Postprint of a Systematic Review of Diabetic Foot Risk Prediction Models

Authors: Lingjun Lin, Guo Jun, Junwei Wang, Gao Yang, Chen Huiying, Wan Yongli, Wan Yongli

Date: 2023-08-28T00:00:00+00:00

Abstract

Background Diabetic foot is a common complication in patients with diabetes, with most patients having severe conditions and rapid disease progression. Well-performing diabetic foot risk prediction models can help healthcare professionals identify high-risk patients and implement early interventions. Objective To systematically evaluate diabetic foot risk prediction models and provide a reference for future model development and optimization. Methods A literature search was conducted in PubMed, Cochrane Library, EMbase, Web of Science, CNKI, and Wanfang Data Knowledge Service Platform for relevant studies on diabetic foot risk prediction models from inception to May 15, 2023. Researchers independently screened the literature and extracted data, using the Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess model quality. Stata 17 software was used to perform a meta-analysis of predictors in the models. Results A total of 13 articles containing 13 models were included, of which 12 models had an AUC > 0.7. Seven models underwent calibration, and eight models underwent validation. PROBAST assessment showed that among the 13 included articles, one had a low risk of bias and the remaining 12 had a high risk of bias; regarding model applicability, one had low applicability. Meta-analysis results showed that age (OR = 1.13, 95% CI = 1.04–1.24), glycated hemoglobin (OR = 1.56, 95% CI = 1.26–1.94), history of foot ulcers (OR = 5.93, 95% CI = 2.85–12.37), history of foot amputation (OR = 7.79, 95% CI = 2.74–22.17), reduced monofilament test sensitivity (OR = 1.59, 95% CI = 1.42–1.78), foot fungal infection (OR = 6.14, 95% CI = 1.71–22.04), and nephropathy (OR = 2.09, 95% CI = 1.65–2.65) were independent risk factors for diabetic foot occurrence. Conclusion Diabetic foot risk prediction models still have limitations, and future model development should focus on predictors such as age, glycated hemoglobin level, history of foot ulcers, history of foot amputation, monofilament test sensitivity, foot fungal infection, and nephropathy.

Full Text

A Systematic Review of Risk Prediction Models for Diabetic Foot Development

LIN Lingjun, GUO Jun, WANG Junwei, GAO Yang, CHEN Huiying, WAN Yongli*

NHC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Diseases, Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin 300134, China

Corresponding author: WAN Yongli, Associate chief physician; E-mail: wanyongli0607@163.com

---

Abstract

Background: Diabetic foot is a common complication among patients with diabetes, characterized by severe conditions and rapid disease progression. A well-performing risk prediction model for diabetic foot development can help healthcare professionals identify high-risk patients and facilitate early interventions.

Objective: To systematically review risk prediction models for diabetic foot and provide references for model construction and optimization.

Methods: We searched PubMed, Cochrane Library, EMbase, Web of Science, CNKI, and WanFang Data for relevant literature on diabetic foot risk prediction models from inception to May 15, 2023. Two researchers independently screened the literature, extracted data, and evaluated model quality using the Prediction Model Risk of Bias Assessment Tool (PROBAST). Meta-analysis of predictors in the models was performed using Stata 17 software.

Results: Thirteen articles were included, containing 13 models, of which 12 had an AUC > 0.7. Seven models reported calibration, and eight models underwent validation. PROBAST assessment revealed that one of the 13 included articles had low risk of bias, while the remaining 12 had high risk of bias; regarding model applicability, only one article demonstrated low applicability. Meta-analysis results showed that age (OR = 1.13, 95%CI = 1.04~1.24), glycated hemoglobin (OR = 1.56, 95%CI = 1.26~1.94), foot ulcer history (OR = 5.93, 95%CI = 2.85~12.37), foot amputation history (OR = 7.79, 95%CI = 2.74~22.17), diminished monofilament test sensitivity (OR = 1.59, 95%CI = 1.42~1.78), foot fungal infection (OR = 6.14, 95%CI = 1.71~22.04), and kidney disease (OR = 2.09, 95%CI = 1.65~2.65) were independent risk factors for diabetic foot development.

Conclusion: Current diabetic foot risk prediction models have notable limitations. Future model development should focus on key predictors including age,

glycated hemoglobin level, foot ulcer history, foot amputation history, monofilament test sensitivity, foot fungal infection, and kidney disease.

Keywords: Diabetic foot; Foot ulcer; Risk assessment; Forecasting; Model; Systematic review

---

Introduction

Diabetic foot refers to foot ulcers, infections, or deep tissue destruction associated with peripheral neuropathy and peripheral vascular disease in the lower extremities [1-2]. In China, the annual prevalence of diabetic foot ulcers is approximately 8.1%, increasing to 31.6% among patients with a history of foot ulcers [3]. Diabetic foot represents a severe complication of diabetes with heavy medical burden and poor prognosis. Patients with diabetes have a 20-fold higher risk of non-traumatic amputation compared to non-diabetic individuals [4], significantly impacting their quality of life and physical and mental health. Prevention is more critical than treatment for diabetic foot [5]; early identification of high-risk patients, strengthened management, and timely preventive measures are essential to reduce incidence or slow progression. Risk prediction models for diabetic foot development can facilitate early identification of high-risk patients in clinical practice. Although numerous studies have developed such models, their clinical applicability remains unclear. Therefore, this systematic review aims to evaluate relevant research on diabetic foot risk prediction models to provide references for selecting well-performing models and identifying high-risk patients early.

Methods

1.1 Search Strategy We conducted comprehensive searches in PubMed, Cochrane Library, EMbase, Web of Science, CNKI, and WanFang Data using a combination of subject headings and keywords. The search was limited to Chinese and English languages from database inception to May 15, 2023. Reference lists of included studies were manually searched. The PubMed search strategy was as follows:

- #1: "Diabetic Foot"[Mesh] Sort by: Most Recent
- #2: ((Foot ulceration[Title/Abstract]) OR (Foot, Diabetic[Title/Abstract])) OR (Diabetic Feet[Title/Abstract]) OR (Feet, Diabetic[Title/Abstract]) OR (Foot Ulcer, Diabetic[Title/Abstract]) OR (diabetic foot ulcer[Title/Abstract])
- #3: #1 OR #2
- #4: ((prediction model[Title/Abstract]) OR (prediction tool[Title/Abstract]) OR (prognostic model[Title/Abstract]) OR (risk prediction[Title/Abstract]) OR (risk assessment[Title/Abstract]) OR (risk score[Title/Abstract]) OR (risk prediction model[Title/Abstract]))
- #5: risk factors[Title/Abstract]

- #6: #4 OR #5
- #7: #3 AND #6

Chinese search terms included: "糖尿病足," "糖尿病足溃疡," "预测模型," "风险预测," "预测因素," "危险因素," "预测工具," "风险评分," "风险评估." English search terms included: "Diabetic Foot/diabetic foot ulcer/prediction model/risk prediction model/risk prediction/risk factors/risk assessment/prognostic model/risk score/prediction tool/nomogram."

1.2 Inclusion and Exclusion Criteria **1.2.1 Inclusion Criteria:** (1) Study population: patients diagnosed with diabetes [6]; (2) Study design: cross-sectional surveys, case-control studies, and cohort studies; (3) Outcome measure: diabetic foot occurrence as the outcome, using diagnostic criteria published by the International Working Group on the Diabetic Foot [7]; (4) Study content: research on diabetic foot risk prediction models (excluding models for progression, recurrence, or prognosis).

1.2.2 Exclusion Criteria: (1) Studies that only explored risk factors without model construction; (2) Reviews, commentaries, news reports, and similar publications; (3) Models developed based on systematic reviews or meta-analyses; (4) Studies where full text was unavailable and abstracts lacked sufficient information; (5) Unpublished literature such as conference abstracts or academic theses; (6) Studies published in languages other than Chinese or English.

1.3 Data Extraction and Analysis Two researchers independently screened literature and extracted data according to inclusion and exclusion criteria, with disagreements resolved by consulting a third reviewer. After finalizing included studies, we developed a standardized form based on the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) checklist [8] to extract data including: first author, publication year, country, study region, study design, study population, follow-up duration, predicted outcome, candidate variables, sample size, missing data and handling methods, modeling approach, variable selection, model performance (AUC with confidence intervals, calibration methods), model validation methods, included predictors, and model presentation format.

1.4 Model Bias Risk and Applicability Assessment We used the Prediction Model Risk of Bias Assessment Tool (PROBAST) [9-10] to evaluate the risk of bias and applicability of included studies. Disagreements were resolved by consulting a third reviewer. PROBAST assesses risk of bias across four domains: participants, predictors, outcomes, and data analysis, with each domain rated as "low," "high," or "unclear" risk. Applicability is assessed across three domains using a similar approach.

1.5 Statistical Analysis We used Stata 17 software to conduct meta-analysis of predictors from included models. Heterogeneity was assessed using I^2 and Z tests. When $I^2 < 50\%$ and $P > 0.05$, indicating no significant heterogeneity, a fixed-effects model was used. When $I^2 \geq 50\%$ or $P < 0.05$, indicating substantial heterogeneity, sensitivity analysis was performed. If heterogeneity could not be eliminated, a random-effects model was applied. Pooled effect sizes were expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$.

Results

2.1 Literature Screening Process and Results The database search yielded 3,337 relevant articles. After initial and detailed screening, 13 articles [11-23] were ultimately included. The literature screening flowchart is shown in [Figure 1: see original paper].

2.2 Basic Characteristics of Included Studies Among the 13 included articles, eight were from China [13-16,18-20,22], two from the United Kingdom [12,21], and one each from the United States, Portugal, and Japan [11,17,23]. Seven studies [13-17,19,21] were retrospective cohort studies, four [11-12,18,22] were prospective cohort studies, and two [20,23] were case-control studies. Three studies [12,21-22] were multicenter, while ten [11,13-20,23] were single-center. Seven articles [13-16,18-20] were published within the last three years. Basic characteristics of included studies are shown in .

2.3 Model Development The 13 articles developed 13 models, including 12 model development studies and one model validation study [17]. The number of potential predictor variables ranged from 10 to 36, total sample sizes from 316 to 17,053, and outcome events from 10 to 1,127. Regarding missing data, one study [13] used multiple imputation, three [11-12,22] used complete case analysis, and four [15,17,20,23] did not report missing data. For continuous variables, nine studies [11-12,14-15,17-19,21-22] maintained continuity, one [13] converted some continuous variables to categorical with predefined grouping criteria, and three [16,20,23] converted some or all continuous variables to categorical. Most studies used logistic regression for model development. For variable selection, five studies [15,18-20,23] were based on univariate analysis. Model development details are shown in .

2.4 Model Performance and Presentation All 13 models reported AUC values ranging from 0.650 to 0.966. Except for HEALD et al. [21] with an AUC of 0.65, the remaining 12 models demonstrated good predictive performance (AUC > 0.70). Seven studies [13-16,18,20-21] reported calibration, primarily presented as calibration plots. Three studies [14-16] also conducted decision curve analysis, and two [13,18] reported Brier scores. For validation, only three studies [13,17,20] performed external validation, while five [11-12,21-23] did not report internal validation. Model presentation varied, with seven studies [13-16,18-20] constructing nomograms for risk estimation based on scores. Details are shown in .

2.5 Bias Risk and Applicability Assessment 2.5.1 Bias Risk: One study [13] had overall low risk of bias, while the remaining 12 had high risk.

- **Participants domain:** One prospective cohort study [18] excluded lost-to-follow-up patients, and another [14] excluded patients with peripheral vascular disease or neuropathy, both potentially introducing selection bias (high risk). The rest were low risk.
- **Predictors domain:** One study [21] had high risk (multicenter retrospective study without standardized predictor assessment), one [23] had unclear risk (blinding status unknown), and the rest were low risk.
- **Outcomes domain:** One study [21] had high risk (possible inconsistent outcome definition/measurement); two [11,21] did not specify whether outcomes were determined without knowledge of predictor information; JIANG et al. [20] did not clarify whether outcomes used predefined or standard definitions.
- **Analysis domain:** One study [13] had low risk. The remaining eight [12,14-17,19-20,22-23] had inadequate sample size with <10 events per variable. Additional issues included: (2) four studies [15-16,20,23] converted continuous variables to categorical without justification; (3) four [15,17,20,23] did not address missing data, while three [11-12,22] used complete case analysis; (4) five [15,18-20,23] selected predictors based solely on univariate analysis; (5) six [11-12,17,19,22-23] did not report calibration assessment; (6) five [11-12,21-23] did not report internal validation, with only two [13,20] conducting both internal and external validation; (7) five studies [11-12,21-23] did not address overfitting or underfitting.

2.5.2 Applicability: Only one study [16] was rated as low applicability due to restricting the study population to patients over 60 years old. Applicability assessment details are shown in .

2.6 Meta-Analysis Results We performed meta-analysis on frequently reported predictors across the 12 studies. Due to large heterogeneity, a random-effects model was used for age, with results shown in [Figure 2: see original paper]. Sensitivity analysis for age showed minimal changes when any single study was removed. Other predictors were similarly meta-analyzed. Disease duration and visual impairment showed no statistical significance after pooling ($P > 0.05$). Kidney disease had low heterogeneity and used a fixed-effects model. Diminished monofilament test sensitivity showed reduced heterogeneity after excluding MONTEIRO-SOARES et al. [17] and used a fixed-effects model. Remaining predictors had substantial heterogeneity and used random-effects models, with minimal changes when individual studies were sequentially removed. Results are shown in .

Discussion

This systematic review identified 13 studies with 13 prediction models for diabetic foot risk, including 12 model development and one model validation study.

AUC values ranged from 0.65 to 0.966; except for HEALD et al. [21] (AUC = 0.65), the remaining 12 models showed good predictive performance (AUC > 0.70). However, 12 of 13 studies had high risk of bias, primarily due to: non-rigorous inclusion/exclusion criteria, non-standardized predictor assessment, insufficient outcome events, inappropriate conversion of continuous to categorical variables, inadequate handling of missing data, suboptimal predictor selection methods, lack of model performance assessment, absence of external validation, and failure to address overfitting. International researchers began exploring diabetic foot prediction models earlier, though early models often lacked calibration and validation. Internal validation examines model reproducibility and prevents overfitting [24], while external validation assesses transportability and generalizability [25]. Chinese research on diabetic foot risk prediction models started later. Among included studies, eight were from China, with seven published in the last three years, indicating rapid growth in this research area with increased attention to model performance assessment and validation. Most models were presented as nomograms, offering more intuitive and convenient personalized risk prediction for effective clinical screening and timely intervention.

The most frequently reported predictors were age, glycated hemoglobin, visual impairment, foot ulcer history, foot amputation history, diminished monofilament test sensitivity, foot fungal infection, diabetes duration, and kidney disease. Meta-analysis identified seven independent risk factors: age, glycated hemoglobin, foot ulcer history, foot amputation history, diminished monofilament test sensitivity, foot fungal infection, and kidney disease. Future prediction model development should prioritize these seven predictors. Disease duration and visual impairment were not statistically significant after pooling, possibly due to varying data types and grouping criteria across studies.

Given that most existing models have high risk of bias, future research should follow PROBAST guidelines [9-10] to minimize bias. Based on our findings, we recommend: (1) carefully defining inclusion/exclusion criteria without excluding patients with comorbidities; (2) using standardized definitions and measurement methods for predictors and outcomes, employing blinding where appropriate, and selecting optimal time points; (3) ensuring adequate sample size (events per variable < 10 may cause overfitting) [26]; (4) maintaining continuous variables as continuous when possible, as conversion to categorical may lose important information and reduce predictive power [27]; if conversion is necessary, predefined grouping criteria should be established rather than converting during analysis, with internal validation and shrinkage of regression coefficients to adjust for overfitting [28]; (5) using multiple or single imputation for missing data to reduce adverse effects on statistical analysis and model stability [29]; (6) avoiding reliance solely on univariate analysis, incorporating clinical knowledge and practical considerations; (7) assessing calibration, conducting internal and external validation, and addressing overfitting and underfitting.

Currently, Chinese diabetic foot risk prediction models show good predictive performance in internal validation but lack external validation. Only two studies [13,20] conducted both internal and external validation, with small external validation samples. Future research should include large-sample, multicenter, multi-regional studies in China to develop and validate models suitable for Chinese populations.

References

[1] KHANOLKAR MP, BAIN SC, STEPHENS JW. The diabetic foot [J]. QJM, 2008, 101(9): 685-695. DOI: 10.1093/qjmed/hcn027.

[2] ZUBAIR M, MALIK A, AHMAD J. Clinico-microbiological study and antimicrobial drug resistance profile of diabetic foot infections in North India [J]. Foot, 2011, 21(1): 6-14. DOI: 10.1016/j.foot.2010.10.003.

[3] JIANG YF, WANG XM, XIA L, et al. A cohort study of diabetic patients and diabetic foot ulceration patients in China [J]. Wound Rep And Reg, 2015, 23(2): 222-230. DOI: 10.1111/wrr.12263.

[4] VEVES A, VAN ROSS ER, BOULTON AJ. Foot pressure measurements in diabetic and nondiabetic amputees [J]. Diabetes Care, 1992, 15(7): 905-907. DOI: 10.2337/diacare.15.7.905.

[5] MEANEY B. Diabetic foot care: prevention is better than cure [J]. J Ren Care, 2012, 38(Suppl 1): 90-98. DOI: 10.1111/j.1755-6686.2012.00276.x.

[6] ALBERTI KG, ZIMMET PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation [J]. Diabet Med, 1998, 15(7): 539-553. DOI: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S.

[7] VAN NETTEN JJ, BUS SA, APELQVIST J, et al. Definitions and criteria for diabetic foot disease [J]. Diabetes Metab Res Rev, 2020, 36(Suppl 1): e3268. DOI: 10.1002/dmrr.3268.

[8] MOONS KG, DE GROOT JA, BOUWMEESTER W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist [J]. PLoS Med, 2014, 11(10): e1001744. DOI: 10.1371/journal.pmed.1001744.

[9] MOONS KGM, WOLFF RF, RILEY RD, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration [J]. Ann Intern Med, 2019, 170(1): W1-33. DOI: 10.7326/M18-1377.

[10] WOLFF RF, MOONS KGM, RILEY RD, et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies [J]. Ann Intern Med, 2019, 170(1): 51-58. DOI: 10.7326/M18-1376.

[11] BOYKO EJ, AHRONI JH, COHEN V, et al. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Dia-

betic Foot Study [J]. Diabetes Care, 2006, 29(6): 1202-1207. DOI: 10.2337/dc05-2031.

[12] CRAWFORD F, MCCOWAN C, DIMITROV BD, et al. The risk of foot ulceration in people with diabetes screened in community settings: findings from a cohort study [J]. QJM, 2011, 104(5): 403-410. DOI: 10.1093/qjmed/hcq227.

[13] XIE Xiaoran, XU Rong, ZHANG Jing, et al. Construction and validation of a diabetic foot risk prediction model [J]. Journal of Nursing Science, 2022, 37(11): 9-14. DOI: 10.3870/j.issn.1001-4152.2022.11.009.

[14] DING Anle, WANG Zan, GUO Peng, et al. Establishment of a predictive model for type 2 diabetic foot disease [J]. Journal of Qiqihar Medical University, 43(22): 2112-2118.

[15] WANG J, XUE T, LI HP, et al. Nomogram prediction for the risk of diabetic foot in patients with type 2 diabetes mellitus [J]. Front Endocrinol, 2022, 13: 890057. DOI: 10.3389/fendo.2022.890057.

[16] SHAO ZC, WANG ZL, BI SX, et al. Establishment and validation of a nomogram for progression to diabetic foot ulcers in elderly diabetic patients [J]. Front Endocrinol, 2023, 14: 1107830. DOI: 10.3389/fendo.2023.1107830.

[17] MONTEIRO-SOARES M, DINIS-RIBEIRO M. External validation and optimisation of a model for predicting foot ulcers in patients with diabetes [J]. Diabetologia, 2010, 53(7): 1525-1533. DOI: 10.1007/s00125-010-1731-y.

[18] LV J, LI R, YUAN L, et al. Development and validation of a risk prediction model for foot ulcers in diabetic patients [J]. J Diabetes Res, 2023, 2023: 1199885. DOI: 10.1155/2023/1199885.

[19] LI MM, YUAN T, LI SP, et al. Nomogram analysis of the influencing factors of diabetic foot in patients with diabetes mellitus [J]. Hormones, 2021, 20(2): 333-338. DOI: 10.1007/s42000-020-00263-1.

[20] JIANG MY, GAN F, GAN MS, et al. Predicting the risk of diabetic foot ulcers from diabetics with dysmetabolism: a retrospective clinical trial [J]. Front Endocrinol, 2022, 13: 929864. DOI: 10.3389/fendo.2022.929864.

[21] HEALD A, LUNT M, RUTTER MK, et al. Developing a foot ulcer risk model: what is needed to do this in a real-world primary care setting? [J]. Diabet Med, 2019, 36(11): 1412-1416. DOI: 10.1111/dme.13837.

[22] ZHOU QH, PENG M, ZHOU LH, et al. Development and validation of a brief diabetic foot ulceration risk checklist among diabetic patients: a multicenter longitudinal study in China [J]. Sci Rep, 2018, 8(1): 962. DOI: 10.1038/s41598-018-19389-8.

[23] TOMITA M, KABEYA Y, OKISUGI M, et al. Development and assessment of a simple scoring system for the risk of developing diabetic foot [J]. Diabetol Int, 2015, 6(3): 212-218. DOI: 10.1007/s13340-014-0189-4.

[24] MOONS KG, KENGNE AP, WOODWARD M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker [J]. Heart, 2012, 98(9): 683-690. DOI: 10.1136/heartjnl-2011-301246.

[25] STEYERBERG EW, HARRELL FE Jr. Prediction models need appropriate internal, internal-external, and external validation [J]. J Clin Epidemiol, 2016, 69: 245-247. DOI: 10.1016/j.jclinepi.2015.04.005.

[26] VITTINGHOFF E, MCCULLOCH CE. Relaxing the rule of ten events per variable in logistic and Cox regression [J]. Am J Epidemiol, 2007, 165(6): 710-718. DOI: 10.1093/aje/kwk052.

[27] MACCALLUM RC, ZHANG SB, PREACHER KJ, et al. On the practice of dichotomization of quantitative variables [J]. Psychol Methods, 2002, 7(1): 19-40. DOI: 10.1037/1082-989X.7.1.19.

[28] CHEN Ru, WANG Shengfeng, ZHOU Jiachen, et al. Interpretation of tools for assessing risk of bias and applicability in prediction model studies [J]. Chinese Journal of Epidemiology, 2020, 41(5): 776-781. DOI: 10.3760/cma.j.cn112338-20190805-00580.

[29] ZHANG Q, WANG LJ. Moderation analysis with missing data in the predictors [J]. Psychol Methods, 2017, 22(4): 649-666. DOI: 10.1037/met0000104.

Funding: Key Project of Integrated Traditional Chinese and Western Medicine, Tianjin Health Commission (2021034); Tianjin Medical Key Discipline (Specialty) Construction Project (TJYXZDXK-032A)

Conflict of interest: None declared.

Received: June 10, 2023; Revised: August 15, 2023

Note: Figure translations are in progress. See original paper for figures.