Peripheral Artery Disease Amputation: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review the current scientific literature concerning peripheral artery disease and its association with amputation, identifying key risk factors, outcomes, and therapeutic approaches. The review utilises 317 studies with 3596028 total participants (naïve ΣN). Peripheral artery disease (PAD) is consistently associated with a substantially increased risk of lower limb amputation, with a risk that is often several-fold higher in affected individuals compared to those without PAD. This risk is significantly compounded by comorbidities, particularly diabetes mellitus and microvascular disease, which exhibit synergistic effects on amputation incidence. The heterogeneity of populations and amputation definitions across studies represents a significant limitation, affecting the certainty and generalizability of pooled quantitative estimates. Clinicians should prioritize early diagnosis and aggressive, multidisciplinary management of PAD and its comorbidities to improve limb salvage rates and reduce the burden of amputation.

Keywords: Peripheral Artery Disease; Amputation; Diabetes Mellitus; Lower Extremity Amputation; Revascularization; Risk Factors; Microvascular Disease; Critical Limb Ischemia; Comorbidities; Racial Disparities

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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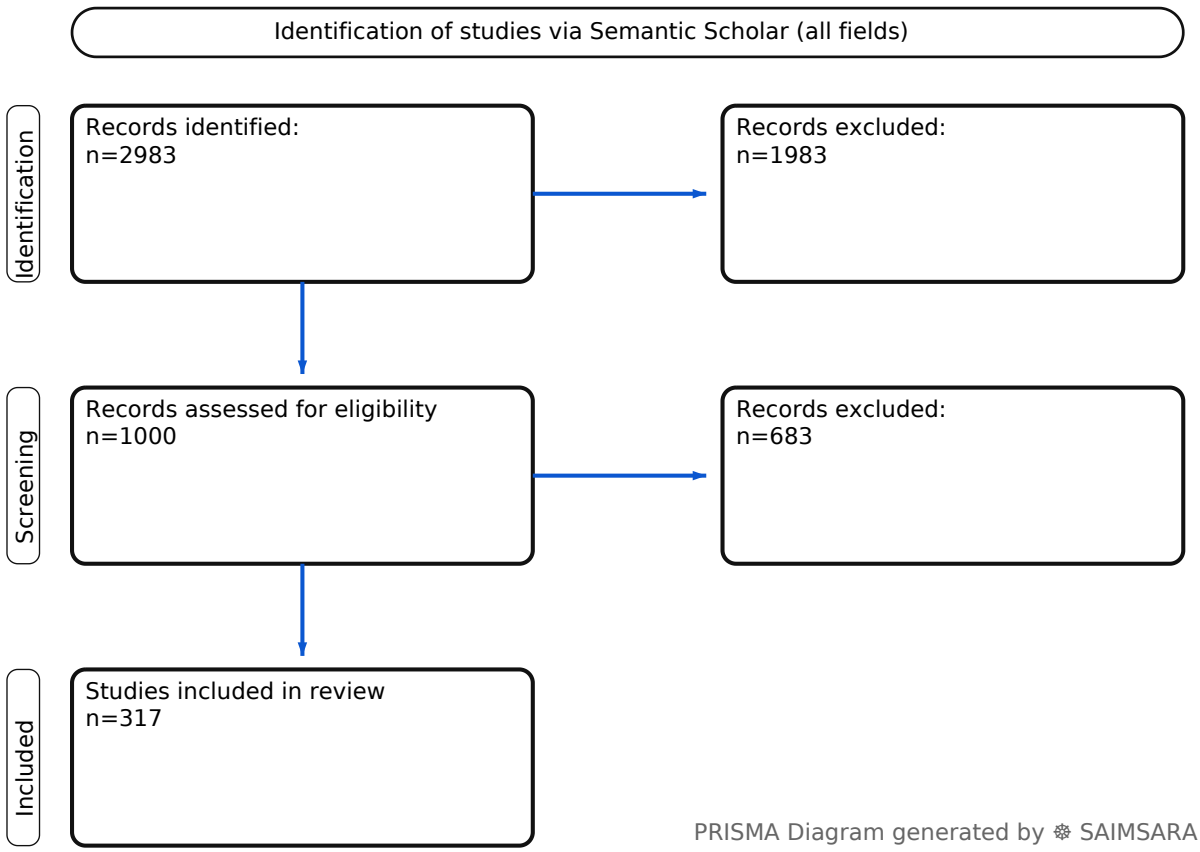
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 317
- Total study participants (naïve ΣN): 3596028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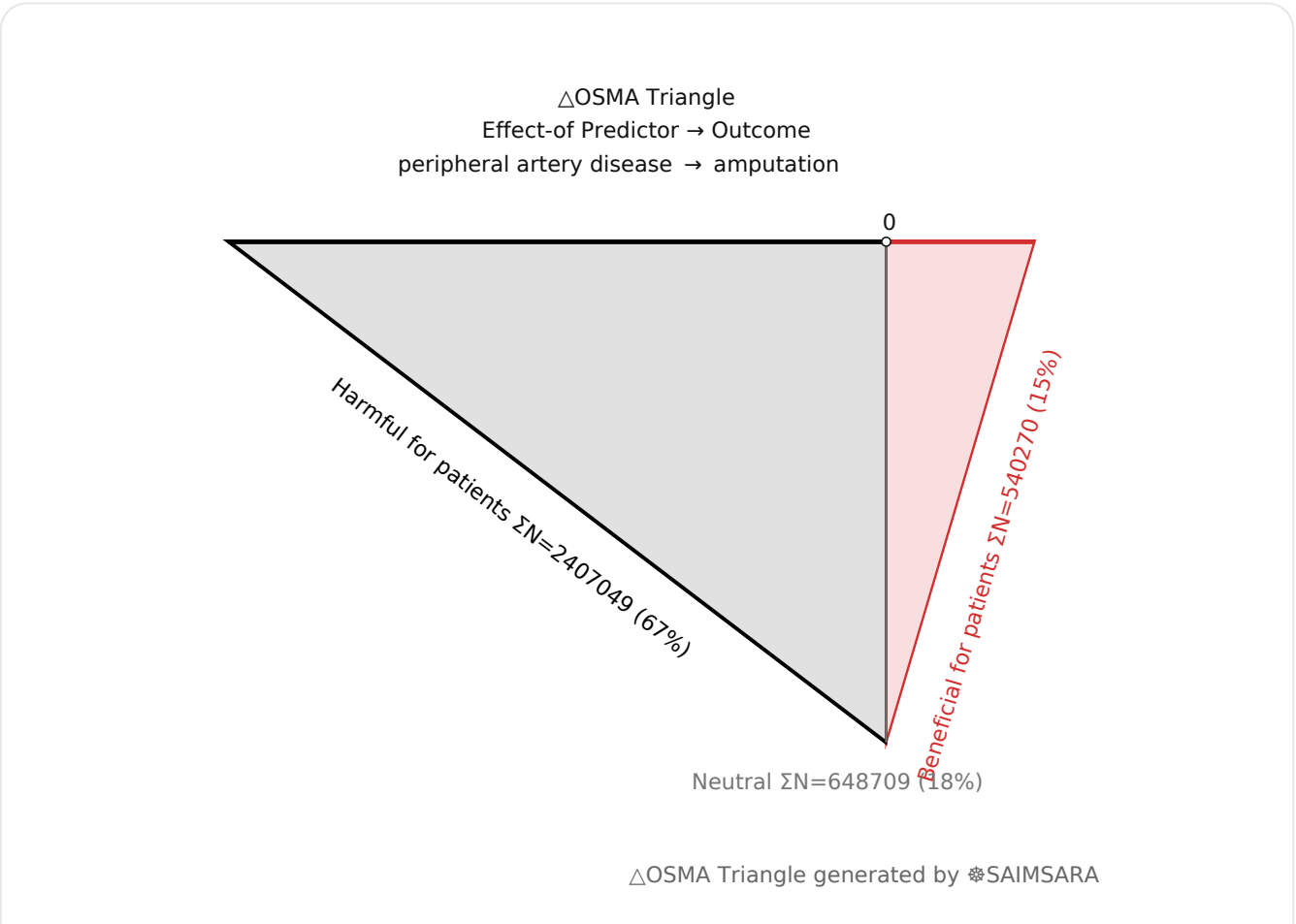
Records excluded:
n=1983
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=683
Included
Studies included in review
n=317
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease → amputation
0
Harmful for patients ΣN=2407049 (67%)
Beneficial for patients ΣN=540270 (15%)
Neutral ΣN=648709 (18%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: amputation Typical timepoints: 1-y, 30-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, healing.

Predictor: peripheral artery disease — exposure/predictor. Doses/units seen: 40 mg. Routes seen: iv. Typical comparator: those without microvascular, white patients, diabetic subjects, patients with neither diabetes....

- **1) Beneficial for patients** — amputation with peripheral artery disease — [6], [20], [36], [37], [48], [53], [54], [56], [69], [70], [71], [72], [77], [84], [89], [97], [132], [136], [151], [159], [161], [166], [167], [168], [170], [191], [194], [197], [210], [212], [214], [215], [219], [230], [231], [235], [240], [241], [254], [256], [257], [263], [265], [267], [268], [273], [298], [303], [306], [309] — ΣN=540270
- **2) Harmful for patients** — amputation with peripheral artery disease — [1], [2], [3], [5], [7], [8], [9], [10], [11], [12], [13], [14], [16], [18], [19], [22], [23], [24], [25], [28], [32], [33], [34], [35], [43], [52], [55], [57], [58], [59], [60], [64], [66], [68], [73], [74], [75], [76], [78], [79], [80], [81], [82], [83], [86], [87], [88], [90], [91], [92], [93], [94], [96], [100], [128], [129], [133], [137], [139], [142], [143], [144], [145], [146], [148], [149], [150], [152], [153], [154], [157], [158], [160], [163], [164], [165], [175], [176], [177], [178], [181], [184], [185], [186], [187], [188], [189], [190], [195], [196], [198], [199], [200], [202], [204], [205], [207], [208], [209], [216], [218], [220], [223], [224], [225], [226], [227], [228], [229], [232], [233], [234], [238], [239], [242], [243], [248], [249], [250], [251], [255], [261], [262], [266], [270], [272], [274], [275], [276], [284], [289], [292], [293], [295], [301], [304], [308], [311], [314], [317] — ΣN=2407049
- **3) No clear effect** — amputation with peripheral artery disease — [4], [15], [17], [21], [26], [27], [29], [30], [31], [38], [39], [40], [41], [42], [44], [45], [46], [47], [49], [50], [51], [61], [62], [63], [65], [67], [85], [95], [98], [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], [126], [127], [130], [131], [134], [135], [138], [140], [141], [147], [155], [156], [162], [169], [171], [172], [173], [174], [179], [180], [182], [183], [192], [193], [201], [203], [206], [211], [213], [217], [221], [222], [236], [237], [244], [245], [246], [247], [252], [253], [258], [259], [260], [264], [269], [271], [277], [278], [279], [280], [281], [282], [283], [285], [286], [287], [288], [290], [291], [294], [296], [297], [299], [300], [302], [305], [307], [310], [312], [313], [315], [316] — ΣN=648709

1) Introduction

Peripheral artery disease (PAD) is a significant global health concern, characterized by narrowing of peripheral arteries, most commonly in the legs. This condition frequently progresses to severe forms such as critical limb ischemia (CLI), leading to chronic non-healing ulcers, gangrene, and ultimately, lower extremity amputation (LEA) [38, 39, 41, 114, 118, 144, 175, 204, 216]. The burden of amputation in PAD patients is substantial, impacting patient morbidity, mortality, and healthcare costs [79, 83, 162]. Comorbidities like diabetes mellitus (DM) and microvascular disease (MVD) profoundly exacerbate the risk of amputation in PAD patients, often leading to an accelerated disease course and worse outcomes [1, 3, 18, 22, 44, 46, 75, 78, 91, 92, 112, 114, 119, 164, 172, 173, 176, 181, 182, 188, 204, 208, 211, 261, 293, 303, 304]. This review synthesizes current evidence on the prevalence, risk factors, and management strategies related to amputation in the context of PAD.

2) Aim

The aim of this paper is to systematically review the current scientific literature concerning peripheral artery disease and its association with amputation, identifying key risk factors, outcomes, and therapeutic approaches.

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.

4) Results

4.1 Study characteristics

The included studies predominantly comprised cohort designs (e.g., [1, 2, 3, 6, 12, 13, 19, 22, 24, 62, 63, 65, 66, 67, 68, 70, 76, 78, 80, 81, 82, 83, 85, 87, 88, 89, 90, 91, 92, 94, 95, 96, 100, 101, 103, 106, 112, 113, 115, 117, 124, 129, 131, 133, 142, 145, 146, 149, 150, 151, 152, 153, 154, 157, 158, 159, 160, 161, 162, 163, 164, 168, 176, 177, 178, 181, 184, 185, 186, 187, 188, 189, 190, 191, 193, 195, 198, 199, 200, 202, 203, 204, 205, 206, 208, 209, 211, 212, 213, 215, 216, 217, 219, 220, 221, 222, 223, 224, 228, 229, 233, 235, 238, 239, 240, 242, 243, 244, 245, 247, 249, 253, 254, 257, 258, 259, 260, 261, 262, 266, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 282, 283, 284, 285, 286, 287, 288, 293, 296, 297, 301, 309, 310, 311, 314, 315, 316), with a notable presence of retrospective and prospective cohort studies. Randomized controlled trials (RCTs) were also identified, particularly for evaluating therapeutic interventions [48, 53, 69, 93, 94, 109, 155, 167, 169, 170, 210, 214, 215, 230, 231, 234, 235, 250, 252, 259, 264, 281, 282, 288, 300, 307, 312]. Populations varied widely, including veterans [1, 145], American Indian adults [2], patients with newly diagnosed type 2

diabetes [3, 6], Medicare beneficiaries [7, 16, 79, 96, 157, 186, 285], and individuals undergoing revascularization procedures [5, 48, 57, 71, 72, 74, 76, 77, 83, 84, 88, 89, 90, 94, 97, 105, 106, 108, 111, 116, 123, 136, 149, 153, 154, 160, 161, 168, 170, 184, 186, 189, 194, 196, 197, 200, 201, 215, 218, 221, 229, 231, 232, 236, 256, 257, 259, 260, 267, 269, 271, 273, 274, 279, 281, 282, 285, 286, 287, 288, 291, 296, 300, 301, 306, 307, 308, 309, 310, 312, 313, 317]. Follow-up periods ranged from 30 days to 28 years, with common durations of 1, 5, and 10 years.

4.2 Main numerical result aligned to the query

Peripheral artery disease (PAD) is consistently associated with a substantially increased risk of lower limb amputation. For instance, PAD alone was associated with a 13.9-fold elevated risk of amputation in veterans [1], and independently with a 7-fold increase in amputation rate in Western Denmark [22]. In patients with type 2 diabetes, PAD was identified as the greatest driver of amputation risk, with more than a 4-fold higher risk [78] and a 5.48-fold higher rate of lower-extremity amputation compared to those without PAD [91]. The coexistence of PAD and microvascular disease (MVD) demonstrated a synergistic effect, increasing amputation risk by 22.7-fold [1] or 12-fold [22] compared to no disease.

4.3 Topic synthesis

- **Comorbidity and Amputation Risk:**
- Microvascular disease (MVD) alone increases amputation risk by 3.7-fold [1], with the combination of PAD and MVD increasing risk to 22.7-fold [1] or 12-fold [22].
- Diabetes mellitus (DM) is a major driver, increasing amputation risk by >4-fold [78] to 5.48-fold [91] in PAD patients, and is an independent risk factor for major limb amputation during revascularization (aOR 1.22 [1.03-1.44]) [90].
- Diabetic retinopathy is associated with a 2.53-fold increased risk of amputation [3].
- Chronic kidney disease (CKD) and hemodialysis patients with PAD show higher amputation rates and mortality [32, 95, 209, 238].
- **Socioeconomic and Demographic Disparities:**
- Black patients have an almost 3-fold higher rate of amputation compared to White patients [16], and Black and Hispanic patients are at greater risk of amputation compared with White patients [7, 31, 73, 74, 153, 157, 186, 309].
- Lower socioeconomic status markers (e.g., lower median household income, distressed communities) are associated with higher amputation rates [11, 157].
- Longer residential distance from a hospital is associated with a 1.35-fold higher risk of amputation [13].
- Men have a higher probability of undergoing lower limb amputations compared to females [10, 133, 224, 270, 274].

- **Prognostic Factors and Biomarkers:**
- Ankle-brachial index (ABI) <0.40 is a strong risk factor for amputation [32], while ABI of 1.4 or greater is also associated with limb amputation [30]. Lower ABI is associated with 3.85-fold to 4.39-fold increased risk of severe ischemic leg outcomes [199].
- Elevated urinary zinc levels (OR 2.36) [2], high growth differentiation factor 15 (GDF15) levels (HR 4.01 [2.05–7.84]) [34], and elevated lipoprotein (a) (Lp(a)) [33] are associated with increased amputation risk.
- Inflammatory markers like monocyte/high density lipoprotein cholesterol ratio (MHR) [28], neutrophil-to-lymphocyte ratio (NLR) [82, 146, 152, 223, 257], and C-reactive protein (CRP) [148, 190] are predictive of amputation.
- Genetic variants like rs6025 (Factor V Leiden) are associated with increased amputation risk (OR 1.54) [35].
- **Treatment Pathways and Interventions:**
- Revascularization procedures are frequently part of amputation pathways [4], with elective revascularization having lower amputation rates (2.7% at 1 year, 5.3% at 5 years) compared to nonelective (15.2% at 1 year, 19.9% at 5 years) [5].
- Rivaroxaban plus aspirin significantly reduced major amputation for vascular causes in PAD patients after revascularization (HR 0.85 [0.76-0.96]) [48, 69, 71, 72, 77, 210, 230].
- Statin therapy is associated with a lower rate of adverse limb outcomes, including amputation, in kidney failure patients with PAD [36].
- Cilostazol use after endovascular therapy (EVT) is associated with a lower risk of major amputation [97, 256] and decreases amputation risk in hemodialysis patients with PAD [70].
- SGLT2 inhibitors were associated with an increased cause-specific hazard of PAD surgeries, including amputation, compared with DPP-4i [145], though another study found a non-significant increase in amputation risk [169], and one study reported lower risks of amputation with SGLT2i compared to DPP4i [240].
- Percutaneous deep vein arterialization resulted in 75% freedom from major amputation in end-stage PAD [37]. Autologous peripheral blood mononuclear cells [56] and CD133+ cells [109] showed promise in reducing amputation risk.
- **Disease Severity and Progression:**
- Critical limb ischemia (CLI) is the most severe form of PAD and carries high 1-year amputation rates (20-25% [165], 30% [175], 45% for no-option CLTI [177], 10.9% for major amputation in diabetic foot ulceration with no-option CLI [311]).
- Gangrene [10, 105, 137, 144, 180, 290] and chronic non-healing ulcers [21, 143, 152, 156, 158, 164, 181, 182, 294] are strong predictors of amputation.
- Medial artery calcification [43, 60, 128, 150, 295, 302] and a greater number of lower extremity lesions [163, 223] are associated with increased amputation risk.
- **Healthcare System and External Factors:**

- Amputation rates vary widely across geographic regions [16, 29, 142, 147, 193, 211, 266] and are influenced by regional prevalence of PAD and diabetes [16].
- The COVID-19 pandemic was associated with increased hospitalizations for advanced PAD and higher amputation rates [227, 228, 289].
- Machine learning models can predict amputation risk [62, 65, 184, 217, 297], and machine learning models can predict major amputation or death after infrainguinal bypass for PAD [47].

5) Discussion

5.1 Principal finding

The central finding is that peripheral artery disease (PAD) is a profound and consistently identified risk factor for lower extremity amputation, with a risk that is often several-fold higher in affected individuals compared to those without PAD [1, 22, 78, 91]. This risk is significantly compounded by comorbidities, particularly diabetes mellitus and microvascular disease, which exhibit synergistic effects on amputation incidence [1, 22, 44, 261].

5.2 Clinical implications

- **Early Diagnosis and Management:** Given the substantial increase in amputation risk, early diagnosis and aggressive management of PAD and its comorbidities (especially diabetes and microvascular disease) are critical for limb salvage [45].
- **Targeted Interventions for High-Risk Groups:** Patients with critical limb ischemia (CLI), non-healing ulcers, or advanced calcification require urgent and specialized interventions, as these conditions are strongly associated with high amputation rates [105, 165, 175, 177, 295].
- **Addressing Disparities in Care:** Significant racial, ethnic, socioeconomic, and geographic disparities in amputation rates highlight the need for equitable access to screening, early intervention, and advanced vascular care, especially in disadvantaged communities [7, 11, 16, 29, 31, 73, 74, 153, 157, 266].
- **Optimizing Pharmacotherapy:** The use of antithrombotic agents like rivaroxaban plus aspirin [48, 69, 71, 72, 77, 210, 230] and cilostazol [70, 97, 256], as well as statins [36], should be considered to reduce amputation risk, particularly post-revascularization.
- **Multidisciplinary Approach:** A multidisciplinary team approach involving vascular specialists, endocrinologists, wound care experts, and podiatrists is crucial for comprehensive management of diabetic foot syndrome and PAD to reduce high amputation frequency [219].

5.3 Research implications / key gaps

- **Standardized Outcome Reporting:** Future studies should standardize the definition and reporting of amputation outcomes (e.g., major vs. minor, specific anatomical levels, timepoints) to enable more robust meta-analyses and comparisons across diverse populations [5, 7, 26, 99, 248].
- **Mechanistic Biomarker Validation:** Further prospective studies are needed to validate the clinical utility of emerging biomarkers (e.g., urinary zinc, GDF15, MHR, NLR, Lp(a), uCystatinC, uFABP3) as independent predictors of amputation risk in diverse PAD populations, exploring their pathophysiological roles [2, 28, 33, 34, 64, 68, 82, 146, 223, 262].
- **Comparative Effectiveness of Revascularization Strategies:** More head-to-head comparative effectiveness research, ideally RCTs, is warranted to determine the optimal revascularization strategy (e.g., endovascular vs. surgical, specific devices like DES, DCB, atherectomy) for different PAD anatomies and patient profiles, focusing on long-term amputation-free survival [170, 271, 282, 301].
- **Interventions for Socioeconomic Disparities:** Research should focus on designing and evaluating interventions that specifically address socioeconomic and systemic barriers to care, aiming to reduce racial/ethnic and geographic disparities in amputation rates [11, 16, 157].
- **Long-term Efficacy of Novel Therapies:** Continued research, including larger RCTs, is needed to assess the long-term efficacy and safety of novel limb salvage interventions, such as percutaneous deep vein arterialization, stem cell therapies, and acupuncture, in preventing amputation [21, 37, 56, 109, 155, 294, 298, 306, 313].

5.4 Limitations

- **Heterogeneity of Populations** — The included studies encompass diverse populations (e.g., veterans, American Indians, Medicare patients, specific geographic regions), limiting direct comparison and generalizability of findings.
- **Variability in Amputation Definitions** — "Amputation" is inconsistently defined, often combining major and minor events or reporting different follow-up durations, which complicates the synthesis of quantitative outcomes.
- **Predominance of Observational Designs** — A large number of studies are cohort or retrospective, which are susceptible to confounding and selection bias, potentially overestimating or underestimating associations.
- **Inconsistent Reporting of Baseline Data** — Many studies lack comprehensive baseline data for all relevant risk factors, making it challenging to fully adjust for confounders and

understand the interplay of multiple risk factors.

- **Geographic Specificity** — Some findings are specific to particular countries or regions (e.g., England, Denmark, Japan, Saudi Arabia, Taiwan, US metropolitan areas), which may not be transferable to other healthcare systems or populations.

5.5 Future directions

- **Standardized Outcome Metrics** — Develop and universally adopt standardized definitions for amputation outcomes (e.g., major, minor, level) and follow-up periods in PAD research.
- **Comparative Effectiveness Research** — Conduct large-scale, pragmatic randomized controlled trials comparing different revascularization strategies and medical therapies for amputation prevention in diverse PAD patient cohorts.
- **Biomarker Validation Studies** — Implement prospective studies to validate the clinical utility and cost-effectiveness of novel biomarkers for predicting amputation risk and guiding personalized treatment.
- **Socioeconomic Intervention Trials** — Design and test interventions aimed at mitigating socioeconomic and racial/ethnic disparities in access to care and amputation rates for PAD patients.
- **Advanced Predictive Analytics** — Utilize machine learning and artificial intelligence on large, integrated datasets to develop more accurate, dynamic predictive models for amputation risk, incorporating a broader range of clinical, socioeconomic, and genetic factors.

6) Conclusion

Peripheral artery disease (PAD) is consistently associated with a substantially increased risk of lower limb amputation, with a risk that is often several-fold higher in affected individuals compared to those without PAD [1, 22, 78, 91]. This risk is significantly compounded by comorbidities, particularly diabetes mellitus and microvascular disease, which exhibit synergistic effects on amputation incidence [1, 22, 44, 261]. The heterogeneity of populations and amputation definitions across studies represents a significant limitation, affecting the certainty and generalizability of pooled quantitative estimates. Clinicians should prioritize early diagnosis and aggressive, multidisciplinary management of PAD and its comorbidities to improve limb salvage rates and reduce the burden of amputation.

References

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Figure 1. Publication-year distribution of included originals

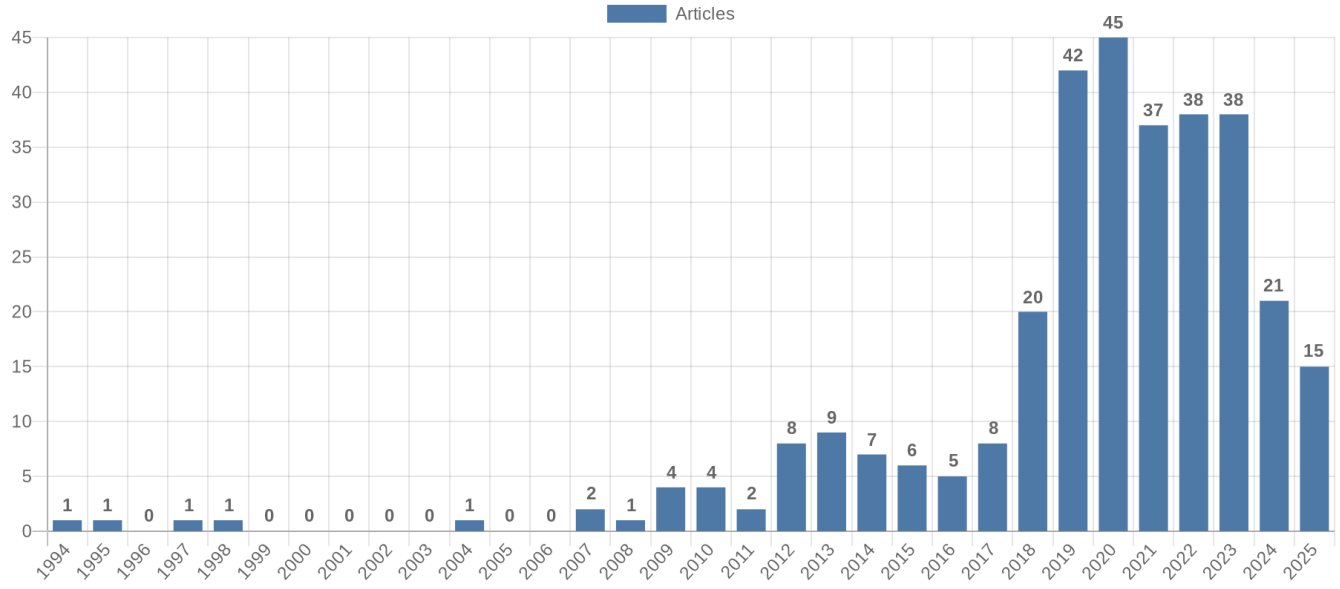

Figure 2. Study-design distribution of included originals

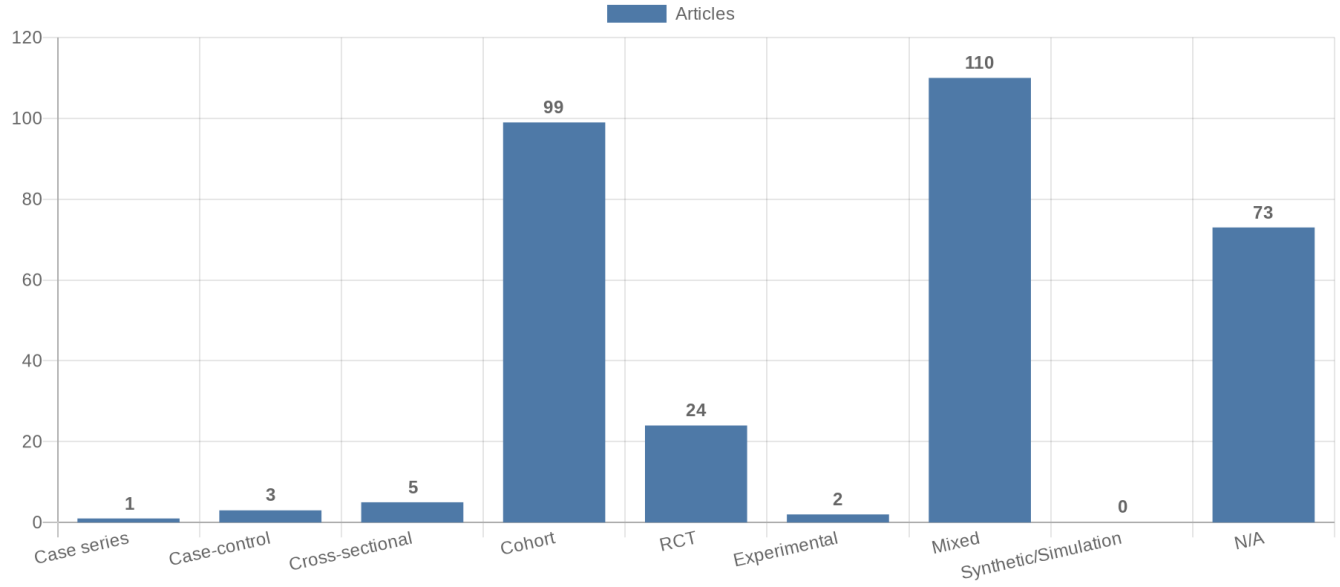

Figure 3. Study-type (directionality) distribution of included originals

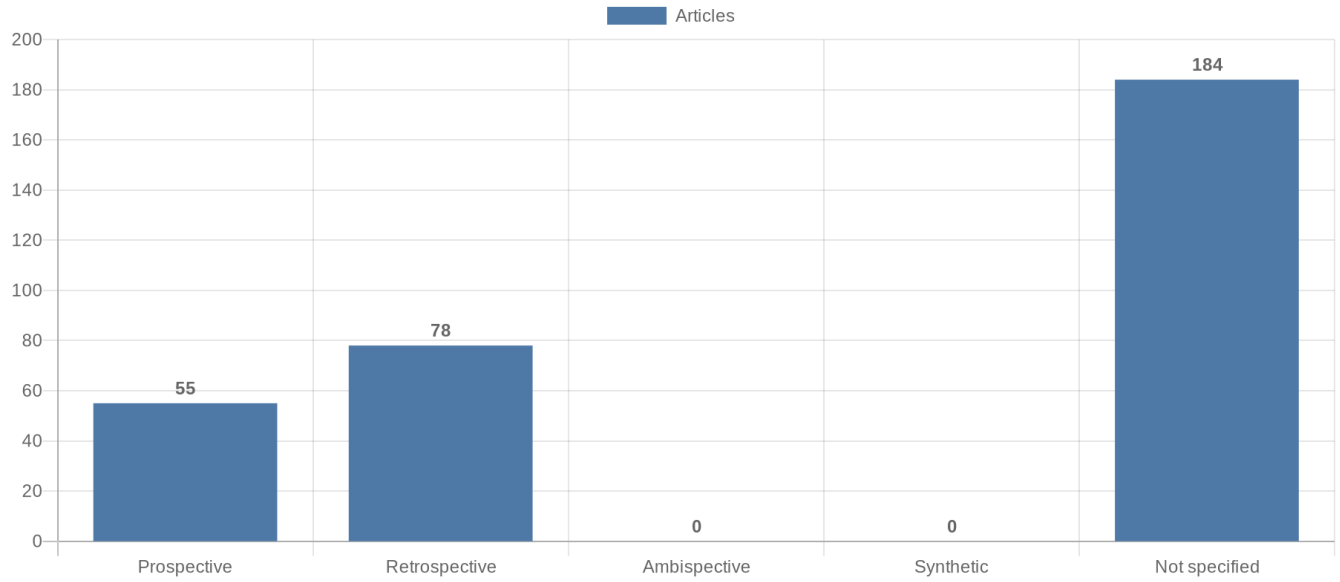

Figure 4. Main extracted research topics

Figure 5. Limitations of current studies (topics)

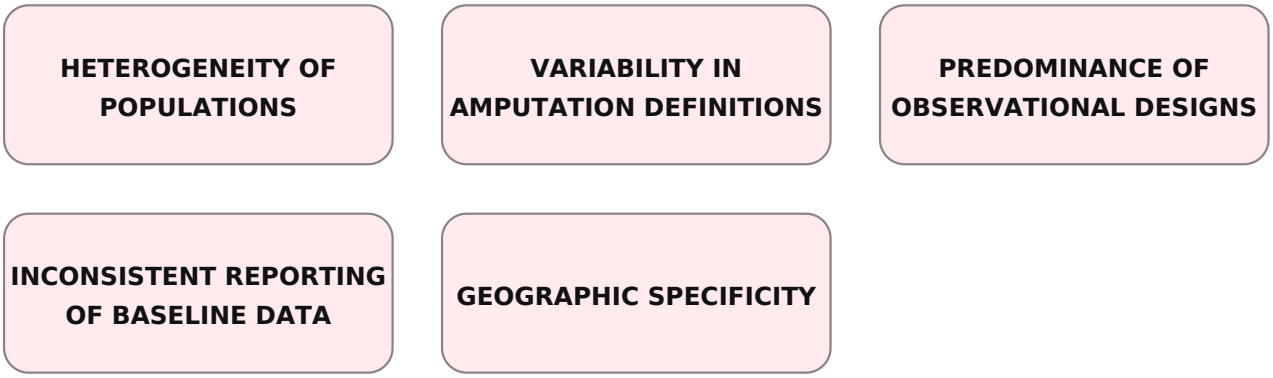

Figure 6. Future research directions (topics)

STANDARDIZED OUTCOME REPORTING

MECHANISTIC BIOMARKER VALIDATION

COMPARATIVE EFFECTIVENESS OF REVASCULARIZATION STRATEGIES

INTERVENTIONS FOR SOCIOECONOMIC DISPARITIES

LONG-TERM EFFICACY OF NOVEL THERAPIES

STANDARDIZED OUTCOME METRICS

COMPARATIVE EFFECTIVENESS RESEARCH