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Original Research Article

Predictors of lower extremity amputation in patients with diabetic foot ulcer

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ABSTRACT

Background: Diabetic foot lesions are responsible for more hospitalisations than any other complication of diabetes and diabetes is a predominant aetiology for non-traumatic lower extremity amputations. Authors, therefore, examined the clinical characteristics that best predict poor outcome in a large population of diabetic foot ulcer patients. The objective of the study was to describe independent predictors for lower extremity amputation in patients with a diabetic foot ulcer and to validate the predictive value of PEDIS (IWGDF) classification system for a diabetic foot ulcer.
Methods: A retrospective study of 197 patients presenting with diabetic foot ulcer presenting to a tertiary care hospital in Mysuru, India. The recorded parameters were age, sex, various risk factors, laboratory parameters, the presence of DM-related complications and ulcer characteristics as determined by PEDIS system. The main outcomes recorded were healed ulcer and amputation.
Results: Authors have found that factors strongly associated with risk of amputation are (in order of strength): PVD, past amputation, nephropathy, past ulcer, ulcer duration, TLC, Hb and sr. creatinine. Authors also validated the PEDIS scoring system as an effective classification system with prognostic value. The PEDIS score of >7 is a highly significant predictor of adverse outcome (amputation) of diabetic foot ulcer.
Conclusions: Several risk factors for lower extremity amputation in a patient with diabetic foot ulcer were identified. An integrated risk-assessment model including the above significant risk factors and PEDIS system can be developed that is both clinically accurate as well as quick to assess for predicting the adverse outcome in a patient of diabetic foot ulcer and providing an opportunity to save the limb.

Keywords: Amputation, Diabetic foot ulcer, Outcome, Prediction

INTRODUCTION

Out of 190 million diabetics worldwide, 65 million live in India, and 10 million more are added every year. About 15% diabetics develop a foot ulcer and 12-24% of them require amputation, making diabetes a predominant aetiology for non-traumatic lower extremity amputations. Diabetic foot lesions are responsible for more hospitalizations than any other complication of diabetes. A diabetic foot ulcer is an independent risk factor for amputation.[1-3]

Eurodiale Study is one of the few large prospective cohort studies on outcome and determinants of outcome in diabetic foot diseases. It studied 1,088 diabetic foot ulcer patients across 14 centres in Europe. Many studies looking into various aspects of the diabetic foot were done from the Eurodiale data.[4-6]

Chuan F et al, conducted a retrospective study in which 364 patients with diabetic foot ulcer were assessed for the validity of PEDIS classification system.[7] When measured using the system, the outcome of diabetic foot ulcer deteriorated with increasing severity of each category.

Martins-Mendes D et al, in their retrospective study of 644 diabetic patients tried to estimate 3-year risk for diabetic foot ulcer (DFU), lower extremity amputation (LEA) and death.[8] They concluded that DFU is more than a marker of complication status, having an independent impact on LEA and mortality risk. They also proposed models that may be applicable in healthcare settings to identify patients at higher risk of DFU, LEA and death.

Prevention of adverse outcome requires identification of variables linked to the outcome and development of tools to predict the outcome. Studies addressing this issue are limited in the Indian scenario and need further validation in other cohorts. The objectives of the study were to describe independent predictors for adverse outcome (lower extremity amputation) in patients with a diabetic foot ulcer. To validate the predictive value of PEDIS (IWGDF) classification system in the prognosis of diabetic foot ulcer.

METHODS

This was a descriptive cohort study where a total of 197 patients with an active diabetic foot ulcer, admitted under the Department of Surgery in J.S.S. Medical College and Hospital, Mysore, India.

Patients presenting with acute limb ischemia, malignant or traumatic ulcer were excluded.

Patient details were retrieved from medical records over a period of 2 years.

Following parameters are noted: Demographics included age (in years) and gender (male or female). History includes diabetes and ulcer duration, past history of ulcer and lower extremity amputation (LEA), tobacco addiction (smoke or non-smoke), alcohol addiction, hypertension (known or newly detected). Clinical examination with ulcer characteristics which were fever, PEDIS classification system[97] (Table 1).

Presence of diabetes-related complications such as metabolic complications (like diabetic ketoacidosis), cerebrovascular disease (history of ischemic stroke), cardiovascular disease (coronary artery disease), peripheral arterial disease (absent/feeble peripheral pulses, intermittent claudication, doppler evidence), nephropathy (CKD, albuminuria), peripheral neuropathy (using tuning fork vibration sensation), retinopathy (low vision, fundoscopy). Laboratory investigations such as total leucocyte count (TLC), Hb, HbA1c, Sr. creatinine.

Table 1: Pedis classification system and scoring system.

Score	Perfusion	Extent	Depth	Infection	Sensation
0	No PAD	Skin Intact	Skin intact	None	No loss
1	PAD, No CLI	<1 cm^2	Superficial	Surface	Loss
2	CLI	1-3 cm^2	Fascia, muscle, tendon	Abscess, fasciitis, septic arthritis	-
3		>3 cm^2	Bone or joint	SIRS	-

Outcomes were categorized as 'healed' (ulcer that is healed or healing at the end of the follow-up period), "non-healing" (those ulcers which remained non-healing), 'minor amputation' (with forefoot and below); 'Major amputation' (at least BKA) or 'death' (patients who expired due to diabetes-related complications). Association between the above-measured parameters and observed outcomes is statistically tested. Missing and indeterminate results were excluded from the analysis.

RESULTS

In this study, a total of 197 subjects with active diabetic ulcer were taken and studied. Of 197 subjects, 100 (50.7%) underwent lower extremity amputation and 86 (43.7%) had their ulcers healed. In only 7 (3.6%) subjects the ulcer remained as non-healing and there were only 4 (2.0%) deaths (Figure 1).

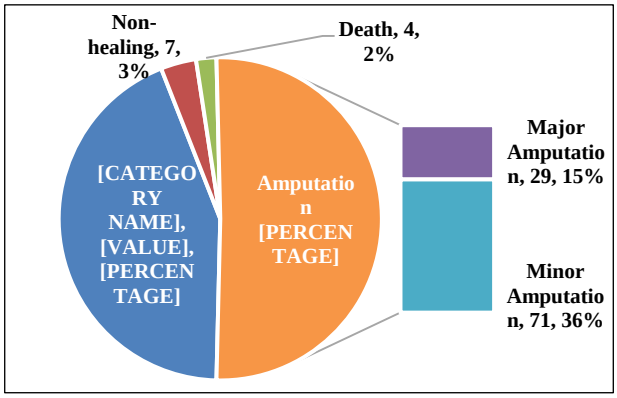

Figure 1: Outcomes of DFU.

The majority of outcomes fall in the group of either healed or amputation, showing more or less a duality of the outcome. To simplify the statistical analysis the other less common outcomes (non-healing and death) have been excluded from analysis. A majority of the subjects (41.6%) belonged to the 6th decade of age with a mean of 60.7 (SD=9.9). But there is no significant difference among the amputation vs healed groups. The duration of ulcer is significantly more in the amputation group (50.6 days) vs healed (24.0 days) group (p=0.0007).

But such a difference is not seen with the duration of diabetes (139.9 months in amputation group vs 133 months in healed group).

Table 2: Amputation vs healed (continuous variables).

Variables	Outcome				P (χ^2 test)
	Amputation		Healed		
	Mean	SD	Mean	SD	
Age (years)	60.6	10.0	60.7	9.8	0.8
Ulcer duration (days)	50.6	72.4	24.0	42.1	0.007
Diabetes duration (months)	139.9	81.7	133.1	85.4	0.5
Hb (g/dL)	10.25	2.11	11.08	2.38	0.01
TLC (per mm^3)	15,915.0	8,114.9	13,084.4	5,556.5	0.007
HbA1c, %	9.7	2.0	11.0	10.3	0.2
Sr. creatinine (mg/dL)	1.50	1.26	1.13	0.84	0.02

Table 3: Amputation vs healed (nominal variables).

Presence of the parameter	Outcome				P (Mann-Whitney test)
	Amputation		Healed		
	N	%	N	%	
Female gender	22	50.0	22	50.0	0.6
Fever	44	56.4	34	43.6	0.5
Previous ulcer	44	67.7	21	32.3	0.005
Previous amputation	38	73.1	14	26.9	0.001
Hypertension	47	58.0	34	42.0	0.3
Tobacco	43	52.4	39	47.6	0.7
Alcohol	41	53.9	35	46.1	0.9
Metabolic	13	65.0	7	35.0	0.3
Cerebrovascular disease	3	50.0	3	50.0	0.9
Cardiovascular disease	14	51.9	13	48.1	0.8
Peripheral vascular disease	53	70.7	22	29.3	0.0001
Nephropathy	39	69.6	17	30.4	0.004
Peripheral neuropathy	18	58.1	13	41.9	0.6
Retinopathy	25	62.5	15	37.5	0.2

In this study, the mean hemoglobin (Hb) is 10.6 ±2.27 g/dL and the amputation group were significantly more anemic than healed group (10.25 vs 11.08 g/dL, respectively). Higher leucocyte counts were found to be significantly associated with higher risk of amputation (15,915/mm^3 in amputee vs 13,084/mm^3 in healed cases, p=0.007). The mean HbA1c among amputee (9.75±2.03%) and healed cases (11.03±10.29%) was not significantly different (p=0.2). Average serum creatinine level was 1.33±1.1 mg/dL and is found to be a significant predictor of amputation (Table 2). In present study, the presence or absence of fever is found to be insignificant in predicting the outcome. Also, there is no gender difference between the outcomes. The occurrence of previous history of ulcer (67.7% in amputation group) or history of previous amputation (73.1% in LEA group) was significantly different among the amputation and healed outcome groups (p=0.001).

Present study showed neither tobacco use, nor alcoholism significantly affect DFU outcome. Of 197, 90 subjects were hypertensive. The difference in the prevalence of hypertension among the outcome groups is insignificant. Most common systemic complication found in patients with DFU was PVD (41.6%). Next common is peripheral neuropathy (17%). But the only systemic complications

with a strong association with amputation following DFU were PVD (p=0.0001, OR=3.07), and nephropathy (p=0.004, OR=2.4) (Table 3).

PEDIS scoring system

The mean PEDIS score is significantly different between healed group and amputation group (6.33 vs 7.47, p=0.0001) (Table 4).

Table 4: Pedis score as a predictor of lea in DFU.

PEDIS score in the group	Mean	SD	P
Amputation	7.47	1.50	<0.0001
Healed	6.33	1.35	

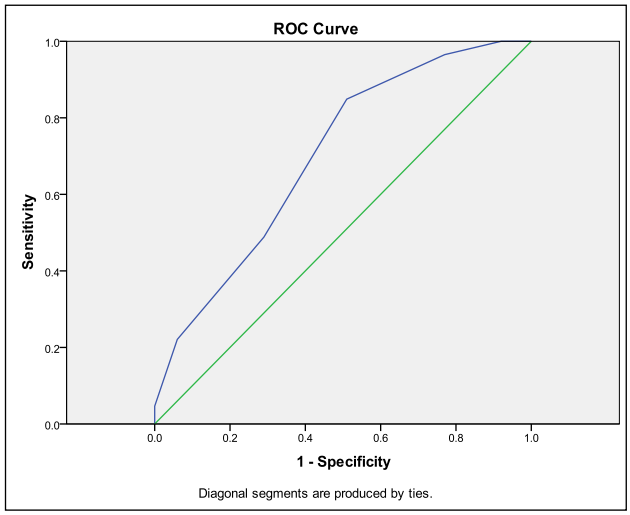

Figure 2: ROC curve of PEDIS score: area under curve = 0.7.

Table 5: Predictive power of PEDIS score >7 as the cut-off.

PEDIS score	Outcome	
	Healed	Amputation
Low risk (<7)	42	29
High risk of amputation (>7)	44	71
Performance of PEDIS score <7 as a test to predict healing		
Parameter	Estimate	Lower - upper 95% CI
Sensitivity	48.84%	(38.55, 59.22)
Specificity	71%	(61.46, 78.99)
Positive predictive value	59.15%	(47.54, 69.83)
Negative predictive value	61.74%	(52.61, 70.11)
Diagnostic accuracy	60.75%	(53.59, 67.48)

It was found that, for the identification of adverse outcomes, the ROC curve of PEDIS score had an area under the curve (AUC) of 0.7 (Figure 2) and a PEDIS score threshold value of 7 has a diagnostic accuracy of 60.75% (48.84% sensitivity, 71% specificity) (Table 5). The ability of the PEDIS score to discriminate between patients who did and did not develop the outcomes of interest was assessed using the area under the receiver operating characteristic curve (ROC) with the 95% confidence interval (CI).

DISCUSSION

The number of patients undergoing amputation in present study (50.7%) is far higher than (23% including, 5% major±8% minor) that seen in Eurodiale study.[5] And, in the Eurodiale study, 71% of the subjects had an outcome of healed ulcer which is much higher than that in present study (43.7%). This could be the result of delayed presentation with more complications in the Indian population, low threshold for amputation considering economics and lack of routine use of advanced treatments.

DFU related mortality in Eurodiale study was 6% and in a study by Young BA et al, was 2.5%, which is more compared to 2.0% in this study.[10] This is probably due to their prolonged period of follow-up.

The observed mean age in present study (60.7±9.9 years) is lower than that in Eurodiale study and other studies by Martins-Mendes D et al, where the average age is 65±12 years.[4,5,8,11] As diabetic foot ulcer is itself considered a complication of diabetic foot, this early occurrence of diabetic foot complication in Indian population can be explained by probable inadequate diabetic control and lack of education.[2]

In the Eurodiale study and Martins-Mendes D et al. study, male constituted 64% and 50% respectively, which is much lower than seen in this study (76%). This is probably due to the relatively higher prevalence of smoking/alcoholism among Indian men compared to the European population. Smoking is an independent risk factor in the development of DFU but not amputation following DFU, per se.

Both age and gender were found to be insignificant predictors of amputation. But in Eurodiale study and study by Chuan F et al, increasing age is found to be associated with higher amputation risk.[7]

In present study, 50% of the patients had a history of diabetes spanning more than 10 years as compared to just <30% of the patients in the Eurodiale study population. Also, the mean diabetes duration was 16.1±10.8 years in Martins-Mendes D et al study in contrast to just 11.4±6.9 years in present study. This again signifies the early occurrence of complications in this study population. In Chuan F et al, study the duration of diabetes is an insignificant determinant of the outcome of DFU, as is found in present study.

The duration of ulcer at the study entry point in the Eurodiale study was <1 week in 17%, 1 week to 3 months in 58% and >3 months in 25%. This is shorter than seen in present study 28%, 59% and 13% respectively. This early presentation to the hospital once ulcer occurs may signify early further complication of the ulcer (like, infection) demanding early medical attention by a specialist due to inadequate primary care. Present study, as well as Chuan F et al, study found that duration of ulcer can predict LEA in patients with DFU.

Previous history of ulcer and amputation

In Martins-Mendes D et al, study 41% had a previous history of ulcer, comparable to 35% in present study. Present study, as well as Martins-Mendes D et al study, found that the history of previous DFU or LEA has a significant predictive value for next LEA.

Tobacco and alcohol use and hypertension

Prevalence of tobacco use in this study is 44.7% which is similar to the national prevalence of 42.4% (Global adult tobacco survey, 2016).[12] But the prevalence of alcoholism is significantly higher in this study population, 42.1% vs 17.2% (Global status report on alcohol and health, 2018).[13]

Tobacco use has not been found to be associated with amputation risk as so in the study by Chuan F et al. But it is strongly associated with PVD and PVD is linked with adverse outcome of DFU. Hence, tobacco use indirectly affects the outcome. DFU was associated with hypertension in nearly half the time (45.7%) which is not different from that of Chuan F et al, study, 49.2% and Young BA et al study, 42.9%.[14] Present study found the presence or absence of HTN has no bearing over the outcome and so is the finding of Chuan F et al, study.

Laboratory parameters

The mean Hb in Chuan F et al, study is higher than in present study (11.4±2.13 vs 10.6±2.27 g/dL), probably representing generally anaemic Indian population. Chuan F et al, also found that Hb is a significant predictor of amputation. This study, as well as Chuan F et al, study found that TLC values predict the risk of amputation.

In present study, the mean HbA1c value of 10.34% is higher than 8.83% found in Chuan F et al, study indicating generally poor glycaemic control in present study population. Present study found no predictive value of HbA1c for amputation in contrary to its significance seen in Chuan F et al, study.

Systemic complications of diabetes

In the Eurodiale study population, PVD and peripheral neuropathy were present in 49% and 86% of the patients, respectively, compared to 41.6% and 17% in present study. Such a low prevalence of peripheral neuropathy could arise from inadequate reporting of the complication. Chuan F et al, study found higher amputation risk associated only with PVD among other systemic complications. In contrast, apart from PVD, the study by Martins-Mendes D et al, found other factors like retinopathy, cardiovascular disease, nephropathy and also peripheral neuropathy to be associated with LEA risk.

PEDIS scoring system

In Chuan F et al, study the ROC curve of total PEDIS score had an area under curve of 0.95 (0.7 in present study) and the threshold value of 7 had a sensitivity of 93% and a specificity of 82% (48.8% and 71% respectively in present study). Though this study shows less diagnostic accuracy of PEDIS score compared to Chuan F et al, study, the validity of the PEDIS scoring system is established as a highly significant predictor of adverse outcome (amputation) of diabetic foot ulcer. The limitations and future direction of this study were lack of uniformity in standards of wound care practiced by different surgeons may have affected our result. Authors did not address the severity of PVD. Also, this study is not population-based and represents patients referred to a tertiary care hospital.

CONCLUSION

Diabetes is a predominant cause for non-traumatic lower extremity amputations (LEA) and diabetic foot pathologies pose a serious health burden for developing countries if not prevented. As seen in this study population, early occurrence of DFU (younger age and shorter duration of diabetes) and significantly more diabetics facing adverse outcome (LEA) in comparison to similar studies in other population, indicates inadequacies in preventive measures including poor diabetic control in-general. Several risk factors for LEA were identified.

Authors have found that factors strongly associated with risk of amputation are (in order of strength): PVD, past amputation, nephropathy, past ulcer, ulcer duration, TLC, Hb and sr. creatinine. As PVD is the most common and significant determinant of outcome, active investigation of each patient is necessary to assess the possibility of revascularization and the probability of wound healing.

Authors also validated the PEDIS scoring system as an effective classification system with prognostic value. The PEDIS score of >7 is a highly significant predictor of adverse outcome (amputation) of diabetic foot ulcer. Above identified significant parameters can be integrated with PEDIS scoring system to develop a risk-assessment model that is both clinically accurate as well as easy and quick to assess for predicting the adverse outcome (amputation). With early identification and intervention, there is an opportunity to save limb in a substantial proportion of patients with a diabetic foot ulcer.

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