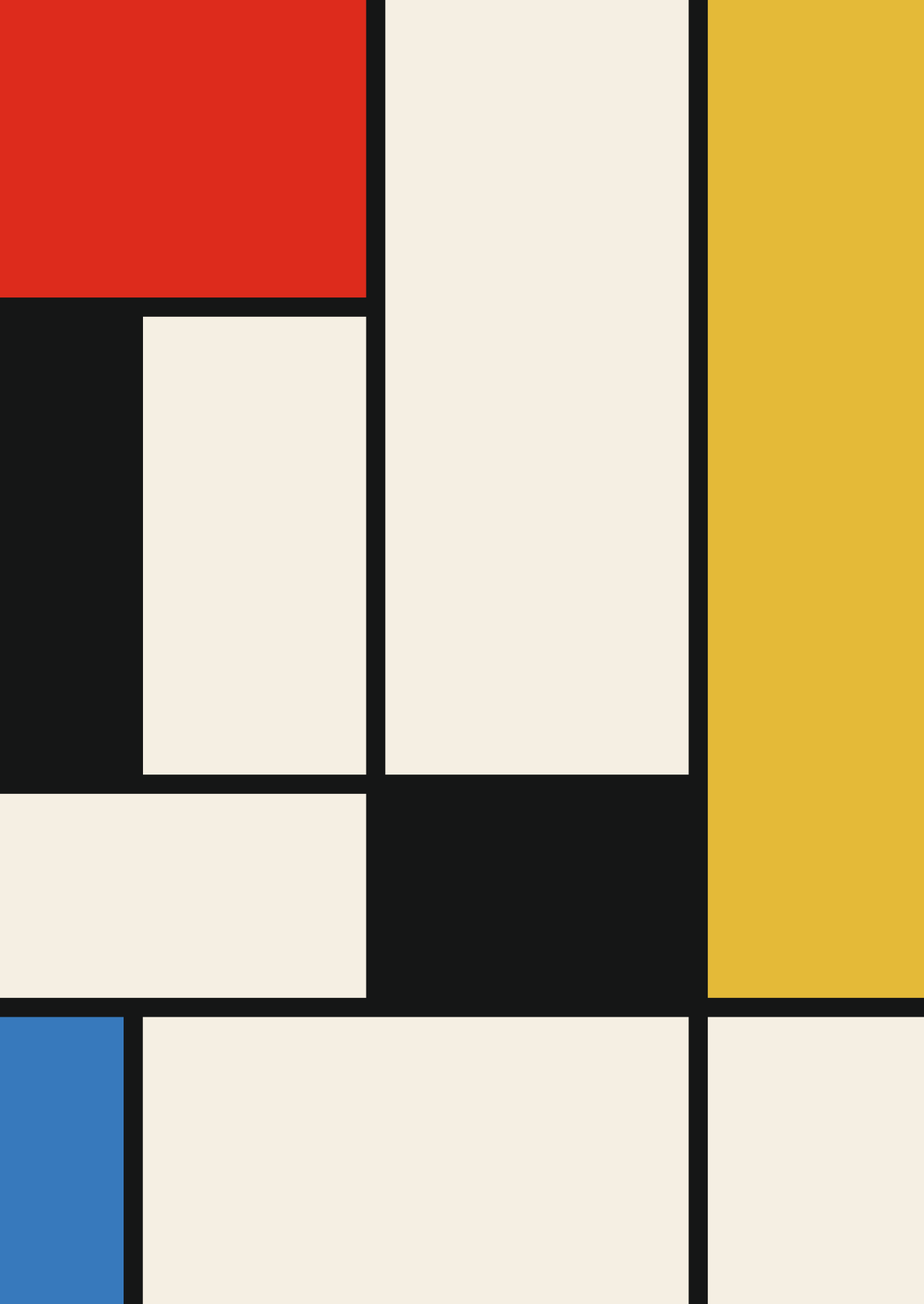
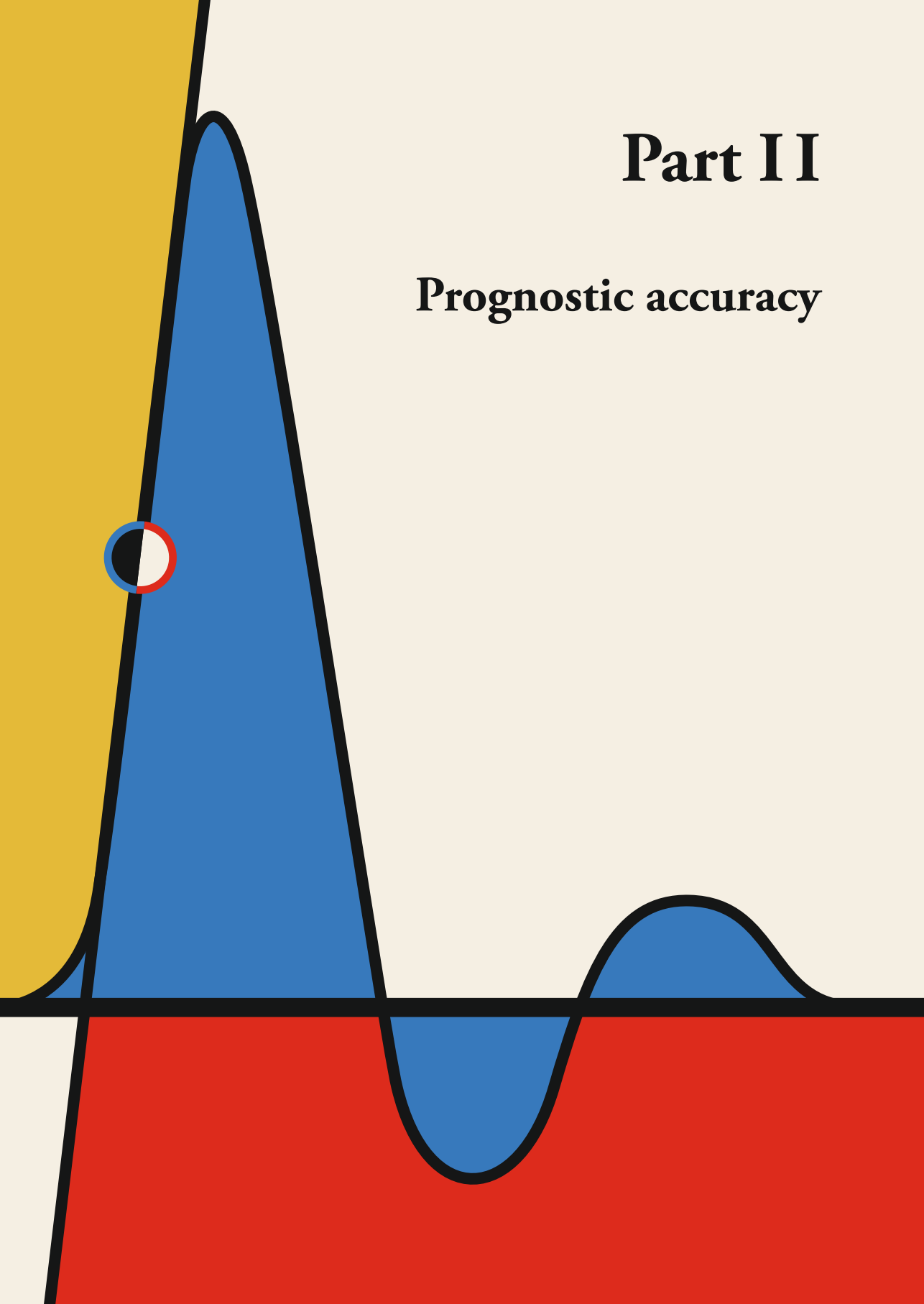
Maximal systolic acceleration in peripheral arterial disease

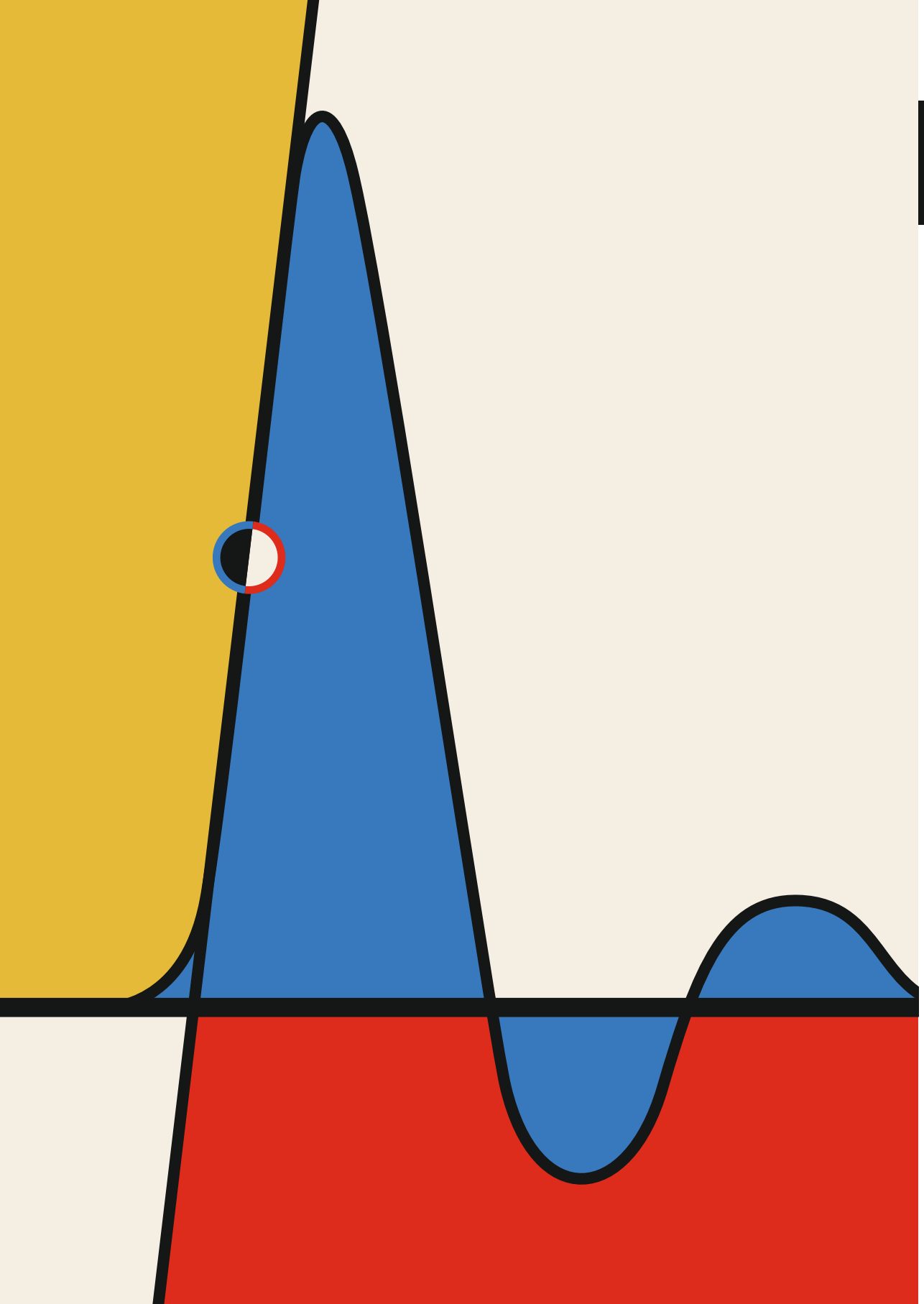
Willems, S.A.



Part II

Prognostic accuracy





Chapter 9

A systematic review of the prognostic performance of bedside tests for predicting ulcer healing and wound healing after minor amputation in patients prone to medial arterial calcification

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ABSTRACT

Foot ulceration is a significant and growing health problem worldwide, particularly due to rises in diabetes mellitus (DM) and peripheral artery disease. The prediction of ulcer healing remains a major challenge. In patients with foot ulcers, medial arterial calcification (MAC) can be present as a result of concomitant DM or chronic kidney disease and is a prognostic factor for unfavourable outcome. This systematic review aimed to evaluate the prognostic reliability of bedside tests to predict ulcer healing and wound healing after minor amputation in patients prone to MAC, following PRISMA guidelines. Primary endpoints were the positive and negative likelihood ratios for ulcer healing. Methodological quality and risk of bias was assessed using the QUIPS tool. A total of 35 studies were included, predominantly investigating, . transcutaneous oxygen pressure ($TcPO_2$), followed by ankle-brachial index and toe pressure. None of these bedside tests effectively provided an acceptable trade-off between predicting healing and non-healing.A $TcPO_2$ below 30 mmHg was most closely associated with non-healing of an ulcer. The same applied to wound healing after minor amputation, in which none of the bedside tests was able to sufficiently predict healing or non-healing. To conclude, currently used bedside tests lack acceptable prognostic performance for ulcer healing and healing after minor amputation in patients prone to MAC. Future prospective studies should establish a clear definition of ulcer healing, utilize a standardized wound classification system and minimize patient heterogeneity. A combined assessment of microvascular and macrovascular perfusion status could improve the prediction of wound healing.

BACKGROUND

Patients with foot ulceration are a growing medical concern worldwide, particularly due to an increase in diabetes mellitus (DM), chronic limb-threatening ischemia (CLTI), or a combination of both.[1, 2] In addition, peripheral artery disease (PAD) is present in up to 50% of patients with diabetic foot ulcers (DFU).[3] Due to demographic trends towards ageing and projected rises in important risk factors for PAD, these patient groups are rapidly expanding.[4] Previous studies showed that the overall rate of ulceration recurrence, risk of limb loss and mortality are strikingly high, causing serious impact on the quality of life in these patients.[5, 6] Therefore, urgent referral to a vascular specialist is of great importance to perform hemodynamic testing, accurately stage the severity of ulceration and to assess the need for revascularization.

In patients with DM and/or PAD, medial arterial calcification (MAC) can be present. MAC is a systemic vascular disorder in which calcification of the tunica media results in arterial stiffness.[7] This process is believed to be associated with aging, but is expedited in patients with DM and chronic kidney disease (CKD).[8-10] Patients with MAC have a notable higher risk of cardiovascular mortality and limb events.[11-13] Previous research also indicates that MAC is strongly associated with a higher risk of major lower limb amputation in patients with PAD.[14] Hence, it is of utmost importance to adequately stage PAD in order to manage foot ulcers in patients with MAC. However, it is well-known that the diagnostic performance of bedside tests to detect PAD can be diminished in these patients.[15-17] An underestimation of its severity could potentially lead to incorrect assumptions about wound ischemia as well.

Currently, a variety of bedside tests are included in the work-up of patients referred for suspected PAD.[18] These include, among others, ankle-brachial index (ABI), toe-brachial index (TBI), toe pressure (TP) and transcutaneous oxygen pressure ($TcPO_2$). These bedside tests are not only used to diagnose PAD, but are also used to predict wound healing. However, in patients prone to MAC (e.g. DM or CKD), it is unclear if these tests are accurate to predict (non-)healing of foot ulcers or minor amputations wounds as well. Therefore, we conducted a systematic review evaluating the prognostic performance of various bedside tests for the prediction of ulcer healing in patients prone to MAC. Secondary, wound healing after minor amputation due to a previously diagnosed foot ulcer was also investigated.

METHODS

Search strategy

This study was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[19] A literature search was performed in PubMed, Embase (OVID-version), Web of Science, Cochrane Library and Emcare for articles published before June 2023. A set of ten key publications was used to validate the search string. Two reviewers (SW, JN) independently screened the titles and abstracts for eligibility of inclusion. Dissimilarities were resolved in a discussion meeting between two reviewers (SW, JN), and if needed, deliberated with a third author (JB). The selected abstracts were independently assessed for definitive inclusion based on full text reading, and the data was extracted. A flow diagram (Figure 1) was maintained for transparency. The search strategy can be found in Supplement S1.

Selection criteria

We aimed to evaluate the prognostic performance of bedside tests to predict (non-traumatic) ulcer healing in patients prone to MAC. Studies investigating primary ulcer healing or wound healing after minor amputation (up to transmetatarsal) were included. Bedside tests were identified as any non-invasive tool that is easily available at the point-of-care. To be eligible for inclusion, studies needed to match the following criteria: I) evaluated a bedside test (e.g. ABI, TBI, ankle pressure (AP), toe pressure (TP), $TcPO_2$); II) included patients (in the (sub)analyses) that were prone to MAC, defined as DM, CKD or ABI > 1.3. If revascularization procedures were performed during the study, new measurements of the bedside test had to be performed after revascularization in order to be included. We excluded articles that reported insufficient data or were case reports. Studies that investigated healing of major amputations were excluded as well, since the bedside tests are not measured at the level of these amputations.

Data extraction and statistical analysis

Data extraction was performed by two investigators (SW, JN) independently. If an article was eligible for inclusion, extracted data contained relevant patient characteristics, the bedside test investigated, and the prognostic performance of that test. In case these parameters were not specified, but could be calculated from the accessible data, data extraction was undertaken. The primary outcomes of interest regarding prognostic performance of ulcer healing were the positive likelihood ratio (PLR) and negative likelihood ratio (NLR). In this review, the PLR reflected the chance of ulcer healing, whereas the NLR indicated that the ulcer did

not heal during follow-up. The interpretation of these likelihood ratios is shown in Table 1.[20] We classified the trade-off between PLR and NLR as poor (PLR <5 and NLR >0.2), moderate (PLR 5-10 and NLR 0.1-0.2) or excellent (PLR >10 and NLR <0.1). Sensitivity and specificity were included in the final evidence table as well. If articles presented their prognostic performance as the chance of non-healing instead of healing (of an ulcer or minor amputation wound), a recalculation was performed to equally compare the results.

Table 1. Interpretation of likelihood ratios and their effect on post-test probability of disease.

Positive likelihood ratio (PLR)	Negative likelihood ratio (NLR)	Interpretation: effect on ability to rule in/rule out disease
>10	<0.1	Large
5 - 10	0.1 – 0.2	Moderate
2 - 5	0.2 – 0.5	Small
1	1	No change

Quality assessment

Methodological quality and risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool.[21] This tool incorporates six domains for critical assessment of study validity and bias including study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis. All domains were judged as low, moderate or high risk of bias. For inclusion in this review, no minimal level of methodological quality was needed. Due to heterogeneity in patient selection, study design and different primary outcome measures, a meta-analysis could not be performed.

RESULTS

Search results

In total, 2121 articles were identified. After removal of duplicates and double publications, 935 studies were assessed for eligibility based on title and abstract. Of these, 91 articles were considered appropriate for full-text review, and 35 could eventually be included in this review. In total, 27 articles evaluated primary ulcer healing and 8 studies investigated wound healing after minor amputation. The PRISMA flow diagram of this process is illustrated in Figure 1.

Overview of studies

A total of 6298 patients were incorporated in this review. The median age of patients was 65 years old (ranging from a minimum of 57 years to a maximum of 77 years) and the majority of patients were male. Five articles did not provide any information about demographic

data of their patient population.[22-26] Except for one article regarding primary ulcer healing in patients with chronic renal failure[23], all studies evaluated DFU or minor amputation wound healing in patients with DM. Classification of these ulcers was presented quite heterogeneously, whereas most studies used the Wagner Scale or Univeristy of Texas Staging System. Overall, primary healing of ulcers varied greatly (between 38% and 83%) with different follow-up periods across the studies. In total, almost half of the articles (16) were published before 2000. Study characteristics and extensive details of the 35 included studies can be found in Supplementary Table S2 and S3. Methodological assessment according to the QUIPS-tool is provided in Table 2.

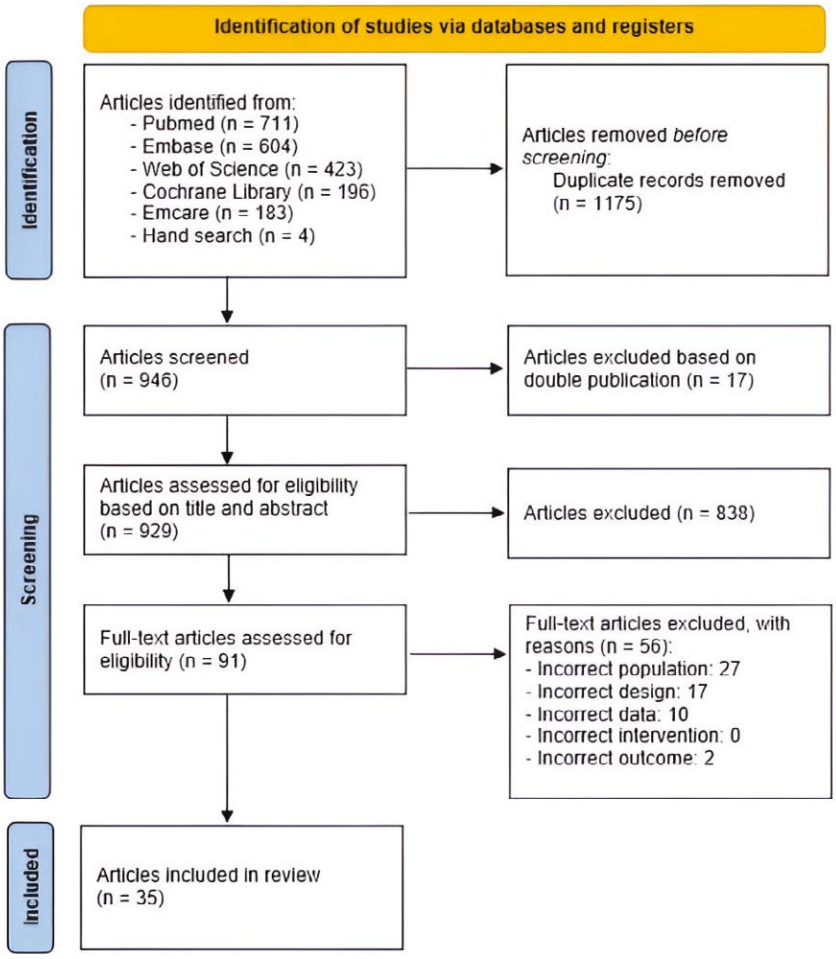

Figure 1. Flow diagram illustrating the inclusion process according to PRISMA guidelines.

Overview of prognostic bedside tests

Most of the studies looked at multiple bedside tests regarding primary ulcer healing. $TcPO_2$ was investigated most frequently (13 studies), followed by ABI (10 studies), TP (8 studies) and AP (7 studies). Other bedside tests were skin perfusion pressure (3 studies), palpable pulses (2 studies) and skin hydration level (2 studies).

Table 2. Methodological assessment of all included studies based on QUIPS-tool.

Reference	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Apelqvist 1989[27]	+++	+++	+++	+++	++	++
Apelqvist 1990[28]	+++	+++	+++	+++	+	+
Ballard 1995[29]	++	+++	+++	+++	++	+++
Bishara 2009[30]	+++	+++	+++	+++	+++	+++
Brechow 2013[37]	+++	+	++	+	+	+
Elghazaly 2023[31]	+++	+++	+++	+++	+++	+++
Elgzyri 2013[47]	++	++	++	++	+	++
Elgzyri 2021[38]	+++	++	++	++	+++	+++
Faris 1985[39]	+	++	+	+	+	+
Gibbons 1979[50]	+	+	++	++	+	+
Holstein 1980[40]	+	+	++	+	+	++
Holstein 1984[51]	++	++	+	+	++	+
Kalani 1999[44]	+	++	++	+	+	++
Karanfilian 1986[45]	+	+	++	+	+	++
Kawai 2017[22]	+	++	+++	+	+	++
Ladurner 2010[32]	+	+	++	++	++	++
Larsson 1993[52]	++	++	++	++	+	++
Lee 2019[48]	+++	++	+++	+++	++	+++
Lee 2022[49]	+++	++	+++	+++	++	+++
Leenstra 2020[33]	++	+++	+++	+++	+++	+++
López-Moral 2022[34]	+	+++	+	+++	++	+++
Manu 2021[41]	++	++	+++	++	++	+++
Mehta 1980[53]	++	++	++	+	+	+
Mennes 2021[35]	++	++	++	+++	++	+++
Nouvong 2009[36]	++	+	++	+++	+	++
Padberg 1996[23]	++	+++	++	++	+	++
Rajagopalan 2018[42]	++	++	++	++	++	++
Thottiyen 2023[46]	++	+++	++	++	++	++
Vincente Jiménez 2015[24]	+	+++	+++	+	++	+
Vitti 1994[54]	+++	++	+++	+	+	+
Wallin 1989[43]	++	+++	+++	+	++	+
Welch 1985[55]	++	+	+++	++	+++	+
Wyss 1988[25]	+	+	+	+	+	++
Yang 2013[26]	++	+++	+++	++	++	+++
Zhang 2019[56]	+++	++	+++	++	+	++

Abbreviations: QUIPS; Quality in Prognosis Studies tool.
All domains were rated according to their potential risk of bias and classified as:
+ = high risk of bias
++ = moderate risk of bias
+++ = low risk of bias

When looking at healing of minor amputation wounds, the most commonly studied bedside test was AP (5 studies), followed by TP (3 studies) and ABI (2 studies). A comprehensive summary of all these tests is shown in Table 3 and the subparagraphs below. Additionally, Table 4 shows an overview of the key features of the most commonly used bedside tests regarding ulcer healing and wound healing after minor amputation.

Definition of primary ulcer healing

Different definitions of primary ulcer healing were seen across the studies. Intact skin with full epithelization within 6 to 12 months was most frequently stated as ulcer healing (11 studies).[23, 27-36]

Seven of the studies regarded healing after the need for a minor amputation as primary ulcer healing as well.[37-43] Improvement of the wound (reduction in size, granulation tissue) was applied as definition in four studies.[26, 44-46] Five studies did not specify the definition of ulcer healing.[24, 32, 47-49]

Quality assessment of included studies

The QUIPS assessment of study validity and risk of bias is shown in Table 2. The quality of studies was generally poor. Only two articles had a low risk of bias on all six domains.[30, 31] Risk of bias was usually moderate or high with respect to study participation, outcome measurement and study confounding. As an example, definition of ulcer healing (outcome measurement) and respective follow-up time varied greatly, which led to differences in prognostic performances across the studies. Also patient selection and ulcer characteristics (including presence of foot infection and neuropathy) were diverse. In general, the scientific evidence for all studies as a whole was rated as low.

PRIMARY ULCER HEALING

Ankle-Brachial Index and Ankle Pressure

A total of ten studies investigated ABI as predictor of ulcer healing.[29, 31, 34-37, 41, 42, 45, 46] Various cut-off values were used (≥0.50 twice,> 0.52 once, ≥0.60 once, >0.65 once, ≥0.90 six times and >1.10 once). Studies of Thottiyen et al. (ABI>0.65), López-Moral et al. (ABI>0.52) and Ballard et al. (ABI≥60) found good NLR's of 0.18, 0.0 and 0.15 and PLR's of 3.6, 4.0 and 1.60 respectively.[29, 34, 46] Despite the good NLR's, there was no acceptable trade off compared to the PLR's. Moreover, NLR in the study of López et al. was merely 0 because there was no healing of wounds observed below ABI 0.52. Therefore, NLR could not be calculated properly. None of the other studies with different cut-off values were able to demonstrate

an acceptable trade-off in predicting ulcer healing. PLR's ranged from 1.06 to 1.9 compared to NLR's ranging from 0.25 to 1.0, indicating insufficient prognostic performance. A comprehensive overview is shown in Table 3.

Ankle pressure was assessed as a predictor for ulcer healing in seven studies.[27, 31, 35, 38, 40, 43, 47]. Cut-off values used were ≥30 (once), ≥40 (once), ≥50 (thrice), ≥70 (once), ≥80 (thrice) and >96 (once) mmHg. Wallin et al. reported the best results for predicting ulcer healing with a cut-off value above 70 mmHg, showing a PLR of 3.4 (NLR 0.1).[43] However, both primary ulcer healing and wound healing after minor amputation were considered as healing, which probably led to an overestimation of the prognostic performance. None of the remaining studies with previously mentioned cut-off values provided an acceptable trade-off in predicting healing vs. non-healing. PLR's and NLR's ranged from 0.8 to 2.7 and 0 to 2.35 respectively. NLR was 0 in the study of Apelqvist et al., mainly because none of the wounds healed in patients with an AP below 40 mmHg.[27] Elghazaly et al. performed a prospective cohort study with the highest degree of methodological quality, investigating AP with a cut-off value below 50 mmHg.[31] This resulted in a PLR of 0.50 and a NLR of 0.92. These results indicate insufficient prognostic performance.

Toe-Brachial Index and Toe Pressure

In total, 4 studies investigated the TBI as predictor for wound healing.[31, 34, 35, 41] All of these studies used different cut-off values (0.51, 0.65, 0.75 and 0.8), however none were able to establish a reasonable trade-off between predicting ulcer healing (highest PLR of 1.58) and non-healing (highest NLR of 0.28).[31, 34] The previously mentioned study by Elghazaly et al. reported an insufficient diagnostic performance of TBI applying a cut-off value of 0.8 (PLR 2.4 and NLR 0.63).

Toe pressure was assessed in 8 studies.[27, 31, 35, 38, 40, 43, 44, 47] Different thresholds for absolute blood pressure were used (15, 20, 30, 40, 45 and 54 mmHg), whereas a toe pressure of 30 mmHg was most frequently applied in four studies.[38, 40, 44, 47] Holstein et al. showed an infinite PLR at this threshold, followed by Kalani et al. (PLR 5.0).[40, 44] The lowest NLR (0.28) was found by Holstein et al. as well, indicating a small effect on the ability to exclude wound healing.[40] When looking at the two studies that used a lower cut-off value (15 and 20 mmHg), lower NLRs were achieved (0.1 and 0.1).[27, 43] This suggests a better capability of predicting non-healing of an ulcer, which is in accordance with the theoretical background of the test. If higher cut-off values for the toe pressure were used (40, 45 and 54 mmHg), no clear conclusions could be made regarding the diagnostic performance, since both lower and higher PLRs and NLRs were found (Table 3).[27, 31, 35, 44]

Transcutaneous Oxygen Pressure

Thirteen studies looked at the $TcPO_2$ as predictor for ulcer healing.[23, 26, 29, 31-35, 42, 44-46, 48] The majority of these studies (7) applied a cut-off value between 25 and 32 mmHg, whereas respectively three[23, 32, 45] and four[31, 33, 42, 48] studies looked at thresholds below and above these values. In general, a highly varied diagnostic performance was seen. Four studies showed high prognostic accuracies with a reasonable trade-off between predicting ulcer healing (PLR > 5) and non-healing (NLR < 0.2).[26, 34, 44, 45] Except for Karanfilian et al. ($TcPO_2$ 10 mmHg), these studies used a cut-off value between 25 and 32 mmHg. However, according to Table 2 (QUIPS-tool), major concerns were seen in all of these studies regarding their potential risk of bias with small patient samples and heterogeneous groups. The other four studies that looked at a threshold between 25 and 32 mmHg showed poor prognostic performances on both predicting healing and non-healing of ulcers (Table 3). Hypothetically, higher cut-off values of the $TcPO_2$ should be more able to predict ulcer healing. However, the studies that investigated these values (40 and 43 mmHg) were not able to prove this.[31, 33, 42, 48] Conversely, in the studies that applied lower thresholds, slightly lower NLRs were found (0.43, 0.58 and 0).[23, 32, 45] An overview of PLR and NLR ranges can be found in Table 3.

Other bedside tests

Skin perfusion pressure (SPP) was investigated by three studies, whom all applied different thresholds (30, 40 and 43 mmHg).[22, 39, 40] Holstein et al. studied a cut-off value of 30 mmHg, leading to a good PLR of 6.4 but insufficient NLR of 0.40. A threshold of 40 mmHg was applied by Faris et al., which showed a PLR of 4.9 and a NLR of 0.04. Although these diagnostic performances are decent, the low number of patients (n = 61), unclear design and outcome definition (healing after local amputation was regarded healing as well) led to a high risk of bias. Kawai et al. used a cut-off value of 43 mmHg, which resulted in a PLR of 11.7 and NLR of 0.35.

The presence of peripheral palpable pulses with respect to ulcer healing was studied by two studies.[28, 29] Apelqvist et al. looked at pulses in the femoral, popliteal and pedal arteries, but could not find any prognostic relevance (all PLRs below 3 and NLRs above 0.4).[28] Ballard et al. investigated the presence of pedal pulses, which led to a PLR of 5.5 and NLR of 0.45.[29]

Skin hydration level (SHL) was studied in two separate articles by the same author.[48, 49] Both studies led to a poor prognostic performance with a PLR of 1.3/2.4 and NLR of 0.72/0.40, respectively.

Three studies explored bedside tests that were not mentioned in other literature. Elgahazaly et al. looked at monophasic or absent waveforms with the podiatry ankle (PAD) scan, which revealed a PLR of 1.29 and NLR of 0.56.[31] The ankle peak systolic velocity (APSV) was studied by Bishara et

al., with a corresponding PLR of 9.88 and NLR of 0.02.[30] Karanfilian et al. investigated the laser doppler velocimetry (LDV) at a threshold of 40 mV, which led to a PLR of 14.9 and NLR of 0.13.

Table 3. Summary of evidence for prognostic performance of different bedside tests with corresponding cut-off values.

Bedside test	Cut-off value	Studies	Primary ulcer healing		Studies	Minor amputation	
			PLR	NLR		PLR	NLR
ABI	> 0.40				1 [61]	1.3	0.07
	≥ 0.50	2 [28, 42]	1.1, 1.2	0.90, 0.61	1 [57]	2.0	0.12
	≥ 0.52	1 [39]	4.0	0			
	≥ 0.60	1 [34]	1.6	0.15			
	≥ 0.65	1 [51]	3.6	0.18			
	> 0.70				1 [61]	4.6	0.2
	≥ 0.90	6 [36, 40-42, 46, 47]	1.05, 1.9, 1.1, 1.7, 1.1, 1.53	0.92, 1.00, 0.78, 0.61, 0.48, 0.25	1 [61]	Infinite	0.87
	> 1.10	1 [28]	1.0	0.98			
AP	≥ 30	1 [50]	0.8	2.35			
	≥ 40	1 [32]	1.1	0.00	1 [60]	1.0	1.1
	≥ 50	3 [36, 45, 52]	0.5, 1.1, 1.3	1.08, 0.48, 0	1 [56]	1.1	0
	≤ 50	1 [36]	0.9	2.2			
	> 60				2 [58, 60]	1.2, 1.0	0.98, 0.9
	≥ 70	1 [48]	3.4	0.10	1 [55]	1.0	1.09
	> 75				1 [57]	2.0	0.16
	≥ 80	3 [32, 43, 45]	1.5, 1.0, 2.7	0.30, 1.09, 0.28			
	≥ 96	1 [40]	1.5	0.4			
TBI	> 0.10				1 [57]	1.9	0.09
	> 0.51	1 [40]	1.5	0.53			
	> 0.65	1 [39]	0	0.28			
	≥ 0.75	1 [46]	0.9	1.05			
	≥ 0.80	1 [36]	2.4	0.63			
TP	> 15	1 [32]	1.4	0.1	1 [57]	1.7	0.10
	≥ 20	1 [48]	4.1	0.2			
	≥ 30	4 [43, 45, 49, 52]	1.1, 0.7, infinite, 5.0	0.88, 1.66, 0.28, 0.88	1 [56]	1.3	0.66
	> 38				1 [59]	2.3	Infinite
	≥ 40	1 [36]	0.92	1.08			
	> 45	2 [32, 49]	3.1, 2.9	0.30, 0.64			
	> 54	1 [40]	1.5	0.40			
$TcPO_2$	> 10	1 [50]	6.0	0			
	> 20	2 [28, 37]	1.7, 2.4	0.43, 0.58			
	> 25 – 30.5	7 [28, 31, 34, 39, 40, 49, 51]	4.3, 5.0, 1.8, 0, 1.2, 6.0, 4.7	0.23, 0.14, 0.05, 0.09, 0.47, 0.09, 0.18			
	≥ 31				1 [30]	5.9	0.2
	≥ 40	4 [36, 38, 47, 53]	1.4, 2.8, 1.5, 1.8	0.70, 0.67, 0.36, 0.39			

Abbreviations: ABI; ankle-brachial index, AP; ankle pressure, NLR; negative likelihood ratio, PLR; positive likelihood ratio, TBI; toe-brachial index, $TcPO_2$; transcutaneous oxygen pressure, TP; toe pressure

In this review, the PLR reflected the chance of wound healing, whereas the NLR indicated the chance that the wound would not heal during follow-up. Mentioned studies are sorted alfabetically and correspond to the position of the reported PLR's and NLR's.

* In the corresponding study, no wound healing was observed below the reported cut-off-value, resulting in an NLR of 0.

Table 4. Overview of the key features of commonly used bedside tests regarding ulcer healing and wound healing after minor amputation.

Bedside test	Technology	Strengths	Weaknesses
ABI	Doppler ultrasound; Index comparison between brachial and ankle blood pressure; external pressure measurement	- High ABIs (>0.7) seem to predict healing after minor amputation	- No acceptable trade-off between PLR/NLR for different cut-off values - No clear correlation between higher/lower cut-off value and prognostic performance
AP	Measurement of absolute blood pressure	- Most studied bedside tests for healing after minor amputation	- No acceptable trade-off between PLR/NLR for different cut-off values - No clear correlation between higher/lower cut-off value and prognostic performance
TBI	Doppler ultrasound ; Index comparison between brachial and toe blood pressure; external pressure measurement	- None	- Few conducted studies - Bad prognostic performances for both primary healing and healing after minor amputation
TP	Measurement of absolute blood pressure	- Lower TPs seem to correlate with lower chances of wound healing (i.e. <30 mmHg)	- Higher TPs do not sufficiently predict ulcer healing - No acceptable trade-off for adequate prognostic performance
$TcPO_2$	Heated electrode to assess oxygen levels just below the skin's surface	- Most studied bedside tests for primary ulcer healing - Lower $TcPO_2$ values seem to correlate with lower chances of wound healing (i.e. <30 mmHg)	- Prediction for healing after minor amputation not known - Higher $TcPO_2$ do sufficiently predict ulcer healing

HEALING OF MINOR AMPUTATION WOUNDS

In total, eight studies looked at wound healing after minor amputations.[25, 50-56]

Ankle-Brachial Index and Ankle Pressure

Ankle pressure was investigated most frequently as bedside test after amputation.[50-53, 55] Only two of the five studies applied the same threshold (60 mmHg).[53, 55] Other included cut-off values were 40, 50, 70 and 75 mmHg. Except for Holstein et al.[51], which revealed a NLR of 0.0 (and PLR of 1.1) at a threshold of 50 mmHg, none of the studies was able to show a reliable prognostic performance regarding amputation healing (all PLRs below 5 and NLRs above 0.1). However, this study had a high risk of bias according to the QUIPS-tool (Table 2), due to an unclear definition of healing, statistical analysis (no pre-specified cut-off value) and participation.

Two studies looked at the ABI, which showed fairly good results regarding non-healing (NLRs of 0.12 and 0.20), but were insufficient in predicting wound healing after minor amputation (PLRs of 2.0 and 4.6) when using cut-off values of 0.5 and 0.7.[52, 56]

Toe-Brachial Index and Toe Pressure

Toe pressure was explored in three studies.[51, 52, 54] All of these used different cut-off values for predicting amputation healing (15, 30 and 38 mmHg). Both Larsson and Vitti et al. showed low NLRs of 0.10 and 0 when applying a threshold of 15 and 38 mmHg, respectively.[52, 54] However, corresponding PLRs were inadequate (1.7 and 2.3) and the quality assessment revealed a high risk of bias for both studies (Table 2). The third study by Holstein et al. applied a threshold of 30 mmHg, which showed a poor prognostic performance (PLR 1.3 and NLR 0.7).[51] Only one study by Larsson et al. investigated the TBI, which resulted in a PLR of 1.9 and NLR of 0.09 when using a cut-off value of 0.10.[52]

Other

Wyss et al. studied the TcPO2 (>31 mmHg), which led to a fairly good prognostic performance (PLR 5.9 and NLR 0.2) in 26 foot or Syme amputations.[25] Many major confounders were not assessed or reported in this study. Pulse volume recordings were investigated by Gibbons et al., showing a PLR of 1.8 and NLR of 0.18.[50] One study investigated the skin blood flow at 12 and 16 mL $100g^{-1}$ min^{-1}, revealing an infinite high PLR, since all wounds healed above the chosen cut-off values.[55] Corresponding NLRs were 0.5 and 0.7, respectively.

DISCUSSION

This systematic review evaluated 35 studies investigating the prognostic performance of bedside tests for primary ulcer and minor amputation wound healing in patients prone to MAC. None of the studied bedside tests were able to show reliable prognostic performances for healing of primary ulcers or minor amputation wounds, indicated by insufficient trade-offs between PLRs and NLRs at different thresholds. This emphasizes the need for better prognostic tools to evaluate wound healing in these patient groups.

The best prognostic performance of the different bedside tests was seen with the $TcPO_2$, particularly in predicting failure of healing. As can be found in Table 3, NLR ranges between 0 and 0.58 were present when applying a threshold around 30 mmHg. Of seven studies that used this cut-off value, five showed a NLR below 0.2 (indicating a moderate to large effect on the ability to rule out ulcer healing). However, only two of these studies had a

PLR above 5.0, thus providing an inadequate trade-off for predicting ulcer healing in a clinical setting. From these results, it can be deducted that in patients prone to MAC and a low $TcPO_2$ measurement, no wait-and-see approach should be applied. Another commonly used bedside test in current clinical practice is the toe pressure. Since digital arteries should theoretically be less susceptible for MAC, it is hypothesized that its diagnostic and prognostic performance should be better (than AP/ABI) in diabetic patients.[15] Ten studies investigated the toe pressure, whereas a pressure of 30 mmHg was most frequently used as cut-off value. This is, to the best of our knowledge, also a threshold that is frequently mentioned in daily practice. Nevertheless, none of those studies provided a reasonable trade-off between proving and excluding ulcer healing. All NLRs were above 0.2, suggesting inadequate performance to predict non-healing. Furthermore, for predicting wound healing, no TP threshold was suitable. The same results were seen for the TBI.

Most of the included studies were of poor to moderate methodological quality. This was mainly caused by the use of unclear definitions in wound healing, use of unclear classification systems regarding ulcer severity and heterogenous study populations without adequate subgroup analyses. Only two of the included studies had a low risk of bias according to the QUIPS-2 tool.[30, 31] Elghazaly et al. investigated ABI, ankle pressure, TBI, toe pressure and $TcPO_2$, but none showed accurate prognostic performance. The ankle peak systolic velocity (APSV) was investigated by Bishara et al., resulting in a high PLR (9.9) and low NLR (0.02), indicating a promising accuracy potentially applicable in daily practice. Unfortunately, this was the only article studying the APSV, limiting its generalizability.

The insufficient prognostic performances of bedside tests to predict ulcer healing in patients prone to MAC are unsurprising, since it is well known that these ulcers have a complex multifactorial etiology. Moreover, most of the bedside tests merely assess macrovascular perfusion, which is just one of the important components in ulcer healing. MAC likely limits the reliability of macrovascular perfusion assessment (ABI, AP, TBI, TP, palpable pulses) because it can cause falsely elevate blood pressure measurements, hampering prognostic capabilities. Furthermore, microvascular perfusion, wound characteristics and infection play major roles in ulcer healing as well. The currently used prognostic bedside tests do not seem to sufficiently address all these factors, and the absence of macrovascular insufficiency does not necessarily mean that an ulcer will heal.

All included studies in this review investigated ulcer or amputation healing in patients prone to MAC. However, almost all studies only investigated patients with DM. CKD and ageing were not studied specifically, but are well-known to increase the likelihood of MAC.[7] Moreover, although falsely normal values can occur, the presence of MAC is often

characterized by an ABI > 1.3. Unfortunately, no studies reported subgroup analyses for these values.[8-10] Only one study investigated healing in a subgroup of patients with chronic renal failure (CRF) using a cut-off value of 1.1 for ABI, demonstrating inadequate predictive capabilities (PLR 1.0, NLR 0.98).[23] Since patients receiving hemodialysis for end stage CKD often develop leg ulcers, it is quite puzzling so little is known about this patient population and ulcer healing. The lack of evidence regarding predictive capabilities of bedside tests concerning wound healing in patients with CKD, advanced age or ABI > 1.3 limits the generalizability of the results of this review for the entire MAC population.

When comparing our review with previous literature, particularly the studies by Chuter et al. and Forsythe et al., we observe both similarities and differences.[57, 58] While those articles focused specifically on diabetic foot ulcer healing, our study broadened the scope to include all patients prone for MAC. Our analysis revealed that most existing research clusters on diabetic patients, and little is known about ulcer healing in patients with CKD or older age. Nonetheless, it is crucial to emphasize the limited understanding of prognostic bedside tests available for these patient groups. This indicates a significant knowledge gap that warrants further investigation. Moreover, our search strategy successfully identified additional relevant articles that contribute to this topic.

To improve future research, various issues encountered in this review should be addressed. First and foremost, the definition of wound healing needs to be clearly described and preferably used uniformly across the research field. Secondly, as a continuation, a standardized classification system of ulcer severity should be used in order to improve applicability in daily practice and comparability of results between studies. This systematic review also highlights the significant heterogeneity of wounds across the included studies, with classification systems being either variable or absent. Current guidelines advise using the WIfI classification system to define ulcer severity and characteristics since this is proven to correlate with probability of wound healing.[59-61] Thirdly, the majority of articles in this review were retrospective cohort studies, introducing multiple risks of bias. Among others, selection bias and the lack of consistent and complete data gathering (dependent on parameters and outcomes recorded in patient files) could have occurred. Future studies should aim to be prospective, incorporate a clear definition of ulcer healing, use a standardized wound classification system and minimalize heterogeneity by separating patients based on underlying etiology. Moreover, these studies could explore the predictive value of combining multiple tests within a prediction model as well.

At last, we believe that new statistical tools could help in better assessment of predictive capabilities in ulcer or amputation healing. An important limitation of current parameters

(sensitivity, specificity and PLR/NLR) is that only information at one threshold based on data from an entire cohort is provided. In the near future, predictive models (for example multistate modelling) can be used to evaluate the chances of important clinical outcomes (ulcer healing, amputation and mortality).[62] A distinct advantage of these models is that they can incorporate individual patient and wound characteristics. Since wound healing is a complex and multifactorial problem, an extensive overview of multiple patient characteristics is needed for accurate prediction. Predictive models can incorporate multiple relevant variables for individual patients, including local wound characteristics, (intra-operative) macrovascular assessment and microvascular perfusion (e.g. near-infrared fluorescence or hyperspectral imaging) to provide a tailor made prognosis.[63, 64] The rise and development of artificial intelligence might aid in creating these tools as well.

CONCLUSION

This review demonstrates that none of the currently used bedside tests have acceptable prognostic performance for ulcer healing in patients prone to MAC. The methodological quality of the included studies in this review raised serious concerns on several important domains, leading to a high risk of bias. Future prospective studies should aim to incorporate a clear definition of ulcer healing, use a standardized wound classification system and minimalize heterogeneity by separating patients based on the underlying etiology of their ulcer. A combined assessment of microvascular and macrovascular perfusion status could improve the prediction of wound healing.

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DISCLOSURES

None.

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SUPPLEMENTS

Search strategy

In cooperation with a trained librarian (JWS), a detailed search strategy was composed. The following databases were searched: PubMed, Embase (OVID-version), Web of Science, Cochrane Library, and Emcare. The query consisted of the combination of the following concepts:

- Predicting wound healing
- Bedside non-invasive diagnostic tests
- Patients prone to medial arterial calcification

These concepts were combined using two search strands in order to maximize relevancy and minimize noise. For the different concepts, all relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases, but the free text word variations of these concepts as well. The search strategy was optimized for all consulted databases, taking into account the differences of the various controlled vocabularies as well as the differences of database-specific technical variations (e.g., the use of quotation marks). The search was limited to English language articles. The final search was performed on June 20th, 2023. The bibliographic databases yielded 943 references. Full details of the search strategy can be found in Appendix A (see below).

APPENDIX A. SEARCH STRATEGY DETAILS.

Database	Search Strategy	Number of references	Number of unique references
PubMed (Continued)	(((“Peripheral Arterial Disease”[majr] OR “Peripheral Arterial Disease”[tiab] OR “Peripheral Arterial Diseases”[tiab] OR “Peripheral Artery Disease”[tiab] OR “Peripheral Artery Diseases”[tiab] OR “Peripheral Arterial Disorder”[tiab] OR “Peripheral Arterial Disorders”[tiab] OR “Peripheral Artery Disorder”[tiab] OR “Peripheral Artery Disorders”[title/abstract:~2] OR (“PAD”[tiab] AND (“artery”[tiab] OR “arteries”[tiab] OR “arterial”[tiab])) OR “peripheral arterial occlusive disease”[tiab] OR “peripheral arterial occlusive diseases”[tiab] OR “peripheral artery occlusive disease”[tiab] OR “peripheral artery occlusive diseases”[tiab] OR “Peripheral Vascular Diseases”[majr:noexp] OR “Peripheral Vascular Disease”[tiab] OR “Peripheral Vascular Diseases”[tiab] OR “Peripheral Vascular Disorder”[tiab] OR “Peripheral Vascular Disorders”[tiab] OR “Peripheral Angiopathies”[tiab] OR “Peripheral Angiopathy”[tiab] OR “Peripheral Arteriopathies”[tiab] OR “Peripheral Arteriopathy”[tiab] OR “Peripheral Vasculopathies”[tiab] OR “Peripheral Vasculopathy”[tiab] OR “Monckeberg Medial Calcific Sclerosis”[majr] OR “Monckeberg’s Medial Calcific Sclerosis”[tiab] OR “Monckeberg’s Sclerosis”[tiab] OR “Monckeberg Sclerosis”[tiab] OR “Monckebergs Sclerosis”[title/abstract:~3] OR “Mönckeberg’s Medial Calcific Sclerosis”[tiab] OR “Mönckeberg’s Sclerosis”[tiab] OR “Mönckeberg Sclerosis”[tiab] OR “Mönckebergs Sclerosis”[title/abstract:~3] OR “Monckeberg”[tiab] OR “Monckeberg*”[tiab] OR “Moenckeberg”[tiab] OR “Moenckeberg*”[tiab] OR “Medial Calcific Sclerosis”[tiab] OR “Medial Calcific Scleroses”[title/abstract:~3] OR “Mönckeberg Medial Calcific Sclerosis”[tiab] OR “incompressible arter*”[tiab] OR “incompressible vessel*”[tiab] OR “medial calcified artery”[title/abstract:~3] OR “medial calcified arteries”[title/abstract:~3] OR ((“Arterial Occlusive Diseases”[majr] OR “Peripheral Vascular Diseases”[majr]) AND (“peripheral”[tiab] OR “peripheral*”[tiab] OR “limbs”[tiab] OR “limb”[tiab] OR “leg”[tiab] OR “legs”[tiab] OR “extremity”[tiab] OR “extremities”[tiab] OR “arm”[tiab] OR “arms”[tiab])) OR “Intermittent Claudication”[majr] OR “Intermittent Claudication”[tiab] OR “Leriche Syndrome”[majr] OR “Leriche Syndrome”[tiab] OR “Leriche’s Syndrome”[tiab] OR “Leriches Syndrome”[tiab] OR “Arteriosclerosis Obliterans”[majr] OR “Arteriosclerosis Obliterans”[tiab] OR ((“Atherosclerosis”[majr] OR “Arteriosclerosis”[majr] OR “Atherosclerosis”[tiab] OR “Arteriosclerosis”[tiab]) AND (“peripheral”[tiab] OR “peripheral*”[tiab] OR “limbs”[tiab] OR “limb”[tiab] OR “leg”[tiab] OR “legs”[tiab] OR “extremity”[tiab] OR “extremities”[tiab] OR “arm”[tiab] OR “arms”[tiab])) OR “Fontaine IV”[tiab] OR “Diabetic Foot”[majr] OR “Diabetic Foot”[tiab] OR “Diabetic Feet”[tiab] OR ((“Diabetes Mellitus”[majr] OR “diabetes”[tiab] OR “diabet*”[tiab] OR “Renal Insufficiency, Chronic”[majr] OR “Chronic Kidney Disease”[tiab] OR “Chronic Kidney Diseases”[tiab] OR “Chronic Kidney Failure”[tiab] OR “Chronic Kidney Insufficiency”[tiab] OR “Chronic Renal Disease”[tiab] OR “Chronic Renal Diseases”[tiab] OR “Chronic Renal Failure”[tiab] OR “Chronic Renal Insufficiency”[tiab] OR “End Stage Kidney Disease”[tiab] OR “End Stage Renal Disease”[tiab] OR “End-Stage Renal Failure”[tiab] OR “End-Stage Kidney Failure”[tiab] OR “ESRD”[tiab]) AND (“peripheral”[tiab] OR “peripheral*”[tiab] OR “Extremities”[majr] OR “Foot Diseases”[majr] OR “limbs”[tiab] OR	711	711

Database	Search Strategy	Number of references	Number of unique references
PubMed (Continued)	"limb"[tiab] OR "leg"[tiab] OR "legs"[tiab] OR "extremity"[tiab] OR "extremities"[tiab] OR "arm"[tiab] OR "arms"[tiab] OR "foot"[tiab] OR "feet"[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "finger"[tiab] OR "fingers"[tiab])))) AND ("Ankle Brachial Index"[mesh] OR "Ankle Brachial Indices"[tw] OR "Ankle-Brachial Index"[tw] OR "Ankle-Brachial Indices"[tw] OR "anklebrachial index"[tw] OR "anklebrachialindex"[tw] OR "ankle brachial"[tw] OR "anklebrachial"[tw] OR "ABI"[tw] OR "Toe Brachial Index"[tw] OR "Toe Brachial Indices"[tw] OR "Toe-Brachial Index"[tw] OR "Toe-Brachial Indices"[tw] OR "Toe Pressure"[tw] OR "toe brachial"[tw] OR "toebrachial"[tw] OR "TBI"[tw] OR "TP"[tw] OR "Oximetry"[mesh] OR "Oximetry"[tw] OR "Oximetries"[tw] OR "Oximetr*"[tw] OR "Pulse Oximetries"[tw] OR "Pulse Oximetry"[tw] OR "transcutaneous oxygen tension"[tw] OR "transcutaneous oxygen"[tw] OR "Pulse"[mesh] OR "Pulse*"[tw] OR "pulsation"[tw] OR "pulsations"[tw] OR "Blood Gas Monitoring, Transcutaneous"[mesh] OR "Transcutaneous Blood Gas Monitoring"[tw] OR "Transcutaneous Capnometry"[tw] OR "PtcO2"[tw] OR "TcPCO2"[tw] OR "Doppler waveform"[tw] OR "Doppler waveforms"[tw] OR "Doppler wave form"[tw] OR "Doppler wave forms"[tw] OR "Ultrasonography, Doppler, Pulsed"[mesh:noexp] OR "Pulsed Doppler"[tw] OR "Doppler Pulsed"[tw] OR "non-invasive"[tw] OR "non-invasiv*"[tw] OR "point-of-care test"[tw] OR "point-of-care tests"[tw] OR "Ankle Pressure"[tw] OR "Ankle Pressures"[tw] OR "Skin Temperature"[Mesh] OR "Skin Temperature"[tw] OR "Skin Temperatures"[tw] OR "Blood Pressure Determination"[Mesh] OR "blood pressure measurement"[tw] OR "blood pressure measurements"[tw]) AND ("Wound Healing"[Mesh] OR "Wound Healing"[tw] OR "Wound Healing"[title/abstract:~4] OR "Wound Heal"[title/abstract:~4] OR "Wound Healed"[title/abstract:~4] OR "Wound Heals"[title/abstract:~4] OR "Wounds Healing"[tw] OR "Wounds Healing"[title/abstract:~4] OR "Wounds Heal"[title/abstract:~4] OR "Wounds Healed"[title/abstract:~4] OR "Wounds Heals"[title/abstract:~4] OR "Ulcer Healing"[tw] OR "Ulcer Healing"[title/abstract:~4] OR "Ulcer Heal"[title/abstract:~4] OR "Ulcer Healed"[title/abstract:~4] OR "Ulcer Heals"[title/abstract:~4] OR "Ulcers Healing"[tw] OR "Ulcers Healing"[title/abstract:~4] OR "Ulcers Heal"[title/abstract:~4] OR "Ulcers Healed"[title/abstract:~4] OR "Ulcers Heals"[title/abstract:~4] OR (("predictor"[tw] OR "predictors"[tw] OR "predictive factor"[tw] OR "predictive factors"[tw] OR "predicting"[tw] OR "Forecasting"[mesh]) AND ("Amputation, Surgical"[Mesh] OR "Amputation"[tw])) OR "Wound Outcome"[title/abstract:~4] OR "Wound Outcomes"[title/abstract:~4] OR "Wounds Outcome"[title/abstract:~4] OR "Wounds Outcomes"[title/abstract:~4] OR "Ulcer Outcome"[tw] OR "Ulcer Outcome"[title/abstract:~4] OR "Ulcer Outcomes"[title/abstract:~4] OR "Ulcers Outcome"[tw] OR "Ulcers Outcome"[title/abstract:~4] OR "Ulcers Outcomes"[title/abstract:~4]) AND ("Sensitivity and Specificity"[mesh] OR "Sensitivity"[tiab] OR "Specificity"[tiab] OR "Predictive Value"[tiab] OR "ROC Curve"[tiab] OR "Signal-To-Noise"[tiab] OR "limit of detection"[tiab] OR "Cohort Studies"[mesh] OR "Follow-Up Studies"[mesh] OR "Longitudinal Studies"[mesh] OR "Prospective Studies"[mesh] OR "Retrospective Studies"[mesh] OR "Cohort"[tiab] OR "Cohorts"[tiab] OR "Follow-Up"[tiab] OR "Longitudinal"[tiab] OR "Prospective"[tiab] OR "Retrospective"[tiab] OR "Cross-Sectional Studies"[mesh] OR "Cross-Sectional"[tiab]		

Database	Search Strategy	Number of references	Number of unique references
PubMed (Continued)	OR "Observational Study"[pt] OR "Observational Studies as Topic"[mesh] OR "Observational Study"[tiab] OR "effectiveness"[tiab] OR "efficacy"[tiab])) **OR** (("Peripheral Arterial Disease"[majr] OR "Peripheral Arterial Disease"[tiab] OR "Peripheral Arterial Diseases"[tiab] OR "Peripheral Artery Disease"[tiab] OR "Peripheral Artery Diseases"[tiab] OR "Peripheral Arterial Disorder"[tiab] OR "Peripheral Arterial Disorders"[tiab] OR "Peripheral Artery Disorder"[tiab] OR "Peripheral Artery Disorders"[title:~2] OR ("PAD"[tiab] AND ("artery"[tiab] OR "arteries"[tiab] OR "arterial"[tiab])) OR "peripheral arterial occlusive disease"[tiab] OR "peripheral arterial occlusive diseases"[tiab] OR "peripheral artery occlusive disease"[tiab] OR "peripheral artery occlusive diseases"[tiab] OR "Peripheral Vascular Diseases"[majr:noexp] OR "Peripheral Vascular Disease"[tiab] OR "Peripheral Vascular Diseases"[tiab] OR "Peripheral Vascular Disorder"[tiab] OR "Peripheral Vascular Disorders"[tiab] OR "Peripheral Angiopathies"[tiab] OR "Peripheral Angiopathy"[tiab] OR "Peripheral Arteriopathies"[tiab] OR "Peripheral Arteriopathy"[tiab] OR "Peripheral Vasculopathies"[tiab] OR "Peripheral Vasculopathy"[tiab] OR "Monckeberg Medial Calcific Sclerosis"[majr] OR "Monckeberg's Medial Calcific Sclerosis"[tiab] OR "Monckeberg's Sclerosis"[tiab] OR "Monckeberg Sclerosis"[tiab] OR "Monckebergs Sclerosis"[title:~3] OR "Mönckeberg's Medial Calcific Sclerosis"[tiab] OR "Mönckeberg's Sclerosis"[tiab] OR "Mönckeberg Sclerosis"[tiab] OR "Mönckebergs Sclerosis"[title:~3] OR "Monckeberg"[tiab] OR "Monckeberg*"[tiab] OR "Moenckeberg"[tiab] OR "Moenckeberg*"[tiab] OR "Medial Calcific Sclerosis"[tiab] OR "Medial Calcific Scleroses"[title:~3] OR "Mönckeberg Medial Calcific Sclerosis"[tiab] OR "incompressible arter*"[tiab] OR "incompressible vessel*"[tiab] OR "medial calcified artery"[title:~3] OR "medial calcified arteries"[title:~3] OR (("Arterial Occlusive Diseases"[majr] OR "Peripheral Vascular Diseases"[majr]) AND ("peripheral"[tiab] OR "peripheral*"[tiab] OR "limbs"[tiab] OR "limb"[tiab] OR "leg"[tiab] OR "legs"[tiab] OR "extremity"[tiab] OR "extremities"[tiab] OR "arm"[tiab] OR "arms"[tiab])) OR "Intermittent Claudication"[majr] OR "Intermittent Claudication"[tiab] OR "Leriche Syndrome"[majr] OR "Leriche Syndrome"[tiab] OR "Leriche's Syndrome"[tiab] OR "Leriches Syndrome"[tiab] OR "Arteriosclerosis Obliterans"[majr] OR "Arteriosclerosis Obliterans"[tiab] OR (("Atherosclerosis"[majr] OR "Arteriosclerosis"[majr] OR "Atherosclerosis"[tiab] OR "Arteriosclerosis"[tiab]) AND ("peripheral"[tiab] OR "peripheral*"[tiab] OR "limbs"[tiab] OR "limb"[tiab] OR "leg"[tiab] OR "legs"[tiab] OR "extremity"[tiab] OR "extremities"[tiab] OR "arm"[tiab] OR "arms"[tiab])) OR "Fontaine IV"[tiab] OR "Diabetic Foot"[majr] OR "Diabetic Foot"[tiab] OR "Diabetic Feet"[tiab] OR (("Diabetes Mellitus"[majr] OR "diabetes"[tiab] OR "diabet*"[tiab] OR "Renal Insufficiency, Chronic"[majr] OR "Chronic Kidney Disease"[tiab] OR "Chronic Kidney Diseases"[tiab] OR "Chronic Kidney Failure"[tiab] OR "Chronic Kidney Insufficiency"[tiab] OR "Chronic Renal Disease"[tiab] OR "Chronic Renal Diseases"[tiab] OR "Chronic Renal Failure"[tiab] OR "Chronic Renal Insufficiency"[tiab] OR "End Stage Kidney Disease"[tiab] OR "End Stage Renal Disease"[tiab] OR "End-Stage Renal Failure"[tiab] OR "End-Stage Kidney Failure"[tiab] OR "ESRD"[tiab]) AND ("peripheral"[tiab] OR "peripheral*"[tiab] OR "Extremities"[majr] OR "Foot Diseases"[majr] OR "limbs"[tiab] OR "limb"[tiab] OR "leg"[tiab] OR "legs"[tiab]		

Database	Search Strategy	Number of references	Number of unique references
PubMed (Continued)	OR "extremity"[tiab] OR "extremities"[tiab] OR "arm"[tiab] OR "arms"[tiab] OR "foot"[tiab] OR "feet"[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "finger"[tiab] OR "fingers"[tiab]))) AND ("Ankle Brachial Index"[mesh] OR "Ankle Brachial Indices"[tw] OR "Ankle-Brachial Index"[tw] OR "Ankle-Brachial Indices"[tw] OR "anklebrachial index"[tw] OR "anklebrachialindex"[tw] OR "ankle brachial"[tw] OR "anklebrachial"[tw] OR "ABI"[tw] OR "Toe Brachial Index"[tw] OR "Toe Brachial Indices"[tw] OR "Toe-Brachial Index"[tw] OR "Toe-Brachial Indices"[tw] OR "Toe Pressure"[tw] OR "toe brachial"[tw] OR "toebrachial"[tw] OR "TBI"[tw] OR "TP"[tw] OR "Oximetry"[mesh] OR "Oximetry"[tw] OR "Oximetries"[tw] OR "Oximetr*"[tw] OR "Pulse Oximetries"[tw] OR "Pulse Oximetry"[tw] OR "transcutaneous oxygen tension"[tw] OR "transcutaneous oxygen"[tw] OR "Pulse"[mesh] OR "Pulse*"[tw] OR "pulsation"[tw] OR "pulsations"[tw] OR "Blood Gas Monitoring, Transcutaneous"[mesh] OR "Transcutaneous Blood Gas Monitoring"[tw] OR "Transcutaneous Capnometry"[tw] OR "PtcO2"[tw] OR "TcPCO2"[tw] OR "Doppler waveform"[tw] OR "Doppler waveforms"[tw] OR "Doppler wave form"[tw] OR "Doppler wave forms"[tw] OR "Ultrasonography, Doppler, Pulsed"[mesh:noexp] OR "Pulsed Doppler"[tw] OR "Doppler Pulsed"[tw] OR "non-invasive"[tw] OR "non-invasiv*"[tw] OR "point-of-care test"[tw] OR "point-of-care tests"[tw] OR "Ankle Pressure"[tw] OR "Ankle Pressures"[tw] OR "Skin Temperature"[Mesh] OR "Skin Temperature"[tw] OR "Skin Temperatures"[tw] OR "Blood Pressure Determination"[Mesh] OR "blood pressure measurement"[tw] OR "blood pressure measurements"[tw]) AND ("Wound Healing"[majr] OR "Wound Healing"[ti] OR "Wound Healing"[title:~4] OR "Wound Heal"[title:~4] OR "Wound Healed"[title:~4] OR "Wound Heals"[title:~4] OR "Wounds Healing"[ti] OR "Wounds Healing"[title:~4] OR "Wounds Heal"[title:~4] OR "Wounds Healed"[title:~4] OR "Wounds Heals"[title:~4] OR "Ulcer Healing"[ti] OR "Ulcer Healing"[title:~4] OR "Ulcer Heal"[title:~4] OR "Ulcer Healed"[title:~4] OR "Ulcer Heals"[title:~4] OR "Ulcers Healing"[ti] OR "Ulcers Healing"[title:~4] OR "Ulcers Heal"[title:~4] OR "Ulcers Healed"[title:~4] OR "Ulcers Heals"[title:~4] OR (("predictor"[ti] OR "predictors"[ti] OR "predictive factor"[ti] OR "predictive factors"[ti] OR "predicting"[ti] OR "Forecasting"[majr]) AND ("Amputation, Surgical"[majr] OR "Amputation"[ti])) OR "Wound Outcome"[title:~4] OR "Wound Outcomes"[title:~4] OR "Wounds Outcome"[title:~4] OR "Wounds Outcomes"[title:~4] OR "Ulcer Outcome"[ti] OR "Ulcer Outcome"[title:~4] OR "Ulcer Outcomes"[title:~4] OR "Ulcers Outcome"[ti] OR "Ulcers Outcome"[title:~4] OR "Ulcers Outcomes"[title:~4]))		
Embase (OVID-version)	(((*"Peripheral Occlusive Artery Disease"/ OR "Peripheral Arterial Disease".ti,ab OR "Peripheral Arterial Diseases".ti,ab OR "Peripheral Artery Disease".ti,ab OR "Peripheral Artery Diseases".ti,ab OR "Peripheral Arterial Disorder".ti,ab OR "Peripheral Arterial Disorders".ti,ab OR "Peripheral Artery Disorder".ti,ab OR ("PAD".ti,ab AND ("artery".ti,ab OR "arteries".ti,ab OR "arterial".ti,ab)) OR "peripheral arterial occlusive disease".ti,ab OR "peripheral arterial occlusive diseases".ti,ab OR "peripheral artery occlusive disease".ti,ab OR "peripheral artery occlusive diseases".ti,ab OR "Peripheral Vascular Disease"/ OR "Peripheral Vascular Disease".ti,ab OR "Peripheral Vascular Diseases".ti,ab OR "Peripheral Vascular Disorder".ti,ab OR "Peripheral Vascular Disorders".ti,ab OR	604	120

Database	Search Strategy	Number of references	Number of unique references
Embase (OVID-version) (Continued)	"Peripheral Angiopathies".ti,ab OR "Peripheral Angiopathy".ti,ab OR "Peripheral Arteriopathies".ti,ab OR "Peripheral Arteriopathy".ti,ab OR "Peripheral Vasculopathies".ti,ab OR "Peripheral Vasculopathy".ti,ab OR *"Monckeberg medial calcific sclerosis"/ OR "Monckeberg's Medial Calcific Sclerosis".ti,ab OR "Monckeberg's Sclerosis".ti,ab OR "Monckeberg Sclerosis".ti,ab OR ("Monckeberg*" ADJ3 "Sclerosis").ti,ab OR "Mönckeberg's Medial Calcific Sclerosis".ti,ab OR "Mönckeberg's Sclerosis".ti,ab OR "Mönckeberg Sclerosis".ti,ab OR ("Mönckeberg*" ADJ3 "Sclerosis").ti,ab OR "Monckeberg".ti,ab OR "Monckeberg*".ti,ab OR "Moenckeberg".ti,ab OR "Moenckeberg*".ti,ab OR "Medial Calcific Sclerosis".ti,ab OR ("Medial" ADJ3 "Calcific" ADJ3 "Scleroses").ti,ab OR "Mönckeberg Medial Calcific Sclerosis".ti,ab OR "incompressible arter*".ti,ab OR "incompressible vessel*".ti,ab OR ("medial" ADJ3 "calcified" ADJ3 "artery").ti,ab OR ("medial" ADJ3 "calcified" ADJ3 "arteries").ti,ab OR *"Intermittent Claudication"/ OR "Intermittent Claudication".ti,ab OR "Leriche Syndrome"/ OR "Leriche Syndrome".ti,ab OR "Leriche's Syndrome".ti,ab OR "Leriches Syndrome".ti,ab OR "Arteriosclerosis Obliterans"/ OR "Arteriosclerosis Obliterans".ti,ab OR ((exp *"Atherosclerosis"/ OR exp *"Arteriosclerosis"/ OR "Atherosclerosis".ti,ab OR "Arteriosclerosis".ti,ab) AND ("peripheral".ti,ab OR "peripheral*".ti,ab OR "limbs".ti,ab OR "limb".ti,ab OR "leg".ti,ab OR "legs".ti,ab OR "extremity".ti,ab OR "extremities".ti,ab OR "arm".ti,ab OR "arms".ti,ab)) OR "Fontaine IV".ti,ab OR *"Diabetic Foot"/ OR "Diabetic Foot".ti,ab OR "Diabetic Feet".ti,ab OR ((exp *"Diabetes Mellitus"/ OR "diabetes".ti,ab OR "diabet*".ti,ab OR exp *"Chronic Kidney Failure"/ OR "Chronic Kidney Disease".ti,ab OR "Chronic Kidney Diseases".ti,ab OR "Chronic Kidney Failure".ti,ab OR "Chronic Kidney Insufficiency".ti,ab OR "Chronic Renal Disease".ti,ab OR "Chronic Renal Diseases".ti,ab OR "Chronic Renal Failure".ti,ab OR "Chronic Renal Insufficiency".ti,ab OR "End Stage Kidney Disease".ti,ab OR "end stage renal disease"/ OR "End Stage Renal Disease".ti,ab OR "End-Stage Renal Failure".ti,ab OR "End-Stage Kidney Failure".ti,ab OR "ESRD".ti,ab) AND ("peripheral".ti,ab OR "peripheral*".ti,ab OR exp *"Limb"/ OR "limbs".ti,ab OR "limb".ti,ab OR "leg".ti,ab OR "legs".ti,ab OR "extremity".ti,ab OR "extremities".ti,ab OR "arm".ti,ab OR "arms".ti,ab OR "foot".ti,ab OR "feet".ti,ab OR "toe".ti,ab OR "toes".ti,ab OR "finger".ti,ab OR "fingers".ti,ab))) AND (*"Ankle Brachial Index"/ OR "Ankle Brachial Indices".ti,ab OR "Ankle-Brachial Index".ti,ab OR "Ankle-Brachial Indices".ti,ab OR "anklebrachial index".ti,ab OR "anklebrachialindex".ti,ab OR "ankle brachial".ti,ab OR "anklebrachial".ti,ab OR "ABI".ti,ab OR "Toe Brachial Index".ti,ab OR "Toe Brachial Indices".ti,ab OR "Toe-Brachial Index".ti,ab OR "Toe-Brachial Indices".ti,ab OR "Toe Pressure".ti,ab OR "toe brachial".ti,ab OR "toebrachial".ti,ab OR "TBI".ti,ab OR "TP".ti,ab OR exp *"Oximetry"/ OR "Oximetry".ti,ab OR "Oximetries".ti,ab OR "Oximetr*".ti,ab OR "Pulse Oximetries".ti,ab OR "Pulse Oximetry".ti,ab OR "transcutaneous oxygen tension".ti,ab OR "transcutaneous oxygen".ti,ab OR *"Pulse"/ OR "Pulse*".ti,ab OR "pulsation".ti,ab OR "pulsations".ti,ab OR *"Transcutaneous Oxygen Monitoring"/ OR "Transcutaneous Blood Gas Monitoring".ti,ab OR "Transcutaneous Capnometry".ti,ab OR "PtcO2".ti,ab OR "TcPCO2".ti,ab OR "Doppler waveform".ti,ab OR "Doppler waveforms".ti,ab OR "Doppler wave form".ti,ab OR "Doppler wave forms".ti,ab OR *"pulsed Doppler echocardiography"/ OR "Pulsed Doppler".ti,ab OR "Doppler Pulsed".ti,ab OR "non-		

Database	Search Strategy	Number of references	Number of unique references
Embase (OVID-version) (Continued)	invasive".ti,ab OR "non-invasiv*".ti,ab OR "point-of-care test".ti,ab OR "point-of-care tests".ti,ab OR *"Ankle Pressure"/ OR "Ankle Pressure".ti,ab OR "Ankle Pressures".ti,ab OR *"Skin Temperature"/ OR "Skin Temperature".ti,ab OR "Skin Temperatures".ti,ab OR exp *"Blood Pressure measurement"/ OR "blood pressure measurement".ti,ab OR "blood pressure measurements".ti,ab) AND (exp *"Wound Healing"/ OR "Wound Healing".ti,ab OR "Wounds Healing".ti,ab OR *"Ulcer Healing"/ OR "Ulcer Healing".ti,ab OR "Ulcers Healing".ti,ab OR (("Wound" ADJ4 "Healing") OR ("Wound" ADJ4 "Heal") OR ("Wound" ADJ4 "Healed") OR ("Wound" ADJ4 "Heals") OR ("Wounds" ADJ4 "Healing") OR ("Wounds" ADJ4 "Heal") OR ("Wounds" ADJ4 "Healed") OR ("Wounds" ADJ4 "Heals") OR ("Ulcer" ADJ4 "Healing") OR ("Ulcer" ADJ4 "Heal") OR ("Ulcer" ADJ4 "Healed") OR ("Ulcer" ADJ4 "Heals") OR ("Ulcers" ADJ4 "Healing") OR ("Ulcers" ADJ4 "Heal") OR ("Ulcers" ADJ4 "Healed") OR ("Ulcers" ADJ4 "Heals")).ti,ab OR (("predictor".ti,ab OR "predictors".ti,ab OR "predictive factor".ti,ab OR "predictive factors".ti,ab OR "predicting".ti,ab OR "Forecasting"/) AND (exp *"Amputation"/ OR "Amputation".ti,ab)) OR "Wound Outcome".ti,ab OR "Wound Outcomes".ti,ab OR "Ulcer Outcome".ti,ab OR "Ulcer Outcomes".ti,ab OR (("Wound" ADJ4 "Outcome") OR ("Wound" ADJ4 "Outcomes") OR ("Wounds" ADJ4 "Outcome") OR ("Wounds" ADJ4 "Outcomes") OR ("Ulcer" ADJ4 "Outcome") OR ("Ulcer" ADJ4 "Outcomes") OR ("Ulcers" ADJ4 "Outcome") OR ("Ulcers" ADJ4 "Outcomes")).ti,ab) AND ("Sensitivity and Specificity"/ OR "Sensitivity".ti,ab OR "Specificity".ti,ab OR "Predictive Value".ti,ab OR "ROC Curve".ti,ab OR "Signal-To-Noise".ti,ab OR "limit of detection".ti,ab OR "Cohort Analysis"/ OR exp "Follow Up"/ OR exp "Longitudinal Study"/ OR exp "Prospective Study"/ OR exp "Retrospective Study"/ OR "Cohort".ti,ab OR "Cohorts".ti,ab OR "Follow-Up".ti,ab OR "Longitudinal".ti,ab OR "Prospective".ti,ab OR "Retrospective".ti,ab OR exp "Cross-Sectional Study"/ OR "Cross-Sectional".ti,ab OR "Observational Study"/ OR "Observational Study".ti,ab OR "effectiveness".ti,ab OR "efficacy".ti,ab)) **OR** ((*"Peripheral Occlusive Artery Disease"/ OR "Peripheral Arterial Disease".ti,ab OR "Peripheral Arterial Diseases".ti,ab OR "Peripheral Artery Disease".ti,ab OR "Peripheral Artery Diseases".ti,ab OR "Peripheral Arterial Disorder".ti,ab OR "Peripheral Arterial Disorders".ti,ab OR "Peripheral Artery Disorder".ti,ab OR ("PAD".ti,ab AND ("artery".ti,ab OR "arteries".ti,ab OR "arterial".ti,ab)) OR "peripheral arterial occlusive disease".ti,ab OR "peripheral arterial occlusive diseases".ti,ab OR "peripheral artery occlusive disease".ti,ab OR "peripheral artery occlusive diseases".ti,ab OR "Peripheral Vascular Disease"/ OR "Peripheral Vascular Disease".ti,ab OR "Peripheral Vascular Diseases".ti,ab OR "Peripheral Vascular Disorder".ti,ab OR "Peripheral Vascular Disorders".ti,ab OR "Peripheral Angiopathies".ti,ab OR "Peripheral Angiopathy".ti,ab OR "Peripheral Arteriopathies".ti,ab OR "Peripheral Arteriopathy".ti,ab OR "Peripheral Vasculopathies".ti,ab OR "Peripheral Vasculopathy".ti,ab OR *"Monckeberg medial calcific sclerosis"/ OR "Monckeberg's Medial Calcific Sclerosis".ti,ab OR "Monckeberg's Sclerosis".ti,ab OR "Monckeberg Sclerosis".ti,ab OR ("Monckeberg*" ADJ3 "Sclerosis").ti,ab OR "Mönckeberg's Medial Calcific Sclerosis".ti,ab OR "Mönckeberg's Sclerosis".ti,ab OR "Mönckeberg Sclerosis".ti,ab OR ("Mönckeberg*" ADJ3 "Sclerosis").ti,ab OR "Monckeberg".ti,ab OR "Monckeberg*".ti,ab OR "Moenckeberg".ti,ab OR "Moenckeberg*".		

Database	Search Strategy	Number of references	Number of unique references
Embase (OVID-version) (Continued)	ti,ab OR "Medial Calcific Sclerosis".ti,ab OR ("Medial" ADJ3 "Calcific" ADJ3 "Scleroses").ti,ab OR "Mönckeberg Medial Calcific Sclerosis".ti,ab OR "incompressible arter*".ti,ab OR "incompressible vessel*".ti,ab OR ("medial" ADJ3 "calcified" ADJ3 "artery").ti,ab OR ("medial" ADJ3 "calcified" ADJ3 "arteries").ti,ab OR *"Intermittent Claudication"/ OR "Intermittent Claudication".ti,ab OR "Leriche Syndrome"/ OR "Leriche Syndrome".ti,ab OR "Leriche's Syndrome". ti,ab OR "Leriches Syndrome".ti,ab OR "Arteriosclerosis Obliterans"/ OR "Arteriosclerosis Obliterans".ti,ab OR ((exp *"Atherosclerosis"/ OR exp *"Arteriosclerosis"/ OR "Atherosclerosis".ti,ab OR "Arteriosclerosis".ti,ab) AND ("peripheral".ti,ab OR "peripheral*". ti,ab OR "limbs".ti,ab OR "limb".ti,ab OR "leg".ti,ab OR "legs". ti,ab OR "extremity".ti,ab OR "extremities".ti,ab OR "arm".ti,ab OR "arms".ti,ab)) OR "Fontaine IV".ti,ab OR *"Diabetic Foot"/ OR "Diabetic Foot".ti,ab OR "Diabetic Feet".ti,ab OR ((exp *"Diabetes Mellitus"/ OR "diabetes".ti,ab OR "diabet*".ti,ab OR exp *"Chronic Kidney Failure"/ OR "Chronic Kidney Disease".ti,ab OR "Chronic Kidney Diseases".ti,ab OR "Chronic Kidney Failure".ti,ab OR "Chronic Kidney Insufficiency".ti,ab OR "Chronic Renal Disease". ti,ab OR "Chronic Renal Diseases".ti,ab OR "Chronic Renal Failure". ti,ab OR "Chronic Renal Insufficiency".ti,ab OR "End Stage Kidney Disease".ti,ab OR "end stage renal disease"/ OR "End Stage Renal Disease".ti,ab OR "End-Stage Renal Failure".ti,ab OR "End-Stage Kidney Failure".ti,ab OR "ESRD".ti,ab) AND ("peripheral".ti,ab OR "peripheral*".ti,ab OR exp *"Limb"/ OR "limbs".ti,ab OR "limb".ti,ab OR "leg".ti,ab OR "legs".ti,ab OR "extremity".ti,ab OR "extremities". ti,ab OR "arm".ti,ab OR "arms".ti,ab OR "foot".ti,ab OR "feet". ti,ab OR "toe".ti,ab OR "toes".ti,ab OR "finger".ti,ab OR "fingers". ti,ab))) AND (*"Ankle Brachial Index"/ OR "Ankle Brachial Indices". ti,ab OR "Ankle-Brachial Index".ti,ab OR "Ankle-Brachial Indices". ti,ab OR "anklebrachial index".ti,ab OR "anklebrachialindex".ti,ab OR "ankle brachial".ti,ab OR "anklebrachial".ti,ab OR "ABI".ti,ab OR "Toe Brachial Index".ti,ab OR "Toe Brachial Indices".ti,ab OR "Toe-Brachial Index".ti,ab OR "Toe-Brachial Indices".ti,ab OR "Toe Pressure".ti,ab OR "toe brachial".ti,ab OR "toebrachial".ti,ab OR "TBI".ti,ab OR "TP".ti,ab OR exp *"Oximetry"/ OR "Oximetry".ti,ab OR "Oximetries".ti,ab OR "Oximetr*".ti,ab OR "Pulse Oximetries". ti,ab OR "Pulse Oximetry".ti,ab OR "transcutaneous oxygen tension". ti,ab OR "transcutaneous oxygen".ti,ab OR *"Pulse"/ OR "Pulse*". ti,ab OR "pulsation".ti,ab OR "pulsations".ti,ab OR*"Transcutaneous Oxygen Monitoring"/ OR "Transcutaneous Blood Gas Monitoring". ti,ab OR "Transcutaneous Capnometry".ti,ab OR "PtcO2".ti,ab OR "TcPCO2".ti,ab OR "Doppler waveform".ti,ab OR "Doppler waveforms".ti,ab OR "Doppler wave form".ti,ab OR "Doppler wave forms".ti,ab OR *"pulsed Doppler echocardiography"/ OR "Pulsed Doppler".ti,ab OR "Doppler Pulsed".ti,ab OR "non-invasive".ti,ab OR "non-invasiv*".ti,ab OR "point-of-care test".ti,ab OR "point-of-care tests".ti,ab OR *"Ankle Pressure"/ OR "Ankle Pressure".ti,ab OR "Ankle Pressures".ti,ab OR *"Skin Temperature"/ OR "Skin Temperature".ti,ab OR "Skin Temperatures".ti,ab OR exp *"Blood Pressure measurement"/ OR "blood pressure measurement".ti,ab OR "blood pressure measurements".ti,ab) AND (exp *"Wound Healing"/ OR "Wound Healing".ti OR "Wounds Healing".ti OR *"Ulcer Healing"/ OR "Ulcer Healing".ti OR "Ulcers Healing".ti OR (("Wound" ADJ4 "Healing") OR ("Wound" ADJ4 "Heal") OR ("Wound" ADJ4 "Healed") OR ("Wound" ADJ4 "Heals") OR		

Database	Search Strategy	Number of references	Number of unique references
Embase (OVID-version) (Continued)	("Wounds" ADJ4 "Healing") OR ("Wounds" ADJ4 "Heal") OR ("Wounds" ADJ4 "Healed") OR ("Wounds" ADJ4 "Heals") OR ("Ulcer" ADJ4 "Healing") OR ("Ulcer" ADJ4 "Heal") OR ("Ulcer" ADJ4 "Healed") OR ("Ulcer" ADJ4 "Heals") OR ("Ulcers" ADJ4 "Healing") OR ("Ulcers" ADJ4 "Heal") OR ("Ulcers" ADJ4 "Healed") OR ("Ulcers" ADJ4 "Heals")).ti OR (("predictor".ti OR "predictors".ti OR "predictive factor".ti OR "predictive factors".ti OR "predicting".ti OR *"Forecasting"/) AND (exp *"Amputation"/ OR "Amputation".ti)) OR "Wound Outcome".ti OR "Wound Outcomes".ti OR "Ulcer Outcome".ti OR "Ulcer Outcomes".ti OR (("Wound" ADJ4 "Outcome") OR ("Wound" ADJ4 "Outcomes") OR ("Wounds" ADJ4 "Outcome") OR ("Wounds" ADJ4 "Outcomes") OR ("Ulcer" ADJ4 "Outcome") OR ("Ulcer" ADJ4 "Outcomes") OR ("Ulcers" ADJ4 "Outcome") OR ("Ulcers" ADJ4 "Outcomes")).ti)))		
Web of Science	(((TI=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial")**) OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND	423	37

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) OR AK=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial"))** OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) OR AB=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial"))** OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral**		

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	**Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) AND (TI=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**) OR AK=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial		

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**) OR AB=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**)) AND (TI=("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes")**		

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	**OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes")))** OR AK=("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes")))** OR AB=("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes"))))** AND (TI=("Sensitivity and Specificity" OR "Sensitivity" OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy") OR AK=("Sensitivity and Specificity" OR "Sensitivity" OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy") OR AB=("Sensitivity and Specificity" OR "Sensitivity"		

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy"))) **OR** ((TI=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial"))** OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) OR AK=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial"))** OR "peripheral arterial occlusive		

Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) OR AB=("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial")**) OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR		

Database	Search Strategy	Number of references	Number of unique references
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Database	Search Strategy	Number of references	Number of unique references
Web of Science (Continued)	Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements")** OR AB=("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements")**) AND TI=("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes"))))**		
Cochrane Library	Three strings coupled to: AND ("Sensitivity and Specificity" OR "Sensitivity" OR "Specificity" OR "Predictive Value" OR "ROC Curve" OR "Signal-To-Noise" OR "limit of detection" OR "Cohort Analysis" OR "Follow Up" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective	196	63

Database	Search Strategy	Number of references	Number of unique references
Cochrane Library (Continued)	Study" OR "Cohort" OR "Cohorts" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "Cross-Sectional Study" OR "Cross-Sectional" OR "Observational Study" OR "Observational Study" OR "effectiveness" OR "efficacy"):ti,ab,kw (("Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" **OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial")**) OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR (Monckeberg* NEAR/3 Sclerosis) OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR (incompressible NEXT arter*) OR (incompressible NEXT vessel*) OR ("medial" NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))) AND ("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse		

Database	Search Strategy	Number of references	Number of unique references
Cochrane Library (Continued)	Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR (non NEXT invasiv*) OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**) AND ("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes"))**):ti,kw ((**"Peripheral Occlusive Artery Disease" OR "Peripheral Arterial Disease" OR "Peripheral Arterial Diseases" OR "Peripheral Artery Disease" OR "Peripheral Artery Diseases" OR "Peripheral Arterial Disorder" OR "Peripheral Arterial Disorders" OR "Peripheral Artery Disorder"** OR ("PAD" **AND ("artery" OR "arteries" OR "arterial")**) OR "peripheral arterial occlusive disease" OR "peripheral arterial occlusive diseases" OR "peripheral artery occlusive disease" OR "peripheral artery occlusive diseases" OR "Peripheral Vascular Disease" **OR "Peripheral Vascular Disease" OR "Peripheral Vascular Diseases" OR "Peripheral Vascular Disorder" OR "Peripheral Vascular Disorders"** OR "Peripheral Angiopathies" OR "Peripheral Angiopathy" OR "Peripheral Arteriopathies" OR "Peripheral Arteriopathy" OR "Peripheral Vasculopathies" OR "Peripheral Vasculopathy" OR "Monckeberg medial calcific sclerosis" OR "Monckeberg's Medial Calcific Sclerosis" OR "Monckeberg's Sclerosis" OR "Monckeberg Sclerosis" OR ("Monckeberg*" NEAR/3 "Sclerosis") OR "Mönckeberg's Medial Calcific Sclerosis" OR "Mönckeberg's Sclerosis" OR "Mönckeberg Sclerosis" OR ("Mönckeberg*" NEAR/3 "Sclerosis") OR "Monckeberg" OR "Monckeberg*" OR "Moenckeberg" OR "Moenckeberg*" OR "Medial Calcific Sclerosis" OR ("Medial" NEAR/3 "Calcific" NEAR/3 "Scleroses") OR "Mönckeberg Medial Calcific Sclerosis" OR "incompressible arter*" OR "incompressible vessel*" OR ("medial"		

Database	Search Strategy	Number of references	Number of unique references
Cochrane Library (Continued)	NEAR/3 "calcified" NEAR/3 "artery") OR ("medial" NEAR/3 "calcified" NEAR/3 "arteries") OR "Intermittent Claudication" OR "Intermittent Claudication" OR "Leriche Syndrome" OR "Leriche Syndrome" OR "Leriche's Syndrome" OR "Leriches Syndrome" OR "Arteriosclerosis Obliterans" OR "Arteriosclerosis Obliterans" OR (("Atherosclerosis" OR "Arteriosclerosis" OR "Atherosclerosis" OR "Arteriosclerosis") AND ("peripheral" OR "peripheral*" OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms")) **OR "Fontaine IV" OR "Diabetic Foot" OR "Diabetic Foot" OR "Diabetic Feet"** OR (("Diabetes Mellitus" OR "diabetes" OR "diabet*" OR "Chronic Kidney Failure" OR "Chronic Kidney Disease" OR "Chronic Kidney Diseases" OR "Chronic Kidney Failure" OR "Chronic Kidney Insufficiency" OR "Chronic Renal Disease" OR "Chronic Renal Diseases" OR "Chronic Renal Failure" OR "Chronic Renal Insufficiency" OR "End Stage Kidney Disease" OR "end stage renal disease" OR "End Stage Renal Disease" OR "End-Stage Renal Failure" OR "End-Stage Kidney Failure" OR "ESRD") AND ("peripheral" OR "peripheral*" **OR "Limb"** OR "limbs" OR "limb" OR "leg" OR "legs" OR "extremity" OR "extremities" OR "arm" OR "arms" **OR "foot" OR "feet" OR "toe" OR "toes" OR "finger" OR "fingers"**))):ti AND ("Ankle Brachial Index" OR "Ankle Brachial Indices" OR "Ankle-Brachial Index" OR "Ankle-Brachial Indices" OR "anklebrachial index" OR "anklebrachialindex" OR "ankle brachial" OR "anklebrachial" OR "ABI" OR "Toe Brachial Index" OR "Toe Brachial Indices" OR "Toe-Brachial Index" OR "Toe-Brachial Indices" OR "Toe Pressure" OR "toe brachial" OR "toebrachial" OR "TBI" OR "TP" OR "Oximetry" OR "Oximetry" OR "Oximetries" OR "Oximetr*" OR "Pulse Oximetries" OR "Pulse Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**):ti,ab,kw AND ("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4**		

Database	Search Strategy	Number of references	Number of unique references
Cochrane Library (Continued)	**"Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes")))**:ti,ab,kw) ((“Peripheral Occlusive Artery Disease” OR “Peripheral Arterial Disease” OR “Peripheral Arterial Diseases” OR “Peripheral Artery Disease” OR “Peripheral Artery Diseases” **OR “Peripheral Arterial Disorder” OR “Peripheral Arterial Disorders” OR “Peripheral Artery Disorder”** OR (“PAD” **AND (“artery” OR “arteries” OR “arterial”))** OR “peripheral arterial occlusive disease” OR “peripheral arterial occlusive diseases” OR “peripheral artery occlusive disease” OR “peripheral artery occlusive diseases” OR “Peripheral Vascular Disease” **OR “Peripheral Vascular Disease” OR “Peripheral Vascular Diseases” OR “Peripheral Vascular Disorder” OR “Peripheral Vascular Disorders”** OR “Peripheral Angiopathies” OR “Peripheral Angiopathy” OR “Peripheral Arteriopathies” OR “Peripheral Arteriopathy” OR “Peripheral Vasculopathies” OR “Peripheral Vasculopathy” OR “Monckeberg medial calcific sclerosis” OR “Monckeberg’s Medial Calcific Sclerosis” OR “Monckeberg’s Sclerosis” OR “Monckeberg Sclerosis” OR (“Monckeberg*” NEAR/3 “Sclerosis”) OR “Mönckeberg’s Medial Calcific Sclerosis” OR “Mönckeberg’s Sclerosis” OR “Mönckeberg Sclerosis” OR (“Mönckeberg*” NEAR/3 “Sclerosis”) OR “Monckeberg” OR “Monckeberg*” OR “Moenckeberg” OR “Moenckeberg*” OR “Medial Calcific Sclerosis” OR (“Medial” NEAR/3 “Calcific” NEAR/3 “Scleroses”) OR “Mönckeberg Medial Calcific Sclerosis” OR “incompressible arter*” OR “incompressible vessel*” OR (“medial” NEAR/3 “calcified” NEAR/3 “artery”) OR (“medial” NEAR/3 “calcified” NEAR/3 “arteries”) OR “Intermittent Claudication” OR “Intermittent Claudication” OR “Leriche Syndrome” OR “Leriche Syndrome” OR “Leriche’s Syndrome” OR “Leriches Syndrome” OR “Arteriosclerosis Obliterans” OR “Arteriosclerosis Obliterans” OR ((“Atherosclerosis” OR “Arteriosclerosis” OR “Atherosclerosis” OR “Arteriosclerosis”) AND (“peripheral” OR “peripheral*” OR “limbs” OR “limb” OR “leg” OR “legs” OR “extremity” OR “extremities” OR “arm” OR “arms”)) **OR “Fontaine IV” OR “Diabetic Foot” OR “Diabetic Foot” OR “Diabetic Feet”** OR ((“Diabetes Mellitus” OR “diabetes” OR “diabet*” OR “Chronic Kidney Failure” OR “Chronic Kidney Disease” OR “Chronic Kidney Diseases” OR “Chronic Kidney Failure” OR “Chronic Kidney Insufficiency” OR “Chronic Renal Disease” OR “Chronic Renal Diseases” OR “Chronic Renal Failure” OR “Chronic Renal Insufficiency” OR “End Stage Kidney Disease” OR “end stage renal disease” OR “End Stage Renal Disease” OR “End-Stage Renal Failure” OR “End-Stage Kidney Failure” OR “ESRD”) AND (“peripheral” OR “peripheral*” **OR “Limb”** OR “limbs” OR “limb” OR “leg” OR “legs” OR “extremity” OR “extremities” OR “arm” OR “arms” **OR “foot” OR “feet” OR “toe” OR “toes” OR “finger” OR “fingers”**)))**:ti,kw AND** (“Ankle Brachial Index” OR “Ankle Brachial Indices” OR “Ankle-Brachial Index” OR “Ankle-Brachial Indices” OR “anklebrachial index” OR “anklebrachialindex” OR “ankle brachial” OR “anklebrachial” OR “ABI” OR “Toe Brachial Index” OR “Toe Brachial Indices” OR “Toe-Brachial Index” OR “Toe-Brachial Indices” OR “Toe Pressure” OR “toe brachial” OR “toebrachial” OR “TBI” OR “TP” OR “Oximetry” OR “Oximetry” OR “Oximetries” OR “Oximetr*” OR “Pulse Oximetries” OR “Pulse		

Database	Search Strategy	Number of references	Number of unique references
Cochrane Library (Continued)	Oximetry" OR "transcutaneous oxygen tension" OR "transcutaneous oxygen" OR "Pulse" OR "Pulse*" OR "pulsation" OR "pulsations" OR "Transcutaneous Oxygen Monitoring" OR "Transcutaneous Blood Gas Monitoring" OR "Transcutaneous Capnometry" OR "PtcO2" OR "TcPCO2" OR "Doppler waveform" OR "Doppler waveforms" OR "Doppler wave form" OR "Doppler wave forms" OR "pulsed Doppler echocardiography" OR "Pulsed Doppler" OR "Doppler Pulsed" OR "non-invasive" OR "non-invasiv*" OR "point-of-care test" OR "point-of-care tests" **OR "Ankle Pressure" OR "Ankle Pressure" OR "Ankle Pressures" OR "Skin Temperature" OR "Skin Temperature" OR "Skin Temperatures" OR "Blood Pressure measurement" OR "blood pressure measurement" OR "blood pressure measurements"**):ti AND ("Wound Healing" OR "Wound Healing" OR "Wounds Healing" OR "Ulcer Healing" OR "Ulcer Healing" OR "Ulcers Healing" OR (("Wound" NEAR/4 "Healing") OR ("Wound" NEAR/4 "Heal") OR ("Wound" NEAR/4 "Healed") OR ("Wound" NEAR/4 "Heals") OR ("Wounds" NEAR/4 "Healing") OR ("Wounds" NEAR/4 "Heal") OR ("Wounds" NEAR/4 "Healed") OR ("Wounds" NEAR/4 "Heals") OR ("Ulcer" NEAR/4 "Healing") OR ("Ulcer" NEAR/4 "Heal") OR ("Ulcer" NEAR/4 "Healed") OR ("Ulcer" NEAR/4 "Heals") OR ("Ulcers" NEAR/4 "Healing") OR ("Ulcers" NEAR/4 "Heal") OR ("Ulcers" NEAR/4 "Healed") OR ("Ulcers" NEAR/4 "Heals")) OR (("predictor" OR "predictors" OR "predictive factor" OR "predictive factors" OR "predicting" OR "Forecasting") AND ("Amputation" OR "Amputation")) **OR "Wound Outcome" OR "Wound Outcomes" OR "Ulcer Outcome" OR "Ulcer Outcomes" OR (("Wound" NEAR/4 "Outcome") OR ("Wound" NEAR/4 "Outcomes") OR ("Wounds" NEAR/4 "Outcome") OR ("Wounds" NEAR/4 "Outcomes") OR ("Ulcer" NEAR/4 "Outcome") OR ("Ulcer" NEAR/4 "Outcomes") OR ("Ulcers" NEAR/4 "Outcome") OR ("Ulcers" NEAR/4 "Outcomes"))**):ti)		
Emcare	See Embase	183	11
Total			942

Table S2. Overview of included studies regarding primary ulcer healing.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Apelqvist 1989[27]	Sweden	Prospective cohort study Follow-up: every 6 months until healing was achieved.	N = 314 DFU patients Mean age: 64 years Male 49.6% Mean DM duration: 17 years	Wagner grading system Grade 1: n = 150 (47.8%) Grade 2: n = 50 (15.9%) Grade 3: n = 46 (14.6%) Grade 4: n = 39 (12.4%) Grade 5: n = 29 (9.2%) Mean duration of ulcers at enrollment: 14.5 weeks.	Wound healing is defined as intact skin for at least 6 months or, for cases when the patient died within that period, as intact skin at the time of death. Patients with several concurrent lesions are represented by the lesion with the worst outcome.	AP ≥ 40 mmHg AP ≥ 80 mmHg TP > 15 mmHg TP > 45 mmHg	AP (40) Sens: 100% Spec: 11.6% PLR: 1.1 NLR: 0.0 TP (15) Sens: 96.1% Spec: 32.6% PLR: 1.4 NLR: 0.1	AP (80) Sens: 87.1% Spec: 42.9% PLR: 1.5 NLR: 0.3 TP (45) Sens: 77.4% Spec: 75.0% PLR: 3.1 NLR: 0.3	Patients were analysed according to their original AP/TP, also after revascularisation procedures. For purposes of calculating predictive capabilities, we reclassified these patients to the group they belong in based on their new AP or TP. Prognostic performance was calculated*.
Apelqvist 1990[28]	Sweden	Prospective cohort study Follow-up: every 6 months until healing was achieved.	N = 314 DFU patients Mean age: 64 years Male: 49.7% Mean DM duration: 17 years	Wagner grading system Grade 1: 47.8% Grade 2: 15.9% Grade 3: 14.6% Grade 4: 12.4% Grade 5: 9.2% Median duration ulceration 5 weeks (range 0 - 208)	Ulcer healing is defined as intact skin for at least 6 months or at time of death Healing after amputation Death before healing	Palpable femoral pulse Palpable popliteal pulse Palpable pedal pulse	Femoral Sens: 98.5% Spec: 3.4% PLR: 1.0 NLR: 0.4 Pedal Sens: 56.5% Spec: 76.2% PLR: 2.4 NLR: 0.6	Popliteal Sens: 73.1% Spec: 58.1% PLR: 1.7 NLR: 0.5	Based on the size of the cohort and period of enrollment this study seems to concern the same cohort as Apelqvist et al. (1989). In this study 4 patients underwent revascularization procedures. This is not described in this article.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Ballard 1995[29]	United States	Prospective cohort study Follow-up ranged from 2 to 15 months (mean 8 months). No loss to follow-up.	N = 55 patients, 66 feet Mean age: 67 years Male: 62% N = 12 patients on dialysis (22%)	Treatment indications: Non-healing ulcer 35 feet (53%) Gangrene 25 feet (38%) Rest pain 6 feet (9%) Determination of treatment based on TcPO2 levels. ³ 30mmHg conservative treatment. 30mmHg operative management with angioplasty or bypass surgery.	Treatment success or failure was defined as complete wound healing or relief of ischemic rest pain.	Palpable pedal pulses ABI ³ 0.60 TcPO2 ³ 30mmHg	Pedal Sens: 60% Spec: 89% PLR: 5.5 NLR: 0.45 $TcPO_2$ Sens: 98% Spec: 44% PLR: 1.8 NLR: 0.05	ABI Sens: 94% Spec: 40% PLR: 1.6 NLR: 0.15	In the conservative group, 36 feet were monitored to end-point due to death 2 and 4 months after treatment initiation. In the operative group, 28 limbs were monitored to end point because of primary lower limb amputation. ABI could only be successfully measured in 41 of 62 eligible limbs due to incompressible vessels.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance	Comments
Bishara 2009[30]	Egypt	Prospective cohort study	N = 100 limbs, 62 patients Mean age: 63 years Male: 67.7% 43 limbs reached endpoint of healing.	Nonischemic lesions Non-healing lesions CLI (rest pain, ischemic ulcers/ gangrene)	Healed wound (fully covered with intact skin) Healing wound (completely covered with healthy granulations, with absence of tissue necrosis or infection) Non-healing (no signs of granulation < 1 month or occurrence of CLI)	APSV ³ 35 cm/s APSV measured before and after revascularization.	APSV Sens: 92.9% Spec: 90.6% PLR: 9.9 NLR: 0.02	If a patient presented with a foot lesion that did not heal and required revascularization, the patient was entered once initially as a non-healed lesion and entered once again after revascularization. If the inclusion criteria were applicable to both limbs in the same patient, each limb was entered separately.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Brechow 2013[37]	Germany	Prospective cohort study 6 monthly check up, total follow-up per patient of 2 years.	N = 678 Mean age: 66 years Male: 69.3% Mean DM duration: 30 years	Modified University of Texas Wound Classification System 1A n = 1 (0.1%) 1B n = 2 (0.3%) 1C n = 12 (1.8%) 1D n = 59 (8.7%) 2B n = 22 (3.2%) 2C n = 36 (5.3% 2D n = 218 (32.1%) 3B n = 16 (2.4%) 3C n = 9 (1.3%) 3D n = 257 (37.9%) 4B n = 2 (0.3%) 4C n= 4 (0.6%) 4D n = 60 (8.8%) Overall 74% of ulcers healed at 2-year follow-up.	Complete healing without major amputation	ABI ³ 0.5 (without signs of MAC) ABI ³ 0.9 (without signs of MAC)	ABI (0.5) Sens: 49.3% Spec: 56.3% PLR: 1.1 NLR: 0.9	ABI (0.9) Sens: 7.5% Spec: 96.0% PLR: 1.9 NLR: 1.0	It is unclear if major amputations occurred after the original wound had healed, or if all major amputations were performed because of primary healing failure. It is unclear if ABI was re-examined after vascular interventions and if severity of PAOD was reclassified before analysis. Prognostic performance was calculated based on estimated numbers in the figures of the article. Therefore, minor errors in our calculations could be present.*

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Elghazaly 2023[31]	United Kingdom	Prospective observational comparison study Follow-up: 12 months	N = 123 DFU Mean age: 68 years Gender: 77% male Mean duration of DM = 18 years	According to Texas Grade: - 0: 0.8% - 1: 62.6% - 2: 8.1% - 3: 28.5% Overall 52.8% of ulcers healed	Ulcer healing was defined as complete healing with full skin epithelialization (intact skin). Healing of a wound after minor or major amputation was not considered healing.	ABI ≥ 0.9 AP ≥ 50 mmHg TBI ≥ 0.8 TP ≥ 40 mmHg $TcPO_2$ ≥ 40 mmHg PAD-scan (monophasic, or absent)	ABI Sens: 64% Spec: 39% PLR: 1.05 NLR: 0.92 TBI Sens: 50% Spec: 79% PLR: 2.4 NLR: 0.63 $TcPO_2$ Sens: 70% Spec: 43% PLR: 1.4 NLR: 0.70	AP Sens: 7% Spec: 86% PLR: 0.50 NLR: 1.08 TP Sens: 50% Spec: 46% PLR: 0.9 NLR: 1.08 PAD-scan Sens: 78% Spec: 40% PLR: 1.3 NLR: 0.56	Follow-up was performed prospectively for 12 months by regular quarterly review of electronic health records. Different thresholds for all point of care tests were analyzed; see reference for full elaboration.
Elgzyri 2013[47]	Sweden	Prospective observational study Continuous follow-up until healing or death	N = 602 DFU Mean age: 77 years Gender: 60% male Mean duration of DM = 15 years	At inclusion, 26% of patients had a deep ulcer (Wagner grade ≥3) Overall 38% of ulcers healed	1) Primary healing (not specified) 2) Healed without major amputation	AP ≥ 50 mmHg TP ≥ 30 mmHg	AP Sens: 93% Spec: 14% PLR: 1.1 NLR: 0.48	TP Sens: 55% Spec: 52% PLR: 1.1 NLR: 0.88	Patients were followed and treated according to a preset standardized protocol. Healed without major amputation results can be obtained in the primary reference as well.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Elgzyri 2021[38]	Sweden	Prospective observational study (retrospectively analysed) Follow-up: average of 41 weeks	N = 476 DFU Mean age: 73 years Gender: 63% male 63% of patients were insulin dependent	100% of ulcers had Wagner grade 4	Primary healing was defined as intact skin with complete epithelialization, also after auto or minor amputation	AP ≥ 80 mmHg TP ≥ 30 mmHg	AP Sens: 71% Spec: 26% PLR: 1.0 NLR: 1.09	TP Sens: 44% Spec: 34% PLR: 0.67 NLR: 1.66	Healed auto or minor amputations were regarded as healing as well. Ten patients were lost at follow-up.
Faris 1985[39]	Australia	Observational study Follow-up time unclear	N = 61 DFU Median age: 72 years Gender: 61% male Median duration of DM = 10 years	Wounds: - 57% ulceration - 43% gangrene	Ulcer healing included both primary healing and healing after local amputation	SPP > 40 mmHg	SPP Sens: 97% Spec: 80% PLR: 4.9 NLR: 0.04		Unclear if design was prospective or retrospective. Healed wounds after amputation were defined as healing as well, leading to an overestimation of prognostic performance.
Holstein 1980[40]	Denmark	Prospective cohort study Follow-up: 45 months maximum	N = 35 DFU Mean age: 68 years Gender: 68% male Mean duration of DM: 62.5% > 10 years 34% of patients were insulin dependent	An ulcer needed to be located on the toes or foot distal to the ankle joint and comprising a skin area of at least 5 by 5 mm and penetrating at least to the subcutis	Healing included minor amputation or resection of the foot as well (i.e. the limb was saved)	AP ≥ 50 mmHg AP ≥ 80 mmHg TP ≥ 30 mmHg SPP ≥ 30 mmHg	AP (50) Sens: 100% Spec: 20% PLR: 1.3 NLR: 0 TP Sens: 72% Spec: 100% PLR: Inf NLR: 0.28	AP (80) Sens: 80% Spec: 70% PLR: 2.7 NLR: 0.28 SPP Sens: 64% Spec: 90% PLR: 6.4 NLR: 0.40	Healed wounds after amputation were defined as healing as well, leading to an overestimation of prognostic performance. Small sample size

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Kalani 1999[44]	Sweden	Prospective observational study Follow-up: 12 months	N = 50 DFU Mean age: 61 years Gender: 74% male Mean duration of DM: 26 years 68% of patients were insulin dependent	Chronic foot ulcers of >2 months duration Average size 230 mm^2	Healed with intact skin or improved ulcer healing	$TcPO_2$ ≥25 mmHg TBP ≥ 30 mmHg and ≥ 45 mmHg	TBP (30) Sens: 15% Spec: 97% PLR: 5.0 NLR: 0.88 TBP (45) Sens: 46% Spec: 84% PLR: 2.9 NLR: 0.64	$TcPO_2$ Sens: 85% Spec: 92% PLR: 6.0 NLR: 0.09	Improved ulcer healing (change of 25% area reduction) after 12 months was still considered 'healed'. Small sample size.
Karanfilian 1986[45]	United States of America	Retrospective observational study Follow-up: maximum of 4 months	N = 37 diabetic patients Mean age: 57 years Gender: 100% male	Chronic foot ulcers, digital and transmetatarsal amputations were all included	Healing was defined as closed wound edges. If after 30 days there was no evidence of healthy granulation tissue, wound contraction, or a viable graft, the ulcer was classified as nonhealing.	$TcPO_2$ > 10 mmHg LDV > 40 mV AP > 30 mmHg	$TcPO_2$ Sens: 100% Spec: 83% PLR: 6.0 NLR: 0.0 LDV Sens: 88% Spec: 94% PLR: 14.9 NLR: 0.13	AP Sens: 65% Spec: 15% PLR: 0.8 NLR: 2.35	Very small sample size Chronic DFU and wounds after amputation were included in the same patient group
Kawai 2017[22]	China	Retrospective cohort study Follow-up: maximum of 10 months	N = 117 DFU (65 patients) Mean age: 70 years Gender: NS	No information about ulcer severity	Definition of healing not specifically mentioned	SPP > 43 mmHg	SPP Sens: 67% Spec: 94% PLR: 11.7 NLR: 0.35		Lack of information about patient inclusion and ulcer severity.
Ladurner 2010[32]	Germany	Prospective cohort study Follow-up: 1 year	N = 141 DFU Mean age: 72 years Gender: 62% male	No information about ulcer severity	Healing was defined as complete epithelization	$TcPO_2$ > 20 mmHg	$TcPO_2$ Sens: 76% Spec: 56% PLR: 1.7 NLR: 0.43		All patients were ineligible for revascularization. Healing after minor and major amputation is not shown here.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Lee 2019[48]	South-Korea	Retrospective observational study Follow-up time unclear	N = 263 DFU Mean age: 62 years Gender: 75% male At least diagnosed with DM for 5 years	Ulcers needed to be located at the forefoot area According to Texas Grade: - 1: 27% - 2: 5% - 3: 67% Average ulcer size was 7.5 cm^2 Average duration of ulcer was 10 weeks	Definition of healing not specifically mentioned	SHL > poor $TcPO_2$ > 40 mmHg	SHL Sens: 62% Spec: 54% PLR: 1.3 NLR: 0.72	$TcPO_2$ Sens: 47% Spec: 68% PLR: 1.5 NLR: 0.78	Only results without revascularization are shown here. Indication to perform major or minor amputation were regarded as non-healing.
Lee 2022[49]	South-Korea	Retrospective observational study Follow-up time unclear	N = 834 DFU Mean age: 62 years Gender: 74% male At least diagnosed with DM for 5 years	Ulcers needed to be located at the forefoot area According to Texas Grade: - 1: 31% - 2: 6% - 3: 63% Average ulcer size was 8.1 cm^2 Average duration of ulcer was 11 weeks	Definition of healing not specifically mentioned	SHL ≥ 21	SHL Sens: 72% Spec: 70% PLR: 2.4 NLR: 0.40		

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Leenstra 2020[33]	The Netherlands	Prospective observational study Follow-up: 12 months	N = 103 DFU Mean age: 70 years Gender: 70% male	Most ulcers were located at the toes The majority of wounds were classified as W1I0/1FI0	Healing was defined as fully healed ulcers and non-healing as ulcers that deteriorated under conservative treatment or that required surgical amputation	$TcPO_2$ > 43 mmHg	$TcPO_2$ Sens: 78% Spec: 56% PLR: 1.8 NLR: 0.39		Patients were excluded if they underwent revascularization or had any clinical signs of sepsis.
López-Moral 2022[34]	Spain	Prospective cohort study Follow-up: 12 months	N = 21 DFU Mean age: 69 years Gender: 81% male Mean duration of DM: 21 years	Average ulcer severity: SINBAD 4±1.09 Average wound area was 2.38 cm^2	Healing was defined as complete epithelization without any drainage confirmed for at least 10 days after closure	ABI > 0.52 TBI > 0.65 $TcPO_2$ > 28.5 mmHg	ABI Sens: 100% Spec: 75% PLR: 4.0 NLR: 0 $TcPO_2$ Sens: 91% Spec: 100% PLR: 0 NLR: 0.09	TBI Sens: 72% Spec: 100% PLR: 0 NLR: 0.28	14% of patients had revascularization during study follow-up Very small sample size
Manu 2021[41]	United Kingdom	Retrospective cohort study Follow-up: 12 months	N = 128 DFU Mean age: 62 years Gender: 79% male Mean duration of DM: 22 years	Most ulcers were located at the toes and sole Median SINBAD score: 3 Median WIfI score: 3	Healing was deducted from clinical notes Healed wounds after amputation were regarded healing as well	ABI ≥ 0.9 TBI ≥ 0.75	ABI (≥ 0.9) Sens: 83% Spec: 22% PLR: 1.1 NLR: 0.78	TBI (≥ 0.75) Sens: 26% Spec: 71% PLR: 0.9 NLR: 1.05	16% of patients were lost to follow-up / no complete data.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Mennes 2021[35]	The Netherlands	Prospective observational study Follow-up: 6 months	N = 53 DFU Mean age: 67 years Gender: 79% male Mean duration of DM: 57% > 10 years	70% of ulcers were UT-classifcation 0 or 1	Healing was defined as complete re-epithelialization and scored at 12 and 26 weeks	ABI > 0.89 TBI > 0.51 TP > 54 mmHg AP > 96 mmHg $TcPO_2$ > 30.5 mmHg	ABI Sens: 62% Spec: 63% PLR: 1.7 NLR: 0.61 AP Sens: 82% Spec: 44% PLR: 1.5 NLR: 0.40 $TcPO_2$ Sens: 85% Spec: 31% PLR: 1.2 NLR: 0.47	TBI Sens: 74% Spec: 50% PLR: 1.5 NLR: 0.53 TP Sens: 82% Spec: 44% PLR: 1.5 NLR: 0.40	Patients with revascularization procedures during follow-up were excluded. Patients with major amputation were excluded.
Nouvong 2009[36]	United States of America	Prospective observational study (blinded) Follow-up: 6 months	N = 73 DFU Mean age: 50 years Gender: 88% male Mean duration of DM: 13 years	Ulcer severity not specified	Healing was defined as complete re-epithelialization and no exudates	ABI > 0.90	ABI Sens: 90% Spec: 21% PLR: 1.1 NLR: 0.48		The treating physicians were blinded to the data. No criteria for wound size or duration were used to select patients.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Padberg 1996[23]	United States of America	Prospective observational study Follow-up time unclear	N = 129 DFU in CLTI patients N = 22 wounds in patients with chronic renal failure Demographic data not presented	Ulcer severity not specified DM 54% of ulcers healed CRF 50% of ulcers healed	Healing was defined as complete wound closure, with epithelialization of the wound surface or a healed suture line	**DM** ABI ~>0.5 $TcPO_2$ ~>20mmHg **CRF** ABI ~>1.1 $TcPO_2$ ~>25mmHg	**DM** ABI Sens: 81% Spec: 31% PLR: 1.2 NLR: 0.61 **CFR** ABI Sens: 46% Spec: 55% PLR: 1.0 NLR: 0.98	$TcPO_2$ Sens: 81% Spec: 81% PLR: 4.3 NLR: 0.23 $TcPO_2$ Sens: 73% Spec: 82% PLR: 4.1 NLR: 0.33	Cut-off values not clearly described. Only estimation on graph possible. Heel ulcers, limbs with uncontrolled foot infections, or those with an obvious neuropathic etiology were excluded.
Rajagopalan 2018[42]	India	Prospective observational study Follow-up: 6 months	N = 564 DFU Mean age: 58 years Gender: 67% male Mean duration of DM: 12 years	Only foot ulcers with Wagner Grade 2 or 3 were included 83% of ulcers healed with 42.6 mean healing days	Healing was defined as complete epithelialization of the ulcer or amputation stump	ABI ≥0.9 $TcPO_2$ >40 mmHg	ABI Sens: 90% Spec: 42% PLR: 1.53 NLR: 0.25	$TcPO_2$ Sens: 84% Spec: 44% PLR: 1.5 NLR: 0.36	Healing of amputation stump was regarded as primary healing as well. 5 patients who underwent revascularization procedures and 13 patients with a non-healing ulcer were excluded. Specificity of 97% was reported for ABI <0.9, however this result could not be reproduced based on available data. A specificity of 90% was calculated based on data provided in the article. Prevalence of PAD was low (18%).

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Thottiyen 2023[46]	India	Longitudinal observational study Follow-up: 3 months	N = 121 DFU Mean age: 65 years Gender: 74% male Chronic Kidney Disease was present in 21% of patients	The ulcer should be below the level of the ankle joint and belong to Wagner's grades 1 to 4 without palpable pulses of the dorsalis pedis and posterior tibial artery.	Healing was defined as complete epithelialization or healing changes such as granulation tissue	ABI >0.65 $TcPO_2$ >27.5 mmHg	ABI Sens: 86% Spec: 76% PLR: 3.6 NLR: 0.18	$TcPO_2$ Sens: 85% Spec: 82% PLR: 4.7 NLR: 0.18	A change in healing status was already defined as 'healing', possibly leading to an overestimation of diagnostic performance. Short follow-up time.
Vincente Jiménez 2015[24]	Spain	Prospective cohort Follow-up time unclear	N = 19 patients Mean age: Not provided Male: 72%	University of Texas classification 1c: 26.1%, n = 5 2c: 10.5%, n = 2 2d: 15.8%, n = 3 3c: 10.5%, n = 2 3d: 36.9%, n = 7 Healing rate: 53% Median time to healing: 103 days	Healing vs. non-healing	$TcPO_2$ ³ 35 mmHg (after revascularization) TcPO2 measured on dorsum of foot before and after revascularization	$TcPO_2$ Sens: 90.0% Spec: 88.9% PLR: 8.1 NLR: 0.11		Small population, mean age not provided, also not possible to calculate. No clear definition of healing. Also not specified if healing after minor amputation was considered healing.
Wallin 1989[43]	Sweden	Prospective cohort Follow-up time unclear	N = 83 Mean age: 70 years Male: 55.4% N = 68 diabetics	No wound classification provided	Major amputation: all amputations above the ankle Healing: Healing without major amputation (either after conservative treatment or minor foot operation including toe/ transmetatarsal amputations)	AP ³ 70 mmHg TP ³ 20 mmHg	AP Sens: 91.7% Spec: 73.3% PLR: 3.4 NLR: 0.1	TP Sens: 87.8% Spec: 78.6% PLR: 4.1 NLR: 0.2	Both primary healing and healing after minor operation are considered healing. Prognostic performance was calculated*.

Table S2. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance	Comments
Yang 2013[26]	China	Prospective cohort Follow-up time: average of 12 months	N = 61 Mean age and gender not reported for entire cohort	Wagner grading system Grade 2 n = 38 (62.2%) Grade 3 n = 8 (13.1%) Grade 4 n = 17 (27.9%)	Ulcers healed with intact skin Improved ulcers (reduction wound size ³ 50%) Unimproved or worsened ulcers	$TcPO_2$ ³ 25 mmHg	$TcPO_2$ Sens: 88.6% Spec: 82.4% PLR: 5.0 NLR: 0.14	

Abbreviations: ABI = ankle branchial index, AP = ankle pressure, APSV = ankle peak systolic velocity, CLI = Critical limb ischemia, DFU = diabetic foot ulcer, DM = diabetes mellitus, LDV = laser doppler velocimetry, PAD = podiatry ankle scan, PAOD = peripheral arterial occlusive disease, PLR = positive likelihood ratio, MAC = medial arterial calcification, NLR = negative likelihood ratio, sens = sensitivity, spec = specificity, SHL = skin hydration level, SPP = skin perfusion pressure, TBI = toe brachial index, TBP = toe blood pressure, TcPO2 = transcutaneous oxygen pressure, TP = toe pressure

* = Predictive capabilities were calculated based on numbers provided in the article. If no clear cut-off values were mentioned, we chose cut-off values based on

1) how clearly we could distinguish the necessary data from the figures or text and

2) the cut-off values commonly used in other articles.

Table S3: Overview of included studies regarding wound healing after minor amputation.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Gibbons 1979[50]	United States of America	Prospective observational study Follow-up time unclear	N = 66 diabetic patients needing forefoot amputation Mean age: 64 years Gender: 67% male Mean duration of DM: 19.5 years 55% of patients were insulin dependent	If clinical assessment indicated a reasonable chance of healing, amputation was performed	Healing of forefoot (toe, metatarsal head or transmetatarsal) amputation	AP ≥70 mmHg PVR (flat or slight)	AP Sens: 64% Spec: 33% PLR: 1.0 NLR: 1.09	PVR Sens: 91% Spec: 50% PLR: 1.8 NLR: 0.18	No description of initial wounds. No explanation on which patients were excluded. In three patients in the healed amputation group, no forefoot pulse volume recording was obtained because of the proximity of the ulcer.
Holstein 1984[51]	Denmark	Retrospective cohort study Follow-up: at least 7 years	N = 102 diabetic patients (109 diabetic feet) Mean age: 65 years Gender: 67% male	Out of the 109 diabetic feet, there were 102 with infection. In 40 feet, the infection was invasive in form of osteitis and/or plantar abscess.	Healing of digital and forefoot amputations Definition of healing not specifically mentioned	SDBP ≥ 30 mmHg (TP) SABP ≥50 mmHg (AP) SPFF ≥ 40 mmHg	SDBP Sens: 67% Spec: 50% PLR: 1.3 NLR: 0.66 SPFF Sens: 56% Spec: 54% PLR: 1.2 NLR: 0.81	SABP Sens: 100% Spec: 9% PLR: 1.1 NLR: 0.00	Subgroup analysis for DM was performed. Statistical analysis not clearly explained. Time and definition of healing was not mentioned.

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Larsson 1993[52]	Sweden	Prospective observational study Follow-up: 6 months	N = 159 DFU requiring amputation Mean age: 70 years Gender: 54% male Mean duration of DM: 18 years	Ulcer severity: 89% had Wagner grade ≥3	Healing was defined as intact skin (after minor amputation)	ABI ≥0.5 AP ≥ 75 mmHg TP ≥ 15 mmHg TBI ≥ 0.10	ABI Sens: 94% Spec: 53% PLR: 2.0 NLR: 0.12 TBI Sens: 96% Spec: 50% PLR: 1.9 NLR: 0.09	AP Sens: 91% Spec: 53% PLR: 2.0 NLR: 0.16 TP Sens: 94% Spec: 43% PLR: 1.7 NLR: 0.10	16% of patients had revascularization before amputation. Primary amputation level was below the ankle in 92 patients and above the ankle in 67 patients.
Mehta 1980[53]	United States of America	Prospective observational study Follow-up: maximum of 30 months	N = 44 DFU Mean age: 59 years Gender: 100% male	45/60 total amputations healed (77% in diabetics)	Definition of healing not specifically mentioned	AP > 60 mmHg	AP Sens: 12% Spec: 90% PLR: 1.2 NLR: 0.98		Diagnostic performance is calculated based on data from figure. Only subgroup analysis (DM) for healed amputation was displayed.
Vitti 1994[54]	United States	Retrospective cohort Follow-up time unclear	N = 136 men Mean age: 64.8 years old Male: 100% DM: n = 110 (81%)	Open wounds after surgery Primarily closed wounds after surgery	Non-healing was defined as incisional breakdown requiring reamputation or failure of secondary wound healing in open amputations.	TP ³ 38 mmHg in non-revascularized diabetics	TP Sens: 100% Spec: 56.8% PLR: 2.3 NLR: -		Cut-off value was not pre-specified but based on outcomes in population. Unclear in how many cases toe used for measurement was amputated. TP only measured pre-operative.

Table S3. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Welch 1985[55]	United Kingdom	Prospective cohort Follow-up time unclear	N = 50 minor foot/ transmetatarsal amputations Mean age: 61 years Male: 58% Diabetic: 68%, n = 34	No wound classification provided	Primary healing: Clean, dry, healed wound on day 14 post-operatively. Delayed healing: Requiring continued treatment without necessity for higher amputation level. Non-healing: Necessity to perform higher level amputation or revascularization	AP ³ 40 mmHg AP ³ 60 mmHg SBF ³ 12 ml $100g^{-1}$ min^{-1} SBF ³ 16 ml $100g^{-1}$ min^{-1}	AP (40) Sens: 88.0% Spec: 11.1% PLR: 1.0 NLR: 1.1 SBF (12) Sens: 54.5% Spec: 100% PLR: inf NLR: 0.5	AP (60) Sens: 80.0% Spec: 22.2% PLR: 1.0 NLR: 0.9 SBF (16) Sens: 27.3% Spec: 100% PLR: inf NLR: 0.7	PLR could not be calculated for SBF and the chosen cut-off values because there was no non-healing above the chosen cut-off value. Lower cut-off values could not be selected because necessary data could not reliably be distinguished from the figures. Small sample size. Prognostic performance was calculated*.

Table S3. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance	Comments
Wyss 1988[25]	United States	Prospective cohort Follow-up time unclear	N = 89 diabetics Mean age: 64 years Male: not provided 112 amputations → 26 foot amputations. Other amputations were major amputations.	Amputation wounds	Healing defined as wound closure with or without additional debridement irrespective of time necessary to heal. Failure defined as necessity of major surgical revision.	$TcPO_2$ ³ 31 mmHg	$TcPO_2$ Sens: 84.2% Spec: 85.7% PLR: 5.9 NLR: 0.2	Large population but only small sample fits criteria of this review (26 foot amputations which are either forefoot or Syme amputations) Definition of major surgical revision unclear. Many major confounders not assessed or reported. Prognostic performance was calculated*.

Table S3. Continued

Author & year (ref)	Country	Study design & setting	Population (n, age, gender, comorbidity)	Ulcer characteristics	Outcome definition	Point of care test	Prognostic performance		Comments
Zhang 2019[56]	China	Prospective cohort Mean follow-up 38 months.	N = 97 DFU Mean age: 67 years old Male: 62% Mean DM-duration: 13 years	No specific grading system regarding the DFU Overall 65% healing after median of 8 months (range 1 – 24 months)	Wound healing after transmetatarsal amputation defined as complete re-epithelialization of the wound	ABI > 0.4 ABI ³ 0.7 ABI > 0.9	ABI (0.4) Sens: 98.4% Spec: 23.6% PLR: 1.3 NLR: 0.07 ABI (0.9) Sens: 12.7% Spec: 100% PLR: inf NLR: 0.87	ABI (0.7) Sens: 81.0% Spec: 82.4% PLR: 4.6 NLR: 0.2	In the ABI > 0.9 group the PLR could not be calculated due to no patients with an ABI > 0.9 experiencing failure to heal of the wound. Prognostic performance was calculated*.

Abbreviations: ABI = ankle branchial index, AP = ankle pressure, DFU = diabetic foot ulcer, DM = diabetes mellitus, Inf = infinite, PLR = positive likelihood ratio, NLR = negative likelihood ratio, PVR = pulse volume recordings, SABP = systolic ankle pressure, SBF = skin blood flow, SDBP = systolic digital blood pressure, sens = sensitivity, spec = specificity, SPFF = skin perfusion pressure on the feet, TBI = toe brachial index, TcPO2 = transcutaneous oxygen pressure, TP = toe pressure
* = Predictive capabilities were calculated based on numbers provided in the article. If no clear cut-off values were mentioned, we chose cut-off values based on
1) how clearly we could distinguish the necessary data from the figures or text and
2) the cut-off values commonly used in other articles.