ORIGINAL ARTICLE

RETROSPECTIVE STUDY OF PREDICTORS FOR FOOT ULCERATION AMONG DIABETIC PATIENTS ATTENDING KUALA LANGAT HEALTH CENTRE FROM 1999 TO 2008

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ABSTRACT

Background : Foot ulcers and its complications are an important cause of morbidity and mortality in diabetes. The aim of this retrospective study is to determine the ulcer-free survival in diabetic foot and its relevant predictors in a cohort of diabetic patients in the primary health care setting.

Methods : Data of newly diagnosed diabetics (n=1121) who received treatment in five health centers in the district of Kuala Langat, Selangor between 1st January 1999 until the 30th June 2008 were studied. Information was gathered by reviewing patient's medical records. All patients were followed until 31st December 2008. The duration of ulcer-free survival was measured from the date of being diagnosed as diabetic until the development of the ulcer.

Results : The total incidence of diabetic foot ulcer was 9.9% (n=111), with an average annual incidence of 1%. The total incidence of amputation was 1.2%. Mean age of being diagnosed having diabetic was 52±10.7 year old and mean age of being diagnosed having diabetic foot ulcer was 54.68±10.16 year old. The mean for overall ulcer-free survival was 99 months (95%CI:96-102). Male gender (LR=6.56; p=0.01), smokers (LR=3.94; p=0.04), low body mass index (LR=4.45; p=0.03), impaired renal function (LR=5.17; p=0.02) and long duration between follow-up (LR=25.10; p<0.0005) predicted the ulcer-free survival. However, with Cox's Proportional Hazard Regression analysis factors independently associated to ulcer-free survival were impaired renal function (HR=1.65)(95%CI:1.09,2.46), poor lipid control (HR=2.36)(95%CI:1.03, 5.41) and duration of follow-up more than six months (HR=4.74)(95%CI:2.28,9.86). Other factors studied were not significant.

Conclusion : In conclusion, about 1% of primary care health center-based diabetic patients developed new ulcers each year. Renal profile and lipid profile can be used as a predictor to ulcer-free survival for diabetic foot ulcer in the primary health care setting. All patients must be given the appropriate duration of follow-up which should not exceed more than six months with emphasis on defaulter tracing to increase the number of patients free from diabetic foot ulcer.

Keywords : Diabetic Foot Ulcer, Ulcer-Free Survival, Primary Health Care, Malaysia.

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INTRODUCTION

Foot ulcers and their complications are another important cause of morbidity and mortality in diabetes. It is also associated with infection that leads to tissue necrosis and end-up with amputation[1]. Clinical studies have consistently identified measures of peripheral neuropathy as predicting diabetic foot ulceration, with some evidence for other association such as peripheral vascular disease, limited joint mobility, foot deformities, duration of diabetes, improper foot wear, trauma, injury due to self treatment, fissure, poor hygiene and infection[2,3,4].

The yearly incidence of diabetic foot ulcer is 1-4% and the prevalence is 4-15%[3,5,6]. The lifetime prevalence of amputation in diabetes is about 6-43% which is 10-20 times higher than community without diabetes[7]. This is due to the non-healing ulcer, where the rates of recurrence are very high[8]. This type of patients has a high mortality following amputation, ranging between 39% and 80% within 5 years[5]. However, compliance and simple preventive foot care program in primary health care center reduces the incidence of diabetic foot ulcer[9] and thus reduces the risk of amputation and death following these complications.

Most research focuses on specific groups of diabetic patients. Indeed such studies are invariably case-controlled in design, or if prospective analyses, assess relatively small, clinic base groups of patients subject to selection bias[1,8]. Relevant risk factors for foot ulceration and their ulcer-free survival in diabetic patients receiving care in community health centers have not yet been determined in Malaysia, even though these are the diabetic patients who are, or should be, screened by family medicine specialist, medical and health officers, medical assistant and practice nurses.

In this retrospective study, a large cohort of diabetic patients receiving health care in Kuala Langat health centers were studied to determine the baseline of yearly incidence of foot ulceration and the predictor of ulcer-free survival.

METHODS

All patients diagnosed with Type 1 or Type 2 diabetes according to World Health Organization (WHO) criteria between 1st January 1999 and 30th June 2008 were targets in five health care centers of Sijangkang, Telok Datok, Kg. Bandar, Bukit Changgang and Jenjarom of Kuala Langat, Selangor. Information was gathered by reviewing patient's diabetic record book (green book) and outpatient records. Direct discussions with clinic health officers were held when any doubts occur. Otherwise, a telephone call or direct interview was used to confirm any information with patients or their family members.

At baseline, all cases were screened to determine the date of diabetes diagnosis. All cases diagnosed from 1st January 1999 to 30th June 2008 (inclusion period) and of Malaysian nationality were short listed. Cases that fulfilled the exclusion criteria were withdrawn. The exclusion criteria were patient, who already developed foot ulcer upon being diagnosed as diabetic, ever had foot ulcers in the past or had undergone amputation at any level due to any cause. Cases were censored if they died, lost to follow-up during the study period or did not develop foot ulcer before the study end.

All patients were followed-up until 31st December 2008. The duration of ulcer-free survival was measured from the date of being diagnosed as diabetic until the foot ulcer developed. The definition of ulcer in this study was any full thickness skin defect at least class I Megitt Wagner classification that required more than two weeks for healing[3]. Ulcer presentation was determined from the statement in patient's diabetic book records. The actual date of diagnosis either for diabetes or foot ulcer was noted. Nevertheless, the appointment date was choose if there was no actual date recorded with assumption that the ulcer was developed between the appointments.

Risk factors identified were recorded for all selected cases. Demographic and lifestyle characteristic include treatment center, age at being diagnosed diabetes, gender, ethnicity, level of education, marital status and smoking status. Other factors studied were presence of hypertension, presence of cardiovascular disease, body mass index (BMI), glycaemic control (HbA1c or fasting blood sugar), lipid control, renal function, statin use, ulcer etiology (presence of neuropathy, ischemia or neuroischemia) and duration between follow-up.

Age was categorized into three groups: less than 30, 30-65 and 65 or older. Three major ethnic groups in Malaysia were taken into account which was Malays/ Bumiputra, Chinese and Indian/ Sikh. BMI was calculated by dividing weight (measured in kilograms) by the square of height (measured in meters) and was further categorized into non obese and obese. A respondent was considered obese if BMI was

27.5kg/m^2 and higher. Parameter for diabetic monitoring was categorized according to clinical practice guidelines by Ministry of Health Malaysia (Table 1). Ethical approval was obtained from the research ethics committee National University of Malaysia (UKM) and National Institute of Health Malaysia. This study also registered to the National Medical Research Registry (NMRR) of Malaysia.

Table 1 Parameter for diabetic monitoring in Malaysia

	Category	
	Normal	**Abnormal**
1. Glycaemic Control		
HbAIc	<6.5%	≥6.5%
Fasting Blood Glucose	4.4-6.1mmol/L	>6.1mmol/L
Random Glucose	4.4-8.0mmol/L	>4.4-8.0mmol/L
2. Lipid		
Cholesterol total	<4.5mmol/L	≥4.5mmol/L
Triglyseride	≤1.7mmol/L	>1.7mmol/L
HDL	≥1.1mmol/L	<1.1mmol/L
LDL	≤2.6mmol/L	>2.6mmol/L
3. Body Mass Index	<23kg/m^2	≥23kg/m^2
4. Renal Function		
Macro/microalbuminuria	-ve	+ve
Serum Urea	2.5-6.7mmol/L	>6.7mmol/L
Serum Creatinine	70-150umol/L	>150umol/L

Source: Ministry of Health Malaysia 2004

Statistical Analysis

Data were analyzed using the SPSS version 12.0. The relationship between baseline variables and incidence of new diabetic foot ulceration was assessed by Kaplan-Meier Survival Curve for each variable separately. The 10-year ulcer-free survival rates were also determined using the Kaplan-Meier survival curve. The equality of survivor functions of the different groups was tested using the Log Rank test. Then, Cox's Proportional Hazard Regression analysis was carried out for variables that gave a p value less or equal to 0.1 with Kaplan-Meier Log Rank test to determine the subset of independent predictors and the hazard ratio of developing foot ulcers.

RESULTS

A total of 4288 diabetic patients' medical records were screened from five health centre in Kuala Langat District of Selangor. Then 1258 cases which diagnosed and registered as diabetics from 1st January 1999 until 30th June 2008 were selected. A total of 137 were dropped according to the exclusion criteria; i) there is a foot ulcer upon diagnosis, ii) ever had diagnosed foot ulcer previously or iii) patient had undergone amputation of any cause. At the end only 1121 cases were selected as respondent.

Jenjarom Health Centre contributed the largest number of diabetic patients diagnosed during the inclusion period which was 350 cases (29%). This was followed by Telok Datok with 323 cases (29%), Kg. Bandar with 198 cases (18%), Bukit Changgang with 145 cases (13%) and the least, Sijangkang with 125 cases (11%). Majority of the respondent, 94.9% (n=1064) were on oral hypoglycemic agent (OHA), whereas only 5.1% (n=57) were prescribed insulin or combination of both insulin and OHA.

Baseline characteristic and other variables were given in table 2. Of the 1121 respondents, 58.2% (n=652) were female and 41.8% (n=469) were male. Diagnosis of diabetes were more common at the age of 30 to 65 year old (86.8%; n=973), followed by aged above 65 year old (11.6%; n=130) and aged below 30 year old (1.6%; n=18). Mean age at being diagnosed having diabetic was 52±10.7 year old. The youngest was 18 year old and the eldest was 85 year old. Meanwhile, the mean age of being diagnosed having diabetic foot ulcer was 54.68±10.16 year old. The youngest was 29 year old and the eldest was 85 year old.

Of the respondents in this study, 61.8% (n=693) were Malays/ Bumiputra, 24.3% (n=272) were Indian/ Sikh and 13.9% (n=156) were Chinese. Main ethnic in most of the health centre were Malays/ Bumiputra. In Telok Datok Health Centre, Indian ethnicity (47.7%; n=154) was more than Malays/ Bumiputra (42.7%; n=138) and Chinese (9.6%; n=31). Whereas in Jenjarom Health Centre, the Chinese ethnicity (32.7%; n=108) was more than Indian/ Sikh (24.5%; n=81).

In terms of highest formal education level, 55.8% (n=626) had achieved secondary school, 27.4% (n=307) had primary or no formal education and 13.2% (n=148) had enter or completed tertiary education. Of all respondents, 91.7% (n=1016) were married and 8.3% (n=92) were single.

The total incidence of diabetic foot ulcer within 10 years in the district was 9.9% (n=111), with an average annual incidence of 1%. Meanwhile, the total incidence of amputation was 1.2%, in which 12.6% from overall patients who developed foot ulcers. Patients start to developed ulcer less than 6 months after being diagnosed as diabetics. The mean for overall ulcer-free survival was 99 months (95%CI:96,102). Figure 1 shows the cumulative ulcer-free survival within 10 year after diabetes had been diagnosed. There were more diabetics developed foot ulcers after eight years as compared to the earlier year.

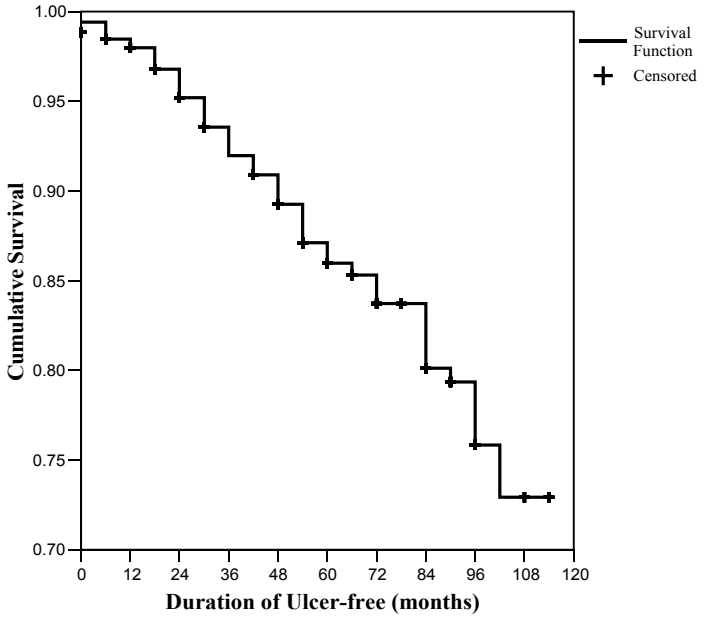

Figure 1 Overall ulcer-free survival in 10 years

Table 2 presents the detailed information on respondent characteristics and their association with the diabetic foot ulcer development. The prevalence of foot ulcer among male (12.4%) were higher than female (8.1%) although there were more female than male in this study (χ^2=5.49; p=0.02). The ages at being diagnosed as neither diabetics nor foot ulcers were not different, as well as glycaemic control. However, female body mass index were found to be higher than male which was 28.49$\pm$5.22 kg/m^2 and 27.31$\pm$4.71 kg/m^2 respectively.

Table 2 Distribution of patients according to sociodemography, behaviour, co-morbidity and treatment

Variables	Patients with diabetic foot ulcers No. of samples (n)	%	Patients without diabetic foot ulcers No. of samples (n)	%	Total (n)	Chi Square (χ^2)	P value
1. Health Centre							
Sijangkang	12	9.6	113	90.4	125	1.67	0.79
Telok Datok	28	8.7	295	91.3	323		
Kg. Bandar	19	9.6	179	90.4	198		
Bukit Changgang	18	12.4	127	87.6	145		
Jenjarom	34	10.3	296	89.7	330		
(n=1121)							
2. Gender							
Male	58	12.4	411	87.6	469	**5.49**	**0.02**
Female	53	8.1	599	91.9	652		
(n=1121)							
3. Age at being diagnosed diabetes							
≤ 65 year old	100	10.1	891	89.9	991	0.34	0.56
> 65 year old	11	8.5	119	91.5	130		
(n=1121)							
4. Ethnicity							
Malays/ Bumiputra	42	9.0	424	91.0	466	5.55	0.06
Chinese	31	11.1	249	88.9	280		
Indian/ Sikh	38	10.1	337	89.9	375		
(n=1121)							
5. Formal Education							
Nil/ Primary	37	12.1	270	87.9	307	2.88	0.24
Secondary	54	8.6	572	91.4	627		
Tertiary	16	10.7	133	89.3	149		
(n=1083)							
6. Marital Status							
Married	103	10.1	913	89.9	1016	0.61	0.79
Unmarried	8	8.7	84	91.3	92		
(n=1108)							
7. Smoking Status							
Smoker	36	12.2	259	87.8	295	2.94	0.09
Non Smoker	70	8.8	730	91.3	800		
(n=1095)							

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8. Co-Morbidity							
Hypertension							
Yes	60	9.2	589	90.8	649	0.75	0.39
No	51	10.8	421	89.2	472		
(n=1121)							
Cardiovascular Dis.							
Yes	24	14.5	141	85.5	165	**4.68**	**0.03**
No	87	9.1	869	90.9	956		
(n=1121)							
9. Parameter of Diabetic Control							
Glycaemic Control							
Normal	22	7.7	265	92.3	285	2.16	0.14
Abnormal	89	10.7	745	89.3	836		
(n=1121)							
Body Mass Index							
Non Obese	61	12.1	445	87.9	506	**4.81**	**0.03**
Obese	39	7.9	455	92.1	494		
(n=1000)							
Lipid Profile							
Normal	7	5.5	120	94.5	127	3.04	0.08
Abnormal	98	10.4	842	89.6	940		
(n=1067)							
Renal Function							
Normal	43	7.3	549	92.7	592	**10.19**	**0.01**
Abnormal	64	13.1	425	86.9	489		
(1081)							
10. Duration Between Follow-up							
< 3 months	3	11.3	417	88.7	470	**22.63**	**<0.0005**
3-6 months	47	7.7	569	92.3	616		
>6 months	11	31.4	24	68.6	35		
(n=1121)							
11. Foot Ulcer Aetiology	45	14.4	273	85.6	319	3.92	0.14
Neuropathy	1	10.0	9	90.0	10		
Ischemia	6	30.0	14	70.0	20		
Neuroischemia							
(n=349)							
12. Statin Group User							
Yes	37	8.8	384	91.2	421	0.89	0.34
No	74	10.6	626	89.4	700		
(n=1121)							

Male was having shorter time to develop foot ulcer after diagnosed being diabetic as compared to female. Their mean ulcer-free survival was 96 months (95%CI:92,100) and 102 months (95%CI:99,105) respectively, where the Log Rank (LR) was 6.46 and p-value of 0.01. Other sociodemographic factor such as place of treatment, aged at being diagnosed diabetes, ethnicity, levels of highest formal education, marital status and smoking status were not associated to the development of diabetic foot

ulcer. There was also no difference between groups of these risk factors on having a shorter time to developed foot ulcer.

However, those of Indian/ Sikh ethnicity were found to have diabetic and ulcer at an earlier age. The Indian/ Sikh were diagnosed as diabetic at the mean age of 49.10±10.98 year old. It was followed by the Malays/ Bumiputra with mean age 52.42±10.26 year old and Chinese with mean age 55.31±11.24 year old. The mean age of being diagnosed ulcer for Indian/ Sikh were 54.68±10.16 year old, followed by 54.85±9.76 year old for Malays/ Bumiputra and 61.15±8.6 year old for Chinese.

About 1095 records stated their smoking status, where 73.1% (n=800) were non smokers and 26.9% (n=295) were smokers. Of the 295 smokers, 60.9% (n=273) were males. Prevalence of smoking among female was only 3.4%. Smoking status alone was not associated with the development of diabetic foot ulcer. However, smokers were developed ulcers earlier than non smokers (Figure 2). The mean ulcer-free survival for smokers was 95 months (95%CI:90,101), whereas mean survival for non smokers was 101 months (95%CI:99,104) with Log Rank 3.94 and p-value of 0.04.

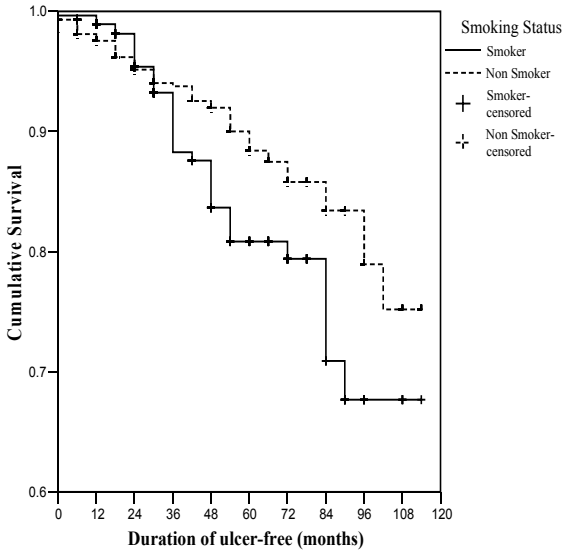

Figure 2 Diabetic-foot-ulcer-free survival according to smoking status

The presence of cardiovascular disease in diabetic patient had an association with the foot ulcer development (χ^2=4.68; p=0.03). Prevalence of ulcer in the presence of cardiovascular disease were 14.5%, whereas in the absence of cardiovascular disease the prevalence were much lower (9.1%). But, there was no difference between presence and absence of cardiovascular disease on having a shorter time to develop foot ulcer (LR=0.49; p=0.48). Mean ulcer-free survival in the presence of cardiovascular disease was 97 months (95%CI:91,103) and mean ulcer-free survival without cardiovascular disease was 100 months (95%CI:98,103).

Most of the respondents were overweight and obese. Mean BMI fall under obese category. Mean BMI for diabetics with ulcer was 27.06±5.35kg/m^2, whereas mean BMI for diabetics without ulcer was 28.09±4.99kg/m^2. There was also an association between body mass index and development of foot ulcer (χ^2=4.81; p=0.03). Non obese respondent was more prone to develop ulcer as compared to obese respondent, in which the prevalence of ulcer were 12.1% and 7.9% respectively. Non obese patient developed ulcer earlier than obese patients (LR=4.45; p=0.03). Mean ulcer-free survival for non obese was 96 months (95%CI:92,101) and mean ulcer-free survival for obese patients was 103 months (95%CI:100,106).

More than half respondents had uncontrolled blood lipid level. About 88.1% (n=940) unable to control their total cholesterol or triglyceride or both. There was only 11.9% (n=127) had a normal lipid level. Prevalence of ulcer among uncontrolled lipid level was 10.4%, whereas only 5.5% among

controlled lipid level (χ^2=3.04; p=0.08). Diabetics with uncontrolled lipid level developed ulcer faster (mean survival 99 months; (95%CI:96,102)) than diabetics with controlled lipid level (mean survival 107 months; (95%CI:102,112)) however it was not statistically significant (LR=3.06; p=0.08).

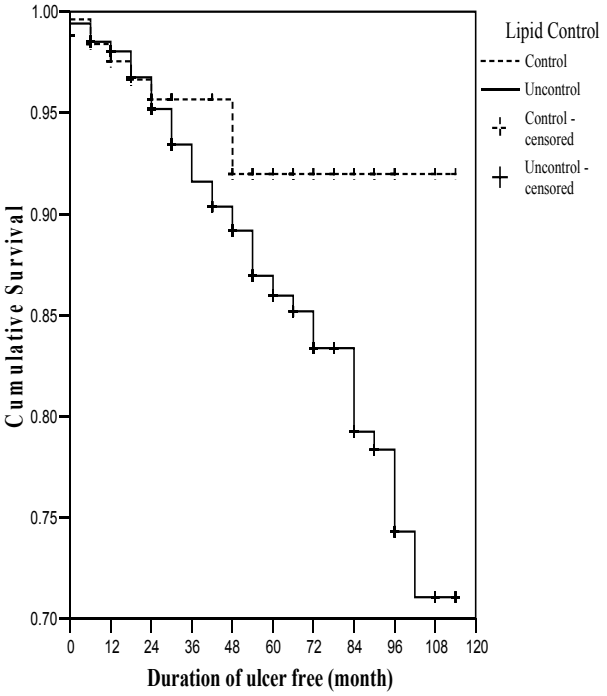

Figure 3 Diabetic-foot-ulcer-free survival according to lipid control

Among this respondent, 37.5% were using statin group for dyslipidemia treatment. Prevalence of ulcer among statin group user was 8.8% and 10.6% among non statin group user (χ^2=0.89; p=0.34). There was also no difference between this two groups in having shorter time to develop foot ulcer (LR=2.95; p=0.13). Mean ulcer-free survival for statin group user was 103 months (95%CI:99,106) and mean for non statin group user was 98 months (95%CI:94,101).

Many diabetics were having renal impairment (45.2%), abnormal urea, excess creatinine and albuminuria. There were significant association between renal function and development of foot ulcer (χ^2=10.19; p=0.001). Diabetics with renal impairment was prone to develop foot ulcer earlier as compared to diabetics without renal impairment (LR=5.17; p=0.02). Mean ulcer-free survival for patients with renal impairment was 97 months (95%CI:93,101), whereas 102 months (95%CI:99,106) in patients without renal impairment.

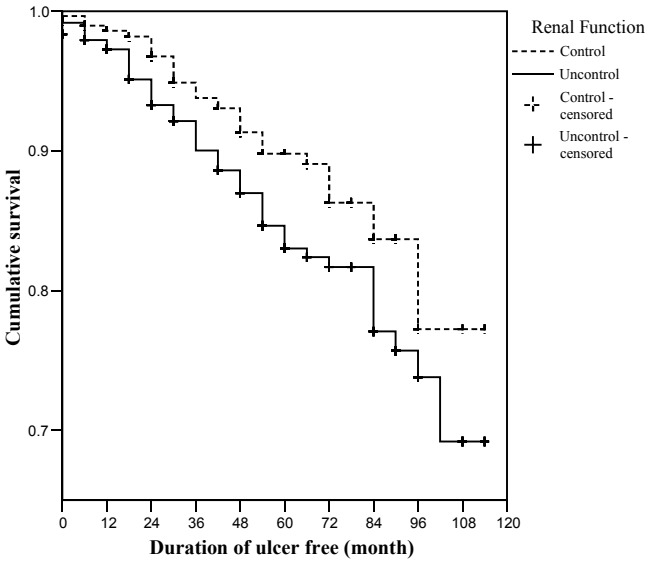

Figure 4 Diabetic foot ulcer-free survival according to renal function

Mean duration between follow-up among diabetics with ulcer found to be longer (3.16±2.65 months) as compared to diabetics without ulcer (2.84±1.44 months) and the difference was statistically significant (t=2.007; p=0.04). The prevalence of ulcer among patients with duration between follow-up more than six months was 31.4%, followed by duration between follow-up less than 3 months 11.3% and duration between follow-up 3-6 months 7.7%. This difference was also statistically significant (χ^2=22.63; p<0.0005).

Patient who had infrequent follow-up was having shorter time to develop foot ulcer. Within 5 year after diabetes diagnosis had been made, 50% of them developed ulcers. Mean ulcer-free survival among them was 62 months (95%CI:51,73) and median 60 months (95%CI:42,77). This was followed by the group with duration of follow-up less than 3 months with mean ulcer-free survival 97 months (95%CI:93,101) and the least was group with duration of follow-up three to six months with mean ulcer-free survival 103 months (95%CI:100,106) and these difference were statistically significant (LR=25.10; p<0.0005).

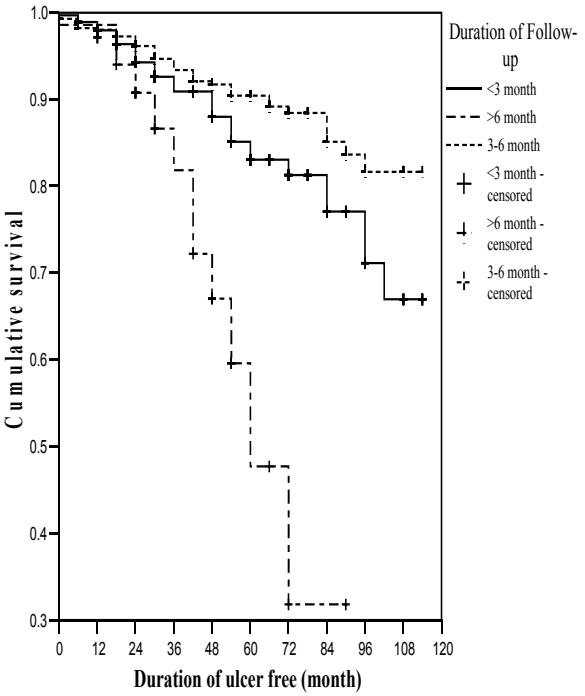

Figure 5 Diabetic-foot-ulcer-free survival according to duration of follow-up

The significant variables influencing ulcer-free survival were smoking status, body mass index, renal function and duration between follow-up. Six variables were entered into the Cox's Proportional Hazard model; including variables that give the p value less than 0.1 in the Kaplan-Meier Log Rank test which were gender and lipid control. The body mass index variable was not included as there was many missing data that might influence the results. Only 7.4% (83 cases) respondent will be dropped from the analysis if this variable not included. Whereas, it will increase to 17.3% (194 cases) if this variable included. The total number of cases included in the final model was 1038 (92.6%), where there were 101 of foot ulcer cases and 83.6% of censored cases.

Patients with duration of follow-up more than six months were 4.74 times (95%CI:2.28,9.86) faster from patients with duration of follow-up 3 to 6 months to develop diabetic foot ulcer ($p<0.005$). Patients with abnormal lipid profile will develop ulcer 2.36 times (95%CI:1.03,5.41) faster than patients with normal lipid profile ($p=0.04$). Diabetics with renal impairment were 1.65 times (95%CI:1.10,2.46) having shorter time to develop an ulcer as compared to the diabetics with normal renal function ($p=0.02$). Other factors; gender, smoking status, statin use and duration of follow-up less than 3 months were not the main predictor for the ulcer-free survival.

Table 3 Kaplan-Meier Log Rank Results

Variables	No. of Sample (N)	Diabetic Foot Ulcer Cases (n)	Survival Mean (95% CI)	Log Rank (LR)	P value
1. Health Centre:	1121	111	102 (99, 105)		
Sijangkang	125	12	96 (90,102)	4.02	0.40
Telok Datok	323	28	102 (98,106)		
Kg. Bandar	198	19	102 (96,107)		
Bkt Changgang	145	18	94 (86,102)		
Jenjaro	330	34	96 (91,102)		
2. Gender:	1121	111			
Male	469	58	96 (92,100)	**6.56**	***0.01**
Female	652	53	102 (99,105)		
3. Age at Diagnosis DM	1121	111			
≤65 year old	991	100	99 (96,102)	0.73	0.39
>65 year old	130	11	103 (97,109)		
4. Ethnicity:	1121	111			
Malays/ Bumiputra	466	42	100 (97,104)	0.97	0.61
Chinese	280	31	97 (92,103)		
Indian/ Sikh	375	38	100 (96,104)		
5. Formal Education	1083	106			
Nil/ Primary	307	37	98 (93,103)	1.33	0.51
Secondary	627	54	101 (97,104)		
Tertiary	149	16	98 (90,105)		
6. Marital Status	1108	111			
Married	92	8	96 (89,104)	0.01	0.91
Unmarried	1016	103	99 (97,102)		
7. Smoking Status	1095	106			
Smoker	295	36	95 (90,101)	**3.94**	***0.04**
Non Smoker	800	70	101 (99,104)		
8. Co-Morbidity Hypertension:	1121	111			
Yes	649	60	101 (97,104)	0.82	0.36
No	472	51	98 (94,102)		
Cardiovascular Dis.:	1121	111			
Yes	165	24	97 (91,103)	0.49	0.48
No	956	87	100 (98,103)		
9. Parameter of Control Diabetic	1121	111			
Glisemik Control:	285	22	102 (98,107)	1.35	0.25
Normal	836	89	99 (96,102)		
Abnormal					
Body Mass Index:	1000	100			
Non Obese	506	61	96 (92,101)	**4.45**	***0.03**
Obese	494	39	103 (100,106)		

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Lipid Profile:	1067	105			
Normal	127	7	107 (102,112)	3.06	0.08
Abnormal	940	98	99 (96,102)		
Renal Function:	1081	107			
Normal	592	43	102 (99,106)	**5.17**	***0.02**
Abnormal	489	64	97 (93,101)		
10. Duration Between Follow-up	1121	111			
<3 months	470	53	97 (93,101)	**25.10**	***<0.0005**
3-6 months	616	47	103 (100,106)		
>6 months	35	11	62 (51,73)		
11. Foot Ulcer Aetiology	348	52			
	319	46	96 (92,101)	4.13	0.13
Neuropathy	10	1	83 (71,96)		
Ischemia	20	6	81 (60,102)		
Neuroischemia					
12. Statin Group User	1121	111			
Yes	420	37	103 (99,106)	2.95	0.09
No	701	74	98 (94,101)		

There was no sign of colinearity effect that may increase or decrease the effect size; all standard error lies between 0.01 and 5.0, hazard ratio value for all predictors were not prominent and the matrix not showing any potential effect. The results of this analysis were shown in Table 4. Other factors studied were found to be not significant.

Table 4 The Cox's Proportional Hazard Regression Analysis Results

Variable	Standard Error	Hazard Ratio	95% Confidence Interval	P value
1. Gender				
Female		1.00		
Male	0.25	1.61	0.98-2.65	0.06
2. Smoking Status				
Non Smokers		1.00		
Smoker	0.27	1.09	0.65-1.86	0.73
3. Serum Lipid				
Normal		1.00		
Abnormal	0.42	2.36	1.03-5.41	***0.04**
4. Renal Function				
Normal		1.00		
Abnormal	0.21	1.65	1.02-2.34	***0.04**
5. Statin Group				
Yes		1.00		
No	0.21	1.40	0.92-2.13	0.11
6. Duration of Follow-up		1.00		
3-6 month	0.21	1.46	0.96-2.24	0.07
< 3 month	0.37	4.74	2.28-9.86	**<0.0005**
> 6 month				

DISCUSSION

The overall incidence and average annual incidence of diabetic foot ulceration in the diabetic cohort in 10 years was about 10% and 1% respectively. Prospective cohort estimation on the annual incidence of diabetic foot ulcers in England was 2.2%[3]. Similar incidence found in Netherlands which was 1.2-3.0%[12]. A retrospective cohort study of 8905 diabetic patients by Ramsey determined similar average annual incidence of foot ulceration (2%), whereas the incidence in a population-based sample of older-onset diabetic patients was higher (2.6%) [13].

The overall mean ulcer-free survival for diabetic patients in Kuala Langat was 8.3 years. This was similar to patients in Netherlands which was 8.9 years and their amputation-free survival was 10.2 years[12]. The strongest independent predictors for ulcer-free survival were abnormal lipid level, renal impairment and duration of follow-up more than 6 months.

Abnormal lipid profile is not the predictor for development of new foot ulceration but it speed-up the time for ulcer development by three times. Nearly 40% diabetics with abnormal lipid profile was using statin group to control dyslipidemia. Statin group use was only introduced about 7 to 8 years ago in the district. In this study, statin group found to reduce the risk for foot ulcer and maintain the state of ulcer-free longer. After 7 years of diabetes diagnosis, there were no more foot ulcer cases in statin group user. Nevertheless, the non statin group users were continuously developed foot ulcers. If we prolonged the study period, the results probably might become significant as the difference become more prominent.

Basically statin group will cause vasodilatation of the blood vessels and improve circulation especially to the vital organ and distal end[14,15]. Thus, reduce the risk of atherosclerosis, artery blockage and ischemia and indirectly reduce the risk of foot ulcer[16]. However, we were unable to demonstrate the temporal cause-effect association properly as the date of statin started in each users was not included in this study.

Almost half of the patients in Kuala Langat were having renal impairment, which was quite similar to American diabetics (40%)[17]. In this study, renal impairment was the predictor for diabetic foot ulcer16. Similar findings by Fernando showed that there was a strong association between microalbuminuria and foot ulcer[22]. This study revealed that diabetics with renal impairment were nearly twice as likely to have shorter time to developed foot ulcer as diabetics without renal impairment. This finding was similar to diabetic community in England which was 2.55 times faster[6]. Both study showed a tight confidence interval secondary to large sample size. Present of renal impairment give a general picture of changes in retina and intima layer of the vessels. Therefore, macroalbuminuria or macroalbuminuria is also a sign of other vascular disease such as peripheral vascular disease that may aggravate the development of foot ulcers[18,19].

The most common duration between follow-up in the district was between 3 to 6 months. This current study found that patients with duration between follow-up more than 6 months were 5 times faster to get diabetic foot ulcer as compared to patient with the usual follow-up. This was the people that defaulted follow-up for many reasons. When there was little monitoring, probability of non compliance to treatment high, delay in detection of complications and no specific prompt treatment given.

A surprising result was patient with frequent follow-up was 1.4 times faster to get foot ulcer as compared to diabetics with 3 to 6 months follow-up. This seems to suggest that frequent attendance may have directly caused foot ulcers, but this is most unlikely. The results probably reflects that ulcers occur more frequently in patients, whom healthcare providers have identified as being “foot at risk” and they were given more frequent appointment for monitoring. However, it is not the main predictor for foot ulceration as it becomes insignificant when other factor were controlled.

More than 2/3 of the defaulters were unable to control their glycaemic level. Almost half of them was having high blood pressure but never diagnosed nor treated and 40% of the hypertensive was poorly controlled. Many patients from this group also had renal impairment (40%) and high lipid level (80%). Moreover, 90% of the defaulters with abnormal lipid level were not using any antilipid agent including statin group. Although the problem were not much difference from the group with duration of follow-up less than 3 months and between 3 to 6 months, their progress were easy to monitor and specific early management can be given.

It was noticeable that prevalence of ulcer in this current study was higher among male, while majority respondents were female. Study in Kuala Lumpur Hospital and Dundee

also has similar results, where male were two times higher to get foot ulcer16[20,21]. This may mean that female patients develop fewer foot ulcers. However, Kumar in 1994 found that both male and female have similar risk to get foot ulcer[22]. Male in Kuala Langat was 1.6 times to get faster diabetic foot ulcer as compared to female but gender was not a strong predictor in this study. Male community in England was significantly 1.4 times to get faster diabetic foot ulcer[3]. This is because they were using a large number of sample (n=9710) that gave a tight confidence interval. However, Boyko in 2006 found that there was no difference in getting faster foot ulcer[23]. Both male and female had their own other risk factors. Prevalence of smoking is high in male which is a known risk factor for ulcer. Whereas female prone to get sole ulcer which is associated with higher BMI[21].

Knowledge of ethnic difference in a multi-ethnic nation such as Malaysia is still not much known. But, this knowledge will help medical staffs manage their patients better with respect to prevention of complications[24]. Indian/ Sikh ethnicity was found to have diabetic and ulcer at an early age as compared to Malay/ Bumiputra and Chinese. This finding is not congruent to study by Hong in Toa Payoh Polyclinic in Singapore where Malays were diagnosed early and followed by Indian and Chinese[26]. Bear in mind that Malays in Malaysia is the majority ethnic group but in Singapore they are the minority group. Ethnic differences in diabetic foot ulcer are most probably due to both genetic and environmental factors. Environmental changes in general able to modify the susceptibility of patients to complications of diabetes.

There was no significant association between age at being diagnosis as diabetes and foot ulcer in this current study. Patients who diagnosed at early age presented with more severe symptom that make it possible for early detection. Therefore they are more susceptible to get foot ulcer earlier. Whereas, elderly diabetics has undergone few changes such as foot deformity, increase blood flow resistant, reduce activities, eye problem, lonely and suffer from other medical problems. Foot ulcer development is more depending on duration of diabetes but not the age at diagnosis[27]. Nevertheless, Abbott showed an association between age and foot ulcer[25].

Most independent predictors of development of foot ulcer and ulcer-free survival have been identified previously by other studies, but there were some surprising findings. We found that lower body mass index is the predictor for ulcer development and ulcer-free survival. This might be due to gluconeogenesis and lipolysis secondary to long term uncontrolled diabetes, so that these kinds of patient were leaner. Otiniano in 2003 also found that obesity alone does not explain the excess prevalence and incidence of diabetes and its complication[26]. Previous studies reported that the propensity of leanness was related to diabetes complications and mortality.

Blood pressure did not have any effect on duration of ulcer development although more than half of the diabetics were also hypertensive. This might be because there were 1/3 of the patients with blood pressure above 130/80mmHg but never been diagnosed. Moreover a lot of hypertensive in diabetes (more than half) was unable to control their blood pressure even with medication and some were fluctuating.

In this study diabetic control was optimal only in 1/3 of the cases. Mean HbA1c was above normal which was 8.5%. Although most of the study revealed that HbA1c level is related to diabetic foot ulcer and other complications, it has not to our knowledge been independently associated with a higher risk of foot ulcer or speed-up the development of foot ulcer. Boyko in 1999 and 2006 in Seattle also found similar results where HbA1c were not associated independently with diabetic foot ulcers[23,27].

Patients with diabetes commonly had a terminal illness that included several renal failure and either severe heart disease or stroke. Heart attack is the most commonly reported cause of death in diabetic Mexican American in Hispanic Established Population for the Epidemiological Study of the elderly in America[26]. Over 15% of patients with diabetes had a history of heart attack and 11% had a history of stroke. Both are known to have significant impact on mortality and disability, particularly in patients with diabetes.

Neuropathy prevalence in our population is about 28%, more or less similar to the rate in England population (22%). Previous studies revealed that neuropathy has a greater effect on diabetic foot ulcer but it was not true in this study. Diabetics with neuropathy were getting ulcer earlier than diabetics without neuropathy[23,28]. Whereas, ischemia might delay the healing process due to lack of nutrient and oxygen secondary to poor blood circulation[1,27]. The combination of both neuropathy and ischaemia will further shortened the duration for ulcer development[1].

Strength and Limitation of Study

In this study a mass screening was undertaken to examine a large sample of patient's record (n=4288) from the primary health care center. Effort were made to minimize selection bias for this cohort by screening all diabetic patient's record as they attended diabetes review in various health care centers in the district; Sijangkang, Telok Datok, Kg. Bandar, Bukit Changgang and Jenjarom. This kind of study of truly primary health care-based sample of newly diagnosed diabetics will in principle produce an unbiased estimate of overall incidence and ulcer-free survival if complete follow-up and data collection can be achieved.

In special clinic-based and hospital-based studies, referral bias is likely to produce higher morbidity and mortality rates than in primary health care-based and community-based studies. Furthermore data from prevalence studies may be misleading because selective survival of diabetic patients with a more favorable risk factors profile. The very severe and complicated diabetics may have died earlier that we cannot include them in prevalence study. Prevalence study, case-control and cohort are only interested in the final event, whether there is event or no event. Whereas the variable of interest in this survival study is the time from diabetes diagnosis until an ulcer occurs. This survival study was able to demonstrate the temporal association between risk factors and the development of foot ulcer. Moreover, the measurement of incidence can be done.

Despite all health centers initially agreeing to take part, we screened at only 4288 cases of the 5 clinics in 6 months due to time constraints. Determination of accurate diabetes population figures was also a problem, due to general lack of accurate registers at this time. We did, however estimates of the total diabetic population (2008) from various sources (Third National Health and Morbidity Survey of Malaysia, Population Survey 2000 of Statistic Department, Diabetic Registry of Kuala Langat Health Centre), and 4288 cases equated of approximately 18.8% of all patients in the district. From the sheer size of the study, this large patient cohort is probably a reasonable representation of the primary-health-care-based diabetes population in Kuala Langat District of Selangor, Malaysia.

This survival study was able to deal with unequal observation time of the subjects under study that makes it incompatible with other conventional study. Moreover, it is capable to adapt with censored data that makes it possible to use all data in the analysis. Although patients are no longer followed because of death, loss of follow-up for unknown reason or no ulcer observed before study ends, the time that is known until the respondent are last observed are still can be used in the analysis. Because, these censored data still carry important information despite their incompleteness. For each respondent, at least we know that respondent's time from diabetes diagnosis to foot ulcer event is greater than duration on observation.

Potential confounders of the multivariate analysis cannot be ignored. Ulcer occurrence would also be influence by other potential risk factors not measured in this study such as healthcare provision, patient behavioral factors, compliance to treatment, foot care and hygiene, improper foot wear, diet, daily activities, exercise and others.

We also have not been able to report on the provision of primary health care services in each health centre. However it is a common knowledge that the process of healthcare in the district is variable in quality and generally of lower standard of supervision as compared to specialist clinic in the hospital that possibly influencing ulcer outcomes. Where patient receive well-organized and regular care with rapid referral to appropriate specialist multidisciplinary teams before problem occurs, ulceration can be prevented and morbidity reduced[27].

We were also unable to review the death certificates to find out other underlying cause of death in diabetic patients. Several studies that reviewed death certificates found that it was very common that death certificates of patients with diabetes did not mention diabetes as an underlying cause. Most of patients records and registries are not up-to-date and do not stated the cause of default. These are important because death is being the competing risk to occurrence of foot ulcer because death preclude subsequent foot ulcer. Death and diabetic foot ulcer also cannot consider as statistically independent unless all deaths arise from completely unrelated condition such as motor vehicle accidents[30]. Because of this reason, we are unable to study this competing risk.

Other issue in this study was information bias from secondary data. We use a secondary data from diabetic book records with no clinical reevaluation in which may exposed to information bias. Some factors will changed during the study period such as smoking status, marital status, glycaemic control, lipid control, renal profile and others. However, we have tried to minimized the

problem by discussing any doubt with clinic's officer, confirmation via phone call or direct interview if patient available in the clinic. Moreover, we have tried to use the mean of all possible continuous measures that may influence the development of ulcer.

CONCLUSION

We have demonstrate that about 1% of a large cohort of diabetic patients seeing in the primary health care setting will develop new foot ulceration each year. About 10% developed foot ulcers within 10 year. Furthermore, we now have important confirmation that a baseline screening measures before diabetic registration; gender, presence of cardiovascular disease, smoking status, body mass index, renal profile and lipid profile can be used to identify the "high risk" patients and predict the onset of diabetic foot ulcer events.

These current findings underscore the importance of enhanced efforts to improve diabetes care as soon as possible after diabetes diagnosis as foot ulcer developed less than 6 months after diagnosis of diabetes has been made. A further prospective survival study of other important risk factors but not included in this study will be very meaningful such as dietary, compliance, foot care, foot hygiene, clinical signs and others.

All patients should be screened regularly for foot complications, given foot care leaflets and useful telephone numbers and contact addresses so that in future foot problems could be addressed immediately, and were referred when appropriate for podiatry and peripheral vascular tests. Thus empowering the patient, easing access to appropriate care, improving attitudes and motivation potentially may influence future ulceration rates for community based patients.

Diabetic screening program also must be improved as the early development of diabetic foot ulcer in this study is a sign of late diagnosis. Another important factor is to review all patients with an adequate follow-up which is less than 6 months. We must also improve and strengthened the defaulter tracing in non-communicable disease in able to prolong the ulcer-free period in diabetics.

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