Journal of Acute Medicine 9(2): 59-63, 2019
DOI:10.6705/j.jacme.201906_9(2).0003
Original Article

Prognostic Factors for Lower Extremity Amputation in Diabetic Foot Ulcer Patients

Anita Kurniawati[1,*], Yoyos Dias Ismiarto[1], I-Lin Hsu[2,3]

[1]Department of Orthopaedics & Traumatology, Faculty of Medicine University Padjadjaran, Dr. Hasan Sadikin Hospital, Bandung, Indonesia
[2]College of Medicine, Department of Emergency Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan
[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Background: Infection and necrosis are common acute complications of diabetic foot ulcer (DFU). Amputation is the last resort treatment to control severe diabetic foot infection. Many risk factors for progression of infection that lead to amputation are disclosed. However, the prediction for the amputation necessity is clinically important to stratify risk and target intervention for limb salvage. Accordingly, this study investigates the predictive risk factors for amputation need in diabetic patients with foot ulcer.
Methods: We retrospectively studied the medical records of the DFU patients from January to December in 2017. The patients were classified as the non-amputation and amputation groups. Patient characteristics, clinical features of vasculopathy and neuropathy (ankle brachial index [ABI] and monofilament test), and laboratory features (hemoglobin A1C [HbA1C], C-reactive protein [CRP], and white blood cell [WBC] counts) were analyzed, using the univariate and multivariate analyses.
Results: Of the eligible 73 cases (age 41 to 76 years), 14 (19.2%) underwent lower limb amputation. Using the multivariate model, significate risk factors included low ABI (< 0.8; adjusted odds ratio [OR] = 17.9; $p = 0.003$), the presence of neuropathy (adjusted OR = 5.6; $p = 0.005$), and HbA1C > 8.0% (adjusted OR = 4.7; $p = 0.016$).
Conclusions: Several predictors, such as vasculopathy, neuropathy, higher HbA1C and CRP, were associated with amputation necessities in DFU patients. Of note, the vasculopathy was found to be the most important powerful. Therefore, identification and correction of these predictors would improve the quality care and patient prognosis.

Key words: *amputation, diabetic foot ulcer, prognostic risk factor*

Introduction

Diabetes mellitus (DM) is vastly linked to lower limbs complication in Indonesia.[1] In the past, DM prevalence is increasing rapidly due to population growth, aging, and increasing prevalence of obesity and physical inactivity.[1] Particularly in Indonesia, the prevalence of DM for all age-groups was estimated to be 5.7% in 2007 and is predicted to be 6.0% in 2030;[2] as well as a projected 8.2 million people living with DM in 2003 and is calculated to rise to 14.1 million in 2035.[3]

One of the most common complications of DM is diabetic foot ulcer (DFU), because it is estimated that 5–15% of patients with DM will be having diabetic foot acute infections or necrosis which often result in amputation as one of the worst and last resort treatment.[4] Accordingly, DM holds a 15- to 20-fold increased risk

Received: July 22, 2018; Revised: August 28, 2018 (2nd); Accepted: August 30, 2018.
*Corresponding author: Anita Kurniawati, MD, Department of Orthopaedics & Traumatology, Faculty of Medicine University Padjadjaran, Dr. Hasan Sadikin Hospital, No. 38, Jl. Pasteur, Bandung, W. Java 40161, Indonesia. E-mail: kurniawatianita85@gmail.com

of lower extremity amputations (LEA),[5] compared to healthy persons. It is interesting, however, that even among foot ulcerations which have been properly debrided, the treatment outcomes can be different greatly.

LEA remains a major problem worldwide, and is associated with significant morbidity and mortality. In addition, patients with LEA had a low quality of life, due to the negative social and psychological impact.[6] Therefore, in daily practice, prediction of the amputation necessity is clinically necessary.[7] Identification of modifiable factors is an important step for the establishment of preventive programs to reduce rate of LEA. However, there was inadequate information associated to risk factors for amputation. Objective of this study is to investigate the associated risk factors for amputation of DFU.

Methods

Setting and Participants

This was a retrospective study, investigated patients with DFU who were hospitalized in Dr. Hasan Sadikin Hospital, Bandung, Indonesia during the period of January 2017 to December 2017.

The inclusion criteria were the following: type 2 DM patients having diabetic foot with Wagner Classification grade 2 and those had been treated conservatively. The exclusion criteria included patients younger than 30 years old, and those having the high fasting blood glucose level (> 200 mg/dL), low albumin serum (< 2.5 g/dL), and low hemoglobin level (< 10.0 g/dL).

Variables

We have conducted a pre-determined review from our patient medical records to collect data included patient characteristics such as the patient age and onset age of DM. Objective clinical data from physical examinations and laboratory results such as ankle brachial index (ABI), Semmes-Weinstein monofilament test, hemoglobin A1C (HbA1C), C-reactive protein (CRP), and white blood cell (WBC) counts were also documented. Neuropathy was evaluated by using 5.07/10.00 g Semmes-Weinstein monofilament test. Capability to locate seven or less sites out of a total of 10 sites indicated the presence of peripheral neuropathy.[8] The presence of angiopathy was assessed with ABI. An ABI < 0.8 were considered has a peripheral ischemic.[9] Data were collected from the DFU patients who met the criteria at the first time of their attendances at emergency department.

These legible patients were categorized into the non-amputation and amputation groups. The patients in the non-amputation group experienced ulcer healing with conservative treatment such as intravenous antibiotic administration, bedside wound debridement and local wound care, use of a negative-pressure device, or surgical methods such as incision and drainage or distal amputation such as toe amputation. Patients failed to conservative treatment and those having the presence of progression stage of the ulcers based on the Wagner Classification System, those underwent a major amputation such as an above-knee amputation and below-knee amputation were classified into the amputation group.

Data Analysis

All collected data was analyzed statistically by using SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test or chi-square analysis was used to determine statistically significant differences between two groups. Multivariate analyses, using the backward stepwise model, were studied for the significant predictors recognized by the univariate analyses. A statistical significance set at *p*-value less than 0.05 ($p < 0.05$).

Results

Of the eligible 73 cases, 14 (19.2%) was categorized as the amputation group consisted of 12 females and two males. In this group, all patients had comorbid type 2 DM for at least eight years. Their mean age at the time of the DM diagnosis was 47 years. Majority of (92.3%) patients had ABI < 0.8, with the mean of 0.768, and had a neuropathy due to the poor Semmes-Weinstein monofilament test result. And most patients had several laboratory tests linked to sepsis. Their mean (standard deviation, SD) of initial HbA1C, WBC counts, and CRP during the hospitalization were 9.8% (2.1), 14,217/mm^3 (1,762), and 8.2 mg/dL (1.9).

The non-amputation group consisted of 59 patients (51 females and eight males), with the mean age of 57.6 years. Their mean age at time of DM diagnosis was 51 years. Eight (13.6%) patients had ABI < 0.8, with the mean of 1.128. Fourteen (23.7%) patients had a neuropathy. Their mean (SD) of initial

HbA1C, WBC counts, and CRP were 7.2% (1.8), 13,837/mm^3 (1,269), and 3.2 mg/dL (1.5).

The clinical predictors linked to amputation need was demonstrated in Table 1, using the univariate and multivariate analyses. In the univariate analyses, four predictors, low ABI (< 0.8), the presence of neuropathy, high HbA1C level (> 8.0%), and high CRP level (> 5 mg/dL), were recognized. Using the multivariate model, significate risk factors included low ABI (< 0.8; adjusted odds ratio [OR] = 17.9; p = 0.003), the presence of neuropathy (adjusted OR = 5.6; p = 0.005), and HbA1C > 8.0% (adjusted OR = 4.7; p = 0.016).

Discussion

As the incidence of DM is increasing worldwide, increase in complications is also undoubted. Overall, 15% of individuals with DM will have foot ulcer during their lifetime.[10] DFU is becoming major concern especially in orthopaedic field. International Diabetes Federation reported that 85% of DM-related LEA were preceded by a foot ulcer.[1,11] Previous experiences revealed that some DFUs healed with conservative treatment while others did not and lead to amputation. Recent studies have indicated that there must be certain factors related to the failure of DFU treatment. This study investigated prognostic risk factors for amputation among DFU patients who were attending to Dr. Hasan Sadikin Hospital Bandung, Indonesia.

Various risk factors have been identified in previous studies. Such variability might be due to the variations in the study designs as well as differences in the genetic profile and cultural features of the populations studied. In addition, inequalities in access to health care are also common among different populations. In our study, the analysis showed that four items were risk factors for LEA.

In our research finding, most of DM patients with DFU were females (72.6%) when compare with males (27.4%) and similar results shown in most of studies done among DFU patients. A study conducted by Khan et al. revealed that the prevalence was significantly higher among the females than the males.[12] This finding may due to more female participation for the study than males.

About 30.7% of patients older than 50 years old underwent amputation surgery in comparison to 25.5% of patients younger than 50 years old. In this study, age was not found to be an important prognostic factor for amputation among DFU patients (p = 0.327). This result is in contrast to studies conducted in Singapore, where Aziz et al. showed that patients older than age 60 years were found to be a significant predictive factor for limb loss.[13] Our findings could be due to the differences in the age variable. The conceptualization of the role of the age variable which we have proposed, however, based on the evaluation of the mean age of the population.

Type 2 DM has traditionally been considered a disease affecting elderly patients. In recent years, however, type 2 DM has become increasingly common in children, adolescents, and young adults, particularly associated with obesity and bad lifestyle. In this study, approximately 38.5% of patients with DM diagnosed before age 50 years underwent major amputation, in comparison with 24.3% of those diag-

Table 1. Prognostic factors for amputation need

Risk factor	Amputation		Unadjusted		Adjusted	
	Yes, n (%)	No, n (%)	OR (95% CI)	p	OR (95% CI)	p
Age > 50 years	6 (25.5)	28 (74.5)	0.7 (0.3–1.5)	0.327	—	—
Onset age of DM < 50 years	4 (38.5)	15 (61.5)	1.9 (0.8–5.0)	0.167	—	—
ABI < 0.8	13 (38.2)	8 (61.8)	9.8 (2.2–44.6)	0.001	17.9 (2.8–139.6)	0.003
Neuropathy	12 (58.8)	14 (41.2)	7.7 (2.9–20.6)	0.001	5.6 (1.7–18.7)	0.005
HbA1C > 8.0%	11 (42.1)	49 (57.9)	3.1 (1.2–7.5)	0.014	4.7 (1.3–16.8)	0.016
WBC > 15,000/mm^3	9 (22.5)	31 (77.5)	1.0 (0.6–3.4)	0.449	—	—
CRP > 5 mg/dL	13 (44.8)	16 (55.2)	3.1 (1.2–8.0)	0.001	No significance	—

ABI: ankle brachial index; CI: confidence interval; CRP: C-reactive protein; DM: diabetes mellitus; HbA1C: hemoglobin A1C; OR: odds ratio; WBC: white blood cell.

nosed after age 50 years who had major amputation. Onset of DM was not found to be a significant factor in predicting limb loss (p = 0.167), opposite to findings by Yusof et al.[14] This differences may due to the lack of awareness, poor communication, and poor education of the patients that often lead to worsening of the ulcers. However, several studies have convincingly shown that young-onset type 2 DM is associated with an extremely adverse metabolic profile and poor long-term outcomes.

ABI less than 0.8 indicates the presence of vasculopathy and is associated with increased mortality, morbidity, and hospitalization. The ABI is a reproducible, non-invasive index used to screen and detect vasculopathy. About 38.2% of patients with ABI < 0.8 underwent LEA, in comparison with 6.3% of patients with ABI ≥ 0.8 who had LEA. The ABI < 0.8 was found to be highly significant as a prognostic risk factor for LEA (p = 0.001). Calcification of the arterial tunica media can falsely elevate the ABI in DM patients. Sharma et al.[15] and Ho and Shanahan[16] found that medial arterial calcification is associated with the increasing risk of ulceration, charcot arthropathy, and mortality in DM patients.

The presence of sensory neuropathy was assessed with Semmes-Weinstein monofilament test. Capability to locate seven or less sites out of a total of 10 sites indicated the presence of peripheral neuropathy. LEA occurred in 58.5% of patients with sensory neuropathy. Numbness in the feet due to nerve damage in diabetic neuropathy can make people less aware of injuries and foot ulcers. These ulcers may fail to heal, which can in turn lead to serious infections. Neuropathy was found to be highly significant in predicting LEA (p = 0.001). Neuropathy is commonly regarded as a main factor that predisposes DFU patients to limb loss, as shown by Nongmaithem et al.[17]

Glycosylated hemoglobin and serum inflammatory markers such as CRP and WBC counts have been used for the diagnosis of foot infections in patients with DM. Limb loss occurred in 42.1% of patients with HbA1C > 8.0%. This study showed that HbA1C was found to be a prognostic risk factor for LEA in DFU patients (p = 0.001). Poor glycemic control had a major role in the development of LEA and this finding is similar to several other studies reported by Pemayun et al.,[18] Sun et al.,[19] and Zhou et al.[20]

Acute phase reactants, including WBC counts and CRP are markers of inflammation that are elevated in response to inflammation, tissue injury, and infections. Diabetic foot infections are associated with high morbidity. About 22.5% of patients with WBC counts ≥ 15,000 mm^3 underwent LEA, in comparison with 15.1% of patients with WBC < 15.000 mm^3 who had LEA. High WBC count was reported as a risk factor of amputation,[19] although WBC was not found to be a predictive risk factor in this study (p = 0.449). Lower limb amputation also occurred in 44.8% of patients who had a CRP > 5 mg/dL was found to be a highly significant prognostic factor for limb loss (p = 0.001). CRP provides a direct index of acute inflammatory process and 91.4% of total amputees had elevated CRP levels. This finding is similar to Sun et al.[19] and Surana and Kasper.[21]

There are several limitations in this study including its retrospective design, small population, and single-centre site. Because of the retrospective design of the study, some important clinical characteristics were not completely recorded. Therefore, we identified only the single most important underlying risk factor with the complete data. Another important risk factors such as smoking and the presence of nephropathy could not be analyzed because there were no sufficient data. However, all the prognostic risk factors that analyzed in our study represent the general prognostic risk factors for amputation in DFU patients. Previous foot care procedures prior to hospitalization was also difficult to estimate. The specific type and duration of antibiotics for patients with infection were also not well documented. Prospective further study with large population and more variables was required.

Conclusions

DFU should be treated aggressively to prevent morbidity and mortality of the patient. We concluded that vasculopathy, neuropathy, high level of HbA1C were prognostic risk factors associated with amputation need in DFU patients. Based on the results of the current study, a prospective study of a large population should be conducted to test these clinical predictors and thereby decrease the need of amputation by the control of these risk factors.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.

2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4-14. doi:10.1016/j.diabres.2009.10.007
3. Mihardja L, Soetrisno U, Soegondo S. Prevalence and clinical profile of diabetes mellitus in productive aged urban Indonesians. *J Diabetes Investig* 2014;5:507-512. doi:10.1111/jdi.12177
4. Thewjitcharoen Y, Krittiyawong S, Porramatikul S, et al. Outcomes of hospitalized diabetic foot patients in a multi-disciplinary team setting: Thailand's experience. *J Clin Transl Endocrinol* 2014;1:187-191. doi:10.1016/j.jcte.2014.10.002
5. Ang Y, Yap CW, Saxena N, Lin LK, Heng BH. Diabetes-related lower extremity amputations in Singapore. *Proc Singapore Healthc* 2017;26:76-80. doi:10.1177/2010105816663521
6. Williams LH, Miller DR, Fincke G, et al. Depression and incident lower limb amputations in veterans with diabetes. *J Diabetes Complications* 2011;25:175-182. doi:10.1016/j.jdiacomp.2010.07.002
7. Brownrigg JRW, Hinchliffe RJ, Apelqvist J, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with foot ulcers in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016;32(Suppl 1):128-135. doi:10.1002/dmrr.2704
8. Fernando ME, Crowther RG, Pappas E, et al. Plantar pressure in diabetic peripheral neuropathy patients with active foot ulceration, previous ulceration and no history of ulceration: a meta-analysis of observational studies. *PLoS One* 2014;9:e99050. doi:10.1371/journal.pone.0099050
9. Pasqualini L, Schillaci G, Pirro M, et al. Prognostic value of low and high ankle-brachial index in hospitalized medical patients. *Eur J Intern Med* 2012;23:240-244. doi:10.1016/j.ejim.2011.09.004
10. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005;293:217-228. doi:10.1001/jama.293.2.217
11. Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations—a review of global variability in incidence. *Diabet Med* 2011;28:1144-1153. doi:10.1111/j.1464-5491.2011.03279.x
12. Khan AR, Al Abdul Lateef ZN, Fatima S, Al Yousuf SAA, Khan Afghan SZ, Al Marghani S. Prevalence of chronic complication among type 2 diabetics attending primary health care centers of Al Ahsa district of Saudi Arabia: a cross sectional survey. *Glob J Health Sci* 2014;6:245-253. doi:10.5539/gjhs.v6n4p245
13. Aziz Z, Lin WK, Nather A, Huak CY. Predictive factors for lower extremity amputations in diabetic foot infections. *Diabet Foot Ankle* 2011;2:7463. doi:10.3402/dfa.v2i0.7463
14. Yusof NM, Rahman JA, Zulkifly AH, et al. Predictors of major lower limb amputation among type II diabetic patients admitted for diabetic foot problems. *Singapore Med J* 2015;56:626-631. doi:10.11622/smedj.2015172
15. Sharma A, Scammell BE, Fairbairn KJ, Seagrave MJ, Game FL, Jeffcoate WJ. Prevalence of calcification in the pedal arteries in diabetes complicated by foot disease. *Diabetes Care* 2010;33:e66. doi:10.2337/dc09-2185
16. Ho CY, Shanahan CM. Medial arterial calcification: an overlooked player in peripheral arterial disease. *Arterioscler Thromb Vasc Biol* 2016;36:1475-1482. doi:10.1161/ATVBAHA.116.306717
17. Nongmaithem M, Bawa APS, Pithwa AK, Bhatia SK, Singh G, Gooptu S. A study of risk factors and foot care behavior among diabetics. *J Family Med Prim Care* 2016;5:399-403. doi:10.4103/2249-4863.192340
18. Pemayun TGD, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital-based case–control study. *Diabet Foot Ankle* 2015;6:29629. doi:10.3402/dfa.v6.29629
19. Sun JH, Tsai JS, Huang CH, et al. Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner Classification. *Diabetes Res Clin Pract* 2012;95:358-363. doi:10.1016/j.diabres.2011.10.034
20. Zhou ZY, Liu YK, Chen HL, Yang HL, Liu F. HbA1c and lower extremity amputation risk in patients with diabetes: a meta-analysis. *Int J Low Extrem Wounds* 2015;14:168-177. doi:10.1177/1534734615593190
21. Surana NK, Kasper DL. Approach to the patient with an infectious disease. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine. Part 8 Infectious Diseases: Section 1 Basic Considerations in Infectious Diseases*. 19th ed. New York, NY: McGraw-Hill Education; 2015:761-764.