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RESEARCH ARTICLE

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Performance of non-invasive bedside vascular testing in the prediction of wound healing or amputation among people with foot ulcers in diabetes: A systematic review

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Abbreviations: ABI, ankle-brachial index; DFU, diabetes-related foot ulcer; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IWGDF, International Working Group on the Diabetic Foot; NLR, negative likelihood ratio; PAD, peripheral artery disease; PICO, population, intervention, comparison, outcome; PLR, positive likelihood ratio; QUIPS, Quality in Prognosis Studies; TBI, toe-brachial index; $TcPO_2$, transcutaneous oxygen pressure; TMA, transmetatarsal amputation.

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Abstract

Introduction: The presence of peripheral artery disease (PAD) confers a significantly increased risk of failure to heal and major lower limb amputation for people with diabetes-related foot ulcer (DFU). Determining performance of non-invasive bedside tests for predicting likely DFU outcomes is therefore key to effective risk stratification of patients with DFU and PAD to guide management decisions. The aim of this systematic review was to determine the performance of non-invasive bedside tests for PAD to predict DFU healing, healing post-minor amputation, or need for minor or major amputation in people with diabetes and DFU or gangrene.

Methods: A database search of Medline and Embase was conducted from 1980 to 30 November 2022. Prospective studies that evaluated non-invasive bedside tests in patients with diabetes, with and without PAD and foot ulceration or gangrene to predict the outcomes of DFU healing, minor amputation, and major amputation with or without revascularisation, were eligible. Included studies were required to have a minimum 6-month follow-up period and report adequate data to calculate the positive likelihood ratio (PLR) and negative likelihood ratio for the outcomes of DFU healing, and minor and major amputation. Methodological quality was assessed using the Quality in Prognosis Studies tool.

Results: From 14,820 abstracts screened 28 prognostic studies met the inclusion criteria. The prognostic tests evaluated by the studies included: ankle-brachial index (ABI) in 9 studies; ankle pressures in 10 studies, toe-brachial index in 4 studies, toe pressure in 9 studies, transcutaneous oxygen pressure ($TcPO_2$) in 7 studies, skin perfusion pressure in 5 studies, continuous wave Doppler (pedal waveforms) in 2 studies, pedal pulses in 3 studies, and ankle peak systolic velocity in 1 study. Study quality was variable. Common reasons for studies having a moderate or high risk of bias were poorly described study participation, attrition rates, and inadequate adjustment for confounders. In people with DFU, toe pressure ≥30 mmHg, $TcPO_2$ ≥25 mmHg, and skin perfusion pressure of ≥40 mmHg were associated with a moderate to large increase in pretest probability of healing in people with DFU. Toe pressure ≥30 mmHg was associated with a moderate increase in healing post-minor amputation. An ABI using a threshold of ≥0.9 did not increase the pretest probability of DFU healing, whereas an ABI <0.5 was associated with a moderate increase in pretest probability of non-healing. Few studies investigated amputation outcomes. An ABI <0.4 demonstrated the largest increase in pretest probability of a major amputation (PLR ≥10).

Conclusions: Prognostic capacity of bedside testing for DFU healing and amputation is variable. A toe pressure ≥30 mmHg, $TcPO_2$ ≥25 mmHg, and skin perfusion pressure of ≥40 mmHg are associated with a moderate to large increase in pretest probability of healing in people with DFU. There are little data available evaluating the prognostic capacity of bedside testing for healing after minor amputation or for major amputation in people with DFU. Current evidence suggests that an ABI <0.4 may be associated with a large increase in risk of major amputation. The findings of this systematic review need to be interpreted in the context of limitations of available evidence, including varying rates of revascularisation, lack of post-revascularisation bedside testing, and heterogenous subpopulations.

KEYWORDS
amputation, diabetes, diabetic foot, foot ulcer, peripheral artery disease, prognosis

1 | INTRODUCTION

Peripheral artery disease (PAD) is known to be present in up to 50% of persons with a diabetes-related foot ulcer (DFU). PAD commonly co-exists with systemic atherosclerosis and underlying generalised endothelial dysfunction due to vascular inflammation and an abnormal metabolic state.[1,2] Together these changes significantly increase the risk of cardiac-related morbidity and mortality.[3] When associated with diabetes, PAD tends to be more diffuse with increased incidence of lower leg arterial involvement[4] and greater severity of the disease process,[5] a high prevalence of co-existent medial artery sclerosis and diminished collateral formation. The presence of PAD confers a significantly increased risk of failure to heal and major lower limb amputation for people with DFU.[1]

There are multiple non-invasive bedside methods of assessing peripheral blood flow in the lower limb to quantify severity of PAD including Doppler ultrasound, the ankle-brachial index (ABI), toe pressures, the toe-brachial index (TBI), and transcutaneous oxygen pressure ($TcPO_2$). Our previous systematic review demonstrated that a skin perfusion pressure of ≥40 mmHg, a toe pressure of ≥30 mmHg, or a $TcPO_2$ of ≥25 mmHg increase the pre-test probability of DFU healing in people with PAD by at least 25% based on limited available data at the time.[6] In addition, evidence of the capacity of bedside vascular assessments to predict healing post-minor amputation in patients with DFU and PAD was found to be variable.[6]

Rapid revascularisation (within 2 weeks) has been demonstrated to have superior outcomes for DFU healing and amputation prevention over more delayed procedures. There are also high rates of post-surgical delayed healing, infection and risk of more proximal amputation post-minor amputation[7,8] and non-healing despite technically successful procedures. Determining performance of non-invasive bedside tests for predicting likely DFU outcomes will assist in identifying individuals that are likely to require revascularisation to achieve healing and those in whom post-revascularisation perfusion may be inadequate. This will assist with effective risk stratification of patients with DFU and PAD to guide management decisions.

The aim of this systematic review was to determine the performance of non-invasive bedside tests to predict healing, minor amputation healing, minor and major amputation outcomes in people with diabetes, PAD and DFU or gangrene. This systematic review forms the basis for developing the intersocietal International Working Group for the Diabetic Foot (IWGDF), European Society of Vascular Surgery, Society of Vascular Surgery guidelines on peripheral artery disease in people with diabetes mellitus and a foot ulcer.

2 | METHODS

2.1 | PICO development

First, the population of interest (P), interventions (I), and outcomes (O) were defined, and clinical questions formulated accordingly by the assessors (i.e., the authors of this paper). These methods are detailed in Supplementary File S1. The PICO that was developed is listed as follows.

2.1.1 | PICO

In a person with diabetes, suspected PAD and a DFU or gangrene, which non-invasive bedside tests, alone or in combination, at any time point (at baseline or after intervention) predict DFU healing, healing after minor amputation and major amputation.

2.2 | Search methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement with content verified using the AMSTAR tool (PROSPERO ID: CRD42023320610). Title and abstract searches of Medline and Embase were conducted from 1 January 1980 to 30 November 2023 using Endnote. The search strings are provided in Supplementary File S1. A validation set of 10 key publications was used to validate the search string. A protocol has not been published separately.

2.3 | Inclusion/exclusion criteria

Included studies were required to be original research that evaluated non-invasive bedside tests in patients with diabetes, and DFU or gangrene to predict the outcomes of DFU healing, minor amputation, and major amputation with or without revascularisation. The minimum follow-up period for a study to be included was 6 months. This timeframe was chosen to capture outcomes of revascularisation occurring after enrolment of participants in the included studies. Revascularisation procedures were considered likely to occur at various time points with shorter follow-up times therefore potentially not reflecting final healing outcomes. For any study to be included, data had to report separately on at least 10 patients with diabetes, or in mixed studies, more than 80% of the cohort were patients with diabetes.

For the purposes of this review, a non-invasive beside test was classified as any test assessing for the presence of PAD in the lower

limb that could be conducted at the bedside. The studies had to report a cut-off value or threshold of the bedside test to predict outcomes and report adequate data to calculate positive and negative likelihood ratios if these data were not reported in outcomes. A limit to human subjects was applied to the database searches.

Studies that did not report data allowing the calculation of likelihood ratios or studies where these data could not be obtained from the study authors were excluded. Studies were also excluded if they evaluated patients with an intact foot (i.e., without an ulcer or gangrene) or did not include a bedside testing measurement.

2.4 | Data collection and analysis

Two reviewers (Vivienne Chuter and Nicolaas Schaper or Robert Fitridge) independently screened the abstracts retrieved for inclusion and a third reviewer adjudicated any conflicts (Nicolaas Schaper or Robert Fitridge). Full-text articles of included abstracts were retrieved and assessed for inclusion independently by the same two reviewers (except where there was a conflict of interest for publications, a reviewer was an author of in which case the third reviewer was used) with the same third reviewer used to adjudicate conflicts where required. Where the third reviewer also had a conflict, another reviewer was to be sought from the authorship group; however, this was not required. Hand searching of the reference list of appropriate articles was also conducted. Data extraction was performed by Vivienne Chuter using a customised data extraction form and cross-checked by Nicolaas Schaper or Robert Fitridge.

To evaluate the prognostic capacity of bedside testing for healing and amputation, the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were used as the primary endpoints.[9] Likelihood ratios were used to express a change in odds of reaching an outcome in the context of a known pre-test probability of disease (i.e., knowledge or estimation of the prevalence of disease in the studied population). The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the NLR expresses a change in odds of experiencing an outcome if the test is negative. PLR is calculated as follows: PLR = sensitivity/(1−specificity); NLR is calculated as follows: NLR = (1−sensitivity)/specificity.

The higher the PLR, the greater the ability of the test to rule in the outcome of interest, whilst a smaller NLR reflects better ability of the test to rule out the outcome. A test was considered to have very good performance if PLR ≥10 (representing a large increase in probability of the specified outcome by around 45% in the presence of a positive test result) and NLR ≤0.1 (representing a large decrease in the probability of the specified outcome of around 45% in the presence of a negative test result)[10–12] (Table 1). A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful diagnostic test. Generally, a minimal change in disease probability can occur when a test is used with a PLR less than 2 or an NLR more than 0.5. The practical application of this is to identify the most useful bedside tests that will inform the healthcare professional as to the probability, or not, of the patient experiencing healing or major amputation.

Due to the anticipated heterogeneity between studies, including differing thresholds, methods for conducting bedside tests, definitions of healing, and study populations, a meta-analysis was not planned. Instead, measures of test performance (sensitivity and specificity and positive likelihood ratio [PLR] and negative likelihood ratio [NLR]) were calculated from the available data and the results for individual beside tests were synthesised. Where the PLR or NLR was calculated, and the PLR was infinite or the NLR zero, respectively, these were reported as a PLR ≥10 or an NLR <0.1.

2.5 | Quality assessment

Methodological quality was assessed using the Quality in Prognosis Studies (QUIPS) tool. This tool uses six domains for critical appraisal of study validity and bias including study participation, study

TABLE 1 Interpretation of likelihood ratios.

	Approximate change in pretest probability of the outcome	Magnitude of effect on posttest probability of the outcome
Negative likelihood ratios		
0.1	−45%	Large decrease
0.2	−30%	Moderate decrease
0.5	−15%	Slight decrease
1	−0%	None
Positive likelihood ratios		
1	+0%	None
2	+15%	Slight increase
5	+30%	Moderate increase
10	+45%	Large increase

Source: McGee, 2002.[12]

attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting with items in each domain rated either yes, partial, no, unsure and an overall, judgement of the risk of bias (high, moderate, or low) within each domain made based on the ratings of the included items.[13] Two reviewers (Vivienne Chuter, Robert Fitridge, or Nicolaas Schaper) independently assessed the quality of the studies with disagreements resolved at a consensus meeting by a third reviewer where required (Nicolaas Schaper or Robert Fitridge). There was no minimum level of quality required for inclusion in the review. The outcome of the QUIPS assessment was used to inform the certainty of evidence applied to evidence statements.

2.6 | Evidence statements

Two investigators (Vivienne Chuter and Robert Fitridge) drew conclusions for each intervention based on the strength of the available evidence, formulated as evidence statements, and accompanying assessment of the quality of the evidence, according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) process.[14] The authors rated the certainty of the evidence for each formulated evidence statement as 'high', 'moderate', 'low', or 'very low' in regard to the strength of confidence in estimates of the effect of a prognostic test on patient-important outcomes.[14,15] GRADE defines 'high' as 'We are very confident that the true effect lies close to that of the estimate of the effect', 'moderate' as 'We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different', 'low' as 'Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect', and 'very low' as 'We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect'.[14] The rating was determined based on the level of evidence, risk of bias, (in)consistency of results, (im)precision, (in) directness (whether the available evidence answers the clinical question), publication bias, effect size, and evidence of dose-response relation.[14] Each evidence statement was phrased in accordance with the methods described by GRADE. When the certainty of evidence was rated as moderate, the evidence statement was generated using the words 'likely results in …'; likewise, when rated with a low certainty of effect, the statement contained 'may result in …'; for evidence rated as having a very low certainty of effect, the statement contained '(very) uncertain'; when the effect or effect size could not be estimated, no evidence statement was provided. All authors discussed these evidence statements until consensus was reached.

3 | RESULTS

3.1 | Search results

The search string utilised for this systematic review identified 14,820 studies. Following screening, 72 studies were deemed appropriate for full-text review, and a final 28 studies met the inclusion criteria. The search and screening strategy is illustrated in a PRISMA flow diagram (Figure 1). Details of the 28 studies, with a total of 6965 participants, are reported in Supplementary Table S1 and the consolidated results are provided in Table 2.

3.2 | Characteristics of included studies

3.2.1 | Participants

The mean or median age of the participants was 61 years, while the proportion of men was between 45.9% and 88%. All except 3 studies reported exclusively on patients with DFU or provided specific data of participants with diabetes. One study with a mixed population with close to 80% of the cohort with diabetes (77.4%)[16] and a second study with a mixed population with 81.92% of the cohort with diabetes were included.[17] The third study observed no difference in healing between patients with diabetes (61.5%) and those without diabetes, so the results of the whole cohort were included.[18] Severity of ulceration was reported in almost 60% of the studies with the majority of studies reporting Wagner grades (n = 12),[19–29] 2 using the SINBAD classification[30,31] and 1 study each utilising the Wound Ischaemia and foot Infection (WIfI) classification system[16] and University of Texas grading systems.[32] Two sets of studies assessed different clinical tests using the same cohort.[19–21,24] Study-specific characteristics can be found in Supplementary Table S1.

3.2.2 | Revascularisation

All but 5 studies[22,25,29,33,34] reported on revascularisation with those studies reporting it describing rates ranging from 4.5% to 100%. Three studies excluded patients who underwent revascularisation,[32,35,36] and 4 others examined cohorts ineligible for revascularisation.[24,37–39] Open, endovascular and hybrid methods were described (Supplementary Table S2).

3.2.3 | Evaluation of prognostic tests

The prognostic tests evaluated by the studies included: ABI in 9 studies[27,30–34,36,39,40]; ankle pressures in 10 studies[17,19,20,23–25,27,32,33,35]; TBI in 4 studies[27,30–32]; toe pressures in 9 studies[17,19,23–25,27,32,35,37]; $TcPO_2$ in 7 studies[29,30,32,33,37,38,41]; skin perfusion pressure in 5 studies[16,18,34,35,42]; continuous wave Doppler (pedal waveforms) in 2 studies[26,28]; pedal pulses in 3 studies;[20,21,41] and Doppler ankle peak systolic velocity (threshold 35 cm/s) by 1 study.[43]

3.2.4 | Clinical outcomes

Supplementary Table S2 presents clinical outcomes by study. Healing rates reported by the studies are varied as some studies report DFU

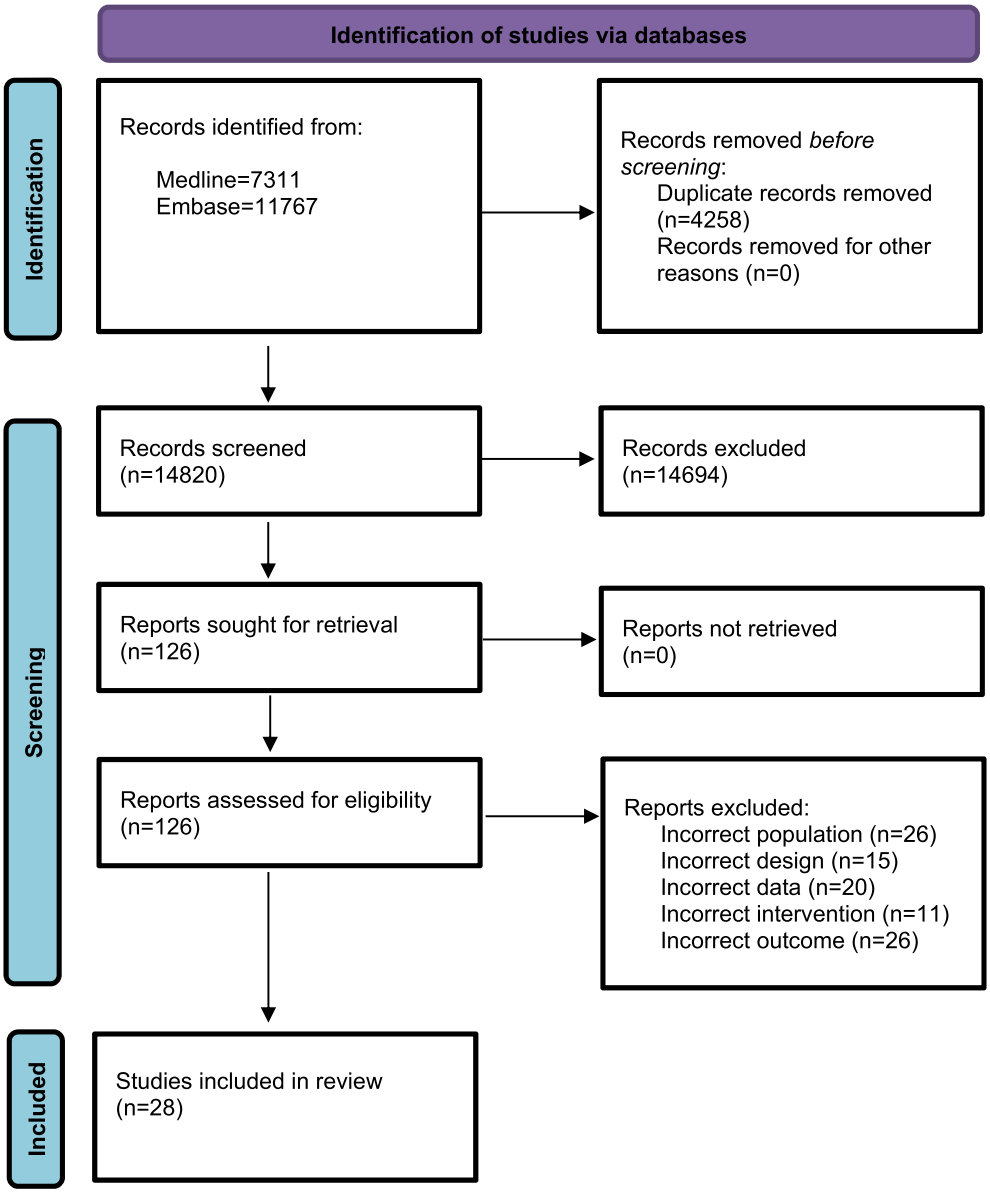

FIGURE 1 PRISMA flow diagram.

healing, others healing including after minor amputation, or healing including after revascularisation or both. The rate of primary healing reported by the studies varied between 38% and 67% with differing follow-up periods used between studies. The rate of major amputation ranged between 0% and 60%. The highest rate of major amputation (60%) was reported by Larsson et al.,[27] who evaluated a high-risk population of patients with diabetes-related foot ulcer requiring amputation.

3.3 | Methodological quality and certainty of evidence

The QUIPS analysis for risk of bias is presented in Table 3. Study quality was variable. The most common reasons for studies having a moderate or high risk of bias were poorly described study participation, attrition rates, and inadequate adjustment for confounders. No bedside testing intervention had consistent outcomes for the prognostic capacity for DFU healing, healing post-minor amputation, minor amputation or major amputation. For example, studies of the prognostic capacity for healing for the ABI reported PLRs ranging from 1.06 to 4.59 suggesting either no effect of the test on post-test probability of healing or a moderate increase.[31,39] This heterogeneity is likely to have been associated with differences in the study population, for example, ischaemia severity, wound severity and presence of co-morbidities (e.g., kidney disease), differences in duration of follow-up (between 6 months and >5 years), and differing study methods including bedside testing measurement thresholds used and control of confounding variables. Interpretation of evidence is also limited by few available studies for the outcomes of minor and major

TABLE 2 Summary of evidence for prognostic capacity of bedside tests at differing thresholds.

		Prognosis—healing			Prognosis—major amputation	
Test	**Threshold**	**PLR range**	**NLR range**	**Threshold**	**PLR range**	**NLR range**
ABI	≥0.50	2.0–4.0	0–0.12	<0.90	1.1–1.3	0–0.92
	>0.70	4.59	0.23	≤0.90 or ≥1.3	2.3	0.64
	≥0.9	1.06–1.67	0.48–0.78			
AP	≥50 mmHg	1.08–1.12	0.34–0.48	<50 mmHg	2.61	0.89
	≥70 mmHg	3.44	0.11	<70 mmHg	8.8	0.29
	≥80 mmHg	1.27–1.5	0.32–0.47	<80 mmHg	2.13	0.76
TBI	>0.65	≥10	0.28			
	≥0.75	0.88	1.05	<0.75	1.44	0.61
Toe pressure	≥30 mmHg	5.0–9.95	0.28–0.88	<30 mmHg	2.90–3.24	0.1–0.75
	≥45 mmHg	1.43–2.87	0.45–0.64	<45 mmHg	2.14	0.67
$TcPO_2$	≥25 mmHg	5.0 to ≥10	0.09–0.14	<20 mmHg	1.87	0.68
	>30 mmHg	1.24–1.60	0.29–0.47			
SPP	≥30 mmHg	≥10	0.36			
	≥40 mmHg	1.3–11.17	0.35–0.62			

Note: The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the negative likelihood ratio (NLR) expresses a change in odds of experiencing an outcome if the test is negative. A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful diagnostic test. Ranges of numbers are provided where more than one study reported positive and negative likelihood ratios.

Abbreviations: ABI, ankle-brachial index; AP, ankle pressure; DFU, diabetes-related foot ulcer; NLR, negative likelihood ratio; PLR, positive likelihood ratio; SPP, skin perfusion pressure; TBI, toe-brachial Index; $TcPO_2$, transcutaneous oxygen pressure.

amputation and a lack of studies for specific bedside tests, for example, continuous wave Doppler. Evidence for all outcomes was rated as low certainty.

3.4 | Non-invasive tests to predict wound healing

Twenty-four studies evaluated non-invasive bedside tests for the prediction of wound healing in people with diabetes and foot ulceration.

3.4.1 | Ankle-brachial index or ankle pressure

In 5[31,32,34,36,40] studies evaluating ABI using a threshold of ≥0.9 healing, a PLR for wound healing of between 1.06 and 1.67 was reported, meaning that there is almost no improvement on the probability of healing when the ABI is above this threshold. Two of these studies investigated healing outcomes in a mixed population including those with DFU and post-minor amputation[31,34] with the remaining studies conducted in people with DFU.[32,36,40] One study examined two separate ABI thresholds for healing post-minor amputation in the same cohort an ABI >0.4 (PLR 1.3) and ABI >0.7 (PLR 4.59) with the higher PLR reflecting an increase in the probability of healing of more than 25%.[39] In this follow-up observational study of 97 patients in China undergoing trans-metatarsal amputation (TMA) for forefoot gangrene who were not eligible for revascularisation, the wound healing rate was 87.8% with an ABI of 0.7–0.9, and all wounds healed where the ABI was 0.91–1.3.[39]

Two studies used lower ABI thresholds to investigate healing post-minor amputation[27] or DFU healing.[30] The studies used similar thresholds for the ABI (ABI ≥0.5,[27] ABI >0.52[30]); the reported PLRs indicated a 15%–25% increase in the probability of healing (PLR: 2.0 and 4.0 and NLR 0.12 and 0). Both the studies also reported low NLRs, suggesting that the chance of *not* healing was increased if the ABI was <0.50. The higher PLR value (4.0) was found in a small cohort of 21 participants, and the ABI cut-off value of >0.52 displayed a sensitivity of 100% and a specificity of 75% as calculated from an ROC curve.[30] A final study used stepwise multiple analysis regression to predict the probability of healing and found an ABI sensitivity and specificity of 81% and 31%, respectively, corresponding to a non-predictive PLR of 1.17.[33] Most studies evaluating ABI as a prognostic factor did not identify a threshold that would indicate a significantly appreciably change of wound healing.

TABLE 3 QUIPS quality assessment results.

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Apelqvist (2011)	++	+++	++	++	++	+
Apelqvist (1990)[a]	++	+++	+++	++	++	+++
Apelqvist (1989)[a]	++	+++	+++	++	++	+++
Bishara (2009)	++	++	+++	+++	+++	+++
Brechow (2013)	++	+	++	+	+	+
Bunt (1996)	+	+	++	+	+	+
Castronuovo (1997)	++	+++	+++	+++	+	++
Chetpet (2018)	++	++	+++	+++	+	+++
Elgzyri (2013)	+++	+++	++	++	+++	++
Elgzyri (2021)	+++	+++	++	+++	+++	+++
Faris (1988)	+	++	+++	+	+	+
Fujii (2021)	+	+	++	+++	++	+++
Gershater (2009)	+++	+++	++	+++	++	+++
Hering (2021)	+	++	+++	++	++	+++
Holstein (1980)	+	++	++	+	+	+
Kalani (1999)	+	++	++	+++	+	++
Kawai (2017)	+	++	+++	+	+	++
Ladurner (2010)	+	+	+++	++	+	++
Larsson (1993)	+++	+++	++	+++	+	++
Lopez-Moral (2022)	+	+++	+	+++	++	+++
Manu (2021)	++	++	+++	++	++	+++
Mennes (2021)	++	++	++	+++	++	++
Nouvong (2009)	++	+	++	+++	+	+++
Padberg (1996)	+	+++	++	+++	+	++
Wallin (1989)	+	+++	++	+	+	+
Tsai (2103)	+++	++	+++	+++	+++	+++
Yang (2013)	+	+	+++	+++	+	++
Zhang (2019)	+++	++	++	+++	+++	+++

Note: +, low quality; ++, moderate quality; +++, high quality.

Abbreviation: QUIPS, Quality in Prognosis Studies tool.

[a]Same cohort, different tests assessed.

Ankle pressure thresholds varied considerably between studies. Two studies investigated a threshold of ankle pressure ≥50 mmHg for DFU healing.[24,25] PLRs (1.08 and 1.12) and NLRs (0.48 and 0.34) indicate ankle pressures at or over this threshold did not increase pretest probability of disease.[24,25] These results were consistent with those of two studies investigating a threshold of ankle pressure ≥80 mmHg for predicting DFU healing with PLRs of 1.27 and 1.5 and NLRs 0.47 and 0.32 indicating little prognostic capacity of the test.[19,25] One study used a threshold of ≥70 mmHg and reported a PLR of 3.44 indicating a 15%–20% increased likelihood of DFU healing in people with pressures over this threshold.[17] Using a higher threshold of ankle pressure (>96 mmHg), another study examining ankle pressures recorded a lower PLR of 1.47.[32] All these results indicate either no increase or only a small increase in the probability of healing using these thresholds. A final study used stepwise multiple regression analysis to predict the probability of healing and found an ankle pressure sensitivity and specificity of 84% and 32%, respectively, corresponding to a non-predictive PLR of 1.23.[33]

For healing post-minor amputation, thresholds for ankle pressure were inconsistent and included ≥75 mmHg and ≥80 mmHg.[23,27] PLRs

indicated little prognostic capacity of the tests (PLR 0.97, 1.25); however, NLRs were inconsistent. Larrson et al.[27] demonstrated that ankle pressure <75 mmHg was strongly prognostic of not healing (NLR 0.16), while Elgyzri et al.[23] found the test to be of no benefit (NLR 1.09). One study evaluated healing in people with DFU or post-minor amputation and reported only a small increase in pre-test probability of healing with an ankle pressure ≥50 mmHg or ankle pressure ≥80 mmHg (PLRs 1.25 and 2.67, respectively).[35] The NLR was 0 for ankle pressure ≥50 mmHg (indicating a much higher probability of *not* healing if the ankle pressure is below this level) and 0.28 for ankle pressure ≥80 mmHg.[35]

3.4.2 | Toe-brachial index or toe pressure

The four studies examining TBI all used different thresholds to predict DFU healing[30–32] and healing post-minor amputation.[27] The TBI thresholds reported, and their respective PLRs were TBI: >0.51, ≥0.65, ≥0.75 and ≥0.1, PLR: 1.47, ≥10, 0.88, 1.9, with most studies indicating almost no increase in the probability of healing when the TBI is above these levels. While one study of DFU healing reported a PLR ≥10 (TBI threshold >0.65), it was a small study ($n = 21$) with no significant difference in the mean TBI between the healed and non-healed groups, and TBI was not associated with healing in a subsequent logistic regression analysis.[30] This study evaluating healing post-minor amputation reported an NLR of 0.09, suggesting a large increased probability of *not* healing post-minor amputation when the TBI is <0.1.[27]

Six studies examined a threshold of toe pressure ≥30 mmHg with three of the studies finding a PLR between 0.67 and 1.29.[23–25] The other three studies reported higher PLRs at this threshold.[17,35,37] Kalani et al.[37] reported a PLR of 5.0, indicating a greater than 25% increase in the probability of healing; however, the corresponding NLR was 0.88, indicating that the toe pressure at this threshold could not predict who did not heal. This same study also found a lower PLR (2.87) at a higher toe pressure threshold of ≥45 mmHg. The authors noted that toe pressure varied considerably in the non-healed group and that there was no significant difference in mean toe pressure between the healed and non-healed groups. Wallin et al.[17] reported a PLR of 9.95 and NLR of 0.31 for this threshold for DFU healing. A further 4 studies that examined a higher toe pressure threshold of ≥45 or >54 mmHg reported a small ability to predict DFU healing (PLR 1.43–3.02).[19,25,32,37] A single study that reported on the use of toe pressure to predict healing post-minor amputation at a threshold of ≥15 mmHg found a low PLR (1.68) in conjunction with a low NLR (0.1), demonstrating that toe pressure values below this threshold indicate a large increase in the probability of *not* healing.[27] In contrast, a PLR ≥10 was reported by Holstein et al.[35] in an investigation of healing post-minor amputation using a ≥30 mmHg threshold, reflecting the fact that all their participants with toe pressures above this level healed ($n = 18$ of 35 feet).

3.4.3 | Transcutaneous oxygen pressure

In a range between 25 and 30.4 mmHg, $TcPO_2$ was shown to have a varied performance for prediction of DFU healing by four studies (PLR: 6, 1.24, 5.03, ≥10).[29,30,32,37] Two of the studies reporting higher PLRs (5.03, 6.0) included both healed ulcers (with intact skin) and improved ulcer healing in their outcome definitions[29,37] in comparison to the other studies that examined healed versus non-healed outcomes, and this may explain the larger PLR results. The PLR ≥10 reported by Lopez-Moral et al.[30] was in a small cohort of 21 participants, and their $TcPO_2$ cut-off value of 28.5 mmHg displayed a sensitivity of 91% and a specificity of 100%. A final study used stepwise multiple regression analysis to predict the probability of healing and found a $TcPO_2$ sensitivity and specificity of 81% and 81%, respectively, corresponding to a PLR of 4.26, which indicates a 25% increase in the probability of healing.[33] The authors concluded that $TcPO_2$ can be used to stratify critically ischaemic limbs for the probability of healing, and at a level of $TcPO_2$ ≥30 mmHg their cohort displayed a 70% probability of healing.[33] One study investigating a $TcPO_2$ threshold of >30 mmHg at baseline or following revascularisation for healing post-minor amputation reported a low PLR (1.60) and NLR of 0.29.[41]

3.4.4 | Skin perfusion pressure

One small study ($n = 22$) of healing post debridement or minor amputation found that where skin perfusion pressure ≥30 mmHg all ulcers healed ($n = 7$), providing a PLR ≥10.[34] Two studies evaluating healing of DFU and/or after minor amputation using a threshold of skin perfusion pressure ≥40 reported a moderate increase in pretest probability of healing (PLR 4.6, 6.4).[16,35] Holstein et al.[35] found only 1 foot of 17 failed to heal with skin perfusion pressure ≥40 mmHg, indicating a greater than 35% increase in the probability of healing. A retrospective study evaluating predictive factors for wound healing, compared patients in a healed group ($n = 88$), occurring primarily or after minor amputation, to a major amputation group ($n = 12$) found that post-revascularisation skin perfusion pressure values were significantly associated with wound healing. A post-revascularisation skin perfusion pressure ≥40 mmHg indicated an almost 30% increase in the pretest probability of healing.[16] A second retrospective study concluded that skin perfusion pressure may be used to determine the appropriate treatment for ischaemic ulcers in people both with and without diabetes as all ulcers with skin perfusion pressure ≥40 mmHg healed.[18] The sensitivity and specificity of a threshold of ≥43 mmHg for a foot ulcer to heal were 67% and 94%, which correspond to a 45% increase in the pretest probability of healing. One additional study with the outcome of survival without limb loss at 6 months used a threshold of skin perfusion pressure ≥40 mmHg with the PLR and NLR indicating the test had a low-to-moderate effect on probability of the outcome (PLR: 1.60, NLR: 0.29).[42]

3.4.5 | Other tests

The presence of palpable pedal pulses in the prediction of healing was evaluated by two studies in relation to DFU healing[21] and healing post-minor amputation.[41] A PLR ≥10 was reported in the study of healing post-minor amputation where all 44 people with palpable pedal pulses healed. The NLR (0.65) corresponds to little change in the probability of healing if pulses are absent.[41] However, the magnitude of the NLR may have been affected by the treatment algorithm, which meant some of those with decreased pulses underwent subsequent revascularisation. The remaining study of DFU healing reported lower PLRs (2.35), indicating only a small improvement in the probability of healing when pedal pulses were palpable.[21]

One study reported a low PLR (1.56) when examining the predictive capability of a biphasic Doppler waveform at the forefoot, for DFU or minor amputation healing following successful PTA of the peroneal artery.[26] An additional study of ankle peak systolic velocity (calculated as the mean of the peak systolic velocities measured across the distal tibial arteries at the ankle level) measured by Doppler using a threshold <35 cm/s demonstrated a large increase in the probability of non-healing DFU below this level, while higher velocities were associated with the opposite effect on the probability of non-healing (PLR 9.9, NLR 0.08).[43]

3.5 | Non-invasive tests to predict lower limb amputation

3.5.1 | Minor amputation

Prediction of minor amputation was investigated by three studies,[26,31,38] which evaluated four non-invasive bedside tests (ABI, TBI, $TcPO_2$, and pedal Doppler waveforms). Manu et al.[31] assessed minor amputation rates at a 5-year follow-up using both ABI <0.9 (PLR 1.3) and TBI <0.75 (PLR 1.1) as threshold values with neither value displaying an increased probability of minor amputation. A $TcPO_2$ <20 mmHg was found only to slightly increase the probability of a minor amputation (PLR 2.5) in one study.[38] The final study found the presence of monophasic pedal Doppler waveforms at the forefoot ineffective (PLR 0.71) for forecasting the probability of a minor amputation.[26]

3.5.2 | Major amputation

Five studies evaluated five non-invasive bedside tests (ABI, AP, TP, $TcPO_2$, and pedal Doppler waveforms) for the prediction of major amputation (amputation of the leg proximal to the ankle) in people with diabetes and foot ulceration.[25,26,28,38,39] One study examined ABI in those undergoing any amputation.[22] Another study assessed predictive capacity of ankle pressure and toe pressure for amputation where the amputation level was not defined.[17] For the outcome of any amputation using a threshold of ≤0.90 or ≥1.30, Chepet et al.[22] reported a PLR of 2.3 and NLR more than 0.5 suggesting that the test did not differentiate those who were not likely to have an amputation from those who were. The study evaluating ABI for the prediction of major amputation used a threshold <0.9 and reported a PLR of 1.1 and NLR of 0 - indicating an ABI <0.9 did not increase the pretest probability of having amputation but an ABI ≥0.9 was associated with a large (45%) increase in the probability of *not* having a major amputation.[39]

The study reporting the outcome of major amputation was a follow-up observational study performed in a cohort of 97 patients in China undergoing TMA for forefoot gangrene who were not eligible for revascularisation.[39] In their cohort, Zhang et al.[39] found all major amputations after TMA (n = 16) occurred in people with an ABI <0.9 (PLR 1.1, NLR 0) indicating no increase in probability of a major amputation for this ABI threshold.[39] However, half of the participants had an ABI ≤0.4, which was associated with a PLR of 40.5 (NLR 0.51), that is, a very high increased probability of major amputation.

Two studies evaluated the predictive capacity of ankle pressure for major amputation.[17,25] Gershater et al.[25] compared the predictive capacity of ankle pressure of <50 and <80 mmHg for major amputation within the same cohort. When the lower threshold was used, there was increased specificity (92% vs. 79%), but this was at the cost of reduced sensitivity (20% vs. 39%). The higher threshold of <80 mmHg performed slightly better (PLR 2.42 vs. 1.83; NLR 0.87 vs. 0.78) regarding the prediction of major amputation; however, these results indicate only a small increased probability of major amputation at these thresholds. Wallin et al.[17] used a threshold of ankle pressure <70 mmHg yielding a PLR of 8.8 for values below this threshold that would increase the pretest probability of major amputation by approximately 45%.

Gershater et al.[25] also compared toe pressure thresholds of <30 mmHg and <45 mmHg within the same cohort and found them broadly equivalent and not strongly predictive of major amputation (PLR 2.63 and 2.08).[25] Similar results were reported by Wallin et al.[17] with a toe pressure of <30 mmHg associated with a PLR of 3.21, indicating a small increase in pretest probability of major amputation. However, the same study reported that an NLR of 0.1 indicating toe pressure ≥30 mmHg is associated with a 45% increase in pretest probability of *not* having a major amputation.

$TcPO_2$ was evaluated in one study of major amputation. $TcPO_2$ <20 mmHg resulted in a PLR of 1.87 and an NLR of 0.68, indicating that this threshold has a poor ability to rule major amputation either in or out.[38] Finally, the presence of monophasic pedal Doppler waveforms at the forefoot or the absence of flow at either of the below the knee arteries did not display a strong predictive value for

major lower extremity amputation in two studies (PLR: 1.56, 2.18, NLR: 0.65, 0.2).[26,28]

3.6 | Evidence statements

In people with DFU:

- an ABI ≥0.9 may not increase the pretest probability of DFU healing or healing after minor amputation[31–34,36,40]
- an ABI <0.9 may not increase the pretest probability of major amputation.[39]
- an ABI <0.5 may be associated with a 30%–45% increase in the pretest probability of non-healing of DFU or non-healing after minor amputation.[27,30]
- an ABI <0.4 may be associated with a large (>45%) increase in the pretest probability of major amputation.[39]

Certainty of evidence: Low.

In people with DFU:

- Ankle pressure ≥50 mmHg is not consistently associated with an increase in the pretest probability of DFU healing or healing after minor amputation.[24,25,35]
- Ankle pressure has variable predictive capacity for major amputation. Thresholds of <50 to <80 mmHg may be associated with a small increase (15%) in the pretest probability of this outcome.[25]

Certainty of evidence: Low.

In people with DFU, there are insufficient data to determine if TBI predicts DFU or minor amputation healing, or minor or major amputation.[27,30–32]

Certainty of evidence: Low.

In people with DFU, a toe pressure ≥30 mmHg may be associated with an increased pretest probability of DFU and post-minor amputation healing of at least 30% and a toe pressure <30 mmHg may be associated with a small increase (15%) in the pretest probability of major amputation.[17,35,37]

Certainty of evidence: Low.

In people with DFU:

- $TcPO_2$ ≥25 mmHg may increase the pretest probability of DFU healing by up to 45%.[29,30,32,37]
- $TcPO_2$ <20 mmHg may increase the pretest probability of minor amputation by a small amount but may not increase the pretest probability of major amputation.[38]
- Skin perfusion pressure of ≥40 mmHg may increase the pretest probability of DFU healing and healing after minor amputation by up to 45%.[16,18,34,35,42]

Certainty of evidence: Low.

In people with DFU it is unlikely that abnormal or absent pedal Doppler waveforms increase the pretest probability of healing or minor or major amputation.[26,28]

Certainty of evidence: Low.

In people with DFU, the presence of pedal pulses may increase the pretest probability of DFU healing by a small amount (15%).[21]

Certainty of evidence: Low.

In people with DFU, the presence of pedal pulses may increase the pretest probability of healing post-minor amputation by a large amount (45).[41]

Certainty of evidence: Low.

4 | DISCUSSION

This systematic review identified 28 studies investigating prognostic capacity of different methods of bedside testing for healing and amputation in people with a DFU or gangrene. Included studies evaluated ABI (n = 10), ankle pressure (n = 9), TBI (n = 4), toe pressure (n = 9), $TcPO_2$ (n = 7), skin perfusion pressure (n = 5), continuous wave Doppler (n = 2), palpation of pedal pulses (n = 2), and ankle peak systolic velocity (n = 1). No test was shown to be superior for this purpose.

The results of this systematic review suggest that the predictive capacity for ABI and ankle pressure for healing and amputation in patients with DFU is variable and dependent on the threshold used. For the ABI, a threshold of ≥0.9 was used in 4 studies investigating the prognostic capacity of the test for DFU healing and healing after minor amputation[31,34,36,40] and <0.9 in 3 studies investigating this for probability of major or any amputation.[22,31,39] For wound healing, an ABI ≥0.9 did not increase the pretest probability of the outcome (PLR 1.06–1.67). For the outcome of amputation, 2 of 3 studies demonstrated no increase in the pretest probability of minor or major amputation with an ABI <0.9 (PLR1.3, 1.1).[31,39] One study reported a small increase in the pretest probability of any amputation with an ABI <0.9 (PLR 2.3).[22] Based on these results, ABI using a threshold of ≥0.9 for healing and <0.9 for amputation does not provide additional information on pretest probability of patient outcomes for DFU and minor amputation healing or amputation. However, several studies demonstrated increased the pretest probability of both *non*-healing (ABI<0.5: 30%–45% increase) in populations in which the revascularisation rate was low (4%–16.4%)[27,30] and amputation (ABI <0.4: 45% increase) in a population not suitable for revascularisation[39] indicating that the test may still have clinical use for this purpose in those with severe disease.

These differing findings may be influenced by several factors. For the purposes of diagnosis of PAD, an ABI of ≤0.90 is recommended as being indicative of the presence of disease.[6] However, in people with diabetes, this threshold has been found to be less accurate for

diagnosing disease in part related to the increased prevalence of medial artery calcification causing falsely elevated ankle pressure and ABI values.[4] In addition, the presence of tibial and pedal stenoses or occlusions may be missed by ankle pressure and ABI testing where they occur at or below the level of the cuff, and disease may be overlooked when the ABI is calculated from the higher of the dorsalis pedis and posterior tibial pressures.[44] These limitations are likely to impact the prognostic capacity of the test for healing or amputation and as well as reducing the diagnostic accuracy.

For ankle pressure, the available studies had heterogenous methodology and found inconsistent results for both healing and amputation outcomes. Thresholds used to investigate the prognostic capacity of ankle pressure for DFU healing, healing after minor amputation, and having a major amputation were highly variable generally ranging from <50 mmHg to <80 mmHg.[17,19,20,23–25,35] Systolic pressures more than these thresholds were not consistently associated with healing, while having pressures <50 mmHg or <80 mmHg was not consistently associated with the increased pretest probability of amputation.[17,25] The lack of prognostic capacity of ankle pressure for healing even at low thresholds is consistent with limitations in diagnostic accuracy of ankle pressure in people with severe ischaemia with a study (55% with diabetes and therefore ineligible for this review), demonstrating ankle pressure alone failed to diagnose chronic limb threatening ischaemia in over 40% of cases.[45]

Other measures of artery function at the ankle were similarly inconsistent. The presence of palpable pedal pulses increased the pretest probability of DFU healing by a small amount (15%). However, it was increased by a large amount for healing after minor amputation where revascularisation had occurred.[21,41] Abnormal or absent pedal Doppler waveforms were shown to have little predictive capacity for healing, or minor or major amputation in 2 studies.[26,28] Of note, one study investigating ankle peak systolic velocity, which averages both tibial arteries at the level of the ankle using a threshold <35 cm/s, demonstrated a high pretest probability of non-healing below this threshold, while higher velocities were associated with a low pretest probability of non-healing (PLR 9.9, NLR 0.08). This test may therefore be of clinical use for determining probability of DFU healing and requires further evaluation as it has not been widely reported on.

Toe pressure was evaluated more with some consistency for healing outcomes across 3 studies using a threshold of ≥30 mmHg. This threshold was associated with an increased pretest probability of DFU healing and healing post-minor amputation of at least 30% as well as a small reduction in the pretest probability of amputation. Two of the 3 studies were conducted in populations that were not revascularised during the follow-up period.[37,38] In the third study, only 5% of the participants were revascularised.[17] With little or no revascularisation to alter peripheral blood flow after baseline measurement in these study populations, the baselines measures are likely to have been a valid estimate of blood flow throughout the follow-up period. This may have contributed to the consistency of results. However, these results need to be considered within the context of the study populations. Most studies investigating toe pressure and TBI were performed in European countries (e.g., Sweden $n = 7$), and the applicability of these findings to other populations/geographic locations is unknown.

The majority ($n = 21$) of studies in this review included participants undergoing revascularisation procedures with these performed in between 4% and 100% of the study participants. As noted in relation to toe pressure outcomes, lack of availability of post-revascularisation bedside testing data means that prognostic outcomes calculated from baseline bedside tests are confounded by any subsequent interventions that were performed on different proportions of study cohorts. In addition, while a minimum 6-month period of follow-up was an inclusion criterion designed to capture revascularisation outcomes, the timing of revascularisation and the follow-up points varied considerably between studies and were in some instances implied by the study design and outcome definitions rather than clearly reported. This is likely to have contributed to the significant heterogeneity between studies for bedside test using similar thresholds. Of the 28 studies included, only 7 were performed in cohorts not undergoing any form of revascularisation.[24,32,35–39] This included 3 studies where participants requiring revascularisation were excluded[32,35,36] and 4 in which participants were considered unsuitable for revascularisation.[24,37–39] These participant populations are likely to have differing levels of ischaemia and comorbidities which would contribute further to the heterogeneity of the results reported in this review.

Four studies of the TBI assessed healing outcomes using different thresholds (>0.51, ≥0.65, ≥0.75 and ≥0.1)[27,30–32] and 1 study evaluated probability of amputation using a threshold of <0.75.[31] Only 1 of the studies that evaluated DFU healing outcomes in a small cohort ($n = 21$) demonstrated that the test increased the pretest probability of the outcome.[30] However, the same study reported TBI was not a significant predictor of healing when controlling for other confounding variables in a data-driven regression model. These results suggest that TBI is of limited use as a prognostic marker of either healing or amputation outcomes and should not be used as primary tests for this purpose. The lack of consistency between TBI and toe pressure results is noteworthy. TBI is calculated as a ratio of toe pressure to brachial systolic pressure. Toe pressure ≥30 mmHg was associated with a moderate increase in the probability of healing. The associated TBI will be affected by the magnitude of the brachial systolic pressure; however, the higher TBI thresholds reported in three of the four studies (>0.51, ≥0.65, ≥0.75) are likely to have included participants with toe pressure significantly higher than 30 mmHg. For studies of toe pressure using higher thresholds, the test was less able to distinguish those who would heal from those who would not.[19,25,32] Consistent with this, 1 study using a threshold of TBI ≥0.1 reported an NLR of 0.09 indicating strong probability of *not* healing below this threshold.[27]

As measures of both macro and microvascular function, $TcPO_2$ and SPP measure perfusion at the tissue level.[46] This may be particularly relevant in people with diabetes where microvascular

disease has been proposed to cause structural and functional changes to the cutaneous blood flow and may occur because of ischaemia.[46,47] Both $TcPO_2$ ≥25 mmHg and SPP of ≥40 mmHg increase the pre-test probability of DFU healing and healing after minor amputation by up to 45%.[16–18,34,35,37,42] However, there are inadequate data to determine the role of these tests in predicting minor or major amputation. Based on current evidence, these measures are more effective than toe pressure in determining probability of healing but are less likely to be available due to requiring more expensive equipment, specific expertise, and the test taking more time to apply.

In addition to revascularisation status, a range of medical and non-medical factors are known to affect DFU healing. These include the presence of infection and wound characteristics (e.g., size and depth), nutrition, co-morbidities, and social determinants many of which were not identified in the studies and will have influenced the outcomes.[48–50] This is well demonstrated in one study by Lopez-Moral et al.,[30] which, although limited by small study size, reported that a TBI ≥0.65 had a PLR of ≥10. However, TBI at this threshold was subsequently not found to be an independent predictor of DFU healing after adjustment for confounding factors. Similarly, poor outcomes for healing post-revascularisation can occur even where there is technical success and unrelated to the severity of ischaemia.[51] As such, amputation remains a therapeutic intervention rather than an outcome and is indicated in a range of clinical scenarios that may be unrelated to vascular supply. The complex nature and identification of potential confounding factors make adequate adjustment for them challenging and often result in residual confounding. Overcoming this challenge requires more detailed assessment of predictors of outcomes, and more thorough follow-up than was included in many of the studies included in this review. It also highlights the utility of classifications systems, such as the WIfI classification system, that includes the assessment of ischaemia, infection severity, and wound severity to apply an overall risk category.[52] Nevertheless, identification of thresholds for various bedside tests that indicate there is a very strong probability of healing or amputation directly due to ischaemia remains central to more timely and effective patient management. A retrospective study by Noronen et al.[53] demonstrated that a delay in revascularisation of more than 2 weeks in people with diabetes results in the increased risk of amputation. These findings are consistent with observational research demonstrating that a shorter time to revascularisation (<8 weeks from DFU presentation) is associated with a higher probability of DFU healing and a lower probability of amputation.[54]

Future research requires careful selection of participant populations and detailed reporting of known confounding factors at baseline and throughout the follow-up periods, including surgical interventions.[55] Use of standardised data sets and establishment of international registries will assist by increasing the amount and quality of available evidence. Directly relevant to bedside testing, reporting of test results post revascularisation and use of clear definitions of DFU healing and minor and major amputation outcomes are needed. The evaluation of the effectiveness of combinations of bedside tests to predict healing and amputation outcomes is required as this may offer a more effective means of identify those at risk of these outcomes.

4.1 | Limitations

While the search methods employed in this study were designed to be robust and included the use of a validation set of studies known to the researchers to test the search strategy, there may be some evidence that was not captured. Researchers in the field were not contacted for unpublished studies; the authors were only contacted where information from included articles was missing, or it was identified that relevant data may have been collected as part of the study. The lack of meta-analysis also limits the extent to which the study findings can be collectively interpreted. Analyses that we conducted as needed of sensitivity and specificity of candidate tests were analysed as univariable associations of PAD markers with clinical outcomes. Whilst we recognise the importance of other confounding factors on clinical outcomes, we lacked individual patient data from which to adjust our analyses for them. Calculation of PLRs and NLRs was also affected by unavailability of data within individual publications, which, in some cases, prevented calculation of endpoints for some outcomes or at certain time points.

5 | CONCLUSIONS

This review has demonstrated that toe pressure ≥30 mmHg, $TcPO_2$ ≥25 mmHg, and skin perfusion pressure of ≥40 mmHg are associated with a moderate to large increase in pretest probability of healing in people with DFU and after minor amputation. There are little data available evaluating the prognostic capacity of bedside testing for minor and major amputation in people with DFU. Current evidence suggests that an ABI <0.4 may be associated with a large increase in the risk of major amputation; however, further research is required to confirm this and to evaluate other bedside tests more thoroughly for both DFU healing and amputation outcomes. The quality of current research is limited by moderate to high risk of bias due to poorly described study participation, attrition rates, and inadequate adjustment for confounders. Findings of this review should also be considered in the context of the numerous factors that are known to affect wound healing.

AUTHOR CONTRIBUTIONS

Vivienne Chuter designed the search strings, performed the literature search, assessed the literature, extracted data, and drew conclusions, checked and completed the risk of bias tables, and wrote the manuscript. Nicolaas Schaper assessed the literature, extracted data, completed the risk of bias tables, and drew conclusions. Robert Fitridge assessed the literature, extracted data, completed the risk of bias tables, drew conclusions, and co-authored the manuscript. All authors were responsible for developing the clinical questions,

selecting the outcomes, formulating the PICO, and all authors critically reviewed the conclusions and the manuscript. Vivienne Chuter acted as the secretary of the working group, Robert Fitridge as the chair of the working group. Vivienne Chuter and Robert Fitridge take full responsibility for the content of the publication.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

Ethics approval was not required for this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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