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REVIEW

From Ulcer to Amputation: A Systematic Review of Prognostic Models for Diabetic Foot Ulcer Amputation

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Aim: To systematically analyze and compare studies on risk prediction models for diabetic foot ulcers progressing to amputation, facilitate clinical decision-making, and provide recommendations for improving modeling strategies in future research.

Methods: We searched Medline, Embase, Cochrane Library, and Clinicaltrials.gov from inception to January 29, 2025, to identify studies on risk prediction models for diabetic foot ulcers progressing to amputation. After study screening and data extraction, we evaluated bias and applicability using the Prediction Model Risk of Bias Assessment Tool.

Results: We included 18 papers comprising 15 development studies and 3 external validation studies. The development studies reported 17 models, while the validation studies externally validated 12 models. The area under the curve of all models ranged from 0.557 to 0.957. The most commonly used predictors were peripheral arterial disease, glycated hemoglobin, infection, Wagner classification, and ulcer depth. All included studies had low concerns regarding applicability but exhibited high risk of bias, primarily due to insufficient events per variable, missing data, inadequate consideration of data complexity, lack of model performance assessment, and absence of internal validation.

Conclusion: Risk prediction model research for diabetic foot ulcer progression to amputation remains in its early stages. Future efforts should prioritize prospectively developing and externally validating models with robust performance and low bias, accompanied by rigorous internal validation and transparent reporting. (Funding: Natural Science Foundation of Hubei Province (2022CFB145) and Research Fund of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (2023D36)).

Keywords: diabetes foot, amputation, forecasting, models, systematic review

Introduction

Diabetic foot ulcer (DFU), a severe chronic complication of diabetes mellitus, represents a critical global health challenge.[1] Lipsky[2] reported amputation rates up to 23% among patients with diabetic foot. In China, the 5-year post-amputation mortality rate in diabetic populations exceeds 40%,[3] highlighting the dual role of DFU-related amputations as a public health challenge and healthcare quality indicator. Beyond mortality, this condition inflicts profound physical disability and psychological trauma, while generating substantial socioeconomic burdens.[4] A review reported that annual hospitalization costs associated with diabetic amputations reached £43.8 million in the UK,[5] a financial strain amplified in low-resource settings where delayed presentations and fragmented multidisciplinary care exacerbate preventable complications.[6]

A prediction model combines various risk factors to calculate the incidence of specific end-point events.[7] Risk prediction models use quantitative research methods, providing more objective results than clinical judgment alone.[8] Predictive models for amputation risk among people with DFU can help medical staff identify high-risk patients, design customized programs for patients with different risk stratifications, and reduce amputation incidence. These tailored

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programs can be adjusted according to different needs, reducing both the risk of under-screening and the cost of over-screening, especially in areas where health resources are scarce.[9]

While numerous amputation prediction models exist for DFU patients, their methodological quality remains uncertain. Previous systematic reviews,[10,11] including Beulens et al's comprehensive analysis,[12] have examined prognostic models for diabetic foot ulcers. We aimed to specifically analyze risk prediction models for DFU progressing to amputation, using PROBAST criteria to assess methodological quality and provide recommendations for future model development.

Methods

Study Design

We conducted this review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[13] the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines,[14] and the Cochrane guidance for prognostic model reviews.[15] The study selection process is illustrated in Figure 1, and the PRISMA checklist is provided in Supplementary Table 1.

Study Selection

Two researchers (XXR and YMF) independently searched Medline, Embase, Cochrane Library, and Clinicaltrials.gov from inception to January 29, 2025, to collect studies on risk prediction models for DFU progressing to amputation. According to the Cochrane guidance,[15] our search strategy was based on Geersing et al[16] and included terms associated with diabetic foot, prognostic model, and amputation. We then conducted a manual search of the references of included studies to obtain additional eligible articles. The complete search strategy is provided in Supplementary File 1.

Inclusion and Exclusion Criteria

We included all studies that developed or validated risk prediction models of amputation in DFU patients. Inclusion criteria were: (1) studies involving adult participants (aged ≥18 years) with DFU; (2) amputation as the primary outcome; (3) cohort or case-control study design.

Exclusion criteria were: (1) studies not focused on model development or validation; (2) models targeting specific disease subgroups (eg, limited to one DFU subtype); (3) conference abstracts, review articles, or letters; (4) basic science studies (eg, cellular/molecular level research); (5) studies with unavailable full text; (6) models containing only a single predictor; (7) non-English language studies.

When development studies did not meet the criteria, we still considered their corresponding external validation studies if they met the inclusion criteria.[17] Two researchers (XXR and YMF) independently selected literature according to the above criteria, with a third referee (ZJ) resolving disagreements.

Data Extraction

We extracted data using the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist.[18] From development studies, we extracted: first author, year, study type, study population, predicted outcome, candidate predictors, sample size, missing data, modeling method, variable selection, model performance, method of internal validation, number of predictors in final model, and model presentation. From external validation articles, we extracted: first author, year, original model, study population, predicted outcome, sample size, missing data, and model performance.

Risk of Bias and Applicability Assessment

Two researchers (XXR and ZJ) assessed risk of bias and applicability concerns using the Prediction model Risk of Bias Assessment Tool (PROBAST).[19] Developed by the Cochrane Prognosis Methods Group in 2019, PROBAST evaluates bias across four domains and applicability across three domains.

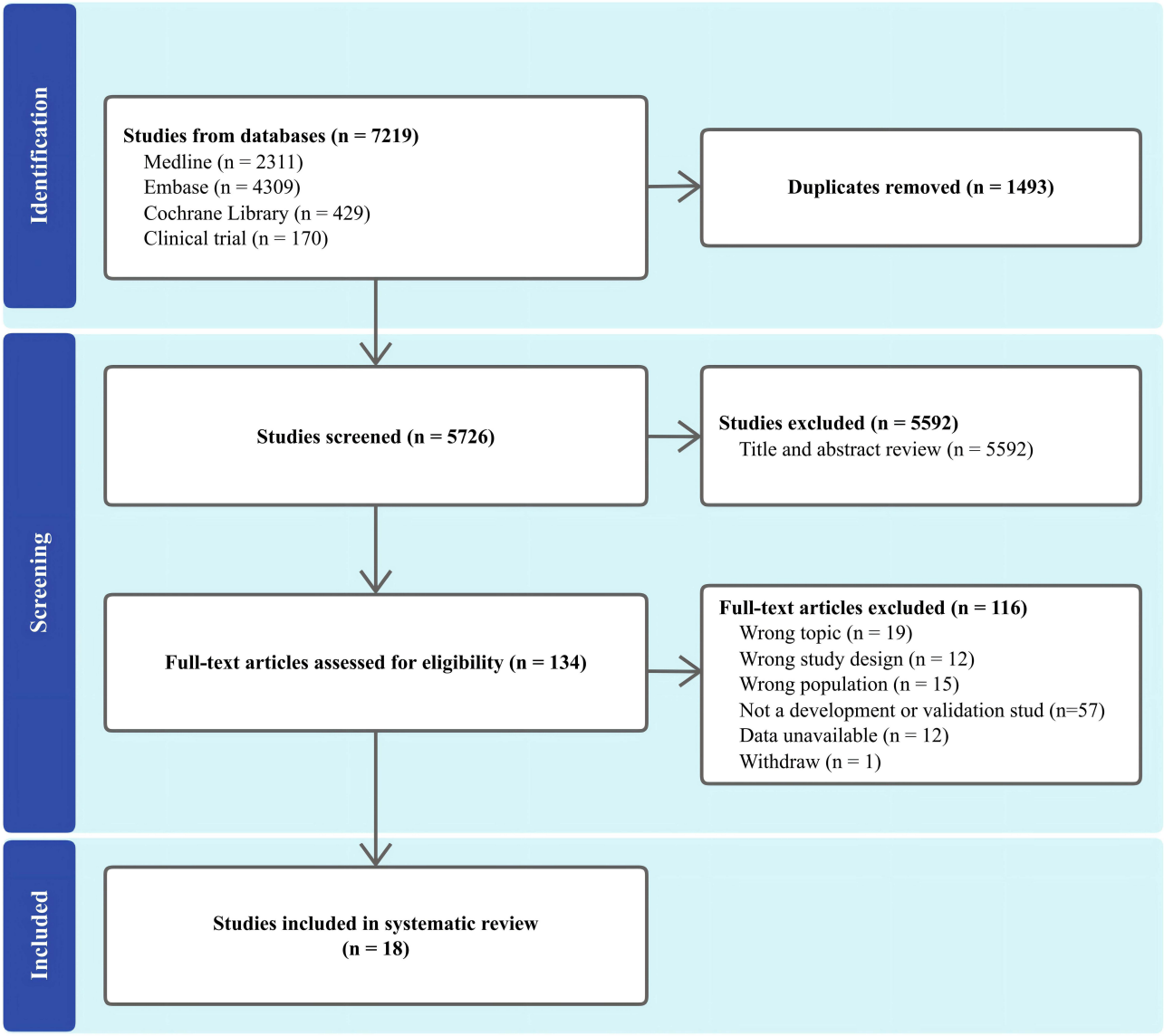

Figure 1 PRISMA flow diagram of study selection process.

Results

Study Selection

Of 7,219 records screened, 18 papers met inclusion criteria (Figure 1). These comprised 15 development studies that reported 17 prediction models and 3 validation studies that externally validated 12 models. Notably, one validation study prospectively validated a model originally developed in one of the included development studies. Overall, we analyzed 28 models across the 18 studies.

Development Studies of Risk Prediction Models for DFU Progressing to Amputation

Characteristics and Predicted Outcome of Development Studies

We included 15 development studies, six published within the past five years. Most were conducted in Western countries (n=7), followed by China (n=4). Fourteen studies adopted cohort designs, and one used a case-control design, with five being multicenter and 10 single-center. Table 1 presents the basic characteristics and predictive outcomes of these development studies.

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Establishment of the Models

The number of candidate predictors ranged from 3 to 39; sample sizes varied from 62 to 326,853; and outcome events ranged from 9 to 19,344. Nine studies did not report missing data. Most models employed logistic regression (n=8), while others used machine learning (n=5), Cox regression (n=1), or variable combination methods (n=1). Table 2 provides detailed information about model development.

Model Performance and Predictors

Four studies assessed calibration, while 11 evaluated discriminations. The area under the curve (AUC) for 12 models ranged from 0.557 to 0.957. Internal validation methods included split-sample validation (n=4), bootstrap resampling (n=2), and cross-validation (n=2); however, seven studies performed no internal validation. Final models included 3 to 33

Table 1 Basic Characteristics and Predicted Outcomes of the Development Studies

Reference	Study Type	Study Population			Predicted Outcome
		Object	Setting	Interval	
Chen et al (2024)[20]	Retrospective cohort	T2DM patients with DFU	China, single center, hospital	2018.1–2023.12	Major amputation
Sánchez et al (2024)[21]	Retrospective cohort	Adult inpatients with DFU	Colombia, multicenter, 2 hospitals	2006 - 2022	Amputation within 30 days
Stefanopoulos et al (2022)[22]	Retrospective study	Adult inpatients with DFU	America, multicenter, NIS database	2008 - 2014	Major amputation
Xie et al (2022)[23]	Retrospective cohort	Adult inpatients with DFU	China, single center, hospital	2009 - 2020	Amputation (major amputation, minor amputation)
Peng et al (2021)[24]	Retrospective case control	T2DM patients with DFU	China, single center, hospital	2015.1–2019.12	Amputation
Lin et al (2020)[25]	Prospective cohort	DFU patients	China, single center, hospital	2018.1–2018.7	Amputation (major amputation, minor amputation)
Monteiro-Soares et al (2016)[26]	Prospective cohort	Active DFU patients	Portugal, single center, diabetic foot clinic	2010.1–2013.3	Amputation (total amputation, minor amputation)
Beaney et al (2016)[27]	Retrospective cohort	DFU patients	England, single center, diabetic foot clinic	2009.9–2011.12	Amputation
Tardivo et al (2015)[28]	Prospective cohort	DFU patients	Brazil, single-center, diabetic foot clinic	2011.3–2013.3	Amputation
Lipsky et al (2011)[29]	Retrospective cohort	DFU patients	USA, multicenter, 97 acute-care hospitals	2003.1–2007.6	Amputation
Van Battum et al (2011)[30]	Prospective cohort	New DFU patients	Europe, multicenter, 14 European centers with longstanding expertise	2003.9–2004.10	Minor amputation
Barberán et al (2010)[31]	Retrospective cohort	Acute DFU patients	Spain, single center, hospital	Clinical records	Amputation
Younes et al (2004)[32]	Prospective cohort	DFU patients	Jordan, single center, hospital	1997.9–2002.12	Amputation
Chetpet et al (2018)[33]	Prospective cohort	DFU patients	India, single center, diabetic foot clinic	2015.10–2016.11	Amputation
Pickwell et al (2015)[34]	Prospective cohort	New DFU patients	Europe, multicenter, 14 European centers with longstanding expertise	2003.9–2004.10	Total LEA, excluding lesser toes

Abbreviations: T2DM, type 2 diabetes mellitus; DFU, diabetic foot ulcer; LEA, lower extremity amputation.

Table 2 Establishment of Prediction Models

Reference	Candidate Predictor (n)	Sample Size		Missing Data		Modeling Method	Variable Selection
		Total(n)	Event(n)	Missing Value (n)	Processing Method		
Chen et al (2024)[20]	39	634	71	NA	NA	Logistic regression	Multivariate analysis
Sánchez et al (2024)[21]	13	573	290	20	Exclude	Classification and Regression Trees	Pruning algorithm
Stefanopoulos et al (2022)[22]	36	326 853	19344	NA	Exclude	Decision tree	LASSO
Xie et al (2022)[23]	37	618	118	NA	Model automatically handle	Light Gradient Boosting Machine	NA
Peng et al (2021)[24]	21	125	58	NA	NA	Logistic regression	Forward stepwise
Lin et al (2020)[25]	33	200	NA	NA	NA	Cox, BPNN, BPNN based on genetic algorithm optimization	Based on univariable analysis
Monteiro-Soares et al (2016)[26]	NA	293	68	9	Complete-case analysis	Logistic regression	Backward stepwise
Beaney et al (2016)[27]	10	165	33	23	Exclude	Logistic regression	Forward stepwise
Tardivo et al (2015)[28]	3	62	9	NA	NA	Combination of three variables	All included
Lipsky et al (2011)[29]	33	3018	646	NA	NA	Logistic regression	Stepwise regression
Van Battum et al (2011)[30]	16	1232	194	< 6%	Multiple imputation	Logistic regression	Backward stepwise
Barberán et al (2010)[31]	20	78	26	NA	NA	Logistic regression	Based on univariable analysis
Younes et al (2004)[32]	4	84	13	NA	NA	Combination of four variables	All included
Chetpet et al (2018)[33]	13	150	44	14	Exclude	Logistic regression	Multivariate analysis
Pickwell et al (2015)[34]	20	575	159	16	Complete-case analysis	Cox regression	Backward stepwise

Abbreviations: BPNN, back propagation neural network; NA, not applicable.

predictors, with peripheral arterial disease (PAD), glycated hemoglobin, infection, Wagner classification, and ulcer depth being most common. Eight models presented results as risk scores. Table 3 summarizes model performance and predictors.

External Validation Studies

Three validation studies externally validated 12 models, all including the University of Texas system.[35] Jeon's[36] study used a retrospective cohort design, while the other two were prospective. Sample sizes ranged from 101 to 293, with 24 to 68 outcome events. All three studies excluded participants with missing data. Carro's[37] validation of the Saint Elian Wound Score System[38] reported the highest AUC (0.893). None assessed calibration. Table 4 summarizes the validation studies' characteristics.

Table 3 Performance and Predictors of Prediction Models

Reference	Model Performance		Method of Internal Validation	Predictor	Presentation
	Discrimination	Calibration			
Chen et al (2024)[20]	0.957	Hosmer-Lemeshow	Split-sample	BMI, ulcer sites, HbA1c, NLR, BUA, EF	Nomogram
Sánchez et al (2024)[21]	0.76	NA	Cross validation	BMI, CKD, CRP, ESR, GFR, GN, HbA1c, HBP, PAD, RA, SBP, Wagner, leukocyte count	Classification And Regression Tree
Stefanopoulos et al (2022)[22]	0.84	NA	Split-sample	Gangrene, Septic Shock, PAD, weight loss, septicemia, systematic infection, Anemia, Age, Bactermia, elective procedure	Prediction algorithm
Xie et al (2022)[23]	Minor amputation:0.85; Major amputation:0.86	Brier score: 0.086	5-fold cross-validation	Age, sex, BMI, diabetes duration, smoking hx, pre-hospital delay, HBP, CAD, HF, cerebral infarction, DN, DR, DPN, PVD, arterial occlusion, gangrene, prior DFU, prior amputation, HbA1c, blood glucose, WBC, neutrophils, Hb, K+, Cr, Na+, albumin, cholesterol, triglyceride, LDL-C, HDL-C, antihyperglycemic drug use, insulin use, Wagner classification system, WIfI classification	Prediction algorithm
Peng et al (2021)[24]	0.876	Calibration curve	Bootstrap	The course of diabetes, PAD, HbA1c, WBC, FIB	Nomogram
Lin et al (2020)[25]	COX:0.557, BPNN: 0.924, BPNN based on genetic algorithm optimization:0.891	NA	Split-sample	Severe ulcer, HbA1c, low-density lipoprotein cholesterol	Equation
Monteiro-Soares et al (2016)[26]	Total amputation:0.87; Major amputation:0.82	NA	NA	DPN, foot deformity, PAD, previous DFU or LEA, multiple DFU, infection, gangrene, bone involvement	Risk score
Beaney et al (2016)[27]	NA	NA	Bootstrap	HbA1c, missing clinic appointments, hypertension, previous revascularization, Charlson index, type of diabetes mellitus, duration of clinic care	Nomogram
Tardivo et al (2015)[28]	NA	NA	NA	Wagner classification, PAD, location of ulcers	Risk score
Lipsky et al (2011)[29]	0.76	Hosmer-Lemeshow	Split-sample	Chronic renal disease, sex, fever, age, infected ulcer versus cellulitis, previous LEA, albumin, PAD, white blood cell count, surgical site vs cellulitis, transferred from other acute-care facilities	Risk score
Van Battum et al (2011)[30]	0.77	NA	NA	Depth of the ulcer, PAD, infection, male	Risk score
Barberán et al (2010)[31]	0.93	NA	NA	Wagner grade 4 or 5, obstruction, elevated sedimentation rate	Risk score
Younes et al (2004)[32]	NA	NA	NA	Depth of the ulcer, extent of bacterial colonization, phase of ulcer healing, associated underlying etiology	Risk score

(*Continued*)

Table 3 (Continued).

Reference	Model Performance		Method of Internal Validation	Predictor	Presentation
	Discrimination	Calibration			
Chetpet et al (2018)[33]	0.903	NA	NA	Age, sensory neuropathy, motor neuropathy, deformity, IDSA infection grade, previous amputation, ulcer depth grade, duration, HbA1c, Rutherford grading, ankle-brachial index	Risk score
Pickwell et al (2015)[34]	Total LEA: 0.8, excluding lesser toes: 0.78	NA	NA	Sex, PAD, pain, peri-wound edema yielding, ulcer size, ulcer depth	Risk score

Abbreviations: BPNN, back propagation neural network; NA, not applicable; DPN, diabetic peripheral neuropathy; PAD, peripheral artery disease; DFU, diabetic foot ulcer; LEA, lower-extremity amputation; IDSA, infectious diseases society of America; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; GN, glomerulonephritis; HBP, hypertension; RA, rheumatoid arthritis; SBP, systolic blood pressure; NLR, neutrophil-lymphocyte ratio; BUA, blood uric acid; EF, ejection fraction; WBC, white blood cell.

Table 4 Characteristics of External Validation Studies

Reference	Original Model	Study Population			Predicted Outcome	Sample Size		Model Performance	
		Object	Setting	Interval		Total(n)	Event(n)	Discrimination	Calibration
Carro et al (2020)[37]	SEWSS, WIFI, Texas	New DFU patients	Argentina, single center, hospital	2019.1–2019.9	Amputation (major amputation, minor amputation)	101	24	SEWSS:0.893	NA
Jeon et al (2017)[36]	DUSS, Texas, Wagner, DEPA, SINBAD	Active DFU patients	Korea, single center, hospital	2010.1–2014.12	Amputation (major amputation, minor amputation)	137	67	DUSS:0.801 Texas:0.886 Wagner:0.892 DEPA:0.890 SINBAD:0.848	NA
Monteiro-Soares et al (2015)[39]	CHS, DEPA, DUSS, IWGDF, Margolis, Wagner, SEWSS, SIGN, SINBAD, Texas, Van Acker	Active DFU patients	Portugal, single-center, hospital	2010.1–2013.3	Amputation (total amputation, minor amputation)	293	68	0.56~0.83	NA

Abbreviations: SEWSS, Saint Elian Wound Score System; WIFI, wound, ischemia, and foot infection; DFU, diabetic foot ulcer; DUSS, diabetic ulcer severity score; DEPA, depth, extent, phase, and the associated underlying etiology; SINBAD, site, ischemia, neuropathy, bacterial infection, and depth; CHS, curative health services; IWGDF, international working group on diabetic foot; SIGN, Scottish intercollegiate guidelines network; NA, not applicable.

Risk of Bias Assessment

All included studies demonstrated high overall risk of bias. While all studies showed low risk of bias for the participant domain, several issues emerged in other domains. For the predictor domain, bias primarily resulted from lack of blinding during predictor assessment (n=9). Similarly, nine studies showed potential outcome bias due to unblinded outcome

Table 5 Risk of Bias and Applicability Concerns Assessment

Reference	Risk of Bias					Applicability			
	Participants	Predictors	Outcomes	Analysis	Overall	Participants	Predictors	Outcomes	Overall
Chen et al (2024)[20]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Sánchez et al (2024)[21]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Stefanopoulos et al (2022)[22]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Xie et al (2022)[23]	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low
Peng et al (2021)[24]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Lin et al (2020)[25]	Low	Low	Low	High	High	Low	Low	Low	Low
Monteiro-Soares et al (2016)[26]	Low	Low	Low	High	High	Low	Low	Low	Low
Beaney et al (2016)[27]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Tardivo et al (2015)[28]	Low	Low	Low	High	High	Low	Low	Low	Low
Lipsky et al (2011)[29]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Van Battum et al (2011)[30]	Low	Low	Low	High	High	Low	Low	Low	Low
Barberán et al (2010)[31]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Younes et al (2004)[32]	Low	Low	Low	High	High	Low	Low	Low	Low
Chetpet et al (2018)[33]	Low	Low	Low	High	High	Low	Low	Low	Low
Pickwell et al (2015)[34]	Low	Low	Low	High	High	Low	Low	Low	Low
Carro et al (2020)[37]	Low	Low	Low	High	High	Low	Low	Low	Low
Jeon et al (2017)[36]	Low	Unclear	Unclear	High	High	Low	Low	Low	Low
Monteiro-Soares et al (2015)[39]	Low	Low	Low	High	High	Low	Low	Low	Low

assessment. Analysis domain concerns included insufficient sample size (n=14), inappropriate handling of censored data (n=14), failure to account for data complexity (n=11), incomplete model performance assessment (n=14), and absence of internal validation (n=11). All models demonstrated low applicability concerns across all domains. Table 5 presents the risk of bias assessment summary, with detailed signaling questions in Supplementary Tables 2 and 3.

Discussion

This systematic review analyzed studies on risk prediction models for DFU progression to amputation. We identified 18 eligible papers including 15 development studies and three external validation studies, totaling 28 models. Discrimination indices ranged from 0.557 to 0.957, with most models achieving AUCs > 0.8, indicating good discriminatory

performance. However, only Lipsky's[29] study reported calibration results. All studies demonstrated high risk of bias, primarily due to insufficient events per variable, missing data, inadequate handling of data complexity, incomplete performance reporting, and lack of internal validation. Consequently, none of the 28 included prediction models can be recommended for clinical use without further validation.

Principal Findings and Future Suggestions

Although diabetic foot amputation incidence remains highest in developing and low-income countries,[40] relatively few models have been developed or validated in Asian or African settings, with most studies conducted in Western countries. Among the 15 development studies, only five were multicenter investigations. Multicenter studies can recruit more participants and cover diverse populations, potentially enhancing generalizability.[41] However, heterogeneity across research settings may introduce higher risk of bias.[42]

Most development models used logistic regression. Lin et al[25] compared Cox regression, backpropagation neural network (BPNN), and genetic algorithm-optimized BPNN, finding that machine learning models exhibited higher AUCs than Cox regression. While machine learning methods offer high prediction accuracy, their lack of transparency may hinder clinical applicability.[43] Whether machine learning consistently outperforms regression models remains contentious.

Predicting amputation among DFU patients is critical for targeting limb salvage interventions. The most frequently reported predictors across all models were PAD, glycated hemoglobin (HbA1c), infection, Wagner classification, and ulcer depth. PAD, present in approximately half of DFU cases, drives both amputation and mortality, making it central to lower limb ischemia management.[44] The pathophysiology underlying these associations is complex and multifactorial. Recent studies have explored broader mechanistic links, including causal relationships between type 2 diabetes and neurological disorders,[45] environmental endocrine disruptors that may induce mitochondrial dysfunction,[46] and systemic metabolic pathways that could influence peripheral complications.[47] These emerging insights suggest that future prediction models might benefit from incorporating biomarkers reflecting these diverse pathophysiological mechanisms.

Poor glycemic control, as measured by HbA1c, represents another established risk factor. Pscherer et al[48] showed that patients with mean HbA1c > 7.5% had 20% higher risk of limb loss compared to those with levels < 7.5%. Elevated white blood cell (WBC) counts also correlate with amputation risk.[49] Eneroth[50] found that WBC counts > 12×10^9/L were associated with increased amputation likelihood. Ulcer depth, a core component of the Wagner classification, strongly predicts outcomes. DFUs are classified by depth (skin, soft tissue, bone), with bone/joint involvement serving as a critical amputation risk indicator.[51]

Infection remains a major modifiable risk factor for amputation. Novel therapeutic approaches are being developed to address this challenge, including glucose-responsive gels that combine photodynamic therapy with hypoxia relief for treating diabetic abscesses[52] and advanced drug delivery systems such as the regulation of selenoproteins.[53] While these therapies are still under investigation, their potential to reduce infection-related amputations could influence future risk stratification models by introducing new modifiable factors.

These widely used predictors are readily measurable in primary care settings, making them practical for routine assessment. Clinicians should prioritize DFU education and proactive management of these risk factors to enhance foot care quality.[54] These validated predictors should form the foundation for future model development.

To our knowledge, this represents the first systematic review specifically evaluating risk prediction models for DFU progression to amputation using PROBAST criteria. Our assessment revealed universal high risk of bias across included studies. For model development, overfitting risk increases when events per variable (EPV) fall below 10, while EPV > 20 enhances result reliability.[55] Validation studies should include at least 100 outcome events to minimize bias in performance estimates,[56] with machine learning models typically requiring larger samples.[57] Although recent methodologies[58,59] enable accurate sample size calculation for prognostic model studies, only four of 18 included studies met recommended sample size criteria.

Six studies reported missing data, with two showing proportions > 10%. Only one study applied multiple imputation, the gold standard for handling missing data, which generates multiple plausible values for each missing observation to appropriately reflect uncertainty.[60,61] Prediction model performance encompasses both discrimination and calibration,[62]

yet only one study assessed calibration. Calibration—measuring accuracy of absolute risk estimates—is as important as discrimination for clinical decision-making.[63] Calibration plots, rather than the Hosmer-Lemeshow test, represent the preferred assessment method.[14] Proper internal validation is essential to correct for optimism bias; without it, model performance will be overestimated.[64] While split-sample validation remains common, cross-validation or bootstrapping provides more robust internal validation. External validation in independent populations remains necessary to establish generalizability.[65]

Future Perspectives

Several priority areas should guide future research in DFU amputation prediction. First, developing artificial intelligence-enhanced models that integrate multimodal data—including clinical parameters, imaging findings, and molecular biomarkers—may substantially improve prediction accuracy.[66] Second, implementation studies are urgently needed to evaluate real-world model performance and impact on patient outcomes. Third, dynamic prediction models that update risk estimates as patient conditions evolve could enable more personalized care delivery. Fourth, international collaborative efforts should establish standardized datasets and validation protocols to ensure model generalizability across diverse populations and healthcare settings. Finally, seamless integration of validated models into clinical decision support systems and electronic health records will be essential for translating research findings into improved patient care.[67]

Limitations of the Review

PROBAST, published by the Cochrane Group in 2019, was not available when most included studies were conducted. Consequently, our methodological quality assessment may appear stricter than if studies had been designed with PROBAST criteria in mind. Despite comprehensive literature searches, we may have missed relevant studies. Meta-analysis was not possible due to sparse calibration reporting and substantial heterogeneity across studies. Our review was restricted to English-language publications, potentially excluding relevant research published in other languages, particularly from non-English speaking countries where diabetic foot disease is highly prevalent. We also acknowledge that certain PRISMA guideline elements were not fully addressed, as our review focused on prediction models rather than interventions, which may have limited search comprehensiveness.

Conclusion

Our review included 18 articles that developed or externally validated 28 models, and summarized their characteristics. The results suggest that the studies on risk prediction models for DFU progressing to amputation are still in the development stage. At present, there is no model that can be applied directly. In the future, prediction models with good performance and low risk of bias should be developed, to identify patients at high risk for diabetic foot amputation as soon as possible and intervene to prevent or delay amputation.

Data Sharing Statement

All data used or generated in this research can be found during this article and its supplementary files.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Specifically, XR and LY designed this study. XR, YMF, and ZJ searched the literature and extracted data. XXR and YMF analyzed data. XXR wrote the first draft of the manuscript. XR and LY supervised and revised the manuscript.

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Disclosure

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