ORIGINAL ARTICLE

Identifying major predictors of lower-extremity amputation in patients with diabetic foot ulcers

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Abstract

Background: The aim of the present study was to investigate the risk factors for amputation in patients with diabetic foot ulcer (DFU).

Methods: Between 2012 and 2017, 646 patients with DFU were admitted to our diabetic foot care center. A retrospective chart review was performed, and the end point was limb salvage and minor or major amputation. Chi-square test, dependent *t* test, and a multivariate logistic regression analysis were performed to identify risk factors in patients with DFUs.

Results: A total of 399 male and 247 female patients (mean age 64.6 years) were included in this study, of whom 159 (24.6%) underwent lower limb amputation (minor, 17.5; major, 7.1%). Independent risk factors of amputation were peripheral arterial disease (PAD) (odds ratio [OR], 3.196; $p < 0.001$), C-reactive protein (CRP) level (OR, 1.046; $p = 0.001$), and hospital stay (OR, 1.019; $p = 0.001$). Subgroup analysis based on all patients with PAD who underwent amputation showed that endovascular intervention (OR, 0.271; $p = 0.049$) was a protective factor for major amputation in addition to CRP level (OR, 1.116; $p = 0.008$).

Conclusion: DFU remains a major medical and public health issue. PAD, CRP level, and hospital stay are independent risk factors for amputation. Endovascular intervention is an independent protective factor against major amputation among patients with PAD who underwent amputation.

Keywords: Amputation; C-reactive protein; Diabetic foot ulcer; Endovascular intervention; Peripheral arterial disease

1. INTRODUCTION

Diabetes mellitus is presently a common metabolic disease diagnosed according to the level of fasting blood sugar or hemoglobin A1C (HbA1C).[1] Patients with poorly controlled diabetes mellitus are at risk of complications such as nephropathy, retinopathy, and neuropathy.[1,2] Due to a lack of protective sensation, skin breakdown over the toes and feet is common in patients with diabetic neuropathy. Furthermore, delayed wound healing secondary to hyperglycemia-induced osmotic diuresis and subsequent low oxygenation and perfusion is common.[3] Wounds below the ankle of patients with diabetes are known as diabetic foot ulcers (DFUs). Approximately 8.8% of patients with diabetes are hospitalized due to foot-related problems and longer than patients with diabetes without foot-related admissions.[4] Moreover, approximately 35% to 40% of DFUs recur within 3 years and up to 70% within 5 years. DFU is the leading cause of nontraumatic lower limb amputations.[5,6]

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Peripheral arterial disease (PAD) is a disease with poor vascular condition secondary to atherosclerosis, calcification, hypertension, inflammation, injury, or smoking, resulting in inadequate circulation of the distal extremities, especially in the lower limbs.[7,8] In these patients, clinical presentation may include pain, paresthesia, poikilothermia, pallor, paralysis, and pulseless. In severe cases, critical ischemia may result in tissue hypoxia and gangrene change, which may require surgical amputation, reducing the patient's quality of life and ambulatory capability and increasing economic burden.[9]

According to a previous study, approximately 50% of patients with DFU were also diagnosed with PAD, which made treatment more complicated.[9] PAD induces not only ischemic status but also immunocompromised status in patients with diabetes, which result in increased infection rate and prolonged healing time. Limb ischemia is a major independent factor of lower limb amputation.[9,10] Conversely, successful revascularization does not ensure a satisfactory outcome of DFU. Other factors, such as wound infection, glycemic control, neuropathy, and impaired renal function, contribute to the outcomes.[3,7,11] The aim of this study was to review patients with DFU in our hospital and to identify possible predictors of clinical outcomes.

2. METHODS

This retrospective study was approved by the Institutional Review Board of the Taipei Veteran General Hospital, a tertiary academic medical center in Taipei City, Taiwan (2017-12-004AC). All patients included in this study were admitted to our plastic ward under the impression of DFU from January

2012 to May 2017. Patients aged <18 years and those with incomplete medical records were excluded from analysis. A total of 1227 patients with diabetes were initially identified during the study period. After reviewing their charts, we excluded from our analysis patients with wounds other than below-ankle level and caused by malignancy, pressure sores, burn, and trauma. A total of 646 patients were included in our study. The corresponding medical records were then reviewed for data related to patient demographics, perioperative variables, and clinical outcomes.

Demographic data included sex, age, body mass index (BMI), active smoking, HbA1C, diagnosis of PAD, diagnosis of osteomyelitis, other comorbidities (hypertension and coronary artery disease), serum level of C-reactive protein (CRP; mg/dL), hospital stay days, and vascular intervention (percutaneous transluminal angioplasty [PTA]). PAD was diagnosed by either computed tomography angiography of the lower limb or Doppler segmental pressure examination. PAD was defined in computed tomography angiography as patients with evidence of vascular stenosis, filling defect, or distal non-enhancement. In contrast, in Doppler segmental pressure examination, the criteria were defined as patients with an ankle-brachial index (ABI) ≤0.8.[6,7]

Our study end point was limb salvage without minor or major amputation. Minor amputation was defined by amputation of the phalanx or metatarsal level, while major amputation represents amputation of the below-knee or above-knee level.

Continuous data are presented as means and standard deviations, while categorical data are presented as frequencies and percentages. Group comparisons were performed using the chi-square test and independent *t* test for categorical and continuous variables, respectively. When identifying possible risk factors, binary logistic regression was used to determine certain covariants associated with the occurrence of amputation. All analyses were performed using SPSS software, version 20 (IBM SPSS Statistics, Armonk, NY, USA). All *p* values were two sided, and values <0.05 were considered statistically significant.

3. RESULTS

The overall demographics and clinical characteristics of patients are shown in Table 1. There were 399 men and 247 women included in this study. All patients were diagnosed with diabetes mellitus and foot ulcers, of whom 259 were diagnosed with PAD. Seventy-seven of the 259 patients received vascular intervention with PTA, while the rest received medication treatment. The average age of the study group was 64.6 years old with an average BMI of 26.2 kg/m². A total of 151 patients had a habit of smoking, while 436 had a history of hypertension, 86 chronic kidney disease, 148 end-stage renal disease (ESRD) under dialysis, and 201 coronary artery disease. A total of 161 patients were diagnosed with both hypertension and coronary artery disease. No patient had overlapping chronic kidney disease and ESRD. The average number of hospital stay days was 24.4 days.

The study group was then divided into two groups based on the limb salvage outcome for possible amputation risk factors by univariate analysis (Table 2). Patients who later underwent amputation (minor or major) during the treatment course were older ($p = 0.031$), had a lower BMI ($p = 0.025$), were diagnosed with ESRD ($p = 0.009$) or PAD ($p < 0.001$), and had a higher CRP level upon admission ($p = 0.020$) and longer hospital stay ($p < 0.001$), and underwent vascular intervention ($p < 0.001$). Further multivariate analysis was performed to define which factors presented as independent risk factors for amputation (Table 3). When all factors were included in the analysis, the remaining independent risk factors were PAD (odds ratio [OR], 3.196; $p < 0.001$), CRP level (OR, 1.046; $p = 0.001$), and hospital stay (OR, 1.019; $p = 0.001$). Patients who received vascular intervention were no longer an independent risk factor for amputation.

Table 1

Patient demographics

Characteristics	Patient numbers (n = 646)
Sex, n (%)	
Male	399 (61.8)
Female	247 (38.2)
Age, y, mean	64.6
BMI, kg/m², mean	26.2
Smoking, n (%)	151 (23.4)
Hypertension, n (%)	436 (67.5)
Diabetic nephropathy, n (%)	86 (13.3)
End-stage renal disease, n (%)	148 (22.9)
Coronary artery disease, n (%)	201 (31.1)
PAD, n (%)	259 (40.1)
Osteomyelitis, n (%)	60 (9.3)
HbA1C (%), mean	8.24
CRP, mg/dL, mean	9.78
Hospital stay, d, mean	24.4
Vascular intervention, n (%)	77 (11.9)
Amputation, n (%)	159 (24.6)
Minor	113 (17.5)
Major	46 (7.1)

BMI = body mass index; CRP = C-reactive protein; HbA1C = hemoglobin A1C; PAD = peripheral arterial disease.

Table 2

Amputation risk of diabetic foot ulcer using univariate analysis

Characteristics	Salvage (n = 487)	Amputation (n = 159)	*p*
Sex, n (%)			0.925
Male	300 (61.6)	99 (62.3)	
Female	187 (38.4)	60 (37.7)	
Age, y, mean ± SD	63.9 ± 14.5	66.7 ± 14.1	0.031
BMI, kg/m², mean ± SD	26.41 ± 5.07	25.36 ± 5.04	0.025
Smoking, n (%)	107 (22.1)	44 (27.7)	0.161
Hypertension, n (%)	321 (65.9)	115 (72.3)	0.144
Diabetic nephropathy, n (%)	59 (12.1)	27 (17.0)	0.139
End-stage renal disease, n (%)	99 (20.3)	49 (30.8)	0.009
Coronary artery disease, n (%)	145 (29.8)	56 (35.2)	0.201
PAD, n (%)	158 (32.4)	101 (63.5)	< 0.001
Osteomyelitis, n (%)	47 (9.7)	13 (8.2)	0.640
HbA1C, %, mean ± SD	8.28 ± 2.24	8.15 ± 2.11	0.543
CRP, mg/dL, mean ± SD	8.50 ± 22.70	13.03 ± 9.57	0.020
Hospital stay, d, mean ± SD	20.74 ± 17.39	35.52 ± 29.07	<0.001
Vascular intervention, n (%)	39 (8.0)	38 (23.9)	<0.001

BMI = body mass index; CRP = C-reactive protein; HbA1C = hemoglobin A1C; PAD = peripheral arterial disease.

Since PAD showed great interference over the outcome of amputation, we performed subgroup analysis based on PAD patients to further identify the risk factors for amputation (Table 4). Elevated CRP level (OR, 1.056; $p = 0.007$) and longer hospital stay (OR, 1.023; $p = 0.006$) were independent risk factors. Besides these, patients with PAD and those who received vascular intervention showed a trend toward amputation (37.6% vs 24.7%), but the difference was not statistically significant ($p = 0.287$).

Major or minor amputations affected patients differently in both physical and mental well-being. Table 5 shows the

Table 3

Amputation risk of diabetic foot ulcer using multivariate analysis

Characteristics	Salvage (n = 487)	Amputation (n = 159)	Odds ratio	CI	*p*
Sex, n (%)			0.969	0.585-1.605	0.903
Male	300 (61.6)	99 (62.3)			
Female	187 (38.4)	60 (37.7)			
Age, y, mean ± SD	63.9 ± 14.5	66.7 ± 14.1	1.007	0.987-1.028	0.491
BMI, kg/m^2, mean ± SD	26.41 ± 5.07	25.36 ± 5.04	0.998	0.949-1.050	0.944
Smoking, n (%)	107 (22.1)	44 (27.7)	1.243	0.716-2.159	0.439
Hypertension, n (%)	321 (65.9)	115 (72.3)	0.765	0.447-1.308	0.328
Diabetic nephropathy, n (%)	59 (12.1)	27 (17.0)	1.090	0.535-2.221	0.812
End-stage renal disease, n (%)	99 (20.3)	49 (30.8)	1.446	0.759-2.755	0.262
Coronary artery disease, n (%)	145 (29.8)	56 (35.2)	0.674	0.393-1.156	0.152
PAD, n (%)	158 (32.4)	101 (63.5)	3.196	1.769-5.776	<0.001
Osteomyelitis, n (%)	47 (9.7)	13 (8.2)	0.871	0.402-1.886	0.726
HbA1C, %, mean ± SD	8.28 ± 2.24	8.15 ± 2.11	0.966	0.864-1.082	0.552
CRP, mg/dL, mean ± SD	8.50 ± 22.70	13.03 ± 9.57	1.046	1.019-1.073	0.001
Hospital stay, d, mean ± SD	20.74 ± 17.39	35.52 ± 29.07	1.019	1.008-1.030	0.001
Vascular intervention, n (%)	39 (8.0)	38 (23.9)	1.489	0.776-2.856	0.231

BMI = body mass index; CRP = C-reactive protein; HbA1C = hemoglobin A1C; PAD = peripheral arterial disease.

Table 4

Amputation risk of diabetic foot ulcers, subgroup of patients with PDA using multivariate analysis

Characteristics	Salvage (n = 158)	Amputation (n = 101)	Odds ratio	CI	*p*
Sex, n (%)			0.888	0.445-1.771	0.736
Male	93 (58.9)	63 (62.4)			
Female	65 (41.1)	38 (37.6)			
Age, y, mean ± SD	70.3 ± 12.9	70.4 ± 13.9	1.015	0.986-1.044	0.329
BMI, kg/m^2, mean ± SD	24.62 ± 4.28	24.79 ± 4.67	0.989	0.912-1.073	0.796
Smoking, n (%)	28 (17.7)	28 (27.7)	1.538	0.702-3.369	0.282
Hypertension, n (%)	121 (76.6)	78 (77.2)	0.475	0.216-1.043	0.064
Diabetic nephropathy, n (%)	18 (11.4)	16 (15.8)	1.012	0.362-2.826	0.982
End-stage renal disease, n (%)	70 (44.3)	43 (42.6)	1.225	0.569-2.637	0.604
Coronary artery disease, n (%)	79 (50.0)	45 (44.6)	0.546	0.284-1.049	0.069
PAD, n (%)	...	...	...	...	...
Osteomyelitis, n (%)	19 (12.0)	10 (9.9)	1.031	0.401-2.647	0.950
HbA1C, %, mean ± SD	7.74 ± 1.94	7.81 ± 1.83	0.940	0.790-1.119	0.485
CRP, mg/dL, mean ± SD	7.43 ± 7.91	11.96 ± 9.08	1.056	1.015-1.100	0.007
Hospital stay, d, mean ± SD	21.77 ± 18.43	36.20 ± 26.48	1.023	1.007-1.039	0.006
Vascular intervention, n (%)	39 (24.7)	38 (37.6)	1.448	0.732-2.863	0.287

BMI = body mass index; CRP = C-reactive protein; HbA1C = hemoglobin A1C; PAD = peripheral arterial disease.

Table 5

Risk of major amputation in patients with PDA using multivariate analysis

Characteristics	Minor (n = 70)	Major (n = 31)	Odds ratio	CI	*p*
Sex, n (%)			0.413	0.106-1.617	0.204
Male	44 (62.9)	19 (61.3)			
Female	26 (37.1)	12 (38.7)			
Age, y, mean ± SD	70.5 ± 15.1	70.2 ± 11.0	1.019	0.960-1.081	0.541
BMI, kg/m^2, mean ± SD	24.88 ± 4.62	24.59 ± 4.87	0.959	0.822-1.119	0.595
Smoking, n (%)	18 (25.7)	10 (32.3)	2.796	0.605-12.922	0.188
Hypertension, n (%)	56 (80.0)	22 (71.0)	0.340	0.078-1.476	0.150
Diabetic nephropathy, n (%)	10 (14.3)	6 (19.4)	0.711	0.106-4.777	0.725
End-stage renal disease, n (%)	32 (45.7)	11 (35.5)	0.208	0.039-1.104	0.065
Coronary artery disease, n (%)	28 (40.0)	17 (54.8)	1.366	0.373-5.000	0.638
PAD, n (%)	...	...	...	...	...
Osteomyelitis, n (%)	9 (12.9)	1 (3.2)	0.228	0.020-2.619	0.235
HbA1C, %, mean ± SD	7.86 ± 1.90	7.68 ± 1.70	0.899	0.636-1.271	0.548
CRP, mg/dL, mean ± SD	9.76 ± 8.13	17.41 ± 9.17	1.116	1.029-1.209	0.008
Hospital stay, d, mean ± SD	33.03 ± 26.06	43.35 ± 26.45	1.023	0.998-1.049	0.068
Vascular intervention, n (%)	30 (42.9)	8 (25.8)	0.271	0.074-0.993	0.049

BMI = body mass index; CRP = C-reactive protein; HbA1C = hemoglobin A1C; PAD = peripheral arterial disease.

independent risk factor of major vs minor amputation in patients with PAD. In addition to CRP level (OR, 1.116; p = 0.008), receiving vascular intervention (OR, 0.271; p = 0.049) was also a protective factor for major amputation.

4. DISCUSSION

The results of this 5-year single-center study present the possible major risk factors of lower limb amputation in patients with DFU. Patients with PAD, higher CRP level upon admission, and longer hospital stay should be addressed properly to reduce the possibility of lower limb amputation, which may cause disability, reduce quality of life, increase hospital expenditure in treatment, and impose significant burden on not only the patients and their families but also the entire healthcare system.[12,13]

Patients with type 2 diabetes have an overall incidence of diabetic foot complications of approximately 2% per year and lower limb amputation of approximately 2-3 per 1000 patients, based on a nationwide study in Taiwan between 2007 and 2014.[13,14] Our study used data from a tertiary medical center and revealed that the overall amputation rate among patients with diabetes accompanied by DFU was 24.6%, which was higher than the previously reported data. Some patients with severe DFU, who had been suggested amputation, came to our institution for a second opinion. We thought that the patients included in this study suffered from more severe DFU, which had to be admitted for treatment. Moreover, most of these patients underwent minor lower limb amputation, which was similar to other reported nationwide studies. Conversely, aggressive vascular intervention among the patients with PAD and DFU may reduce the amputation rate based on our cohort and previous studies.[14–16]

Among our patients, PAD, CRP level, and hospital stay were independent risk factors of amputation. In previous studies, almost half of the patients with DFU had PAD, a risk factor of poor wound healing and future amputation.[3,11,14] In our study, the overall incidence of PAD was 40.1%, which however increased to 63.5% in patients who underwent amputation, acting as an independent risk factor. Furthermore, severe infection status with a higher CRP level with a cutoff value of 50 mg/L before PTA was presented as a major predictor of major amputation.[11] In our study, regardless of the overall analysis or the subgroup analysis, elevated CRP level acted as an independent risk factor for amputation, similar to previous reports.[11,17]

Hinchliffe et al[18] reported that the 1-year limb salvage rates were a median of 85% (interquartile range, 80%-90%) following open surgery, while the rates were 78% (70%-89%) following endovascular revascularization. There are insufficient data to recommend one method of revascularization over another. Butt et al also reported that endovascular surgery first and open vascular surgery first strategies were associated with similar long-term results in a large cohort of patients with DFU and PAD undergoing revascularization. Rapid revascularization reduces the risk of amputation.[19–22] In our study, 77 patients with PAD underwent endovascular revascularization, and 39 of them were not amputated. The salvage rate was 50.6%. As shown in Table 4, in the subgroup of patients with PAD, endovascular revascularization was not an independent risk factor of amputation but showed a trend of more amputation (p = 0.287) in comparison to no intervention (37.6% vs 24.7%). A possible explanation is that it is a retrospective study; patients were not randomly assigned to vascular intervention, and patients with less severe PAD might be treated medically. Moreover, further subgroup analysis in Table 5 demonstrated that endovascular intervention will reduce the possibility of major amputation in DFU patients with PAD who eventually underwent amputation, 25.8% major vs 42.9% minor amputation.

Other possible risk factors for lower limb amputation, including older age, gangrene appearance, nutritional status, and deterioration in renal function, have been reported.[3,5,13,19] In our study, no significant difference was found between age (p = 0.491) and chronic kidney disease (p = 0.812 for diabetic nephropathy, p = 0.262 for ESRD).

This study has some limitations. First, this was a single-center study, which may lead to treatment and patient selection bias. Second, there was no objective evidence of successful endovascular intervention provided in this study (e.g., TcPO2, ABI), which affects the interpretation of PTA as a protective factor for amputation. Lastly, this is a retrospective study with less strength of evidence and more bias.

In conclusion, DFU remains a major medical and public health issue. PAD, CRP level, and hospital stay have been shown as independent risk factors of amputation. Endovascular intervention is an independent protective factor against major amputation among patients with PAD who underwent amputation.

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