PREDICTIVE FACTORS AND LEVELS OF AMPUTATION IN PATIENTS WITH DIABETIC FOOT ULCER

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Abstract
Background: Diabetes mellitus complicated by diabetic foot ulcer leading to amputation carries socio-financial implications. The spectrum of the issue extends globally. Knowledge of burden of factors leading to amputations at various level is vital in understanding the gravity of the problem. **Objective:** To determine the frequency of predictive factors and levels of amputation in patients with diabetic foot ulcer. **Materials and methods:** This cross sectional study was carried out at department of surgery, Khyber Teaching Hospital, during the period 13th June 2022 till 12th December 2022. A total of 180 male and female patients in the age range 30 to 60 years undergoing amputation for diabetic foot ulcer were enrolled. Predictive factors and level of amputation were noted. Data was analyzed using SPSS version 25. **RESULTS:** Mean age of the patients was 46.68 ± 10.239 years. The number of female participants was 101 (56.1%). Most common predictive factor observed was peripheral arterial disease in 75 (41.7%) patients while below knee amputation was most common procedure performed in 85 (47.2%) patients. **CONCLUSION:** Female patients with grade 3 and above Wagner diabetic foot with peripheral arterial disease were more likely having lower limb amputation. Amputation below knee was most common.

Keywords: Diabetic Foot Ulcer (DFU), Predictive Factors, Level of Amputation

INTRODUCTION
Diabetes related complications are commonly encountered owing to rampant increase in the prevalence of the disease and lack of appropriate and timely medical care. Sedentary life style and change in dietary pattern with westernization of food are major factors leading to diabetes. The burden of disease has grown to critical levels in Pakistan almost 33 million (one-fourth of overall population). Presentation to hospital is often delayed due to lack of clinical symptoms unless later stages of the disease in the form of complications like diabetic foot ulcer and chronic kidney disease.(1, 2)
Diabetic foot ulcer (DFU) is a chronic ulcer of the foot in patients with uncontrolled diabetes. Though avoidable with adequate diabetes control, a significant proportion of patients present with non-healing infected and gangrenous stage, ultimately leading to amputation of the limb. There is 25% probability of diabetic patient for developing diabetic foot ulcer during the life-time.(3)
Diabetic foot ulcer is a crippling disease. It carries substantial socio-financial implications in terms of high mortality, recurrent extended hospitalizations, leave of job, and reduce productivity and burden on care-giver.(4, 5) Numerous factors have been analyzed that could potentially predict the wanted outcomes of DFU. Among them, infection is leading cause occurring in more than half of the patients

with initial stage. Up to 82% cases have been mentioned in the literature in hospitalized patients with chronic ulcers.(6) Other potential factors of clinical importance are peripheral neuropathy, leukocytosis, proteinuria and peripheral arterial disease. In a study by Ejiofor Ojwu and colleagues, peripheral arterial disease was reported in 49.4% patients who underwent lower limb amputation for diabetic foot. Neuropathy was reported in 35.5% patients.(3) In another study by Pickwell et al, peripheral arterial disease was reported in 55.8% diabetic patient who underwent lower limb amputation followed by wound infection in 35.8% patients.(6)

Diabetes-related lower limb amputation rates have significantly declined in many countries over the years. This is however not the case in our country where DFU-related lower limb amputation rates are still very high. Efforts to prevent this unpleasant scenario therefore deserve utmost attention, and this could be partly accomplished by predictive factors identification. Regrettably, not much has been done in this direction in our country especially in our local population. Hence the study was planned. This study aimed to determine the frequency of predictive factors and levels of amputation in patients with diabetic foot ulcer.

MATERIALS AND METHODS

Study design and settings
This cross sectional study was carried out at the department of Surgery, Khyber Teaching Hospital, Peshawar, during the period 13th June 2022 till 12th December 2022. Approval for the conduct of the study was granted by research review committed vide letter no: ___, dated _____.

Sampling
A total of 180 male and female participants in the age range 30 to 60 years diagnosed with diabetic foot ulcer admitted for lower limb amputation were enrolled. Patients with prior history of amputation in the same foot, patients with prothrombotic conditions, patients with rheumatic conditions like Raynaud's disease, SLE, rheumatoid arthritis and patients taking blood thinners like Coumadin and antiplatelets and patients vascular pathologies like varicose veins were excluded. Sample size was 180, calculated using WHO sample formula, using the proportion (expected frequency of peripheral arterial disease) p = 35.5%,(3) margin of error = 7.5% and 5% level of significance.Participants were enrolled using non – probability consecutive sampling technique.

Diabetic foot ulcer was diagnosed clinically by the presence of wound (erythema, gangrene, seroanguinous or pustular discharge) extending below the dermis at the level of ankle or below. DFU was graded as per Wagner classification. Patients with Wagner grade 2 to 5 DFU were considered significant. The predictive factors of amputation were noted in terms of: 1) Peripheral Arterial Disease: The presence of diminished or impalpable dorsalis pedis and/or posterior tibial artery pulsations on manual examination, the presence of significant arterial narrowing ($> 50\%$) on Doppler ultrasonography of the lower limbs was considered confirmatory for the presence of peripheral arterial disease. 2) Peripheral Neuropathy: Peripheral neuropathy was diagnosed by loss of pressure perception in the foot to Semmes-Weinstein 10 g monofilament test or diminished vibration sense using the 128 Hz tuning fork. 3) Wound Infection: The presence of purulent exudates or any two or more of the following: peri-wound edema, peri-wound redness, local warmth, foul smell, pain or tenderness on palpation and fever (body temperature more than 38° C on thermometer). The level of Amputation were noted in terms of: 1) Toe Amputation: Amputation through the meta-tarsal bones. 2) Below Knee Amputation: Amputation at any level from knee to ankle. 3) Knee Disarticulation: Amputation at the level of knee joint. 4) Above Knee Amputation: Amputation at any level from hip joint to knee joint.

Data Collection Procedure
Informed consent was taken from all study participants and baseline demographics including age, gender, BMI, foot laterality and duration of ulcer (months) were noted. Detailed physical examination of the ulcer was carried out for shape, size, location and Wagner grade. For wound infection, signs of infection including peri-wound edema, discharge and fever was recorded. A monofilament

examination was performed four separate sites (1st, 3rd and 5th metatarsal head and plantar side of greater toe) followed by doppler ultrasound of the limb to look for peripheral arterial disease. Keeping in view of clinical, laboratory and radiological findings, MDT was arranged for every case and level of amputation was decided. Loss of anatomical plane of the lower extremity was noted. Presence of predictive factor and level of amputation was noted as per operational definitions. All the data was recorded using especially proforma.

Data Analysis Procedure
Statistical analysis was carried out using SPSS version 23. Categorical data was presented as frequencies and percentages while continuous data was presented as mean and standard deviation. Tests of statistical significance was chi square test applied at 5% level of significance.

RESULTS
In this study, age of the patients ranged from 40 to 75 year. Mean age was 46.68 ± 10.239 years, mean weight 72.07 ± 6.463 kg, mean height was 170.55 ± 7.883 cm, mean BMI was 24.865 ± 2.6605 kg/m^2 as shown in Table-I.

Table- I: Mean ± SD of patients according to age, height, weight and BMI. (N = 180)

BASELINE DEMOGRAPHICS AND CHARACTERISTICS	MEAN ±STD. DEVIATION
1. Patient Age (years)	46.68 ± 10.239
2. Patient Height (cm)	170.55 ± 7.883
3. Patient Weight (kg)	72.07 ± 6.463
4. Patient BMI (kg/m^2)	24.865 ± 2.6605

Frequency and percentage of patients according to various clinic demographic parameters is summarized in table 2. Gender-wise female participants were higher in proportion (n = 101, 56.1%) while right foot ulcers were more frequent than left (n = 103, 57.2%). Majority of the patients had BMI >23.0kg/m^2 (n = 131, 72.8%). 97 patients (53.9%) had ulcer duration more than 6 months. Regarding the Wagner classification, grade 4 and 5 ulcers were more frequent (n = 139, 77.2%).

Table 2. Frequency and %age of patients according to various clinic-demographic parameter (N = 180)

Parameters	Subgroups	Frequency (%)
Gender	Male	79 (43.9%)
	Female	101 (56.1%)
Age (years)	Male	65 (36.1%)
	Female	115 (63.9%)
Foot laterality	Right	103 (57.2%)
	Left	77 (42.8%)
BMI (kg/m^2)	23.0 or below	49 (27.2%)
	More than 23.0	131 (72.8%)
Ulcer duration (months)	≤6	83 (46.1%)
	>6	97 (53.9%)
Wagner classification	2 - 3	41 (22.8%)
	4 - 5	139 (77.2%)

Predictors and levels of amputations are reported in table 3 in terms of frequencies and percentages. Peripheral arterial disease was the most commonly recorded factor in 75 patients (41.7%) followed by wound infection (n = 60, 33.3%). Least common was peripheral neuropathy in 45 patients (25.0%). Below knee amputation (BKA) was most frequent (n = 85, 47.2%), followed by toe amputation (n = 40, 22.2%). Knee disarticulation was least common recorded in 25 participants (13.9%).

Table 3. Frequencies and percentages of patients according to outcome variables (predictive factors and levels of amputation), (N = 180)

Outcome variables	Subgroups	Frequency (%)
PREDICTIVE FACTORS	Peripheral arterial disease	75 (41.7%)
	Peripheral neuropathy	45 (25.0%)
	Wound infection	60 (33.3%)
LEVELS OF AMPUTATION	Toe amputation	40 (22.2%)
	Below knee amputation	85 (47.2%)
	Knee disarticulation	25 (13.9%)
	Above knee amputation	30 (16.7%)

The subgroup analysis of predictive factors with various with clinic-demographic parameters is illustrated in table 4. 26 patients (57.8%) male patients had peripheral neuropathy compared to 19 female patients (42.2%). The chi square p value for association between gender and peripheral neuropathy was 0.030. No statistically significant association was obtained other parameters and predictors of amputation.

Table 4. Stratification of predictive factors various clinic-demographic parameters, (n = 180)

		AGE (years)		Total	p value
		≤45	>45		
PAD	YES	28(37.3%)	47(62.7%)	75(100.0%)	0.772
	NO	37(35.2%)	68(64.8%)	105(100.0%)	
PN	YES	18(40.0%)	27(60.0%)	45(100.0%)	0.530
	NO	47(34.8%)	88(65.2%)	135(100.0%)	
WI	YES	19(31.7%)	41(68.3%)	60(100.0%)	0.380
	NO	46(38.3%)	74(61.7%)	120(100.0%)	
		GENDER			
		Male	Female		
PAD	YES	29 (38.7%)	46(61.3%)	75(100.0%)	0.232
	NO	50(47.6%)	55(52.4%)	105(100.0%)	
PN	YES	26(57.8%)	19(42.2%)	45(100.0%)	0.030
	NO	53(39.2%)	82(60.8%)	135(100.0%)	
WI	YES	24(40.0%)	36(60.0%)	60(100.0%)	0.457
	NO	55(45.8%)	65(54.2%)	120(100.0%)	
		BMI (kg/m^2)			
		≤23	>23		
PAD	YES	23(30.7%)	52(69.3%)	75(100.0%)	0.380
	NO	26(24.8%)	79(75.2%)	105(100.0%)	
PN	YES	09(20.0%)	36(80.0%)	45(100.0%)	0.208
	NO	40(29.6%)	95(70.4%)	135(100.0%)	
WI	YES	17(28.3%)	43(71.7%)	60(100.0%)	0.812
	NO	32(26.6%)	88(73.4%)	120(100.0%)	
		ULCER DURATION			
		≤6 MONTHS	>6 MONTHS		
PAD	YES	31(41.3%)	44(58.7%)	75(100.0%)	0.277
	NO	52(49.5%)	53(50.5%)	105(100.0%)	
PN	YES	20(44.4%)	25(55.6%)	45(100.0%)	0.795
	NO	63(46.7%)	72(53.3%)	135(100.0%)	
WI	YES	32(53.3%)	28(46.7%)	60(100.0%)	0.169
	NO	51(42.5%)	69(57.5%)	120(100.0%)	

		WAGNER CLASSIFICATION			
		2-3	4-5		
PAD	YES	17(22.7%)	58(77.3%)	75(100.0%)	0.976
	NO	24(22.8%)	81(77.2%)	105(100.0%)	
PN	YES	11(24.4%)	34(75.6%)	45(100.0%)	0.758
	NO	30(22.2%)	105(77.8%)	135(100.0%)	
WI	YES	13(21.7%)	47(78.3%)	60(100.0%)	0.801
	NO	28(23.3%)	92(76.7%)	120(100.0%)	

As presented in table 5, the p value for association between level of association and gender of the patient was 0.009. Out of total 79 male patients with amputation, 37 (46.85) had below knee amputation compared to 48 female patients (46.8%). Toe amputation was recorded in 12 (15.2%) male patients versus 28 (27.7%) female patients while 21 male patients (26.6%) had above knee amputation compared to 09 female patients (8.9%).

Table – 5: Stratification of level of amputation with various clinic-demographic parameters (N= 180)

		LEVEL OF AMPUTATION				Total	P value
		TA	BKA	KD	AKA		
AGE (years)	≤45	19(29.2%)	28(43.1%)	05(7.7%)	13(20.0%)	65(100%)	0.106
	>45	21(18.3%)	57(49.6%)	20(17.4%)	17(14.8%)	115(100%)	
TOTAL		40(22.2%)	85(47.2%)	25(13.9%)	30(16.7%)	180(100%)	
GENDER	Male	12(15.2%)	37(46.8%)	09(11.4%)	21(26.6%)	79(100%)	0.009
	Female	28(27.7%)	48(47.5%)	16(15.8%)	09(8.9%)	101(100%)	
TOTAL		40(22.2%)	85(47.2%)	25(13.9%)	30(16.7%)	180(100%)	
BMI (kg/m^2)	≤23	11(22.4%)	20(40.8%)	07(14.3%)	12(24.5%)	49(100%)	0.391
	>23	29(22.1%)	65(49.6%)	18(13.7%)	18(13.7%)	131(100%)	
TOTAL		40(22.2%)	85(47.2%)	25(13.9%)	30(16.7%)	180(100%)	
ULCER DURATION (months)	≤6	23(27.7%)	39(46.9%)	10(12.0%)	11(13.2%)	83(100%)	0.315
	>6	17(17.5%)	46(47.4%)	15(15.5%)	19(19.6%)	97(100%)	
TOTAL		40(22.2%)	85(47.2%)	25(13.9%)	30(16.7%)	180(100%)	
WAGNER CLASSIFI-CATION	2-3	11(26.8%)	17(41.5%)	08(19.5%)	05(12.2%)	41(100%)	0.435
	4-5	29(20.9%)	68(48.9%)	17(12.2%)	25(17.9%)	139(100%)	
TOTAL		40(22.2%)	85(47.2%)	25(13.9%)	30(16.7%)	180(100%)	

DISCUSSION

In this study, among 180 patients who underwent amputation the most frequent predictive factor for amputation was peripheral arterial disease recorded in 75 patients (41.7%) followed by wound infection (n = 60, 33.3%) and peripheral neuropathy (n = 45, 25.0%). In a study by Yesil and colleagues, peripheral arterial disease in 80.8% patients followed by peripheral neuropathy (77.5%) and osteomyelitis (62.4% patients).(7) The trend in the occurrence of various predictive factors was similar to our study though the proportion was much higher compared to our study. Our results are however, in contrast to the observations of Sun et al. where they reported peripheral neuropathy as most frequent factor recorded in 84.2% patients.(8) Jiang and colleagues reported infection in 84.9% patients. (9) Zubair et al reported neuropathy in 69.5% patients, peripheral arterial disease in 10.6% patients and wound infection in 58.6% participants. (10) The difference in pattern of risk factors compared to our study may be attributed to the fact that the later studies are carried out at western population with better infection control measures leading to lower infection rates. Resistance to antibiotics in our settings may be the potential contributors for higher infection rate.

Below knee amputation was most frequently performed procedure among our cohort of patients recorded in 85 patients (47.2%) followed by toe amputation in 40 patients (22.2%) and above knee amputation in 30 participants (16.7%). In a study by Ahmed et al, out of total 138 patients, 65 patients (32.5%) had minor amputations (below ankle) and 73 patients (36.5%) had major amputations (above ankle). Their results are much lower compared to our observation. This difference in findings may be due to difference in allocation of all patients with below knee amputation in the same group in our study.(11) Out results are however, quite similar to the findings of Ali et al who reported below knee amputation as the most common procedure in 55 patients (34.8%) patients, toe amputation in 42 patients (26.6%) and above knee amputation in 34 participants (21.5%).(12)

The number of female patients (n = 115, 63.9%) undergoing amputation was higher than men in our study. In an Ethopian study, the ratio was however, reverse compared to our observations.(13) We could not draw any significant reason for this difference in gender-wise amputation between the two studies. Perhaps the difference in overall prevalence of diabetes in both the counties may have contributed this effect. In a hospital based case control study by Pemayun, the proportion of female patients who underwent amputation was higher compared to male (59.6% female versus 40.4% male) similar to our findings.(14)

Majority of the patient who underwent amputations had grade 3 or above ulcers as per Wagner classification. Priti Shah and colleagues reported that all patients (100.0%) who underwent amputation for diabetic foot ulcer had grade 3 and above ulcers. (15) Sawsen et al showed Wagner grade 4 and 5 as single independent predictive factor for lower limb amputation.(16) In another study, taking grade 3 as cut off, the sensitivity and specificity of Wagner classification for predicting lower limb amputation was 69.0% and 75.0% respectively.(17)

Though the study provides insights about useful information about amputation in diabetic foot ulcer, the carries certain limitations like a single center study with small sample size. Inclusion of a control group could have improved the results. The study also fails to provide to information like size and exact site of ulcer. Multicenter large sample size study with control group are required to establish our findings.

CONCLUSION
Lower limb amputation is frequently performed procedure for diabetic foot ulcer in out settings. Peripheral arterial disease and wound infection were the most common predictive factor for amputation. Below knee amputation and toe amputation were most common sites for amputation. Female patients with grade 3 and above Wagner ulcer were more likely having lower limb amputation.

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