A systematic review and narrative synthesis of risk prediction tools used to estimate mortality, morbidity and other outcomes following major lower limb amputation

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What does this study/review add to the existing literature and how will it influence future clinical practice:

This systematic review and narrative synthesis has identified 13 risk prediction tools that provide objective predictions for several important outcomes following amputation. Most tools demonstrated at least acceptable discrimination for objectively predicting important post-operative outcomes. Nine tools predicted mortality outcomes, with fewer predicting morbidity, necessity for revision surgery and successful ambulation outcomes. Despite their promising performance, the majority of risk prediction tools lack adequate external validation. We therefore cannot recommend the implementation of the majority of these tools into clinical practice without additional robust external validation to support their clinical utility.

Abstract

Objectives: The decision to undertake a major lower limb amputation can be complex. This review evaluates the performance of risk prediction tools for estimating mortality, morbidity and other outcomes following amputation.

Methods: A systematic review was performed following PRISMA guidelines. MEDLINE, Embase and Cochrane databases were searched to identify studies reporting on risk prediction tools that predict outcomes following amputation. Outcome measures included the accuracy of risk tools in predicting a range of post-operative complications, including; mortality (both short-term and long-term), perioperative morbidity, need for re-amputation and ambulation success. A narrative synthesis was performed in accordance with the Guidance on the Conduct of Narrative Synthesis In Systematic Reviews.

Results: The search identified 518 database records. 12 observational studies, evaluating 13 risk prediction tools in a total cohort of 61 099 amputations, were included. One study performed external validation of an existing risk prediction tool whilst all other studies developed novel tools or modified pre-existing generic calculators. Two studies conducted external validation of the novel/modified tools. Nine tools provided risk estimations for mortality, two tools provided predictions for postoperative morbidity, two for likelihood of ambulation, and one for re-amputation to the same or higher level. Most mortality prediction tools demonstrated acceptable discrimination performance with C-statistic values ranging from 0.65 – 0.81. Tools estimating the risk of post-operative complications (0.65 – 0.74) and necessity for re-amputation (0.72) also performed acceptably. The BLARt (Blatchford Allman Russell tool) demonstrated outstanding discrimination for predicting functional mobility outcomes post-amputation (0.94). Overall, most studies were at high risk of bias with poor external validity.

Conclusions: This review has identified several risk prediction tools that demonstrate

acceptable to outstanding discrimination for objectively predicting an array of important postoperative outcomes. However, methodological quality of some studies were poor, external validation studies are generally lacking, and there are no tools predicting other important outcomes, especially quality of life.

Introduction

Deciding whether major lower limb amputation is the best option for a patient with end-stage chronic limb threatening ischaemia (CLTI), or diabetic foot disease, can be complex. These patients often face a challenging decision between further attempts at revascularization and limb salvage, definitive amputation, ongoing wound care only, or palliation. Amputation is associated with morbidity and mortality rates of up to 50% at one-year following amputation [1,2]. The appropriate level of amputation also needs to be considered by clinicians to provide the correct balance between chance of wound healing and successful ambulation.

Previous studies have highlighted that clinician understanding of factors that lead to adverse outcomes following amputation, such as mortality, is lacking [1,2]. Poor decision making around amputation can dramatically reduce quality of life (QoL), and also prove to be very costly to healthcare providers [3,4]. Key interventions, such as high-quality palliative care, have been shown to have been under-utilized in amputees despite good evidence for its benefit [5,6].

Modern clinical management should involve shared decision making between the multidisciplinary clinical team and the patient with their family or carers [7]. An important component of shared decision making involves providing patients with predictions regarding likely outcomes. Risk predictions regarding mortality, need for revision surgery, chances of successful ambulation with a prosthesis and overall QoL, are generally estimated by the healthcare professional based on their experience and intuition (‘gestalt’) [8]. However, a recent systematic review revealed that whilst, in general, surgeons are good at predicting short term perioperative risk, they are poor at predicting long term outcomes [8]. This review found no specific studies addressing the accuracy of surgeon gestalt for predicting postoperative outcomes following amputation. Objective risk prediction calculators have been shown to frequently perform better than surgeon's gestalt, which is subject to many biases that can affect risk prediction accuracy [8]. Despite this, risk prediction calculators are rarely used in daily vascular surgical clinical practice before performing amputation.

The aim, therefore, of this systematic review was to identify and evaluate the performance of risk prediction tools for estimating outcomes following major lower limb amputation.

Methods

Search strategy

This systematic review was undertaken, and is reported, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9,10]. The review was registered with PROSPERO (CRD42020166399). Publications which reported on risk prediction tools to estimate outcomes post-amputation were identified. Risk prediction tools were defined as: "a scoring system or model used to predict an outcome after surgery, and which contains at least two different risk factors". Amputation was defined as any major amputation occurring above the ankle joint, including; transtibial (TT), through knee amputation (TKA), transfemoral (TF) and hip disarticulation. The following databases were searched: Ovid, Ovid MEDLINE, MEDLINE (via PubMed), Embase, the Cochrane Library Database, and the Cochrane Collaboration Central Register of Controlled Clinical Trials, and PubMed without restrictions on date, language or publication type, with the last search date as 5th March 2020.

The search term used was (Amputation [MeSH terms] AND (tool* OR scor*) AND (risk* OR predict* OR stratif*) AND (mortality OR morbidity OR ambulat* OR outcome* OR healing OR reamputation*).

The search was complemented by an exhaustive review of the bibliography in included articles and also by using the 'related articles' function in PubMed of the included papers. Articles that cited included publications were also reviewed.

Inclusion and exclusion criteria

All studies of patients undergoing an amputation in which a risk prediction tool was used in the preoperative, or immediate post-operative (within 90 days) period to estimate the probability of post-operative outcome(s) were included. This would encompass both development and validation studies. Studies which included patients undergoing amputation for CLTI, diabetes and or/trauma, via emergency or elective surgery were included. Full papers and abstracts in English were included. Non-English papers were only included if they had an English abstract with extractable data.

Papers describing the risk assessment of theoretical cases or patient vignettes were excluded, as were studies in which there were insufficient data on patient outcome(s). Any single or multiple variable studies presented as 'generalised risk factors' without presentation of a scoring system were also excluded.

Data extraction and assessment of study quality

For each stage of the review, two of the three authors (RAP, ND, CAW) performed each step independently, and compared results. These stages included: literature search, data extraction and methodological quality assessment. Any disagreements between the first two reviewers were resolved by the senior author (DCB).

The following baseline data were extracted for each study: first author, year of publication, geographical location, study design and type (single or multiple centres, number of surgeons involved, whether consecutive patients were enrolled, whether patients were selected randomly), data collection period, sample size, study population (age, sex, current illness leading to amputation [CLTI/diabetes/trauma/cancer/congenital/other]), type of enrolled patients (first amputation only vs. previous amputees included), and any other key inclusion/exclusion criteria of the study. Further data collected included details pertaining to the risk prediction tool, i.e. timing of tool use (pre-amputation vs. post-amputation), and the components of the risk prediction tool (variables used to estimate risk).

The discriminatory ability of the various tools was quantified using the concordance (C-statistic) value which is equivalent to the area under the receiver operator curve (AUROC). The C-statistic represents the probability that a prediction tool will predict a higher risk for a randomly selected individual who experiences an outcome of interest than another randomly selected individual who does not [11]. It thereby measures the concordance between observed events and tool-based risk predictions. Threshold values for tool discrimination have previously been defined as; $C \geq 0{\cdot}9$ indicating outstanding discrimination, $0{\cdot}8 \leq C < 0{\cdot}9$ as excellent discrimination, $0{\cdot}7 \leq C < 0.8$ as acceptable discrimination, $0.5 \leq C < 0.7$ as poor discrimination and $C < 0{\cdot}5$ indicating no discriminatory performance [11].

The study quality was assessed using PROBAST (Prediction model study Risk Of Bias Assessment Tool) which was utilized to assess the risk of bias and the applicability/generalizability of the prediction model studies. PROBAST assesses for bias arising from the study participants, risk predictors, outcomes and the analysis [12,13].

Outcome measures

A list of potential outcome measures of particular interest was drafted before undertaking the review. These included: postoperative mortality (both short-term i.e. < 30 days and long-term i.e. ≥ 30 days), postoperative morbidity/complications (usually defined as within 30 days of surgery), wound healing, need for revision surgery and/or re-amputation, ambulation with a prosthesis (which would include both the likelihood of achieving ambulation, and the time to achieving ambulation), overall mobility (i.e. mobility with frame, wheelchair etc.), and QoL. Outcomes reported in at least one study were collected herein.

Narrative Synthesis

Meta-analysis was deemed not appropriate given the significant heterogeneity within the included patient populations, method of risk prediction tool assessment and outcomes assessed. Therefore, a narrative synthesis was conducted according to the Guidance on the Conduct of Narrative Synthesis In Systematic Reviews [14]. Two authors (RAP, CAW) systematically summarized key aspects of each study's methodology and results. The senior author (DCB) then identified and grouped common themes based on outcomes.

Results

A total of 518 articles were identified from the initial search. Figure 1 details a flow diagram demonstrating article exclusions. 12 studies, comprised 61 099 amputations, met the inclusion criteria, all of which were observational cohort studies [15-26]. These 12 studies described 13 risk prediction tools, the details of which (including the variables used in the calculation of each tool) are presented in Supplementary Table 1. Study baseline demographic data is detailed in Table 1. Most studies analysed patients undergoing amputation for CLTI or diabetes. Four studies included patients only undergoing their first amputation [15,18,22,26] and three studies included patients who had undergone revision amputation (see Table 1) [16,21,23]. No specific data was reported in any of the studies regarding the number of patients who had undergone prior amputation of the contralateral leg.

Study design

Only one study solely performed external validation of an existing risk prediction tool without novel tool development [15]. The eleven remaining studies all developed novel tools or modified pre-existing ones. Two of these studies solely developed new tools without performing separate validation analyses [16,17]. Five studies conducted internal validation of their new/modified tools [18-22]. Two studies developed new tools and simultaneously undertook external validation of pre-existing tools [23,24]. The two remaining studies were the only ones to develop a new tool and conduct external validation [25,26]. All but two studies were published in the past ten years and, therefore, given the small number of studies, no attempt was made to try and compare tools developed at different times.

Risk of bias

Table 2 details risk of bias and concerns regarding study applicability as assessed by the PROBAST tool. Overall, the largely retrospective methodology employed in many included studies meant that most were at high risk of bias. The use of certain large national data sets (such as the Veterans Affair database) limited applicability of study results to the wider CLTI patient population given the extremely low proportion of female participants included (see Table 1) [16,18,21,22,26].

Outcome data

Nine tools provided risk estimations for mortality [15,16,17,19-21,23,24,26], two tools provided predictions for postoperative morbidity [15,23] two for ambulation [22,25], and one for re-amputation to the same or higher level (i.e. TT to TF) [18]. No tools were identified to predict QoL or wound healing. Table 3 details the performance of the risk calculation tools in predicting outcomes. All but one [15] risk prediction tool could be applied in the preoperative period; the Surgical Apgar Score, however, used to predict 30-day major complications and death post-amputation, relies on intra-operative variables and therefore cannot be used to inform pre-operative shared decision-making discussions [15].

Mortality prediction tools

Nine tools, examining 55 102 amputations, evaluated mortality outcomes [15-17,19-21,23,24,26]. Eight tools provided short-term perioperative mortality risk predictions (30 days or in-hospital) [15,16,17,19-21,23,24], with only one study predicting one-year outcomes [26]. Most mortality prediction tools demonstrated acceptable discrimination performance with C-statistic values ranging from 0.65 [15] – 0.81 [16,20]. There was no mortality prediction tool with standout performance and overall, five tools of relatively similar methodological quality performed best with C-statistic values ranging 0.75 – 0.81 [16,20,23,24,26]. Three of these tools demonstrated excellent discrimination with C-statistic ≥0.80 [16,20,24]. Six tools provided percentage risk predictions of mortality [19-21,23,24,26], with the remaining three tools categorizing their predictions (either I-IV risk groups or low / moderate / high / very high risk) [15,16,21]. Two studies only included patients undergoing their first amputation [15, 26] and one excluded patients undergoing emergency amputations [21].

Morbidity prediction tools

Two tools (9529 amputations) looked at predicting post-operative morbidity after amputation [15,23]. Ambler et al demonstrated acceptable discriminatory performance of their tool to predict in-hospital cardiac and renal complications post-amputation (C-statistic 0.74 for both) but borderline poor discrimination for respiratory complications (C-statistic 0.69) [23]. External validation of the Surgical Apgar Score to predict 30-day major post-operative complications demonstrated it to have poor overall discriminatory performance with C-statistic 0.65 (95% confidence interval [CI] 0.56-0.73) [15]. However, its discrimination performance was better for TF with C-statistic 0.71 (95% CI: 0.61-0.81) as opposed to TT; 0.47 (95% CI: 0.38-0.67) [15].

Post-operative ambulation prediction tools

Two tools (737 amputations) looked at predicting successful ambulation rates after amputation [22,25]. The best performing tool was the BLARt for predicting ability to walk with a prosthesis 12 months post-amputation [25]. This tool (designed to be used pre-operatively) was developed from a cohort of amputees that had been referred for prosthetic rehabilitation. Nonfunctional mobility outcomes were defined as patients who had died or had a Special Interest Group in Amputee Medicine (SIGAM) grade A/B (non-prosthesis user or only using it to transfer). Poor functional outcomes were classed as SIGAM grade less than grade D (impaired walking of up to 50m or more with a walking aid) [25]. The tool demonstrated outstanding discrimination in identifying both poor (0.94) and non-functional outcomes (0.91) [25]. It should, however, be noted that this study included patients with a broad range of mobility capabilities that were referred for prosthetic rehabilitation, which will have inflated its C-statistic in contrast to other tools which do not filter patients in this way [27].

The AMPREDICT-Mobility tool predicts patient performance at independently performing a series of basic (iBASIC) or advanced (iADVANCED) mobility tasks (as previously defined by the Locomotor Capabilities Index 5-level (LCI-5) scale [28]) 12 months post-amputation [22]. It incorporates medical factors along with social and psychological factors (e.g. marital status and education level) and provides clinicians with a preoperative probability of achieving independent mobility tasks for various amputation levels. During internal validation, the tools optimism-adjusted C statistic for iBASIC and iADVANCED mobility was 0.74 and 0.71, respectively (raw C statistic values were 0.85 and 0.82, respectively).

Re-amputation prediction tools

One tool, examining 5260 amputations, predicted reamputation rates within 12 months for patients undergoing their first unilateral amputation [18]. 1283 required ipsilateral reamputation to the same or higher level within one year and the risk prediction tool demonstrated acceptable discrimination with C-statistic 0.72.

Discussion

This is the first systematic review to report on the existence and performance of risk prediction tools for patients undergoing amputation. 13 tools, from 12 studies, were identified that demonstrated acceptable to outstanding discrimination for predicting various important post-operative outcomes. However, most studies were at high risk of bias, just under half were judged not to be not widely applicable, and few tools have been externally validated. Furthermore, whilst there are many 30-day and in-hospital mortality risk tools, other important outcomes, such as 1-year mortality, ambulation and re-amputation, are poorly studied, and there were no tools identified that predicted other important outcomes like wound healing or QoL after amputation.

Several of the risk prediction tools demonstrated acceptable discrimination for predicting perioperative 30-day mortality [16,20,23,24] and major complications [23]. With C-statistic values ranging 0.75-0.80, these tools could provide clinicians with useful perioperative decision aids. For the longer-term outcomes, such as reamputation [18] and mobility [22,25], prediction tool discrimination performance was also at least acceptable. Indeed, the BLARt was the best performing tool with outstanding discrimination for predicting poor mobility outcomes [25]. However, the BLARt tool study only included a cohort of amputees that had been referred for prosthetic rehabilitation and the study also received support from the commercial Blatchford Group which may have introduced bias. Nevertheless, the encouraging performance of these tools for predicting long-term functional outcomes is interesting, especially given that surgeons have been shown to typically be poor at predicting these type of outcomes [8].

Amputation is a life changing event and poor decision making can impact the QoL for both patients and their families [3]. The James Lind Alliance Priority Setting Partnership for Vascular Surgery's interim clinician-led Delphi process has identified amputation surgery as one of the key areas lacking good-quality evidence to guide decision making at present [29]. Patients at high risk for dying in the early post-operative period may prefer a palliative approach. Those at high risk of one-year mortality may put more emphasis on achieving wound healing and not needing to undergo additional amputation procedures rather than attaining functional mobility in their remaining life years, whilst balancing the benefits a longer residual limb can provide. Understanding the risks and benefits of the potential amputation levels on other key outcomes such as chance of requiring further amputations or achieving meaningful functional mobility will aid in the shared decision process as the patient can weigh these risks against their individual values and priorities.

In order to facilitate shared decision making, surgeons and other healthcare professionals should provide estimates of likely outcomes with different treatment options. However, this process is heavily dependent upon the surgeon's subjective predictions for the risk of various post-operative outcomes such as mortality, ambulation and QoL. Indeed, amputation decision making differs considerably between vascular surgeons given the same clinical vignettes [30]. Given the importance of risk prediction, it is interesting that a recent systematic review has shown that whilst surgeons are good at predicting short term perioperative risks, they are poor at predicting long term outcomes and are often outperformed by risk prediction tools [8]. These tools are not susceptible to the various clinical biases that affect routine clinical decision making and remove a degree of subjectivity from the process [8]. Prediction models provide the evidence base for clinical decision support tools which play an important role in complex clinical decision making by presenting personalized outcomes at the point of care during physician/patient shared decision-making encounters.

Whilst these tools will never completely replace clinical decision making, there is a growing appreciation for the use of risk prediction calculators within surgery. For example, following the results of the National Emergency Laparotomy Audit (NELA), all patients undergoing emergency laparotomies in the United Kingdom (UK) should have their preoperative mortality risk calculated by the NELA RISK calculator and subsequently be admitted to critical care post-operatively if their risk of death is ≥5% to increase their chance of survival [31]. The use of such tools within vascular surgery, and particularly amputation surgery, is less commonplace.

The findings of this review are limited by the high risk of bias and significant heterogeneity amongst the included studies, in addition to the general lack of external validation. Whilst mainly including patients undergoing amputation for diabetes and CLTI, a small proportion of studies included patients undergoing amputation for trauma, congenital and neoplastic causes. These are likely to represent a different population of patients with perhaps more focus on other pertinent issues such as risk of cancer recurrence (which, of note, no tools examine). We included these studies as they were often a small proportion of patients in larger diabetic/CLTI study groups and we did not want to exclude any prediction tools in this initial review on the topic. However, attempting to apply risk prediction tools to such heterogenous cohorts may have limited their performance and it may be pertinent for future work to focus tools on specific cohorts of patients. This work does, however, emphasize the comparative absence of predictive tools in the group of patients undergoing amputation for trauma, congenital and neoplastic causes. Finally, outcome definition and statistical analysis varied between studies with poor reporting of other useful analyses (such as predictive values, sensitivity/specificity etc.).

Ensuring prediction tools are externally validated is of utmost priority prior to implementation into surgical practice. External validation can be performed in multiple ways, but is most commonly performed through prospective studies or retrospective analysis of 'big' datasets [32]. It can also be conducted either temporally (in the same population/region during a different time period) or geographically (in another population geographically removed). However, only two of the novel tools identified in this review had undergone external validation [25,26], thus limiting the generalizability of these tools currently. The lack of external validation is a common problem with risk prediction tool development research [32]. It likely stems from the limited number of outcome events that occur within a data set, hence leaving researchers using all their data for model development rather than validation [31]. Several mortality prediction tools for amputation are non-validated which invariably limits acceptance of their use in routine clinical practice. Furthermore, five of the studies included herein developed their models from Veterans' Affairs databases, which includes tiny numbers of female patients, hence severely limiting the generalizability of their tools in the absence of external validation [16,18,21,22,26]. It will be important for clinicians to consider whether the cohorts included in future external validation studies are applicable to their local patient populations.

The VERN (Vascular and Endovascular Research Network) trainee research collaborative has recently launched the PERCEIVE study (PrEdiction of Risk and Communication of outcome following major lower limb amputation a collaboratIVE study) [33]. This international study is aiming to determine the accuracy of postoperative outcome predictions following amputation made by both a range of healthcare professionals (surgeons, anaesthetists and physiotherapists) and also by risk prediction tools. It is hoped this study will provide important external validation data for the use of these tools, and also quantify how good healthcare gestalt is when considering amputation.

The use of large datasets (often retrospective) such as the Veterans' Affairs databases to develop risk prediction tools means that many of the included studies were susceptible to various types of bias, including misclassification bias (when a value mistakenly placed into an incorrect category) and confounding bias (influence of extra unaccounted factors on associations).

There is a noticeable predilection within the literature to develop mortality predicting tools which likely stems from the ease of measuring this outcome from databases. Only one tool estimated necessity for revision surgery [18] and just two for chances of postoperative morbidity [15,23] or successful ambulation [22,25]. Whilst mortality is an important outcome following amputation, QoL and its inherent link to functional independence are arguably equally important to patients and their families. Patients often report a desire to have more of an active role in decisions regarding amputation [3]. Therefore, incorporating calculator estimates for these functional outcomes within the shared decision model may enhance patient experience and empower patients to make better choices. The AMPREDICT team have developed a coherent set of three calculators estimating mortality [26], re-amputation [18] and ambulation [22] following amputation. Whilst still requiring further external validation work, the prospect of having all three calculators within one simple user-friendly application that clinicians can conveniently calculate prior to consultations is an attractive prospect [22].

This review mainly focused on comparing the C-statistic for identified tools. It is important to mention that this only measures one domain of prediction model performance and is associated with its own limitations. The C-statistic does not measure tool calibration and, therefore, does not determine how accurately the overall magnitude of risk is predicted [27]. Other important variable such as tool predictive values, sensitivity and specificity were poorly reported amongst the identified studies.

None of the studies included in this review conducted separate risk prediction analyses based upon indication for amputation and this may be interesting work to undertake in future studies given the risks for a dysvascular amputation are likely to be very different to a traumatic amputation. Furthermore, no studies compared the accuracy of predictions made in the pre- versus post-operative period. Previous work on non-amputation surgery suggests that post-operative predictions are generally more accurate [8]. When appropriately validated risk prediction tools are available (be that based on either pre- or post-operative patient variables), providing patients with an awareness of estimates regarding specific post-operative outcomes will further empower them in the shared decision-making process to be considered along with their own individualized preferences. As mentioned previously, the PERCEIVE study [33] will compare the pre-operative predictions made by a range of healthcare professionals involved in amputation surgery (surgeons, anaesthetists and physiotherapists) and will compare these predictions to those made by several risk prediction tools.

Conclusion

This systematic review has identified several risk prediction tools for estimating outcomes following amputation. 13 tools were identified that demonstrated acceptable to outstanding discrimination for predicting important post-operative outcomes including mortality, necessity for revision surgery and successful ambulation. Despite these tools showing promising performance, their methodological quality was generally weak and there is a significant lack of external validation studies assessing these existing tools which urgently needs addressing with prospective studies. Therefore, we cannot currently recommend the implementation of these tools into routine clinical practice outside of a research capacity. Additionally, further efforts need to be invested into delivering the calculations through convenient user-friendly platforms.

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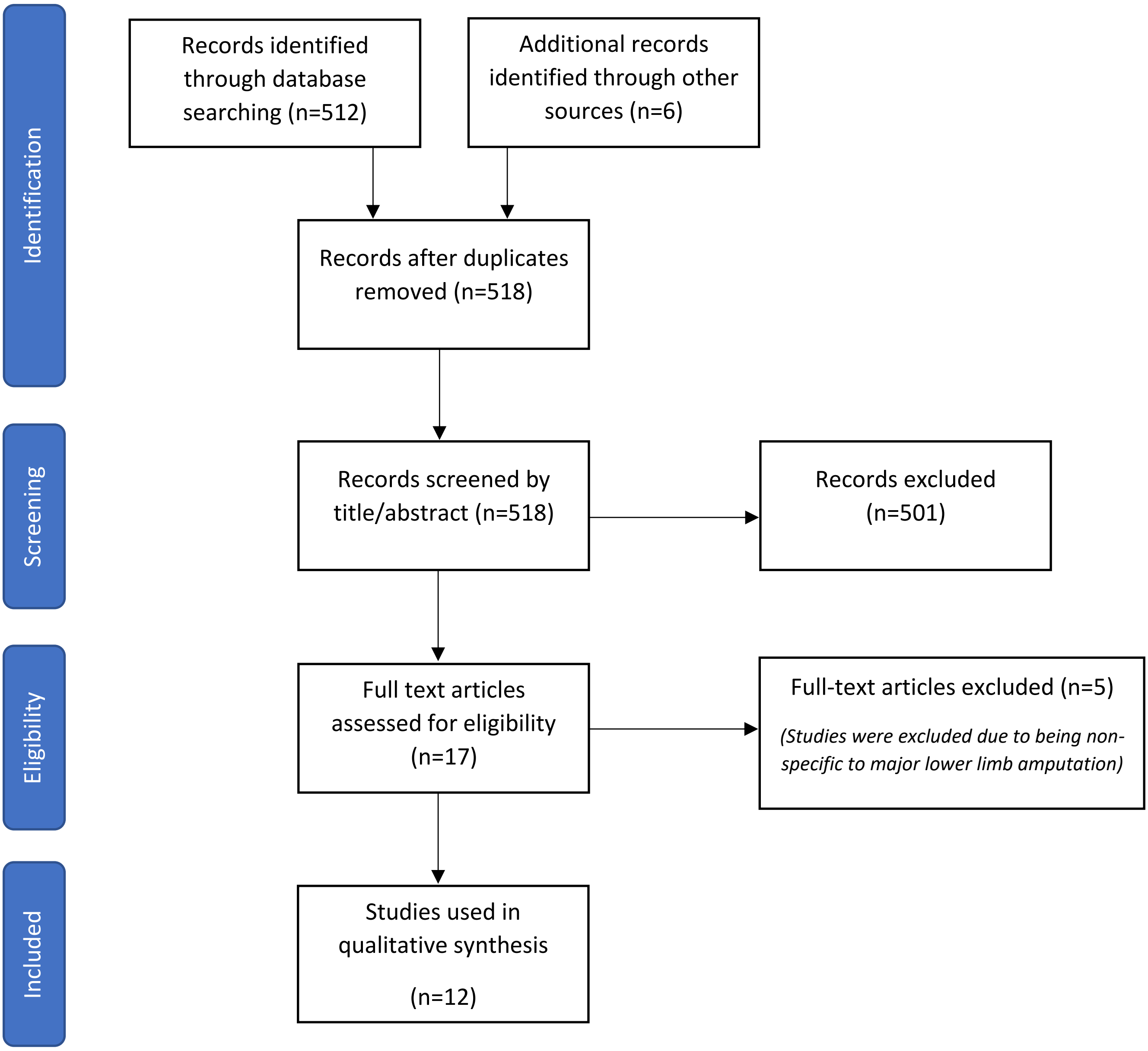

Figure 1. Flow diagram detailing lower limb amputation outcome risk prediction tool study inclusion and exclusion

Table 1. Lower limb amputation risk prediction tool study demographic details

Study	Tool used	Study design (1 Retrospective observational, 2 Prospective observational)	Centres	Sample size	Mean Age	Gender (Male:Female)	Amputation aetiology (1 PVD, 2 DM, 3 Trauma, 4 Cancer, 5 Congenital)	Amputation history (1 first amputation only, 2 amputation revision also, 3 not detailed)	Outcomes predicted (1 mortality, 2 morbidity, 3 ambulation, 4 amputation revision)
Feinglass (2001) [16]	Novel tool (un-named)	1	Multiple	4061	67.8	4061:0	1, 2	2	1
Tang (2009) [19]	Novel modified 'VBHOM'	2	Multiple	538	75	309:229	1	3	1
Nelson (2012) [20]	Novel tool (un-named)	1	Multiple	9368 (development), 1373 (validation)	TF 70.5 TT 65.0	TF 2226:1806, TT 3527:1809	1, 2, 3, 4	3	1
Patterson (2012) [24]	VBHOM and a novel modified VBHOM	1	Single	306	78	184:122	1	3	1
Easterlin (2013) [17]	Novel tool (un-named)	1	Multiple	9244	66	6102:3142	1	3	1
Wied (2016) [15]	Surgical Apgar Score	1	Single	170	74	96:74	1, 2	1	2
Czerniecki (2017) [22]	Novel 'AMPREDICT-Mobility'	2	Multiple	200	62.9	192:8	1, 2	1	3
Norvell (2019) [26]	Novel 'AMPREDICT-Mortality'	1	Multiple	5028 (development), 2140 (validation)	68	7103:65	1, 2	1	1

Jolissaint (2019) [21]	Novel tool (un-named)	1	Multiple	9890 (Derivation set) 5000 (validation set)	66.6	9783:107 (derivation set) 4957:43 (validation set)	1, 2	2	1
Czerniecki (2019) [18]	Novel 'AMPREDICT-Reamputation'	1	Multiple	5260 (including 1283 reamputations)	65.8	3937:40	1, 2	1	4
Bowrey (2019) [25]	Novel 'BLARt' score	1 (with prospective validation)	Multiple	338 in tool development 199 in tool validation	TF 69.5 TT 65	TF 109:43 TT 144:42	1, 2, 3, 4, 5	3	3
Ambler (2020) [23]	Novel 'UKAmpRisk'	1	Multiple	9549	70	6729:2820	1, 2, 3	2	1, 2

TF = Transfemoral, TT = Transtibial, VBHOM = Vascular Biochemistry and Haematology Outcome Models, BLARt = Blatchford Allman Russell tool

Table 2. Prediction model risk of bias assessment tool (PROBAST) detailing risk of bias and concern regarding study applicability of included studies examining outcomes following lower limb amputation

Study	Risk of Bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of Bias	Applicability
Feinglass (2001) [16]	-	-	-	-	-	+	+	-	-
Tang (2009) [19]	+	+	+	-	+	+	+	-	+
Nelson (2012) [20]	+	+	+	-	+	+	+	-	+
Patterson (2012) [24]	+	+	+	-	+	+	+	-	+
Easterlin (2013) [17]	+	+	+	-	+	+	+	-	+
Wied (2016) [15]	+	+	+	-	+	+	+	-	+
Czerniecki (2017) [22]	+	-	+	-	-	-	+	-	-
Norvell (2019) [26]	+	+	+	-	-	+	+	-	-
Jolissaint (2019) [21]	+	+	+	-	-	+	+	-	-
Czerniecki (2019) [18]	-	-	+	-	-	+	+	-	-
Bowrey (2019) [25]	+	+	+	-	+	+	+	-	+
Ambler (2020) [23]	+	-	-	+	+	+	+	-	+

+ indicates low risk of bias/concern regarding applicability
- indicates high risk of bias/concern regarding applicability

Table 3. Discriminatory performance of outcome risk prediction calculators for patients undergoing lower limb amputation			
Outcome	**Study**	**Outcome timing**	**C-statistic value (95% CI)**
Mortality	Wied (2016) [15]	30 days	Overall: 0.65 (0.56-0.73) TF: 0.71 (0.61-0.81) TT: 0.47 (0.38-0.67)
	Nelson (2012) [20]	30 days	TF: Derivation sample – 0.78 Validation sample - 0.75 TT: Development sample – 0.80 Validation sample - 0.81
	Jolissaint (2019) [21]	30 days	Development sample – 0.74 Validation sample - 0.74
	Easterlin (2013) [17]	30 days	0.74
	Feinglass (2001) [16]	30 days	TF: 0.79 TT: 0.81
	Ambler (2020) [23]	In hospital	0.79 (0.77-0.80) External validation of other tools: VBHOM - 0.59 (0.56-0.61) VBHOM2 - 0.65 (0.63-0.67) VAM - 0.68 (0.66-0.70) NSQIP - 0.65 (0.64-0.68)
	Tang (2009) [19]	In-hospital or ≤30 day	Derivation sample - 0.70 Validation sample - 0.68
	Patterson (2012) [24]	In-hospital or ≤30 day	VBHOM: 0.67 Modified VBHOM: 0.80
	Norvell (2019) [26]	1 year	Derivation sample - 0.77 Validation sample - 0.76
Major complication	Wied (2016) [15]	30 days	Overall: 0.65 (0.56-0.73) TF: 0.71 (0.61-0.81) TT: 0.47 (0.38-0.67)
	Ambler (2020) [23]	In hospital	Cardiac complications – 0.74, Respiratory complications – 0.69 Renal complications - 0.74
Reamputation	Czerniecki (2019) [18]	1 year	0.72
Ambulation	Bowrey (2019) [25]	1 year	Non-functional outcome - 0.91 (0.87-0.95) Poor functional outcome - 0.94 (0.91-0.97)
	Czerniecki (2017) [22]	1 year	iBASIC mobility – 0.74* iADVANCED mobility - 0.71*

Supplementary Table 1. Risk prediction calculators and factors involved in risk prediction following lower limb amputation

Study	Tool used	Outcomes predicted	Predictors included in risk tool
Feinglass (2001) [16]	Novel tool (un-named)	30-day Mortality	TT 30-day mortality: *Comorbidities:* Current smoker, Dyspneoa at rest, Totally dependent functional health status, COPD, Previous revascularization/amputation, Gangrene, Hepatomegaly, HTN (requiring treatment), Dialysis, CVA with no neurological deficit, Impaired sensorium, Disseminated cancer, ASA IV or V *Investigations:* Albumin TF 30-day mortality: *Demographics:* Age, DNR status, Emergency operation *Comorbidities:* Current pneumonia, Ventilator dependent, HTN (requiring treatment), Disseminated cancer, ASA IV *Investigations:* Bilirubin, K, Urea, WCC
Tang (2009) [19]	Novel modified 'VBHOM'	30-day Mortality	*Demographics:* Age, gender, mode of admission *Investigations:* Hb, WCC, Urea, Creatinine, Na, K
Nelson (2012) [20]	Novel tool (un-named)	30-day Mortality	*Demographics:* Age *Comorbidities:* Dependent functional status, dialysis, steroid use, preoperative sepsis, impaired sensorium (confusion/delirium), DNR status *Investigations:* Thrombocytopenia, increased INR, and azotemia
Patterson (2012) [24]	VBHOM and a novel modified VBHOM	30-day Mortality	*Demographics:* Age *Investigations:* Na, K, creatinine, albumin
Easterlin (2013) [17]	Novel tool (un-named)	30-day Mortality	*Demographics:* Age *Comorbidites:* CHF, COPD, major cardiac surgery, steroid use, dependent functional status, dyspnea, dialysis, impaired sensorium, preoperative sepsis
Wied (2016) [15]	Surgical Apgar Score	30-day Mortality & Major Morbidity	*Operative factors:* Estimated blood loss, intraoperative lowest mean arterial pressure, intraoperative lowest heart rate
Czerniecki (2017) [22]	Novel 'AMPREDICT-Mobility'	One-year ambulation	*Demographics:* Age, BMI, race, married/partnered *Comorbidities:* DM, dialysis, COPD, treatment for anxiety/depression, self-rated health *Operative factors:* Amputation level
Norvell (2019) [26]	Novel 'AMPREDICT-Mortality'	One-year Mortality	*Demographics:* Age, BMI, race *Comorbidities:* Functional status, CHF, dialysis *Investigations:* Urea, WCC and platelet count *Operative factors:* Amputation level

Jolissaint (2019) [21]	Novel tool (un-named)	30-day Mortality	*Demographics:* Age, DNR status *Comorbidities:* CKD, COPD, CHF, CAD, dependent living status *Operative factors:* Amputation level (TF)
Czerniecki (2019) [18]	Novel 'AMPREDICT-Reamputation'	One-year reamputation rates	*Demographics:* Sex *Comorbidites:* Current smoker, Alcohol abuse, Rest pain/gangrene, Anticoagulant therapy, DM, COPD, CKD, Previous revascularization *Investigations:* WCC *Operative Factors:* Amputation level
Bowrey (2019) [25]	Novel 'BLARt' score	One-year ambulation	*Demographics:* Age, Gender, BMI *Comorbidities:* Cause of amputations (Trauma, congenital, orthopaedic, cancer, vascular), Cognitive capacity, Pre-amputation mobility, Severe respiratory disease, Dialysis, CVA/neurological disease, Recent MI/Angina, Contralateral Limb Problem Operative Factors: Amputation level
Ambler (2020) [23]	Novel 'UKAmpRisk'	In-hospital Mortality & Major Morbidity	*Demographics:* Age, Emergency admission, Weight *Comorbidites:* Abnormal ECG, Albumin, ASA grade *Investigations:* Creatinine, WCC, Previous Ipsilateral Intervention *Operative factors:* Bilateral/Unilateral operation, amputation level

* VBHOM = Vascular Biochemistry and Haematology Outcome Models, BLARt = Blatchford Allman Russell tool, Hb - Haemoglobin, WCC – White cell count, Na – Serum sodium, K – Serum potassium, BMI – Body mass index, DM – diabetes mellitus, COPD – chronic obstructive pulmonary disease, DNR – Do not attempt resuscitation order, INR – International normalized ratio, CHF – Congestive heart failure, CAD – Coronary artery disease, TF - Transfemoral, TT – Transtibial, ASA – American Society of Anaesthesiologists, HTN - Hypertension, CVA – Cerebrovascular accident, MI – Myocardial Infarction