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SYSTEMATIC REVIEW

Editor's Choice – Prognostic Factors and Models to Predict Mortality Outcomes in Patients with Peripheral Arterial Disease: A Systematic Review

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WHAT THIS PAPER ADDS

This systematic review summarises current knowledge on predictive factors and models for mortality outcomes in people with peripheral arterial disease (PAD) Fontaine stage I — III or Rutherford category 0 — 4. The review identifies over 80 prognostic factors and eight models. Age, sex, smoking, diabetes mellitus, and hypertension were often reported in the studies on prognostic factors as predictors of mortality outcomes. Age consistently appears in studies on prognostic models, whereas sex, smoking status, and diabetes do not. The study offers a concise and comprehensive analysis of mortality prediction in PAD, highlighting key factors and suggesting improvements for prognostic models.

Objective: Predicting adverse outcomes in patients with peripheral arterial disease (PAD) is a complex task owing to the heterogeneity in patient and disease characteristics. This systematic review aimed to identify prognostic factors and prognostic models to predict mortality outcomes in patients with PAD Fontaine stage I — III or Rutherford category 0 — 4.

Data Sources: PubMed, Embase, and Cochrane Database of Systematic Reviews were searched to identify studies examining individual prognostic factors or studies aiming to develop or validate a prognostic model for mortality outcomes in patients with PAD.

Review Methods: Information on study design, patient population, prognostic factors, and prognostic model characteristics was extracted, and risk of bias was evaluated.

Results: Sixty nine studies investigated prognostic factors for mortality outcomes in PAD. Over 80 single prognostic factors were identified, with age as a predictor of death in most of the studies. Other common factors included sex, diabetes, and smoking status. Six studies had low risk of bias in all domains, and the remainder had an unclear or high risk of bias in at least one domain. Eight studies developed or validated a prognostic model. All models included age in their primary model, but not sex. All studies had similar discrimination levels of > 70%. Five of the studies on prognostic models had an overall high risk of bias, whereas two studies had an overall unclear risk of bias.

Conclusion: This systematic review shows that a large number of prognostic studies have been published, with heterogeneity in patient populations, outcomes, and risk of bias. Factors such as sex, age, diabetes, hypertension, and smoking are significant in predicting mortality risk among patients with PAD Fontaine stage I — III or Rutherford category 0 — 4.

Keywords: Mortality predictors, Peripheral arterial disease, Prognostic factors, Prognostic models, Systematic review
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INTRODUCTION

Peripheral arterial disease (PAD) affects over 236 million people worldwide and is the third most common manifestation of atherosclerosis following coronary artery disease and stroke.[1,2] The prognosis for individuals with PAD is generally poor, with mortality rates of around 30% at five years[3–5] and over 50% at 10 years.[6] Additionally, the risk of major adverse cardiovascular and limb events is high, especially in those with chronic limb threatening ischaemia (CLTI).[7]

Predicting adverse outcomes in patients with PAD is challenging because of the wide range of factors that vary across patients, such as symptom presentation and patient characteristics.[8–10] Prognostic factors refer to the parameters that are associated with the risk of future outcomes in individuals with a specific health condition.[11] These factors are combined in mathematical algorithms to estimate individual risk of a particular outcome, resulting in prognostic models.[12]

Some prognostic factors, such as demographic characteristics and comorbidities, have been identified as predictors of health outcomes in PAD. For instance, age is a well established prognostic factor, as older individuals have a higher risk of adverse outcomes such as amputation, cardiovascular events, and death.[13,14] Diabetes is also a significant predictor of worse outcomes in PAD, including a higher risk of amputation.[1,6,15,16]

Despite studies investigating the prognostic value of patient disease characteristics and new models that aim to improve prognostication in patients with PAD, more clarity on all existing predictor factors and models is needed to predict mortality outcomes accurately in this high risk population.[17] Lack of a comprehensive overview of published research on this topic may explain this. Therefore, this systematic review aimed to investigate prognostic factors and prognostic models of mortality outcomes, such as all cause mortality, cardiovascular related mortality, short term mortality, or in hospital mortality in patients with PAD Fontaine stage I — III or Rutherford category 0 — 4.

METHODS

The protocol for this systematic review was registered with PROSPERO (CRD42022353663). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to ensure transparent reporting of review methods (Supplementary Table S1).[18]

Search strategy and eligibility criteria

A literature search was conducted on 1 August 2022 in PubMed, Embase, and Cochrane Database of Systematic Reviews. Studies that were published between 1 January 2010 and 1 August 2022 were searched (Supplementary Table S2). On 21 November 2023, an update search was conducted using the same strategy for studies published between August 2022 and November 2023 (Supplementary Table S3). Inclusion of studies was restricted to those published from 2010 onwards, as studies on the prognosis of PAD before 2010 would not inform current clinical practice.

The eligible studies were those that investigated factors predicting mortality outcomes in adult patients (> 18 years) with PAD Fontaine stage I — III or Rutherford category 0 — 4. The mortality outcomes included all cause mortality, in hospital mortality, short term mortality, long term mortality, cardiovascular mortality, and non-cardiovascular mortality. Studies that developed or validated prognostic models for predicting mortality outcomes were also considered. Studies that focused only on patients with CLTI or those who had previously undergone major amputation were excluded to minimise heterogeneity among the selected studies. For studies that included patients with all PAD stages, including CLTI, only the results for Fontaine stage I — III or Rutherford category 0 — 4 were reported. If a study did not conduct subgroup analysis by PAD stage, it was still included and the result from the entire population was reported. Finally, studies with limited sample sizes that prevented adjustment for traditional risk factors were excluded.

For the studies on prognostic models, both internal validation, i.e., assessment of the performance of a prognostic model using the same data that were used to develop the model,[19] and external validation, i.e., testing the performance of a prognostic model on an independent dataset that was not used to develop the model,[12] were considered. The study selection process was conducted by two independent reviewers (C.P.P. and R.W.V.M.) who screened titles, abstracts, and full text articles to identify potentially eligible studies. In cases of disagreement, reviewers resolved the issue by reaching a consensus.

Data extraction and quality assessment

Data were extracted independently by two reviewers (C.P.P. and R.W.V.V.) and cross checked for accuracy. From all the included studies, the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) guidance[20] was followed, and data related to general information, i.e., authors, year of publication, and title, were extracted. Other data extracted included study characteristics (study design, sample size, eligibility criteria, and outcome definition) and information about single predictors and model characteristics (predictor under study, number of predictors in the model, rationale for selecting the predictors, methods for internal or external validation, and performance measures).

The predictors were classified into six groups: demographics (age, sex, and race), medical history (comorbidities), clinical features (body mass index [BMI], blood pressure, ankle brachial index [ABI]), medication (antiplatelets, antihypertensives, and lipid lowering drugs), biomarkers and laboratory measurements (C reactive protein [CRP], estimated glomerular filtration rate [eGFR]), and other factors (scores, arterial stiffness assessed by systolic pulse wave analysis, and flow mediated dilation assessed by ultrasound).

The quality of studies evaluating prognostic factors was assessed independently by two reviewers (C.P.P. and R.W.M.V.) using the Quality in Prognosis Studies (QUIPS) tool,[21] resulting in a low, unclear, or high risk of bias for each domain. To assess the risk of bias and applicability of

studies to prognostic models, the Prediction model Risk Of Bias ASsessment Tool (PROBAST) was used.[22] Each model was evaluated on four domains (participants, predictors, outcome, and analysis), and bias and applicability per domain was rated as low, unclear, or high. Finally, the overall risk of bias and applicability based on the level of concern in each domain were evaluated.

Data synthesis

A descriptive analysis of the identified prognostic factors and model studies was conducted. From the studies on prognostic factors, all the predictors included in the multivariable model were extracted, along with their effect estimates, i.e., hazard ratio (HR), risk ratio, odds ratio (OR), or area under the receiver operating characteristic curve (AUC) with respective 95% confidence interval (CI). Furthermore, all the variables used for adjustment in the final multivariable models were extracted. For the studies on prognostic models, the model characteristics were thoroughly examined, including all the predictors considered and their validation methods. Discriminatory values were assessed, such as concordance statistic (C statistic) or AUC, indicators of a model's predictive accuracy. Additionally, calibration was evaluated to understand how predicted outcomes align with observed outcomes. Because of the expected differences in patient demographics, disease characteristics, outcome definitions, and investigated predictors, a decision was made not to conduct a meta-analysis. The varied methodologies and outcome measures used by the studies could introduce significant variability, making statistical pooling unsuitable.

RESULTS

Literature search results

A total of 4 538 unique studies were reviewed, from which 4 390 were excluded after the screening of titles and abstracts. Subsequently, 148 full text articles were assessed. Among these, 86 articles were excluded for various reasons, such as the availability of only abstracts, incorrect outcome or population, or inadequate sample size (Supplementary Table S4). The first phase of the search included 56 studies focusing on prognostic factors, along with six studies (comprising five models) dedicated to developing or validating a prognostic model.

In a subsequent search update, 699 studies were identified, and 31 studies were chosen for full text evaluation. Of these, 15 studies met the inclusion criteria, encompassing 13 on prognostic factors and two on prognostic models. A total of 77 studies were included, with 69 studies on prognostic factors[23–91] and eight studies developing or validating prognostic a model[92–99] for mortality outcomes (Fig. 1).

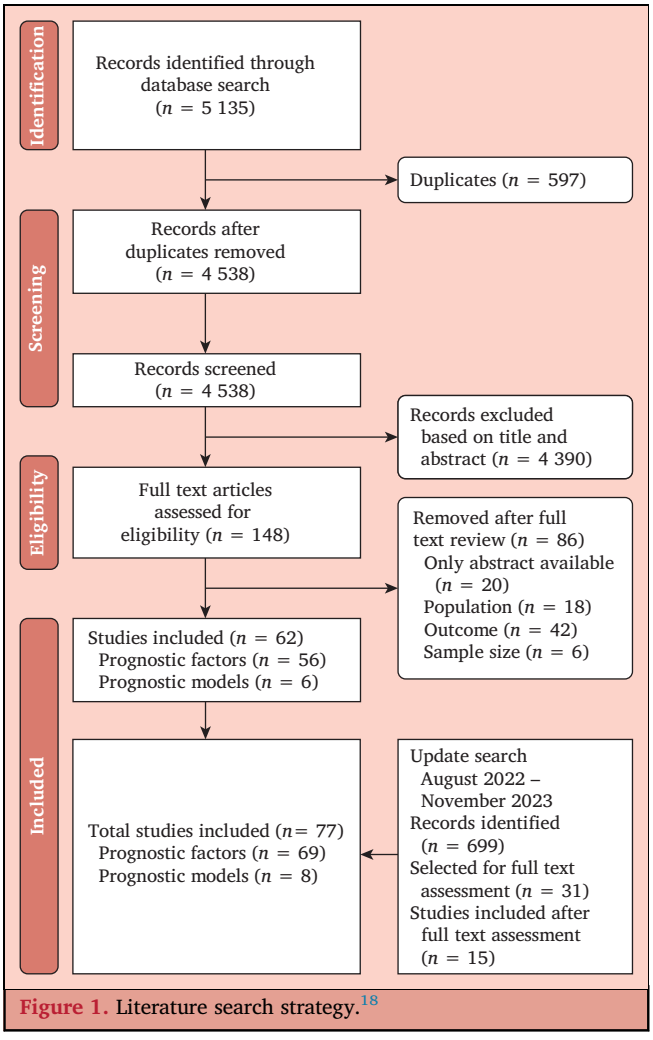

Figure 1. Literature search strategy.[18]

Study characteristics

Among the studies investigating prognostic factors, 44 (64%) were prospective cohorts, 22 (32%) were retrospective cohorts, and three (4.3%) were case—control studies. The sample size across these studies ranged from 101 — 134 081 patients, with the proportion of men varying from 42 — 100%. The mean age ranged from 61 — 79 years, and the mean follow up duration spanned from 1 — 135.6 months.

The prevalence of hypertension was significantly variable, ranging from 27 — 90%, whereas seven studies (10%) did not report it. Similarly, the prevalence of diabetes varied from 13 — 78%, with seven studies (10%) omitting the reporting of diabetes prevalence. Chronic kidney disease showed a wide range, from 0.8 — 75%; 31 studies (45%) did not provide information on its prevalence (Table 1). Regarding mortality outcomes under study, the most frequently studied was all cause mortality in 38 studies (55%), cardiovascular mortality in 24 studies (35%), and overall mortality in 13 studies (19%) (Table 2).

In the studies that described prognostic models, the sample size varied from 129 — 150 921. The male population ranged from 0 — 76%, and the mean age ranged between 69 years and 72 years. The prevalence of hypertension ranged from 39 — 97%, with one study (13%)

Table 1. Baseline characteristics of 69 studies of prognostic factors in patients with peripheral arterial disease.

Author (year)	Outcome of interest	Study population	Sample size	Men — %	Follow up — mo (mean)	Mean age — y	Hypertension — %	Diabetes — %	Smoking — %	Heart failure — %	Coronary artery disease — %	Chronic kidney disease — %
Criqui *et al.* (2010)[32]	All cause, cardiovascular and non-cardiovascular death at 2 and 6.6 y	Patients with PAD	397	87	79.2	68.7†	77†	36†	NR	NR	NR	NR
de Liefde *et al.* (2010)[33]	All cause and cardiac death at 5 y	Patients with PAD	261	62	72	61†	36†	23†	40†	6†	NR	5†
McDermott *et al.* (2011)[64]	All cause death and mobility loss at 97 mo	Patients with PAD	440	57	72 (50–97)	NR	NR	32	16	21	24	NR
Singh *et al.* (2010)[75]	All cause death at 5 y	Patients with PAD	410	60	60 (22.6)	71.8 (8.2)†	NR	36†	14†	27†	27†	NR
Skau *et al.* (2020)[76]	All cause death	Outpatients with PAD	436	59	120	70.1 (7.2)	78	25	76	NR	18	NR
Winkel *et al.* (2010)[89]	Cardiovascular death at 2 y	Patients with symptomatic PAD	3 655	75	24	67.7 (9.6)†	61†	NR	20†	42†	NR	NR
de Liefde *et al.* (2012)[34]	Long term death	Patients with PAD	2 165	67	60 (61–68)	62 (11)†	37†	19†	32†	6†	NR	7†
Mui *et al.* (2011)[67]	Death at 12 y	Patients with PAD undergoing angiography	488	68	72 (40.8)	66 (11.3)†	58†	31†	60†	NR	23†	NR
Urbonaviciene *et al.* (2011)[82]	All cause and cardiovascular death at 120 mo	Patients with intermittent claudication or critical limb ischaemia	295	58	73.2 (25.2)	67 (9.6)	51	15	60	NR	15	NR
Urbonaviciene *et al.* (2011)[83]	All cause and cardiovascular death at 100 mo	Patients with intermittent claudication or critical limb ischaemia	378	61	60 (20.4)	65.7 (8.8)†	56†	24†	56†	NR	18†	NR
Ye *et al.* (2011)[90]	All cause death	Patients with PAD	13 039	61	66*	69.5 (11.9)†	74†	35†	81†	16†	56†	9.8†
Jain *et al.* (2012)[48]	Long term all cause and cardiovascular death	Patients with PAD	679	56	54	72.7 (8.4)†	NR	35†	20†	26†	23†	NR
Urbonaviciene *et al.* (2012)[81]	All cause and cardiovascular death at 120 mo	Patients with intermittent claudication or critical limb ischaemia	463	58	73.2	65.6 (9.5)†	51†	13†	58†	NR	14	NR
Valentijn *et al.* (2012)[84]	Death at 4 y	Patients with PAD requiring vascular surgery	1 172	73	1	68.6 (10.1)†	70†	23†	45†	9†	NR	31†
Jain *et al.* (2013)[47]	Long term death	Patients with PAD	442	58	56.4	72.7 (8.2)†	27†	32†	17†	20†	24†	NR
Leeper *et al.* (2013)[59]	All cause and cardiovascular death at 12 y	Patients with PAD by history or by claudication	725	98	135 (74.4)	62 (9.1)	65	16	67	8	NR	NR
de Vos *et al.* (2014)[35]	Death at 5 y	Patients with established PAD	252	73	61.2 (60–63.6)	66 (11)	91	29	50	NR	28	NR
Desormais *et al.* (2014)[36]	Combined 1 y death and major amputation	Patients with PAD Rutherford III–VI	925	71	12	71 (12.8)	77	44	25	13	38	NR
Erturk *et al.* (2014)[37]	Cardiovascular	Patients with PAD	508	81	20 (12–27)	64 (57–71)*	61†	42†	52†	NR	41†	21.6†
Kals *et al.* (2014)[52]	Death at 8 y	Patients with PAD Fontaine stage II –IV	117	100	49.2 (26.4)	62.1 (7.6)†	39†	NR	97†	NR	20†	NR
Linnemann *et al.* (2014)[61]	Total death and amputation at 1 y	Patients with PAD Rutherford II–V	1 041	63	12	70.7 (10.8)	85	41	24	NR	45	38
Mueller *et al.* (2014)[66]	All cause death	Patients with PAD Rutherford I–VI	487	70	60	70 (38–94)*	61	NR	41	NR	31	NR

Table 1-*continued*

Author (year)	Outcome of interest	Study population	Sample size	Men — %	Follow up — mo (mean)	Mean age — y	Hypertension — %	Diabetes — %	Smoking — %	Heart failure — %	Coronary artery disease — %	Chronic kidney disease — %
Pohlhammer *et al.* (2014)[68]	All cause death	Patients with PAD Fontaine stage IIa—IIb	235	100	84	58.3 (6.3)	86	16	52	NR	29	NR
Jones *et al.* (2015)[51]	Composite of death, myocardial infraction, and stroke at 8 y	Patients with PAD undergoing revascularisation	908	57	40.8	68.6 (10.1)	89	41	31	NR	14	21
Kim *et al.* (2015)[53]	All cause of death	Patients with intermittent claudication or critical limb ischaemia	240	81	17 (15.4—18.5)	66.8 (11.3)	73	48	55	NR	38	NR
Lacroix *et al.* (2013)[57]	Death and amputation at 1 y	Patients with PAD Rutherford III—VI	1 010	71	12	70.7 (2.8)	77	44	25	13	37	NR
Smolderen *et al.* (2015)[77]	Cardiovascular and other causes of death at 60 mo	Patients with PAD	756	65	38.4	65 (9.8)	60	24	50	5	19	9
Staniszewska *et al.* (2015)[78]	All cause death at 10 y	Patients with symptomatic PAD	238	66	83*	69 (62—75)	65	14	NR	NR	31	NR
Amrock *et al.* (2016)[26]	Long term all cause and cardiovascular death	Patients with PAD	556	50	87.6	70.9 (11.3)	78	30	22	NR	NR	31
Hackl *et al.* (2016)[42]	Death at 5 y	Patients with PAD	184	67	94.8 (86.4—104.4)	68 (61—76)*	81	35	40	NR	21	NR
Jalkanen *et al.* (2016)[49]	Death at 36 mo	Patients with PAD undergoing endovascular intervention	887	57	36	72.4	70	43	27	NR	43	10
McDermott *et al.* (2016)[63]	All cause and cardiovascular death at 70 mo	Patients with PAD	951	61	32.4 (14.4)	71.29 (9.14)	34	34	21	20	23	NR
Senthong *et al.* (2016)[73]	All cause death at 5 y	Patients with PAD	821	66	60	66 (10)	83	43	74	NR	90	NR
Ali *et al.* (2018)[24]	30 d death after lower extremity bypass surgery	Patients with PAD	4 704	64	1	67.9 (11.7)	85	NR	41	NR	NR	7
Amrock *et al.* (2017)[25]	All cause and cardiovascular death	Patients with PAD	647	42	86.4	67.8	77	30	25	NR	NR	30
Chowdhury *et al.* (2017)[31]	Cardiovascular and all cause death	Patients with symptomatic PAD	220	66	46 (31—64)*	69 (63—88)	71	23	86	NR	36	17
Senda *et al.* (2018)[72]	All cause and cardiovascular death at 5 y	Patients with intermittent claudication	441	81	42 (22.8)	74 (67—80)	74	43	59	10	31	NR
Senthong *et al.* (2017)[74]	All cause death at 5 y	Patients with PAD undergoing coronary angiography	771	66	60	66 (10)	83	43	74	31	90	NR
Wickström *et al.* (2017)[87]	All death at 80 mo	Patients with PAD admitted for DSA	887	NR	84	72.4	NR	NR	NR	NR	NR	NR
Wickström *et al.* (2017)[88]	All cause and cardiovascular death at 40 mo	Patients with symptomatic PAD	732	58	40	72 (11)	40	41	29	NR	43	10
Esteban *et al.* (2019)[38]	Death and amputation	Patients with PAD	518	80	14.5	NR	79	57	63	11	26	26
Hemstra *et al.* (2018)[43]	Cardiovascular death	Patients with symptomatic PAD	286	57†	84†	67	49†	16†	58†	NR	NR	NR

Continued

Table 1-*continued*

Author (year)	Outcome of interest	Study population	Sample size	Men — %	Follow up — mo (mean)	Mean age — y	Hypertension — %	Diabetes — %	Smoking — %	Heart failure — %	Coronary artery disease — %	Chronic kidney disease — %
Higashitani *et al.* (2018)[44]	All cause, cardiovascular, and non-cardiovascular death, and MACE	Patients with PAD undergoing endovascular intervention	2 238	72	10.4	73.3 (9.3)	83	57	23	12	47	27
Höbaus *et al.* (2018)[45]	MACE and all cause of death at 5 y	Patients with PAD Rutherford I–III	366	66	60	69 (10)	NR	NR	NR	NR	32[†]	NR
Hu *et al.* (2019)[46]	Long term amputation and death	Patients with PAD	16 888	53	65 (41.1)	63.4 (14.5)	68	26	NR	10	NR	19
Pourafkari *et al.* (2018)[69]	All cause death at 10 y, and MACE	Patients with PAD undergoing revascularisation	1 228	99	20[*]	67[†]	77[†]	52[†]	NR	9[†]	55[†]	32[†]
Tern *et al.* (2018)[80]	All cause death at 90 mo	Patients with clinical diagnosis of PAD	678	60	69.9[*]	74 (64–82)[*]	NR	42	NR	11	NR	NR
Mizobuchi *et al.* (2019)[65]	Any death at 1 000 d	Patient with PAD undergoing endovascular therapy	628	69	69	69 (10)	83	71	38	NR	NR	75
Roncal *et al.* (2019)[71]	Cardiovascular death at 96 mo	Patients with PAD	262	87	48	70 (11)	74	53	32	NR	28	39
Golledge *et al.* (2020)[41]	MACE, amputation, and all cause death	Patients with PAD	1 533	75	39.6 (12–85.2)	69[†]	75[†]	35[†]	31[†]	NR	45[†]	0.8[†]
Malik *et al.* (2020)[62]	All cause death at 4 y	Patients with symptomatic PAD	765	58	48	68.4 (9.7)	89	39	31	14	NR	15
Chi *et al.* (2021)[30]	All cause and cardiovascular death	Patients with abnormal low and high ABI	195	66	90	66.4 (13)[†]	82[†]	42[†]	12[†]	NR	NR	NR
Fukase *et al.* (2021)[40]	All cause of death, MACE	Patients with PAD undergoing endovascular intervention	335	82	43.2 (12–74.4)	72 (8)	84	56	89	NR	NR	36
Koivunen *et al.* (2021)[54]	Cardiovascular death	Patients with PAD Rutherford II–VI	729	58	80	74.9 (10.5)	70	41	29	NR	43	9
Rammos *et al.* (2021)[70]	Death at 24 mo	Patients with PAD	246	59	12.5 (0.1–24)	75 (6.5)[†]	90[†]	36[†]	23[†]	NR	54[†]	39[†]
Al-Damluji *et al.* (2022)[23]	Peri-operative death	Patients with PAD undergoing endovascular intervention	134 081	60	NR	68.4 (11.1)	88	52	79	19	32	14
Aursulesei *et al.* (2022)[27]	Death risk at 10 y	Patients with PAD	101	52	6	70.6 (9.2)	76	38	43	26	24	17
Balasundaram *et al.* (2023)[28]	30 d death after revascularisation	Patients with PAD all stages	11 947	60	1	69[*]	84	56	30	4	NR	10
Kotov *et al.* (2022)[55]	Overall death, amputation or death, and MACE	Patients revascularised for PAD	4 354	68	7.4 (0–12)[*]	69 (62–77)	NR	37	20	17	16	22
Lapébie *et al.* (2022)[58]	All cause death, and MACE	Patients with PAD all stages	2 494	75	9.5 (4.4)	70.6 (12.8)	86	40	25	12	37	40
Vieira-Cardoso *et al.* (2023)[85]	All cause death, and long term MACE	Patients with PAD Rutherford III–VI	107	95	57 (34.4 –69.6)[*]	62.2 (8.8)	65	32	90	12	29	15
Chang *et al.* (2023)[29]	All cause of death, MACE	Patients with lower extremity artery disease	504	47	37.8 (19.8–65)[*]	79.9 (6.2)[†]	88[†]	67[†]	28[†]	14[†]	39[†]	70

Table 1-*continued*

Author (year)	Outcome of interest	Study population	Sample size	Men — %	Follow up — mo (mean)	Mean age — y	Hypertension — %	Diabetes — %	Smoking — %	Heart failure — %	Coronary artery disease — %	Chronic kidney disease — %
Evans *et al.* (2023)[39]	All cause and cardiovascular death	Patients with PAD following endovascular intervention for limiting claudication or critical limb ischaemia	202	78	111 (81.6 −133)*	68*	96	49	26	NR	73	26
Jang *et al.* (2023)[50]	Death at 1, 2, 3, 4, and 5 y	Patients with lower extremity PAD (claudicants and critical limb ischaemia)	214	53	45.6 (27−68)*	71.2 (11.8)	84	78	38	16	53	40
Kurokawa *et al.* (2023)[56]	Death, MALE, MACE	Patients with lower extremity artery disease all stages	288	77	22.4 (8.7 −42.8)*	73 (9)	85	46	22	NR	30	24
Leiherer *et al.* (2023)[60]	All cause and cardiovascular death, and MACE	Patients with PAD all stages	379	72	108 (63.6 −120)*	67*	94	40	31	NR	NR	20
Tasbulak *et al.* (2022)[79]	Long term death, restenosis	Patients with lower extremity artery disease undergoing endovascular intervention	723	89	40.2 (14.9)*	61.6 (9.3)	74	58	58	NR	66	24
Welch *et al.* (2023)[86]	All cause death at 6 mo	Patients with PAD Rutherford III−VI	148	61	6	70.3 (11)	72	NR	75	NR	30	10
Zierfuss *et al.* (2023)[91]	All cause and cardiovascular death	Patients with intermittent claudication and critical limb ischaemia	1 028	61	55*	68 (9.0)†	90†	42†	36†	11†	13†	NR

PAD = peripheral arterial disease; NR = not reported; DSA = digital subtraction angiography; MACE = major adverse cardiovascular event; ABI = ankle brachial index; MALE = major adverse limb event.

* Median.

† Pooled results.

not reporting it. The prevalence of diabetes ranged from 21 — 53%. Chronic kidney disease was reported in four studies (50%), with a prevalence ranging from 6 — 33% (Table 3).

Prognostic factors for mortality outcomes

In multivariable models, over 80 prognostic factors were associated with increased mortality outcomes (Supplementary Table S5).

Sixty three studies (91%) investigated the predictive value of age.[23−26,28−30,32−55,57,59−78,80−84,86−91] Twenty two studies included age as a predictor in the primary model;[24,28,32,35,37−39,43,44,49−52,59,62,63,65,67,69,76,80,89] the remainder adjusted their multivariable model for age. Of the studies that included age in their primary model, 21 showed that as age increased, mortality risk increased. One study's results were not statistically significant (HR 1.04, 95% CI 1.00 — 1.1).[49]

Sex or gender was the second most examined demographic factor, included in 40 (58%) studies, with 31 studies[23,25,26,30,33,34,36,40,41,45−48,53,54,57,60,64,71−74,77,78,81−84,86,90,91] adjusting their multivariable model for sex or gender, and nine studies[27,32,37,43,50,62,63,65,89] including it as a predictor. In terms of the prognostic relevance of sex or gender, two studies established that females faced a lower mortality risk at six years (women *vs.* men, HR 0.45, $p < .05$;[32] men *vs.* women, HR 1.73, 95% CI 1.27 — 2.37[63]), whereas the remaining studies did not yield statistically significant results.

Race/ethnicity was a predictor included in nine studies (13%), where five adjusted their multivariable model for race,[26,47,48,64,75] whereas four included it in their primary model.[24,28,62,63] In one study, other races (compared with White people) had a lower mortality risk (OR 0.69, $p = .022$).[28] The results from the other studies, however, were not statistically significant.

Factors related to previous and current medical history were also predictors of mortality outcomes. Forty four studies (64%) reported the predictive value of diabetes.[25−27,30,32−34,36,37,40,41,44,46,49,51,53−55,57,58,60−64,66,67,69,71,73−75,77−83,87−91] Twenty nine adjusted their multivariable model for diabetes status and 15 studies[25,27,32,37,44,49,51,58,62,63,67,69,79,80,89] included it as a predictor. The results on the effect of diabetes differed among the studies. Although seven studies

Table 2. Individual predictors identified in 69 studies assessing prognostic factors to predict death in patients with peripheral arterial disease (PAD).

Prognostic factor	Total studies assessing prognostic factor (n = 69)	Mortality outcomes described in the included studies						
		All cause death (n = 38; 55%)	Cardio-vascular death (n = 24; 35%)	Death (n = 13; 19%)	Long term death (n = 7; 10%)	30 d death (n = 3; 4%)	In hospital death (n = 2; 3%)	Non-cardio-vascular death (n = 1; 1%)
Demographic factors								
Age	63 (91)	39	16	11	3	3	1	1
Sex	40 (58)	32	8	5	2	2		
Race/ethnicity	9 (13)	6	1			3		
Medical history factors								
Diabetes mellitus	44 (64)	20	11	8	2		1	
Smoking history	32 (47)	19	11	7	1			
Coronary artery disease	24 (35)	11	6	5	1	2	1	
Heart failure	20 (29)	20	3	4	1		1	
Hypertension	17 (25)	7	7	4	1			
Stroke or transient ischaemic attack	13 (19)	8	2	2	1			
Dyslipidaemia	13 (19)	5	3	3	2			
Chronic kidney disease	11 (16)	6	2	5				1
Renal failure	11 (16)	3	3	2	1	1	1	
COPD	8 (12)	4	1	2	1			
Dialysis	7 (10)	4		1		2		
Left ventriclar ejection fraction	6 (9)	4		1		1		
History of intervention	6 (9)	2		2		1	1	
Non-specified cardiovascular disease	5 (7)	3	2					
History of cancer	5 (7)	4		1				
History of angina	4 (6)	2	1			1		
History of amputation	4 (6)	1		1	1		1	
Atrial fibrillation	3 (4)	1	1	1				
Anaemia	2 (3)	1		1				
Musculoskeletal disease	1 (1)			1				
Previous PAD	1 (1)				1			
Post-operative complications	1 (1)			1				
Clinical factors								
BMI	24 (35)	15	4	1				
Ankle brachial index	18 (26)	12	5	1		1		
PAD stage	15 (22)	7	2	6				
Functional performance	8 (12)	6	1	1				
Blood pressure	9 (13)	8	1					
Heartbeat	3 (4)	2	1	1				
Site and number of lesions	3 (4)	2	1					
Physical activity	3 (4)	3	1					
Weight	2 (3)	1		1				
Toe pressure	3 (4)		2			1		
Toe brachial index	2 (3)		2					
Crural index	2 (3)		1	1	1			
Clinical symptoms	2 (3)	1	1					
Depressive symptoms	2 (3)	2	1					
Pulse pressure	1 (1)	1	1					
Biomarkers and laboratory factors								
Glomerular filtration rate and or creatinine	18 (26)	11	4	2				
Non-high density lipoprotein cholesterol	11 (16)	10	3	1				
High sensitivity CRP	11 (16)	6	2	2				1
BNP and NT-proBNP	6 (9)	6		1				
High density lipoprotein cholesterol	5 (7)	4	1					
High neutrophil:lymphocyte ratio	4 (6)	3	1					
Haemoglobin	3 (4)	1		2				
Cardiac troponin	3 (4)	2		1				
Cystatin level	3 (4)	3	2					
Glucose levels and orglycated haemoglobin	3 (4)	2		1				
Triglycerides	2 (3)	1		1				
Red cell distribution width	2 (3)	2						
High trimethylamine N-oxide	2 (3)	1	1					
Urea	1 (1)	1						
High homocysteine	1 (1)	1						
High urine albumin:creatinine ratio	1 (1)	1	1					
White blood cell count	1 (1)	1						
Angiopoietin-2	1 (1)	1						
Symmetric dimethylarginine	1 (1)	1						

Table 2-*continued*

Prognostic factor	Total studies assessing prognostic factor (n = 69)	Mortality outcomes described in the included studies						
		All cause death (n = 38; 55%)	Cardio-vascular death (n = 24; 35%)	Death (n = 13; 19%)	Long term death (n = 7; 10%)	30 d death (n = 3; 4%)	In hospital death (n = 2; 3%)	Non-cardio-vascular death (n = 1; 1%)
α-Defensin	1 (1)	1	1					
Tumour necrosis factor and or sTWEAK	1 (1)		1					
Skin autofluorescence	1 (1)	1						
Protein biomarkers	1 (1)	1						
Microfibril associated glycoprotein 4	1 (1)		1					
Medication factors								
Lipid lowering drug use	12 (18)	7	3	4	1			
Antiplatelet agent use	7 (10)	3		3				
ACEi or ARB use	4 (6)	3	1		1			
Beta blocker use	2 (3)			1	1			
Diuretic	1 (1)	1			1			
Antihypertensive	1 (1)	1						
RAAS inhibitors	1 (1)			1				
Anticoagulants	1 (1)	1						
Hyperbaric oxygen	1 (1)			1				
Other factors								
Scores	13 (19)	6	2	3	1	2		
Frailty measure by mortality frailty index	3 (4)			1				
Apolipoprotein	2 (3)	2				2		
Myeloperoxidase	2 (3)	2						
QT interval	1 (1)	1						
Flow mediated dilatation	1 (1)			1	1			
Renal artery stenosis	1 (1)							
Oxidised low density lipoprotein cholesterol	1 (1)	1			1			
Small arterial stiffness	1 (1)	1						
Aortic valve calcium	1 (1)						1	
Chronic stress	1 (1)			1				
Financial situation	1 (1)							

Data are presented as n (%) or n. The cells that are empty indicate that the prognostic factor in the first column was not included in any study investigating that specific mortality outcome. COPD = chronic obstructive pulmonary disease; PAD = peripheral arterial disease; BMI = body mass index; CRP = C reactive protein; BNP = B type natriuretic peptide; NT-proBNP = N-terminal pro B type natriuretic peptide; s/TWEAK = serum tumour necrosis factor like weak inducer of apoptosis; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; RAAS = renin–angiotensin–aldosterone system.

showed that diabetes increased mortality risk,[27,32,49,51,58,69,79] others did not show a significant association.

Thirty eight studies (55%) assessed the predictive value of smoking status.[23,25–27,32,33,37,40,41,43,47–49,51,52,54,55,57,59–64,67,68,71,73,74,77,81–83,87–91] Twelve included it as a predictor[25,27,32,37,43,49,51,59,62,63,67,89] and the remainder adjusted for it in the multivariable model. Four studies showed a higher mortality risk among smokers.[25,27,49,89] In other studies, however, no statistically significant differences were found between smokers and non-smokers.

History of coronary artery disease, including myocardial infarction and ischaemic heart disease, was assessed in 24 (35%) studies.[23,24,29,36–38,49–51,54,62,63,67,69,73,75–77,80,81,83,87–89] Of these, 13 assessed the predictive value of coronary artery disease,[24,37,38,49–51,62,63,67,69,76,80,89] but only five found that history of coronary artery disease increased mortality risk.[24,38,62,69,76]

BMI was assessed in 24 studies (35%). Nine of these 24 studies examined its predictive value,[25,30,43,44,50,52,63,65,72] whereas 15 adjusted their multivariable model for it.[26,29,47,48,60,64,75,77,78,81–83,86,90,91] Two studies reported that underweight (BMI < 18 kg/m^2) was associated with higher all cause mortality and cardiovascular mortality risk compared with normal weight.[44,72] BMI was also assessed as a continuous variable in five studies.[30,43,52,63,65] Chi *et al.*[30] showed that a decrease in BMI was associated with a lower overall mortality risk (HR 0.94, 95% CI 0.88 – 0.99). The study by McDermott *et al.*[63] also showed a lower all cause mortality risk associated with BMI (HR 0.96, 95% CI 0.93 – 0.99), but no information was available about the direction of the effect. The studies by Amrock *et al.*[25] and Senda *et al.*[72] compared BMI > 30 kg/m^2 *vs*. $18.5 \leq$ BMI < 25.0 kg/m^2, but their results were not statistically significant.

The predictive value of ABI was assessed in 18 studies (26%).[25,32–34,47–49,54,62–64,75–78,81–83] Nine studies adjusted their multivariable analyses for it and nine studies assessed ABI as a primary predictor. Abnormally low ABI was associated with higher mortality risk in four studies.[33,49,54,76] Two studies showed that ABI > 0.90 was associated with a lower all cause mortality risk (HR 0.14, $p < .05$;[32] and HR 0.35, 95% CI 0.13 – 0.96[34]). The results from the remaining three studies were not statistically significant.

Toe pressure and toe brachial index were assessed in three[49,54,88] and two[54,88] studies, respectively. Toe pressure < 30 mmHg *vs*. > 50 mmHg was found to be associated with a higher risk of cardiovascular death (HR 2.31, 95% CI 1.36 – 3.94;[54] and HR 2.84, 95% CI 1.75 – 4.61[88]). Similarly,

Table 3. Baseline characteristics of 69 studies on prognostic models of patients with peripheral arterial disease (PAD).

Author	Outcome of interest	Study population	Predictors included in final model	Sample size	Men — %	Follow up (mean) — mo	Age (mean) — y	Hypertension — %	Diabetes — %	Smoking — %	Heart failure — %	Coronary artery disease — %	Chronic kidney disease — %
Abbas *et al.* (2011)[92]	Death after endovascular intervention	Women with symptomatic PAD undergoing endovascular intervention	Age, congestive heart failure, pre-procedural creatinine	292	0	45 (27)	71 (11)	97	47	61	27	76	26
Dopheide *et al.* (2020)[94]	All cause and cardiovascular death	Patients with PAD Rutherford I–VI	Age, Rutherford class, atherosclerosis extent	1 310	64	50 (26)	72 (11.7)	85	30	62	NR	43	NR
Gupta *et al.* (2012)[95]	Perioperative death	Patients with PAD undergoing elective bypass grafting	Age, chronic corticosteroid use, COPD, SIRS, dialysis dependence, functional status, rest pain	9 556	64	1	68 (60–77)*	84	21	42	2	2	6
Hackl *et al.* (2015)[96]	Cardiovascular events and long term death	Patients with PAD Rutherford II–III	Age, history of myocardial infarction, CRP, ABI, eGFR, and APA, statin, and RAAS inhibitor use	129	71	105 (8.4)	66 (60–76)*	78	31	40	NR	9	NR
Pros *et al.* (2013)[97]	All cause death at 1 y	Patients with PAD	Age, history of myocardial infarction, CRP, ABI, eGFR, and APA, statin, and RAAS inhibitor use	Development cohort, 640; validating cohort, 517	Development cohort, 68; validating cohort, 76	12	Development cohort, 70.2 (13); validating cohort, 70.5 (12)	Development cohort, 70; validating cohort, 71	Development cohort, 42; validating cohort, 48	Development cohort, 26; validating cohort, 23	Development cohort, 11; validating cohort, 11	NR	Development cohort, 17; validating cohort, 14
Wisman *et al.* (2015)[98]	All cause death at 10 y	Patients with PAD undergoing peripheral bypass surgery	Age, chronic limb ischaemia, diabetes, vascular intervention	Development cohort, 482; validating cohort, 2 088	Development cohort, 65; validating cohort, 64	79*	Development cohort, 69 (10); validating cohort, 69 (10)	Development cohort, 39; validating cohort, 39	Development cohort, 23; validating cohort, 27	Development cohort, 60; validating cohort, 53	NR	Development cohort, 16; validating cohort, 18	NR
Cox *et al.* (2022)[93]	30 d death and re-admission after endovascular intervention	Patients with PAD in electronic healthcare records	Physiological high risk factors, elective surgery, functional status, creatinine, INR, blood urea nitrogen, diabetes, claudication, haematocrit, age, renal comorbidities, albumin	14 444	59	NR	69.1 (11.4)	83†	53†	30†	NR	NR	NR
Zhang *et al.* (2022)[99]	In hospital death	Patients with PAD all stages identified from hospital registries	Total number of ICD-10 diagnoses, total of ICD-10 procedure, age, endovascular revascularisation, congestive heart failure, diabetes, region of the hospital, teaching status of the hospital, emergency department use record	150 921	60	Not reported	67.2 (12.9)	NR	38	NR	74	14	33

PAD = peripheral arterial disease; NR = not reported; COPD = chronic obstructive pulmonary disease; SIRS = systemic inflammatory response syndrome; CRP = C reactive protein; ABI = ankle brachial index; eGFR = estimated glomerular filtration rate; APA = antiplatelet agent; RAAS = renin–angiotensin–aldosterone system; INR = international normalised ratio; ICD-10 = International Classification of Diseases, 10th revision.

* Median.

† Pooled results.

toe brachial index < 0.25 *vs.* > 0.50 was associated with a higher risk of cardiovascular death (HR 3.20, 95% CI 1.34 — 7.63;[54] and HR 3.68, 95% CI 1.48 — 9.19[88]).

PAD stage assessed by Rutherford classification or Fontaine stage was investigated in 15 studies (22%).[23,28,29,36,37,39,44,50,53,55,57,61,82,83,91] Of five studies that included the PAD stage as a predictor, four found that a worse PAD stage was associated with a higher risk of mortality outcomes.[28,37,39,44]

Clinical factors, such as blood pressure measurements, were evaluated in nine studies (12%), but different measures, including systolic, diastolic, or mean blood pressure, were used to assess its predictive value.[25,26,30,33,45,52,73,74,77] Six studies adjusted their multivariable model for blood pressure, and three[25,30,52] investigated its predictive value. Kals *et al.*[52] showed that including mean arterial blood pressure in a model aiming to predict the all cause and cardiovascular mortality rate incremented the discrimination abilities of the model (AUC 0.70, 95% CI 0.60 — 0.80). The results from Chi *et al.*[30] and Amrock *et al.*[25] were not statistically significant.

Laboratory values such as creatinine, eGFR, and CRP were predictors of mortality outcomes in 18 (26%)[27,45,51,53,57,61,65,67,68,71—74,76,78,82,83,91] and 14 (20%) studies,[25,26,32,40,50,57,66,71—74,76,81,83] respectively. Two studies showed that eGFR < 30 mL/min/1.73m^2 was associated with higher mortality risk compared with eGFR > 90 mL/min/1.73m^2.[51,57] The prognostic value of brain natriuretic peptide (BNP), haemoglobin, and anaemia were evaluated in six (9%)[65,66,68,70,74,91] and five (7%)[36,57,65,72,90] studies, respectively. High BNP levels were associated with higher mortality risk in four studies.[65,66,70,91] Other factors such as scores, e.g., $CHADS_2$, R_2CHADS_2, and lower limb arterial calcification scores, and chronic stress were assessed in 13 studies (19%)[23,28,30,31,42,46,49,51,55,65,80,86,87] and one study (1%),[62] respectively.

Risk of bias assessment of studies on prognostic factors

Six studies had low risk of bias in all domains[29,58,60,62,77,80] and the remainder had an unclear or high risk of bias in at least one domain. Most of the studies were downgraded due to inadequate reporting of differences between participants who completed the study and those who did not, lack of description of loss to follow up, or no explanation of how missing data were handled by the authors (Fig. 2).

Prognostic models

Eight studies were identified on prognostic models to predict mortality outcomes. The number of predictors included in each model ranged between three and 12. Age was the only predictor present in all models. Sex and race were not included in the final models. Each model contained at least one medical history factor, such as diabetes, history of myocardial infarction, and chronic obstructive pulmonary disease. Laboratory measurement factors, specifically creatinine and CRP, were included in four (50%) and two (25%) models, respectively. Two studies used machine learning techniques to predict 30 day and in hospital mortality rates, respectively.[93,99] These studies identified physiological high risk factors and total number of International Classification of Diseases, Tenth Revision (ICD-10) diagnoses as the most important predictors for 30 day and in hospital mortality rate, respectively.

All models demonstrated acceptable discrimination with AUC from 0.70 — 078. Five studies (50%) conducted internal model validation, split population was used in four models, and bootstrapping in one study.[93—95,98,99] Two studies externally validated the Cohorte de Patients Artériopathes (COPART) risk score in an external cohort in another country.[96,97] In both populations, the model had a satisfactory performance in discrimination (C statistic 0.74) and calibration. All studies provided a statistical syntax, a web interface, or a simple scoring system to calculate an individual risk.

Risk of bias assessment of studies on prognostic models

Five of the studies describing a prognostic model had an overall high risk of bias, whereas two studies had an overall unclear risk of bias.[98,99] Particularly, the items regarding analyses were suboptimal, including the categorisation of

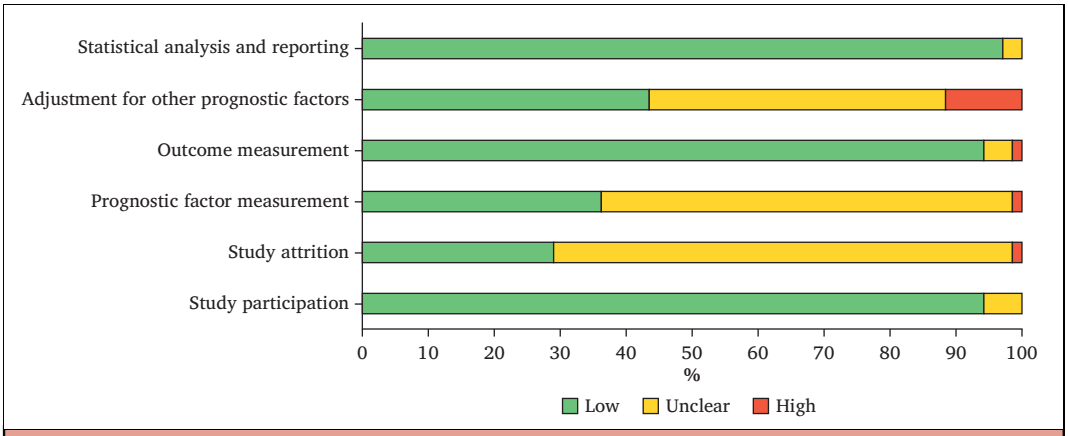

Figure 2. Quality in Prognosis Studies risk of bias for studies on prognostic factors. Low = low risk of bias; unclear = unclear risk of bias; high = high risk of bias.

continuous variables, lack of reporting on missing data, and the use of univariable analysis for selecting predictors. Most of the studies were considered of low concern for applicability, meaning that the participants, predictors, and outcomes reflected clinical practice. Except for the study by Abbas *et al.*,[92] applicability was unclear owing to inadequate information on participants and settings (Table 4).

DISCUSSION

This systematic review summarises evidence from 69 studies that investigated prognostic factors for death in PAD, as well as eight studies that developed or validated prognostic models. Over 80 single prognostic factors were identified, with age, sex, diabetes, hypertension, and smoking status consistently emerging as predictors of mortality outcomes. These factors can be considered when deciding which models provide incremental predictive accuracy and are more precise and suitable for specific patient populations or outcomes.

Prognostic factors

Age, which constitutes an essential and natural prognostic factor, was the only factor present in more than 90% of the studies. It has been found that in patients with PAD, mortality risk increases after the age of 65 years, with each year reflecting worse outcomes in older patients. This suggests that early diagnosis and intervention might provide benefits, such as reducing the severity of symptoms, improving physical functioning and quality of life, and lowering the mortality risk.

Smoking and diabetes are recognised risk factors for PAD and are associated with disease severity.[100,101] In this systematic review, several included studies described the predictive value of these factors, and their findings confirmed the associations between diabetes and smoking status and poor outcomes in patients with PAD. It is surprising, however, that over 40% of the studies did not include them as variables in their analyses. While this discrepancy could be caused by population differences, study designs, and specific research objectives, it raises a critical concern about the potential oversight of crucial determinants that significantly contribute to accurate risk prediction in patients with PAD. Refining predictive models for PAD is imperative, and including smoking status and diabetes as essential variables in future research ensures that predictive models accurately capture the multifaceted nature of PAD and its associated risk factors.

In the included studies, elevated levels of CRP and BNP were associated with increased mortality risk. A notable challenge arises in determining cutoff levels, specifically for predictors with a continuous unit of analysis, or changing units that effectively discriminate between individuals at high and low risk of death. This challenge is attributed to differences in statistical modelling approaches and the unique characteristics of diverse study populations. This complicates the clinical interpretation of CRP and BNP levels and hinders their seamless integration into routine risk stratification practices for patients with PAD. Future research efforts should focus on establishing consensus on standardised cutoff levels or changing units, considering variations in statistical methodologies and population demographics.

Prognostic factors such as race, ethnicity, and socio-economic status were barely assessed in any study. Only 13% and 1% of studies, respectively, have reported on these factors, despite their known significant roles in health disparities and outcomes. For instance, Asian American patients with PAD have been found to have higher in hospital mortality rates, whereas Black and Hispanic patients have a higher percentage of CLTI than non-Hispanic White patients.[102]

Additionally, low socio-economic status has been linked to an increased risk of amputation.[103] Neglecting these factors can lead to an incomplete understanding of how they affect the overall prognosis of PAD. Therefore, to ensure that medical interventions are tailored to the needs of a diverse patient population, they need to be explored further.

Prognostic models

Relying on a single prognostic factor often falls short in providing a comprehensive prognosis for all patients with PAD.[104] A more informative approach involves integrating relevant factors into existing models, and ideally externally

Table 4. The Prediction model Risk Of Bias ASsessment Tool (PROBAST) for studies on prognostic factors.

Study	Risk of bias				Applicability			Overall	
	Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	Risk of bias	Applicability
Pros *et al.* (2013)[97]	+	+	+	−	+	+	+	−	+
Hackl *et al.* (2015)[96]	+	+	+	−	+	+	+	−	+
Abbas *et al.* (2011)[92]	−	?	+	−	?	?	+	−	?
Wisman *et al.* (2015)[98]	+	+	+	?	+	+	+	?	+
Dopheide *et al.* (2020)[94]	+	+	+	−	+	+	+	−	+
Gupta *et al.* (2012)[95]	−	?	+	−	+	+	+	−	+
Cox *et al.* (2022)[93]	+	?	+	+	+	+	+	+	+
Zhang *et al.* (2022)[99]	+	?	+	?	+	+	+	?	+

(+) = low risk of bias and low concern about applicability; (−) = high risk of bias and high concern about applicability; (?) = unclear risk of bias and unclear concern about applicability.

validating them. Eight studies were identified on prognostic models to predict mortality outcomes with similar discrimination and calibration abilities. Although all models had methodological limitations, particularly in statistical analyses, including handling missing data and predictor selection, future prognostic models can improve their methodological approaches by addressing these specific concerns.

From a clinical perspective, the identified prognostic models are easy to use in clinical practice because simple scoring systems with points or percentages to assign risk levels are used, with predictors that are commonly available in clinical practice. All the models included age in the primary model and at least one of the identified medical history factors and or clinical factors. Sex was notably absent from all models except for the study conducted by Abbas *et al.*,[92] which was specifically developed for a female population. The absence of sex as a variable in most models raises questions about the comprehensiveness and applicability of existing prognostic tools across diverse populations. The unique physiological characteristics of women and men, and potential differences in clinical presentation, emphasise the necessity of incorporating sex specific factors into prognostic models.

The investigation of prognostic models developed for other cardiovascular diseases offers a promising avenue for exploration in the context of PAD. Chi *et al.*[30] evaluated the predictive value of $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc scores, originally designed for assessing stroke risk in patients with atrial fibrillation, within the context of patients with both low and abnormally high ABI. They found that $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc scores were significant predictors of cardiovascular and all cause mortality, and had additional predictive values to conventional parameters for predicting cardiovascular and all cause death. The results of this research approach show the potential applicability of predictive models across different cardiovascular conditions.

The use of machine learning techniques in medical research has become increasingly popular, particularly in developing and validating models. In predicting mortality risks among patients with PAD, machine learning has been found to be effective. Two studies exemplify the application of machine learning in predicting mortality outcomes in patients with PAD.[93,99] These studies have shown that incorporating new predictors apart from traditional prognostic factors such as age can improve the predictive capacity of a model. For instance, Zhang *et al.*[99] found that the total number of ICD-10-CM diagnoses and the total number of ICD-10-CM procedures were top predictors of in hospital death. Similarly, Cox *et al.*[93] identified physiological high risk as the most important predictive factor of 30 day death. Interestingly, none of the identified studies that examined single prognostic factors assessed the predictive abilities of the abovementioned. These findings demonstrate the significance of machine learning in prognostic research. Machine learning has the potential to extract valuable insights that may not be noticeable through traditional statistical methods. Moreover, incorporating new parameters along with demographic and clinical characteristics can significantly enhance prognostic models.

Current recommendations and perspectives towards the future

The 2024 guideline of the European Society for Vascular Surgery (ESVS) on the management of asymptomatic lower limb PAD and intermittent claudication mentioned the role of some of the prognostic factors in relation to the prognosis of PAD.[105] This concerns all the factors that were identified in the present systematic review. For instance, biomarkers such as CRP and NT-proBNP (N-terminal prohormone of BNP) are discussed; however, because of insufficient data on the added value of prognosis, laboratory biomarkers are not recommended for clinical risk stratification. This was confirmed in the present systematic review, with only 16% and 9% of the identified studies investigating the predictive value of CRP and NT-proBNP, respectively. Tobacco smoking is described as an essential risk factor for progression and poorer outcomes in patients with PAD, and clear recommendations about smoking cessation are given to improve prognosis in this population. According to the guideline, the role of sex needs to be better identified, with conflicting research results, something that was confirmed in the review. One of the explanations for this may be the under representation of women in epidemiological studies. Therefore, the ESVS guideline recommends balancing the proportion of women and men in clinical studies.

The current guidelines do not recommend any prognostic model to be used in clinical practice in patients with PAD. Similarly, in the latest global vascular guideline for CLTI management, the list of most important predictors of death is included as part of the patient risk estimation.[106] Similar to the present results, no specific tool or model is recommended because of the lack of studies prospectively testing their models across the spectrum of CLTI. This systematic review is a starting point for healthcare professionals to identify the current state of risk prediction tools in clinical practice, and to continue research efforts to refine and validate these tools, ultimately enhancing their utility and effect in guiding clinical decision making for patients with PAD and CLTI.

Strengths and limitations

To the best of our knowledge, this is the first systematic review investigating the prognostic factors and models for predicting mortality outcomes in patients with PAD. The main strength of the study is the rigorous systematic review methodology used to identify, describe, and assess the risk of bias of all studies. Some limitations are acknowledged in this systematic review. The studies were too heterogeneous to conduct any meta-analysis. The inherent variability in data presentation, outcome measures, and participant

characteristics among the studies contributed to this heterogeneity. To improve this, it is recommended that authors adhere to reporting guidelines, such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,[107] to maintain the completeness of their reporting. Standardising outcome definitions to promote consistency among diverse studies is also advocated. And the stratification of patient groups based on relevant characteristics is also suggested, such as sex, disease stage, or comorbidities. This stratification will enable more refined subgroup analyses, allowing a deeper understanding of how a specific factor performs in different populations. Secondly, only studies published in English and Spanish were considered, potentially excluding relevant studies in other languages. Studies with small sample sizes were excluded; however, full text screening identified that all assessed predictors were also considered in the excluded studies. This systematic review only considered studies that were published from 2010 onwards. While this approach allowed us to focus on the most recent evidence, it may have resulted in the exclusion of relevant studies that were conducted before this period. Consequently, the ability to capture the complete range of prognostic factors and models in PAD may have been affected by this limitation. To determine whether many studies were missed, the same search strategy was conducted on PubMed to identify studies published between 1980 and 2009 that contained the keywords of interest in their title or abstract. This search yielded 190 studies, of which most could be excluded based on a quick scan. This is probably because prognostic research in the setting of PAD is rather novel. Therefore, not many references were missed by limiting the search to studies published from 2010 onwards. Furthermore, the review excluded studies that exclusively focused on patients with CLTI. This specific exclusion criterion might limit the generalisability of the findings to this subset of patients. Patients with CLTI often represent a distinct and advanced stage of PAD, characterised by severe limb ischaemia and associated with higher morbidity and mortality rates. By excluding studies exclusively focused on CLTI, this systematic review may only partially capture the unique prognostic factors and models relevant to this specific subgroup. Researchers and clinicians should be aware of this exclusion when applying the findings to populations with CLTI. Future studies explicitly focusing on CLTI could provide valuable insights into prognostic factors specific to this severe manifestation of PAD. Although the identified prognostic models report acceptable performance abilities, they differ significantly in their outcome definitions, the included patient population, and the considered variables. Moreover, only two of the models were externally validated. Therefore, it cannot be conclusively determined which model would perform best in clinical practice. We urge clinicians to select a model that matches each patient's individual characteristics and emphasise that externally validated models are more likely to provide an accurate prediction.

Conclusion

Sex, age, diabetes, hypertension, and smoking are consistently identified as key prognostic factors that influence mortality outcomes in patients with PAD Fontaine stage I — III or Rutherford category 0 — 4. A strategic approach of continuously updating and validating existing models is recommended. This involves a dynamic process that periodically reviews and refines the models, considering the evolving nature of medical knowledge and patient demographics. We suggest exploring the integration of additional prognostic factors with robust predictive capabilities for mortality outcomes. This proactive approach aims to determine whether incorporating these factors significantly improves the refinement and precision of prognostication, leading to more reliable and relevant models.

CONFLICT OF INTEREST

None declared.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2024.05.029.

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