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Development and validation of a clinical prediction rule for development of diabetic foot ulceration: an analysis of data from five cohort studies

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ABSTRACT

Introduction The aim of the study was to develop and validate a clinical prediction rule (CPR) for foot ulceration in people with diabetes.

Research design and methods Development of a CPR using individual participant data from four international cohort studies identified by systematic review, with validation in a fifth study. Development cohorts were from primary and secondary care foot clinics in Europe and the USA (n=8255, adults over 18 years old, with diabetes, ulcer free at recruitment). Using data from monofilament testing, presence/absence of pulses, and participant history of previous ulcer and/or amputation, we developed a simple CPR to predict who will develop a foot ulcer within 2 years of initial assessment and validated it in a fifth study (n=3324). The CPR's performance was assessed with C-statistics, calibration slopes, calibration-in-the-large, and a net benefit analysis.

Results CPR scores of 0, 1, 2, 3, and 4 had a risk of ulcer within 2 years of 2.4% (95% CI 1.5% to 3.9%), 6.0% (95% CI 3.5% to 9.5%), 14.0% (95% CI 8.5% to 21.3%), 29.2% (95% CI 19.2% to 41.0%), and 51.1% (95% CI 37.9% to 64.1%), respectively. In the validation dataset, calibration-in-the-large was −0.374 (95% CI −0.561 to −0.187) and calibration slope 1.139 (95% CI 0.994 to 1.283). The C-statistic was 0.829 (95% CI 0.790 to 0.868). The net benefit analysis suggested that people with a CPR score of 1 or more (risk of ulceration 6.0% or more) should be referred for treatment.

Conclusion The clinical prediction rule is simple, using routinely obtained data, and could help prevent foot ulcers by redirecting care to patients with scores of 1 or above. It has been validated in a community setting, and requires further validation in secondary care settings.

Significance of this study

What is already known about this subject?

- Foot ulcers can lead to amputation and are costly to healthcare providers.
- Prediction of who will develop an ulcer means preventative therapies can be targeted appropriately.
- Current prediction models do not give precise risk estimates but a descriptive term instead, for example, 'intermediate risk', which is hard to interpret.

What are the new findings?

- A simple, validated clinical prediction rule that quantifies risk with scores 0 to 4 using the sum of:
  Score 1 if insensitive to a 10 g monofilament.
  Score 1 if any pedal pulse is absent.
  Score 2 if there is history of previous ulcer or amputation.
- Risks of developing an ulcer for each score are:
  Score 0—risk is 2.4% (95% CI 1.4% to 3.9%).
  Score 1—risk is 6.0% (95% CI 3.5% to 9.5%).
  Score 2—risk is 14% (95% CI 8.5% to 21%).
  Score 3—risk is 29% (95% CI 19% to 41%).
  Score 4—risk is 51% (95% CI 38% to 64%).
- Patients with a score of 1 or more could benefit from preventative treatment.

How might these results change the focus of research or clinical practice?

- Health professionals will be able to quickly and easily estimate risk of foot ulceration and so direct preventative therapies at those most likely to benefit.

INTRODUCTION

Diabetes-related foot ulcers have severe consequences for the individual and healthcare systems providing foot care.[1] Some ulcers lead to lower extremity amputation and ulcers have been linked with higher rates of mortality.[2] Moreover, diabetes-related amputations are now increasing in young and middle-aged adults.[3] In 2016, there were 130 000 people with diabetes discharged from a US hospital with a lower extremity amputation.[4] Estimated costs of treating ulcers vary from $10 000 to $35 000 per ulcer,[5] and the annual direct costs in the USA alone of $176 billion, of which up to a third are related to the lower extremity.[6] Similar costs per capita are seen globally,[7 8] and the National

Health Service in England could save £250 million per year if the prevalence of foot ulceration was reduced by one third.[1]

Since the early 1990s, researchers have been developing tools to predict the risk of a diabetes-related foot ulceration or lower extremity amputation. These tools vary in complexity and include a range of patient data.[9] For example, the QDiabetes tool will calculate risk of amputation or blindness within the next 10 years, though it does not give risk of foot ulceration. Seven predictive tools for foot ulcer (including the American Diabetes Association, the University of Texas Foot Risk System, and the International Working Group on the Diabetic Foot risk classification systems) were tested in a population of 446 people in Portugal. The models all demonstrated relatively high levels of accuracy with C-statistics between 0.75 and 0.86. However, the number of elements required by each predictive model varied from 4 to 15. This variation is reflected in current diabetes clinical guidelines, which recommend the use of between 8 and 10 individual elements from the patients' history or test results, or different combinations of the same, for risk assessment.[10–12] None of these predictive models gives a quantified risk, but a descriptive term such as 'high risk' or a recommendation such as 'refer to foot clinic'.

Certain interventions have been shown to reduce the incidence of foot ulcers. A recent systematic review and meta-analysis found some evidence of effective interventions to prevent foot ulceration. Meta-analyses of dermal infrared thermometry (relative risk 0.41 (95% CI 0.19, 0.86)), complex interventions (relative risk 0.59 (95% CI 0.38, 0.90), and custom-made footwear and offloading insoles (relative risk 0.53 (95% CI 0.33, 0.85)) all reduced the incidence of foot ulcers.[13] Given this existing knowledge of predisposing factors for foot ulceration and the availability of preventative interventions, our aim was to develop and validate a prognostic model and subsequent clinical prediction rule (CPR) to provide a risk estimate for an individual using his or her own data. The CPR should be accurate, simple to use, inexpensive, and produce a quantified risk of foot ulceration within a meaningful timeframe, for patients in primary and secondary care settings.

RESEARCH DESIGN AND METHODS

Source of data

This PODUS 2020 (Prediction of Diabetic foot Ulcerations) project used individual participant data (IPD) from the PODUS 2015 project, which identified predictors of foot ulceration in diabetes by systematic review and meta-analysis (see the online supplemental material for details of PODUS 2015).[14] The search strategies for Medline and Embase were rerun to find new studies published since 2015 and searched to May 2017. We identified one eligible study but a request for data was unsuccessful.[15] The PODUS 2020 inclusion criteria were:

- Studies that recruited people 18 years old or older with a diagnosis of diabetes.
- Participants were ulcer-free at time of recruitment (or if the study recruited some individuals with a current ulcer, it was possible to remove those individuals from the analysis), participants with a history of previous ulcer were eligible.
- Predictors of foot ulcer were assessed at baseline.
- Foot ulcer presence/absence was ascertained at follow-up.

Data from four cohort studies were used to develop the prognostic model and subsequent CPR.[16–19] Data from a fifth cohort study, only available remotely via a Safe Haven facility, were used for external validation.[10 20] The validation dataset was an electronic register, which had taken data from General Practice records and Information Services Division NHS Scotland. The other PODUS 2015 studies were either no longer available[21] or did not have the required predictors.[22–25]

All studies were assessed for their risk of bias using the Prediction model Risk of Bias Assessment Tool (PROBAST).[26] Recruitment dates ranged from May 1995 to November 2007 in the development datasets, and the last follow-up date was December 2008. In the validation dataset, recruitment dates ranged from January 2001 to December 2006 and the final follow-up date was 2007. These studies are described extensively elsewhere.[14]

Participants

Of the four studies used for model development, two studies collected data from people who received care in UK community settings[16 17] and two collected data from people in hospital foot clinics set in mainland Europe and the USA.[18 19] The validation dataset had data from a UK electronic health register. Participants met the above criteria and received standard care for the setting.

Outcome

The outcome was any definition of foot ulceration as used by the contributing studies occurring within 2 years of baseline, as assessed by podiatrists or self-report questionnaires. The largest contributing study,[16] with 6478 participants comprising 78% of the total model development dataset, had data on whether an ulcer had developed within 2 years from baseline, but not the precise date of ulceration. The other development and validation studies either gave time to ulceration or date of last follow-up, so that their data could be harmonized with the largest dataset.[16]

In three of the development datasets,[16 17 19] the assessment of outcome was blinded to predictors where possible. One of the predictors included amputation, which cannot be hidden from the assessor of ulcer outcome.

Selection of predictors

We chose three binary predictors for inclusion in prognostic model and subsequent CPR based on their clinical

plausibility, availability, and testing in PODUS 2015 (see the online supplemental material).[14] The three predictors were (a) insensitivity to a 10 g monofilament, (b) an absent pedal pulse in either foot, and (c) previous history of ulceration or amputation.

Healthcare professionals carried out the test of touch sensation using a 10 g monofilament by applying the monofilament to the plantar aspect of the foot at a variety of sites. Participants then confirmed whether they felt the monofilament.

Healthcare professionals palpated two pulses in each foot, the dorsalis pedis and the posterior tibial pulses. However, a minority may be missing the dorsalis pedis pulse and be healthy.[27]

Previous history of ulceration or amputation was ascertained either at initial assessment or from patient records. Patients were test-positive for previous history if either a foot ulcer or a lower extremity amputation had occurred prior to baseline data collection.

Statistical analyses methods—handling of predictors

The studies varied in the data recorded for insensitivity to 10 g monofilaments and absent pedal pulses. For monofilaments, the number and place of sites on the foot tested by monofilament varied between studies. For pulses, some studies gave the total number of pulses per person, and others had recorded the absence/presence of the two individual pulses on each foot. However, for consistency across studies, the following coding was adopted:

- Insensitivity to monofilaments was coded as 1 if the participant was insensate anywhere on the foot and 0 if the participant could feel the monofilament at all sites.
- Absent pulses was coded as 1 if any of the four pulses (two on each foot) were missing and 0 if all four were present.

Previous history (ulcer and amputation) was consistently coded in the different studies. Data on previous foot ulceration and previous amputation were combined because of the association of amputation with ulceration—they both suggest a propensity to ulcerate.[28] For the prognostic model analysis, previous history was coded as 1 if the participant had a previous ulcer or amputation, and 0 if the participant had never had an ulcer or amputation.

Summary statistics were calculated for all the predictors and an extensive description of all the datasets can be found elsewhere.[14]

Statistical analyses methods—underlying statistical model

The prediction model was logistic regression with the binary outcome of ulcer by 2 years. The predictors were monofilaments, pulses, and previous history of ulcer or amputation, which were forced into the model regardless of statistical significance. We checked with shrinkage factors that the size of the dataset and number of outcomes were adequate to fit the model. See the online supplemental material for details.

Statistical analyses methods—conversion of the prognostic model to a CPR

A general method for converting a prognostic model to a CPR is described by Steyerberg.[29] In essence, the coefficients of the prediction model are used to generate a scoring system (see the online supplemental material), by rounding coefficients and creating risk groups.

Statistical analyses methods—validation of predictive performance

For each participant in the validation dataset,[10 20] we calculated the CPR score from the individual's results for monofilaments, pulses, and previous history.

For each score, the actual risk of ulcer in the validation dataset was compared with the predicted risk of ulcer. Discrimination was assessed by calculating the C-statistic and visual examination of a receiver operating characteristic (ROC) plot. A perfectly discriminating CPR would have a C-statistic of 1, while a CPR with no discrimination beyond chance would have a C-statistic of 0.5. Calibration was assessed with calibration-in-the-large, calibration slope, and calibration plots.[29] A perfectly calibrated CPR would have a calibration slope of 1 and a calibration-in-the-large of 0.

The CPR is a simplification of the prognostic model and so may result in a loss of information. Hence, the performance of the prognostic model was compared with the CPR score in the validation dataset.

Statistical analyses methods—net benefit and decision curve

Finally, we conducted a net benefit analysis to investigate how useful the CPR could be in practice.[30] The net benefit analysis compared a 'treat all' and 'treat none' strategy to 'treat some' where who does and does not receive treatment is decided by the CPR score. The net benefit analysis indicated whether the CPR could have a clinical impact and was assessed with decision curves.[30]

Reporting and software

This study adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines and include a TRIPOD checklist in the online supplemental

Table 1 Demographic results for the development studies (Abbott, Crawford, Monteiro-Soares, Pham)[16–19] and the validation study (Leese)[10 20]

Study	Age (years) mean±SD	Duration of diabetes (years) mean±SD	Men, N (%)
Abbott	61.3±13.2	8.2±8.2	3515 (53.2)
Crawford	70.5±10.0	8.8±8.4	611 (51.2)
Monteiro-Soares	64.3±10.4	15.8±10.4	164 (45.6)
Pham	58.3±12.5	13.9±10.8	124 (50.0)
All development	62.7±13.1	8.8±8.6	4414 (52.5)
Leese	65.1±13.1	6.8±7.8	1931 (56.6)

material.[31] Software used were SAS V.9.4 (www.sas.com) and R V.3.4.2 (https://cran.r-project.org/) for all analyses. The pROC,[32] meta,[33] and rms[34] packages in R were used.

RESULTS

Results of the critical appraisal with the PROBAST tool are given in the online supplemental material. Overall, studies were considered to be at a low risk of bias and applicable to the research purpose. In one development dataset and the validation dataset, outcome was assessed with knowledge of the predictors.[10 18 20]

Participants

Participant flow diagrams for four studies are given in the online supplemental material. These show how many participants did and did not have complete data. One study did not need a flow diagram as it had complete data for the outcome and all three predictors.[18] The number of patients in the development datasets was 8404, and the number who contributed to the analyses was 8255 (98%). The percentage with complete data in the validation dataset was 3324 (97.4%), again high enough not to require multiple imputation.

The median age of the participants was older in the validation dataset (67 years) versus development (64 years) datasets. The percentage of men ranged from 45.6% to 56.6% in the five datasets (see table 1).

The community-based studies[16 17] had smaller percentages of people insensitive to monofilaments or with previous history compared with the secondary care-based studies,[18 19] but broadly comparable percentages with absent pulses (see table 2). The risk of ulcer in the community-based studies[16 17] was at least 10% lower than the secondary based care based studies. The results from the validation dataset[10 20] were more similar to the results from the community based studies[16 17] than the secondary care based studies.[18 19]

Prognostic model development

The number of patients from the development datasets used in the logistic regression models was 8255, with 430 people developing ulcers and 7825 people remaining ulcer-free.

On the log-odds scale, for the logistic regression model using the three clinical predictors, the coefficient for monofilaments was 1.11, for pulses 0.70, and previous history 1.95. These correspond to ORs of 3.00 (95% CI 2.39 to 3.76), 2.01 (95% CI 1.62 to 2.51), and 7.02 (95% CI 5.40 to 9.13), respectively. The estimate of baseline risk was 2.2% (95% 1.7% to 2.8%). See the online supplemental material for the underlying logistic regression equation that forms the prognostic model.

CPR development

After examination of the prognostic model coefficients and the corresponding risks of developing an ulcer given in the online supplemental material, a CPR was created based on the following scoring system:

- Score 1 if insensitive to a 10 g monofilament.
- Score 1 if any pedal pulse is absent.
- Score 2 if there is history of previous ulcer or amputation.

This CPR therefore gives scores from zero to four. The modeling procedure was repeated (see the online supplemental material) with CPR score as the only predictor. Baseline risk was 2.4% (95% CI 1.7% to 3.4%), and the OR for CPR score was 2.57 (95% CI 2.36 to 2.81). Risk of ulceration for each score is given in table 3.

Shrinkage factors for both the prognostic model and the CPR were very close to 1, showing that the sample size was adequate for the analyses (see the online supplemental material for details).

Validation of the CPR in the validation dataset

In the validation dataset, there were 3324 participants with suitable data, of whom 128 had an ulcer by 2 years and 3196 remained ulcer-free.[10 20] The validation plot suggests excellent calibration of risks in the lower risk groups, but slight miscalibration at higher risk groups (see figure 1); however, the net benefit analysis below would recommend the same clinical pathway despite any miscalibration. The calibration slope was 1.139 (95% CI 0.994 to 1.283) and calibration-in-the-large was −0.374 (95% CI −0.561 to −0.187). See the online supplemental

Table 2 Predictor and outcome data in the development studies (Abbott, Crawford, Monteiro-Soares, Pham)[16–19] and validation study (Leese)[10 20]

Study	N in study	% (n) insensitive to monofilament	% (n) missing at least one foot pulse	% (n) with previous ulcer or amputation	% (n) with ulcer outcome at 2 years	% (n) with complete data
Abbott	6603	19.4 (1278)	29.6 (1957)	4.7 (312)	4.4 (291)	98.1 (6478)
Crawford	1193	22.3 (266)	18.8 (224)	7.2 (86)	1.9 (23)	98.5 (1175)
Monteiro-Soares	360	46.1 (166)	20.3 (73)	38.1 (137)	14.4 (52)	100 (360)
Pham	248	74.6 (185)	14.5 (36)	71.4 (177)	27.8 (69)	97.6 (242)
All development studies	8404	22.5 (1895)	27.2 (2290)	8.5 (712)	5.2 (435)	98.2 (8255)
Leese	3412	20.7 (707)	14.0 (478)	5.7 (196)	3.9 (133)	97.4 (3324)

Table 3 Population-based probability of ulcer at 2 years for each CPR score, calculated using Pavlou's method for population-average estimates

CPR score	N patients	Probability of ulcer at 2 years	95% CI
0	4646	0.024	(0.014 to 0.039)
1	2406	0.060	(0.035 to 0.095)
2	676	0.140	(0.085 to 0.213)
3	358	0.292	(0.192 to 0.410)
4	169	0.511	(0.379 to 0.641)

CPR, clinical prediction rule.

material for calibration results in the prognostic model, which are very similar to those of the CPR.

Examination of the ROC curve (see the online supplemental material) suggests very little loss of discrimination performance when using the CPR compared with the prognostic model. The area under the ROC curve for the CPR was 0.829 (95% CI 0.790 to 0.868) and for the prognostic model was 0.834 (95% CI 0.794 to 0.873).

Potential impact of the CPR

The net benefit analysis aimed to balance the risk of not offering treatment to people who would develop an ulcer against treating people who would not develop an ulcer. If the overall risk of ulceration is very high, there will be a benefit to treating everyone. If the overall risk of ulceration is very low, it may not be worth offering treatment to anyone. Between these two extremes, the net benefit analysis suggests that offering treatment to those people with a risk of 6% or more, that is, a CPR score of 1 or more, would correctly weigh risk of ulceration against unnecessary treatment (see online supplemental material).

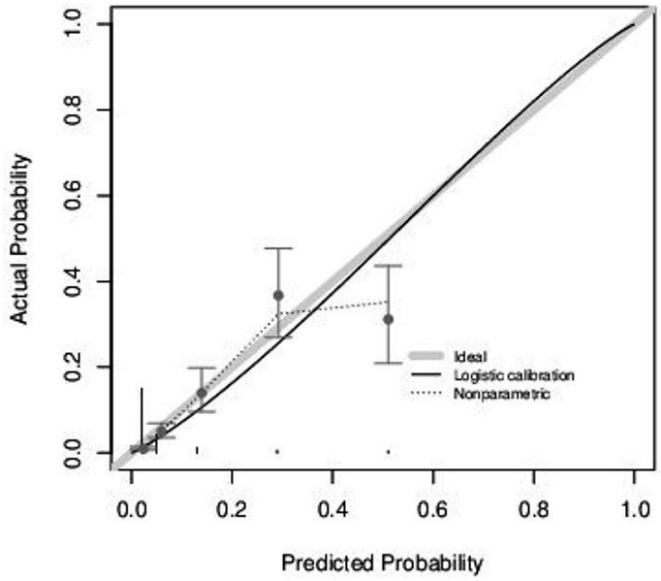

Figure 1 Calibration plot from the external validation of the CPR. Gray line indicates perfect calibration; black curve is the estimated calibration curve. The five groups correspond to CPR scores of 0–4, and vertical lines show the width of the 95% CI. CPR, clinical prediction rule.

CONCLUSION

A CPR was developed and validated to predict foot ulceration within 2 years in people with diabetes. The data came from a large international dataset, which was assembled using a systematic review and IPD meta-analyses.[14 35] The three predictors that form the CPR are easy to collect during patient foot examinations, are usually recorded in health records and therefore this CPR can be applied at the point of care. The 10 g monofilament test is inexpensive and widely used in foot risk assessments (eg, https://gpnotebook.com/simplepage.cfm?ID=x20200630104981911 28), and the assessment of pedal pulses is a standard part of routine foot care. A history of lower extremity amputation or foot ulceration is both well-known risk factors and is highly likely to have been recorded in patient's health records across different healthcare settings.

Other advantages of this CPR are that it requires very little calculation by the end-user and quantifies a person's risk of foot ulceration over a 2-year timescale in a way that is easy to understand. Simplicity, ease-of-use, and cost are all important factors that can affect whether or not a CPR is used in clinical practice. This is especially true in the context of the global health environments, where a CPR using only three predictors may be particularly useful. Furthermore, an analysis of routinely collected foot risk assessment data conducted by the wider research group found only 5% of people at low risk of foot ulceration changed their risk score during a 2-year period.[36] This suggests that biennial, as opposed to annual foot risk assessment for those at low risk of foot ulceration may be adequate.[36] If this simplified CPR was used biennially to assess risk of foot ulceration, the burden on diabetes services across primary care, community and hospital settings could be greatly reduced.

CPRs are a form of Clinical Decision Support System (CDSS), but these can be underused unless they are integrated into existing clinical systems. For example, CDSSs requiring computing software need to be embedded into the IT systems and the healthcare professionals are obliged to use in routine care.[37 38] A CPR that can be used independently of electronic equipment is of value because of the very wide range of IT availability for healthcare professionals across all clinical settings worldwide. In this manuscript, there is a print version of the CPR for use in the consulting room (online supplemental material), and any healthcare professional could learn the risk estimates for each individual score quickly. However, the CPR could also be integrated into existing electronic foot screening programs such as SCI-diabetes (https://www.sci-diabetes.scot.nhs.uk/).

The CPR was developed using individual patient data from three different countries and healthcare systems to make a better assessment of the generalizability and

applicability across different healthcare settings and populations.[39] The authors are unaware of any other CPRs for foot ulceration in diabetes that are equally simple to use and that have had such a robust process of development and validation.

The four international cohort studies which were used in the analyses were designed specifically to identify predictive factors of foot ulceration in people with diabetes. These structured datasets had very few missing values, a characteristic of routinely collected datasets which can undermine the process of validation for prognostic models.[40]

Strengths and limitations

Despite being derived from only three binary predictors, the discrimination and calibration of the CPR were excellent when externally validated in a UK population. There was slight miscalibration in those with the highest risks, but this is acceptable if clinical risk thresholds are likely to be much lower. Indeed, the net benefit analysis suggests that the use of the CPR to identify people who score 1 or above (ie, predicted risk of 6% or above) for subsequent treatment with preventative interventions could bring greater clinical benefits than either treat-all or treat-none strategies and thus is likely to have clinical utility in practice. Further validation in countries other than the UK, Portugal, or the USA would be welcome.

The weaknesses of the CPR and the underlying statistical model lie in its simplicity; as it has only three binary predictors, it will not give predictions across the entire 0 to 1 probability range. However, there are no prognostic models that predict foot ulceration with 100% accuracy and all comprise more sophisticated and expensive tests than this CPR. Also, many outcomes in diabetes are dependent on self-care, and in particular, the maintenance of a tight HbA1c and a body mass index (BMI) lower than 27. Individuals can exert some control over these parameters. HbA1c has a known association with the development of peripheral neuropathy (the main etiology for foot ulceration in diabetes).[41] Initially, HbA1c and BMI were considered for the model in PODUS 2015; however, neither were collected in the largest study.

As CPRs are not treatments in themselves, they do not directly influence clinical outcomes unless they are linked to clinical decision thresholds. The net benefit analysis shows that the CPR has the potential to have clinical utility when a score of one or above is used to trigger treatment, but further evaluation is required where preventative interventions are targeted at those with a score of one or more. As death has also been linked to foot ulceration, ideally, an impact study would account for those participants who died before the end of the 2 years' follow-up and would analyze time-to-ulceration events and incorporate a competing risk model.

The use of this CPR in conjunction with effective preventative interventions could improve patient outcomes by reducing the number of foot ulcers and generate financial savings for the NHS. The simplicity of the CPR means that the cost implications of implementing it in clinical practice are minimal.

The CPR was developed and validated in a large international dataset, but an evaluation of its clinical impact in different patient populations would assess its therapeutic impact. This should be assessed in a prospective comparative study, preferably a randomized controlled trial.

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ONLINE SUPPLEMENT

Background to PODUS 2020

This PODUS 2020 project is a continuation of the work started in the PODUS 2015 project. The results of the PODUS 2015 project have been published as part of the NIHR HTA monograph series (https://doi.org/10.3310/hta19570).

Studies were identified via systematic review and the authors of eight studies[1-8] agreed to give their data. A ninth study was made available via a Safe Haven facility,[9, 10] and the author of a tenth study could not make the data available, but SAS programs (www.sas.com) were supplied to the study statistician so that she could run analyses and return the results to the PODUS team [11].

Selection of predictors

For PODUS 2015, a list of the potential predictors of foot ulceration was made based on clinical plausibility and availability in the datasets. These predictors were:

Age	Insulin regime	Biothesiometer
Sex	Duration of diabetes	Ankle reflexes
Body mass index	Eye problems	Ankle-brachial index
Smoking	Kidney problems	Peak plantar pressure
Height	Insensitivity to a 10g monofilament	Previous ulcer
Weight		Previous amputation
Alcohol use	Absent pedal pulses	Foot deformity
HbA1c	Tuning fork	

These predictors were discussed at an investigators' meeting to choose which should be included in the final model. Several were rejected at this stage for inconsistency of definition across the studies. For example, "eye problems" ranged from overt retinopathy to wearing glasses. Other predictors had been collected in only one or two studies and so were also rejected at this stage. The final PODUS 2015 model had six predictors:

Age	Duration of diabetes	Absent pedal pulses
Sex	Monofilaments	Previous ulcer/amputation

The PODUS 2015 outcome variable was development of a new foot ulcer at any time during the study follow-up. The statistician of the tenth study tested these six predictors using SAS programs supplied by the PODUS team, and she was not otherwise involved in PODUS.

Results were considered to be replicated if the results in the tenth study coincided with those from the eight PODUS studies. The coefficient for each predictor had to be in the same direction in both the PODUS analyses and those from the tenth study, the confidence intervals had to overlap, and the predictor had to achieve statistical significance in the tenth dataset. This process replicated three predictors:

Monofilaments	Absent pedal pulses	Previous ulcer/amputation

Age was not a statistically significant predictor in either the PODUS analyses or in the tenth study. Increasing duration of diabetes increased the odds of foot ulcer in our analyses, but decreased the odds in the tenth dataset. Non-linearity in relationships was checked as an explanation of these results, but no evidence was found of any non-linearity.[12] It turned out that the tenth dataset had very few women (<2%) and so could not be used to confirm sex as a predictor.

Sample size

There was no sample size calculation as the datasets were pre-existing and the analysis simply used all the data available. However, recent sample size guidance [13, 14] was checked, and the size of the dataset and number of outcomes were adequate for the analyses.

The development datasets had 8255 participants, who had 430 ulcer outcomes, which gave 143 events per predictor parameter. Assuming a conservative model performance (Cox-Snell R^2 of 15%), this exceeded the recommended minimum sample size for model development.[14]

In the validation dataset, 295 participants were removed from the analysis as they had already contributed data to one of the development datasets.[2] This reduced the validation dataset from 3707 to 3412. The validation dataset had 128 ulcer outcomes, again exceeding the recommendation of at least 100 events and 100 non-events to validate model performance in an external dataset.[15]

Missing data

The percentage of participants that had missing data for predictors or outcome was calculated. Some participants were missing data on previous history of ulceration or amputation. As both ulceration and amputation are important to record, it was judged that missing data on these events meant that the participant had no previous history of ulceration or amputation. Therefore missing data for history was recoded as negative for this predictor. For the other predictors, other methods for dealing with missing data, such as multiple imputation, would have been considered, but as the proportion of missing data in the development studies was <2.4% and in the validation dataset <2.6%, a complete-case analysis was performed.

Participant flowcharts for each study (see supplementary material) show where data were missing and the effect of recoding of missing data for previous history.

Handling competing risk of death

Some participants died in each study before the end of follow-up. In the community-based studies, one death was recorded in the largest dataset over its two year follow-up period,[1] and 59 people died in the dataset with one year follow-up.[2] In the two secondary care studies, one recorded that 13 people had died,[6] but death was not recorded in the other study.[5] Since death was not systematically recorded in all studies, participants were included whether or not it was known they had died, provided they had complete data on the predictors and outcome before their death. The total number of known deaths (73) comprised less than 1% of the analysis dataset. The CPR therefore assumes that people who died before developing a foot ulcer would not have a foot ulcer by two years.

During the two-year follow-up period of the validation dataset, 95 patients died, 2.8% of 3412. We applied the same method as to the development datasets, and included these people in the analyses if they had complete data on predictors and outcome.

Statistical analysis plan

The analysis used a logistic regression model with random effects on the intercept, so that each study could have a different baseline risk of ulcer by two years. However, one of the development studies only had follow-up for one year, not two[2]. This study did not contribute to the overall estimate of baseline risk in the prognostic model, but it was allowed to contribute to the estimates of odds ratios (see supplementary material), which were deemed similar enough at one year or two years to combine (and preferable to simply excluding the study and losing a large number of participants).

After model development, the potential for overfitting was estimated by calculating a heuristic shrinkage factor. Shrinkage estimates close to one suggest that the model's estimates are not optimistic (i.e. overfitting is of little concern), whereas smaller shrinkage estimates suggest that the model's predictions are optimistic and should be shrunk.

When calculating risks for each score of the CPR, population-averaged risk estimates were calculated, which use the random effects distribution of baseline risks rather than one summary estimate of baseline risk, to allow for the data being clustered in studies. Population-averaged estimates are considered to be more generalizable to participants in new studies.[16]

Steyerberg's method for developing a clinical prediction rule from a statistical model was used [17]. However, the step where the coefficients of predictors are made smaller to compensate for overfitting was omitted. Overfitting is a named given to the phenomenon where statistical models tend to perform better in the datasets they were derived from than independent datasets. This is a particular problem for small datasets, complex models, or large numbers of predictors. The CPR dataset was large, the model simple, and the number of predictors small, and the extent of overfitting with shrinkage factors was estimated and found it to be negligible. Shrinkage was >0.999 in all cases.

Shrinkage was estimated by: [18]

$$\frac{Likelihood\ ratio\ \chi^2 - number\ of\ predictor\ parameters}{Likelihood\ ratio\ \chi^2}$$

Where overfitting occurs, it is recommended that the coefficients of the model are adjusted by multiplying by the shrinkage factor.

As the development dataset comes from four studies, this was accounted for in the analysis by allowing the individual studies to have different baseline risk of ulcer by two years. However, in one of the studies the length of follow-up was only one year [2], Therefore, the baseline risk of ulcer in this study was lower than in the other studies as the participants had less time to develop an ulcer. To address this, the study's Principal Investigator attempted to obtain longer-term follow-up data with limited success, and the PODUS 2020 steering committee advised not to use the longer-term follow-up data.

The prediction model's baseline risk of ulcer at two years was estimated with data from the three studies with at least two-year follow-up [1, 5, 6]. First, a logistic regression model was fitted with study as a predictor in addition to the three clinical predictors to obtain baseline risk estimates for each study. Then a random effects meta-analysis of the three study-specific baseline risk estimates was conducted to obtain an overall baseline risk estimate for the prediction model, giving an estimated risk at two years conditional on the three clinical predictors. The estimates for the three

clinical predictors used all four studies. Heterogeneity in the effect of the clinical predictors was not modelled.

The implementation of Steyerberg's method was:

1. Fit the logistic regression model with monofilament, pulses, previous history of ulcer/amputation, and study as predictors. This gives coefficients showing by how much the log odds changes when monofilaments, pulses, or history change from test-negative to test-positive and estimates of baseline risk for each study. The software used was SAS PROC LOGISTIC (SAS 9.4 www.sas.com) with maximum likelihood estimation.
2. Perform a random-effects meta-analysis of the three estimates from the studies with two years of follow-up to get a single overall estimate of baseline risk.
3. Use this overall estimate and the regression coefficients for the three predictors to calculate the probability of ulcer for each possible predictor combination. There are three binary predictors and therefore eight possible predictor combinations.
4. Multiply and round the coefficients of the predictors to get a CPR scoring scheme, bearing in mind that predictor combinations with similar risk of ulcer should have the same score.
5. Repeat Step 1 and Step 2, only using the CPR score instead of monofilaments, pulses, and history.
6. Calculate probability of ulcer for each score using a population average method.[16] The population average method should produce estimates with better calibration in external datasets and generalisability to people recruited to new studies than simply using the CPR logistic regression equation.

Risk of bias assessment with PROBAST tool

Table 1 Results of PROBAST[19] evaluation for the development studies (Abbott, Crawford, Monteiro-Soares, Pham) and validation study (Leese)

Study	Risk of bias			Applicability			Overall	
	Participants	Predictors	Outcome	Participants	Predictors	Outcome	Risk of bias	Applicability
Abbott	+	+	+	+	+	+	+	+
Crawford	+	+	+	+	+	+	+	+
Monteiro-Soares	+	+	+	+	+	+	+	+
Pham	+	+	+	+	+	+	+	+
Leese	+	+	-	+	+	+	-	+

Flowcharts of participants for each study.

Note that a flowchart for the Monteiro-Soares study was omitted as there were no missing data.

Figure S1 Flow of patients in Abbott dataset. All patients had two year ulcer outcome recorded. Not all patients are shown at each stage.

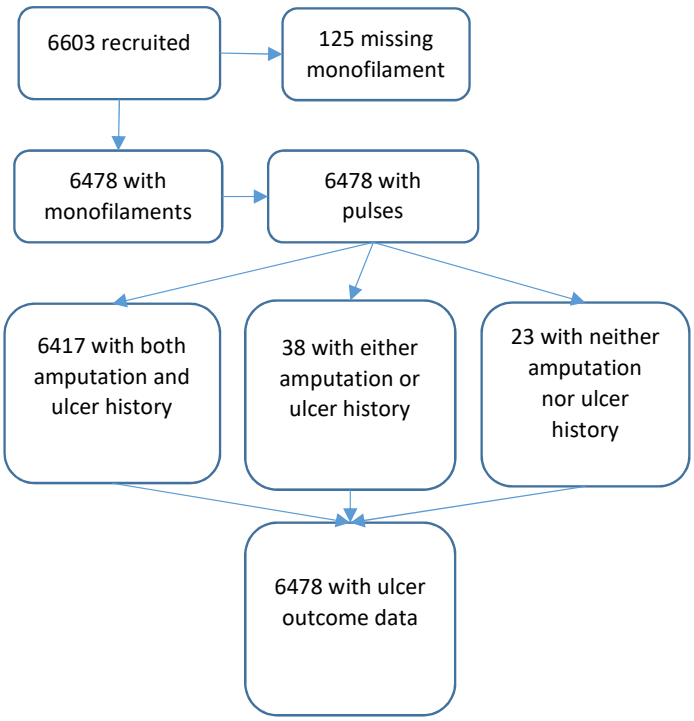


Figure S2 Flow of patients in the Crawford dataset. Not all patients are shown at each stage.

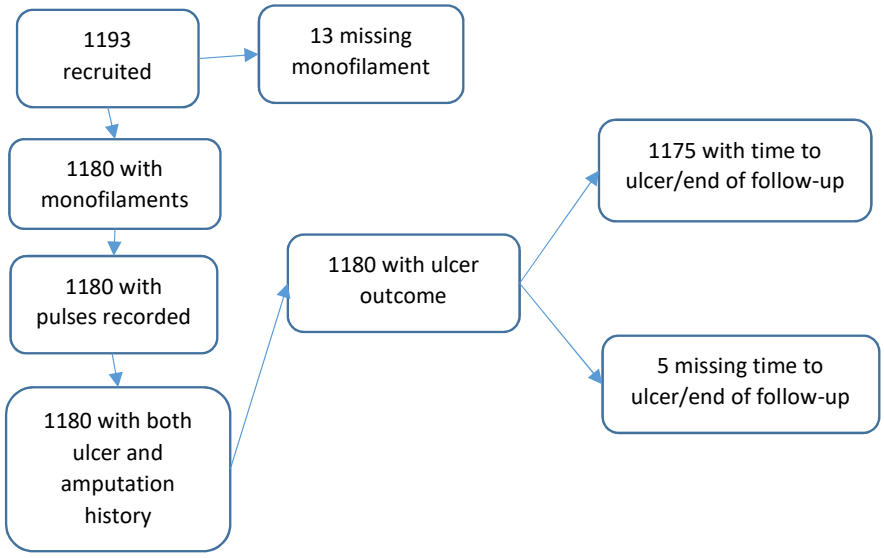


Figure S3 Flow of patients in the Pham study. Not all patients are shown at each stage.

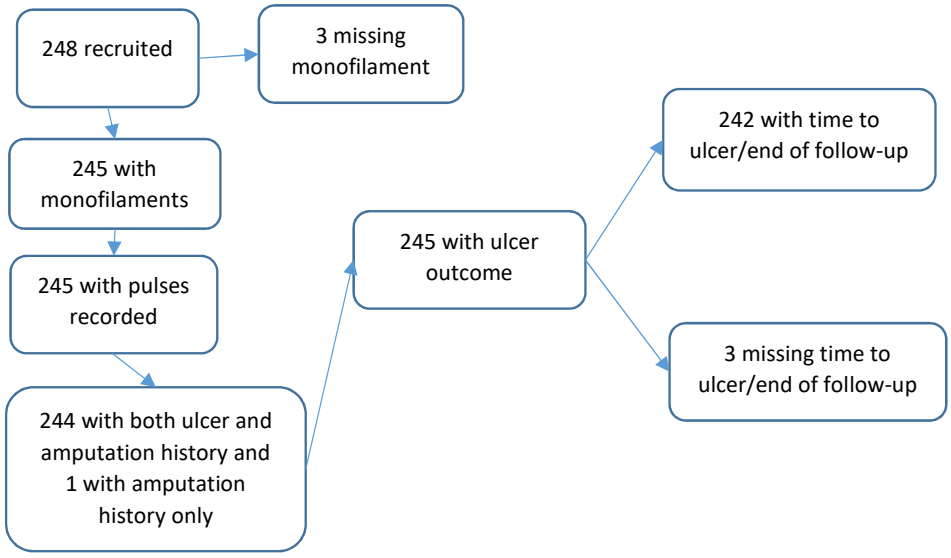
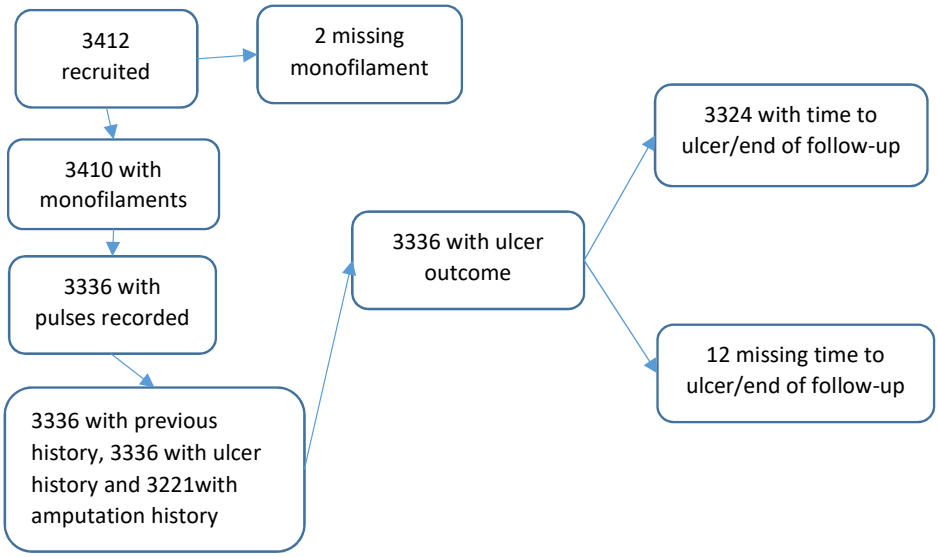


Figure S4 Flow of patients in the Leese study. Not all patients are shown at each stage.



Development of the CPR from the prognostic logistic regression model

Overfitting in the logistic regression model was negligible, with shrinkage estimated as > 0.999, so there was no need to adjust coefficients.

On the log odds scale, the initial logistic regression model with original predictors (coded 0 if test-negative and 1 if test positive so that a 1 always indicated "disease") was:

$$Log\ odds\ of\ ulcer\ by\ two\ years = -3.81 + 1.11 * mono + 0.70 * pulse + 1.95 * history$$

The intercept of -3.81 came from the random effects meta-analysis of study-specific baseline risk of the three studies with two-year follow-up data. Based on this model, predicted risks are:

$$Risk\ of\ ulcer\ at\ two\ years = \frac{1}{1 + e^{-(-3.81+1.11*mono+\ .70*pulse\ \ \ .95*history)}}$$

Repeating the analysis with CPR score gave this equation:

$$Risk\ of\ ulcer\ at\ two\ years = \frac{1}{1 + e^{-(-3.73+0.944*score)}}$$

Again, overfitting for the model with CPR score as assessed by the shrinkage factor (>0.999) was negligible. This equation was not used directly to calculate the risk of ulcer, but instead the population averaged method of Pavlou et al.[16] Here both approaches give similar results. The Pavlou method uses the distribution of random effects rather than just the point estimate of -3.73 when estimating the risks. The risk of ulceration for each score is given in Table 3 of the manuscript.

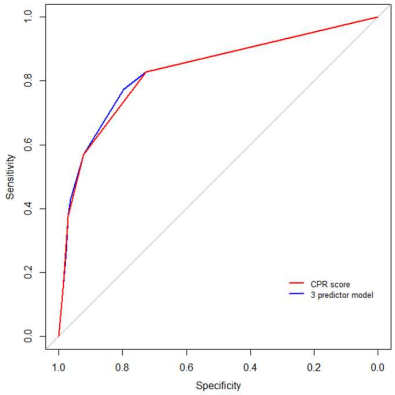
Calibration in the validation dataset of the prognostic model and CPR score

Table 2 External data calibration statistics for the three predictor and CPR models.

Model	Calibration-in-the-large (95% CI)	Calibration slope (95% CI)
Full prognostic model	-0.269 (-0.457 to -0.082)	1.133 (0.990 to 1.276)
CPR score	-0.374 (-0.561 to -0.187)	1.139 (0.994 to 1.283)

Discrimination in the validation dataset of the prognostic model and CPR score.

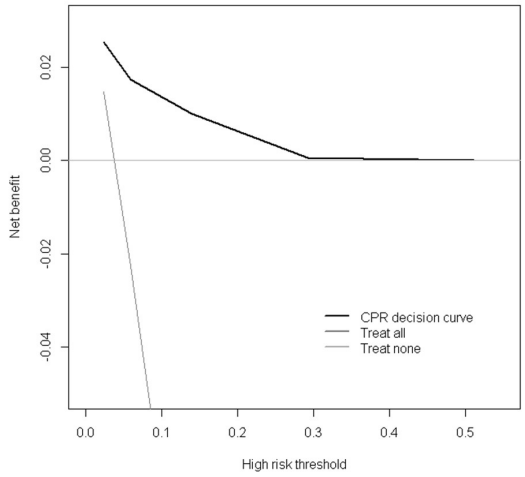
Figure S5 External validation ROC plot from the validation dataset for both the prognostic model with three predictors and the CPR score.



Net benefit

The potential clinical utility of the CPR was assessed with a net benefit analysis. At a risk threshold of 6% the net benefit is 0 for treat none, and < 0 for treat all, but 0.015 for using the CPR. This can be interpreted as the decision was to treat patients with CPR scores of 1 and above, then 15 additional cases of ulcer at 2 years would be correctly identified for treatment by the CPR, without increasing the number treated unnecessarily, per 1000 individuals. At a risk threshold of 14%, the number of additional cases of ulcer at 2 years correctly identified for treatment would be 10 per 1000 individuals. See decision curves in Figure S6.

Figure S6 Net benefit plot with decision curves for "treat none", "treat all", and "treat according to CPR score".



Printable CPR

PODUS Clinical Prediction Rule	Score
Test with 10g monofilament Insensitive at any site(s) – score 1 point Sensitive at all sites – score 0 points	
Check pedal pulses Any pulse(s) missing – score 1 point 4 pulses present – score 0 points	
Has there been an ulcer or amputation previously? Any ulcer or amputation – score 2 points No ulcer or amputation – score 0 points	
Total score out of 4	

Score	Risk of ulcer at two years
0	2%
1	6%
2	14%
3	29%
4	51%

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