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*Original Article*

# Analysis of risk factors of morality in elderly patients with type 2 diabetic foot and transverse tibial bone transport technique

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**Abstract:** Objective: To evaluate the risk factors for morality in elderly patients with a type 2 diabetic foot (DF) and transverse tibial bone transport surgery. Methods: A total of 102 hospitalized elderly patients with DF and transverse tibial bone transport technique in the Longfu Hospital from 2018 to 2021, were divided into the non-survival group (9 patients) and survival group (93 patients). The risk factors were screened using univariate regression analysis and multivariate cox regression analysis based on the clinical data of patients in the two groups. Results: The age, glycosylated hemoglobin (HbAlc), small Low Density Lipoprotein cholesterol (smLDL-c), superoxide dismutase (SOD), albumin (ALb), prealbumin (PA), procalcitonin (PCT), hemoglobin (HGB) and the course of diabetes in the non-survival group were higher than those in the survival group. The grading of the diabetic foot, the history of smoking, the past history of hypertension (HTN), hyperlipidemia and coronary heart disease (CHD) were significant difference between the survival group and the non-survival group. The results of univariate regression analysis showed age, smLDL-c, SOD, PCT, anaemia, hypoproteinemia, the past history of CHD were risk factors for all of the elderly patients with a type 2 DF and transverse tibial bone transport technique surgery. Multivariate regression analysis showed that age, the history of CHD, PCT, HGB, SOD, and smLDL-c were major risk factors for the non-survival group. Conclusion: The mortality of the elderly patients with type 2 DF and transverse tibial bone transport technique is affected by many factors; early identification and comprehensive management of related risk factors have important significance in decreasing the mortality with these patients.

**Keywords:** Diabetic foot, tibia lateral bone transport, risk factors

## Introduction

Diabetic foot (DF) is defined as foot infections, ulceration or deep tissue destruction associated with nerve abnormalities in the foot below the ankle and varying degrees of peripheral vascular disease. DF is one of the serious complications in the elder patients with type II diabetes, and it is associated with the primary cause of non-traumatic toe amputation, with a high rate of teratogenicity, disability, mortality, costs, and reduced quality of life. Transverse tibial bone transport technique is the most effective way to treat DF in our hospital. The transverse tibial bone transport technique was derived from the law of tension-stress first found by Ilizarov [1]. This tension-stress can activate and enhance the regenerative capacity of living tissues, leading to growth or regeneration of muscles, fascia, blood vessels, and nerves simultaneously [1-3]. This technique offers a new direction for the treatment of diabetic foot combinations. Most patients retain the affected limb successfully after surgical treatment, which reduces the amputation rate and improves the quality of life. However, patients after surgical treatment are also at risk of fracture, non-healing wounds, and infection at the surgical site. Moreover, a few patients died in the perioperative period. Therefore, a total of 102 elderly patients with type 2 DF were included. The aim of this study was to explore risk factors by analyzing the clinical data in the elderly patients of type 2 DF with transverse tibial bone transport technique.

## Material and methods

### *Ethics approval and informed consent*

The protocol has been approved by the Longfu Hospital institutional review board (LFLL2021-

**Table 1.** Wagner ulcer classification system

| Grade | Lesion |
|---|---|
| 0 | No open lesions; may have deformity or cellulitis |
| 1 | Superficial diabetic ulcer (partial or full thickness) |
| 2 | Ulcer extension to the ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis |
| 3 | Deep ulcer with abscess, osteomyelitis, or joint sepsis |
| 4 | Gangrene localized to the portion of the forefoot or heel |
| 5 | Extensive gangrenous involvement of the entire foot |

22). All patients will gave written informed consent before recruitment, for publishing data.

*Patients*

From 2018 to 2021, 102 elderly patients with type 2 DF with transverse tibial bone transport technique were enrolled in our hospital. They were divided into the survival group (n = 93) and the non-survival group (n = 9). In the survival group, the patients were 67.97±10.49 years old, including 56 males and 37 females. In the non-survival group, the patients were 78.56±7.58 years old, including 6 males and 3 females.

*Collection of clinical indexes*

The general information of every patient, including age, gender, smoking history, medical history (coronary heart disease (CHD), hypertension (HTN), hyperlipidemia, cerebrovascular disease), course of diabetes, grading of the DF, and diabetic complications (diabetic retinopathy, diabetic peripheral neuropathy, diabetic peripheral vascular disease, diabetic nephropathy). Laboratory test results, including glycosylated hemoglobin (HbAlc), total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), small and dense low density lipoprotein (smLDL-c), superoxide dismutase (SOD), serum creatinine (Cr), urea nitrogen (BUN), pre-albumin (PA), plasma albumin (ALb), blood uric acid (UA), C-reactive protein (CRP), procalcitonin (PCT), neutrophil proportion (N%), white blood cell count (WBC), hemoglobin (Hb), and platelet count (PLT).

Grading of the diabetic foot was performed after examination of the wound using Wagner classification [4], as shown in **Table 1**.

*Statistical analyses*

The statistical calculations were performed using SPSS 20.0 statistical software. Normally distributed continuous variables were expressed as mean ± SD values and were compared between two groups using a t test. Categorical data were compared using chi-square test. A univariate logistic regression was performed for clinical data, and then the multivariate binary logistic regression analysis was performed. For all statistical analyses, a value of $P < 0.05$ was regarded as statistically significant.

## Results

*The change of clinical indexes in the survival and non-survival group*

A total of 102 type 2 DF patients undergoing transverse tibial bone transport technique were enrolled, and the basic biochemical characteristics were shown in **Tables 2** and **3**. As seen in **Table 2**, clinical indicators including age, HbA1c, smLDL-C, SOD, PCT, and the course of DM were higher in the non-survival group than in the survival group, while Alb, PA, and HGB were lower than in the survival group ($P < 0.05$). These results suggested that patients in the non-survival group were older, had a longer history of diabetes, poor control of blood glucose and lipids, higher levels of oxidative stress, nutritional bias, and more severe infections.

As exhibited in **Table 3**, compared with the survival group, the non-survival group had a longer history of smoking, higher grade of DF, and more complicated diseases ($P < 0.05$).

*Logistic regression analysis for risk factors of type 2 DF after transverse tibial bone transport technique*

Results of univariate binary logistic regression analysis are presented in **Table 4**. Univariate binary logistic analysis showed statistically significant differences in age, smLDL-C, SOD, Alb, PA, PCT, HGB, history of CHD, HTN and hyperlipidemia.

**Table 2.** Basic biochemical characteristics of the studied population

| Variables | Survival group (n = 93) | Non-survival group (n = 9) | *P* value |
|---|---|---|---|
| Age | 67.97±10.49 | 78.56±7.58*** | 0.004 |
| HbA1c | 7.63±0.85 | 8.22±0.81* | 0.049 |
| TC | 3.89±0.66 | 4.30±0.75 | 0.081 |
| TG | 1.64±0.38 | 1.82±0.27** | 0.176 |
| HDL-C | 0.86±0.16 | 0.85±0.14 | 0.810 |
| LDL-C | 2.41±0.47 | 2.65±0.49 | 0.145 |
| smLDL-C | 0.71±0.09 | 0.93±0.20* | 0.012 |
| Hcy | 14.92±2.57 | 16.71±4.60* | 0.284 |
| SOD | 147.22±15.23 | 158.46±16.83*** | 0.039 |
| Alb | 37.76±4.78 | 34.00±3.64* | 0.024 |
| PA | 163.66±16.31 | 149.00±13.87*** | 0.011 |
| Cr | 88.41±17.19 | 92.11±18.13 | 0.541 |
| BUN | 6.72±1.23 | 6.88±1.23 | 0.721 |
| UA | 278.82±30.00 | 296.67±54.05 | 0.120 |
| PCT | 0.16±0.05 | 0.21±0.05*** | 0.002 |
| WBC | 9.16±1.11 | 9.64±1.04** | 0.223 |
| N% | 75.88±4.72 | 77.88±3.51*** | 0.221 |
| HGB | 104.38±8.87 | 97.44±9.13** | 0.028 |
| PLT | 297.44±28.39 | 316.78±31.53* | 0.056 |
| CRP | 38.85±5.71 | 42.00±6.96* | 0.124 |
| the course of DM | 11.17±2.83 | 13.22±3.42* | 0.044 |

*P < 0.05, **P < 0.01, ***P < 0.001 vs survival group.

**Table 3.** Basic clinical characteristics of the studied population

| | $X^2$ | *P* value |
|---|---|---|
| Sex | 3.176 | 0.075 |
| Smoking history | 6.627 | 0.010 |
| HTN | 5.647 | 0.017 |
| Hyperlipidemia | 10.039 | 0.002 |
| CAD | 7.686 | 0.006 |
| Cerebrovascular disease | 2.510 | 0.113 |
| Wagner classification | 4.745 | 0.029 |

Results of multivariate binary logistic regression are presented in **Table 5**. Variables that were statistically significant risk factors for the death were later used in multiple binary logistic regression analysis in order to find the major factors. The results showed that the age, history of CHD, PCT, HGB, SOD and smLDL-c are the major factors for the non-survival group.

Additionally, the analysis of the cause of death showed that acute cardiovascular events in 5 cases (55.55%), septic shock in 3 cases (33.33%), and anemia in 1 case (11.11%).

## Discussion

DF is the most and severe common complication of diabetes mellitus [5]. The pathogenesis of DF is neuropathy, vascular lesions, infection, metabolic disorders, combined with a variety of inducing factors, which eventually lead to ulceration, infection or damage of deep tissues in the foot below the ankle in a patient with DM [6]. It can occur in a variety of issues and is the leading cause of hospitalization in diabetic patients, causing complex treatment, healthcare budget burden, reduced quality of life of many individuals, and even the death [7]. As a new treatment method, transverse tibial bone transport has been gradually applied in the clinic. Through transverse tibial bone transport technique, tibiae are formed into movable bone flaps to be transversely transported correspondingly, which repeatedly stimulates the regeneration of tibial bone marrow [8], promotes neovascularization and bone tissue formation, achieves the reconstruction of peripheral blood circulation [9], to improve limb blood supply, radically eradicate the source of ischemic diseases in lower limbs and promote blood circulation, therefore playing a role in clinical treatment [10].

This study aims to analyze the risk factors in elderly patients with type 2 DF and transverse tibial bone transport technique and to help guide the appropriate use of resources for clinicians to use and for examples to exist.

*Age and smoking*

Studies have shown that age is a risk factor for the occurrence and death of DF patients, forever, the incidence gradually increases with increasing age [7]. This study indicated that the age of the non-survival group was statistically higher than the survival group. Both univariate and multivariate binary logistic regression analysis showed that age was an important risk factor for the death.

**Table 4.** The results of univariate regression analysis risk factors of the non-survival group

| | OR | P | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Up |
| Age | 1.160 | 0.006 | 1.044 | 1.288 |
| HbA1c | 2.067 | 0.056 | 0.981 | 4.359 |
| TC | 2.237 | 0.089 | 0.884 | 5.665 |
| TG | 3.263 | 0.179 | 0.581 | 18.311 |
| HDL | 0.569 | 0.808 | 0.006 | 53.046 |
| LDL | 2.600 | 0.152 | 0.703 | 9.611 |
| SmLDL-C | 533711.577 | 0.001 | 249.483 | 1141755410 |
| Hcy | 1.228 | 0.082 | 1.013 | 1.255 |
| SOD | 1.052 | 0.049 | 1.000 | 1.107 |
| Alb | 0.821 | 0.031 | 0.685 | 0.983 |
| PA | 0.951 | 0.017 | 0.913 | 0.991 |
| Cr | 1.011 | 0.538 | 0.975 | 1.049 |
| BUN | 1.102 | 0.718 | 0.650 | 1.870 |
| UA | 1.015 | 0.128 | 0.996 | 1.035 |
| PCT | 232399944.1 | 0.006 | 225.293 | 2.397E+14 |
| WBC | 1.449 | 0.225 | 0.796 | 2.638 |
| N% | 1.097 | 0.223 | 0.945 | 1.274 |
| HGB | 0.906 | 0.036 | 0.827 | 0.993 |
| PLT | 1.022 | 0.065 | 0.999 | 1.046 |
| CRP | 1.091 | 0.131 | 0.975 | 1.220 |
| the course of DM | 1.238 | 0.054 | 0.997 | 1.537 |
| Sex | 1.892 | 0.365 | 0.477 | 7.511 |
| Smoking history | 2.211 | 0.339 | 0.435 | 11.236 |
| HTN | 6.672 | 0.022 | 1.309 | 34.007 |
| Hyperlipidemia | 4.414 | 0.045 | 1.032 | 18.886 |
| CAD | 17.655 | 0.008 | 2.109 | 147.773 |
| Cerebrovascular disease | 1.809 | 0.399 | 0.456 | 7.179 |
| Wagner classification | 1.321 | 0.706 | 0.311 | 5.615 |

**Table 5.** Multivariate regression analysis the major risk factors of the non-survival group

| | OR | P | 95% CI | |
|---|---|---|---|---|
| | | | Lower | Up |
| Age | 0.767 | 0.042 | 0.595 | 0.990 |
| CAD | 13.263 | 0.028 | 1.314 | 133.920 |
| PCT | 4.028 | 0.029 | 0.579 | 550.794 |
| HGB | 0.888 | 0.002 | 0.824 | 0.957 |
| SOD | 0.820 | 0.049 | 0.657 | 1.023 |
| SmLDL | 0.968 | 0.040 | 0.938 | 0.999 |

It has been widely acknowledged that smoking is a leading and independent risk factor for diabetic foot ulcer and amputation [10]. The reason is that carbon monoxide, nicotine, tar and other harmful substances reduce the oxidative stress reaction of inflammatory cells, weaken the ability of neutrophils, macrophages and pathogens, and decrease the rate of wound healing, promote ulcer surface formation by cytotoxic effects [11, 12]. This study suggests that there was a statistical difference in smoking history between the two groups.

*Hyperlipidemia and oxidative stress*

TC and LDL-c increase vascular wall viscosity and vascular wall permeability, damage vascular endothelial cells, decrease NO concentration, which lead to endothelial dysfunction (ED) in the patients with hypercholesterolemia; TC and LDL-c also directly damage vascular endothelial cells, which also leads to ED. ED is an initiation factor for atherosclerosis (AS) and is an independent predictor of cardiovascular events in high-risk populations. Studies have shown that [13] a large number of reactive oxygen species (ROS) such as superoxide anions are generated in patients with hypercholesterolemia. As the elevated level of ROS, excessive ROS can reduce NO production, accelerate NO degradation, interfere and inactivate NO, reduce NO bioavailability, inhibit endogenous nitric oxide synthase (eNOS) activity and so on, which can cause ED and initiate AS [14].

Oxidative stress refers to the process of oxidative damage caused by the accumulation of reactive oxygen species *in vivo* or cells. ROS includes free radicals such as superoxide (O2-), hydroxyl radicals (Ho-), and non-free radicals such as hydrogen peroxide ($H_2O_2$), nitrite peroxide (peroxynitrite) and hypochlorite (HClO-). In this study, compared with the survival group, SOD (the oxidative stress index) levels were all

increased significantly in the non-survival group. In addition, univariate and multivariate binary logistic regression analysis indicated that SOD was included in the regression equation, suggesting that SOD was an important risk factor for the dead patients with transverse tibial bone transport technique. This may be related to the oxidative stress response throughout the whole process of AS (from the formation of lipid streaks to the rupture of severe plaques lesions). There were statistical differences in smLDL-c and SOD between the two groups, and univariate and multivariate binary Logistic regression analysis indicated that smDL-c and SOD were important risk factors for the death. Therefore, controlling blood lipids and reduction of oxidative stress levels are helpful to improve the prognosis of such patients.

*Level of blood glucose, Course of diabetic and Hypertension*

Chronic hyperglycemia lead to macrovascular and microvascular complications in patients with type 2 DF by damaging vascular endothelial cells, oxidative stress, promoting platelet adhesion, activating coagulation mechanism, promoting thrombosis and other mechanisms, which promote the occurrence and development of DF, and increase mortality [15, 16]. Elevated HbA1c will reduce blood fibrinolytic activity, increase red blood cell aggregation form microthrombosis, aggravate lower limb circulation disturbances, and perpetuate diabetic foot conditions. In addition, hypertension can increase vascular wall stress and shear force as well as sympathetic nerve excitability, which lead to structural and functional changes of lower limb arteries, promote the development of AS [17], and then accelerating the occurrence of DF. Our study indicated that there were statistical differences in HbAlc, the course of diabetes and the history of HTN. These results suggest that hypertension, hyperglycemia and a long course of diabetes mellitus are all risk factors for the death.

*Cardiovascular diseases*

Cardiovascular disease is still the main cause of death in elderly patients with type 2 DF. The basic pathology is AS with microvascular lesions. Patients with type 2 diabetes mellitus are relatively insulin deficient or insulin resistant, which can increase free fatty acids, reduce the activities of lipoprotein enzyme and lecithin cholesterol transacylase, increase the activity of liver lipase, and cause lipid metabolism disorders. The disorder of lipid metabolism is an important risk factor for diabetic macrovascular complications, especially the increase of triglycerides and the decrease of high-density lipoprotein, which leads to the damage of vascular endothelium and smooth muscle cells, and promotes the formation of arterial plaques. Elevated blood pressure leaded to endothelium-dependent vasodilation dysfunction and increased arterial intima media thickness, which can also cause AS and promote the development and development of DF. Long-term hyperglycemia, hyperlipidemia, hypertension, high oxidative stress and other factors accelerate the process of AS. The deposition of transparent substances in the inner layer of the great vessel wall leads to a decrease in coronary blood flow, increased blood viscosity, high coagulation state, and thrombosis, which result in sudden cardiac death. Microvascular lesions aggravate myocardial ischemia and hypoxia, which lead to increase sudden death rates and painless myocardial infarction rates in such patients complicated with CHD, as well as rapid progression, poor prognosis and high mortality [16]. Moreover, the sympathetic and parasympathetic fibers that regulate cardiac function are damaged in elderly patients with type 2 DF, so arrhythmias are prone to occur [17]. In the non-survival group, 5 persons died because of acute cardiovascular events, and univariate and multivariate binary logistic regression analysis indicated that CHD history was included in the regression equation, suggesting that CHD history was an important risk factor for the death of patients after tibial bone transport.

*Infection*

When DF combined with infection occurs, the macrophages play a role in defense, at the same time, releasing toxic particles. This makes bacteria proliferate easy under high sugar conditions, inflammation responses expand, and severe tissue damage occurs [18]. Eventually it is hard to control infection, thus septic shock can happen. In this study, 3 patients died because of septic shock. Our study showed that PCT in the non-survival group was significantly higher than those in the survival group,

and PCT entered into the equation in univariate and multivariate binary logistic regression analysis. Hemodynamics are affected by enhanced coagulation mechanisms, increased blood viscosity, edema and compression of vessel walls in the state of infection, which results in ischemia aggravating, even inducing the occurrence and development of cardiovascular and cerebrovascular diseases [19-21]. Therefore, timely control of infection can significantly reduce the risk of postoperative death.

*Nutritive factors*

In this study, 1 person died due to aggravation of anemia, and hemoglobin was significantly lower in the non-survival group compared with the survival group. Univariate and multivariate binary Logistic regression analysis indicated that hemoglobin was included in the regression equation, suggesting that the reduction of hemoglobin was an important factor for death.

We speculated that the reason of lower hemoglobin in the non-survival group might be due to the effects of various factors on erythrocyte membrane proteins such as oxidative stress, endotoxin and glycoylation, which prolonged the damage of hyperglycemia on red blood cell function [22]. Therefore, it has a protective effect in improving anemia for the elderly patients of DF after tibial bone transport. Protein is essential for the synthesis of enzymes, which are involved in cell proliferation, collagen synthesis and healing. Studies have found that malnutrition can aggravate the severity of diabetic foot by changing the utilization pathway of protein and fat [23]. In this study, there were statistically significant differences in serum albumin and prealbumin in the non-survival group compared with the survival group. Thus, improving the nutritional status of surgery patients plays a crucial role in their prognosis.

In conclusion, whereas none of the factors listed in this study alone will result in the prognosis of the elderly patients with type 2 diabetes undergoing tibial bone transport, it is the interaction and combination of risk factors working together that leads to death. Therefore, it's beneficial to reduce the mortality for such elderly patients by early active smoking cessation, reduction of oxidative stress, controlling infection, correction of anemia, improvement of nutritional status, controlling blood glucose, blood pressure and blood lipids, standardized treatment of cardiovascular diseases, etc.

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## Disclosure of conflict of interest

None.

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