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REVIEW ARTICLE

Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review

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Abstract

As a progressive disease process, early diagnosis and ongoing monitoring and treatment of lower limb peripheral artery disease (PAD) is critical to reduce the risk

Abbreviations: ABI, ankle-brachial index; CDUS, colour Duplex ultrasound; CTA, computed tomography angiography; DFU, diabetes-related foot ulcer; DSA, digital subtraction angiography; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; IWGDF, International Working Group on the Diabetic Foot; MRA, magnetic resonance angiography; NLR, negative likelihood ratio; PAD, peripheral artery disease; PICO, population, intervention, comparison, outcome; PLR, positive likelihood ratio; QAREL, Quality Appraisal of Reliability; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; TBI, toe-brachial index; $TcPO_2$, transcutaneous oxygen pressure.

of diabetes-related foot ulcer (DFU) development, non-healing of wounds, infection and amputation, in addition to cardiovascular complications. There are a variety of non-invasive tests available to diagnose PAD at the bedside, but there is no consensus as to the most diagnostically accurate of these bedside investigations or their reliability for use as a method of ongoing monitoring. Therefore, the aim of this systematic review was to first determine the diagnostic accuracy of non-invasive bedside tests for identifying PAD compared to an imaging reference test and second to determine the intra- and inter-rater reliability of non-invasive bedside tests in adults with diabetes. A database search of Medline and Embase was conducted from 1980 to 30 November 2022. Prospective and retrospective investigations of the diagnostic accuracy of bedside testing in people with diabetes using an imaging reference standard and reliability studies of bedside testing techniques conducted in people with diabetes were eligible. Included studies of diagnostic accuracy were required to report adequate data to calculate the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) which were the primary endpoints. The quality appraisal was conducted using the Quality Assessment of Diagnostic Accuracy Studies and Quality Appraisal of Reliability quality appraisal tools. From a total of 8517 abstracts retrieved, 40 studies met the inclusion criteria for the diagnostic accuracy component of the review and seven studies met the inclusion criteria for the reliability component of the review. Most studies investigated the diagnostic accuracy of ankle -brachial index (ABI) ($N = 38$). In people with and without DFU, PLRs ranged from 1.69 to 19.9 and NLRs from 0.29 to 0.84 indicating an ABI <0.9 increases the likelihood of disease (but the extent of the increase ranges from a small to large amount) and an ABI within the normal range (≥0.90 and <1.3) does not exclude PAD. For toe-brachial index (TBI), a threshold of <0.70 has a moderate ability to rule PAD in and out; however, this is based on limited evidence. Similarly, a small number of studies indicate that one or more monophasic Doppler waveforms in the pedal arteries is associated with the presence of PAD, whereas tri- or biphasic waveform suggests that PAD is less likely. Several forms of bedside testing may also be useful as adjunct tests and 7 studies were identified that investigated the reliability of bedside tests including ABI, toe pressure, TBI, transcutaneous oxygen pressure ($TcPO_2$) and pulse palpation. Inter-rater reliability was poor for pulse palpation and moderate for $TcPO_2$. The ABI, toe pressure and TBI may have good inter- and intra-rater reliability, but margins of error are wide, requiring a large change in the measurement for it to be considered a true change rather than error. There is currently no single bedside test or a combination of bedside tests that has been shown to have superior diagnostic accuracy for PAD in people with diabetes with or without DFU. However, an ABI <0.9 or >1.3, TBI of <0.70, and absent or monophasic pedal Doppler waveforms are useful to identify the presence of disease. The ability of the tests to exclude disease is variable and although reliability may be acceptable, evidence of error in the measurements means test results that are within normal limits should be considered with caution and in the context of other vascular assessment findings (e.g., pedal pulse palpation and clinical signs) and progress of DFU healing.

KEYWORDS
amputation, diabetes, diagnosis, foot ulcer, peripheral artery disease, reliability

1 | INTRODUCTION

Globally, diabetes mellitus is estimated to affect 537 million people at a rate of 1 in 10 adults, with an expected increase to 783 million people by 2045.[1] Diabetes is associated with a significant risk of diabetes-related foot disease, including peripheral neuropathy, ischaemia and infection. In combination with increased biomechanical stress and trauma, these factors play a central role in the development of a foot ulcer; the life-time incidence of such an ulcer can be up to 34% in persons with diabetes.[2] In people with diabetes, up to 85% of amputations are preceded by a diabetes-related foot ulcer (DFU).[3] DFU healing can be compromised by infection and peripheral artery disease (PAD).[3]

Diabetes is strongly associated with the presence of PAD. In people with diabetes, the prevalence of PAD, as diagnosed by bedside non-invasive testing, has been shown to exceed 20% and a longer duration of diabetes is associated with an increasing risk of disease.[4] Compared to PAD in the general population, PAD in individuals with diabetes has a more severe disease presentation and runs a more aggressive course of disease, with a more diffuse distribution of the anatomical lesions.[5,6] PAD is an independent risk factor for the development of DFU, which has a worse outcome compared to neuropathic ulcers, with impaired wound healing, foot infection, and amputation.[2,3,7] It is also an indicator of other atherosclerotic diseases including coronary artery, renovascular and cerebrovascular diseases as well as higher all-cause mortality.[2,8]

Up to half of the persons with a DFU have PAD, usually in combination with neuropathy.[7] Early diagnosis and treatment are critical in these patients to reduce the risk of non-healing and amputation.[9-13] In addition, diagnosing PAD in persons without a DFU will impact their risk stratification with more intensive monitoring required and additional measures taken to reduce the risk of ulcer development.[14] However, diagnosing PAD in a person with diabetes, in particular in those with a DFU, is challenging due its altered disease presentation and the interaction with other complications such as peripheral neuropathy.[7,15] Many patients have few symptoms, probably due to peripheral neuropathy masking typical symptoms such as intermittent claudication and rest pain[7,15]. Non-invasive bedside tests such as the ankle-brachial index (ABI) and/or toe pressures are often recommended as an initial diagnostic test for PAD and can also be used for ongoing monitoring.[16,17] Several of these bedside tests are widely available, have low-cost, are non-invasive, and can be used for triage of individuals requiring more advanced testing. The majority of patients with a DFU have below the knee and pedal disease, frequently in combination with medial artery calcification, and many have oedema of the lower leg, which can all affect the diagnostic accuracy of commonly used non-invasive bedside tests for PAD.[6,18,19] Furthermore, the examiner-dependent nature of bedside testing, the variability of methods used when conducting these tests, pre-measurement blood pressure stabilisation, caffeine and nicotine consumption and exercise as well as environmental factors such as ambient temperature can all affect the reliability of these tests when monitoring for disease progression.[20-22]

Given the atypical presentation of PAD in many of those with diabetes and its large impact on DFU healing, clinicians treating these patients will in many cases have to rely on clinical examination and non-invasive measurement of peripheral circulation as an initial screening tool. Therefore, the aims of this systematic review were to firstly determine the diagnostic accuracy of clinical examination and non-invasive bedside tests for identifying PAD compared to an imaging reference test, and, secondly, to determine the intra- and inter-rater reliability of these non-invasive bedside tests, in adults with diabetes with and without DFU. 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), comparison (C) and outcomes (O) were defined, and clinical questions were formulated accordingly by the assessors (i.e., the authors of this paper). Methods for this are detailed in Supplementary File S1. The PICOs that were developed are listed below.

1. **PICO:** In a person with diabetes with or without DFU does clinical examination (including pulse palpation) compared to an imaging reference standard (digital subtraction angiography (DSA), computed tomography angiography (CTA), magnetic resonance angiography (MRA), or colour Duplex ultrasound (CDUS)) accurately identify the presence of PAD or exclude it?
2. **PICO:** In a person with diabetes with or without DFU does bedside testing compared to an imaging reference standard (DSA, CTA, MRA, CDUS) accurately identify the presence of PAD or exclude it?
3. **PICO:** Does bedside testing reliably assess PAD in a person with diabetes with or without DFU?

2.2 | Search methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis

(PRISMA) statement and the PRISMA-DTA statement with content verified using the AMSTAR tool (PROSPERO ID: CRD420 23400976). Title and abstract searches of Medline and Embase were conducted from 1980 to 30th November 2022. Due to the expansion of this review from the previous iteration to include people with diabetes without foot ulcer, and to add reliability outcomes, new search strings were used and records were searched again from the original start date of 1980.[12] The search strings are provided in Supplementary File S1. A set of 20 key publications was used to validate the search string. A protocol has not been published separately.

2.3 | Inclusion and exclusion criteria

For the purposes of this review a non-invasive bedside test was defined as any non-invasive test assessing for PAD using a measure of blood flow that could be conducted at the bedside. PAD was defined as obstructive atherosclerotic disease of the arteries from the distal aorta to the foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular testing or medical imaging, resulting in disturbed or impaired circulation to one or both of the lower extremities. For any study to be included, data had to be reported separately on at least 10 patients with diabetes or, in studies of participants with and without diabetes, more than 80% of the cohort were patients with diabetes. A limit to human subjects was applied to the database searches.

To evaluate the diagnostic accuracy of clinical examination, pedal pulse palpation and bedside tests, a study was included if it were original research evaluating an aspect of diagnostic accuracy of clinical examination and/or pedal pulse palpation and/or one or more non-invasive bedside tests against a reference standard and if it included adults with diabetes, with or without foot ulcer. Reference tests for the diagnosis of PAD included DSA, CTA, MRA, or CDUS. No threshold for the severity of PAD was applied.

To evaluate the reliability of non-invasive bedside testing, a study was included if it was original research reporting the reliability (inter- or intra-rater reliability) of one or more non-invasive bedside tests in adults with diabetes. Studies of diagnostic accuracy were excluded if there was a comparison between bedside tests only or if there was inadequate data to calculate the predictive diagnostic outcomes. Studies of reliability were excluded if the test-retest timeframe made it likely that the results might be affected by disease progression, for example, >6 months. Studies measuring microvascular function were excluded.

2.4 | Data collection and analysis

Two reviewers (Vivienne Chuter and Robert Fitridge) independently screened the abstracts for inclusion and a third reviewer (Nicolaas Schaper) adjudicated any conflicts. Full-text articles of included abstracts were retrieved and assessed for inclusion independently by the same two reviewers (except where 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 and Robert Fitridge and cross-checked by Nicolaas Schaper or Robert Fitridge using one of two customised extraction forms (for diagnostic accuracy studies and reliability studies).

For diagnostic accuracy outcomes the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were the primary endpoints. In order to assess the usefulness of bedside tests, likelihood ratios were used, which reflect the ability of a diagnostic test to rule in or rule out disease.[23] Likelihood ratios were used to express a change in odds of reaching an outcome, in the context of 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. 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. Where PLRs and NLRs were calculated as infinite, these are reported as PLR $\geq$10 and NLR $\leq$0.1.

A test was considered to have very good performance if PLR $\geq$10 (representing an increased probability of the specified outcome by around 45% in the presence of a positive test result) and NLR $\leq$ 0.1 (representing a decrease in the probability of the specified outcome of around 45% in the presence of a negative test result).[24–26] Generally, minimal change in disease probability can occur when a test is used with a PLR between 1 and 2 or an NLR between 0.5 and 1. The PLR and NLR therefore provide a more meaningful assessment of diagnostic utility than sensitivity or specificity when used with the aim of disease-probability revision. Due to the anticipated heterogeneity between studies including differing thresholds for diagnosis of index and reference tests, different reference tests, methods of measurement and study populations as well as the need for measures of uncertainty around the outcomes measures a meta-analysis was considered not to be appropriate.

For studies of reliability, it was pre-determined that a meta-analysis of reliability outcomes for inter- and intra-rater reliability would be conducted provided there were sufficient studies that reported the estimator of interest, and that a measure of uncertainty for this estimator (e.g. standard error, 95% confidence interval, non-truncated *p*-value) was available. Given the expectation for a high degree of study heterogeneity, it was pre-determined that a fixed effect meta-analysis would generally not be appropriate so we aimed to only pool estimates using a random effect approach, provided there were at least five studies.[27] For the assessment of individual study reliability intraclass correlation coefficient (ICC) values were

interpreted according to cut-offs: >0.75 denotes good reliability, 0.50 to 0.75 suggests moderate reliability, and values below 0.50 represent poor reliability.[28] Kappa values were interpreted as none (0–0.20), minimal (0.21–0.39), weak (0.40–0.59), moderate (0.60–0.79), strong (0.80–0.90) and almost perfect (>0.90).[29] Any kappa values >0.60 were considered acceptable, in accordance with the conservative thresholds suggested for health research and practice.[29]

2.5 | Quality assessment

For studies of diagnostic accuracy the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was used.[30] This tool consists of four domains: patient selection, index test, reference standard and flow and timing. Each domain is assessed in terms of the risk of bias. The first three domains also include assessment of applicability. A summary quality score is not generated; instead, studies are rated as having a low, high, or unclear risk of bias and applicability. Two reviewers (Vivienne Chuter, Robert Fitridge or David Russell) independently assessed the quality of the studies, with disagreements resolved at a consensus meeting by a third reviewer where required (Nicolaas Schaper). There was no minimum level of quality required for inclusion in the review.

Studies of reliability were appraised for risk of bias using the Quality Appraisal of Reliability (QAREL) Checklist and qualitative methodological assessment.[31] The QAREL tool is an 11-item checklist that covers seven key domains; the spectrum of participants and assessors; assessor blinding; the order effects of examination; the suitability of the time-interval between repeated measurements; appropriate test application and interpretation; and appropriate statistical analysis.

2.6 | Evidence statements

Two investigators (Vivienne Chuter & 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 GRADE.[32] The authors rated the certainty of the evidence for each formulated evidence statement as 'high', 'moderate', 'low', or 'very low' in relation to the strength of confidence in estimates of the effect of a diagnostic test strategy or the reliability of a bedside test on patient-important outcomes. 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'.[32] The rating was determined based on the study design, the risk of bias, (in)consistency of results, (im)precision, (in)directness, publication bias, effect size and evidence of dose-response relation.[33] 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'. All authors discussed these evidence statements until consensus was reached.

3 | RESULTS

3.1 | Search results

From a total 8517 abstracts retrieved, 40 studies met the inclusion criteria for the diagnostic accuracy component of the review and 7 studies met the inclusion criteria for the reliability component of the review (Figure 1, Supplementary Tables S1 and S2).

3.2 | Diagnostic accuracy

3.2.1 | Characteristics of included studies

Of the 40 studies relating to diagnostic accuracy undertaken in populations with diabetes,[33–72] 28 of the studies used prospective recruitment[33,36–39,41–44,46,47,52–60,62,65,67–72] and the remainder used retrospective recruitment.[34,35,40,45,48–51,61,63,64,66] Eight studies reported including participants with active DFU,[39,43,44,48,57,58,69,72] with the proportion of the study population affected ranging from 6.6% to 100%.[39,69] Two studies reported a low prevalence of a history of DFU.[37,64] Two studies excluded participants with DFU.[33,67] DFU status was not reported in the remaining studies. Detailed characteristics of the included studies are provided in Supplementary Table S1. A summary of diagnostic accuracy findings for objective tests in people with diabetes with or without DFU is provided in Table 1.

Thirty-five studies[34-37,39-50,52-62,64,65,67-72] involving 3905 participants and 3 studies[33,38,51] including 497 limbs (number of participants not reported) investigated the ability of the ABI to identify PAD. Seven studies involving 1372 people[34,39,44,57,58,65,69] and 1 study of 89 limbs (number of participants not reported)[33] investigated the diagnostic accuracy of the TBI. Three studies (n = 315) assessed toe pressure.[44,63,69] Four studies involving 585 participants[57,61,66,69] and 1 study of 89 limbs[33] investigated the diagnostic accuracy of pedal Doppler waveforms measured by continuous wave Doppler. Pulse palpation was assessed in three studies of 565 participants[37,57,69] and 1 study of 89 limbs.[33] Other bedside tests investigated for diagnostic accuracy included; ankle pressure,[44,69] post-exercise ankle pressure,[35] post-exercise ABI,[64] resting and post-exercise transcutaneous oxygen pressure ($TcPO_2$),[43,69] pulse volume recording waveforms above and below the knee,[45] pulse oximetry at

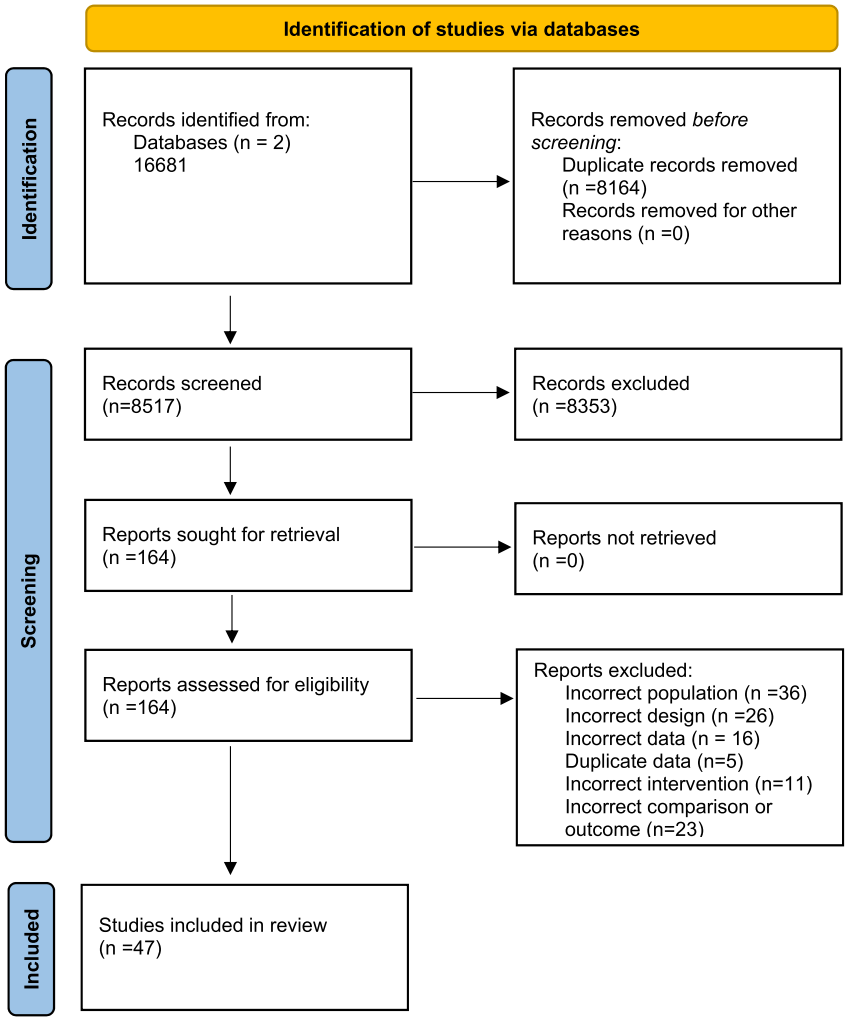

FIGURE 1 PRISMA flow diagram.

Test	Threshold	Diagnosis no DFU		Diagnosis with DFU	
		PLR range	NLR range	PLR range	NLR range
ABI	≤0.90	1.28 to ≥10	0–0.56	2.18	0.75
	≤0.90 to ≥1.3	2.11 to ≥10	0.19–0.72	1.69–2.32	0.53–0.54
AP	<70 mmHg			2.25	0.67
TBI	<0.70	2.0–3.55	0.28–0.44	1.62	0.24
	≤0.75	1.62–2.60	0.14–0.24		
Toe pressure	<50 mmHg			17.55	0.56
	≤60 mmHg	3.1	0.39		
$TcPO_2$	<30 mmHg	2.66	0.40		
	<60 mmHg			0.81	1.10

TABLE 1 Summary of evidence for the diagnostic capacity of bedside tests at differing thresholds.

Note: Ranges of numbers are provided were more than one study reported positive and negative likelihood ratios. Studies in people with and without DFU (mixed) populations and where DFU status is not reported are not included.

Abbreviations: ABI, Ankle -brachial Index; AP, ankle pressure; NLR, negative likelihood ratio; PLR, positive likelihood ration; TBI, toe -brachial Index; $TcPO_2$, Transcutaneous oxygen pressure.

the hallux,[52] functional photoplethysmography,[36] photoplethysmography waveforms,[61] pulse volume waveform analysis,[39] the pole -test at the ankle, capillary refill time, venous filling time and clinical signs including hair loss, skin atrophy, skin temperature-dependent rubor and blue/purple skin[69]. The diagnostic accuracy of combinations of tests was assessed in four studies, which included ABI and TBI[34] pulse palpation and ABI,[37] ABI and pulse volume recording waveforms[45] and pulse oximetry and ABI.[52] In addition, 3 studies investigated the comparative diagnostic accuracy of ABI calculated from the highest of the two ankle systolic pressures (dorsalis pedis and posterior tibial) and the lowest of the two systolic ankle pressures.[47,50,54]

For the 38 studies using the ABI as an index test, the threshold used to indicate a positive (i.e., abnormal) test varied. Nine studies used a threshold of <0.9,[38,42,54,56,59,60,70–72] 8 studies used a threshold of ≤0.9,[34,39,41,43,52,53,58,64,65] 7 studies use a threshold of <0.9 and >1.3,[33,46,50,55,57,61,69] 2 studies used a threshold of ≤0.9 and ≥1.3,[37,40] 3 studies used a threshold of <0.9 and >1.4[51,62,65] one used ≤0.9 and ≥1.4[48] and the remainder did not state a threshold. Two studies compared the diagnostic accuracy of ABI ≤0.9 and ABI ≤0.90 or >1.3/1.4.[34,43] Eight studies used the TBI as the index test with inconsistent thresholds for a positive test result between studies.[33,34,39,44,57,58,65,69] One study used a threshold of ≤0.6,[58] 2 studies <0.70,[34,65] another 2 studies used <0.75[33,57] and 1 study used ≤0.75.[69] One study,[39] used a threshold calculated from a ROC analysis (0.38) and 1 study did not report the diagnostic threshold.[44] Similarly, thresholds for toe pressure were heterogenous and ranged from <50 to 97 mmHg across 3 observational studies.[44,63,69] In the 5 studies using continuous wave Doppler as the index test, 3 used an absent or monophasic waveform[57,66,69] and 1 study used the loss of a triphasic waveform[33] as the threshold for diagnosis of PAD. One study considered any of the following diagnostic for PAD[1]: loss of triphasic pattern,[2] decreased amplitude of >50% compared with the contralateral side, or[3] loss of reverse flow component as.[61] Audible and visual Doppler waveforms were investigated in 1 study[57] and visual Doppler waveforms in the remaining 4studies.[33,61,66,69]

The majority of included studies used CDUS as a reference standard (n = 31) with diagnostic threshold variables but most commonly presence of one or more stenoses of ≥50%.[33,34,37–39,41–44,46–48,52–57,59,60,62–72] Five studies used DSA[36,40,45,50,58] 2 studies used CTA[49,61] and 1 study used CTA or MRA.[35] Where reported in the study the diagnostic thresholds used for these tests are included in Supplementary Table S1.

3.2.2 | Methodological quality

Methodological quality was variable between studies. Potential for bias was related to the lack of confirmed consecutive recruitment of participants, lack of reporting of participant characteristics, a lack of description of blinding of assessors of the index test to the reference standard and vice versa, partial verification bias from restricting reference testing to those with abnormal index tests and uncertainty over the interval between the tests.[73] With respect to the index test (bedside test) and reference standard, the primary concerns were a lack of description of methodology to undertake the measurements and threshold values used to classify disease status. The results of the QUADAS-2 assessment are summarised in Table 2.

All included studies were observational cross-sectional studies with prospective or retrospective recruitment and there was variable or unreported prevalence of PAD and DFU in study populations. No bedside testing technique was consistently demonstrated to have equivalent sensitivity and specificity to the imaging reference standard and therefore resulted in increased risk of false positive and false negative test outcomes.[32] False positive results may lead to unnecessary follow-up testing and additional intervention as well as stress and anxiety to the person. False negative results mean disease is undiagnosed which may contribute to an increased risk of DFU and amputation. There was also a significant heterogeneity of the primary endpoints (PLRs and NLRs) between studies for all bedside tests where two or more studies evaluated the same bedside test as the index test. Due to the number of studies with small populations or where few studies had evaluated a bedside test, publication bias was considered probable. Based on these factors affecting all included studies and the results of the risk of bias assessment, the certainty of evidence was graded as low for all evidence statements.

3.2.3 | Diagnostic accuracy results

Clinical examination

Two studies in populations with diabetes but without DFU demonstrated that the presence of palpable pulses does not necessarily rule out PAD (NLR 0.25–0.43) and that when a foot pulse is absent or weak there is a small increase in the likelihood of disease (PLR 1.84–2.46).[33,37] In a population with DFU, 1 study reported that pulse palpation and evaluation of other clinical signs of PAD (hair loss, muscle atrophy and reduced peripheral skin temperature) had a small ability to increase the pre-test probability of disease, but these tests could not exclude PAD.[69]

Ankle-brachial index

Of the 38 studies investigating diagnostic accuracy of the ABI, 3 studies were performed in a population in which all or most participants had DFU.[58,69,72] For this population, PLRs ranged from 1.69 to 2.32 and NLRs from 0.53 to 0.75.[58,69,72] For studies reporting a population without DFU or with very low incidence of DFU, PLRs ranged from 2.1 to 19.9 and NLRs from 0.29 to 0.84.[33,37,39,43,48,52,67] Three studies compared the diagnostic accuracy of the ABI when calculated from the highest or the lowest systolic blood pressure of either the dorsal pedis or posterior tibial artery.[47,50,54] Using the lowest pressure to calculate ABI was associated with a slightly higher PLR in 2 of the 3 studies (1.47 and 2.66 vs. 1.28 and 1.93).[50,54]

TABLE 2 Representation of Quality Assessment of Diagnostic Accuracy Studies-2 results.

Study	Risk of Bias				Applicability		
	Patient Selection	Index Test	Reference Standard	Flow & Timing	Patient Selection	Index Test	Reference Standard
AbuRahma 2020	?	?	?	?	☺	☺	☺
Aday 2018	☹	?	?	?	☹	☺	☺
Alnaeb 2007	?	?	?	☺	?	☺	☺
Aubert 2014	?	☺	☺	☺	☺	☺	☺
Ayati 2021	?	?	?	?	☺	☺	☺
Babaei 2020	?	☺	☺	☺	☺	☺	☺
Buschmann 2018	☹	☹	?	☺	☹	☺	☺
Clairotte 2009	☺	?	?	☺	☺	☺	☺
Dhanowar 2016	☺	?	☹	?	☺	☺	☹
Dinesh 2021	☺	?	?	?	☺	☺	☺
Fejfarova 2021	☹	☹	?	?	☺	☺	☺
Goyal 2013	?	?	?	?	☺	?	☺
Gupta 2017	☺	?	?	☺	☺	☺	☺
Homza 2018	☺	☺	?	☺	☺	☺	☺
Hur 2018	☹	?	?	?	☺	☺	☺
Ichihashi 2014	☺	☺	☺	☺	☺	☺	☺
Jeevanathan 2014	☺	☺	☺	☺	☹	☺	☺
Kiuchi 2016	☹	☺	☺	☺	☺	☺	☺
Kumar 2016	☺	?	?	?	☺	☺	☺
Lewis 2016	☺	☺	☺	☺	☺	☺	☺
Machaczka 2021	?	?	?	?	☺	☺	☺
Manfredini 2017	☹	☹	☺	☺	☹	☺	☺
Mishra 2019	?	?	?	?	☺	?	?
Normahani 2020	☺	☺	☺	☺	☺	☺	☺
Park 2012	?	?	?	?	?	☺	?
Potier 2009	☺	?	?	?	☺	?	☺
Premanath 2010	☹	?	?	☹	☺	☺	☺
Premathala 2002	?	?	?	☺	☹	☺	☺
Ro 2013	☹	?	?	☺	☹	☺	☺
Santoro 2018	☹	?	?	?	☹	☺	☺
Sonter 2017	?	☺	☺	☺	☺	☺	☺
Tehan 2016	☹	?	?	☺	☺	☺	☺
Tehan 2017	☹	?	?	?	☺	☺	☺
Tehan 2018	☹	?	☹	☺	☺	☺	☺
Uwgu	?	?	?	☺	☺	☺	☺
Vega 2011	☺	?	?	☺	☹	☺	☺
Vriens 2018	☹	☺	☺	☺	☹	☺	☺
Williams 2005	☹	?	?	☺	?	☺	☺
Williamson 2022	☹	?	?	?	☺	☺	☺
Zhang 2010	☺	?	?	☺	☺	?	☺

Note: Risk of bias: Low Risk: ☺ , High Risk: ☹ , Unclear Risk: ?.

Toe pressures and toe-brachial index

Three studies investigated toe pressure in persons with DFU,[69] in those with and without DFU[44] and in persons in whom DFU status was not reported.[63] The PLRs ranged from 2.67 to 17.55 and NLRs from 0.36 to 0.56. Of the 8 studies investigating diagnostic accuracy of the TBI in populations with DFU or in those with and without DFU, the PLRs ranged from 1.62 to ≥10 and NLRs from 0 to 0.70, with highly variable diagnostic thresholds for the index test: ≤0.38 to ≤0.75.[44,57,58,69] Similarly in populations without DFU, where DFU prevalence was very low (6.6%) or where DFU status was unknown the diagnostic accuracy of the TBI was inconsistent, with PLRs ranging from 2 to 23.81, and NLRs from 0 to 0.44.[33,34,39,65]

Continuous wave Doppler

For continuous wave Doppler, the PLRs and NLRs indicated a moderate to high ability of visual assessment of pedal Doppler waveforms to identify the presence of PAD and to rule it out (PLR range 2.93 to ≥10, NLR range 0–0.35).[33,61,66,69] One study[57] reported likelihood ratios for visual and audible Doppler waveforms to be similar to both methods. In this study peak systolic velocity ratio measured using CDUS was used as a reference test. The highest PLRs were observed when a diagnostic threshold of a peak systolic velocity ratio ≥2 (indicating 50% stenosis) was used (audible PLR 3.04, visual PLR 3.28), with a peak systolic velocity ratio ≥3 or peak systolic velocity ratio ≥4 the PLRs were lower (i.e.<2).

Other tests and combinations of tests

Of studies investigating the diagnostic accuracy of other types of bedside testing, post-exercise ankle pressure,[35,64] pulse-volume waveform analysis[39] and the pole-test[69] increased the pre-test probability of disease with a positive test result (PLR range 3.48 to ≥10), however, these tests were more variable in their ability to exclude disease (NLR range 0.2–0.93). Only 1 study in people with DFU investigated the diagnostic accuracy of clinical signs of PAD.[69] Hair loss, atrophy and cool skin were found to have a small ability to diagnose disease but limited capacity to exclude it (PLR:1.46–3.9, NLR:0.57–0.78); however, dependent rubor, purple/blue skin, and venous filling were not found to be not discriminatory.[69]

Combinations of tests had variable diagnostic accuracy with the use of ABI and pulse-volume recording waveforms, demonstrating the greatest ability to identify and exclude PAD. However, results for combinations of tests are based on individual studies of low quality.[34,37,45,52]

3.3 | Diagnostic accuracy evidence statements

3.3.1 | Statement

In people with diabetes with and without DFU, weak or absent pedal pulses may increase the likelihood of PAD by a small amount; however, the presence of palpable pulses does not rule out PAD.[33,37,57,69]

Certainty of evidence: Low

3.3.2 | Statement

In people without DFU, an ABI of <0.90 may be associated with a moderate to large increase in the likelihood of PAD; however, a value between 0.9 and 1.3 does not rule out PAD.[32,34,38,43,47,62,65]

Certainty of evidence: Low

In people with DFU, the combination of either an ABI of <0.90 or >1.3 may be associated with a small to moderate increase in the likelihood of PAD; however, a value between 0.9 and 1.3 does not rule out PAD.[58,69,72]

Certainty of evidence: Low

In people with diabetes with and without DFU, using the lowest systolic pressures of either the dorsalis pedis or the posterior tibial arteries to calculate the ABI slightly improves the ability to rule the presence of PAD in and out, compared to an ABI calculated with the highest systolic pressures of the dorsalis pedis and posterior tibial arteries.[47,50,54]

Certainty of evidence: Low

In people with DFU, the ability of a TBI to rule PAD in or out is variable.[58,69]

Certainty of evidence: Low

In people without DFU a TBI <0.70 is associated with a moderate increase in the likelihood of PAD and has a moderate ability to rule PAD out.[33,39]

Certainty of evidence: Low

In people with DFU, a toe pressure ≤50 mmHg is associated with a large likelihood of ruling disease in, but >50 mmHg does not rule out PAD.[69]

Certainty of evidence: Low

In people with diabetes with and without DFU, a toe pressure of ≤60 mmHg is associated with a small likelihood of ruling PAD both in and out.[44]

Certainty of evidence: Low

In people with DFU, the presence of one or more monophasic Doppler waveforms in the pedal arteries is associated with the presence of PAD. A tri- or biphasic waveform suggests PAD is less likely.[69]

Certainty of evidence: Low

In people with diabetes without DFU, the presence of one or more monophasic Doppler waveforms in the pedal arteries is associated with the presence of PAD. A tri- or biphasic waveform suggests PAD is less likely.[33,66]

Certainty of evidence: Low

In people with diabetes with or without DFU:

- there was insufficient evidence to draw conclusions on the diagnostic accuracy for PAD of resting and post-exercise $TcPO_2$,[43,69] functional photoplethysmography,[36] post exercise ABI[64] ankle pressure[44] and pulse-volume recordings.[45]
- post-exercise ankle pressure,[35,64] photoplethysmography,[61] pulse-volume waveform recording,[39] pulse oximetry[52] and the pole-test[69] may have a moderate to large ability to identify the presence of PAD, however, a normal result does not exclude disease;
- there was insufficient evidence found to draw conclusions for the abilities of combinations of bedside tests to rule PAD in or out.[34,37,45,52]

Certainty of evidence: Low

3.4 | Reliability

3.4.1 | Characteristics of included studies

Of the 7 studies examining the reliability of bedside testing for PAD in 277 participants with diabetes (Table 2), 1 study reported the reliability of palpation pulses of dorsalis pedis and posterior tibial pulses.[74] Two studies investigated intra-rater[75,76] and 1 study assessed inter-rater reliability of the ABI.[74] Inter-rater reliability of the TBI was assessed in 4 studies,[74,77,78] and 3 studies investigated intra-rater reliability.[77,78] Three studies investigated inter- and intra-rater reliability of toe pressure[77,78] and 1 additional study assessed inter-rater reliability of $TcPO_2$.[79] No studies included people with DFU. Two studies reported participants having diabetes-related complications including neuropathy, nephropathy, retinopathy[74,75] and one study reported previous history of vascular surgery (36.7%), intermittent claudication symptoms (36.7%), rest pain symptoms (3.3%).[77]

There was little consistency in the training and qualifications of the raters. The tests were performed using students,[77] inexperienced and experienced podiatrists,[75,78] diabetes educator, vascular sonographer,[76] and vascular technologists.[79] The majority of studies used manual methods for performing the measurements with 1 study reporting the use of automated devices. Four studies reported pre-measurement procedures, including the avoidance of caffeine, exercise and pre-measurement rest.[75,77-79]

3.4.2 | Methodological quality

The methodological quality of the included studies was variable with inconsistent blinding of single raters to their own results. However, most studies reported adequate randomisation of the order of examination and detailed the time between repeated measurements (Table 2). Three of these studies related to the reliability of toe pressure and TBI and one study to intra-rater reliability of the ABI.[63,75,77] In addition, most studies used appropriate statistical measures of agreement, with complete reporting of results (Table 3). Due to inconsistency and imprecision in results, small study sizes and the quality appraisal outcomes, the certainty of evidence was rated as low.

3.5 | Reliability results

Meta-analysis of reliability was not conducted due to the insufficient number of available studies for specific bedside tests and therefore narrative synthesis of results was undertaken. One study investigating the reliability of pulse palpation observed moderate agreement for palpation of the posterior tibial pulse (kappa 0.45) and weak agreement for dorsalis pedis (0.30).

The intra-rater reliability of the ABI was reported in 1 study with an intra-class correlation coefficient of 0.82 (95% confidence interval [CI]: 0.70–0.90) and 95% limits of agreement 0.15 to 0.15. These data indicate that an ABI measured by the same rater requires a change of 0.15 to be considered a true change and not a measurement error.[75] The inter-rater reliability of the ABI, measured by three raters, was in one study fair to moderate in three groups of persons with diabetes: those with diabetes only, with PAD, and with medial artery

TABLE 3 Quality Appraisal of Reliability checklist.

Item	Alvaro-Afonso et al. (2018)	Casey et al. (2021)	De Meijer et al. (2008)	Faccenda et al. (1988)	Romanos et al. (2010)	Scanlon et al. (2012)	Sonter et al. (2015)
1. Was the test evaluated in a sample of subjects who were representative of those to whom the authors intended the results to be applied?	Y	Y	Y	Y	Y	Y	Y
2. Was the test performed by raters who were representative of those to whom the authors intended the results to be applied?	U	Y	Y	U	Y	Y	Y
3. Were raters blinded to the findings of other raters during the study?	U	N/A	U	N/A	Y	Y	Y
4. Were raters blinded to their own prior findings of the test under evaluation?	N/A	Y	N/A	U	N	N	N
5. Were raters blinded to the results of the reference standard for the target disorder (or variable) being evaluated?	N/A	U	U	N/A	N/A	N/A	N/A
6. Were raters blinded to clinical information that was not intended to be provided as part of the testing procedure or study design?	U	U	U	U	U	U	Y
7. Were raters blinded to additional cues that were not part of the test?	U	U	U	U	U	U	U
8. Was the order of examination varied?	U	Y	U	U	Y	Y	Y
9. Was the time interval between repeated measurements compatible with the stability (or theoretical stability) of the variable being measured?	Y	Y	Y	Y	Y	Y	Y
10. Was the test applied correctly and interpreted appropriately?	Y	Y	y	N	Y	Y	Y
11. Were appropriate statistical measures of agreement used?	Y	Y	P	P	Y	Y	Y

Abbreviations: N, No; N/A, Not applicable; P, Partly; U, Unclear; Y, Yes.

calcification (diabetes only: Kappa 0.4, diabetes with PAD 0.45, diabetes with medial artery calcification 0.43).[74]

The intra- rater reliability of the TBI was moderate to good with ICCs ranging from 0.51 to 0.77. One study reported fair to moderate reliability of the TBI in groups of people with diabetes and those with diabetes with PAD or with medial artery calcification (diabetes only: Kappa 0.45, diabetes with PAD 0.65, diabetes with medial artery calcification 0.60). TBI inter-rater reliability was also good with the majority of studies reporting ICCs ranging from 0.77 to 0.85.[77] Two studies reported 95% limits of agreement for intra- and interrater reliability, indicating that a TBI requires an observed change of up to 0.30 by the same rater or 0.22 between raters for it to be considered a true change.[77,78]

For toe pressure inter- and intra-rater reliability was reported as good to excellent, ranging from ICC 0.78–0.87 and 0.88–0.93 respectively.[77,78] Two studies reported 95% limits of agreement for intra- and inter-rater reliability indicating that toe pressure requires an observed change of up to 27 mmHg by the same rater or 29 mmHg between raters for it to be considered a true change.[77,78]

One study investigating the inter-rater reliability of $TcPO_2$ reported an ICC of 0.60 indicating moderate reliability.[79]

3.6 | Reliability evidence statements

In people with diabetes without DFU:

- ABI, toe pressure and TBI may have good inter- and intra-rater reliability but margins of error are wide.[74-78]
- $TcPO_2$ may have moderate inter-rater reliability but the margins of error are wide.[79]
- Pulse palpation may have weak to moderate inter-rater reliability.[74]
- An ABI may require an observed change of 0.15 by the same rater for this to be considered a true change and not a measurement error.[75]
- A toe pressure may require an observed change of up to 27 mmHg by the same rater or 29 mmHg between raters for this to be considered a true change and not a measurement error.[77,78]
- A TBI may require a change of up to 0.28 by the same rater or 0.22 between raters to be considered a true change and not a measurement error.[77,78]

Certainty of evidence: Low

4 | DISCUSSION

This systematic review identified 40 studies investigating the diagnostic accuracy of various bedside tests for PAD in people with diabetes. The majority of studies (n = 37) evaluated diagnostic accuracy of the ABI, which was found to be variable across populations of people with and without DFU. In particular in patients with DFU its diagnostic accuracy may be inadequate. Fewer studies are available investigating the diagnostic accuracy of other methods of bedside testing including pulse palpation, TBI, toe pressure and $TcPO_2$, but there is no test that has been shown to be superior for diagnosing PAD in people with diabetes with and without DFU. Similarly, few studies of the reliability of bedside testing techniques were identified (n = 7) with data relating to ABI, TBI, toe pressure and $TcPO_2$ only, and no studies were identified investigating any of these testing methods in a population with DFU.

Evidence for the diagnostic accuracy of pulse palpation for PAD in people with diabetes and with or without DFU is limited. The included studies suggest an increased likelihood of disease in those with absent or weak pulses, but the presence of pulses does not rule out disease.[33,37,57,69] Similarly, there is limited evidence to support the use of some other clinical examinations such as hair loss, muscle atrophy and reduced peripheral skin temperature to assist in diagnosing PAD. However, the effect of these tests on the pre-test probability of disease is small and normal test results do not exclude the presence of disease. In part this may be due to the subjective nature of these tests and the presence of other diabetes-related complications such as neuropathy which may cause similar abnormalities in the foot.

Numerous methods of bedside testing are available for assessing vascular status of the lower limb and in our systematic review most studies assessed the diagnostic accuracy of the ABI. The synthesis of the results indicates that for people with diabetes without DFU or where DFU status was not reported, an ABI <0.9 increases the pre-test probability by a moderate to large amount, that is, the person is likely to have PAD[33–35,37,38,40–43,46,48,50,51,53,54,56,59,60,62,64,65,67,69,70] and therefore may be a useful test for diagnosing PAD. In contrast, for populations with DFU, the same ABI threshold (<0.9) appears to increase the pre-test probability of disease by a relatively small amount. However, this conclusion is based on a limited number of studies (n = 3), one with a moderate risk of bias and two with a high risk.[58,69,72] Across the included studies for both people with diabetes and with or without DFU, NLRs did not reach the threshold that is indicative of a test that is able to effectively rule out or exclude disease. Therefore, in the presence of a 'normal ABI result' that is, a result >0.90 and <1.3, it cannot be assumed that a person with a DFU does not have the disease and given the impact of PAD on ulcer outcome, it must be excluded with higher certainty. It is important to recognise that the current body of evidence is limited by high methodological heterogeneity and incomplete reporting of patient characteristics, for example, DFU status, the methodology of measurement and diagnostic thresholds for both index and reference tests. For example, thresholds for the ABI were variable across studies or the threshold was not stated. Quality appraisal of the included studies demonstrated mixed study quality, with several sources of potential bias in many including patient selection, (potential) lack of assessor blinding and partial verification bias.

One explanation for the limited diagnostic accuracy of the ABI could be the decrease in compressibility of the arteries in the lower

leg due to medial arterial calcification which is frequently observed in persons with DFU.[6,15] Nearly all patients with DFU have neuropathy which is also associated with medial artery calcification and it frequently co-exists with PAD due to shared risk factors including chronic hyperglycaemia. Medial artery calcification can affect the accuracy of non-invasive tests such as the ABI by causing elevation of ankle and digital pressures.[16] While the presence of medial artery calcification is likely when the ABI is in excess of 1.3, in circumstances where there is co-existent PAD the combination of the conditions may result in elevation of the ABI to within the normal range. It is also noteworthy that an ABI >1.3 caused by the presence of medial artery calcification has similar outcomes to a low ABI in terms of amputation outcomes and cardiovascular morbidity and mortality. Therefore, elevated ABI results are also indicative of vascular pathology that requires ongoing management.[79,80] The choice of reference test used in this review is also likely to have influenced diagnostic accuracy outcomes for all index tests. The Global Vascular Guidelines identify catheter digital subtraction angiography (DSA) as the gold standard imaging technique for imaging prior to revascularisation. However, the majority of studies on diagnostic accuracy used CDUS. In people with diabetes CDUS and CTA can be affected by (severe) medial artery calcification which is frequently present in the smaller arteries of the leg in people with DFU. MRA images are also incapable of defining the extent of calcification and it is likely that there were in accuracies in these tests as well.[80] In addition, the index tests investigated in this review measure haemodynamics, while the reference tests provide anatomic information on disease location and severity. As inherently different measures it is expected there will be some disagreement between them. The severity of stenosis used as the threshold of diagnosis of PAD is also likely to have affected the diagnostic accuracy of these tests with less severe disease potentially not causing a noticeable change in haemodynamic parameters measured by the index tests.

International guidelines for PAD testing in the general population recommend that for each lower limb the highest of the dorsalis pedis or posterior tibial artery systolic pressures is used as the numerator, whilst the highest of the left and right brachial pressures is used as the denominator in the calculation (high ABI method).[81] Using the highest ankle pressure rather than the lowest creates a 'best case scenario' when there may be distally distributed disease (below the tibial trifurcation). In such a situation, the cumulative reduction in pressure distally in all arteries associated with proximal disease does not occur; however, distal ischaemia may be present.[82] To accurately capture disease below the knee (where one of the vessels measured may be more significantly affected), which often occurs in patients with diabetes, use of the lowest of the ankle pressures in the ABI calculation has been proposed (low ABI).[83] Several studies in this review investigated the high and low ABI methods of calculating the ABI on diagnostic accuracy.[47,50,54] Based on the limited available evidence, an ABI calculated using the low ABI method has a slightly improved ability to rule the presence of PAD both in and out than an ABI calculated using the high ABI methods. Therefore, this latter method seems preferable to diagnose PAD. However, this finding needs to be confirmed through more comprehensive evaluation of ABI calculation methods in people with diabetes and DFU as well as evaluating the use of the average of dorsalis pedis and posterior tibial systolic pressure measurements.

Continuous wave Doppler, TBI, toe pressure and $TcPO_2$ are other bedside testing methods which were investigated in multiple studies. The diagnostic accuracy of continuous wave Doppler was assessed using multiple methods to classify a pathological result. In people with diabetes without DFU, absent/monophasic or biphasic pedal Doppler waveforms were associated with a moderate to large likelihood of PAD, while a triphasic waveform indicated that disease was unlikely.[33,66] In people with DFU, absent or monophasic pedal Doppler waveforms were associated with a high likelihood of disease and bi- or triphasic waveforms suggested that PAD was unlikely.[69] Of note, there was also evidence to suggest that in people with diabetes with neuropathy, continuous wave Doppler is less able to identify disease (diabetes, no neuropathy: PLR:12.5, NLR <0.1 vs. diabetes and neuropathy PLR:2.76, NLR: <0.1).[33]

For TBI measurements we suggest that a threshold of <0.7 is suggestive for PAD, (PLR 2.0–3.55) however, this conclusion is based on two low-quality studies.[34,65] Further research is necessary to determine this threshold conclusively. Data relating to toe pressure was similarly affected by high heterogeneity between studies including use of differing study populations and differing thresholds for the index test. A threshold of ≤60 mmHg had a limited effect on the pre-test probability of disease in a population of people with diabetes with and without DFU (PLR 3.1, NLR 0.39).[44] A toe pressure threshold ≤50 mmHg in a population with DFU increased the pre-test probability of disease by a large amount (PLR 17.55); however, values above this threshold do not exclude disease (NLR 0.56).[69] There are not adequate data to determine how well lower thresholds of the TBI and toe pressure reflect the increasing severity of ischaemia in relation to diagnostic accuracy. However, pragmatically it is essential to consider the dual purpose of the tests in predicting wound healing and amputation risk[10,84] and the role of such measures in the application of classification systems such as WIfI which utilise other measurement thresholds.[85]

The findings of this review highlight the need to avoid relying on a single test to assess the presence of PAD with no commonly used bedside test being demonstrated to be superior for the diagnosis of PAD. Several less widely used bedside testing methods were investigated in single studies. Post-exercise ankle pressure,[30,59] photoplethysmography,[56] pulse volume waveform analysis recording[34] and the pole-test[64] were reported to have a moderate to large ability to identify the presence of disease. These may be useful adjunct tests in the clinical setting, warranting further investigation of the diagnostic accuracy of these methods. In addition, clinical signs including cool skin and atrophy were demonstrated to have a small ability to identify the presence of disease in one study.[69] However, as clinical signs are subjective, and similar changes can occur as a result of neuropathy, clinical examination should be used in conjunction with other objective tests for PAD.

The progressive nature of PAD and the use of repeat testing to monitor lower limb status means that the reliability of bedside testing techniques is central to determine the nature of a change in a measurement that is, whether a change between two or more time points when testing occurs is a true change or related to error in the measurement. The magnitude of the error then dictates the magnitude of measurement change required for the difference to reflect a true change in the variable being measured. We found little data investigating the reliability of bedside testing techniques for lower limb vascular disease, specifically in diabetes cohorts. Based on current evidence for people with diabetes (no data was identified in those with DFU) we found that $TcPO_2$ has moderate inter-rater reliability[79] while ABI, toe pressure and TBI may have good inter- and intra-rater reliability but margins of error are wide.[74-78] Observed changes required to be considered a true change and not a measurement error were 0.15 for an ABI measured by the same clinician[75] for toe pressure 26 mmHg by the same clinician or 30 mmHg between clinicians and up to 0.28 by the same clinician or 0.22 between clinician for the TBI.[77,78] This would impact the interpretation of ABI, toe pressure and TBIs, particularly where thresholds for severe ischaemia/non-healing are being considered and over- or underestimation of blood flow may affect patient management. It is unclear if the use of multiple or serial measures would increase reliability. We could not find evidence of this being assessed. Further research is required to determine the reliability of bedside measures in populations with DFU and in cohorts that include participants with greater severity of PAD as it is unknown if the reliability and measurement error reported in this review occur in other subpopulations. The investigation of methods to improve reliability for example, training or through use of automated devices are warranted, and clear measurement protocols that can be implemented in clinical practice need to be developed.

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, 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.

5 | CONCLUSIONS

This systematic review has demonstrated that no single bedside test or a combination of bedside tests has been shown to have superior diagnostic accuracy for PAD. However, an ABI <0.9 or >1.3, TBI of <0.70 and absent or monophasic pedal waveforms indicated by continuous wave Doppler are useful to identify the presence of disease. The ability of these tests to exclude disease is variable and therefore test results that are within normal limits should be considered with caution. This review also identified palpation of pedal pulses and some clinical signs (e.g., skin temperature) only increase the pre-test probability of disease by a small extent. Further testing should therefore be used where disease is suspected. Other beside tests, such as TBI, also have limitations in diagnostic accuracy, highlighting the need to avoid relying on a single test to assess for the presence of PAD. There are limited data that have investigated the effect of combining tests on diagnostic accuracy and further investigation needs to be undertaken to determine this. However, the variability in diagnostic accuracy demonstrated across different tests in this review and the specific limitations of individual testing techniques support the use of multiple tests to determine the presence of disease. Test results should also be considered in the context of clinical examination findings and medical history. Several other tests, including pulse oximetry and post-exercise ankle pressure, may be useful as adjunct tests and should be included in future research. In addition, there is a clear need for improved reporting and further studies of diagnostic tests for PAD in patients with diabetes and DFU to support more robust conclusions in the future. Evidence of the reliability of bedside tests in people with diabetes is limited and there is a lack of evidence in people with DFU. Available data suggest that reliability is acceptable for several tests (e.g. ABI, TBI and toe pressure), but these tests are affected by measurement error and change in test results requires careful interpretation. Further research is required on the reliability of bedside testing in people with DFU.

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. Robert Fitridge assessed the literature, extracted data, completed the risk of bias tables and drew conclusions. David Russell completed the risk of bias tables. Nicolaas Schaper assessed the literature, drew conclusions, and co-authored reviewed the manuscript. All authors were responsible for developing the clinical questions, selecting the outcomes, formulating the PICOS, and all authors critically reviewed the conclusions and the manuscript. Vivienne Chuter acted as the secretary of the working group and 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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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethics approval was not required for this work.

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SUPPORTING INFORMATION

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