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Biomarker Prediction of Postoperative Healing of Diabetic Foot Ulcers

A Retrospective Observational Study of Serum Albumin

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ABSTRACT

PURPOSE: The purpose of this study was to investigate the relationship and to determine potential usefulness of serum albumin as a biomarker for predicting postoperative diabetic foot ulcer (DFU) healing.

DESIGN: A retrospective study.

SUBJECTS AND SETTING: The sample comprised 266 inpatients with type 2 diabetes receiving care in The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Among them, 174 had DFUs and underwent surgery for foot DFUs including amputation, skin grafting, and flap procedures. A comparison group consisted of 92 inpatients without a DFU or surgery.

METHODS: The association between healing and preoperative albumin levels was analyzed via a logistic regression model and receiver operating characteristic (ROC) curve.

RESULTS: The albumin value of patients with DFU grade 3 or more (3.23 ± 0.58 g/dL) was lower than that of patients with DFU grade 1-2 (3.58 ± 0.5 g/dL), and both were lower than that of the comparison group (3.89 ± 0.3 g/dL). Patients with a DFU with hypoalbuminemia (<3.5 g/dL) had a 2.5-fold higher risk of nonhealing at postoperative 28 days than patients with normal levels (odds ratio = 3.51; 95% confidence interval, 1.75-7.06; $P < .001$). For patients with a DFU overall, the ROC curve showed a preoperative albumin cutoff of 3.44 g/dL for DFU wound healing.

CONCLUSIONS: For patients with a DFU undergoing surgery, preoperative serum albumin may be used as a biomarker for predicting postoperative healing.

KEY WORDS: Albumin, Diabetic foot ulcer, Preoperative evaluation, Wound healing.

INTRODUCTION

Diabetic foot ulcer (DFU) is the most common complication associated with diabetes. Because of the high health costs of preventing long-term complications, the International Diabetes Federation announced the need for increased awareness about strategies to prevent DFUs.[1] Among them, the most devastating complication is lower-limb amputation, which affects between 40% and 70% of individuals with a DFU.[2-4] The prevalence of DFUs among patients with diabetes is reported to be as high as 10%; the lifetime risk of DFUs is even higher, affecting 25% of individuals with diabetes.[5,6] In the United States, only about 50% of DFUs heal within 1 year.[7] In cases of chronic nonhealing DFUs, hospitalization, surgical intervention, and subsequent amputation may be required. Therefore, for early assessment of wound healing of a DFU, and when an amputation occurs, vigilant assessment of the surgical site is essential, but these timely assessments remain a difficult challenge for clinicians. Thus, factors that predict healing, in

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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particular, biomarkers, may improve the precision of clinical assessments for patients with a DFU.

One such biomarker is human albumin, a small globular protein composed of 609 amino acids, that accounts for 50% of plasma proteins, and is synthesized in the liver and released into the blood vessels.[8] Albumin is a multifunctional protein involved in detoxification, antioxidation, inflammation and blood coagulation regulation, stabilization of endothelial cells, wound healing, and immune regulation.[9] The ability of albumin to regulate inflammation, interfere in neutrophil adhesion, and reduce oxidative damage may enhance endothelial function.[10,11] Studies in vitro support that albumin stabilizes vascular endothelial cells by moderating the intrinsic inflammatory response.[12] In diabetes, the pathology of DFUs is related to peripheral neuropathy and peripheral vascular lesions, which affect endothelial cell function. Albumin has the ability to maintain the function of endothelial cells. A study showed that physiological concentrations of albumin selectively inhibit TNF-α–induced upregulation of VCAM-1 expression and monocyte adhesion, most likely by inhibiting NF-κB activation in a GSH-independent manner, thereby acting as an anti-inflammatory agent toward endothelial cells.[13]

There is increasing evidence that hypoproteinemia is closely related to wound healing because it contributes to reduced collagen formation and wound dehiscence and results in poor wound-healing rates after abdominal[14] and lumbar surgeries[15] and in perineal wound healing.[16,17] Recent studies of patients with a DFU showed that serum albumin level was significantly lower than that in diabetic patients without a DFU[18] and that low albumin level was an independent predictor for delayed wound healing.[19] Thus, albumin may be a marker of prognosis in patients with a DFU. However, no study has evaluated whether preoperative serum albumin may affect postoperative outcomes of DFUs.

In this study, we aimed to investigate whether the serum albumin concentration of patients with a DFU may predict postoperative healing in patients undergoing surgery for their DFU. We also compared other commonly used inflammatory markers such as white blood cells (WBCs), neutrophils, and fibrinogen because studies have shown that WBCs and neutrophils are commonly used as predictors of amputation, and fibrinogen levels might be a valuable tool for assessing the disease severity in patients with a DFU.[20]

METHODS

In this retrospective study of 174 Chinese inpatients with a DFU, we evaluated the predictive value of albumin and other biomarkers in postoperative healing.

The sample size calculation was based on the results from our preliminary work (unpublished data) with a power of 80% and α of .05. Accordingly, it was estimated that 170 or more patients were required in the study. We then matched 92 inpatients with diabetes and without a DFU or having surgery by sex and age to determine differences in albumin, WBC, neutrophil, and fibrinogen outcomes.

Inclusion criteria were patients 18 years or older with diabetes mellitus. We did not restrict the type of diabetes; however, all patients had type 2 diabetes. Exclusion criteria were blood coagulation or neoplastic disorders, severe hypertension, liver disease or preexistent renal failure, use of aspirin or other acetylsalicylic acid within 1 month before surgery, or serum creatinine concentration of 1.5 mg/dL or more before surgery. Data such as patient demographics, vital signs, duration of diabetes, history of smoking and drinking alcohol, lab test results, *ICD-10* diagnosis codes, *ICD-9-CM* surgical procedure codes, medications, and mortality were obtained from hospital databases. The institutional review board (IRB) of The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China (IRB#2021-136), approved this retrospective study on February 5, 2021. We analyzed previously collected data from December 2016 through December 2019.

Study Procedures

The study population comprised 266 patients with type 2 diabetes. Among them, 174 patients had a DFU and underwent surgery, including amputation, skin grafting, pedicled flap (during flap formation and transfer, a portion of the flap must be attached to the donor site, called the pedicle, in order to maintain blood supply), or free flap. The DFUs were graded according to Wagner's classification. The surgical procedures were the same as those in our previous study described elsewhere.[21] Prior to reconstructive surgery, all the patients received standard care for DFUs, including systemic glucose control, off-loading, infection control, and local wound care and had adequate circulation assessed by transcutaneous oxygen test of 30 mm Hg or more and ankle brachial index values of 0.9 or more. Mechanical debridement was performed in all 174 cases, and negative pressure wound therapy was used in 116 patients prior to surgery to obtain clean, healthy granulation tissue. Procedures included 153 skin grafts, 16 pedicled flaps, and 5 free flaps. In addition, 62 large or small amputations were performed because of poor healing in 32 patients with skin grafting, 13 with pedicled flap, and 3 with free flap after amputation.

Measurement and Evaluation

Body mass index was calculated as weight (kg) divided by height $(m)^2$. Blood samples were taken after 8 to 10 hours overnight fasting for examination of plasma glucose, glycated hemoglobin (HbA_{1c}), complete blood cell count (hemoglobin, WBCs, neutrophil), albumin, and fibrinogen. Serum albumin concentration was measured with the bromocresol green dye-binding method, the most commonly used method for determining serum protein concentration. The reference range for the albumin assay was 3.5 to 5.0 g/dL. The Clauss method, with Diagnostica Stago (Asnieres, France) equipment and reagent, was used to measure serum fibrinogen levels in accordance with the Diagnostica Stago guidelines. The reference range for the fibrinogen assay was 2.0 to 4.0 g/L. All tests were performed in the biochemistry laboratory of our hospital. Wound healing at 28 days after surgery was judged as complete (full reepithelialization, with no need of dressing) or incomplete. Complete wound closure was defined as the stage at which 100% reepithelialization of the injured skin was achieved without any drainage or need for dressings.[21]

Statistical Analysis

Data analysis was performed using SPSS 25 for Windows software (IBM, Armonk, New York). Continuous variables are described as mean ± standard deviation (SD) and median (minimum-maximum). Categorical variables are shown as numbers (percentage). The Kolmogorov-Smirnov test was used to determine the normality of continuous variables. Continuous variables were tested with Student's *t* test to evaluate differences in means. The chi-squared test was applied for categorical variables to evaluate differences in percentage

TABLE 1.
Demographic and Laboratory Characteristics in the Surgical and Comparison Groups

	Total	DFU (n = 174)	Control (n = 92)	
Age, y				
Min-max (median)	33-90 (63)	33-90 (65)	36-88 (60)	.124
Mean ± SD	62.90 ± 11.96	63.72 ± 11.33	61.35 ± 13.00	
Sex, n (%)				
Male	174 (65.4)	119 (68.4)	55 (9.8)	.16
Female	92 (34.6)	55 (31.6)	37 (40.2)	
Duration of diabetes, y				
Min-max (median)	1-40 (10)	1-40 (10)	1-30 (9)	.123
Mean ± SD	10.77 ± 7.15	11.28 ± 6.71	9.78 ± 7.86	
Smoking, n (%)				
Never	211 (79.3)	144 (82.8)	67 (72.8)	.057
Ever (former + current)	55 (20.7)	30 (17.2)	25 (27.2)	
Drinking, n (%)				
Never	228 (85.7)	149 (85.6)	79 (85.9)	.958
Ever (former + current)	38 (14.3)	25 (14.4)	13 (14.1)	
BMI, kg/m^2				
Min-max (median)	16.97-40.02 (23.04)	17.72-36.99 (22.89)	16.97-40.02 (24.08)	.013
Mean ± SD	23.69 ± 3.35	23.29 ± 3.05	24.44 ± 3.77	
SBP, mm Hg				
Min-max (median)	92-208 (134.5)	92-203 (136)	98-208 (133.5)	.489
Mean ± SD	136.5 ± 22.17	137.19 ± 22.54	135.21 ± 21.50	
DBP, mm Hg				
Min-max (median)	50-115 (77)	50-112 (76)	53-115 (77)	.526
Mean ± SD	77.49 ± 11.98	77.15 ± 11.55	78.13 ± 12.79	
FBG, mmol/L				
Min-max (median)	2.6-33.7 (7.2)	2.7-29.3 (7.15)	2.6-33.7 (7.6)	.12
Mean ± SD	8.45 ± 4.40	8.15 ± 3.83	9.03 ± 5.28	
Albumin, g/dL				
Min-max (median)	1.40-4.79 (3.64)	1.40-4.79 (3.36)	2.79-4.7 (3.9)	<.001
Mean ± SD	3.51 ± 0.57	3.32 ± 0.58	3.89 ± 0.30	
WBC count (×10^9/L)				
Min-max (median)	3.13-36.61 (7.70)	3.13-36.61 (8.85)	3.83-11.32 (6.79)	<.001
Mean ± SD	9.11 ± 4.93	10.36 ± 5.63	6.74 ± 1.39	
Neutrophil (×10^9/L)				
Min-max (median)	0.73-33.02 (4.71)	0.73-33.02 (6.02)	1.90-7.64 (3.97)	<.001
Mean ± SD	6.39 ± 4.95	7.61 ± 5.69	4.08 ± 1.22	
Fibrinogen, g/L				
Min-max (median)	1.84-10.44 (4.14)	2.37-10.44 (4.85)	1.84-7.34 (3.04)	<.001
Mean ± SD	4.45 ± 1.62	5.07 ± 1.58	3.27 ± 0.88	
Hemoglobin, g/L				
Min-max (median)	42-187 (120.5)	42-166 (112.5)	62-187 (137.5)	<.001
Mean ± SD	118.31 ± 25.68	109.76 ± 23.42	134.48 ± 21.78	
HbA_{1c}, %				
Min-max (median)	5-18 (8.2)	5-18 (8.5)	5.8-14.8 (7.55)	.216
Mean ± SD	8.62 ± 1.95	8.74 ± 1.87	8.41 ± 2.08	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DFU, diabetic foot ulcer; FBG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; SBP, systolic blood pressure; WBC, white blood cell.

rates. To evaluate whether certain variables could predict postoperative DFU healing, multivariate analyses were performed using a logistic regression model with a forward stepwise procedure; the entry and removal probabilities were .05 and .10, respectively.

Because the reference range for the albumin assay was 3.5 to 5.0 g/dL, the multivariate analyses were performed using less than 3.5 g/dL and 3.5 g/dL or more. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff values of the preoperative serum albumin for wound healing at 28 days after surgery in 174 patients with a DFU. A value of $P < .05$ was deemed statistically significant.

RESULTS

Patient Characteristics

The final study population comprised 174 patients with a DFU (surgical group; 119 males; 55 females) and 92 patients without a DFU (comparison group; 55 males; 37 females; Table 1). The surgical and comparison groups were comparable in duration of diabetes, smoking, alcohol intake, blood pressure, fasting blood glucose, and HbA_{1c}. The following features of the surgical group were significantly higher than those of the control: WBC count ($P < .001$); neutrophils ($P < .001$); and fibrinogen ($P < .001$). The following measures were significantly lower than those of the comparison group: body mass index ($P = .013$); albumin ($P < .001$); and hemoglobin ($P < .001$).

Of the 174 patients in the surgical group, 42 had a DFU grade 1-2, and 132 had DFU grade 3 or more (Figure 1). The mean albumin level of surgical patients with DFU grade 3 or more (mean = 3.23 ± 0.58 g/dL) was less than that of patients with DFU grade 1-2 (mean = 3.58 ± 0.5 g/dL), and each of these was less than that of the comparison group (mean = 3.89 ± 0.3 g/dL).

For the surgical group overall, the healing rate at 28 days after surgery was positively associated with the preoperative serum albumin concentration, suggesting the lower the preoperative serum albumin concentration, the lower the postoperative healing rate of patients with a DFU (Figure 2).

Predictors

The logistic regression model showed that serum albumin was an independent prognostic factor for complete wound healing

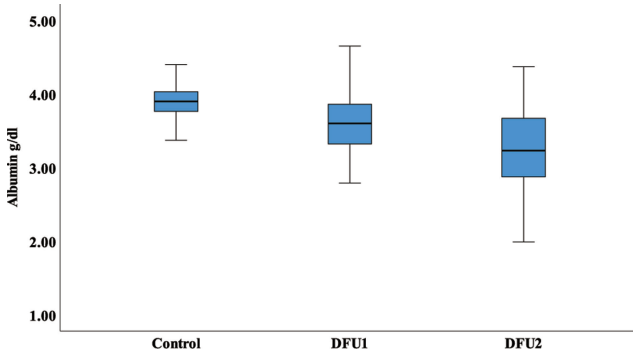
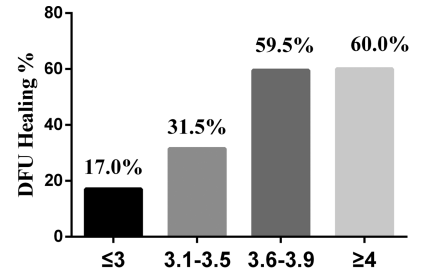


Figure 1. Patients in the test subgroup with DFU grade 3 or more (DFU2) had a lower mean albumin level compared with test patients with DFU grades 1-2 (DFU1). The mean albumin values of both the test subgroups were lower than those of the control patients. DFU indicates diabetic foot ulcer.



Healing(n)	9	17	25	15
Total(n)	53	54	42	25

Figure 2. Rate of complete healing at postoperative day 28 in the test group was positively associated with preoperative serum albumin level. DFU indicates diabetic foot ulcer.

at 28 days after surgery. According to the final multivariate analysis with adjustment for covariates such as age and sex, patients with a DFU with hypoalbuminemia (<3.5 g/dL) had a 251% higher risk of nonhealing compared with patients with normal levels (odd ratio [OR] = 3.51; 95% confidence interval [CI], 1.75-7.06; $P < .001$; Table 2). Patients with a DFU with WBCs 10 $\times 10^9$/L or more had a 333% higher risk of nonhealing compared with patients with normal levels (OR = 4.33; 95% CI, 1.94-9.69; $P < .001$; Table 2). Preoperative fibrinogen levels were not associated with postoperative healing in patients with a DFU ($P = .529$).

Postoperative Healing

The ROC curve analysis was used to evaluate wound healing at 28 days after surgery in the surgical group. The AUC (area bound by the coordinate axis under the ROC curve) revealed ranges between 0.5 and 1. The closer the AUC is to 1.0, the higher the authenticity of the detection method; preoperative serum albumin was 0.727 to estimate wound healing at 28 days after surgery (Figure 3). In addition, the preoperative albumin cutoff for DFU wound healing 28 days after surgery in the surgical group overall was 3.44 g/dL, with sensitivity, specificity, positive predictive values, and negative predictive values of 68.2%, 71.3%, 59.2%, and 78.6%, respectively (Figure 3).

DISCUSSION

To our knowledge, this study is the first to evaluate the significance of serum albumin for predicting the postoperative prognosis of patients with a DFU. Among patients with type 2 diabetes, those with a DFU had a significantly higher mean WBC count, neutrophils, and fibrinogen compared with patients without a DFU; albumin, hemoglobin, and body mass index were significantly lower in the surgical group with a DFU compared to those in the comparison group with diabetes and similar comorbid conditions. The mean preoperative serum albumin level appeared to decrease with the severity of a DFU. The percentage of patients with DFUs who experienced complete healing 28 days after surgery was positively associated with preoperative albumin; the lower the preoperative serum albumin concentration, the lower the postoperative healing rate of patients with a DFU. On the contrary, the higher the preoperative serum albumin concentration, the higher the postoperative healing rate of a DFU. Serum albumin was an

TABLE 2.
Multivariate Analysis of Nonhealing at 28 Days After Surgery in the Surgical Group

	Mean ± SD	*P*	OR (95%CI)		Mean ± SD	*P*	OR (95%CI)
Albumin <3.5 g/dL	3.32 ± 0.58	<.001	3.51 (1.75-7.06)	Albumin <3.5 g/dL	3.32 ± 0.58	<.001	3.51 (1.75-7.06)
WBC count ≥10 × 10^9/L	10.36 ± 5.63	<.001	4.33 (1.94-9.69)	WBC count ≥10 × 10^9 /L	10.36 ± 5.63	<.001	4.33 (1.94-9.69)
Fibrinogen ≥4 g/L	5.07 ± 1.58	.529		Fibrinogen ≥4 g/L	5.07 ± 1.58	.529	
Age, y	63.72 ± 11.33	.119		Age, y	63.72 ± 11.33	.119	
Duration of diabetes, y	11.28 ± 6.71	.918		Duration of diabetes, y	11.28 ± 6.71	.918	

Abbreviations: CI, confidence interval; OR, odds ratio; WBC: white blood cell.

independent prognostic factor for complete wound healing. Patients with a DFU and hypoalbuminemia had a 2.5-fold higher risk of nonhealing compared with patients with normal albumin levels.

In our current study, we performed univariate, multivariate regression, and ROC curve analyses of data from a large cohort of 174 patients with a DFU who underwent 3 types of surgical procedures for their wounds.

Ischemia modified albumin is a novel marker of tissue ischemia, which is detected based on testing the binding capacity of albumin and cobalt. Studies have shown that this binding affinity changes under different pathological conditions, indicating a decline in the physiological function of albumin as it relates to the prognosis of DFU amputation.[22] However, due to the inconvenience of using this technique for monitoring ischemia-modified albumin in the clinic, we looked for common indicators of albumin to predict DFU prognosis directly. We found that patients with diabetes and DFU and undergoing surgery for nonhealing wounds have lower serum albumin levels compared with those without a DFU. The preoperative serum albumin level may predict the prognosis for wound healing within 28 days after surgery.

Our findings are similar to those reported in a study conducted by Shiraki and colleagues[19] of serum albumin levels. Results suggest that a low serum albumin level of less than 3 g/dL (hazard ratio = 1.42; 95% CI, 1.08-1.86) was an independent predictor for delayed wound healing after endovascular therapy in patients with a DFU and critical limb ischemia. These results were supported by Brookes and colleagues,[18] who determined that 61.5% of patients with a DFU who required amputation had hypoalbuminemia, with an average albumin level of 2.87 g/dL. However, the investigators could not conclude that hypoalbuminemia may prognosticate postoperative wound healing; they did not perform a multivariate regression analysis of multiple factors that may have contributed to a healing prediction model and the sample size was small.

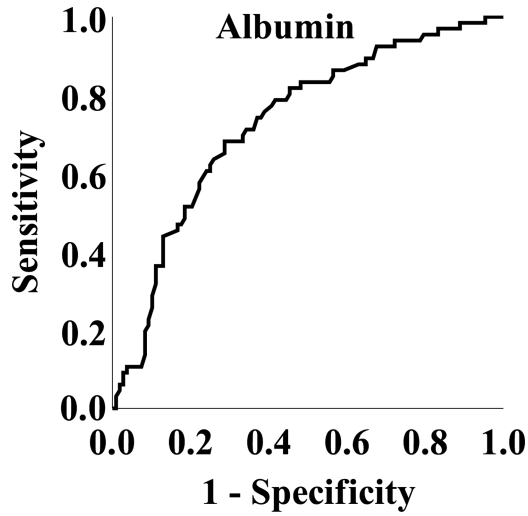


Figure 3. Receiver operating characteristic curve analysis of the test group to evaluate wound healing at 28 days after surgery. The area under the receiver operating characteristic curve for preoperative serum albumin was 0.727 to estimate wound healing at 28 days after surgery.

In our study, the logistic regression model suggested that serum albumin was an independent prognostic factor for whether the wound was completely healed 28 days after surgery in patients with a DFU. The ROC curve for preoperative albumin levels predicted postoperative healing with an AUC of 0.727, with sensitivity of 68.2%, specificity of 71.3%, and a cutoff of 3.44 g/dL. The higher the sensitivity, the lower the rate of missed diagnosis. The higher the specificity, the lower the misdiagnosis rate. The cutoff value is an equilibrium point between the sensitivity and specificity of using the ROC curve. Using the cutoff value to predict postoperative healing of DFUs was the most accurate. The overall accuracy of preoperative albumin in the determination of postoperative healing was 70.11%, indicating albumin is a good predictor of healing. We posit that low preoperative albumin level may be a biomarker for predicting postoperative healing in patients with a DFU.

We also point out that hypoalbuminemia may be associated with the development of DFUs. It is well-known that a DFU is associated with multiple risk factors, such as peripheral neuropathy, peripheral vascular disease, impaired resistance to infection, ischemia, peripheral edema, kidney disease, foot deformity, and poor glycemic control.[23,24] Albumin plays a crucial role in maintaining colloid osmotic pressure, while hypoalbuminemia can lead to edema.[10] Albumin also improves microcirculatory blood flow and reduces inflammation and oxidative damage.[25,26] Albumin has platelet function inhibition and antithrombotic function.[27] In a study conducted by Brookes and colleagues[18] of patients with DFUs, hypoalbuminemia was found to be associated with micronutrient deficiencies and is thought to contribute to amputation. Findings from their study showed that preoperative albumin supplementation promoted DFU healing. Specifically, serum albumin supplementation of more than 3.44 g/dL in patients with a DFU was significantly associated with postoperative healing. The researchers concluded that adequate albumin supplementation in diabetic patients may be a reasonable strategy to prevent the formation of DFUs.

In routine clinical practice, fibrinogen, WBCs, and neutrophils are used for determining DFU disease progression. These parameters can change according to the degree of the inflammation state, but they do not adequately reflect postoperative healing because of lacking data on their sensitivity and specificity. In our study, preoperative fibrinogen levels were not associated with postoperative healing in DFUs ($P = .529$).

STRENGTHS AND LIMITATIONS

This study provides evidence of a significant correlation between serum albumin and DFU disease severity in a cohort of patients with diabetes, comparing those with and without a DFU. We used data from a cohort of patients in our large database; our results require confirmation in a larger diverse sample of patients (our patients were from Asia), which may constitute a selection bias and results may not be generalized to those from other ethnic and racial groups. In addition, postoperative follow-up time was short; outcomes may be different at various postoperative time periods. The age of the population may also contribute to serum albumin findings; thus, more comprehensive prospective clinical and laboratory studies are required to determine the biological function and mechanism of serum albumin in DFUs.

CONCLUSION

Data from our study demonstrated a significant correlation between serum albumin and postoperative healing of DFUs. Preoperative serum albumin can be used as a biomarker to predict postoperative healing of DFU patients. If our data are validated by further trials, we believe that a standardized cutoff value for albumin will help monitor the disease progression and influence treatment. Therefore, we believe that serum albumin is a valuable tool in predicting postoperative healing of DFUs.

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