Peripheral Artery Disease Prognosis: Systematic Review with ☸SAIMSARA.

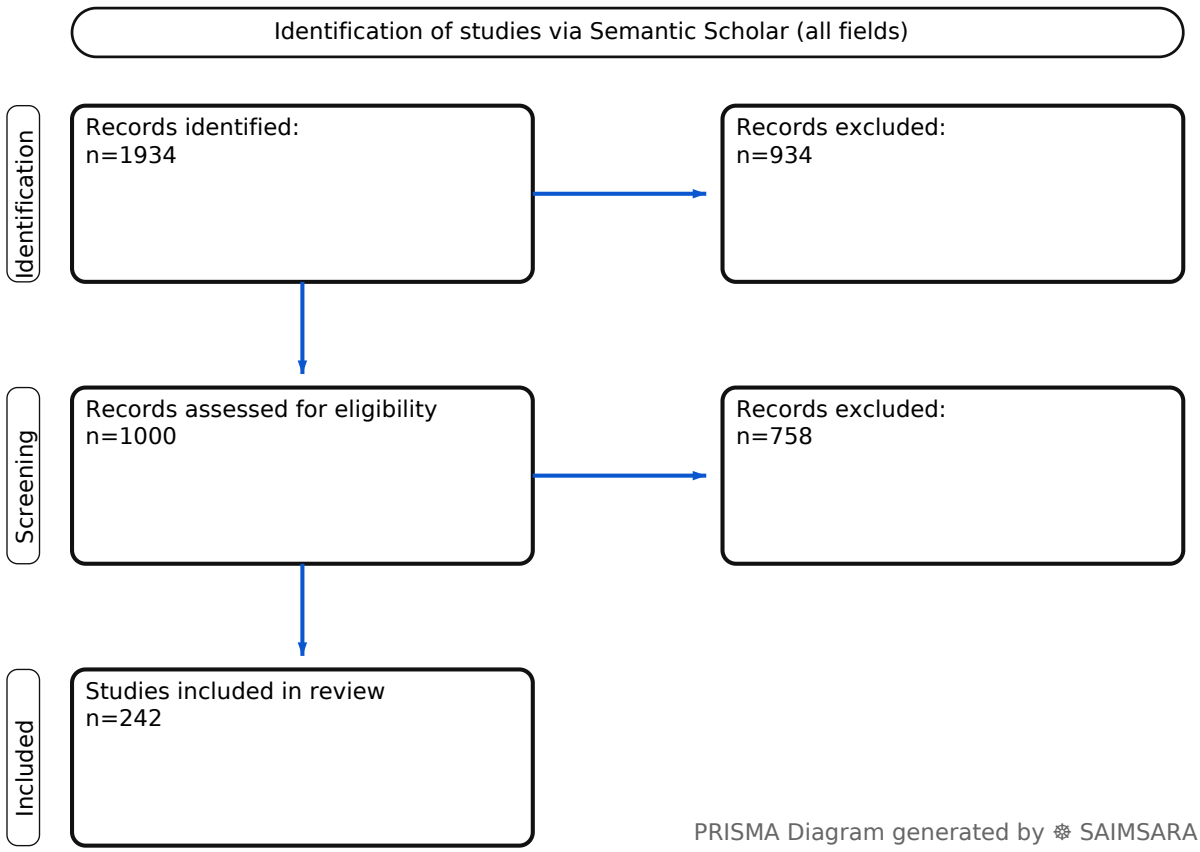
saimsara.com • Download PDF • URL

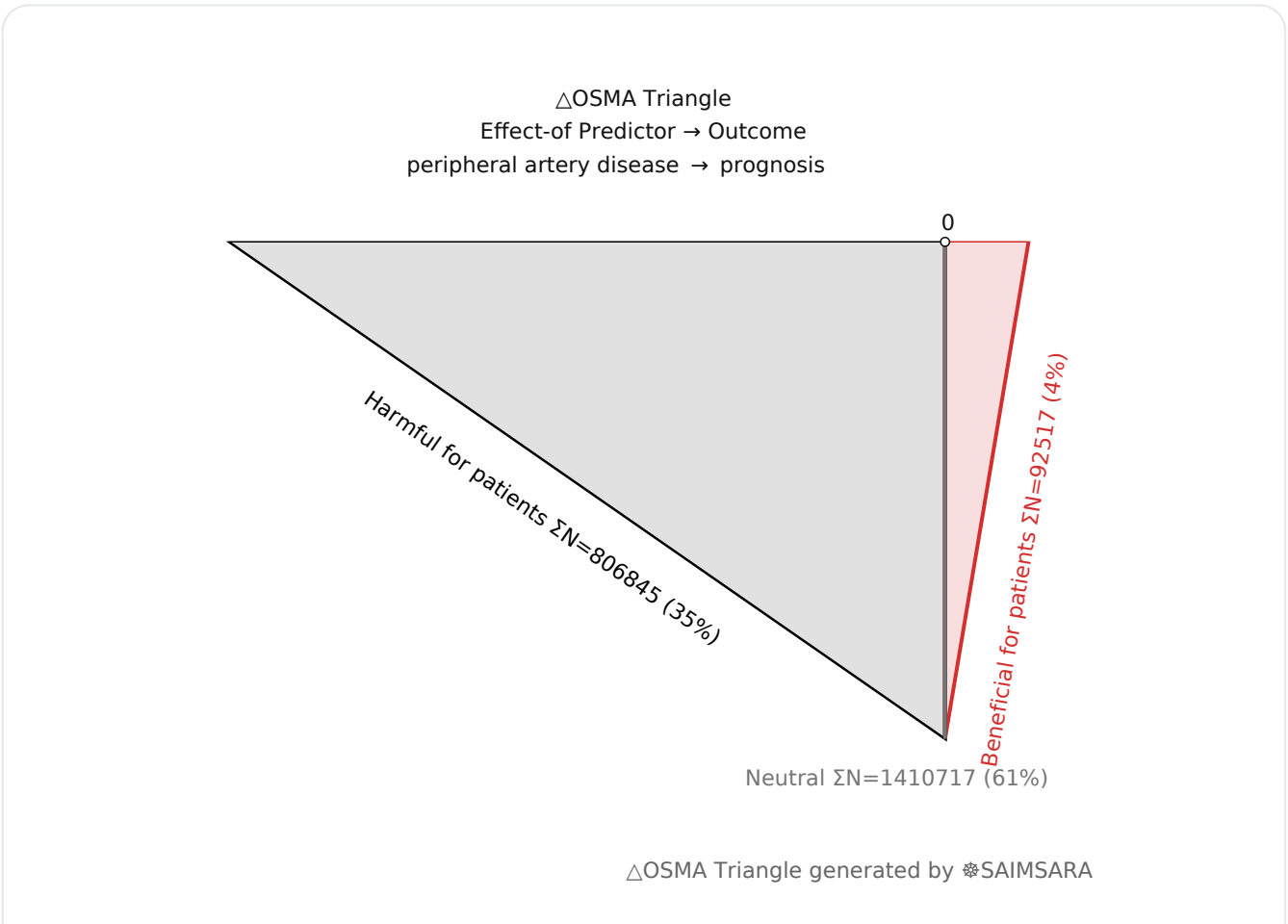
Abstract: This paper aims to synthesize current research on peripheral artery disease prognosis, identifying key risk factors, biomarkers, and management strategies that influence patient outcomes. The review utilises 242 studies with 2310079 total participants (naïve ΣN). Direct numerical comparison of a single central value for peripheral artery disease prognosis is challenging due to the high heterogeneity in patient populations, specific endpoints (e.g., all-cause mortality, cardiovascular mortality, major adverse limb events, major adverse cardiovascular events), and follow-up durations across studies. However, a consistent theme is that PAD is associated with significantly elevated mortality and adverse event rates. This dire prognosis extends across diverse patient populations, including those with significant comorbidities like diabetes, hemodialysis, and coronary artery disease. The most impactful limitation affecting certainty is the inherent heterogeneity in study designs, patient cohorts, and reported outcomes, which precludes a single, universally applicable prognostic figure. Clinicians should prioritize comprehensive risk assessment, including evaluation of comorbidities, inflammatory markers, and nutritional status, to guide intensified, personalized management strategies for patients with peripheral artery disease.

Keywords: Peripheral Artery Disease; Prognosis; Mortality; Major Adverse Limb Events; Major Adverse Cardiovascular Events; Biomarkers; Risk Factors; Endovascular Treatment; Hemodialysis; Inflammation

Review Stats

- Generated: 2026-01-30 17:30:12 CET
- Plan: Pro (expanded craft tokens; source: Semantic Scholar)
- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 1934
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 242
- Total study participants (naïve ΣN): 2310079


Identification of studies via Semantic Scholar (all fields)
Identification
Records identified:
n=1934
Records excluded:
n=934
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=758
Included
Studies included in review
n=242
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease → prognosis
0
Harmful for patients ΣN=806845 (35%)
Beneficial for patients ΣN=92517 (4%)
Neutral ΣN=1410717 (61%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar

Outcome: prognosis Typical timepoints: 1-y, 5-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, survival.

Predictor: peripheral artery disease — exposure/predictor. Typical comparator: non-dialysis patients., management by a surgeon, other inflammatory indices, dipeptidyl peptidase-4….

- **1) Beneficial for patients** — prognosis with peripheral artery disease — [8], [13], [18], [24], [73], [80], [82], [88], [91], [133], [137], [177], [183], [198], [217], [222], [242] — ΣN=92517
- **2) Harmful for patients** — prognosis with peripheral artery disease — [1], [3], [4], [6], [10], [11], [12], [14], [15], [16], [20], [22], [25], [54], [56], [57], [62], [63], [64], [67], [68], [75], [76], [78], [79], [81], [87], [89], [90], [93], [98], [100], [126], [127], [131], [136], [138], [143], [144], [146], [149], [150], [159], [160], [161], [163], [165], [171], [172], [175], [176], [180], [185], [186], [187], [189], [190], [192], [193], [195], [196], [197], [201], [202], [203], [204], [205], [207], [209], [210], [211], [212], [213], [219], [221], [224], [225], [226], [227], [229], [230], [232], [233], [234], [236], [237], [239], [240], [241] — ΣN=806845
- **3) No clear effect** — prognosis with peripheral artery disease — [2], [5], [7], [9], [17], [19], [21], [23], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [55], [58], [59], [60], [61], [65], [66], [69], [70], [71], [72], [74], [77], [83], [84], [85], [86], [92], [94], [95], [96], [97], [99], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [128], [129], [130], [132], [134], [135], [139], [140], [141], [142], [145], [147], [148], [151], [152], [153], [154], [155], [156], [157], [158], [162], [164], [166], [167], [168], [169], [170], [173], [174], [178], [179], [181], [182], [184], [188], [191], [194], [199], [200], [206], [208], [214], [215], [216], [218], [220], [223], [228], [231], [235], [238] — ΣN=1410717

1) Introduction

Peripheral artery disease (PAD) represents a significant global health burden, characterized by progressive atherosclerosis affecting arteries outside of the heart and brain [50, 125, 129]. Its prevalence is notably high in underserved populations [30] and among individuals with comorbidities such as diabetes mellitus (DM), chronic kidney disease (CKD), and coronary artery disease (CAD) [36,

58, 99]. PAD is consistently associated with a poor prognosis, marked by increased risks of major adverse cardiovascular events (MACE), major adverse limb events (MALE), amputation, and all-cause mortality [46, 117, 172]. Understanding the multifaceted determinants of prognosis in PAD is crucial for effective risk stratification, personalized management strategies, and ultimately, improving patient outcomes.

2) Aim

This paper aims to synthesize current research on peripheral artery disease prognosis, identifying key risk factors, biomarkers, and management strategies that influence patient outcomes.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields. Retrospective designs were common [1, 4, 6, 10, 12, 45, 62, 69, 74, 84, 86, 87, 88, 90, 96, 100, 101, 103, 107, 110, 114, 118, 119, 123, 131, 136, 142, 144, 149, 156, 159, 160, 161, 167, 175, 176, 177, 178, 188, 190, 192, 194, 195, 197, 201, 202, 205, 207, 212, 214, 216, 217, 219, 221, 224, 226, 228, 230, 231, 232, 236, 239, 240, 241], introducing potential for selection and recall bias. Prospective cohort studies [3, 5, 11, 13, 15, 24, 37, 38, 39, 41, 44, 56, 64, 73, 76, 78, 79, 81, 82, 85, 89, 92, 99, 108, 109, 115, 116, 120, 121, 126, 128, 133, 134, 136, 137, 138, 140, 142, 143, 144, 146, 147, 152, 156, 159, 160, 161, 163, 164, 165, 166, 169, 171, 173, 176, 177, 180, 184, 185, 186, 189, 190, 192, 193, 196, 198, 203, 204, 208, 210, 211, 212, 213, 214, 215, 229, 235, 240] and randomized controlled trials (RCTs) [27, 80, 91, 94, 109, 121, 133, 173, 176, 177] generally offer higher levels of evidence. Many studies did not specify study type or directionality [2, 7, 9, 17, 18, 19, 20, 21, 22, 26, 29, 31, 33, 34, 35, 42, 43, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 57, 59, 60, 61, 63, 65, 66, 68, 70, 71, 72, 75, 77, 83, 93, 95, 97, 98, 102, 104, 105, 106, 111, 112, 113, 117, 122, 124, 125, 127, 128, 129, 130, 132, 135, 139, 141, 145, 148, 150, 151, 153, 154, 155, 157, 158, 162, 166, 168, 170, 172, 174, 179, 181, 182, 183, 187, 191, 194, 199, 200, 206, 207, 209, 218, 220, 222, 223, 225, 233, 234, 237, 238, 242], limiting certainty about their robustness. Sample sizes varied widely, from small cohorts [16, 18, 35, 39, 41, 43, 54, 60, 63, 77, 95, 103, 105, 107, 109, 111, 123, 124, 128, 141, 145, 146, 147, 164, 174, 178, 181, 182, 188, 193, 199, 204, 208, 215, 219, 229] to large registries [1, 6, 13, 23, 27, 28, 38, 44, 64, 74, 75, 76, 82, 84, 87, 88, 89, 90, 92, 96, 97, 98, 99, 100, 101, 106, 108, 110, 113, 114, 115, 116, 118, 119, 120, 121, 126, 127, 131, 133, 134, 136, 137, 138, 140, 142, 143, 144, 149, 150, 156, 157, 158, 159, 160, 161, 162, 163, 165, 166, 167, 169, 171, 173, 175, 176, 179, 180, 183, 185, 189, 190, 192, 195, 196, 198, 202, 205, 206, 207, 210, 212, 213, 214, 216, 221, 224, 226, 227, 230, 231, 232, 235, 236,

239], impacting generalizability.

4) Results

4.1 Study characteristics:

The included studies predominantly employed cohort designs, with a mix of retrospective and prospective approaches, alongside some mixed-design studies and randomized controlled trials. Populations frequently included patients with peripheral artery disease (PAD) and various comorbidities such as diabetes, chronic kidney disease (CKD), hemodialysis (HD), coronary artery disease (CAD), acute coronary syndromes (ACS), and those undergoing revascularization procedures. Follow-up periods ranged from short-term (e.g., 30 days, 3 months, 6 months) to long-term (e.g., 1 year, 2 years, 5 years, 10 years, and up to 16 years).

4.2 Main numerical result aligned to the query:

Direct numerical comparison of a single central value for peripheral artery disease prognosis is challenging due to the high heterogeneity in patient populations, specific endpoints (e.g., all-cause mortality, cardiovascular mortality, major adverse limb events, major adverse cardiovascular events), and follow-up durations across studies. However, a consistent theme is that PAD is associated with significantly elevated mortality and adverse event rates. For instance, 10-year cumulative mortality rates after cardiovascular surgery in hemodialysis patients with PAD treated with lower extremity bypass (LEB) reached 58.9%, compared to 15.6% in non-HD CABG patients [1]. In patients with non-ST-segment elevation acute coronary syndromes (NSTEMI), 1-year mortality was 16.2% in PAD patients versus 6.2% in non-PAD patients [6]. For patients with chronic limb-threatening ischemia (CLTI), 5-year amputation-free survival can be as low as 43% [49], with 1-year survival rates without major amputation reported at 45% [122].

4.3 Topic synthesis:

- **Comorbidity Burden and Mortality:** Peripheral artery disease is an independent predictor of mortality, with risks significantly amplified by comorbidities such as hemodialysis (adjusted HR 3.04 for HD vs non-HD; 10-year cumulative mortality up to 58.9% in LEB HD patients) [1, 9, 38, 93], acute coronary syndromes (1-year mortality 16.2% vs 6.2% in NSTEMI PAD vs non-PAD) [6, 227], and heart failure (independent predictor of cardiac and all-cause mortality) [22, 235]. Diabetes mellitus further exacerbates risks, particularly for amputation (4.43-fold higher amputation event rate in diabetic PAD) [112, 149, 165, 185, 192].
- **Inflammatory and Nutritional Biomarkers:** Various biomarkers predict adverse outcomes. Elevated Interleukin-7 (IL-7) (HR 1.56 for 2-year MALE) [3], Interleukin-27 (IL-27)

(HR 2.95 for MACE) [15], Trimethylamine-N-Oxide (TMAO) (sub-hazard ratios ≥2 for cardiovascular death) [31], and the pan-immune inflammation value (PIV) (HR 1.89 for mortality) [12] are associated with poorer prognosis. Nutritional status, assessed by geriatric nutritional risk index (GNRI) [4, 118] or controlling nutritional status (CONUT) score [197], and inflammation-based scores like C-reactive protein/albumin ratio (CAR) [131] and HALP score [16] also independently predict MALE, amputation, and mortality.

- **Predictive Models and Risk Stratification:** Advanced models incorporating clinical features and inflammatory biomarkers (AUROC 0.84 for 2-year MALE) [2], IL-7 and clinical features (F1 score 0.829) [3], and machine learning techniques [75, 96, 101, 179] demonstrate high accuracy in predicting adverse events. Scores like the PAD3D score (4.5-fold increase in all-cause and CV mortality) [40], CHA2DS2-VASc score (HR 1.28 for MACE) [90], and ceramide-based risk score CERT (HR 1.35 for 10-year mortality per category increase) [25] effectively stratify risk.
- **Anatomical and Functional Predictors:** Severity and extent of atherosclerosis are critical. A greater number of lower extremity lesions (≥3) is associated with increased adverse prognosis (adjusted HR 1.60) [89]. Severe vascular stenosis leads to reduced muscle mass [14], and decreased psoas muscle CT value predicts major adverse cardiovascular and limb events (MACLE) [43]. Ankle-brachial index (ABI) <0.9 is a dominant risk factor for cardiovascular outcomes (adjusted HR 2.39 for composite events, 3.27 for all-cause mortality) [116, 196] and amputation risk (ABI <0.40 had highest amputation risk) [165].
- **Impact of Interventions and Management:** Dual antiplatelet therapy (DAPT) is associated with lower rates of all-cause mortality (HR 0.86), MALE (HR 0.60), and major amputation (HR 0.78) [27]. Rivaroxaban combined with aspirin improved prognosis and reduced amputations [91, 242], and rivaroxaban reduced acute limb ischemia by 33% after revascularization [133]. Complete coronary revascularization (HR 0.56 for MACE) [24] and optimal medical therapy (OMT) (HR 0.688 for MACE, HR 0.626 for mortality) [198] improve outcomes. Regular cardiologist visits improved 3-year prognosis [8, 137, 183].
- **Psychological and Social Factors:** Depression and anxiety symptoms are underestimated risk factors for postoperative prognosis in diabetic PAD patients undergoing amputation [5]. PAD in hemodialysis patients has a significant social impact due to its dismal prognosis [9].
- **Emerging Risk Factors and Therapeutic Targets:** Elevated growth differentiation factor 15 (GDF15) levels are associated with increased PAD risk in diabetic patients (OR 1.13) [11]. The RNF213 p.R4810K variant is associated with large-artery atherosclerosis [214]. Receptor for advanced glycation end products (RAGE) ligands [148] and TRPC3/6 channel inhibitors [105] are potential therapeutic targets.

5) Discussion

5.1 Principal finding:

The central finding is that peripheral artery disease is consistently associated with a poor prognosis, characterized by significantly elevated risks of mortality, major adverse cardiovascular events (MACE), and major adverse limb events (MALE), with specific rates varying widely based on patient characteristics and disease severity [1, 6, 46, 117, 172].

5.2 Clinical implications:

- **Early Risk Stratification:** Clinicians should utilize predictive models and biomarkers, such as IL-7 [3], PIV [12], and the HALP score [16], alongside clinical features to identify high-risk PAD patients for intensified management.
- **Aggressive Comorbidity Management:** Given the profound impact of comorbidities like hemodialysis [1, 9], diabetes [112, 165], and coronary artery disease [6, 24], integrated and aggressive management of these conditions is paramount to improve PAD prognosis.
- **Nutritional and Mental Health Screening:** Routine screening for malnutrition (e.g., using GNRI [4, 118] or CONUT score [197]) and psychological distress (depression, anxiety) [5] is crucial, as these factors independently worsen outcomes in PAD patients.
- **Optimized Antithrombotic Strategies:** Dual antiplatelet therapy [27] and rivaroxaban-based regimens [91, 133, 242] should be considered in appropriate PAD patients to reduce MACE, MALE, and amputation rates.
- **Cardiologist-Led Outpatient Care:** Outpatient management by a cardiologist is associated with improved prognosis, including fewer deaths and adverse events [8, 137, 183], suggesting a multidisciplinary approach with cardiology involvement is beneficial.

5.3 Research implications / key gaps:

- **Standardized Prognostic Metrics:** Future studies should aim for more standardized reporting of key prognostic endpoints (e.g., 1-year all-cause mortality, 2-year MALE) across diverse PAD populations to enable more robust meta-analyses and comparisons.
- **Validation of Novel Biomarkers:** Prospective, large-scale studies are needed to validate emerging biomarkers (e.g., GDF15 [11], RAGE ligands [148], Elabela [128]) for their independent prognostic value and clinical utility in diverse PAD cohorts.
- **Impact of Comprehensive Interventions:** Research should investigate the combined effect of addressing multiple prognostic factors (e.g., optimal medical therapy, nutritional support, psychological interventions, and revascularization) on long-term outcomes in PAD.
- **Machine Learning Model Implementation:** Studies are needed to evaluate the real-world implementation and cost-effectiveness of machine learning-based prognostic models [75,

96, 101] in routine clinical practice for PAD.

- **Sex-Specific Prognostic Factors:** Further research is warranted to explore sex-specific differences in PAD risk factors and prognosis [23, 128], and how these influence management strategies and outcomes.

5.4 Limitations:

- **Heterogeneous Endpoints** — The variability in reported endpoints (MACE, MALE, mortality) and follow-up durations limits direct quantitative synthesis.
- **Retrospective Study Designs** — A significant number of studies were retrospective, introducing potential for selection and information bias.
- **Population Specificity** — Many studies focused on highly specific patient subgroups (e.g., hemodialysis, diabetes, post-surgical), limiting generalizability to the broader PAD population.
- **Missing Data** — Several summaries indicated "N/A" for sample size or follow-up, hindering comprehensive assessment of study quality.
- **Lack of Causal Inference** — Most studies identify associations, but do not establish causality for prognostic factors or interventions.

5.5 Future directions:

- **Prospective Biomarker Validation** — Conduct large prospective studies to validate novel inflammatory and metabolic biomarkers.
- **Comparative Effectiveness Research** — Compare long-term outcomes of different revascularization strategies in specific PAD subgroups.
- **Integrated Care Pathway Trials** — Design trials evaluating multidisciplinary care pathways incorporating nutritional and psychological support.
- **Machine Learning Clinical Integration** — Develop and test clinical decision support tools based on validated machine learning prognostic models.
- **Sex-Specific Risk Factor Analysis** — Investigate how sex-specific risk factors influence PAD progression and treatment response.

6) Conclusion

Direct numerical comparison of a single central value for peripheral artery disease prognosis is challenging due to the high heterogeneity in patient populations, specific endpoints (e.g., all-cause

mortality, cardiovascular mortality, major adverse limb events, major adverse cardiovascular events), and follow-up durations across studies. However, a consistent theme is that PAD is associated with significantly elevated mortality and adverse event rates [1, 6, 46, 117, 172]. This dire prognosis extends across diverse patient populations, including those with significant comorbidities like diabetes, hemodialysis, and coronary artery disease. The most impactful limitation affecting certainty is the inherent heterogeneity in study designs, patient cohorts, and reported outcomes, which precludes a single, universally applicable prognostic figure. Clinicians should prioritize comprehensive risk assessment, including evaluation of comorbidities, inflammatory markers, and nutritional status, to guide intensified, personalized management strategies for patients with peripheral artery disease.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

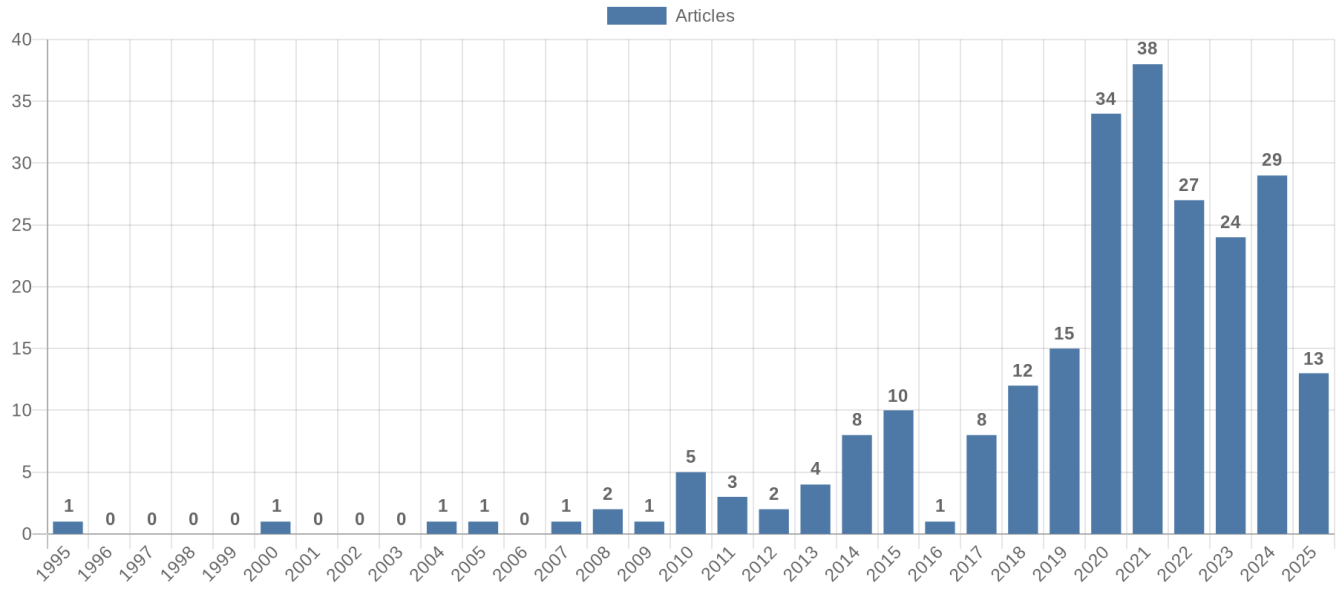


Figure 2. Study-design distribution of included originals

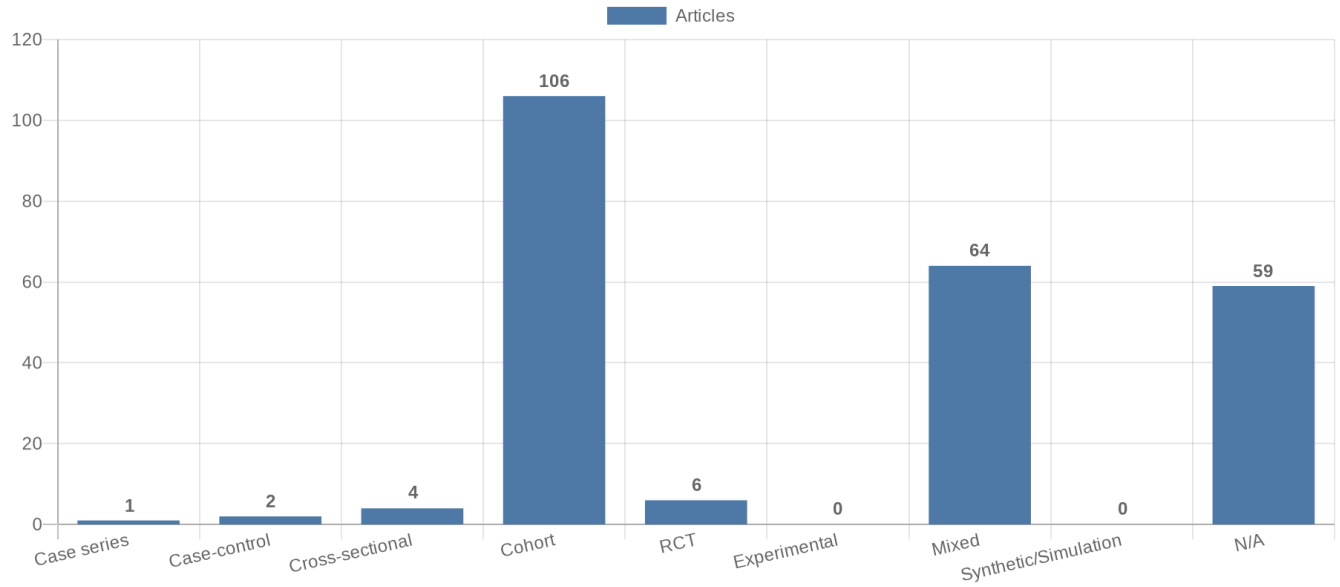


Figure 3. Study-type (directionality) distribution of included originals

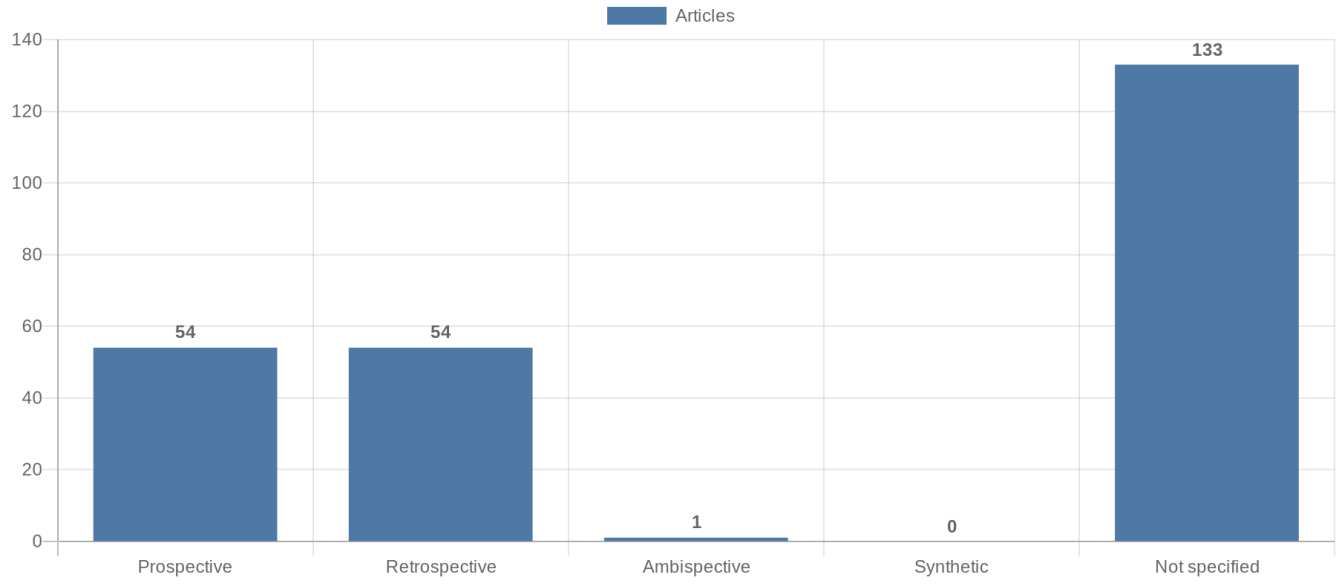


Figure 4. Main extracted research topics

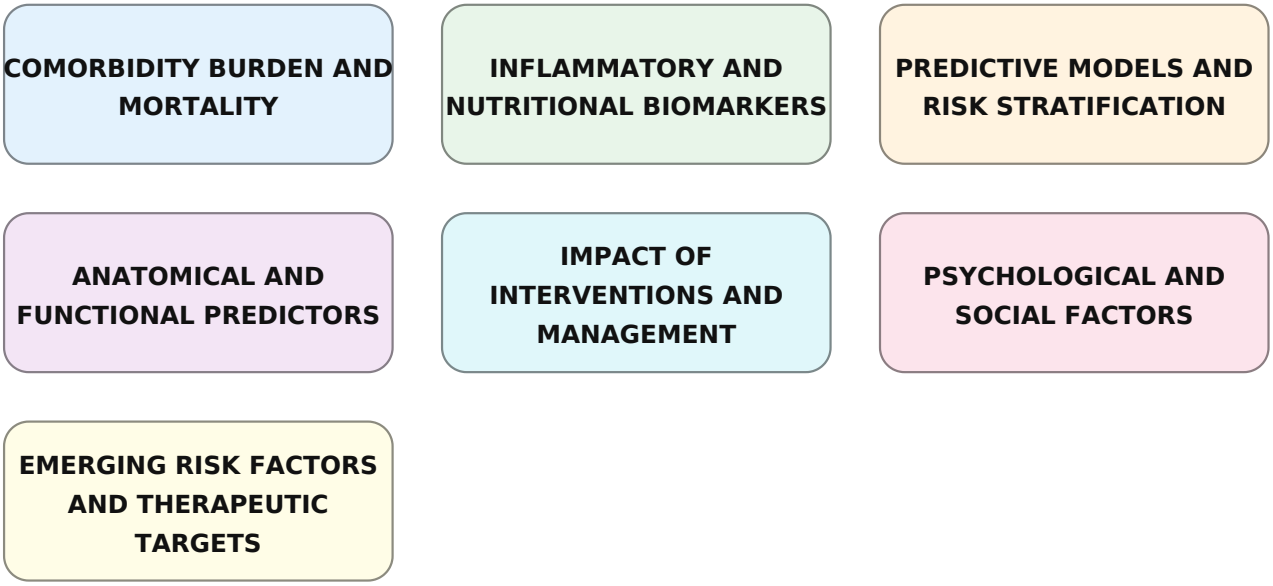


Figure 5. Limitations of current studies (topics)

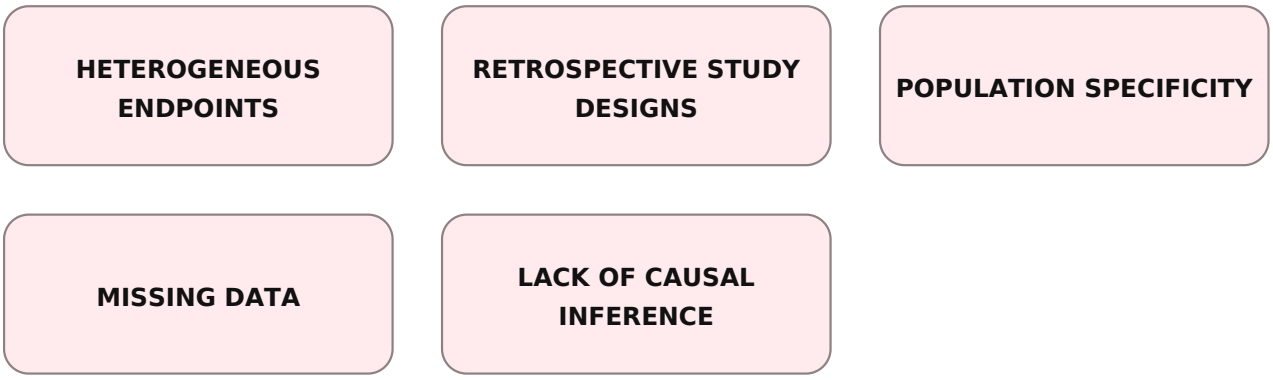


Figure 6. Future research directions (topics)