ORIGINAL ARTICLE

PROGNOSTIC FACTORS OF MAJOR AMPUTATION AMONG HOSPITALIZED DIABETIC FOOT PATIENTS IN A TERTIARY TEACHING HOSPITAL, MALAYSIA

Nor HakimahAbRahman[1],AnizaAbd. Aziz[2], Wan MohdZahiruddin W Mohammad[1] , Abdul NawfarSadagatullah[1],Wisam Abdul Kadder Yassin[2] , Zawawi Nordin[2]

1School of Medical Sciences, Health Campus, UniversitiSains Malaysia, 16150 KubangKerian, Kelantan, Malaysia , 2Faculty of Medicine, Medical Campus, Universiti Sultan ZainalAbidin, 20400, Kuala Terengganu, Malaysia

ABSTRACT

Diabetic foot ulcer is a major health care problem leading to hospitalization, morbidity, amputation and mortality in diabetic patients. The aim of this study is to determine the amputation-free probability and prognostic factors of major amputation among hospitalized diabetic foot patients in a tertiary teaching hospital in Malaysia. A retrospective record review study was conducted among 231 hospitalized diabetic foot patients in Hospital Universiti Sains Malaysia from 1st January 2007 until 31st December 2011 followed by 1 year follow up. Patients' medical records were retrieved and reviewed. Socio-demographic, clinical characteristics and amputation endpoint status were recorded. The duration of amputation-free time was measured from the date of being diagnosed as diabetic foot until the date of amputation.Simple and Multiple Cox regression were performed to determine the prognostic factors of major amputation. The patients' age ranged from 21 to 83, with mean (SD) was 56.9 (10.4) years. Majority were male (51.5%) and Malays (95.7%). The overall proportion of amputation due to diabetic foot was 88.7% which comprised of minor (76.6%) and major amputation (13.7%). The adjusted prognostic factors that were found to be significantly influence the risk of having major amputation among hospitalized diabetic foot patients in HUSM were age at diagnosed of DFU (Adjusted HR: 1.05, 95% CI: 1.00, 1.09, P=0.033), gender (Adjusted HR: 0.21, 95% CI: 0.07,0.66, P=0.007), duration of DM (Adjusted HR: 2.76, 95% CI: 1.25, 6.12, P=0.012), smoking status(Adjusted HR: 4.19, 95% CI: 1.12, 15.65, P=0.033) and status of DFU (Adjusted HR: 2.55, 95% CI: 1.10, 6.07, P=0.029). Older diabetic patients, female, having diabetes more than 10 years, smoker and recurrent DFU were at higher risk of major amputation.

Keywords: *diabetic foot ulcer, amputation-free time, major amputation, prognostic factors*

INTRODUCTION

Diabetes mellitus (DM) is a significant burden of health care due to its epidemic proportions and related end-organ damage[1]. The most alarming condition is the steady increase in type 2 DM, especially in developing countries including Malaysia. Globally, over 200 million people is estimated are suffering from DM and it was predicted that figure will reach to 366 million by 2030[1]. This prediction is due to population growth, aging, urbanization and increasing the prevalence of obesity and physical inactivity[2]. The National Health and Morbidity Survey (NHMS) revealed the increment of diabetis mellitus prevalence among Malaysian adults 30 years of age and above from 6.3% (1986) to 8.3% (1996) to 14.9% (2006)[3-5]. A newer statistics showed further increment by about 31% during 5 years extended from 2006 to 2011[6]. These numbers have been projected to increase sharply over the years[7].

Diabetic foot (DF) is one of the most common major endpoints among diabetic complications. Complications of DF have been reported to form 12% of all complication among diabetics who were admitted in the hospitals in Malaysia[8]. The incidence and prevalence of DF vary between countries, but the trend is consistently increasing[2]. Diabetic foot ulcer (DFU) is characterized by skin and tissue loss that extends into or through the dermis into deeper tissue. The main etiologic factors of foot ulceration are diabetic neuropathy and peripheral vascular disease. Other factors such as biomechanical abnormalities limited joint mobility and increased susceptibility to infection lead to foot ulcer[9]. The occurrence of foot ulcers in different populations were reported ranges from 2% to 10%[10-11]. An estimated 15% of patients with diabetes will develop a lower extremity ulcer during their disease[12-14].

Foot ulcers may become complicated by infection and / or gangrene. Ideally, incurable lower extremity infection and or gangrene are treated by amputation. Internationally, it is described that more than a million amputations conducted annually as a result of diabetes. It means that every 30 seconds a lower limb is lost due to diabetes somewhere in the world[15]. According to the Third National Health and Morbidity Survey in 2006, the prevalence of lower extremity amputation among patients with diabetes in Malaysia was 4.3%[5,16]. A survey done locally found that 66 % of the patients who undergone amputation were diabetic and related to diabetic

foot conditions, whereas 34% were not known to have diabetes mellitus[17]. In India, about 10.5% of their diabetic foot (DF) patients underwent major amputations [18].

The increasing global incidence of DM corresponds with rising in its disabling complications. Lower-extremity amputations among the most feared and cost intensive complications of diabetes. Approximately 25% of patients with diabetes will develop foot ulcer sometime during their lives and among them up to 2% of patients may already have undergone amputation[19]. Besides that, DF has a significant impact on the quality of life (QOL). For example, the restriction of movement associated with foot ulcers disturbs the patients' ability to accomplish simple, everyday tasks including relaxation events. Some studies reported that patients with DFUs had poorer QOL than those who had no diabetic complications[20].Diabetic foot problems adversely affect the patients' physical and mental health conditions[21].

Quantifying the prognosis of DF and its consequences is essential for rational management by the surgeon as well as planning and allocation of resources by health decision maker. Identifying the prognostic factors for DF amputation allows further recommendation for prevention of foot amputation among DF patients in a local setting. Necessary actions could be suggested based on the study findings to reduce and prevent the number of amputations among diabetics. Prevention of limb loss will maintain considerable diabetic patient's good quality of life. Thus, this study aims to identify the prognostic factors of major amputation among hospitalized diabetic foot patients in a tertiary hospital.

METHODOLOGY

A retrospective record review study was conducted among 231 hospitalized diabetic foot patients in Hospital UniversitiSains Malaysia (Hospital USM) from 1st January 2007 until 31st December 2011 followed by 1 year follow up. This study included patients who ever had foot ulcers in the past and the patients were followed up in Diabetic Clinic, Hospital USM for their diabetic management. Patients who died before amputation and had incomplete data records for the main variables of interest more than 30% were excluded from the study. Patients' were selected using simple random sampling and their medical records were retrieved from the record office. Socio-demographic, clinical characteristics and amputation endpoint status were recorded by a researcher into a standardized case report form. Major amputation was defined as amputation of the lower limb above the ankle in diabetic patients[22]. Minor amputation was defined as amputation of the lower limb below the ankle; most commonly involve toes in diabetic patients[22]. Concurrent diabetes complications during DF diagnosis were reported as documented in the medical folders by the attending medical officer or physician. The variables included hypertension, hyperlipidemia, diabetic nephropathy, heart disease, stroke, retinopathy, peripheral vascular disease (PVD) and neuropathy.

The duration of amputation-free time was measured from the date of being diagnosed as diabetic foot until the date of amputation. Simple and Multiple Cox Proportional Hazard regression were performed to determine the significant prognostic factors of major amputation. The event for the Cox regression analysis was major amputation and the censored were minor amputations, observations not amputated and lost to follow-up at the end of the study. The variables chosen for the Cox Regression analysis were based on literature and their clinical importance. The analyses were performed using SPSS version 20.0.

RESULTS

Two hundred and thirty one patients diagnosed with diabetic foot hospitalized in Hospital USM were included in this study. The amputation status of patient's during follow-up was summarized in Table 1. The main endpoint or event for the prognostic factors evaluation for this study was major amputation due to diabetic foot 28(12.1%). There were 203(87.9%) patients who did not experience the event (censored observations). Those in the censored observations were patient who undergo minor amputation (76.6%), patients who were not amputated at the end of study (6.1%), and those who were loss to follow-up (5.2%).

Table 1: Amputation status of subjects (n=231)

Amputation Status	Event n(%)	Censored n(%)	Total n(%)
Major amputation	28(100.0)[a]	-	**28(12.1)[c]**
Minor amputation	-	177(87.2%)[b]	**177(76.6)[c]**
Not amputated at the end of the study	-	14(6.9)[b]	**14(6.1)[c]**
Loss to follow up	-	12(5.9)[b]	**12(5.2)[c]**
Total	**28(12.1)[c]**	**203(87.9)[c]**	**231(100.0)[c]**

[a]*Percentage from total event*
[b]*Percentage from total censored*
[c]*Percentage from total subjects*

Descriptive statistics

The study respondents comprised of 119 male and 112 female; a total of 231 patients. Table 2 and 3 shows the socio-demographic and clinical

characteristics of the diabetic foot patients respectively. Male to female ratio was 1:1.06. The overall mean (SD) age was 56.9 (10.4) years. Most of the patients were Malays (95.2%). Out of 231 patients, 203(87.9%) of them were married, 17(7.4%) were widowed, 10(4.3%) were single and 1(0.5%) were divorced. Majority of the patients were unemployed 110(88.2%). Most of patients were having hypertension 178 (77.1%) , 47.6% having retinopathy, 35.1% having heart diseases, 8.2% having stroke, 40.1% having nephropathy, 15.2% neuropathy. There were 8(3.5%) patients have peripheral vascular disease. About 39% of our patient also had hyperlipidemia.Approximately more than half of the patients (81.4%) were non current smoker. Patients that had family history of diabetes mellitus 149(67.4%) were higher than patients who did not have family history of diabetes mellitus 72(32.6).

Table 2: Socio-demographics Characteristics of subjects (n=231)

Variables	Overall n(%)	Major Amputation n(%)	Censored n(%)
SOCIO-DEMOGRAPHIC			
Age at diagnosis (years)	56.9 (10.4)[a]		
Gender			
Female	5112(48.5)	19(17.0)	93(83.0)
Male	119(51.5)	9(7.6)	110(92.4)
Ethnicity			
Non Malay	10(4.3)	2(20.0)	8(80.0)
Malay	220(95.7)	26(11.8)	194(88.2)
Marital Status			
Single	10(4.3)	0(0.0)	10(100.0)
Married	203(87.9)	24(11.8)	179(88.2)
Widowed	18(7.8)	4(22.2)	14(77.8)
Occupation			
Unemployed	110(50.2)	13(11.8)	97(88.2)
Self employed	74(33.8)	12(16.2)	62(83.8)
Government sector	26(11.9)	1(3.9)	25(96.2)
Private sector	9(4.1)	0(0.0)	9(100.0)
CLINICAL			
Type of diabetes			
Type I	1(0.4)	0(0.0)	1(100.0)
Type II	230(99.6)	28(12.2)	202(87.8)
Family history of DM			
Yes	149(67.4)	20(13.4)	129(86.6)
No	72(32.6)	7(9.7)	65(90.3)
Duration of DM			
< 10 years	124(53.7)	10(8.1)	114(91.9)
≥ 10 years	107(46.3)	18(16.8)	89(83.2)
Smoking status			
Non current smoker	184(81.4)	22(11.96)	162(88.04)
Current smoker	42(18.6)	6(14.29)	36(85.71)
Insulin at diagnosis			
Yes	111(50.0)	16(14.4)	95(85.6)
No	111(50.0)	10(9.0)	101(91.0)
HbA1c			
Normal (less than 6.5%)	15(6.9)	2(13.3)	13(86.7)
Abnormal (more/equal 6.5%)	203(93.1)	24(11.8)	179(88.2)
Total Cholesterol			
Normal	131(74.9)	11(8.4)	120(91.6)
Abnormal	44(25.1)	5(11.4)	39(88.6)

[a]*Mean (SD)*

Table 3: Co-morbidity and complication of subjects (n=231)

Variables	Overall n(%)	Major Amputation n(%)	Censored n(%)
CO-MORBIDITY			
Hypertension			
Yes	178(77.1)	25(14.0)	153(86.0)
No	53(22.9)	3(5.7)	50(94.3)
Hyperlipidemia			
Yes	90(39.0)	9(10.0)	81(90.0)
No	141(61.0)	19(13.5)	122(86.5)
COMPLICATION			
Heart disease			
Yes	81(35.1)	9(11.1)	72(88.9)
No	150(64.9)	19(12.7)	131(87.3)
Stroke			
Yes	19(8.2)	3(15.8)	16(84.2)
No	212(91.8)	25(11.8)	187(88.2)
Peripheral vascular disease			
Yes	8(3.5)	1(12.5)	7(87.5)
No	223(96.5)	27(12.1)	196(87.9)
Nephropathy			
Yes	93(40.1)	13(14.0)	80(86.0)
No	138(59.9)	15(10.9)	123(89.1)
Neuropathy			
Yes	35(15.2)	4(11.4)	31(88.6)
No	196(84.8)	24(12.2)	172(87.8)
Retinopathy			
Yes	110(47.6)	15(13.6)	95(86.4)
No	121(52.4)	13(10.7)	108(89.3)

Prognostic factors of major amputation among diabetic patients

The final model of the prognostic factors for major amputation among hospitalized diabetic foot patients in Hospital USM is shown in Table 4. Those diabetic foot patients at older age, female, having diabetes more than 10 years, currently smoke and had history of DF were at higher risk of major amputation.

DISCUSSION

The present study described the risk of having major amputation among hospitalized DF patients. There were a number of studies that assessed the prognosis of amputation (either major, minor or overall amputation) among diabetic foot patients and its related factors. However, majority of the study took major amputation as their main endpoint or event to be studied[22]. Major amputation leads to a more disabling condition than those who experience minor amputation. It leads to significant physical disability and emotional disturbance as it affect larger limbs as compared with amputation of toes only. Hence, this study explored the possible factors influence the major amputation for prevention strategy.

The prevalence of diabetic complications in current study population was higher compared to other local study. The Diabcare 2008 study in Malaysia revealed the prevalence of myocardial infarction and angioplasty were 5.5% and 7.1% respectively[23]. Cerebral stroke was reported at 3.4%, absent foot pulse was 2.7%, microabuminuria was 10.2% and non -proliferative diabetic retinopathy was 16.3%[23]. Hence, it was observed that the present study was reviewing a group of patients who at higher rate of particularly macrovascular diabetic complications. Nevertheless, none of the above mentioned complications showed significant increase risk of major amputation. In contrast, the prevalence of neuropathy, hypertension and hyperlipidemia in the present respondents were lower than in Diabcare 2008 group; 15.2% vs 24.1%, 77.1% vs 80.3% and 39% vs 96.1% respectively[23].

Table 4: Prognostic factors of hospitalized diabetic foot patients for major amputation in Hospital USM by Simple and Multivariable Cox Proportional Hazard Regression Model (n=231)

Variables	Simple Cox Regression			Multivariable Cox Regression		
	b[a] (SE)[b]	Crude HR[c] (95% CI)	*P* value[d]	b[a] (SE)[b]	Adjusted HR[e] (95% CI)	*P* value[f]
Age at diagnosis	0.03 (0.02)	1.04 (1.00,1.07)	**0.058**	0.04 (0.02)	1.05 (1.00,1.09)	**0.033**
Gender						
Male	-	1	-		1	-
Female	0.89 (0.40)	2.44 (1.10,5.40)	**0.027**	1.56 (0.58)	4.77 (1.52,14.96)	**0.007**
Duration of DM						
< 10 years	-	1	-		1	-
≥ 10 years	0.78 (0.39)	2.18(1.01, 4.72)	**0.048**	1.02 (0.41)	2.76 (1.25,6.12)	**0.012**
Smoking status						
Non smoker	-	1	-		1	-
Smoker	0.25 (0.46)	1.28(0.52, 3.17)	0.588	1.43 (0.67)	4.19 (1.12, 15.65)	**0.033**
Status of DF						
New		1	-		1	-
Recurrent	0.69 (0.42)	2.00(0.88,4.54)	0.099	0.95 (0.43)	2.59 (1.10, 6.07)	**0.029**

CI Confidence Interval
[a] Coefficient regression [b] Standard error
[c]Crude Hazard ratio of Simple Cox Hazard Regression
[d]p value of Wald statistic in Simple Cox Proportional Hazard Regression
[e]Adjusted Hazard Ratio of Multiple Cox Proportional Hazard Regression
[f]p value of Wald statistic in Multiple Cox Proportional Hazard Regression
Two-way interactions and multicollinearity were checked and not found.
Log-minus-log plot, hazard function plot and schoenfeld residuals were applied to check for the model assumption.

Prognostic Factors of Major Amputation among Hospitalized Diabetic Foot Patients

The adjusted prognostic factors that determine the risk of major amputation in DF patients found in this study were older age at diagnosed DF, being female, longer duration of DM, smoking, and recurrence of DF. Generally, these variables which were identified as being associated with major amputation were consistent as those reported by other comparable observational study[24].

Older DF patients in the present study had higher risk of major amputation compared to younger DF patients. Several studies reported significant difference of age at diagnosed DF[24, 25]. Their older age patients (aged 50 years old above) were at higher risk to have overall (major and minor) amputation. Approximately 30% of all patients with DM aged older than 50 years have some degree of lower-limb sensory neuropathy. It is also well known that older diabetic patients have longer DM duration with more complications.

The Fremantle Diabetes study showed that patients requiring amputation had longer durations of diabetes with worse glycaemic control and higher systolic blood pressure. These patients were also more likely to have nephropathy, neuropathy, retinopathy, peripheral arterial disease and cardiovascular disease[26]. Majority of the studies demonstrated patients with longer duration of DM (more than 10 years) were at increased risk to undergo major amputation[27]. These findings support our results that those having diabetes for more than 10 years were almost three times likely to end up with major amputation.

Smoking status and recurrence status were also significant prognostic factors in the present study. A similar result was revealed by a previous study that the DF patients who smoke had significantly increased their risk of amputation by four to five times [28]. It is well documented that cigarette smoking increases risk of peripheral arterial disease (PAD) which delay wound healing in diabetics. Patients who had recurrent DF had higher risk of amputation and this finding was similar with the findings [29-30] reported by Ghanassia*et. al* (2008) and Shojaiefard*et. al* (2008).

The influence of gender as a risk factor of major amputation was rarely reported. Otherwise, the effects of nephropathy, neuropathy and PVD on major amputation were consistently described in the recent studies[30-32]. However, this study did not found statistical significant association of these comorbidities with major amputation.

LIMITATION OF THE STUDY

A number of limitations of our methodology and result were those related to any retrospective study. Missing values was a problem that had to be faced and in handling secondary data. However, the sample size still achieved acceptable final required power of study. Patients with incomplete data on prognostic factors were excluded from the analysis. The excluded group may have a worse prognosis and this may have resulted in an underestimation of the potential confounders during this study and had a tendency for bias in our results with regards to prognostic factors. Even though obesity had been reported as a significant prognostic factor in previous studies, this variable was not included for analysis in this study since the information of weight and height were difficult to obtain because it is not written in more than half of the patients' medical records. Others variable that were not included in the study were level of education and household income. Samples were based on patients who were admitted to hospital. Therefore, it will lead to hospital bias and there are possibility that the results from the study could not be used to infer to the populations.

CONCLUSION AND RECOMMENDATION

Older diabetic patients, female, having diabetes more than 10 years, smoker and recurrent DF were at higher risk of major amputation.
DF was found to be related to increased re-ulceration rate and lifelong disability. Thus, multidisciplinary approach including preventive strategy such as tight glycaemic control, smoking cessation, proper footwear, patient and staff education, and treatment of foot ulcers are the recommended strategies to reduce foot ulcers and the amputation rate. An emphasis on the importance of early detection of DF by increasing public awareness and the formulation of a better screening program may help to increase amputation-free time.

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