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ORIGINAL ARTICLE

What characteristics are most important in stratifying patients into groups with different risk of diabetic foot ulceration?

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ABSTRACT

Aims/Introduction: This study aimed to assess if patients can be divided into different strata, and to explore if these correspond to the risk of diabetic foot complications.

Materials and Methods: A set of 28 demographic, vascular, neurological and biomechanical measures from 2,284 (1,310 men, 974 women) patients were included in this study. A two-step cluster analysis technique was utilised to divide the patients into groups, each with similar characteristics.

Results: Only two distinct groups: group 1 (n = 1,199; 669 men, 530 women) and group 2 (n = 1,072; 636 men, 436 women) were identified. From continuous variables, the most important predictors of grouping were: ankle vibration perception threshold (16.9 ± 4.1 V vs 31.9 ± 7.4 V); hallux vibration perception threshold (16.1 ± 4.7 V vs 33.1 ± 7.9 V); knee vibration perception threshold (18.2 ± 5.1 V vs 30.1 ± 6.5 V); average temperature sensation threshold to cold (29.2 ± 1.1°C vs 26.7 ± 0.7°C) and hot (35.4 ± 1.8°C vs 39.5 ± 1.0°C) stimuli, and average temperature tolerance threshold to hot stimuli at the foot (43.4 ± 0.9°C vs 46.6 ± 1.3°C). From categorical variables, only impaired sensation to touch was found to have importance at the highest levels: 87.4% of those with normal sensation were in group 1; whereas group 2 comprised 95.1%, 99.3% and 90.5% of those with decreased, highly-decreased and absent sensation to touch, respectively. In addition, neuropathy (monofilament) was a moderately important predictor (importance level 0.52) of grouping with 26.2% of participants with neuropathy in group 1 versus 73.5% of participants with neuropathy in group 2. Ulceration during follow up was almost fivefold higher in group 2 versus group 1.

Conclusions: Impaired sensations to temperature, vibration and touch were shown to be the strongest factors in stratifying patients into two groups with one group having almost 5-fold risk of future foot ulceration compared to the other.

INTRODUCTION

The lifetime prevalence of diabetic foot ulcer (DFU) is estimated to be 15–25% in people with diabetes[1]. DFU is the main cause of lower limb amputation in patients with diabetes worldwide[1]. The presence of DFU in diabetes patients increases the risk of death at 5 years by 2.5-fold[2]. To decrease the socioeconomic cost associated with DFUs, a knowledge of the clinical characteristics of individual patients with higher risk of developing DFU is necessary. In an earlier study, neuropathy, foot deformity, history of amputation, poor diabetes control, duration of diabetes and elevated plantar pressure were found to be associated with DFU risk[3]. Also, longer diabetes duration and poorer glycemic control were associated with DFU history[4]. In another study, patients with active foot ulcers were independently associated with symptoms of peripheral arterial disease[5].

A previous systematic review of the DFU risk stratification systems identified: (1) foot deformity, (2) peripheral neuropathy

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(vibration perception threshold [VPT] or cutaneous insensitivity to monofilament), (3) peripheral arterial disease (pulses and/or ankle-brachial index), (4) previous amputation, (5) the presence of callus, (6) glycated hemoglobin, (7) tinea pedis, and (h) onychomycosis as prognostic factors that are commonly used to predict the risk of ulceration[6]. A recent systematic review of the literature and meta-analysis reported insensitivity to a 10-g monofilament or one absent pedal pulse as prognostic factors to identify patients with moderate or intermediate risk of foot ulceration[7]. Also, a history of DFUs or lower-extremity amputations was reported to be sufficient to identify those at high risk of developing DFU[7].

Despite these findings to date, all systematic reviews and meta analyses used conventional statistics, where the DFU future incident was treated as the outcome measure in a prospective setting[8]. There is a scarcity of studies in which all variables describing the patient status in conjunction with the DFU incident are investigated to assess whether similarities and differences between those can be used to classify patients into risk groups.

The aim of the present study was to assess if patients can be divided into different strata based on a variy of measures and if the strata correspond to the risk of DFU. The first objective was to assess if patients can be stratified into distinct strata based on similarities and differences in common characteristics.

The second objective was to investigate if these strata are associated with the risk of future DFU.

MATERIALS AND METHODS

Participants

A total of 2,281 (1,307 men, 974 women) diabetes patients who attended a diabetic foot service at Abbas Medical Center – a specialist clinic in Dar-es-Salam, Tanzania – between January 2011 and December 2015 participated in the present study. This clinic had a comprehensive outpatient capacity, and is one of the main diabetic foot clinics in Eastern, Western and Central Africa with a focus on diabetic foot complications as a result of diabetes. The primary inclusion criterion was the patient being diagnosed with diabetes. Sample size calculations were carried out using a sample size calculator for cluster analyses (Kohn MA, Senyak J. Sample Size Calculators: https://www.sample-size.net) with an alpha level of 5% and beta level (type II error rate) 20%; and assuming an effect size of 0.12, at least 2,180 participants were needed.

Ethical approval was sought and granted by the local ethics committee. This study used secondary anonymized data and received ethical approval from an independent ethics committee constituted at Abbas Medical Center (Ref: Ethics/StaffsUni/03-2016). All data were collected by a clinical research assistant employed at the center, and data collection from each participant took 90 min, including the preparation and consent. Foot ulcer was defined as a full-thickness wound involving the foot or the ankle, distal to and including the malleoli.

Data collection

A combination of categorical and continuous measures (as follows) were collected from the participants at a single visit at baseline.

Categorical measures

The general categorical measures were: diabetes type (type 1 or type 2), smoking (current smoker, never smoked, previous smoker), alcohol habits (currently drinks, never drank, in the past), previous amputation and history of ulceration.

The foot-specific categorical measures included: pedal pulse, foot deformity, Charcot foot, skin status (dry, normal), swelling and presence of callus.

Specific categorical measures for each participant were defined as if these occurred on either or both feet for each participant.

Continuous measures

The general continuous measures included: age, body mass, height, shoe size, duration of diabetes and body mass index. The foot-specific continuous measures were: ankle-brachial index, vibration perception threshold, temperature sensation and tolerance thresholds, and barefoot plantar pressure.

The vibration perception threshold was measured using a clinically accepted device neuropathy analyzer (Vibrotherm Dx; Diabetic Foot Care India Pvt Ltd, Chennai, India) at the wrist, knee, ankle and big toe. This device was also used to measure the temperature sensation and temperature tolerance thresholds to cold/warm stimuli at: the hallux, third toe, fifth toe, underneath the arch and heel.

A plantar pressure platform (EMED; Novel, Munich, Germany) was used to measure the average peak plantar pressure during the stance phase of walking at 16 sites (hallux, 2nd toe, 3rd toe, 4th toe, 5th toe, 1st metatarsal head [MTH], 2nd metatarsal head, 3rd metatarsal head, 4th metatarsal head, 5th metatarsal head, lateral midfoot, centre of the midfoot, medial midfoot, lateral hindfoot, medical hindfoot, center of the hindfoot). The participants were asked to walk over the platform using a two-step protocol. The mean of the average pressures from three stance phases from each foot was calculated based on which peak pressures were reported.

Neuropathy was assessed using 10-g monofilament for loss of sensation[9]. This was assessed on both feet at 10 sites including: hallux, third toe, fifth toe, first MTH, third MTH, fifth MTH, lateral midfoot, medial midfoot, center of the hindfoot and dorsum of the foot[10]. The Ipswich Touch Test involved lightly touching/resting the tip of the index finger for 1–2 s on the tips of the first, third and fifth toes[11]. Touch sense status was defined as follows: normal as 0 insensate sites, decreased as one to three insensate sites, highly decreased as four or five insensate sites and absent as six insensate sites from the total six sites tested.

The specific continuous measurements were averaged between the left and right feet. The patients were then followed for a median of 133 days (range 2,904 days) until their first ulcer occurrence, where 166 patients ulcerated.

Statistical analysis

All statistical tests were carried out using IBM® SPSS®v.28 (IBM Corp., Armonk, NY, USA).

Cluster analysis

A two-step cluster analysis technique was used to divide the participants into subgroups, where participants in each subgroup showed similar characteristics. The two-step cluster analysis procedure is an exploratory tool designed to show natural groupings (or clusters) within a dataset that would otherwise not be apparent. The algorithm used can handle both the categorical and continuous variables, and the selection of a number of clusters is automatic by comparing the values of a model-choice criterion across different clustering solutions. Therefore, the grouping and the number of groups are not forced.

The two-step cluster analysis procedure is summarized as follows:

Step 1. The procedure begins with the construction of a cluster features tree by placing the first case at the root of the tree in a leaf node that contains variable information about that case. Based on similarity to existing nodes and using the distance measure as the similarity criterion, each successive case is then added either to an existing node or forms a new node.

Step 2. The leaf nodes of the cluster features tree were then grouped using an agglomerative clustering algorithm. The agglomerative clustering can be used to produce a range of solutions. To determine which number of clusters is “best”, each of these cluster solutions is compared using Schwarz’s Bayesian criterion clustering criterion. The autoclustering process created the Schwarz’s Bayesian criterion changes for scenarios from two to 15 clusters, and identified that when the number of clusters showed as two, the best reduction in Schwarz’s Bayesian criterion was achieved (Table 1).

After completing the procedure, only two clusters were identified.

Test of differences between the two identified clusters

The χ^2-test for independence with Yates’s continuity correction was used to identify a significant ($P < 0.05$) association between categorical variables between the two clusters.

Furthermore, given the normal distribution of the data, an independent T-test was used to assess significant ($P < 0.05$) differences in continuous variables between the two clusters. The differences between the two clusters are highlighted in (Tables 2–5). Further information is provided in the Results section, and the tables are explained in the text and in the legends in the relevant section. The significance level for the P Value was 0.05 and those appear in Bold in (Tables 2–6). In addition (Figures 1–3) also provide a graphic description of the two clusters in relation to the specific measures.

Table 1 | The auto-clustering process showing the Schwarz’s Bayesian criterion changes for scenarios from two to 15 clusters.

No. clusters	BIC	BIC change[†]	Ratio of BIC changes[‡]	Ratio of distance measures[§]
1	114,107.637			
2	**88,513.939**	**−25,593.698**	**1.000**	**8.431**
3	86,496.035	−2,017.904	0.079	1.094
4	84,749.700	−1,746.335	0.068	1.291
5	83,656.836	−1,092.864	0.043	1.639
6	83,439.912	−216.923	0.008	1.031
7	83,263.997	−175.915	0.007	1.103
8	83,212.210	−51.787	0.002	1.135
9	83,304.225	92.015	−0.004	1.241
10	83,602.880	298.654	−0.012	1.013
11	83,912.317	309.437	−0.012	1.391
12	84,459.503	547.186	−0.021	1.241
13	85,124.786	665.283	−0.026	1.031
14	85,804.956	680.169	−0.027	1.022
15	86,495.530	690.574	−0.027	1.031

It is clear that when the number of clusters is two, the best reduction in Schwarz’s Bayesian criterion was achieved. BIC, Schwarz’s Bayesian criterion. †The changes are from the previous number of clusters in the table. ‡The ratios of changes are relative to the change for the two-cluster solution. §The ratios of distance measures are based on the current number of clusters against the previous number of clusters.

RESULTS

The cluster sizes were 1,199 patients (669 men, 530 women) in cluster 1, and 1,072 patients (636 men, 436 women) in cluster 2, with 13 (5 men, 8 women) who did not belong to any of the two clusters and were considered as outliers (Table 2). Figure 1 shows the distribution of patients at different levels of neuropathy assess with touch sensation across the two clusters.

The size ratio between the two clusters was 1.12. (Tables 2 and 3) represent the results related to the test of differences in categorical variables. (Tables 4 and 5) show the differences in the continuous variables.

Categorical variables

The strength of categorical variables in identifying the cluster

From the categorical measures, only two specific categorical measures, including the neuropathy (assessed using monofilament; importance 0.52) and touch sensation level (importance 1.00; Figure 1), were shown to be most important in identifying which cluster the patient belongs to (Table 3).

The differences in the categorical variables between the two clusters

In relation to ulceration, a significantly lower proportion of the patients in cluster 1 had a current ulcer or ulcerated during

Table 2 | General categorical variables, including the previous ulceration, callus and amputation history, along with lifestyle factors, such as smoking and drinking habits, for all participants and for participants in each cluster

	All (2,271)		Cluster 1 (1,199–52.8%)		Cluster 2 (1,072–47.2%)		Importance in predicting cluster	χ^2-test of independence			
	Count	%	Count	%	Count	%	Range 0–1 with 1 being the most important predictor	χ^2	*P*-value	Effect size Phi/ Cramér's V†	Effect size category‡
Male	1,307	57.5	636	59.3	671	55.9	0.00	2.548	0.110	−0.034	Small
Previous ulceration	20	0.9	4	0.3	16	1.5	0.01	7.441	**0.006**	−0.062	**Small**
Amputation	14	0.6	1	0.1	13	1.2	0.01	10.019	**0.002**	−0.072	**Small**
Current ulcer	164	7.2	27	2.2	137	12.8	0.07	92.153	**0.000**	−0.203	**Medium**
Presence of callus	363	16.0	181	15.1	182	17.0	0.00	1.373	0.241	−0.026	Small
Current smoker	133	5.8	81	6.7	52	4.8	0.01	18.612	**0.000**	0.090	**Small**
Never smoked	1,742	76.6	946	78.8	796	74.2					
Past smoker	399	17.5	174	14.5	225	21.0					
Current alcohol cons.	292	12.8	167	13.9	125	11.6	0.01	15.533	**0.000**	0.082	**Small**
No alcohol consumption	1,257	55.3	694	57.8	563	52.5					
Past alcohol consumption	725	31.9	340	28.3	385	35.9					
Dry skin	2,055	90.4	1,081	90.0	974	90.8	0.00098	0.298	0.585	0.013	Small
Future ulcer at follow up	166	7.3	32	2.7	134	12.5	0.06	79.376	**0.00**	0.189	**Medium**

P-values <0.05 show a significant association and are shown in bold in the table. †The χ^2-test of independence (with Yates's continuity correction). ‡Effect size for χ^2 (Phi) number of rows = 2, Two categories: 0.01 small, 0.30 medium, large 0.50; effect sizes for χ^2 (Cramér's V); number of rows equal to 3–3; categories: 0.07 small, 0.21 medium, 0.35 large; effect sizes for χ^2 (Cramér's V); number of rows equal to 4–4; categories: 0.06 small, 0.17 medium, 0.29 large.

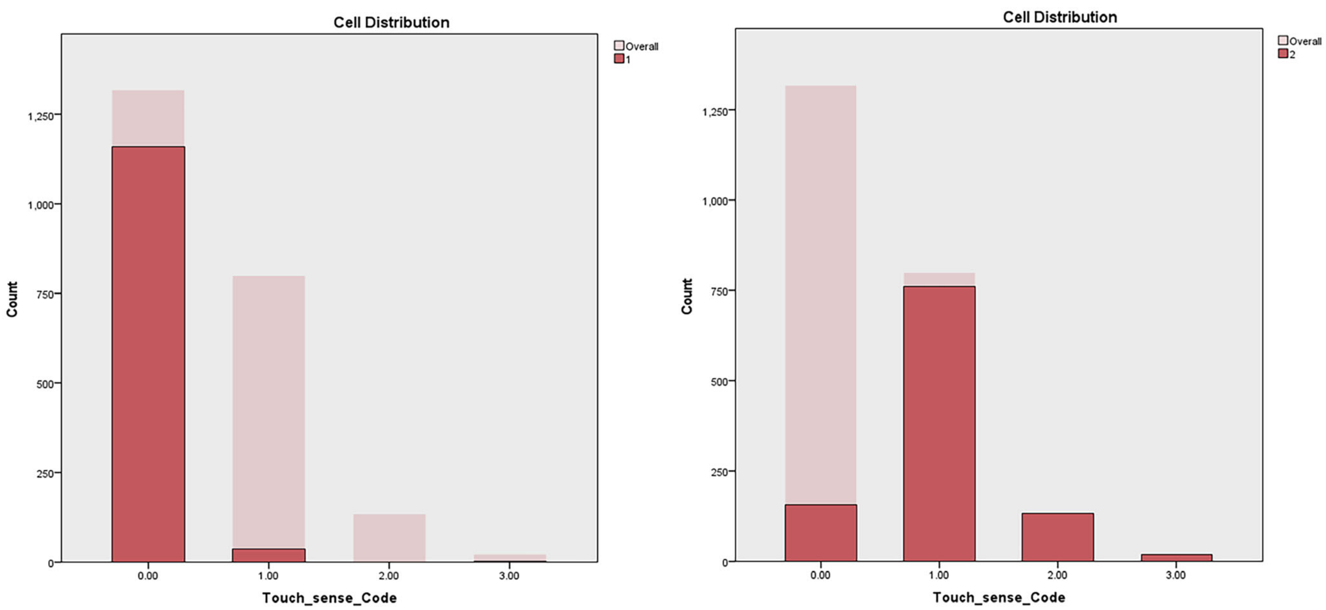

Figure 1 | Distribution of participants across four different levels of sensations: normal (0), decreased (1), highly decreased (2) and absent (3) - Left: Group 1 in solid versus total shaded and Right: Group 2 solid versus total shaded. This shows the proportion of patients with impaired sensation is much higher in Group 2.

follow up, both with a medium effect size compared with cluster 2 (Table 2). A significantly higher proportion of patients in cluster 2 had neuropathy, and compromised touch sensation, both with a large effect size (Table 3). With a medium effect size, A significantly higher proportion of patients in Cluster 2 had foot swelling or limited ankle mobility (Table 3).

Table 3 | Specific categorical variables indicating neuropathy, nail ingrowth, mycosis and foot deformity, along with biomechanical factors, such as foot swelling, and for all participants and for paticipants in each cluster

Categorical variable	All (2,271)		Cluster 1 (1,199–52.8%)		Cluster 2 (1,072–47.2%)		Importance in predicting cluster	χ^2-test of independence			
	Count	%	Count	%	Count	%	Range 0–1 with 1 being the most important predictor	χ^2	*P*-value	Effect size (Phi/ Cramér's V)†	Effect size category‡
Neuropathy	1,215	53.4	318	26.5	897	83.6	0.52	740.775	**0.000**	0.572	**Large**
Foot deformity	43	1.9	20	1.7	23	2.1	0.00	0.461	0.497	0.017	Small
Mycosis	55	2.4	16	1.3	39	3.6	0.01	11.772	**0.001**	–0.075	**Small**
Nail ingrowth	15	0.7	4	0.3	11	1.0	0.00	3.154	0.076	–0.043	Small
Charcot foot	3	0.1	1	0.1	2	0.2	0.00098	0.010	0.922	0.014	Small
Foot swelling	150	6.6	25	2.1	125	11.6	0.07	82.657	**0.000**	–0.192	**Medium**
Limited ankle mobility	155	6.8	27	2.2	128	11.9	0.04	93.512	**0.000**	0.203	**Medium**
Limited MTP joint mobility	417	18.3	149	12.4	268	25.0	0.05	58.961	**0.000**	0.162	**Medium**
Normal touch sensation	1,321	58.1	1,162	96.8	159	14.8	1.00	1563.588	**0.000**	0.829	**Large**
Decreased touch sensation	798	35.1	36	3.0	762	71.0					
Highly decreased touch sensation	134	5.9	1	0.1	133	12.4					
Absent sensation	21	0.9	2	0.2	19	1.8					

P-values <0.05 show a significant association and are shown in bold in the table. MTP, metatarsophalangeal. †χ^2-test of independence (with Yates's continuity correction). ‡Effect size for χ^2 (Phi); number of rows = 2; Two categories: 0.01 small, 0.30 medium, large 0.50; effect sizes for χ^2 (Cramér's V); number of rows equal to 3–3; categories: 0.07 small, 0.21 medium, 0.35 large; effect sizes for χ^2 (Cramér's V); number of rows equal to 4–4; categories: 0.06 small, 0.17 medium, 0.29 large.

A significantly higher proportion of patients in cluster 1 had normal sensation to touch compared with patients in cluster 2, with a large effect size (Table 3).

Continuous variables

The strength of categorical variables in identifying the cluster

From the continuous measures, vibration perception threshold at the ankle (Figure 2), knee and wrist, and average vibration perception threshold were all strong predictors of the cluster with an importance of 1. Temperature sensation threshold to cold, temperature sensation threshold to hot and temperature tolerance threshold to hot were shown to be the important predictors of clusters (importance 1; Table 4).

After those, temperature tolerance threshold to cold (importance 0.79), vibration perception threshold at wrist (importance 0.51) and duration of diabetes (importance 0.24) were the most important predictors of clusters (Table 4).

The differences in the ankle sensitivity measures as VPT (Volts) between the two clusters

The patients in cluster 1 were shown to have significantly lower VPT average (by 16.7 V), duration of diabetes (by 1687.3 days), (TST) Temperature Sensatio Threshold to hot probe average (by 4.1°C), (TTT) Temperature Tolerance Theshold to hot probe average (by 3.2°C), wrist VPT (by 3.2 V), knee VPT (by 11.8 V), ankle VPT (by 15.0 V) and hallux VPT (by 17.1 V).

In addition, the patients in cluster 1 were shown to have a significantly higher TST to cold probe average (by 2.5°C) and TTT to cold probe average (by 3.0°C), shown in (Table 4).

Cluster 1 had a significantly higher plantar pressure at all toes, and at medial midfoot, lateral hindfoot, center of hindfoot, medial hindfoot and at the second MTH, all with small effect size (Table 5). Cluster 1 had a significantly lower in 5th MTH, with small effect size (Table 5).

Clusters and the association to future foot ulceration

Patients in cluster 2 were 4.6-fold more likely to have future foot ulcers during follow up, as shown in (Figure 3) and as highlighted in (Table 2).

DISCUSSION

Only two distinct clusters were identified where a majority of important predictors (importance level 1.0) of grouping were associated to the neuropathy-related characteristics.

Sensation to touch; temperature sensation threshold to warm and cold stimuli; temperature tolerance threshold to hot stimuli; VPTs at the ankle, knee and hallux; and average VPT were the strongest predictors of the cluster to which the patient belonged. These findings are interesting and are in line with the previous systematic review of literature where peripheral neuropathy assessed using VPT was reported as a criterion associated with stratification of patients based on the risk of

Table 4 | Continuous parameters including the age, duration of diabetes along with weight, height and body mass index, along with the neuropathy-related variables for all participants and for participants in each cluster

Continuous variables	Mean	All (2,271)	Cluster 1 (1,199–52.8%)		Cluster 2 (1,072–47.2%)		Importance in predicting Cluster	Independent sample *t*-test			Effect size category[†]
		SD	Mean	SD	Mean	SD	Range 0–1 with 1 being the most important predictor of cluster	Mean difference	*P*-Differences	Effect size Cohen's *d*	
Age (years)	51.8	12.0	49.0	12.5	55.0	10.6	0.11	–6.0	**0.000**	–0.512	**Medium**
Height (m)	1.59	0.09	1.58	0.09	1.59	0.09	0.01	–0.02	**0.000**	–0.174	**Small**
Weight (kg)	74.7	16.0	75.4	16.2	73.9	15.8	0.00	1.5	**0.030**	0.091	**Very Small**
Body mass index (kg/m²)	29.8	6.2	30.3	6.3	29.1	6.1	0.02	1.1	**0.000**	0.184	**Small**
Ankle-brachial index	1.08	0.13	1.09	0.12	1.07	0.14	0.02	0.02	**0.000**	0.184	**Small**
Vibration perception threshold average (V)	23.2	10.6	15.3	4.8	32.0	8.0	1.00	–16.7	**0.000**	–2.551	**Large**
Duration of diabetes (days)	2,051	2,313	1,250	1,749	2,959	2,531	0.24	–1687.3	**0.000**	–0.784	**Large**
TST to cold probe average (°C)	28.7	30.5	29.2	1.1	26.8	0.7	1.00	2.5	**0.000**	2.649	**Large**
TST to hot probe average (°C)	37.4	4.0	35.4	1.8	39.5	1.1	1.00	–4.1	**0.000**	–2.704	**Large**
TTT to cold probe average (°C)	20.0	3.8	21.4	2.6	18.3	0.8	0.79	**3.0**	**0.000**	1.493	**Large**
TTT to hot probe average (°C)	45.0	2.8	43.5	1.0	46.7	1.4	1.00	**–3.2**	**0.000**	–2.765	**Large**
Vibration perception threshold wrist (V)	11.6	3.1	10.1	2.4	13.3	2.8	0.51	**–3.2**	**0.000**	–1.223	**Large**
Vibration perception threshold knee (V)	23.8	8.3	18.2	5.1	30.1	6.5	1.00	**–11.8**	**0.000**	–2.032	**Large**
Vibration perception threshold ankle (V)	24.0	9.6	16.9	4.2	32.0	7.5	1.00	**–15.0**	**0.000**	–2.513	**Large**
Vibration perception threshold hallux (V)	24.1	10.7	16.1	4.8	33.2	7.9	1.00	**–17.1**	**0.000**	–2.640	**Large**
Blood glucose level (mmol/L)	15.1	8.1	14.5	7.7	15.7	8.4	0.01	**–1.283**	**0.000**	–0.159	**Small**

P-values <0.05 show a significant association and are shown in bold in the table. †Cohen's *d* categories as small = 0.2; medium = 0.5; large = 0.8. TTT, Temperature Tolerance Theshold; TST, Temperature Sensatio Threshold.

DFU[6]. Also, VPT at the wrist was found to be an important predictor (importance 0.51) for identifying the cluster to which the patients belong to. This is an interesting finding that shows that peripheral neuropathy in general is associated with clustering.

The results regarding the temperature sensation threshold to cold stimuli is in line with our own previous studies where these were associated with the presence of DFU[12] or with an increased risk of future DFU[13]. Also, the results of the present study where the temperature sensation threshold to warm stimuli, and both the temperature sensation and tolerance threshold to hot stimuli were the strongest predictors of cluster are in line with our previous study, where these are associated with increased risk of future DFU[13]. In addition, the findings of the current study are in line with our previous study in which temperature sensation and tolerance thresholds to cold stimuli were shown to significantly decrease the risk of future ulcer occurrence[13].

In addition, the findings of the current study in relation to the strength of the sensation to touch variable in clustering

Table 5 | Peak plantar pressure during walking at different regions of the foot for all participants and for participants in each cluster

Continuous variables	All (2,271)		Cluster 1 (1,199–52.8%)		Cluster 2 (1,072–47.2%)		Importance in predicting cluster	Independent sample *t*-test			
	Mean	SD	Mean	SD	Mean	SD	Range 0–1 with 1 being the most important predictor	Mean difference	*P* differences[a]	Effect size Cohen's *d*	Effect size category
Plantar pressure at hallux (KPa)	269.9	125.3	281.6	125.2	256.8	124.4	0.02	24.2	**0.000**	0.194	**Small**
Plantar pressure at 2nd toe (KPa)	145.5	76.9	151.2	78.7	139.0	74.4	0.01	11.9	**0.000**	0.155	**Small**
Plantar pressure at 3rd toe (KPa)	98.2	57.0	102.0	57.5	94.0	56.2	0.01	7.9	**0.000**	0.138	**Small**
Plantar pressure at 4th toe (KPa)	64.9	41.4	68.5	42.2	60.8	40.3	0.02	7.6	**0.000**	0.183	**Small**
Plantar pressure at 5th toe (KPa)	36.9	30.2	39.9	32.1	33.7	27.5	0.02	6.2	**0.000**	0.207	**Small**
Plantar pressure 1st MTH (KPa)	174.6	79.9	172.2	75.3	177.5	85.1	0.00	−5.3	0.119	−0.066	Very small
Plantar pressure at 2nd MTH (KPa)	213.9	74.5	217.0	72.7	210.2	76.5	0.00	7.0	**0.025**	0.094	**Very Small**
Plantar pressure at 3rd MTH (KPa)	232.0	75.8	234.3	71.3	229.2	80.4	0.00	5.5	0.086	0.073	Very Small
Plantar pressure at 4th MTH (KPa)	221.8	74.5	220.6	67.8	223.0	81.4	0.00	−1.8	0.568	−0.024	Very Small
Plantar pressure at 5th MTH (KPa)	207.4	103.6	200.7	91.4	215.2	115.6	0.01	−15.0	**0.001**	−0.145	**Very Small**
Plantar pressure at lateral midfoot (KPa)	80.6	35.8	81.4	34.1	79.7	37.8	0.00	1.8	0.237	0.050	Very Small
Plantar pressure at center of midfoot (KPa)	105.4	47.3	105.5	45.4	105.3	49.5	0.00	0.4	0.854	0.008	Very Small
Plantar pressure at medial midfoot (KPa)	69.1	27.9	70.8	27.9	67.1	27.8	0.01	3.6	**0.002**	0.131	**Very Small**
Plantar pressure at lateral hindfoot (KPa)	118.8	40.0	122.9	39.4	114.2	40.3	0.02	8.6	**0.000**	0.217	**Small**
Plantar pressure at center of hindfoot (KPa)	172.4	47.2	175.9	47.9	168.4	45.9	0.01	6.9	**0.000**	0.147	**Small**
Plantar pressure at medical hind foot (KPa)	126.6	45.6	130.7	46.0	121.9	44.7	0.02	8.7	**0.000**	0.192	**Small**

P-values <0.05 show a significant association and are shown in bold in the table. [a]Signifcance at *P* <0.05. MTH, metatarsal head; SD, standard deviation. Cohen's *d* categories as small = 0.2; medium = 0.5; large = 0.8.

patients is in line with our previous study, where decreased, highly decreased and absent sensation to touch increased the risk of future DFU by at least three-, five and ninefold compared with patients with intact touch sensation[13].

With a lower-strength neuropathy, assessed as impaired sensation to a monofilament, was found to be one of the predictors (importance 0.52), which is in line with the systematic review of the literature, where insensitivity to a 10-g monofilament was reported as a prognostic factor to identify patients with moderate or intermediate risk of foot ulceration[7]. This result on neuropathy is also in line with our previous study, where the presence of neuropathy was reported to increase the risk of future DFU BY 2.5-fold[13].

The results of the present study show that the two clusters were significantly different in relation to neuropathy, measured as impaired sensation to a monofilament with a large effect size. This is in line with our previous studies in which neuropathy was associated with either the presence of ulcer[12] or with the future incidence of ulcer[13]. In a previous study, we found that having neuropathy increases the risk of future DFU by 2.5-fold[13], and that is in line with the current study, in which only 2.7% of the patients in cluster 1 versus 12.5% of the patients in cluster 2 had DFU during follow up.

The results are also in line with another previous study in which we found that having neuropathy is significantly associated with DFU with a large effect size[12], and that is in line with

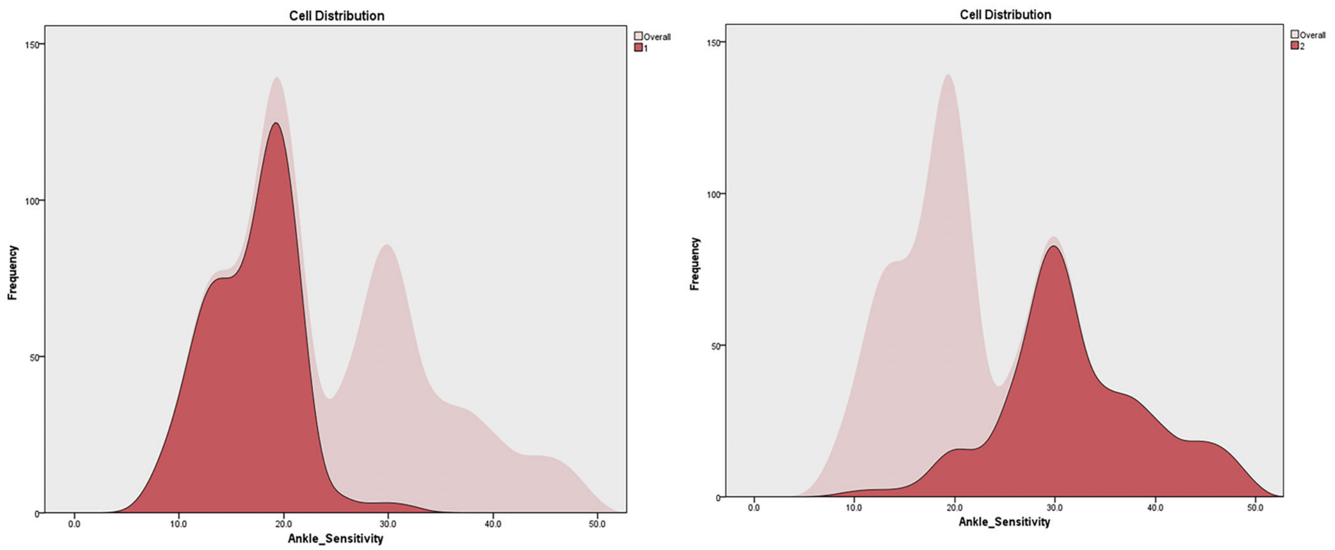

Figure 2 | Distribution Of vibration perception threshold (VPT) at the ankle (in Volts) in Left: group 1 solid versus total shaded and Right: group 2 solid versus total shaded. This shows the vibration perception threshold for patients in group 2 is much higher compared with patients in group 1.

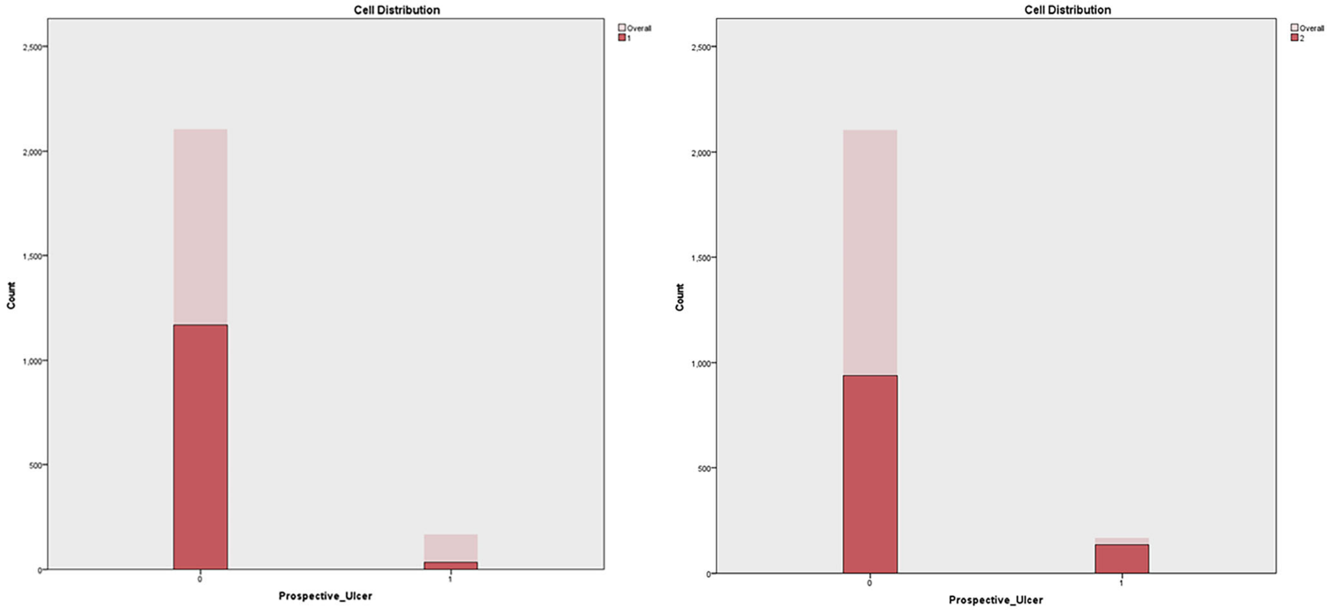

Figure 3 | Distribution of participants across without and with future ulcers. Left: Group 1 in solid versus total shaded and Right: Group 2 solid versus total shaded. This shows the proportion of patients with future ulcers is much higher in Group 2.

the current study in which only 2.2% of the patients in cluster 1 versus 12.8% of patients in cluster 2 had current DFU with medium effect size.

The results of the current study where foot swelling was 5.5-fold more prevalent in cluster 2 compared with cluster 1 is in line with the previous study, where foot swelling was associated with current ulcer with a large effect size[12] or was shown to increase the risk of future DFU by 3.3-fold[13].

In addition, the results of the current study on limited ankle and metatarsophalangeal joint mobility were 5.4- and twofold more prevalent in cluster 2 compared with cluster 1, respectively, are in line with the previous study, where these variables were associated with increased risk of future DFU by 1.7- and 2.7-fold[13].

Also, these results are in line with the previous study, where having current ulcers was associated with an increased likelihood of having limited range of motion of the ankle joint[12].

The average, TTT and TST to cold probe was significantly lower for cluster 1, whereas the corresponding values for TTT and TST to hot probe were significantly higher in cluster 2 (all with large effect size). This is in line with the findings in which significantly higher thermal sensitivity in patients with active DFU[12] and in those with increased risk of future DFU[13] are reported.

In the current study, the values of VPT at the wrist, knee, ankle and hallux were significantly lower in cluster 1 (large effect size), which are in line with the finding that cluster 1 had fewer patients with neuropathy. Specifically, the difference in VPT seems to be 17.1 V, which is the highest VPT difference out of the four sites tested. Although, the fact that the blood glucose level was shown to be significantly lower in cluster 1 (small effect size) seems to indicate a lower level of diabetes severity in this cluster.

The results of the current study on plantar pressure, where patients in cluster 1 (with a generally lower level of neuropathy) showed higher plantar pressure at the majority of regions compared with patients in cluster 2 (with generally higher level of neuropathy) in general, are somehow in contradiction with the results of a previous systematic review[14].

Meta-analysis for plantar pressure at the forefoot showed greater plantar pressure in the forefoot of DPN patients (n = 177) at moderate effect levels compared with diabetes patients with no neuropathy (n = 102)[14]. This is in contrast to the present study, where the pressure at all toes and at the second MTH was found to be significantly lower in cluster 2, but in line with the results of the current study, where the plantar pressure at the fifth MTH was significantly higher in cluster 2 (with higher levels of neuropathy)[14].

The results of the current study, where the plantar pressure was found to be significantly lower at the medial midfoot in cluster 2 (with generally higher levels of neuropathy), are in contrast to the meta-analysis results, where greater plantar pressure in DPN patients (n = 108) compared with those with diabetes (n = 55) was reported at the midfoot[14].

In relation to the lower plantar pressure in cluster 2 at the rearfoot, the results of the current study are in contrast to the reported higher rearfoot plantar pressure in patients with DPN (n = 108) compared with those with diabetes (n = 55) with moderate effect sizes[14].

Overall, the results of the present study on peak plantar pressure are in contrast with the previous systematic review of literature[14]. However it needs to be taken into account that the reported results are based on a smaller sample of participants; that is, <200[14], compared with the current study, where >2,000 patients were included.

As shown in the Results section, the patients in cluster 2 were found to have 4.6-fold the risk of future DFU. This is interesting, and indicates that the cluster analyses proposed here can identify the patients in the medium- and high-risk category[7].

As shown earlier, a recent systematic review of literature and meta-analysis (Prediction of Diabetic Foot Ulcerations [PODUS]) reported sensitivity to a 10-g monofilament or one absent pedal pulse as prognostic factors to identify patients with moderate or intermediate risk of foot ulceration[7]. Although, a history of DFUs or lower-extremity amputations were reported to be sufficient to identify those at high risk of developing DFU[7].

To compare how the two clusters differ with regard to diabetic foot risk classification, the PODUS risk score[7] and Clinical Prediction Rule scores[15] were calculated for each participant. (Table 6) shows the comparative results of the PODUS and Clinical Prediction Rules for predicting DFU for the two clusters. As shown in (Table 6), a significantly higher proportion of patients in cluster 2 versus cluster 1 are in the PODUS high-risk category (2.2% vs 0.3%). Also, a significantly higher proportion of patients in cluster 2 versus cluster 1 are in the PODUS medium-risk category (82.7% vs 27.1%), as shown in (Table 6). By contrast, a significantly higher proportion of patients in cluster 1 versus cluster 2 are in the PODUS low-risk category (72.6% vs 15.1%), as shown in (Table 6).

In fact, when the average PODUS score between the clusters was calculated, it was found that the average PODUS score in cluster 1 was found to be 0.277 ± 0.455, which was significantly lower than the PODUS score for cluster 2, which was found to be 0.817 ± 0.396.

In addition, when the clinical prediction rule based on the scoring from monofilament testing, presence/absence of pulses, and participant history of previous ulcer and/or amputation[15], was used, there were significant differences between the two clusters.

This indicated that 72.6% of patients had a risk score of 0 (where the chance of ulcer in 2 years was reported be 2.4%) in cluster 1, which was significantly higher than the 45.1% with a risk score of 0 in cluster 2 (Table 6). In contrast, 79.1% of patients in cluster 2 were shown to have a risk score of 1 (where the chance of DFU in 2 years is 6%[15]), which is a significantly higher proportion than the related 26.3% proportion in cluster 1 (Table 6). Similarly, 3.7% of patients in cluster 2 had a risk score of 2 (where the chance of DFU in 2 years is 14%[15]), which is a significantly higher proportion than the related 0.9% proportion in cluster 1 (Table 6). In addition, 2.1% of patients in cluster 2 had a risk score of 3 (where the chance of DFU in 2 years is 51%[15]), which is a significantly higher proportion than the related 0.2% proportion in cluster 1 (Table 6). The average CPR score for predicting DFU in cluster 1 was found to be 0.286 ± 0.482, which was significantly lower than the score for cluster 2, which was calculated to be 0.927 ± 0.515.

Table 6 | Prediction of Diabetic Foot Ulcerations and Clinical Prediction Rule (CPR) scores for all participants and for paticipants in each cluster

Categorical variable	All (2,271)		Cluster 1 (1,199–52.8%)		Cluster 2 (1,072–47.2%)		χ^2-test of independence			
	Count	%	Count	%	Count	%	χ^2	*P*-value	Effect size (Phi/ Cramér's V)[†]	Effect size category[‡]
PODUS score 0 (low risk)	1,043	45.6	872	72.6	162	15.1	759.391	**0.000**	0.407	**Large**
PODUS score 1 (moderate risk)	1,217	53.2	325	27.1	887	82.7				
PODUS score 2 (high risk)	28	1.2	4	0.3	24	2.2				
Clinical prediction rule score 0	1,043	45.6	872	72.6	162	45.1	763.483	**0.000**	0.408	**Large**
Clinical prediction rule score 1	1,169	51.1	316	26.3	849	79.1				
Clinical prediction rule score 2	52	2.3	11	0.9	40	3.7				
Clinical prediction rule score 3	24	1.0	2	0.2	22	2.1				
Clinical prediction rule score 4	0	0	0	0	0	0				

[†]χ^2-test of independence (with Yates's continuity correction). [‡]Effect size for Chi square (Phi); number of rows = 2; two categories: 0.01 small, 0.30 medium, large 0.50; Effect sizes for Chi square (Cramer's V) number of rows equal to 3 – 3 Categories: 0.07 small, 0.21 medium, 0.35 large.

The two-step cluster analysis procedure is an exploratory tool designed to reveal natural groupings (or clusters) within a dataset that would otherwise not be apparent. The algorithm works by comparing the values of a model-choice criterion across different clustering solutions, where the procedure can automatically determine the optimal number of clusters, using the criterion specified in the clustering criterion group. although the two-step cluster analysis works with both continuous and categorical variables, the likelihood distance measure assumes that variables in the cluster model are independent. Also, the continuous variables are assumed to have a normal (Gaussian) distribution, and the categorical variables are assumed to have a multinomial distribution. Although the sources of bias for other clustering methods were highlighted by Lorimer et al.[16], for the two-step cluster analyses, the empirical internal testing shows that the procedure is fairly robust to violations of both independence and the distributional assumptions.

In the present study, it was found that patients can be divided into two strata identified by the two clusters that correspond to the risk of DFU. We showed that without imposing any restriction or promoting any specific number of clusters, the patients can be stratified into distinct groups based on similarities and differences in a few common characteristics. The strongest predictors of clusters were related to neuropathy. It was found that the risk score and vulnerability to future DFU, and the incidence of DFU during follow up were significantly higher in cluster 2, in which neuropathy was more prevalent.

Although neuropathy can be assessed through a variety of means, the inclusion of different ways of assessing neuropathy in the present study was essential to ensure that there was no bias for or against any of the methods of neuropathy assessment. Specifically, assessing neuropathy through VPT and touch sensation can be more directly associated with assessment of large fibers impairments. However, temperature perception threshold can assess small fiber neuropathy. It is interesting that the results of this study showed that both the tests related to small and large fiber impairments were among the most important predictors of grouping. In a sense, the results of this study can indicate that small- and large-fiber neuropathy are both linked to the severity of diabetic foot complications, as shown through the associations with a higher prevalence of ulcers and future ulcers in cluster 2.

The clustering technique proposed here can be used to identify the cluster to which the patient belongs, and can have implications in stratifying patients into lower- and higher-risk categories for future DFU. Impaired sensations to temperature, vibration and touch were shown to be the strongest factors in stratifying patients into groups, which also reflects the risk of future foot ulceration.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: This study used secondary anonymized data from a wider study carried out at Abbas Medical Center, Dar es Salaam, Tanzania. It received ethical approval from an independent ethics committee constituted at Abbas Medical Centre (Ref: Ethics/StaffsUni/03-2016).
Informed consent: All participants gave informed consent before taking part.
Approval date of registry and the registration no. N/A.
Animal studies: N/A.

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