Received: 12 January 2023 | Revised: 26 March 2023 | Accepted: 26 April 2023

DOI: 10.1002/dmrr.3674

WILEY

REVIEW ARTICLE

Predicting diabetic foot ulceration using routinely collected data in a foot clinic. What level of prognostic accuracy can be achieved?

Roozbeh Naemi[1] | Gayathri Balasubramanian[1] | Tracey Darvel[2] | Nachiappan Chockalingam[1]

[1]Centre for Biomechanics and Rehabilitation Technologies, School of Health Science and Wellbeing, Science Centre, Staffordshire University, Stoke-on-Trent, UK

[2]The Hillingdon Hospital, Central and North West London NHS Foundation Trust, Uxbridge, UK

Correspondence
Roozbeh Naemi, Staffordshire University Ringgold Standard Institution, Stoke-on-Trent ST4 2DE, UK.
Email: r.naemi@staffs.ac.uk

Abstract

This study aimed to investigate the efficacy of using routinely collected clinical data in predicting the risk of diabetic foot ulcer (DFU). The first objective was to develop a prognostic model based on the most important risk factors objectively selected from a set of 39 clinical measures. The second objective was to compare the prediction accuracy of the developed model against that of a model based on only the 3 risk factors that were suggested in the systematic review and meta-analyses study (PODUS). In a cohort study, a set of 12 continuous and 27 categorical data from patients (n = 203 M/F:99/104) who attended a specialised diabetic foot clinic were collected at baseline. These patients were then followed-up for 24 months during which 24 (M/F:17/7) patients had DFU. Multivariate logistic regression was used to develop a prognostic model using the identified risk factors that achieved $p < 0.2$ based on univariate logistic regression. The final prognostic model included 4 risk factors (Adjusted-OR [95% CI]; p) in total. Impaired sensation (116.082 [12.06–1117.287]; $p = 0.000$) and presence of callus (6.257 [1.312–29.836]; $p = 0.021$) were significant ($p < 0.05$), while having dry skin (5.497 [0.866–34.89]; $p = 0.071$) and Onychomycosis (6.386 [0.856–47.670]; $p = 0.071$) that stayed in the model were not significant. The accuracy of the model with these 4 risk factors was 92.3%, where sensitivity and specificity were 78.9%, and 94.0% respectively. The 78.9% sensitivity of our prognostic 4-risk factor model was superior to the 50% sensitivity that was achieved when the three risk factors proposed by PODUS were used. Also our proposed model based on the above 4 risk factors showed to predict the DFU with higher overall prognostic accuracy. These findings have implications for developing prognostic models and clinical prediction rules in specific patient populations to more accurately predict DFU.

KEYWORDS
clinical prediction rules, diabetic foot, prognostic model, risk factor, stratification, ulcers

1 | INTRODUCTION

Diabetic Foot Ulcer (DFU) is the main cause of non-traumatic lower limb amputation worldwide.

The lifetime prevalence of DFU is reported to be between 15% and 25%[1] in a person with diabetes, while a recent study estimates this figure to be higher.[2] Nearly half of the diabetic foot ulcers become infected[3] and one in five moderate or severe diabetic foot infections lead to amputation.[4,5] It has been reported that the presence of DFU increases the risk of death at 5 years by 2.5 times.[6]

Systematic reviews of existing literature identify many predictive factors including impaired sensation, peripheral vascular disease, peak plantar pressure, foot deformities and fasting blood sugar as risk factors for diabetic foot ulcers.[7,8] Also, age, duration of diabetes, height, body weight and Body Mass Index (BMI) have been associated with the risk of DFU occurrence.[7,8] An earlier systematic review of the risk factors for diabetic foot ulceration identified foot deformity, peripheral neuropathy (Vibration Perception Threshold-VPT or cutaneous insensitivity to monofilament), peripheral arterial disease (pulses and/or ankle brachial index), previous amputation, the presence of callus, HbA1c, Tinea pedis, and onychomycosis as prognostic factors that can predict the risk of ulceration.[9]

In studies focusing on validation and comparison of existing diabetic foot risk models, it was concluded that the existing models show high efficacy represented as the area below receiver operating characteristic (ROC) ranging from 0.73 to 0.86 and with no significant difference in accuracy between them.[10] However, in a later multicentre prospective cohort study the authors reported considerable differences in the efficacy of predictions when they applied to a hospital versus community settings i.e. the area below the ROC curve could differ between 0.46 in a community setting for a risk prediction model and 0.86 for another model.[10,11] Recently, the prognostic factors for foot ulceration in people with diabetes were investigated as part of the international research collaboration for the prediction of diabetic foot ulcerations known as PODUS.[12]

This investigation proposed a multivariable prognostic model based on a systematic review and meta-analysis using individual patient data from 10 studies to predict foot ulceration.[12] In PODUS, the history of DFU, insensitivity to a 10-g monofilament and any absent pedal pulse were identified as consistent independent predictors of DFU.[12] This 3 risk-factor prognostic model proposed in PODUS was reported to have a sensitivity of 90.0%–95.3% and a specificity of 12.1%–63.9%.[12] This prognostic model was reported to compare favourably with the more complex approaches to foot risk assessment recommended in clinical diabetes guidelines.[12] However, the data in those studies were collected during a period no later than 2008 within a mix of settings from the hospital to primary care, outpatients, and tertiary care units.[12]

This indicates that although this 3-risk factor prognostic model proposed by PODUS compares favourably with more complex models in general,[12] the variability which was previously reported for existing risk models across different settings[11] can also exist. These indicate that there is a need for assessing the efficacy of using routinely collected data in predicting the risk of DFU in the first place and to compare the accuracy of such against that of proposed by the 3-risk factor PODUS prognostic model.

Hence, this study aimed to assess the efficacy of using routinely collected clinical data at a foot clinic setting in predicting DFU. The first objective was to develop a prognostic model based on the most important risk factors that are objectively selected from a set of routinely collected clinical data. The second objective was to compare the prediction accuracy of the developed model against that of a model based on only the 3 risk factors that were suggested in PODUS.[12]

2 | MATERIALS AND METHODS

Data from a routine NHS clinic in England was analysed as a part of this work. This audit received necessary governance approvals prior to any data reduction and synthesis. Data from patients ($n = 203$, M/F:99/104) who attended the specialised diabetic foot clinic were included in this study. The primary exclusion criterion was the presence of any DFU at baseline. Diabetic foot ulcer was defined as a full-thickness wound involving the foot or the ankle, distal to and including the malleoli. The sample size was calculated using logistic regression with a power of 0.95 and Alpha 0.05, Odds Ratio of 1.8 for future ulceration. This resulted in a sample size of 203 participants who would also provide 80% power to detect hazard ratios of 1.6.

An initial database that included 211 patients was identified. Eight patients had missing data and were removed from the data set and the participants with complete and no missing data set were 203 patients who were all included in the study.

The baseline characteristics of the patients were collected during their initial visit between January 2017 and December 2018. The categorical and continuous measures are shown in Tables 1 and 2. The primary inclusion criteria were that the patient was diagnosed with diabetes.

The categorical and continuous parameters assessed are shown in Tables 1 and 2. In addition, data related to previous ulceration, and amputation along with foot-specific characteristics such as muscle weakness and foot deformity were also assessed. Twenty-five out of 203 participants in the study had a history of previous ulceration (Table 2).

Skin status was considered as Dry when the epidermis lacked moisture or sebum; and Normal when the skin was well-balanced eudermic that is neither too oily nor too dry.[13] Tinea pedis and onychomycosis[14] and the presence of callus were recorded.[15,16]

A 10-g monofilament was used on 10 sites for each foot and sensation in less than 8 out of 10 sites was considered as neuropathy.[17] The vibratory and blunt sensations were tested over the tip of the great toe bilaterally and the abnormal response was defined as when the patient loses sensation.[1,18]

The foot-specific categorical parameters for each participant were defined as if these occurred on either or both feet for each participant. The presence of triphasic, biphasic, monophasic, or

TABLE 1 Continuous measures and the corresponding values for all participants and for those with and without ulcer incident during follow-up.

	All			No ulcer incident			With ulcer incident			Mann-Whitney *U* test		Univariate logistic regression	
Continuous variable	Med	IQR	*N*	Med	IQR	*N*	Med	IQR	*N*	*p*	Effect size (*r*)	Odd ratio (95% CI)	*p* value
Age (years)	76	17	203	76	15	179	74	27	24	0.868	−0.01	0.998 (0.964–1.033)	0.946
Weight (kg)	84.5	21.15	69	80.85	23.69	52	89	40.5	17	0.008	−0.32	1.041 (1.011–1.072)	**0.007**
BMI (kg/m^2)	30.5	9.57	68	30.3	9.5	54	31.9	13.3	14	0.299	−0.13	1.042 (0.979–1.109)	0.186
HbA1c (mmol/mol)	58	23	170	57.00	22.25	150	67.50	26.25	20	**0.01**	−0.20	1.024 (1.004–1.046)	**0.019**
Creatinine (μmol/L)	79	31	105	78.50	29.50	96	102.00	54.50	9	0.05	−0.19	1.013 (0.999–1.027)	0.055
Duration since the diagnosis of diabetes (years)	13	15	181	12	15	160	19	15	21	0.359	−0.07	1.009 (0.971–1.049)	0.637
Left dorsal pedis systolic pressure (mm HG)	150	26	197	149	26	173	153	39	24	0.448	−0.05	1.008 (0.991–1.026)	0.349
Right dorsal pedis systolic pressure (mm HG)	150	27	198	149.5	28	174	150	22	24	0.691	−0.03	1.004 (0.986–1.022)	0.678
Left posterior tibialis systolic pressure (mm HG)	153	34	198	152.5	34	174	158	36	24	0.581	−0.04	1.002 (0.984–1.019)	0.862
Right posterior tibialis systolic pressure (mm HG)	152	30	198	151	30	174	160	27	24	0.382	−0.06	1.008 (0.99–1.026)	0.411
Brachial systolic pressure (mm HG)	132	20	200	134	20	176	130	18	24	0.533	−0.04	1 (0.972–1.028)	0.993
Brachial diastolic pressure (mm HG)	72	15	52	73	14	47	70	16	5	0.554	−0.08	0.979 (0.888–1.08)	0.673
Left dorsalis pedis ABI	1.14	0.21	199	1.13	0.21	175	1.18	0.21	24	0.492	−0.05	2.273 (0.213–24.216)	0.496
Left posterior tibialis ABI	1.15	0.19	200	1.15	0.20	176	1.18	0.19	24	0.945	0.00	0.962 (0.096–9.675)	0.974
Right dorsalis pedis ABI	1.13	0.20	199	1.13	0.20	175	1.11	0.21	24	0.982	0.00	1.452 (0.112–18.793)	0.775
Right posterior tibialis ABI	1.16	0.19	199	1.16	0.20	175	1.19	0.18	24	0.474	−0.05	2.941 (0.233–37.155)	0.405

Note: The results from the test of difference (Mann-Whitney) and univariate logistic regression are also shown. The values in bold show the significant parameters for the corresponding test. The underlined values show the parameters that achieved $p < 0.2$ in Univariate analyses which were also included in the Multivariate analyses.

Abbreviation: ABI, ankle brachial index; mm Hg, millimeters of mercury.

absence of pulse in the dorsalis and posterior tibiali arteries were collected. Neuropathy was assessed as the presence or absence of sensation to: 10-g monofilament, vibration, sharp/blunt sensation felt on Hallux, 1st and 3rd Metatarsophalangeal joint. Also, the presence of Paraesthesia, numbness, burning sensation, pain, and proprioception was assessed.

Gender, Smoking habits (Current smoker, Never smoked, Previous smoker) as well as the Type of diabetes (Type 1 or 2), Presence or absence of other comorbidities or pathological conditions, angina, hyperlipidaemia, hypertension, retinopathy, and history of surgery data were also collected.

Age, body mass, duration of Diabetes and BMI as well as the clinical characteristics including HbA1c and Creatinine were measured. The vascular parameters were Brachial systolic and diastolic pressure, the systolic pressure in dorsalis pedis and posterior tibiali arteries and Ankle Brachial Pressure Index were also collected.

During 24 months of follow-up, 24 (M/F:17/7) patients had DFU. DFUs were 7 on the right foot only, 16 on the left foot only, and 1 on both feet. The majority of ulcers were at the forefoot with only 5 at the rear-foot. Because of the limitations in the number of ulcers at each site, this study did not consider the location of ulcers in the analyses. Using IBM® SPSS®v.26, a Chi-square test for independence with Yates Continuity Correction was utilised to identify significant ($p < 0.05$) differences in categorical measures between the two groups (with and without DFU during follow-up). Furthermore, given the non-normal distribution of the data, which was established through the test of normality (Kolmogorov-Smirnov, $p < 0.05$), Mann-Whitney *U*-Test was utilised to assess significant ($p < 0.05$) differences in continuous measures between the patients with and without DFU during follow-up. Univariate Logistic Regression was utilised to identify parameters and their odds ratio contributed to predict the DFU risk during follow-up.

Multiple logistic regression analysis was utilised to find the contributory factors to DFU during follow-up. The purposeful selection of parameters in the multiple logistic regression model was

TABLE 2 Categorical measures and the corresponding values for all participants and for those with and without ulcer incident during follow-up.

	Total (203)		No ulcer occurrence 179 (88.18%)		With ulcer occurrence 24 (11.82%)		Univariate logistic regression		Chi square test of independence			
Categorical variable	Count	%	Count	%	Count	%	*p* value	Odd ratio (95% CI)	Chi value	*p* value for differences	Effect size for differences	Effect size
I. General (non-clinical) categorical parameters												
Gender (ref male)	99	48.77%	82	45.81%	17	70.83%	**0.026**	2.873 (1.136–7.267)	5.304	**0.021**	0.162[a]	Small
Smoker (ref smoker)	10	0.49%	7	0.39%	3	0.125%	0.267	2.642 (1.231–4.053)	4.323	0.115	0.147[b]	Medium
Type diabetes (ref type 2)	186	91.63%	164	91.62%	22	91.67%	0.936	0.936 (0.20–4.411)	0.006	0.936	−0.006[a]	Small
Presence of other comorbidities/other conditions (ref yes)	199	98.03%	175	97.77%	24	100.00%	0.999	N/A	0.411	0.522	0.045[a]	Small
Presence of angina (ref yes)	19	9.36%	18	10.06%	1	4.17%	0.366	0.386 (0.049–3.034)	0.877	0.349	−0.066[a]	Small
Hyperlipidaemia (ref yes)	166	81.77%	148	82.68%	18	75.00%	0.331	0.608 (0.223–1.659)	0.958	0.328	−0.069[a]	Small
Hypertension (ref yes)	165	81.28%	145	81.01%	20	83.33%	0.824	1.138 (0.365–3.551)	0.050	0.824	0.016[a]	Small
Retinopathy eye (ref yes)	35	17.24%	27	15.08%	8	33.33%	0.034	2.778 (1.082–7.128)	4.804	**0.028**	0.155[a]	Small
III. General foot characteristics												
Muscle wasting in the limb (ref yes)	5	2.46%	2	1.12%	3	12.50%	**0.006**	13.125 (2.068–83.309)	11.852	**0.001**	0.243[a]	Small
Dry skin in the foot (ref yes)	110	54.19%	89	49.72%	21	87.50%	**0.002**	7.000 (2.016–24.308)	11.991	**0.001**	0.244[a]	Small
Tinea pedis (ref yes)	24	11.82%	22	12.29%	2	8.33%	0.570	0.645 (0.142–2.932)	0.327	0.567	−0.040[a]	Small
Skin onychomycosis (ref yes)	12	5.91%	9	5.03%	3	12.50%	0.162	2.683 (0.673–10.696)	2.097	0.148	0.102[a]	Small
Foot deformity (ref yes)	23	11.33%	18	10.06%	5	20.83%	0.130	2.339 (0.779–7.021)	2.409	0.121	0.109[a]	Small
Callus in the foot (ref yes)	97	47.78%	82	45.81%	15	62.50%	0.135	1.951 (0.811–4.692)	2.288	0.130	0.106[a]	Small
Nail deformity (ref yes)	74	36.45%	67	37.43%	7	29.17%	0.421	0.682 (0.269–1.731)	0.654	0.419	−0.057[a]	Small
IV. Ulcer history												
Previous history of foot ulcer (ref yes)	25	12.32%	11	6.15%	14	58.33%	**0.00**	21.382 (7.747–59.012)	53.376	**0.000**	0.513[a]	Large
V. Amputation history												
Previous history of foot amputation (ref yes)	3	1.48%	1	0.56%	2	8.33%	**0.025**	16.182 (1.409–185.837)	8.786	**0.003**	0.208[a]	Small
VI. Vascular characteristics												
Dorsalis pulse (ref absent or monophasic)	1	0.49%	1	0.56%	0	0%	1	0	0.135	0.714	−0.026[a]	Small
Posterior tibialis pulse (ref absent or monophasic)	2	0.98%	1	0.56%	1	4.17%	0.153	7.739 (0.468–127.985)	2.824	0.093	0.118[a]	Small
VIII. Neuropathy parameters												
Impaired monofilament sensation (ref abnormal)	54	26.60%	33	18.44%	21	87.50%	**0.000**	30.738 (8.660–109.239)	51.349	**0.000**	0.504[a]	Large
Absent vibration perception (128 Hz) (ref absent)	67	33.99%	46	25.70%	21	87.50%	**0.000**	20.087 (5.724–70.490)	36.270	**0.000**	0.424[a]	Medium

TABLE 2 (Continued)

Categorical variable	Total (203)		No ulcer occurrence 179 (88.18%)		With ulcer occurrence 24 (11.82%)		Univariate logistic regression		Chi square test of independence			
	Count	%	Count	%	Count	%	*p* value	Odd ratio (95% CI)	Chi value	*p* value for differences	Effect size for differences	Effect size
Absent sharp/blunt sensation (ref absent)	62	30.54%	41	22.91%	21	87.50%	**0.000**	23.390 (6.641–82.380)	41.317	**0.000**	0.452[a]	Medium
Paraesthesia (ref yes)	24	11.82%	17	9.50%	7	29.17%	**0.008**	3.900 (1.417–10.731)	7.773	**0.005**	0.196[a]	Small
Numbness (ref yes)	38	18.72%	26	14.53%	12	50.00%	**0.000**	5.846 (2.373–14.405)	17.346	**0.000**	0.293[a]	Medium
Burning sensation (ref yes)	13	6.40%	11	6.15%	2	8.33%	0.688	1.380 (0.287–6.640)	0.163	0.687	0.028[a]	Very small
Pain sensation (ref yes)	20	9.85%	12	6.70%	8	33.33%	**0.000**	6.917 (2.466–19.399)	16.764	**0.000**	0.288[a]	Medium
Proprioception (ref absent)	6	2.96%	5	2.79%	1	4.17%	0.675	1.600 (0.178–14.360)	0.179	0.672	0.030[a]	Very small

Note: The results from the test of association (Chi-square) and univariate logistic regression are also shown. The values in bold show the significant parameters in the corresponding test. The underlined values show the parameters that achieved $p < 0.2$ in Univariate analyse which were also included in the Multivariate analyses.

[a]Effect size as the Phi coefficient, with Small = 0.01, Medium = 0.30, Large = 0.50.

[b]Effect size as Cramer's V coefficient (three categories), where Small = 0.07, Medium = 0.21, Large = 0.35.

based on the univariate analyses in which variables with $p < 0.2$ were selected.[19]

There were a total of 20 parameters where the Univariate analyses resulted in $p < 0.2$ added to the multivariate mode. These included 4 continuous parameters (as highlighted in Table 1) and 16 categorical parameters (as highlighted in Table 2). An automated backward stepwise Wald's selection algorithm where variables with $p < 0.05$ were retained based on the probability of the Wald statistic was used to perform multivariate logistic regression analyses using the 20 parameters (which showed $p < 0.2$ in prior Univariate analyses). These 20 parameters, were analysed in the multivariate analyses using the backward stepwise Wald's selection algorithm to ensure that any interrelationship and co-dependencies between parameters that may be interrelated are taken into account.

The logistic regression is based on the Backward stepwise method in which the parameters were selected based on the backward elimination that begins by entering all terms specified on the stepwise list into the model first. From there, the algorithm alternates between forward entry (with *p* value threshold for stepwise entry at 0.05) on the terms left out of the model and backward elimination (with *p* value threshold for stepwise removal at 0.10) on the stepwise terms in the model. This continues until no terms meet the entry or removal criteria and where the final model can be identified. Hence, the final model will include parameters with significance at $p < 0.1$ out of which some may be significant at $p < 0.05$.

3 | RESULTS

All results related to the categorical and continuous measures are presented in Tables 1 and 2 respectively.

Whilst comparing the continuous parameters between the groups with and without ulcer using Mann-Whitney *U*-Test, weight and HbA1C were significantly ($p < 0.05$) higher in the group with a future ulcer when compared to the group without ulcers; all with small to moderate effect size.

Also, the Chi-square test for independence showed a significantly higher proportion of those who ulcerated were male, had Retinopathy, muscle wasting, dry skin, history of ulceration, history of amputation, insensitivity to monofilament, vibration, and sharp blunt objects, paraesthesia, numbness, and pain.

Univariate Logistic Regression indicated that patients with any of the above characteristics had a significantly higher chance of having diabetic foot ulcers during follow-up (Table 2). Multiple logistic regression (Multivariate) analysis indicated that in the final model (Adjusted-OR [95% CI]), the absence of sensation to monofilament (116.082 [12.06–1117.287]), and the presence of callus (6.257 [1.312–29.836]) in the foot were the only parameters that were statistically significant ($p < 0.05$) predictors of DFU. However, the presence of dry skin (5.497 [0.866–34.89]) and Onychomycosis (6.386 [0.856–47.670]) while stayed in the model, their contribution to predicting DFU was non-significant ($p \geq 0.05$) (Table 3).

TABLE 3 Logistic regression model predicting the likelihood of developing diabetic foot ulcer.

Model parameters	B	S.E.	Wald	Sig.	Exp (B)	95% CI exp (B)	
						Lower	Upper
Dry skin	1.704	0.943	3.266	0.071	5.497	0.866	34.896
Onychomycosis	1.854	1.026	3.268	0.071	6.386	0.856	47.670
Callus	1.834	0.797	5.295	**0.021**	6.257	1.312	29.836
Monofilament	4.754	1.155	16.935	**0.000**	116.082	12.060	1117.287
Constant	−7.780	1.669	21.719	0.000	0.000		

Note: The Odds Ratio is presented as Exp (B) and the B values are coefficients in the logistic regression equation to calculate the probability of a case falling into a specific category. The values in bold show the significant values at $P < 0.05$.

The model's accuracy in the classification was 92.3% with a sensitivity of 78.9% and a specificity of 94.0%. The area under ROC for the model was 0.876. The multiple logistic regression model that included all 4 risk factors was statistically significant (Omnibus Tests of Model Coefficients showed $\chi^2 = 62.179$, $p < 0.0005$). Furthermore, the model explained 61.1% (Nagelkerke R^2) of the variance in future ulcers during follow-up.

4 | DISCUSSION

4.1 | Differences in patients with DFU and with no-DFU during follow-up

The present study highlights that the patients with future DFU occurrence had distinctive characteristics in a set of parameters, majority of which were related to an impaired sensation that is in line with the previous studies[11] in European, Middle Eastern[20] and African population.[21] In addition, a significantly higher proportion of patients who incurred future DFU had a history of ulceration (Large effect size), which is in line with the findings in the European[10,11] Middle Eastern[20] and African[21] populations.

Also with medium effect size, the significant majority of patients who incurred future DFU had shown absent sensation to vibration perception (in line with findings in Middle Eastern[20] and European population[10]) or to Sharp/Blunt sensation; or having numbness or pain sensation that is in line with studies in European population.[11]

However, with a small effect size, the significant majority of patients who incurred future DFU showed paraesthesia. Interestingly, the number of patients who had impairments with regard to proprioception and burning sensation were not significantly different between the two groups.

From the other categorical parameters, only muscle wasting and dry skin were proportionately higher in the group with future ulceration. The result on dry skin is in line with the study in African[21] and in the European[11] populations.

Also with a small effect size, the group who ulcerated was associated with having a higher proportion of patients with a history of amputation, which is generally in line with previous studies in the European population[10] and with the studies in Middle Eastern[20] and African[21] populations.

The results of the current study indicate that a significantly higher proportion of participants with retinopathy develop future DFU, which is in line with the studies in the Middle Eastern population[20] and generally in line with the previous observations on the association of DFU with visual impairment.[11]

The results of the present study also highlight that the group vulnerable to future diabetic foot ulcers have significantly higher HbA1C and creatinine levels, which is in line with the previous finding in the European[11] population.

In addition, the results of the current study also indicate that a significantly higher proportion of participants who developed a future ulcer were males, which is in line with the previous findings in the Middle Eastern population.[20] However, these results of our study is contrary to the previous studies on the European population showed no association between sex and future DFU.[10,11]

We also found that the group with future DFU was significantly heavier (with a large effect size), which contradicts the results of a previous study in which no significant differences in weight were found for those with future DFU in the European[10,11] Middle Eastern[20] and African[21] populations.

4.2 | Independent risk factors associated with increased likelihood (odds) of future diabetic foot ulcer

The associations between weight and HbA1C with increasing the likelihood of DFU occurrence found in the present study are in line with a study conducted on the pooled patient data from Europe and North America.[12]

Also, in the current study, male gender and retinopathy were associated with increased likelihood (OR:2.873 and OR:2.778 respectively) of future DFU that is in line with the results of pooled patient data from Europe and North America (OR:1.69 and OR:2.09 respectively).[12]

In this study muscle wasting was also found to significantly increase the likelihood of future ulceration (OR:13.125) in line with our

previous observations on the effect of diabetes on decreasing muscle strength.[22]

Our results also indicate that having dry skin increases the risk of ulceration (OR:7.000), which is in line with our previous observation in the African population (OR:2.344).[21] Furthermore, the results of this study in which impaired sensation to monofilament (OR:30.738) was found to be in line but much higher compared to the previous studies where (OR:5.61)[11] and (OR:2.525)[21] were reported. Also, impaired sensation to vibration (OR:20.087) that was associated with an increased likelihood of future DFU in this study is higher compared to OR:7.61 previously reported.[12]

In the current study, we also found that insensitivity to sharp/blunt (OR:23.390), paraesthesia (OR:3.900), numbness (OR:5.846), and pain sensation (OR:6.917) increase the likelihood of future DFU that have not been commonly assessed in previous studies.

On the other hand, amputation (OR:16.182) and ulceration history (OR:21.382) were found to be associated with future DFU, which is generally in line with but higher than what was reported in studies of pooled patient data from Europe and North America for the presence of amputation (OR:10.31) and for the history of ulceration (OR:13.74).[12]

4.3 | Prognostic model to predict patients with future DFU

Multiple logistic regression analysis indicated that the prediction accuracy of the current model was 92.3% with a sensitivity of 78.9% and specificity of 94.0%. The logistic regression model contained 4 predictor variables including insensitivity to monofilament, presence of callus, presence of dry skin, and Onychomycosis.

The absence of sensation to monofilament (Adjusted OR:116.082 [12.060–1117.287]), and the presence of callus (Adjusted OR:6.257 [1.312–29.836]) were the only predictor variables that were statistically significant in the model, while the dry skin (Adjusted OR:5.497 [0.866–34.896]) and Onychomycosis (Adjusted OR:6386 [0.856–47.670]) non-significantly contributed to the model in predicting the future incident of diabetic foot ulceration. Whilst the assessment of skin condition is fairly simple and routinely checked in a clinic, the data itself is not recorded systematically and not available in larger cohorts. Therefore, it is difficult to compare our results on skin status against the literature.[13] Although this data is not available routinely in larger cohorts, it is difficult to compare the result of this study on skin status with the literature. However, in our previous prospective cohort study of patients in Africa, we established that the dry skin contributes to increased ulcer risk in patients with diabetic foot disease and is a predictor of DFU.[21]

It should be mentioned that the multivariate logistic regression takes into account the effect of interrelationship between confounding variables. The collinearities, interrelationships and co-dependence between parameters were taken care of by the automated backward stepwise selection algorithm. Also, the possible interdependency between variables was taken care of by this model, as explained in the methodology section that may be interrelated are taken into account.

Our proposed model outperformed the model based on three risk factors PODUS multivariable prognostic model that is based on a systematic review and individual patient data meta-analyses.[12] When the insensitivity to monofilament, absence of any pedal pulse, and history of ulcer or amputation were used in our study (based on what was proposed by PODUS), the sensitivity was only 50% and the specificity was 96.1%, while the overall prediction accuracy was 90.6%. This meant that when only three risk factors proposed in PODUS[12] were to be used for the patient population in the current study, only 1 out of 2 patients who ulcerated in 2 years of follow-up could be identified.

Interestingly, the sensitivity and specificity, which were found in this study based on the three risk factors PODUS-proposed model, were respectively lower than 90.9%–95.6% and higher than 13.2%–63.9% as reported in PODUS study.[12]

Overall it is clear that both sensitivity (78.9%) and overall prediction accuracy (92.3%) that were achieved in the current study using the four risk factors (Insensitivity to monofilament, Presence of callus, Presence of dry skin and Onychomycosis) are higher than what is achieved using the three risk factors (absent pedal pulse, history of ulcer and monofilament insensitivity) based on PODUS.[12]

The area under ROC (area [95% CI]) for the model developed in this study was 0.876 [0.789–0.963], which was higher than the range 0.834 [0.794–0.873] as reported in the PODUS model.[23] However, when the data from the current study and using the three risk factors (absent pedal pulse, history of ulcer, and monofilament insensitivity) as suggested by PODUS[12] were used, the area under the ROC was 0.907 [0.852–0.963]. While this can indicate overall better quality of the model based on three risk factors as proposed by PODUS[12] mainly due to marginally better specificity (i.e. 96.1% vs. 94% in the current study), the 4 risk factor model proposed in the current study shows to be more accurate due to better sensitivity and overall prediction accuracy.

A recent study focused on the development and validation of a clinical prediction rule for diabetic foot ulceration and was validated for community settings.[23] While it is envisaged that there is a need for validation of such models in secondary settings,[23] bespoke prognostic models such as the one developed in the current study are needed to allow more accurate DFU predictions in the first place. The prognostic model proposed in the current study can have such implications. It is foreseeable that upon further validation, developing a clinical prediction rule bespoke to predicting the risk of DFU in diabetic foot clinics at hospital settings could be materialised.

The 78.9% sensitivity achieved here in our study is much higher than the 50% based on 3 risk factors suggested by the PODUS model.[12] However, this is still low, where at least 1 in 5 patients with future DFU are missed in the prediction. In the future, the inclusion of mechanical properties of plantar soft tissue[24] should be considered, which could increase the model sensitivity.

When the average risk of DFU at 2 years of follow-up was calculated based on the three risk factor PODUS model,[12] the

predicted risk was 11.87 ± 20.36%. The risk predicted by the proposed model in this study based on 4 risk factors was 11.20 ± 21.67%. These predicted values are very close to 11.82% (24 out of 203 participants ulcerated in 24 months) prevalence of DFU in this study.

While in the present study the history of previous ulcer was shown to be significant through univariate analyses, this parameter did not stay in the final multivariate model. This is contrary to the PODUS model[12] where one of the risk factors for future ulceration was reported to be a history of ulceration. However, the finding in the current study may be because the presence of callus and neuropathy already accounted for the contribution that the history of previous ulcer could have in the model and hence history of previous ulcer did not stay in the final multivariate model. This would point to the need for separate prognostic models in the future where the risk of first ulcer or the risk of recurrence can be assessed for a specific population. This knowledge combined with the established strategies through systematic reviews such as insole intervention[25] and home monitoring of foot temperature[26] can be effective in decreasing the risk of ulceration in different risk category populations.

Overall, we report that the models proposed based on the 4 parameters in the current study can more accurately predict the risk of ulceration compared to what was proposed in PODUS.[12] While these have implications for developing stratification algorithms and clinical prediction rules[23] for specific patient populations, bigger cohort studies can shed more light on the efficacy of such models in accurately predicting DFU.

AUTHOR CONTRIBUTIONS

Roozbeh Naemi conceived, designed and wrote the first draft of the manuscript and oversaw the process of statistical analyses and the data curation process. Gayathri Balasubramanian performed data clean-up and statistical analyses and compiled and wrote the Results section. Tracey Darvel: Performed the data curation. Nachiappan Chockalingam: Contributed to the revision of the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

None reported.

ETHICS STATEMENT

Ethical approval for analysing the fully anonymised dataset was granted by the University Research Ethics Committee at Staffordshire University.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Roozbeh Naemi https://orcid.org/0000-0002-2998-2883
Gayathri Balasubramanian https://orcid.org/0000-0002-0916-0479
Nachiappan Chockalingam https://orcid.org/0000-0002-7072-1271

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3674.

REFERENCES

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005;293(2):217. https://doi.org/10.1001/jama.293.2.217
2. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375. https://doi.org/10.1056/NEJMra1615439
3. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia*. 2007;50(1):18-25. https://doi.org/10.1007/s00125-006-0491-1
4. Lipsky BA, Berendt AR, Cornia PB, et al. Infectious diseases society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54(12):e132-e173. https://doi.org/10.1093/cid/cis346
5. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJM. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care*. 2003;26(4):1069-1073. https://doi.org/10.2337/diacare.26.4.1069
6. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet Med*. 2016;33(11):1493-1498. https://doi.org/10.1111/dme.13054
7. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. *Diabetologia*. 2011;54(5):1190-1199. https://doi.org/10.1007/s00125-010-2030-3
8. Crawford F, Cezard G, Chappell FM, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). *Health Technol Assess*. 2015;19(57):1-210. https://doi.org/10.3310/hta19570
9. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. *Diabetes Metab Res Rev*. 2012;28(7):574-600. https://doi.org/10.1002/dmrr.2319
10. Monteiro-Soares M, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development. *Eur J*. 2012;167(3):401-407. https://doi.org/10.1530/eje-12-0279
11. Monteiro-Soares M, Ribas R, Pereira da Silva C, et al. Diabetic foot ulcer development risk classifications' validation: a multicentre prospective cohort study. *Diabetes Res Clin Pract*. 2017;127:105-114. https://doi.org/10.1016/J.DIABRES.2017.02.034
12. Crawford F, Cezard G, Chappell FM, PODUS Group. The development and validation of a multivariable prognostic model to predict foot ulceration in diabetes using a systematic review and individual patient data meta-analyses. *Diabet Med*. 2018;35(11):1480-1493. https://doi.org/10.1111/dme.13797

13. Pendsey SP. Understanding diabetic foot. *Int J Diabetes Dev Ctries*. 2010;30(2):75-79. https://doi.org/10.4103/0973-3930.62596
14. Akkus G, Evran M, Gungor D, Karakas M, Sert M, Tetiker T. Tinea pedis and onychomycosis frequency in diabetes mellitus patients and diabetic foot ulcers: a cross sectional - observational study. *Pak J Med Sci*. 2016;32(4):891. https://doi.org/10.12669/pjms.324.10027
15. Edmonds ME, Foster AVM. Diabetic foot ulcers. *Br Med J*. 2006;332(7538):407-410. https://doi.org/10.1136/bmj.332.7538.407
16. Bus SA, van Netten JJ, Lavery LA, et al. IWGDF guidance on the prevention of foot ulcers in at-risk patients with diabetes. *Diabetes Metab Res Rev*. 2016;32:16-24. https://doi.org/10.1002/dmrr.2696
17. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg*. 2006;45(5 Suppl l):S1-S66. https://doi.org/10.1016/S1067-2516(07)60001-5
18. Abbott CA, Carrington AL, Ashe H, et al. The north-west diabetes foot care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med*. 2002;19(5):377-384. https://doi.org/10.1046/j.1464-5491.2002.00698.x
19. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17. https://doi.org/10.1186/1751-0473-3-17
20. Yazdanpanah L, Shahbazian H, Nazari I, et al. Incidence and risk factors of diabetic foot ulcer: a population-based diabetic foot cohort (ADFC study)—two-year follow-up study. *Int J Endocrinol*. 2018;2018:1-9. https://doi.org/10.1155/2018/7631659
21. Naemi R, Chockalingam N, Lutale JK, Abbas ZG. Predicting the risk of future diabetic foot ulcer occurrence: a prospective cohort study of patients with diabetes in Tanzania. *BMJ Open Diabetes Res Care*. 2020;8(1):e001122. https://doi.org/10.1136/bmjdrc-2019-001122
22. Błazkiewicz M, Sundar L, Healy A, Ramachandran A, Chockalingam N, Naemi R. Assessment of lower leg muscle force distribution during isometric ankle dorsi and plantar flexion in patients with diabetes: a preliminary study. *J Diabetes Complications*. 2015;29(2):282-287. https://doi.org/10.1016/J.JDIACOMP.2014.10.007
23. Chappell FM, Crawford F, Horne M, et al. Development and validation of a clinical prediction rule for development of diabetic foot ulceration: an analysis of data from five cohort studies. *BMJ Open Diabetes Res Care*. 2021;9(1):e002150. https://doi.org/10.1136/BMJDRC-2021-002150
24. Naemi R, Chatzistergos P, Suresh S, Sundar L, Chockalingam N, Ramachandran A. Can plantar soft tissue mechanics enhance prognosis of diabetic foot ulcer? *Diabetes Res Clin Pract*. 2017;126:182-191. https://doi.org/10.1016/j.diabres.2017.02.002
25. Crawford F, Nicolson DJ, Amanna AE, et al. Preventing foot ulceration in diabetes: systematic review and meta-analyses of RCT data. *Diabetologia*. 2020;63(1):49-64. https://doi.org/10.1007/S00125-019-05020-7/FIGURES/3
26. Golledge J, Fernando ME, Alahakoon C, et al. Efficacy of at home monitoring of foot temperature for risk reduction of diabetes-related foot ulcer: a meta-analysis. *Diabetes Metab Res Rev*. 2022;38(6):e3549. https://doi.org/10.1002/DMRR.3549

How to cite this article: Naemi R, Balasubramanian G, Darvel T, Chockalingam N. Predicting diabetic foot ulceration using routinely collected data in a foot clinic. What level of prognostic accuracy can be achieved? *Diabetes Metab Res Rev*. 2023;e3674. https://doi.org/10.1002/dmrr.3674