4 in 33.3%, 44%, and 22.6% of the patients, respectively.

Age and gender were not found to be statistically significant with the type of amputation ($p=0.638$, $p=0.122$, respectively). Although no significant difference was found for comorbidities like CKD and CAD regarding the type of amputation, a significant difference was found for PAD ($p<0.001$). PAD was present in 41.7% of patients who underwent debridement and/or minor amputation, whereas this rate was 75.0% in the major amputation group. A statistically significant difference was observed between the types of surgery and the presence of neuropathy, ischemia, infection, osteomyelitis, Wagner score, albumin, CRP, leukocyte count, platelet count, hemoglobin, neutrophil

Table 1 Surgical type-based comparison of variables

Variables	Surgery type		Overall population	*p* value
	Debridement and/or minor amputation	Major amputation		
Age, mean ± SD	66.54 ± 10.77	65.71 ± 12.58	66.39 ± 11.12	0.749[b]
Gender	158 (77.5)	42 (87.5)	200 (79.4)	0.122[c]
Male	46 (22.5)	6 (12.5)	52 (20.6)	
Female				
PAD, n(%)	96 (47.1)	36 (75.0)	132 (52.4)	**< 0.001[c]**
CKD, n(%)	32 (15.7)	6 (12.5)	38 (15.1)	0.579[c]
CAD, n(%)	102 (50.0)	24 (50.0)	126 (50.0)	1.000[c]
Neuropathy, n(%)	82 (40.2)	42 (87.5)	124 (49.2)	**< 0.001[c]**
Ischemia, n(%)	129 (63.2)	47 (97.9)	176 (69.8)	**< 0.001[c]**
Infection, n(%)	138 (67.6)	46 (95.8)	184 (73.0)	**< 0.001[c]**
Osteomyelitis, n(%)	119 (58.3)	48 (100.0)	167 (66.3)	**< 0.001[c]**
Wagner score, n(%)	84 (41.2)	0 (0.0)	84 (33.3)	**< 0.001[c]**
2	108 (52.9)	3 (6.2)	111 (44.0)	
3	12 (5.9)	45 (93.8)	57 (22.7)	
4				
Creatinine, mean ± SD	1.50 ± 1.47	1.27 ± 0.91	1.46 ± 1.38	0.551[b]
Albumin, mean ± SD	35.22 ± 5.74	30.00 ± 5.46	34.22 ± 6.04	**< 0.001[b]**
CRP, mean ± SD	60.33 ± 67.10	137.92 ± 61.98	75.11 ± 72.75	**< 0.001[b]**
Hba1c, mean ± SD	8.94 ± 1.96	9.28 ± 1.87	9.01 ± 1.94	0.167[b]
Leukocyte, mean ± SD	10.23 ± 4.89	12.41 ± 4.76	10.65 ± 4.93	**< 0.001[b]**
Platelet, mean ± SD	306.56 ± 121.28	375.06 ± 181.66	319.61 ± 137.12	**0.019[b]**
Hemoglobin, mean ± SD	11.58 ± 1.98	9.60 ± 1.70	11.21 ± 2.08	**< 0.001[a]**
Lymphocyte, mean ± SD	1.88 ± 0.85	1.76 ± 0.83	1.86 ± 0.85	0.385[b]
Neutrophil, mean ± SD	7.16 ± 4.46	9.27 ± 4.57	7.56 ± 4.55	**0.001[b]**
HALP, mean ± SD	28.99 ± 18.46	15.54 ± 9.81	26.43 ± 17.94	**< 0.001[b]**
CRP/Albumin, mean ± SD	1.89 ± 2.25	4.78 ± 2.31	2.44 ± 2.53	**< 0.001[b]**
CALLY, mean ± SD	3.10 ± 3.21	0.47 ± 0.35	2.60 ± 3.07	**< 0.001[b]**

SD standard deviation, *PAD* peripheral artery disease, *CKD* chronic kidney disease, *CAD* coronary artery disease, *CRP* C-reactive protein, *HALP* hemoglobin-albumin-lymphocyte-platelet, *CALLY* C-reactive protein-albumin-lymphocyte, [a] student-t test, [b] mann-Whitney U test, [c] ki-square test

count, HALP score, CRP/albumin ratio and CALLY index ($p < 0.05$). Neuropathy was observed in 40.2% of patients with debridement and/or minor amputations, compared to 87.5% in those who underwent major amputation. The rates of ischemia, infection, and osteomyelitis were significantly higher in the major amputation group (Table 1).

The mean HALP score values calculated from the existing laboratory data were 28.99 ± 18.46 for the debridement-minor amputation group and 15.54 ± 9.81 for the major amputation group ($p < 0.001$). The mean CRP/Albumin ratio values were 1.89 ± 2.25 for the debridement-minor amputation group and 4.78 ± 2.31 for the major amputation group ($p < 0.001$). The mean CALLY index was calculated as 3.10 in the debridement and/or minor amputation group, whereas it was 0.47 in the major amputation group ($p < 0.001$) (Table 1).

A moderate and statistically significant negative correlation was observed between the HALP score and the CRP/Albumin ratio ($p < 0.001$), indicating that as the HALP score increased, the CRP/Albumin ratio decreased. Conversely, a moderate and significant positive correlation was identified between the HALP score and the CALLY index ($p < 0.001$), suggesting that higher HALP scores were associated with higher CALLY index values. Additionally, a strong and statistically significant negative correlation was found between the CALLY index and the CRP/Albumin ratio ($p < 0.001$), demonstrating that increases in the CALLY index were associated with decreases in the CRP/Albumin ratio (Table 2).

Table 2 Statistics regarding the association between HALP score, CRP/Albumin ratio, and CALLY index

Variables		HALP score	CRP/Albumin	CALLY index
HALP		-	−0.584	0.706
	p value	-	**< 0.001[a]**	**< 0.001[a]**
CRP/Albumin		-	-	−0.940
	p value	-	-	**< 0.001[a]**
CALLY		-	-	-
	p value	-	-	-

HALP hemoglobin-albumin-lymphocyte-platelet, *CRP* C-reactive protein, *CALLY* C-reactive protein-albumin-lymphocyte, [a]spearman correlation test

ROC analyses performed according to surgical type revealed statistically significant areas under the curve (AUC)

Table 3 ROC analysis results for variables according to surgical type

Variables	Area	SE	*p* value	%95 CI Min - Max	Sensitivity	Specificity	Cut-off
HALP	0.750	0.037	<0.001	0.678–0.821	0.771	0.618	19.96
CRP/Albumin	0.853	0.023	<0.001	0.807–0.898	0.917	0.745	2.29
CALLY	0.830	0.026	0.001	0.780–0.880	0.854	0.725	0.71
CRP	0.843	0.024	<0.001	0.796–0.890	0.896	0.760	77.10
Albumin	0.742	0.040	<0.001	0.664–0.819	0.604	0.765	30.95
Wagner score	0.952	0.015	<0.001	0.922–0.982	0.938	0.941	3.50

HALP hemoglobin-albumin-lymphocyte-platelet, *CRP* C-reactive protein, *CALLY* C-reactive protein-albumin-lymphocyte, *SE* standard error, *CI* confidence interval, *Min* minimum, *Max* maximum

for the HALP score, CRP/Albumin ratio, and CALLY index ($p<0.001$, $p<0.001$, and $p=0.001$, respectively). For the HALP score, the cut-off value was determined to be 19.96, with a sensitivity of 77.1% and specificity of 61.8%. Patients with HALP scores≤19.96 were more frequently in the major amputation group, while those with scores>19.96 were more commonly in the debridement and/or minor amputation group. For the CRP/Albumin ratio, the cut-off value was 2.29, with a sensitivity of 91.7% and specificity of 74.5%; values above 2.29 were associated with major amputation, whereas values below were associated with debridement and/or minor amputation. The CALLY index cut-off was 0.71, with a sensitivity of 85.4% and specificity of 72.5%; values≤0.71 were associated with major amputation, while values>0.71 were more often observed in the debridement and/or minor amputation group. ROC analysis for CRP, albumin, and Wagner score according to the type of surgery revealed statistically significant areas under the curve ($p<0.001$). The corresponding sensitivity values were 0.896, 0.604, and 0.938; specificity values were 0.760, 0.765, and 0.941; and cutoff points were identified as 77.10, 30.95, and 3.5, respectively. Patients with a CRP level≤77.10 were classified as candidates for debridement and/or minor amputation, whereas those with levels>77.10 were considered candidates for major amputation. Similarly, an albumin level≤30.95 indicated candidacy for major amputation, while patients with levels>30.95 were more likely to undergo debridement and/or minor amputation. A Wagner score≤3.5 was associated with eligibility for debridement and/or minor amputation, whereas scores>3.5 corresponded to major amputation candidacy (Table 3).

When patients were grouped according to the cut-off values of the HALP score, CRP/Albumin ratio, and CALLY index, statistically significant differences were found in several clinical and laboratory variables, including ischemia, infection, Wagner score, albumin, CRP, leukocyte count, platelet count, hemoglobin, lymphocyte and neutrophil counts, CRP/Albumin ratio, and CALLY index ($p<0.05$). Among patients with a HALP score≤19.96, ischemia (77.4%), infection (80.0%), and Wagner grade 4 ulcers (34.8%) were more prevalent. In this group, the mean albumin level was 30.97 g/L (reference: 35–52 g/L), and the mean CRP level was 108.98 mg/L (reference: 0–5 mg/L). Leukocyte, platelet, and neutrophil counts were also significantly higher (Table 4).

Table 4 Comparison of variables according to HALP score

Variables	HALP score		*p* value
	≤19.96	>19.96	
Age, mean±SD	66. 78±10.61	66.06±11.56	0.607[a]
Gender	90 (78.3)	110 (80.3)	0.691[c]
Male	25 (21.7)	27 (19.7)	
Female			
PAD, n(%)	59 (51.3)	73 (53.3)	0.754[c]
CKD, n(%)	17 (14.8)	21 (15.3)	0.904[c]
CAD, n(%)	58 (50.4)	68 (49.6)	0.899[c]
Neuropathy, n(%)	63 (54.8)	61 (44.5)	0.105[c]
Ischemia, n(%)	89 (77.4)	87 (63.5)	**0.017[c]**
Infection, n(%)	92 (80.0)	92 (67.2)	**0.022[c]**
Osteomyelitis, n(%)	83 (72.2)	84 (61.3)	0.069[c]
Wagner score, n(%)	25 (21.7)	59 (43.1)	**<0.001[c]**
2	50 (43.5)	61 (44.5)	
3	40 (34.8)	17 (12.4)	
4			
Creatinine, mean±SD	1.33±1.07	1.56±1.59	0.282[b]
Albumin, mean±SD	30.97±5.09	36.95±5.39	**<0.001[a]**
CRP, mean±SD	108.98±75.32	46.68±56.81	**<0.001[b]**
Hba1c, mean±SD	9.18±1.87	8.86±2.00	0.062[b]
Leukocyte, mean±SD	12.21±5.64	9.34±3.79	**<0.001[b]**
Platelet, mean±SD	383.27±157.23	266.18±87.61	**<0.001[b]**
Hemoglobin, mean±SD	10.19±1.78	12.06±1.93	**<0.001[a]**
Lymphocyte, mean±SD	1.47±0.66	2.18±0.86	**<0.001[b]**
Neutrophil, mean±SD	9.60±5.21	5.86±3.02	**<0.001[b]**
CRP/Albumin, mean±SD	3.76±2.76	1.33±1.65	**<0.001[b]**
CALLY, mean±SD	0.90±1.15	4.03±3.44	**<0.001[b]**

HALP hemoglobin-albumin-lymphocyte-platelet, *SD* standard deviation, *PAD* peripheral artery disease, *CKD* chronic kidney disease, *CAD* coronary artery disease, *CRP* C-reactive protein, *CALLY* C-reactive protein-albumin-lymphocyte, [a]student-t test, [b]mann-Whitney U test, [c]ki-square test

Similarly, patients with a CRP/Albumin ratio > 2.29 exhibited significantly higher rates of neuropathy, ischemia, infection, and osteomyelitis, with Wagner grade 4 detected in 49.0% of these cases. In this group, CRP, HbA1c, leukocyte, platelet, and neutrophil levels were also significantly elevated, while no significant differences were observed for age, PAD, CKD, CAD, or creatinine (Table 5).

Consistent with these findings, patients with a CALLY index ≤ 0.71 had significantly higher rates of neuropathy, ischemia, infection, and osteomyelitis, with Wagner grade 4 present in 45.4% of cases. In this group, CRP, leukocyte and neutrophil counts, and CRP/Albumin ratios were significantly higher. However, no significant differences were found in age, PAD, CKD, CAD, creatinine, HbA1c, or platelet levels (Table 6).

Table 5 Comparison of variables according to CRP/albumin ratio

Variables	CRP/Albumin ratio		*p* value
	≤2.29	>2.29	
Age, mean ± SD	66.59 ± 10.96	66.06 ± 11.42	0.602[b]
Gender	115 (73.7)	85 (88.5)	**0.005**[c]
Male	41 (26.3)	11 (11.5)	
Female			
PAD, n(%)	76 (48.7)	56 (58.3)	0.138[c]
CKD, n(%)	25 (16.0)	13 (13.5)	0.593[c]
CAD, n(%)	80 (51.3)	46 (47.9)	0.604[c]
Neuropathy, n(%)	60 (38.5)	64 (66.7)	**< 0.001**[c]
Ischemia, n(%)	95 (60.9)	81 (84.4)	**< 0.001**[c]
Infection, n(%)	95 (60.9)	81 (84.4)	**0.001**[c]
Osteomyelitis, n(%)	89 (57.1)	78 (81.2)	**< 0.001**[c]
Wagner score, n(%)	70 (44.9)	14 (14.5)	**< 0.001**[c]
2	76 (48.7)	35 (36.5)	
3	10 (6.4)	47 (49.0)	
4			
Creatinine, mean ± SD	1.45 ± 1.46	1.47 ± 1.26	0.461[b]
Albumin, mean ± SD	36.75 ± 5.37	30.11 ± 4.66	**< 0.001**[a]
CRP, mean ± SD	28.71 ± 18.74	150.51 ± 64.26	**< 0.001**[b]
Hba1c, mean ± SD	8.85 ± 1.96	9.26 ± 1.89	**0.044**[b]
Leukocyte, mean ± SD	8.64 ± 2.87	13.92 ± 5.77	**< 0.001**[b]
Platelet, mean ± SD	294.95 ± 115.61	359.69 ± 158.91	**0.001**[b]
Hemoglobin, mean ± SD	11.74 ± 2.08	10.34 ± 1.77	**< 0.001**[a]
Lymphocyte, mean ± SD	1.98 ± 0.88	1.65 ± 0.76	**0.001**[b]
Neutrophil, mean ± SD	5.69 ± 2.34	10.61 ± 5.54	**< 0.001**[b]
HALP, mean ± SD	32.68 ± 18.86	16.27 ± 10.06	**< 0.001**[b]
CALLY, mean ± SD	3.97 ± 3.22	0.38 ± 0.22	**< 0.001**[b]

HALP hemoglobin-albumin-lymphocyte-platelet, *SD* standard deviation, *PAD* peripheral artery disease, *CKD* chronic kidney disease, *CAD* coronary artery disease, *CRP* C-reactive protein, *CALLY* C-reactive protein-albumin-lymphocyte, [a] Student-t test, [b] mann-Whitney U test, [c] ki-square test

Discussion

Diabetic foot is one of the chronic complications of DM and is a multifactorial problem that can threaten the lower extremity. Several classification systems are used to assess the severity of DFU, but no biomarker can predict the type of amputation needed for treatment. Our study aimed to evaluate the relationship between amputation type, and HALP score and CRP/Albumin ratio and CALLY index in DFU patients. Among the 252 patients with DFU, a higher major amputation rates were found for those with a HALP score ≤ 19.96, a CRP/Albumin ratio > 2.29 and a CALLY index ≤ 0.71 ($p < 0.001$, $p < 0.001$, and $p = 0.001$, respectively).

Given that the HALP score, the CRP/Albumin ratio and CALLY index are derived from biomarkers that are acutely responsive to systemic inflammation, their levels may be significantly influenced by transient inflammatory states such as acute infection or tissue injury. This potential variability should be carefully considered when interpreting their prognostic value, as such fluctuations may not necessarily reflect the underlying chronic disease burden but rather the acute-phase response at the time of measurement.

Albumin, a component of all the HALP score, the CRP/Albumin ratio and CALLY index, was found to be lower in patients who underwent major amputation (30.97 ± 5.09, 30.11 ± 4.66 and 30.22 ± 54.76, respectively). Hypoalbuminemia, a common condition among hospitalized patients, appears to be related with adverse clinical outcomes. Serum albumin levels are used for assessing malnutrition in daily practice. Acute and chronic inflammatory conditions affect hepatic protein metabolism, altering serum albumin levels [5]. Therefore, albumin can be used as an indicator of disease severity in inflammatory states. In this study, the low albumin levels in major amputation group led to a reduction in HALP score and CALLY index with an increase in CRP/Albumin ratio.

CRP, a plasma protein of hepatic origin, is a marker that can rise to 1000 times its normal value in cases of tissue damage, inflammation, and infection. Numerous studies have investigated the relationship between CRP and different diseases, and it has been shown that high CRP levels are associated with diabetes [4]. In a study comparing healthy individuals with DM patients with or without increased risk for DFU, they mentioned that low basal CRP levels are related with improved wound healing and may serve as a biomarker indicating prognosis in DFU [19]. The current study has shown that the high CRP level is significant in terms of the necessity of major amputation ($p < 0.001$). A study on the effects of inflammation and malnutrition on albumin levels found that patients with low albumin levels had significantly higher CRP values compared to those

Table 6 Comparison of variables according to CALLY index

Variables	CALLY index		*p* value
	≤0.71	>0.71	
Age, mean±SD	66.40±10.90	66.38±11.29	0.988[a]
Gender	84 (86.6)	116 (74.8)	**0.025**[c]
Male	13 (13.4)	39 (25.2)	
Female			
PAD, n(%)	56 (57.7)	76 (49.0)	0.178[c]
CKD, n(%)	15 (15.5)	23 (14.8)	0.893[c]
CAD, n(%)	48 (49.5)	78 (50.3)	0.897[c]
Neuropathy, n(%)	61 (62.9)	63 (40.6)	**0.001**[c]
Ischemia, n(%)	82 (84.5)	94 (60.6)	**<0.001**[c]
Infection, n(%)	78 (80.4)	106 (68.4)	**0.036**[c]
Osteomyelitis, n(%)	79 (81.4)	88 (56.8)	**<0.001**[c]
Wagner score, n(%)	14 (14.4)	70 (45.2)	**<0.001**[c]
2	39 (40.2)	72 (46.5)	
3	44 (45.4)	13 (8.3)	
4			
Creatinine, mean±SD	1.50±1.28	1.43±1.45	0.421[b]
Albumin, mean±SD	30.22±4.76	36.73±5.37	**<0.001**[a]
CRP, mean±SD	146.47±67.52	30.45±23.85	**<0.001**[b]
Hba1c, mean±SD	9.21±1.84	8.87±2.00	0.061[b]
Leukocyte, mean±SD	13.22±5.90	9.04±3.34	**<0.001**[b]
Platelet, mean±SD	342.41±154.82	305.34±123.17	0.101[b]
Hemoglobin, mean±SD	10.24±1.71	11.81±2.07	**<0.001**[a]
Lymphocyte, mean±SD	1.50±0.71	2.08±0.86	**<0.001**[b]
Neutrophil, mean±SD	10.28±5.52	5.86±2.68	**<0.001**[b]
HALP, mean±SD	15.47±9.84	33.28±18.47	**<0.001**[b]
CRP/Albumin, mean±SD	4.95±2.33	0.87±0.74	**<0.001**[b]

HALP hemoglobin-albumin-lymphocyte-platelet, *SD* standard deviation, *PAD* peripheral artery disease, *CKD* chronic kidney disease, *CAD* coronary artery disease, *CRP* C-reactive protein, *CALLY* C-reactive protein-albumin-lymphocyte, [a] student-t test, [b] mann-Whitney U test, [c] ki-square test

with normal albumin levels (median 67 mg/L vs. 6 mg/L, $p < 0.001$). A strong negative correlation was also found between serum albumin and CRP ($p < 0.001$) [5]. Similarly, Gong et al. [20] reported that DFU patients who underwent amputation had significantly lower albumin levels, and higher platelet and CRP levels ($p < 0.001$).

While CRP, albumin, and the Wagner score individually exhibited significant associations with major amputation, the composite indices evaluated in this study demonstrated superior discriminative performance. Although the reliability of albumin and CRP as separate parameters has been documented, it has been suggested that the CRP/Albumin ratio would be more useful for predicting prognosis because both parameters can be influenced by different variables. Notably, the CRP/Albumin ratio yielded an AUC of 0.853, surpassing the predictive capacity of CRP or albumin when considered alone. In addition, the HALP and CALLY indices incorporate hematologic, inflammatory, and immunologic parameters, thereby providing a more integrated assessment of the patient's systemic inflammatory and nutritional status.

The CRP/Albumin ratio has been shown to predict mortality and severity of multi-organ dysfunction in patients admitted to intensive care unit, and 90-day mortality in patients with sepsis [21, 22]. Similarly, Donlon et al. [21] found that the CRP/Albumin ratio was a good indicator for identifying patients at risk for surgical site infections after major abdominal surgeries. In this study, it was shown that patients with a CRP/Albumin ratio >2.29 were at higher risk for major amputation. The CRP/albumin ratio has been shown to be a predictive factor for all amputations and osteomyelitis in DFU patients. Eren et al. [23] showed that a CRP/albumin ratio of 1.74 and above predicted the diagnosis of osteomyelitis with 92.0% sensitivity and 80.9% specificity in DFU patients. Karaca et al. [24] reported that a high CRP/albumin ratio was an independent predictor of all amputation in diabetic foot infection. The CRP/albumin can be used as a biomarker indicating disease progression and poor prognosis in DFU patients.

In critical illnesses, the inflammatory and nutritional status of patients is important, as catabolic conditions caused by inflammation and stress can lead to malnutrition and short-term morbidity/mortality. The development of DFU is inextricably linked to inflammation and nutrition. Lin et al. [25] used the albumin/neutrophil to lymphocyte ratio, which combines inflammation and nutritional markers, to assess the risk of DFU. Given that inflammation and albumin can affect each other, the need for parameters that include both variables are obvious. Accordingly, during the study design, it was decided to incorporate the HALP score and CALLY index assessments, as both indices encompass parameters reflecting the two variables of interest.

The HALP score which reflects both inflammation and nutritional status is calculated by hemoglobin, albumin, lymphocyte and platelet count. Currently, most studies evaluating the efficiency of HALP score have primarily concentrated on cancer patients [26–28]. In a meta-analysis including cancer patients, it was shown that a low HALP score is associated with decreased overall survival, disease-free survival, and relapse-free survival [29]. The HALP score has been studied in several aspects such as poor prognosis, determination of surgical treatment and treatment success in inflammatory disease. Benli et al. [30] showed that HALP score below the cut-off value of 31.2 was associated with acute appendicitis complications and postoperative morbidity ($p < 0.001$). Keskin et al. [14] examining surgical morbidity in patients with acute cholecystitis, it was shown that the conversion rates from laparoscopic cholecystectomy to open cholecystectomy increased when the

HALP score was below the cut-off value of 34.43. Although several studies have shown that a low HALP score is associated with poor prognosis, some have reported no predictive value [31, 32]. Nevertheless, studies exist in which the HALP score has been assessed but determined to have no predictive value [13, 33]. To the best of our knowledge, the present study represents one of the earliest investigations to assess the prognostic utility of the HALP score specifically within the context of diabetic foot ulcers. This innovative application extends the scope of the HALP score beyond its conventional use in oncology, underscoring its potential relevance in chronic inflammatory disorders characterized by concomitant vascular compromise and nutritional impairment. Such findings broaden the clinical applicability of the HALP score and support its integration into risk stratification frameworks for non-malignant, inflammation-driven conditions. This study showed that the risk of major amputation increased in patients with a HALP score below the cut-off value of 19.96. This cutoff value is lower than in other studies, which can be explained by the rapid progression of DFU leading to untreatable infections and tissue loss, converting into a systemic disease that threatens both the limb and life. As HALP is a novel scoring system, no universal cut-off value has been determined yet.

The CALLY index is composed of three key parameters: C-reactive protein (CRP), which reflects systemic inflammation; serum albumin, indicative of nutritional status; and lymphocyte count, representing immune function [34]. Since these components are thought to be more susceptible to malignant processes, most existing studies have focused on oncological conditions [7, 34, 35]. For instance, research in colorectal cancer patients has demonstrated that higher CALLY index values are associated with improved prognosis and increased survival rates [34]. However, given the index's components, it is evident that the CALLY index also reflects the systemic inflammatory state. Recently, studies have begun to explore the validity of the CALLY index in benign inflammatory conditions, revealing its potential superiority over other inflammatory biomarkers such as the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio [36, 37]. In the present study, the CALLY index was found to be a significant predictor of surgical approach in patients with DFU, a benign inflammatory condition.

Major lower extremity amputations result in decreased quality of life and increased healthcare costs. Estimating the risk of amputation in DFU patients and identifying predictive factors is a critical issue that guides the management process. Depending on our results, patients with a HALP score $\leq$ 19.96, a CRP/Albumin ratio >2.29 and a CALLY index $\leq$ 0.71 appear to have higher risk for major amputation. In patients diagnosed with DFU, it is possible to predict major amputation using biomarkers obtained from routine laboratory data. Demirkol et al. [38] found that patients who underwent amputation had higher leukocyte count and CRP levels compared to those who did not. Similarly, Karacaer et al. [39] evaluated diabetic foot infections and observed that amputation was performed more frequently in patients with higher leukocyte and CRP levels, with osteomyelitis, and peripheral arterial disease. A study on the prognosis of acute diabetic foot conditions indicated that patients with CRP levels >100 mg/L should receive urgent debridement within 24 h [40]. A study examining the efficiency of DFU classification systems on predicting amputation requirement found a significant relationship between the higher DFU grade and the need for lower limb amputation [41]. The lack of a universal scoring system for predicting amputation needs and levels has opened a new field to be explored for innovative studies. Lee et al. [42] reported that five existing classification systems and the newly developed coding system can effectively predict LEA, and the Wagner system was the most useful tool for predicting LEA in patients with DFU. In our study, we demonstrated that low HALP scores and CALLY index, high CRP/Albumin ratios is related with higher risk of major amputation. Guided by the cut-off values of these biomarkers, we can follow the course of the disease and plan the necessary treatment options.

Limitations

The retrospective design of this study inherently limits the ability to control for potential confounding factors that may have influenced the patients' inflammatory status at the time of surgical decision-making. Furthermore, the single-center nature of the study and the inclusion of only those patients who underwent surgical intervention restrict the generalizability of the findings. Another important limitation is the absence of longitudinal follow-up data, which precluded an evaluation of whether the assessed scores could reliably predict progression to major amputation in patients who initially underwent minor procedures. The lack of temporal monitoring of inflammatory and nutritional biomarkers also limits our ability to determine their dynamic prognostic value over the course of disease evolution.

Conclusion

As the severity of diabetic foot ulceration increases, so does the risk of tissue loss and major amputation. One of the key clinical challenges in managing this patient group is determining the appropriate timing and extent of surgical intervention. While clinical examination and imaging remain

central to this decision-making process, the inclusion of objective laboratory-based biomarkers may enhance prognostic assessment. While individual biomarkers are predictive, the composite scores may enhance risk stratification and facilitate earlier identification of high-risk patients. Our study demonstrated that HALP score ≤ 19.96, CRP/Albumin ratio > 2.29 and CALLY index ≤ 0.71 were significantly associated with major amputation. HALP score, CRP/Albumin ratio and CALLY index can be used as valuable biomarkers in predicting amputation level in DFU patients. Further prospective studies are needed to determine whether these scores can be used to identify patients at risk for future major amputation at the time of their initial minor procedures.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval For this type of study formal consent is not required. Ankara University Human Research Ethics Committee approval was received with the decision number İ11-809-23.

Informed consent This study has obtained IRB approval from Ankara University Human Research Ethics Committee and the need for informed consent was waived.

Consent for publication For this type of study consent for publication is not required.

Competing interests The authors declare no competing interests.

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