Association between anemia and the risk and outcomes of diabetic foot in patients with type 2 diabetes mellitus

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Abstract. The aim of the present study was to explore the association between anemia and the risks and outcomes of diabetic foot (DF) in patients with type 2 diabetes mellitus (T2DM). A total of 145 patients with T2DM were recruited between January and December 2021 and divided into the DF and non-DF groups according to whether they were diagnosed with DF. Individual patient data were extracted and blood samples were evaluated in a biochemical center for routine biochemical and blood-related indicators. The patients' survival rates were followed up until December 2022. An independent-samples t-test and χ^2 test were used to compare the differences between the two groups. The association between the various clinical indicators for the DF and non-DF groups was evaluated using single-factor binary logistic regression analysis. Multi-factor binary logistic regression analysis was used to analyze the association between hemoglobin (Hb) and the risk for DF. A Kaplan-Meier survival curve was used to analyze the impact of anemia and DF on the 1-year survival rate. The diabetes duration, number of patients who smoked and consumed alcohol, and serum creatinine and C-reactive protein levels in the DF group were significantly higher than those in the non-DF group ($P<0.05$). By contrast, the estimated glomerular filtration rate (eGFR) and Hb, albumin (Alb) and total cholesterol levels, were lower in the DF group when compared with those in the non-DF group ($P<0.05$). All of the study participants were divided into two groups, according to their baseline eGFR [eGFR ≥90 or <90 ml/(min x 1.73 m^2)]. It was found that, independently of renal function, lower Hb and Alb levels were associated with a higher incidence of DF. The 1-year survival rate for DF with anemia was significantly lower when compared with that in patients with DF without anemia ($P<0.05$). In conclusion, the Hb level in patients with T2DM is a protective factor against DF and anemia is an independent risk factor for DF. The present study suggested that anemia is associated with a decrease in the survival rate of patients with DF. This finding provided a theoretical basis for the clinical correction of anemia and improvement of DF prognosis (clinical trial no. 20220003).

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Abbreviations: DF, diabetic foot; DM, diabetes mellitus; T2DM, type 2 DM; BMI, body mass index; Hb, hemoglobin; Scr, serum creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Alb, albumin; TC, total cholesterol; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Key words: anemia, diabetic foot, type 2 diabetes mellitus, risk factors, survival rate

Introduction

Diabetes is a chronic endocrine/metabolic disease characterized by hyperglycemia due to insulin action and/or insulin secretion defects. Diabetes is frequently accompanied by visceral lesions, which may lead to serious complications and death (1). Diabetic foot (DF), a serious complication of diabetes mellitus (DM), causes a significant economic, social and psychological burden due to its high incidence, disability and mortality rates (2). The pathophysiology of foot ulcer and soft tissue infection in diabetes is due to neuropathy, trauma and peripheral arterial occlusive disease in numerous patients. Diabetes neuropathy may lead to foot deformity, resulting in increased skin pressure when walking. Once foot ulcers occur,

there is a high risk of invasive infection in the limbs. When the condition is combined with peripheral arterial occlusive disease, patients should be considered to have severe limb ischemia (3). DF destroys the skin and deep tissues of the patient's ankle joints and is frequently accompanied by infection and/or varying degrees of lower limb arterial occlusion. In severe cases, the muscle and bone tissue are involved (2). In patients with DM aged >50 years, the incidence of DF may be as high as 8.1%, and ~32/100 patients with DF who achieve healing exhibit recurrence within 1 year (4). It is noteworthy that the annual mortality rate of patients with DF is as high as 11% (4). The major risk factors for the progression of DF are male sex, prolonged history of DM, smoking, drinking, visual impairment, comorbidities and complications. Certain partial risk factors for DF, including neuropathy, peripheral arterial disease, history of toe amputation, abnormal plantar pressure and lower extremity venous insufficiency, accelerate its progression (2,5). Although interventions have been developed to target these risk factors, the incidence of DF is still annually increasing (4). Therefore, it is imperative that studies actively seek to establish new risk factors for DF. The different causes and clinical manifestations of DF require a multidisciplinary approach to address the ultimate goal of treatment, prevention of amputation and maintenance of functional foot with load-bearing capacity (6).

Previous studies have reported that the prevalence of anemia in patients with DF was as high as 51.9-85.3% (7), and the rate of adverse outcomes was even higher (8). However, it has remained to be clarified whether anemia is a poor prognostic factor for DF, and whether it affects DF outcomes and reduces the survival rate. The aim of the present study was to analyze the clinical characteristics and risk factors of DF in patients with type 2 DM (T2DM) and explore the association between anemia and the risks and outcomes of DF, as this information may provide a theoretical clinical basis for the prevention and treatment of DF and the improvement of its outcomes.

Materials and methods

Study population. Between January and December 2021, a total of 145 patients with T2DM were admitted to Suqian First Hospital in (Suqian, China). Patients were divided into the DF and non-DF groups (n=80 and 65, respectively), based on whether they had DF. The inclusion criteria were as follows: i) Diagnosis of T2DM based on the Guidelines for the Prevention and Treatment of T2DM in China (9); ii) diagnosis of DF according to the International Working Group on the DF guidelines (2); and iii) aged between 18 and 80 years. The exclusion criteria were as follows: i) Diagnosis of type 1, gestational or any special type of diabetes; ii) pregnancy or lactation; iii) hematological disease; iv) recent consumption of iron, folic acid or B12 supplements; v) DF secondary to severe injury, such as trauma; vi) dehydration and nutritional disorders; vii) other causes of anemia, including chronic renal failure, chronic liver disease, malabsorption, insufficient meat intake and strict vegetarian diet.

Data collection and measurement. The patients' body weight and height were measured using a height and weight scale. During the weight and height measurements, patients were requested to remove heavy clothes, shoes, bags or any other heavy items. These data were accurate to 0.1 of their respective units. The body mass index (BMI) was calculated by dividing the body weight in kg by the squared body height in m^2. The blood pressure was measured in the supine position at rest using a mercury sphygmomanometer. The mean of three measurements (at least 3 min apart) was used for the analysis. Other basic characteristics, such as age, sex, course of diabetes and history of smoking and drinking, were collected by trained investigators using a standard questionnaire. Fasting venous blood samples were collected on the first day after admission to determine the patients' fasting plasma glucose (FPG) levels and the related biochemical parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), albumin (Alb), hemoglobin A1c (HbA1c), Hb and C-reactive protein (CRP) levels (VARIANT II and D-10 Systems; Bio-Rad Laboratories, Inc.).

The estimated glomerular filtration rate (eGFR) was calculated from the Scr levels using the Chinese version of the simplified Modification of Diet in Renal Disease formula (10). Anemia was defined as a Hb concentration of <130 and <120 g/l in men and women, respectively (7,11).

Statistical analysis. Statistical analysis was performed using SPSS version 24.0 (IBM Corp.). Continuous and categorical variables were expressed as the mean ± SD and as n (%), respectively. Comparisons between the groups were made using a Student's t-test and the χ^2 test for continuous and categorical data, respectively. The median (interquartile range) was used for non-normally distributed variables and the Wilcoxon rank-sum test was used for comparison between the groups. Single-factor binary logistic regression analysis was performed to assess the impact of the clinical indicators on the risk of DF. Multivariate binary logistic regression analysis was performed to evaluate the association between Hb and a high DF risk. Kaplan-Meier plots were used to examine patient survival. Log-rank tests were performed to assess statistically significant differences between survival curves. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Study participant characteristics. A total of 145 patients with T2DM were analyzed in the present study, including 76 women and 78 men, and divided into two groups (DF and non-DF). The mean age was 67.92±11.75 years and the mean diabetes duration was 12.06±7.34 years. As presented in Table I, the duration of DM, age, history of smoking and alcohol consumption, and Scr and CRP levels in the DF group were significantly higher compared with those in the non-DF group, while the eGFR, as well as the Hb, Alb and TC levels, exhibited the opposite trend (i.e., lower in the DF group compared to the non-DF group). No significant differences were observed in terms of number of men, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, FPG, TG, HDL-C or LDL-C.

Single-factor binary logistic regression analysis of the clinical data and DF. As presented in Table II, a single-factor binary

Table I. Comparison of the general data from the patients with type 2 diabetes mellitus in the DF and non-DF groups.

Parameter	Non-DF group (n=65)	DF group (n=80)	T/χ^2	P-value
Male sex	30.00 (46.15)	48.00 (60.00)	2.766[a]	0.096
Age, years	66.46±10.04	69.10±12.92	-1.383[b]	0.024
BMI, kg/m^2	26.38±3.39	24.64±4.60	2.536[b]	0.254
Diabetes duration, years	10.00 (7.83, 12.51)	12.00 (8.24, 13.16)	-2.383[c]	0.017
History of smoking, years	12.00 (9.24, 20.16)	31.00 (17.64, 41.58)	7.076[a]	0.008
History of drinking, years	8.00 (6.51, 12.31)	21.00 (17.16, 26.25)	4.004[a]	0.045
SBP, mmHg	134.00 (21.00)	137.50 (23.75)	-1.014[c]	0.310
DBP, mmHg	76.03±9.22	75.66±10.01	0.228[b]	0.426
HbA1c, %	8.00 (3.30)	8.30 (3.35)	-0.639[c]	0.523
FPG, mmol/l	8.00 (6.67)	7.97 (5.26)	-0.634[c]	0.526
Scr, mg/l	0.70 (0.31)	0.96 (0.63)	-4.475[c]	<0.001
eGFR, ml/(min x 1.73 m^2)	117.97±42.09	87.56±52.81	3.770[b]	<0.001
Hb, g/l	133.15±25.01	117.25±22.00	4.040[b]	<0.001
Alb, g/l	41.50 (4.65)	35.75 (7.15)	-6.040[c]	<0.001
TG, mmol/l	1.35 (1.39)	1.35 (0.91)	-1.263[c]	0.207
TC, mmol/l	4.46±1.25	3.96±1.13	2.550[b]	0.010
HDL-C, mmol/l	1.09 (0.47)	1.14 (0.46)	-0.925[c]	0.355
LDL-C, mmol/l	2.55±0.86	2.37±0.92	1.140[b]	0.260
CRP, mg/l	4.90 (2.95)	9.60 (14.80)	-3.872[c]	<0.001

[a]Pearson's Chi-square test; [b]t-test; [c]Wilcoxon rank-sum test. Variables are expressed as n (%) for categorical data or the mean ± standard deviation or median (interquartile range) for continuous data with or without normal distributions, respectively. DF, diabetic foot; BMI, body mass index; Hb, hemoglobin; Scr, serum creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Alb, albumin; TC, total cholesterol; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

logistic regression analysis was performed with DF as the dependent variable and different clinical indicators of patients from the two groups as independent variables. The duration of DM, and Scr and CRP levels were significant risk factors for DF, while the eGFR, Hb, Alb and TC levels were protective factors against DF.

Multivariate binary logistic regression analysis following eGFR stratification. According to the single-factor binary logistic regression analysis, the Scr level was a significant risk factor for DF. Therefore, to exclude the influence of renal function, all participants were stratified according to their eGFRs and divided into two groups (H-90 and L-90). The H-90 group was defined as having an eGFR ≥90 ml/(min x 1.73 m^2) and the L-90 group as having an eGFR <90 ml/(min x 1.73 m^2).

As indicated in Fig. 1, after adjusting for DM duration, and Scr, Hb, Alb, TC and CRP levels, it was found that Hb and Alb levels were protective factors against the risk of DF in the H-90 group (odds ratio=0.932 and 0.740, 95% CI=0.877-0.991 and 0.599-0.914, respectively, P=0.024 for both). However, no statistical significance was observed for the L-90 group.

Survival curve analysis for all patients with or without DF. As presented in Fig. 2A, the 1-year survival rate of the patients with anemia was significantly lower than that of the control group (83.33 vs. 93.7%; P=0.002) in all patients. Similarly, the 1-year survival rate of the patients with DF was significantly lower than that of the control group (85 vs. 100%, P=0.002; Fig. 2B) in all of the patients. In the DF group, the 1-year survival rate of the patients with anemia was significantly lower than that of the patients without anemia (79.25 vs. 96.25%, P=0.044; Fig. 2C).

Discussion

DF, one of the most serious complications of T2DM, is associated with a variety of factors, such as loss of protective sensation, peripheral arterial disease, foot deformities and foot ulcers (12). It is associated with significant costs and high disability rates, as well as poor prognosis, all of which affect the quality of life of patients. Recently, an increasing number of studies demonstrated a high prevalence of anemia in patients with DF (9). The present study indicated that the prevalence of anemia in the DF group was as high as 53%, which was markedly higher than the 13% in the non-DF group. A previous study indicated that low Hb levels cause a false reduction in the HbA1c levels, reduce tissue oxygenation, weaken the antioxidant system and accelerate nerve damage (13). In addition, anemia and DF may share a common pathophysiological mechanism (8). Studies suggested that the incidence of anemia in patients with DF is high, and anemia should be investigated as a risk factor for DF. With changes in the microcirculation, the potential negative effects of anemia may hinder ulcer healing, leading

Table II. Single-factor binary logistic regression analysis of the influence on the risk of DF.

Variable	B	SE	Wald	Exp(B)	P-value
Male sex	-0.560	0.338	2.747	0.571	0.097
Age, years	0.019	0.014	1.799	1.020	0.180
Diabetes duration, years	0.053	0.024	4.761	1.055	0.029
BMI, kg/m^2	-0.116	0.480	5.957	0.890	0.150
SBP, mmHg	0.012	0.010	1.317	1.012	0.251
DBP, mmHg	-0.004	0.017	0.053	0.996	0.818
HbA1c, %	0.069	0.072	0.903	1.071	0.342
FPG, mmol/l	-0.007	0.037	0.039	0.993	0.844
Scr, mg/dl	2.057	0.579	12.606	7.825	<0.001
eGFR, ml/(min x 1.73 m^2)	-0.014	0.004	11.637	0.986	0.001
Hb, g/l	-0.033	0.009	13.559	0.968	<0.001
Alb, g/l	-0.245	0.048	26.692	0.782	<0.001
TG, mmol/l	0.018	0.032	0.321	1.018	0.571
TC, mmol/l	-0.373	0.154	5.840	0.688	0.016
HDL-C, mmol/l	-0.573	0.538	1.132	0.564	0.287
LDL-C, mmol/l	-0.233	0.205	1.293	0.792	0.256
CRP, mg/l	0.078	0.028	7.921	1.082	0.005

BMI, body mass index; Hb, hemoglobin; Scr, serum creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Alb, albumin; TC, total cholesterol; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

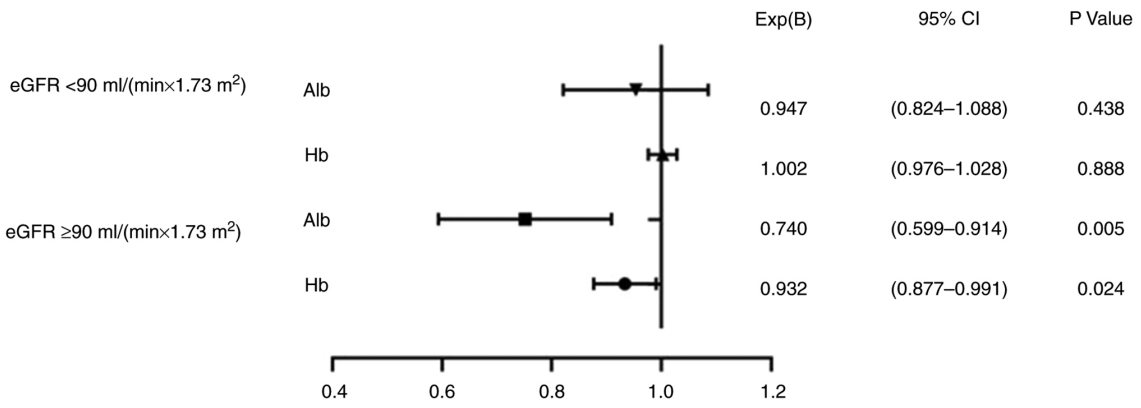

Figure 1. Multivariate binary logistic regression analysis following eGFR stratification. eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Alb, albumin.

to higher amputation and mortality rates (14,15). The severity of anemia has been proven to be associated with the severity of DF (16). Therefore, determining whether Hb is a protective factor against DF may prove useful in terms of the prevention, delay and improvement of the occurrence and development of DF.

In the present study, high eGFR, Hb and Alb levels protected against DF. As the serum Hb level increased, the risk of DF dropped to 96.8%. By contrast, the Scr, TC and CRP levels were risk factors for the development of DF. However, there is still a lack of studies on the survival rate in relation to the Hb level and DF.

There is still controversy around the mechanism of anemia in patients with DM. Alsayegh *et al* (17) proposed that anemia in patients with DM is mainly associated with renal insufficiency, glomerular hyperfiltration, chronic inflammation, microvascular injury, autonomic neuropathy and decreased erythropoietin synthesis caused by an abnormal renin-angiotensin-aldosterone system or other abnormalities (18). In diabetic patients with normal renal function, the prevalence of anemia is high. Studies suggested that abnormal iron storage, albuminuria, hyperglycemia and neuropathy may increase the prevalence of anemia. After adjusting for the eGFR, no obvious association was found between anemia and nephropathy (19,20). The present study demonstrated that the Scr level and eGFR were significant risk factors for DF. To further analyze the relationship between renal insufficiency, anemia and DF, all participants

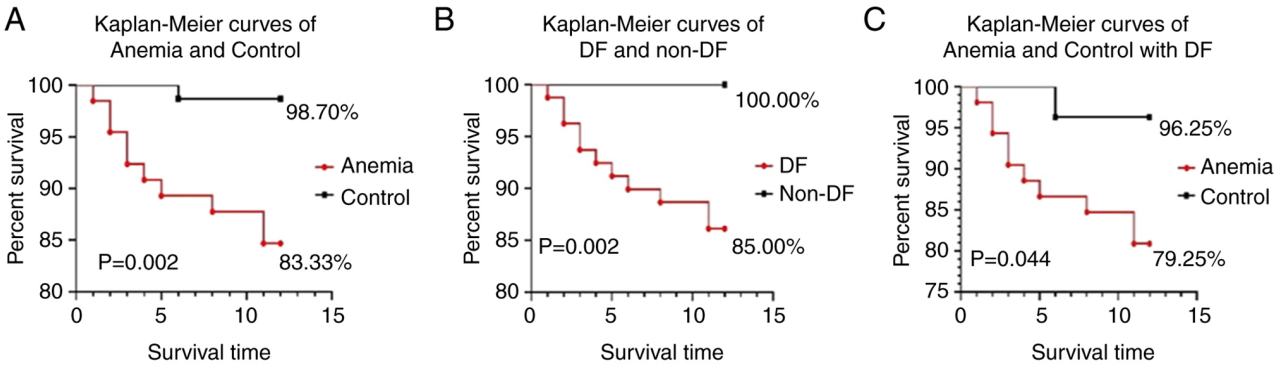

Figure 2. Probability of 1-year survival in all patients with or without DF. (A) Comparison of 1-year survival rate between the anemia and control groups. (B) Comparison of 1-year survival rate between the DF and control groups. (C) Comparison of 1-year survival rate between anemia and non-anemia patients in the DF group. DF, diabetic foot.

were stratified according to their eGFR and the association between certain clinical indicators, such as Hb and Alb levels, and the risk of DF was analyzed. In the group with eGFR ≥90 ml/(min x 1.73 m^2), the odds ratios for the Alb and Hb levels were 0.740 and 0.932, respectively ($P<0.05$). This meant that when the renal function was normal, both the Hb and Alb levels protected against DF.

According to the survival curve plotted for the present study, in the DF group, the 1-year survival rate of the patients with anemia was significantly lower than that of the patients without anemia (79.25 vs. 96.25%), suggesting that anemia was a risk factor for DF-related mortality. However, the mechanism behind the relationship between anemia and DF remains unclear. The possible mechanisms are as follows: i) Anemia may result in reduced skin oxygenation and capillary blood flow, increased hypoxia-inducible factors, aggravated lower limb ischemia, infections and hindered wound healing (21). Decreased oxygenation may also lead to endoneurial hypoxia and a weakened antioxidant system, resulting in increased free radical production, endothelial dysfunction and nerve damage (13,22). ii) Anemia may cause a false decrease in HbA1c levels, leading to insufficient hypoglycemic strength, and accelerated progression of microvascular and macrovascular complications (23) that increase the prevalence of myocardial infarction, stroke, DF and other diseases. iii) The internal environment of patients with DF features chronic inflammation, and certain pro-inflammatory cytokines both inhibit hematopoietic function and reduce the level of the raw material for hematopoiesis, namely iron (24-26). In a hyperglycemic state, the end products of glycosylation on the red blood cell membrane continue to accumulate, leading to changes in the red blood cell rheology and quantity (27).

The present study differed from previous research. To the best of our knowledge, it was the first clinical study on the association between Hb, DF risk and survival rates in Asia. It was found that the Hb level was a protective factor for DF, independently of renal function, which suggested that anemia is associated with a decrease in the survival rate of patients with DF. However, the present study had certain limitations. First, the sample size was small and the selected respondents only resided in China. Furthermore, the causal relationship between the Hb level and DF, or the effect of correcting anemia on DF prognosis, could not be elucidated. In addition, the follow-up time in the present study was short at just 1 year. Therefore, further clinical studies and basic experiments are needed to investigate the causal relationship between the Hb level and DF. Finally, multiple factor analysis was not conducted on anemia and other risk factors, such as the risk of infection and delayed wound healing. Follow-ups should be performed after anemia correction. Moreover, the sample size should be expanded to determine the optimal Hb level required to reduce the risk for DF. A multivariate analysis of anemia and other risk factors should be supplemented. Furthermore, interventional research will be required to explore whether the clinical correction of anemia may reduce the incidence of DF and improve its outcome and prognosis. This information may provide evidence-based medicine for the early prevention of DF.

In conclusion, the present study found that, in patients with T2DM, the Hb level was a protective factor against DF, and a low Hb level was found to be an independent risk factor for DF. The present study suggested that anemia is associated with a decrease in the survival rate of patients with DF. These results should prompt clinicians to pay close attention to the Hb levels of patients with DM and encourage a timely correction of anemia in that population. Such interventions may have a positive role in the prevention of DF and improvement of its survival rate.

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Availability of data and materials

Not applicable.

Authors' contributions

JL, MG and SM were responsible for the conceptualization of the study. ZZ, YL,CC and JW were responsible for data organization and statistical analysis. JL and ZZ wrote the original

draft. ZZ, JW, SM and MG wrote, reviewed and edited the manuscript. MG and SM checked and confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was in accordance with the Declaration of Helsinki and was approved by the ethics committee of Suqian First Hospital (Suqian, China; clinical trial no. 20220003). The participants all provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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