Universiteit Utrecht

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MSc Epidemiology

Writing Assignment

Mortality Risk in Patients with Peripheral Artery Disease: A literature review on prognostic models

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Layman´s summary

Peripheral arterial disease (PAD) is a medical condition characterized by the narrowing or blockage of the vessels (arteries) that carry blood to the legs, arms, and neck. PAD affects millions of people worldwide. The mortality among these patients is similar to mortality in people with heart problems.

Predicting mortality in these patients is relevant to doctors and the patients themselves. Prediction models are an essential tool that can help calculate, for instance, the risk of death or loss of a limb in patients with PAD. A prediction model is a mathematical model to anticipate the future. It uses a combination of factors (e.g., age, gender, or test results) that serves to detect future situations (e.g., death risk of bleeding or risk of fall) and helps make projections based on the information. Prediction models can be used for different purposes, in several sciences, and with various techniques. In medicine, prediction models have a critical relevance because they help doctors, policymakers, and patients make clinical decisions.

In this work, our objective was to identify and describe prediction models for mortality in patients with PAD. To do this, we searched the literature published between January 2010 and May 2022 using three databases (PubMed, EMBASE, Cochrane). This literature review allowed us to identify four studies that described three predictive models. One development study, i.e., a study that develops a new predictive model. One validation study, i.e., a study that aims to evaluate how well an existing model works in other people. And two developing and validating studies, i.e., a study developing a new model and then validating it in the same patients, using statistical techniques, or in different patients. All models had an adequate performance, which means they could predict mortality. However, the validated models demonstrated an optimal prediction of death among other PAD patients, different to those included first to develop the model.

The strengths of the models identified in this literature review include that they were short (with three to six factors), easy to use and had a classification of risk that is easy to understand (low, medium, high risk). We also consider some limitations, such as the lack of validation in all models and the high risk of bias in the models, which means that the features of the study design or conduct of the study might give misleading results.

This literature review permitted us to conclude that, when validated, the available models are adequate to predict mortality. However, validation studies and updates including new factors can be performed in the future.

Abstract

Background

Several prognostic factors are associated with predicting mortality in patients with peripheral artery disease (PAD), and some are included in prediction models for mortality risk. Still, there is not literature about the prognostic models for mortality in PAD in the last decade. We present a summary of the available models, make a comparison of the performance between them, and assess their risk of bias.

Objective

We aim to identify prognostic models for mortality in patients with PAD, give an overview of the model, present a comparative discussion to establish common predictors factors for mortality and appraise the risk of bias of the model.

Methods

We searched PubMed, EMBASE, and the Cochrane library to identify studies developing or internally/externally validating prognostic models for mortality in patients with PAD. We extracted information on study design, population characteristics, and model characteristics, and used the Risk Of Bias ASsessment Tool for prediction model (PROBAST) to assess the risk of bias of the identified models.

Results

In total, four studies (three models) met the inclusion criteria. Two studies developed and externally validated a model, namely the CORPAT and BOA-RC2 models, one study developed a model for predicting mortality in females, and the last was an external validation study of the CORPAT model. The identified models predicted mortality or the combined outcome of mortality and non-fatal cardiovascular events at different moments (1, 2, 5 and 10 years). Age was included as predictor in all models. Other frequently used predictor was kidney function but even so, there was no agreement in the age categories neither in the measures of kidney function used. Discrimination performance was comparable across studies and risk of bias was high in all models.

Conclusion

Despite the high risk of bias, the validated prognostic models demonstrate optimal performance in predicting mortality among patients with PAD. Existing models need to be validated more

often and if necessary, the authors should consider update by adding new predictors not contained in existing models.

Introduction

Peripheral artery disease (PAD) - characterized by the narrowing of the arteries supplying blood to the lower limbs, usually secondary to atherosclerotic disease [1]- is the third most common manifestation of atherosclerosis after coronary artery disease (CAD) and stroke. PAD affects over 236 million people worldwide, [2] and the mortality rate, risk of myocardial infarction (MI) and risk of stroke in patients with PAD are equivalent to the risk of those outcomes for patients with CAD.[3] In 2010, Vaartjes et al. [4] described that 28-days and one-year mortality risks among patients with PAD were lower than in patients with MI and stroke, whereas the five-year mortality risk among males with PAD was comparable to males with MI. To accurately estimate individualized risk of mortality in patients with PAD, prognostic models can help. A prognostic model is a mathematical algorithm that relates patients' characteristics (called predictor factors) to a future outcome (for instance, mortality, bleeding, or a new atherothrombotic event). Other names for prognostic models include prediction model, prediction rule, or prognostic index. Different forms to present them exist, e.g. a risk chart, nomogram, risk calculator. [5] Some prognostic models are used daily in clinical practice, as is the case of the Framingham risk score [6] used to determined cardiovascular risk or the Apgar score [7] to predict a neonatal adverse outcome. Prognostic models are important in medicine because they might inform clinical decision-making for clinicians, patients, and policymakers. However, the number of existing models makes it hard for researchers to validate, test their impact, and know which one to use. PAD is no exception to this phenomenon.

Several prognostic factors such as age, history of diabetes or ankle-brachial index (ABI) among other [8,9] are associated with predicting mortality in patients with PAD, and some are included in prediction models for mortality risk, amputation risk, disease recurrence and CVD events. Even though PAD has been widely studied, and a significant number of literature reviews on different topics related to it exist, there is no clear overview of prognostic models to predict mortality. Additionally, a summary of the quality, utility, practicality, and applicability of these models is also unavailable. Knowing this, we aimed to conduct a literature review to identify prognostic models for mortality in patients with PAD.

Methods

Selection criteria

We included studies which aimed to develop or validate models predicting the risk of mortality in patients with PAD. A study was eligible if it included patients ≥18 years; and if it included patients with PAD in all stages. Studies were excluded if they reported solely a predictor factor, or if they only included patients with critical limb ischemia (CLI).We restricted the inclusion of studies to those published in full text in English or Spanish. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] was used to ensure transparent reporting of review methods.

Search strategy

A literature search was conducted on 16 June 2022 in PubMed, EMBASE and the Cochrane library. We searched for studies published between the 1st of January 2010 and the 31st of May 2022 using the terms related to prediction model and combined these with mortality and peripheral artery disease using the Boolean operators AND/OR. The complete search strategy in described in Appendix **A1**. The screening of titles and abstracts was carried out by a single author (CP) using the Rayyan tool[11] and discussed with the supervisors.

Data extraction and quality assessment

We extracted data of the included studies related to general information (authors, years of publication, country, title); study characteristics (study design, sample size, inclusion, and exclusion criteria); eligibility criteria for patients included in the studies; and model characteristics (predictors in the model, rationale of selecting the predictors, and performance measures).

We assessed the risk of bias and applicability of the included studies using the Risk Of Bias ASsessment Tool for prediction model (PROBAST).[12] Each model was evaluated on four domains: participants, predictors, outcome, and analysis. We rated the level of concern regarding bias and applicability per domain as low, unclear, or high. Finally, the overall risk of bias and applicability was considered based on the level of concern in each domain.

Results

Literature search results

The search strategy identified 1236 studies. After deduplication, 1,000 studies were left for screening. 938 studies were excluded after reading the titles, 32 after reading the abstracts, and 30 articles were full text assessed. After a full-text review, 25 articles were excluded (12 described independent prognostic factors, seven only abstracts were available, three included

only CLI patients, and three for other reasons). A further study was discarded because the authors did not report intercept, so it was not possible to calculate prediction risk. Finally, four studies[13-16] met the inclusion criteria and were included in the literature review. See **figure 1**.

Study characteristics

We identified three prognostic models in the four studies included. Two studies developed and externally validated a model, namely the CORPAT [15] and BOA-RC2 [16] models, one study developed a model for predicting mortality in females,[13] and the last was an external validation study of the CORPAT model.[14] The studies were published between 2011 and 2015, with sample sizes ranging from 292 to 640 in development and 129 to 2083 in validation studies. All the studies included patients with different stages of PAD and focussed on patients who underwent surgical procedures due to PAD. In the study by Abbas A. et al.,[13] the whole population included females, while the population in the other studies were predominantly males. The primary aim of the models was to predict mortality at 10-years,[13] 1-year mortality or non-fatal cardiovascular events,[15] long-term (ten years) mortality or non-fatal cardiovascular events,[14] and mid-long-term (2,5,10 years) mortality or non-fatal MI or ischemic stroke.[16]
One study was a single-center retrospective cohort [13], one single-center prospective cohort [14] and two multicentre prospective cohorts.[15,16] See **Table 1**.

Risk of bias of the included studies

We assessed the risk of bias among the studies using PROBAST. We found a high risk of bias and low concern regarding applicability in three studies, [14-16] and a high risk of bias and unclear concern regarding applicability in one study.[13] See appendix **A2**.

Prognostic models for mortality

The mortality risk score for females undergoing endovascular interventions (EI) [13] is the first prognostic model developed to predict mortality in female patients. This study included 292 hospitalised patients who underwent an endovascular intervention due to PAD between June 1999 and November 2009. In the first step, the authors selected predictors based on univariable analysis with a p-value <.01. In the backward stepwise multivariable logistic regression model, predictors with a p-value >.05 were excluded. The final model includes the three variables age, Congestive Heart Failure (CHF), and Chronic Kidney Disease (CKD). The authors provided a score based on the odds ratio estimate from the model (see **table 2**). Thus, patients aged < 50 years old receive 0-points, and for every decade over 50 years, 1-point; a history of CHF gets

4-points and for patients without CHF 0-points; CKD was categorized, patients with creatinine levels <1.5mg/dl get 0-points and those with creatinine levels ≥ 1.5 obtain 4-points. This model allows a score ranging from 0 to 12 points and classifies patients as low-risk (0-2 points), medium-risk (3-5 points) and high-risk (6-12 points). The discrimination ability of this model was 77% (c-statistic 0.77). Within this study, 76 patients were classified as low-risk, 102 as medium-risk, and 112 high-risk and mortality at 10-years was 5.3%, 15.7% and 39% in low-medium-high risk, respectively.

The COhorte de Patients ARTériopathes (CORPAT) Risk Score was first developed and externally validated by Pros, N. et al.[15] In a multicentre prospective cohort study, the authors selected patients older than 18 years hospitalized for PAD at different stages of the disease. They included two groups, the development cohort consisted of 640 patients hospitalized in the center of Toulouse, and the validation cohort included 517 patients hospitalized in the centers of Bordeaux and Limoges. They performed univariable analysis to identify which factors were associated with the outcome in the first year of follow-up. For the final model, only the variables independently associated with the outcome (1-year mortality, cardiovascular event) at a significant level, p-value <.05, were included. The model includes six predictors, namely age, previous MI, glomerular filtration rate (eGFR), ankle-brachial index (ABI), C-reactive protein (CRP), and medication (statins, antiplatelet agents, and renin-angiotensin system inhibitors). Each predictor received points based on the beta estimates (**table 2)**. Subsequently, they divided the risk score into low-risk (≤0 points), medium-risk (0.5-2 points), high-risk (2.5-4 points), and very high risk (≥4.5 points). In the development cohort, the rates of the outcome according to the score were 2%, 12.8%, 23% and 42.2%, respectively. Similar rates were observed in the validation cohort, i.e., 1.4%, 18.3%, 30.2%, 44.4%, respectively. The performance was similar in both cohorts (C-statistic 0.76 in the development cohort and 0.74 in the validation cohort).

Hackl, G. et al.,[14] validated the CORPAT risk score for assessing long-term (10-years) mortality risk in patients with PAD. They included 129 patients in the study (patients that presented at the outpatient clinic of the Division of Angiology, with intermittent claudication (Rutherford stages 2-3) and those hospitalised who underwent a first endovascular procedure) and followed them up for ten years. This time, the authors decided to present only three risk groups, namely low-risk (≤ 0 points), medium-risk (0.5-2 points) and high-risk (≥ 2.5 points), under the assumption that in clinical practice, there are no prognostic differences between high- and very-high-risk patients in the long-term. At the end of the follow-up, 23.1%, 34.1% and 63.9% of patients of the low-medium-high risk groups, respectively, had died. The authors

subsequently updated the model by excluding the predictors CRP and medication because these two variables were not significant when comparing between groups (low-risk, medium-risk and high-risk), but they did not find significant changes in the results, mortality results were not influenced by omitting these parameters.

The Bypass Oral anticoagulants or Aspirin Risk Chart (BOA-RC2) for assessing composite mortality risk at three different time horizons (2, 5 and 10 years) was developed and validated by Wisman, P. et al.[16] In this study, the authors included 2650 patients from the Dutch BOA trial, 482 for the development cohort and 2168 for the validation cohort. They performed Cox proportional hazard models and included variables with p-values <.20 from the univariable analysis in the multivariable analysis. Age, diabetes mellitus (DM), CLI and a previous vascular intervention were independent predictors of the outcome (p-value <.05) and were eligible for the final model. Unlike the other models described above, the BOA-RC2 quantify the risk. For instance, the five-year risk for a patient 68 years old with DM, intermittent claudication, and a prior vascular intervention is 45% (average risk). The 10-year risk for the same patient is 82% (average risk). **Figure 2** (Wisman, P. et al.)[16] gives a complete description of the risk chart. The discriminatory performance of the model was evaluated with the area under the receiver operator (AUC-ROC). The AUC-ROC in the development cohort was 0.78 (95% CI 0.73-0.82) and 0.73 (95% CI 0.71-0.75) in the validation cohort. The BOA-RC2 showed good calibration in the validation cohort, the calibration plot showed similar predicted (1395) and observed (1372) outcome events.

Discussion

The primary purpose of this review was to identify models available for predicting mortality in patients with PAD, make a comparison between them in terms of risk of bias and discrimination performance, and identify common predictors between them.

All models included a limited set of three to six predictors and are easy to apply because they use scoring systems with points or percentages to assign a risk level. The models shared only one common predictive factor systematically included in the multivariable analyses, age. Kidney function was included in the final models of three studies (two models).[13-15] Even so, each model used different cut-points to categorize age and different measures of kidney function (i.e., creatinine levels and eGFR), which make them not easily comparable.

The sample sizes were adequate in all studies achieving an EPV ratio of 10. But this was due to the models included few variables in their multivariable analyses. The distribution of the population was also similar, one study included only females[13] and in the others, males were

more represented. This may be explained by the fact that although women present PAD at least as often as men, still treatment disparities exist between sexes, and males receive more often EV procedures. [17,18] Regarding performance assessment, we found similar discrimination ability between the models, and none excelled over the others.

The strengths of the models include, first, their performance discrimination, without significant differences between them. Second, the predictors included in all models, which are easy to measure and available in all hospital settings. Finally, applicability concerns were low, and the models were presented in an easy-to-understand way.

We also acknowledge some limitations, the risk of bias being one of them. All models were at high risk of bias, mainly due to concerns in the analysis domain. The models were developed and, some but not all of them, validated in patients with advanced stages of PAD and hospital settings; therefore, the performance of the models in less severe patients or their transportability to other populations is unknown. Finally, they presented a risk stratification into low, medium, and high, but only one model provides the mortality risk in absolute numbers, which are easy to interpret.

Several prognostic factors have been associated with increased mortality in patients with PAD. (Age, multiple biomarkers (Neutrophil-to-leukocyte ratio, CRP, Homocysteine, Urinary albumin-to-creatinine ratio), nutritional status, and stress levels).[19-23] As a single factor is not precise enough to provide prognostic information, predictive models are necessary. Our literature review does not confirm that the mentioned variables predict mortality when used in multivariable analysis because, except for age and kidney function, none was part of or was a common factor among the identified models because they were not considered in the model or were excluded because they did not reach significance. This might be considered a consequence of the review limitations because we focus on studies published from 2010 onwards. Yet, we believe it is unlikely as trends show that most of the prognosis-related studies were published in the last decade, and only in 2021 in PubMed 10869 results have the terms prognostic models.

Conclusion

Validated models demonstrate optimal performance in predicting mortality among patients with advanced-stage PAD or after a surgical procedure due to PAD. There are still some concerns regarding the risk of bias; therefore, this must be considered when using the models. Age and renal function are prognostic factors for mortality. Existing models need to be

validated more often and if necessary, the authors should consider update by adding new predictors not contained in existing models.

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Figures

Figure 1: Flow diagram of the literature search strategy to identify studies on prognostic models of mortality in patients with peripheral artery disease. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. [10]

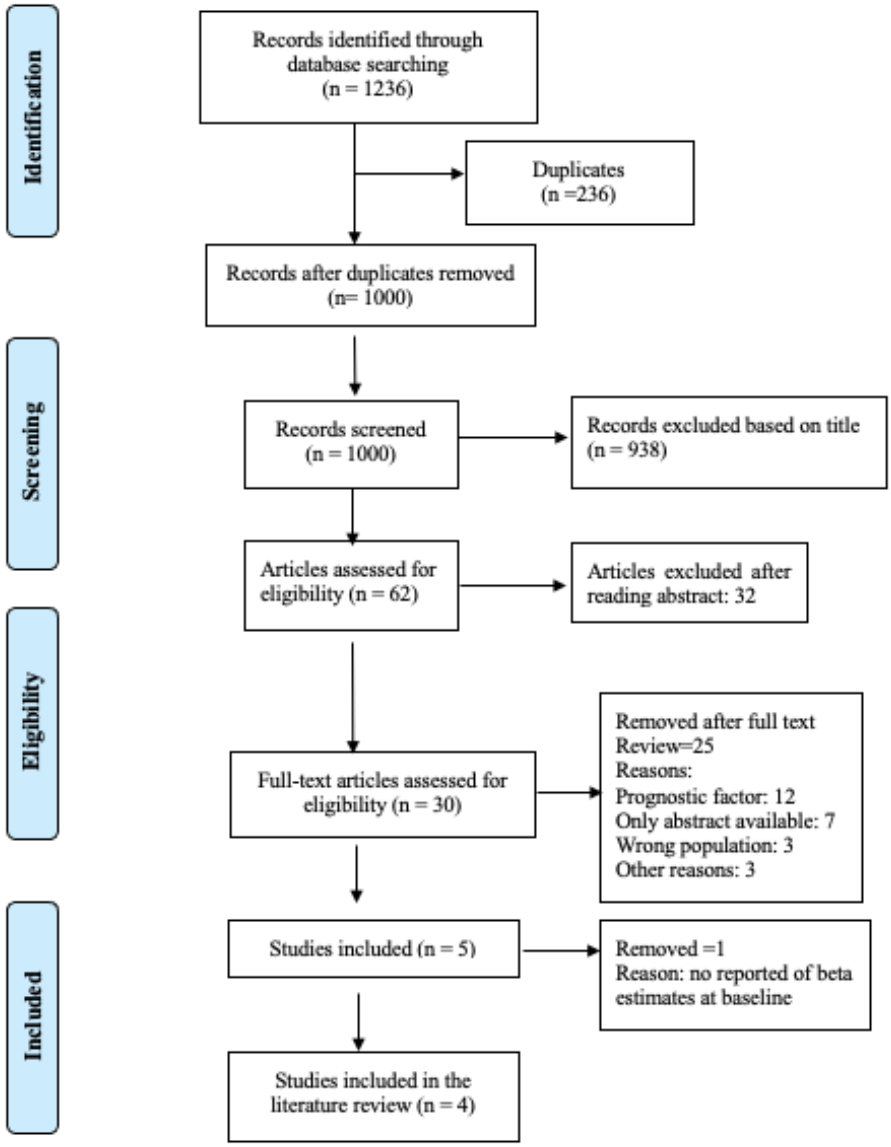
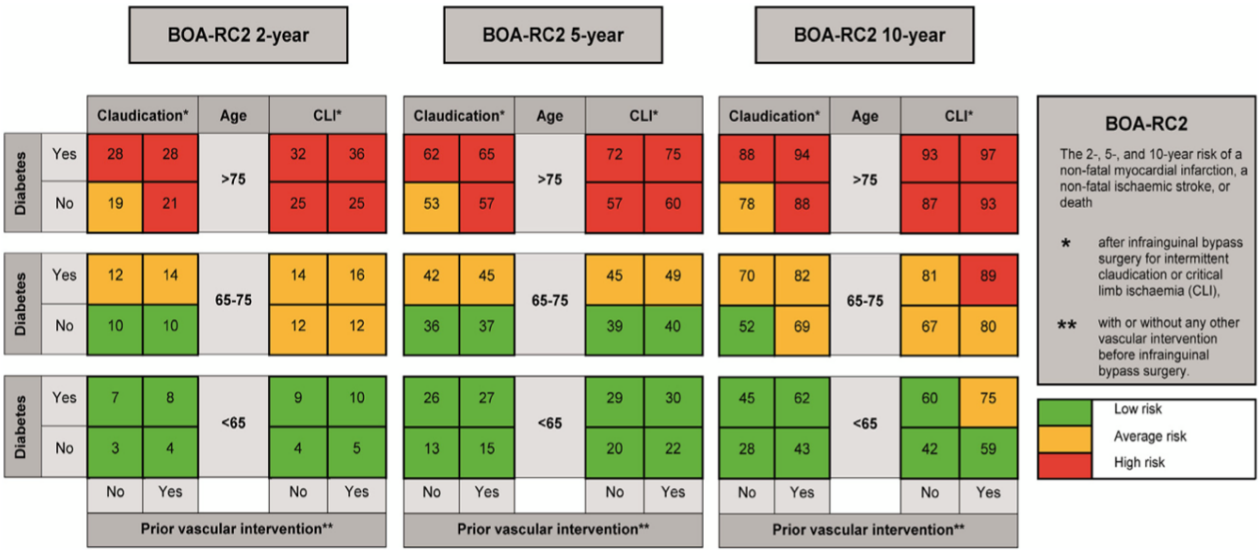


Figure 2: The BOA-RC2



Taken from Wisman, P. et al [16]; CLI: critical limb ischemia

Tables

Table 1: Study characteristics

Author	Abbas, A et al (2011) [13]	Pros, N et al (2013) [15]	Hackl, G. et al (2015) [14]	Wisman, P et al (2015) [16]
Model	Mortality risk score for females undergoing endovascular interventions.	CORPAT Risk Score	CORPAT Risk Score.	BOA-RC2 Mortality risk
Objective	Development	Development/Validation	Validation	Development/Validation
Outcome	10 years mortality	1-year mortality or cardiovascular event	Long term mortality or cardiovascular event (10 years)	Risk mortality (2,5,10 years), non-fatal myocardial infarction, non-fatal ischemic stroke
Sample size	292 females	640 (68.4% males) / 517 (76.4% males)	129 (71.3% males)	482 (65% males) / 2083 (64% males)
Study design	Single center retrospective cohort study	Multicenter prospective cohort study	Single center prospective cohort study	Multicenter prospective cohort study
Inclusion criteria	PAD patients who underwent lower extremity endovascular intervention between 1999 and 2009	Patients with PAD. The clinical presentations included either an IC, rest pain, or ulceration and gangrene or acute lower-limb ischaemia. Patients following an endovascular procedure were also included	Patients with PAD (Rutherford 2-3). And patients who had to undergo their first endovascular procedure of the pelvic and/ or femoropopliteal arteries	Patients with PAD who underwent infrainguinal bypass surgery
Exclusion criteria		Patients for whom follow-up was improbable, those with arterial occlusive disease not related to atherosclerosis, those with acute ischaemia without lower-limb atherosclerosis (embolic) and those refusing to participate.	Unstable angina or poststroke, malignant hypertension, life exp <1-year, wound infection, contraindication for anticoagulants or antiplatelets agents.	

PAD: peripheral artery disease; IC: intermittent claudication

Table 2: Multivariable analyses

Mortality risk score for female undergoing endovascular interventions [13]			
Predictor	**Odd ratio (95% CI)**	**Beta estimate**	**Points**
Age (for every decade over 50 add one point)	1.43 (1.06-1.92)	0.35	+1
History of CHF	4.03 (2.22-7.32)	1.39	+4
Creatinine ≥1.5	3.74 (1.9-7.23)	1.32	+4
CORPAT risk score [14,15]			
Predictor	**Odds ratio (95% CI)**	**Beta estimate**	**Points**
Age 75-84 years	3.09 (1.28-7.47)	1.13	+2
Age ≥85 years	4.69 (1.8-12.2)	1.54	+3
History of MI	1.73 (1.03-2.9)	0.55	+1
CRP ≥ 70mg/L	2.35 (1.17-4.7)	0.85	+2
ABI <0.3	2.54 (1.36-4.76)	0.68	+2
ABI 03.-0.49	1.97 (1.04-3.72)	0.93	+1.5
ABI ≥1.3	2.65 (1.26-5.58)	0.97	+2
eGFR >30-60 ml $min^{-1}1.73m^{-2}$	1.68 (1.03-2.74)	0.52	+1
eGFR ≤30 ml $min^{-1}1.73m^{-2}$	2.29 (1.21-4.31)	0.82	+1.5
Medication	0.46 (0.29-0.7)	0.73	-1.5

CI: confidence interval; CHF: chronic heart disease; CRP: C-reactive protein; ABI: ankle-brachial index; eGFR: glomerular filtration rate.

Appendix

A1: Search strategy

PubMed. Search date: 16/06/2022		
Concept	Keywords	Total
#1	(((((((clinical prediction rule[MeSH Terms]) OR (Prognostic model[Title/Abstract])) OR (Predictive model[Title/Abstract])) OR (Prediction model[Title/Abstract])) OR (Prediction rule[Title/Abstract])) OR (Index score[Title/Abstract])) OR (Score[Title/Abstract])) OR (nomogram[Title/Abstract]))	738,053
#2	((((((determinants, mortality[MeSH Terms]) OR (Fatal*[Title/Abstract])) OR (Dead[Title/Abstract])) OR (Death[Title/Abstract])) OR (Short term mortality[Title/Abstract])) OR (Long term mortality[Title/Abstract])) OR (Loss of life[Title/Abstract]))	1,326,895
#3	(((((((disease, peripheral artery[MeSH Terms]) OR (peripheral occlusive arter* disease[Title/Abstract])) OR (Lower extremity arter* disease[Title/Abstract])) OR (intermittent claudication[Title/Abstract])) OR (lower limb peripheral artery disease[Title/Abstract])) OR (peripheral vascular disease[Title/Abstract])) OR (lower extremity peripheral artery disease[Title/Abstract]))	35,296
EMBASE Search date: 16/06/2022		
Concept	Keywords	Total
#1	('clinical prediction rule':ti,ab OR 'prognostic model':ti,ab OR 'predictive model':ti,ab OR 'prediction model':ti,ab OR 'prediction rule':ti,ab OR 'prognostic factor':ti,ab OR 'score':ti,ab OR 'nomogram':ti,ab) AND ([english]/lim OR [Spanish]/lim) AND [01-01-2010]/sd	1'020,904
#2	('determinants, mortality':ti,ab OR 'fatal*':ti,ab OR 'dead':ti,ab OR 'death':ti,ab OR 'short term mortality':ti,ab OR 'long term mortality':ti,ab) AND ([english]/lim OR [Spanish]/lim) AND [01-01-2010]/sd NOT [01-06-2022]/sd	920,578
#3	('peripheral arterial disease':ti,ab OR 'peripheral artery disease':ti,ab OR 'lower extremity arterial disease':ti,ab OR 'peripheral vascular diseas*':ti,ab OR 'lower limb peripheral artery disease':ti,ab OR 'intermittent claudication':ti,ab OR 'peripheral occlusive arter* disease':ti,ab OR 'lower extremity peripheral artery disease':ti,ab) AND ([english]/lim OR [Spanish]/lim) AND [01-01-2010]/sd	30,041
Cochrane library Search date: 16/06/2022		
Concept	Keywords	Total
#1	'clinical prediction rule':ti,ab OR 'prognostic model':ti,ab OR 'predictive model':ti,ab OR 'prediction model':ti,ab OR 'prediction rule':ti,ab OR 'prognostic factor':ti,ab OR 'score':ti,ab OR 'nomogram':ti,ab	1426
#2	'determinants, mortality':ti,ab OR 'fatal*':ti,ab OR 'dead':ti,ab OR 'death':ti,ab OR 'short term mortality':ti,ab OR 'long term mortality':ti,ab	2557
#3	'peripheral arterial disease':ti,ab OR 'peripheral artery disease':ti,ab OR 'lower extremity arterial disease':ti,ab OR 'peripheral vascular diseas*':ti,ab OR 'lower limb peripheral artery disease':ti,ab OR 'intermittent claudication':ti,ab OR 'peripheral occlusive arter* disease':ti,ab OR 'lower extremity peripheral artery disease':ti,ab	516
#4	#1 AND #2 AND #3	68

With Cochrane Library publication date from Jan 2010 to May 2022, in Cochrane Reviews

A2: PROBAST Risk of bias assessment

	Pros, N et al (2013). CORPAT Risk Score. 1 year mortality [15]	**Hackl. G (2015). CORPAT Risk score. Long term mortality [14]**	**Abbas, A (2011). Mortality risk score for female [13]**	**Wisman, P (2015). BOA RC-2 [16]**
Type of prediction study				
Development			X	
Development and validation	X			X
Validation		X		
Publication reference				
Model of interest	CORPAT Risk Score	CORPAT Risk Score	Novel mortality risk score for female	BOA Risk Chart 2
Outcome of interest	All cause of mortality, no fatal stroke, no fatal MI	all-cause mortality and cardiovascular (CV) death	Mortality after EI	All cause death, non-fatal myocardial infarction, or non-fatal ischaemic stroke during a 10 year follow up
DOMAIN 1: Participants				
Risk of Bias				
Describe source of data and criteria for participant selection	The COPART is a multicentre registry prospectively collecting exhaustive data about all patients consecutively hospitalised for PAD.	Patients presented at the outpatient clinic of the Division of Angiology, Graz with intermittent claudication (Rutherford Stages 2e3), and those who had to undergo their first EV procedure of the pelvic and/ or femoropopliteal arteries	A single-center retrospective chart review of all consecutive female patients who underwent EI for symptomatic PAD over the last decade (November 1999–June 2009).	Patients from the Dutch BOA trial. The derivation cohort consisted of 482 patients (18%) from the Dutch BOA trial. The follow up data of these 482 patients were extended from 1998 to 2009 and collected from the vascular surgeon, general practitioner, patient, or relatives and acquaintances in a stepwise manner
Where appropriate data sources used?	Yes	Yes	No (retrospective study)	Yes
Where all inclusion and exclusions of participants appropriated.	Yes	Yes	Not stated	Yes (described in previous study)
RoB introduced by selection of participants	**Low**	**Low**	**High**	**Low**
Rationale of RoB			Single center retrospective study, without specification of exclusion or inclusion criteria.	
Applicability				

Described included participants, setting and dates.	age >18 years, consent to participate in the study and referred to the hospital specifically for clinical PAD of atherosclerotic origin. The clinical presentations included either an intermittent claudication (IC), associated with an abnormal ankle brachial index (ABI) <0.90 or >1.30 or, in the case of normal ABI at rest, a positive treadmill test and/or an arterial stenosis >50% revealed by duplex ultrasound and/or angiography, or ischaemic rest pain, or ulceration and gangrene or acute lower-limb ischaemia related to a documented PAD with significant arterial stenosis. Setting: University hospital	Between March 2002 and November 2004, 129 consecutive patients were included in a prospective observational study of death or a CV event (myocardial infarction, stroke, amputation). Patients presented at the outpatient clinic of the Division of Angiology	All consecutive female patients who underwent EI for symptomatic PAD between 1999 and 2009.	Patients after infrainguinal bypass surgery from 77 medical centres throughout the Netherlands between 1995 and 1998.
Concern that included participants and setting do not match the research question	Low	Low	**Unclear**	**Low**
Rationale of applicability rating	Appropriate description of patients, inclusion, and exclusions criteria	Appropriate description of patients, inclusions, and exclusions criteria.	Lack of information about the included participants and setting	Appropriate description of patients.
DOMAIN 2: Predictors				
Risk of Bias				
List and describe predictors included in the final model	Age, prior history of MI, CRP level, ABI, eGFR, Medication	Age, prior history of MI, CRP level, ABI, eGFR, Medication	Age, Congestive Heart Failure, Chronic Kidney Disease	Age, Critical limb ischemia after intervention, Diabetes mellitus, prior vascular intervention
Were predictors defined and assessed in a similar way for all participants	Yes	Yes	Yes	Yes
Were predictors assessments made without knowledge of outcome data	Yes	Yes	No	Yes
Are all predictors available at the time the model is intended to be used?	Yes	Yes	Yes	Yes
RoB introduced by predictors of their assessment	Low	Low	Low	**Low**
Rationale of bias rating	Predictors well defined and assessed in the same way for all participants.			
Applicability				
Concern that definition, assessment or timing of predictors do not match RQ	**Low**	**Low**	**Low**	**Low**
Rationale of applicability rating				
DOMAIN 3: Outcome				
Risk of Bias				

Describe the outcome, how it was defined, determined and the time between predictor assessment and outcome determination	Mortality, nonfatal stroke, nonfatal MI at 1 year	Mortality, cardiovascular event. Follow up 2002 to 2011	Mortality after EI	all cause death, non-fatal myocardial infarction, or non-fatal ischaemic stroke during a 10 year
Was the outcome determine appropriately?	Yes	Yes	Yes	Yes
Was a prep-spec of standard outcome definition used?	Yes	Yes	Yes	Yes
Outcome defined similar for all participants?	Yes	Yes	Yes	Yes
Was the time interval between predictor assessment and outcome appropriate?	Yes	Yes	Yes	Yes
RoB introduced by the outcome or its determinants	**Low**	**Low**	**Low**	**Low**
Rationale of bias rating	Hard outcome, thus the risk of bias is low	Hard outcome	Hard outcome	Hard outcome
Applicability				
At what time point was the outcome determined?	1 year follow up	Long term	Retrospective study	2, 5, 10 years
Concern that the outcome, its definition, timing, or determination do not match RQ	**Low**	**Low**	**Low**	**Low**
Rationale of applicability rating				
DOMAIN 4: Analysis				
Risk of Bias				
Describe the numbers of participants, number of candidate predictors, outcome events and events per candidate predictor.	Participants: 1167 (640 development cohort; 517 validation cohort). Candidate predictors: 20; Outcome events: all-cause mortality and non-fatal cardiovascular events had occurred in 123 (19.2%) and 105 (20.3%) of the participants in the derivation and validation cohorts, respectively	Participants: 129; Candidate predictors: 6: Outcome events: Forty-nine patients (38%) died during the observation period, and 30 (23.3%) suffered CV death.	Participants: 292 females (221 survived, 71 died). Overall, 76 patients (26%) fell into the low-risk category and had a 5.3% mortality, 102 patients (35%) fell into the moderate-risk group with a mortality of 15.7%, and 112 patients (39%) fell into the high-risk group with a mortality of 45.5%	Participants: 482 development cohort; 2083 validation cohort. Candidate predictors: 4; Outcome events: Development: The primary outcome event consisted of 242 deaths (50.2%), 44 myocardial infarctions (9.1%), and 35 strokes (7.3%). The primary outcome event occurred within the first 30 days of peripheral bypass surgery in seven patients (0.2%). Validation: The commonest primary outcome event was death (53.0%; N 1,105) followed by myocardial infarction (7.6%; N 159) and stroke (5.1%; N 107). During the first 30 days the primary outcome event occurred in 35 patients (0.2%).

Describe how the model was developed (modelling technique, predictor selection)	In the derivation cohort, a backward stepwise logistic regression was used to identify factors independently associated with the outcome occurrence. Only factors remaining independently associated with the outcome occurrence with a 5% significance level ($p < 0.05$) were retained in the final model	Survival analysis was assessed by Kaplan Meier curves and Log-rank statistics. Statistical significance was set at $p < .05$.	Backward stepwise multivariable logistic regression analyses were completed to determine the strongest predictors of death. Using a Kaplan-Meier analysis (Fig. 3A, B), survival estimates were performed	Cox proportional hazards model and associated variables that yielded p <.20 in the univariate analysis were included in the multivariate analysis. Independent predictors of the primary outcome event (p <.05) were identified using backward stepwise elimination. The regression coefficients of the independent predictors were reduced with a uniform shrinkage factor
Described whether and how the model was validated either internally or externally	External validation in a different setting	N/A	No validation described	Validated in the remain patients of the complete cohort of the BOA trial
Describe the perfomance measure of the model (calibration, discrimination, net benefit...)	Discrimination (C-statistic 0.76 for the derivation cohort and 0.74 for the validation cohort). Calibration: no significant differences were found between observed and calculated composite end-point rates in the validation cohort (Hosmer Lemeshow test: p = 0.65)	No information	C-statistic 0-77	The performance of the BOA-RC2 was good with a Brier score of 0.19, an area under the curve of 0.73, and a Hosmer Lemeshow statistic of p .9.
Describe any participants who were excluded from the analysis	111 patients were excluded because of deviation from the protocol, 34 were lost to follow-up, 165 did not reach the 1-year anniversary date of follow-up and 64 died during hospitalisation.	Patients suffering from angina pectoris, previous stroke, malignant hypertension, heart failure were excluded	No information	No information
Describe missing data on predictors and oucomes as well as methods used for missing data	No information	No information	No information	Missing ankle brachial index (ABI) data of 81 patients in the derivation cohort were imputed with mul- tiple imputations.
Were there a reasonable of participant with the outcome?	Yes	Yes	Yes	Yes
Continous and categorical variables handled appropriated?	No (they categorize continous variables)	No (they categorized continous variables	No (they categorized continous variables)	No (they categorized continous variables)
Were all enrrolled participants included in the analysis?	Yes	Yes	Yes	Yes
Were participants with missing data handled appropriated?	No information	No information	No information	Yes
Was selection of predictors based on univivariable avoided?	No	N/A	Yes	Yes

Were complexities in the data accounted appropriately?	No information	Yes	No information	No information
Were relevant model performance measures evaluated appropriately?	Yes	No	No	Yes
Were model overfitting and optimism in model perfomance accounted for?	No	N/A	No	No
Do predictors, and their assigned weights in the final model correspond to the results from multivariable analysis?	Yes	N/A	Yes	Yes
RoB introduced by the analysis	**High**	**High**	**High**	**High**
Rationale of bias rating	They used univariate to select predictors. There was no description about missing data or how this was handled. Also, there is no information about complexities in the data. They categorized continuous variables	No information about performance. There was no description about missing data or how this was handled. They categorized continuous variables.	They do not describe any validation, categorized continuous variables, do not described missing data nor complexities in the data.	They do not describe patients excluded from de analysis, categorized continuous variables, no described complexities in the data nor how overfitting was accounted.
Overall judgment of RoB	**High risk of bias**	**High risk of bias**	**High risk of bias**	**High risk of bias**
Overall judgment of applicability	**Low concerns regarding applicability**	**Low concerns regarding applicability**	**Unclear concerns regarding applicability**	**Low concerns regarding applicability**