Chronic Limb Threatening Ischemia: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to systematically review and synthesize current evidence on the diagnosis, treatment strategies, prognostic factors, and novel interventions for chronic limb-threatening ischemia. The review utilises 507 studies with 558889 total participants (naïve ΣN). The 1-year amputation-free survival (AFS) rate in patients with chronic limb-threatening ischemia (CLTI) ranged from 37% to 91.5%, underscoring the severe and varied prognosis of this condition. While surgical and endovascular revascularization remain cornerstones of therapy, novel interventions for "no-option" CLTI and improved prognostic tools are continually emerging, offering hope for improved limb salvage and patient outcomes across diverse populations. The heterogeneity in study designs and outcome reporting represents a significant limitation, affecting the certainty of current evidence. Clinicians should integrate prognostic tools like WIfI and GLASS classifications to guide personalized treatment strategies, while future research should prioritize large-scale randomized controlled trials to establish the comparative effectiveness of novel therapies.

Keywords: Chronic Limb-Threatening Ischemia; Peripheral Artery Disease; Revascularization; Limb Salvage; Amputation; Endovascular Therapy; Surgical Bypass; Wound Healing; Major Adverse Limb Events; Inflammation

Review Stats

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- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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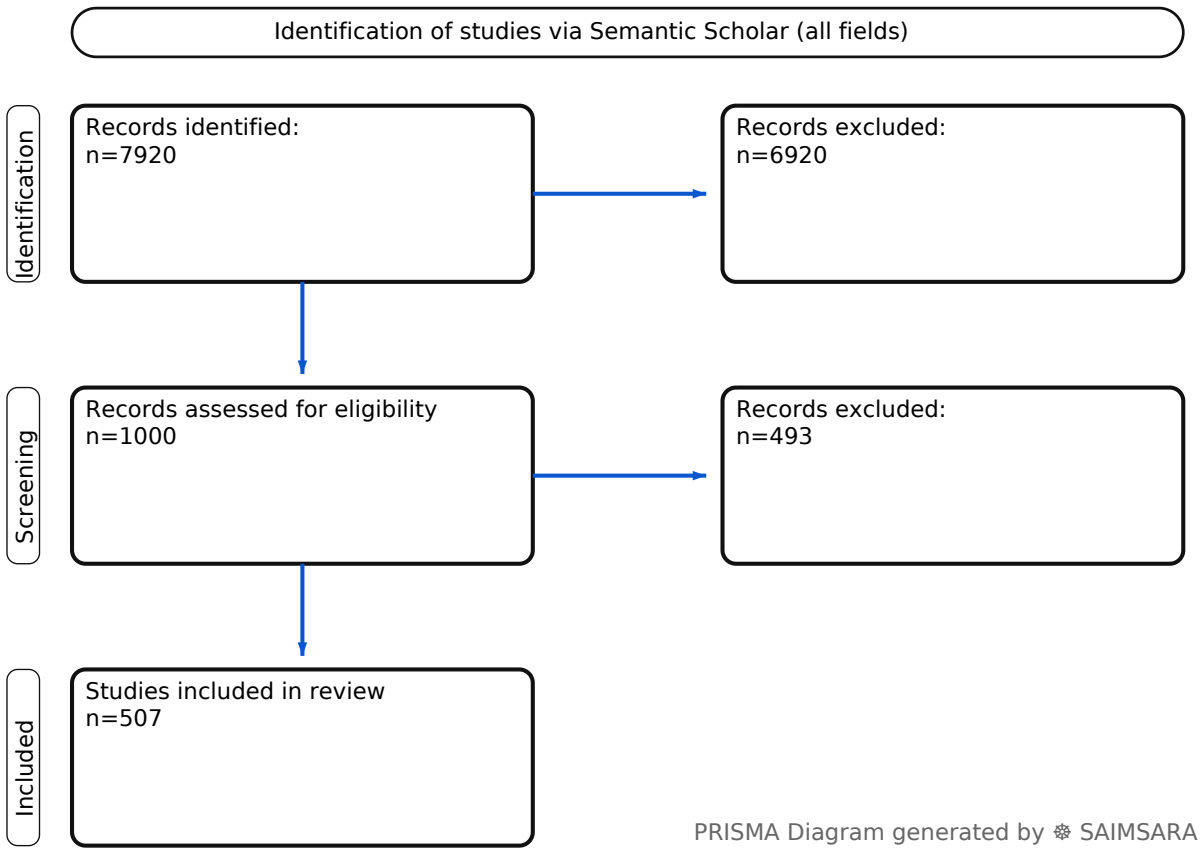
- Included original Abstracts/Papers: 507
- Total study participants (naïve ΣN): 558889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Records excluded:
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Screening
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Records excluded:
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Included
Studies included in review
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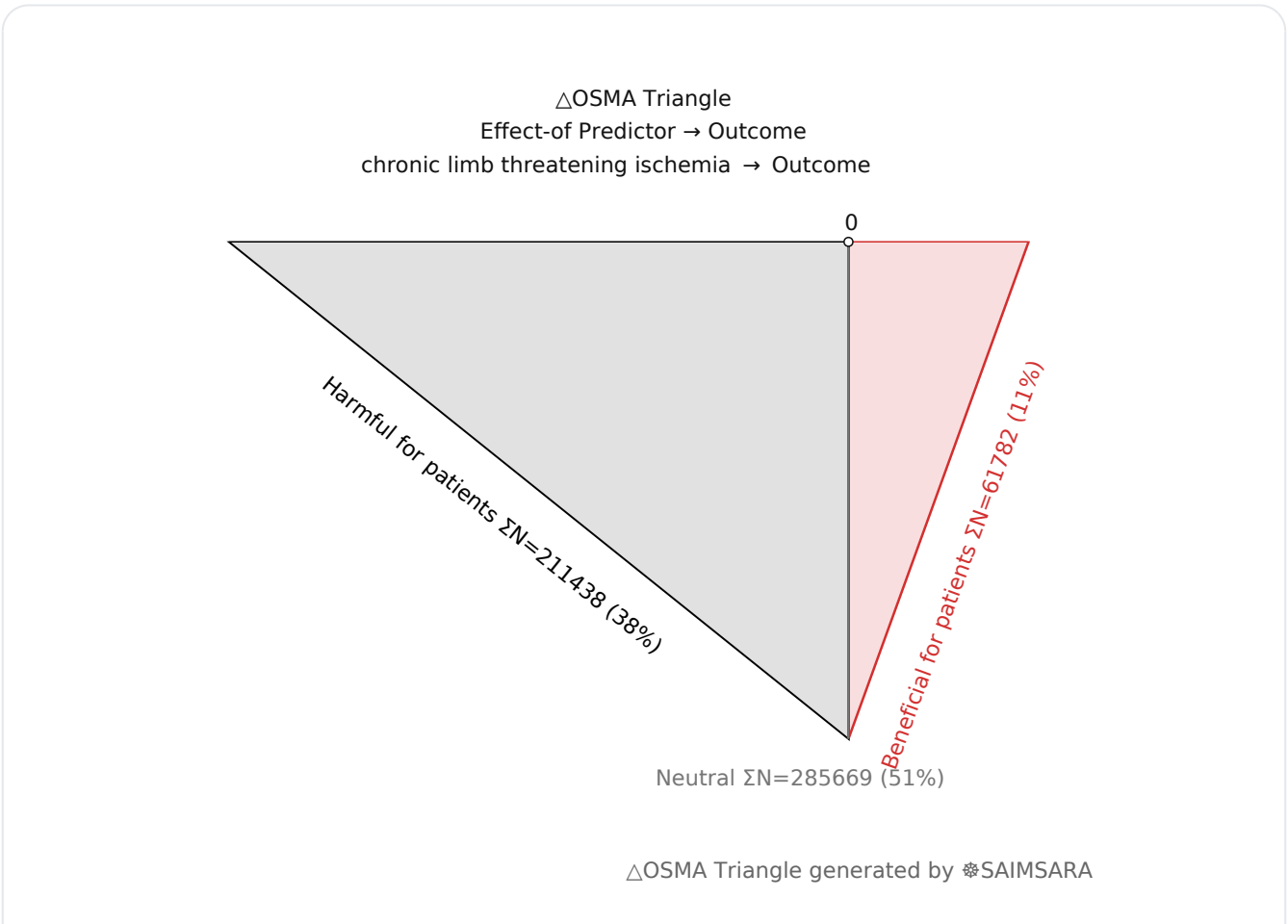
△OSMA Triangle
Effect-of Predictor → Outcome
chronic limb threatening ischemia → Outcome
0
Harmful for patients ΣN=211438 (38%)
Beneficial for patients ΣN=61782 (11%)
Neutral ΣN=285669 (51%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Outcome Typical timepoints: 1-y, 12-mo. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: survival, mortality, healing.

Predictor: chronic limb threatening ischemia — exposure/predictor. Routes seen: intramuscular, im, iv. Typical comparator: endovascular therapy. outcomes, non-angioplasty, endovascular intervention in, claudication patients....

- **1) Beneficial for patients** — Outcome with chronic limb threatening ischemia — [1], [2], [4], [6], [7], [20], [24], [25], [53], [57], [58], [60], [63], [66], [70], [72], [73], [75], [77], [78], [80], [81], [83], [84], [85], [86], [100], [112], [114], [117], [155], [160], [162], [174], [211], [214], [216], [219], [221], [222], [225], [377], [384], [386], [387], [389], [390], [391], [395], [397], [398], [399], [400], [401], [403], [405], [406], [407], [410], [411], [413], [419], [420], [425], [426], [431], [434], [436], [438], [440], [441], [443], [451], [456], [458], [460], [461], [462], [463], [469], [475] — ΣN=61782
- **2) Harmful for patients** — Outcome with chronic limb threatening ischemia — [3], [5], [8], [9], [12], [13], [16], [23], [51], [59], [61], [62], [65], [69], [71], [76], [79], [82], [87], [88], [97], [98], [124], [125], [151], [152], [153], [154], [156], [157], [159], [165], [204], [207], [212], [218], [220], [224], [376], [378], [379], [385], [388], [392], [402], [404], [409], [417], [421], [423], [424], [432], [433], [435], [437], [439], [442], [445], [448], [449], [452], [453], [454], [457], [459], [465], [467], [474] — ΣN=211438
- **3) No clear effect** — Outcome with chronic limb threatening ischemia — [10], [11], [14], [15], [17], [18], [19], [21], [22], [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], [52], [54], [55], [56], [64], [67], [68], [74], [89], [90], [91], [92], [93], [94], [95], [96], [99], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [113], [115], [116], [118], [119], [120], [121], [122], [123], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [158], [161], [163], [164], [166], [167], [168], [169], [170], [171], [172], [173], [175], [176], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [197], [198], [199], [200], [201], [202], [203], [205], [206], [208], [209], [210], [213], [215], [217], [223], [226], [227], [228], [229], [230], [231], [232], [233], [234], [235], [236], [237], [238], [239], [240], [241], [242], [243], [244], [245], [246], [247], [248], [249], [250], [251], [252], [253], [254], [255], [256], [257], [258], [259], [260], [261], [262], [263], [264], [265], [266], [267], [268], [269], [270], [271], [272], [273], [274], [275], [276], [277], [278], [279], [280], [281], [282], [283], [284], [285],

[286], [287], [288], [289], [290], [291], [292], [293], [294], [295], [296], [297], [298], [299], [300], [301], [302], [303], [304], [305], [306], [307], [308], [309], [310], [311], [312], [313], [314], [315], [316], [317], [318], [319], [320], [321], [322], [323], [324], [325], [326], [327], [328], [329], [330], [331], [332], [333], [334], [335], [336], [337], [338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373], [374], [375], [380], [381], [382], [383], [393], [394], [396], [408], [412], [414], [415], [416], [418], [422], [427], [428], [429], [430], [444], [446], [447], [450], [455], [464], [466], [468], [470], [471], [472], [473], [476], [477], [478], [479], [480], [481], [482], [483], [484], [485], [486], [487], [488], [489], [490], [491], [492], [493], [494], [495], [496], [497], [498], [499], [500], [501], [502], [503], [504], [505], [506], [507] — ΣN=285669

1) Introduction

Chronic limb-threatening ischemia (CLTI) represents the most severe manifestation of peripheral artery disease (PAD), characterized by chronic ischemic rest pain, non-healing wounds, or gangrene, and is a significant cause of morbidity, limb loss, and mortality [55, 122]. Patients with CLTI often face complex clinical challenges, including advanced age, multiple comorbidities such as diabetes mellitus (DM) and end-stage renal disease (ESRD), and a high risk of major adverse limb events (MALE) and major adverse cardiovascular events (MACE) [35, 190, 424]. The management of CLTI is multifaceted, involving revascularization strategies (surgical or endovascular), wound care, and novel therapeutic approaches, with a primary goal of limb salvage and improved quality of life [47, 56]. Despite advancements, a substantial proportion of patients, particularly those with "no-option" CLTI where conventional revascularization is not feasible, continue to experience poor outcomes, highlighting an urgent need for effective interventions and refined prognostic tools [3, 56, 116].

2) Aim

This paper aims to systematically review and synthesize current evidence on the diagnosis, treatment strategies, prognostic factors, and novel interventions for chronic limb-threatening ischemia.

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 cohort studies and case series, which constitute a significant portion of the evidence, are inherently susceptible to selection bias and confounding, limiting the strength of causal inferences. Variability in follow-up duration and outcome definitions across studies also introduces heterogeneity. Randomized controlled trials (RCTs) offer higher levels of evidence but are less frequent for all interventions.

4) Results

4.1 Study characteristics

The evidence base for chronic limb-threatening ischemia (CLTI) is diverse, comprising numerous cohort studies (retrospective and prospective), randomized controlled trials (RCTs), and mixed-design studies. Populations frequently include patients with infrainguinal peripheral artery disease, no-option CLTI, diabetic patients, and those with specific lesion types (e.g., infrapopliteal, femoropopliteal, inframalleolar). Follow-up periods typically range from 6 months to 2 years, with some studies extending to 5 years or more.

4.2 Main numerical result aligned to the query

The 1-year amputation-free survival (AFS) rate in patients with chronic limb-threatening ischemia (CLTI) undergoing various interventions or management strategies exhibited a wide range, from 37% [3] to 91.5% [73]. The median 1-year AFS rate across comparable studies was 75% (e.g., 71% [86], 79% [431]). This considerable heterogeneity reflects differences in patient populations, disease severity, intervention types, and outcome definitions.

4.3 Topic synthesis

- **Revascularization Strategies & Efficacy:**
- Surgical revascularization, particularly with adequate great saphenous vein (GSV) conduit, significantly lowers major adverse limb events (MALE) or death compared to endovascular therapy (HR, 0.68; 95% CI, 0.59 to 0.79; P<0.001) [1, 6, 25]. Bypass with alternative conduit (AC) was associated with increased major amputation (HR=1.82 [95% CI, 1.36-2.44]; P<.001) compared to endovascular therapy (ET) [25].
- Endovascular therapy (EVT) for infrapopliteal (IP) lesions shows variable outcomes; balloon angioplasty for inframalleolar (IM) stenotic lesions did not significantly improve wound healing or AFS but was associated with higher lesion morphology progression (39.3% vs. 12.9%; p=0.035) [5]. Drug-coated balloons (DCBs) demonstrated improved primary patency (75.0% vs. 28.3%; p<0.001) and freedom from clinically-driven target lesion revascularization (CD-TLR) (91.5% vs. 76.8%; p=0.03) in infrapopliteal lesions compared to

conventional angioplasty [426].

- Direct revascularization is associated with improved amputation-free survival (OR=2.632), wound healing (OR=2.262), and overall survival (OR=1.757) compared to indirect approaches [63].
- **No-Option CLTI Interventions:**
- Transcatheter arterialization of the deep veins (TADF) achieved 6-month AFS of 66.1% in patients with no conventional revascularization options [4]. Percutaneous deep venous arterialization (pDVA) using the LimFlow device showed 12-month AFS of 71.0% and limb salvage of 86.8% [86].
- Autologous cell therapy (ACT) improved limb ischemia and wound healing in diabetic patients with no-option CLTI [80, 84, 189]. Bone marrow-derived mesenchymal stem cell (BM-MSC) therapy achieved 92.85% AFS and 78.5% ulcer healing at 2 years [24].
- Spinal cord stimulation (SCS) improved limb survival (92.3% at 1 year), pain control, and quality of life in diabetic CLTI patients unsuitable for revascularization [75, 222].
- **Prognostic Factors & Risk Stratification:**
- Elevated inflammatory markers (C-reactive protein, fibrinogen, Lp(a), HMGB-1, sortilin, TNF-α, IL-6) are associated with worse outcomes, including delayed wound healing, MALE, MACE, and mortality [8, 16, 43, 49, 190, 218, 224, 339, 424, 437, 439, 455].
- Frailty (Clinical Frailty Scale, CFS) is a strong independent predictor of poor outcomes, including lower wound healing rates and increased mortality [123, 142, 157, 342, 356]. Malnutrition, assessed by CONUT or GNRI scores, also predicts worse outcomes and mortality [133, 147, 151, 157, 220, 285].
- The WIfI (Wound, Ischemia, and Foot Infection) classification system is a clinically meaningful tool for predicting outcomes, guiding management, and correlating with amputation risk and mortality, especially in diabetic patients [13, 129, 157, 197, 370, 447]. Higher Global Limb Anatomic Staging System (GLASS) grades are associated with lower technical success, patency, and higher amputation and mortality rates [76, 134, 156, 240, 261].
- **Wound Healing & Limb Salvage:**
- Wound healing rates vary widely, from 25% at 6 months for TADF [4] to 86.7% with successful pedal arch revascularization (PAR) [58]. Angiographic wound blush (WB) is a predictor of better 12-month limb-based patency (31.6% vs 9.7%) and AFS (54.1% vs 22.2%) [83].
- Negative pressure wound therapy with instillation and dwell time (NPWTi-d) using an antiseptic solution shortened treatment duration [44].
- Infected ulcers, particularly with Gram-negative bacteria, are associated with higher amputation rates (52% freedom from amputation in GNB vs 72% in GPB) [59, 65, 165].
- **Health Disparities & Socioeconomic Factors:**

- Black women had the highest rate of post-revascularization progression from claudication to CLTI (11.8%) [23]. Black and Hispanic patients undergoing infrainguinal revascularization had worse limb outcomes and higher amputation rates compared to White patients, even with similar disease severity [409, 417].
- Patients from rural areas experience significantly worse inpatient outcomes, including higher mortality (aOR=1.35) and major amputation (aOR=1.38), compared to urban patients [82]. Socioeconomic deprivation is a major driver of CLTI disparities in diabetic patients [141].
- Low-income status, male sex, and care at safety-net hospitals were associated with lower intensity of vascular care before amputation, linked to worse long-term survival [85].
- **Novel Diagnostic & Therapeutic Approaches:**
- Apheresis with the Rheocarna device reduced LDL-C and fibrinogen, improving ABI and SPP, leading to wound healing [2, 66, 89, 407].
- Low-intensity pulsed ultrasound (LIPUS) improved clinical symptoms, inflammation, perfusion parameters, and vascular function, with high 1-year survival and limb survival rates (88.9% and 88.6% respectively) [7].
- Circulating miRNA-1827 is significantly elevated in CLTI patients [234]. Elevated serum fatty acid synthase (cFAS) is independently associated with CLTI [229]. Specific serum metabolites can differentiate CLTI from intermittent claudication [200].

5) Discussion

5.1 Principal finding

The median 1-year amputation-free survival (AFS) rate for patients with chronic limb-threatening ischemia (CLTI) was 75%, ranging from 37% to 91.5% [3, 73], indicating a high degree of variability in outcomes depending on patient characteristics, disease severity, and treatment modalities.

5.2 Clinical implications

- **Revascularization Strategy Tailoring:** Surgical bypass with an adequate great saphenous vein conduit should be considered the preferred revascularization strategy for CLTI patients with suitable anatomy due to superior long-term limb outcomes [1, 6, 25].
- **Aggressive Management for No-Option CLTI:** For patients without conventional revascularization options, novel therapies like transcatheter arterialization of deep veins, cell-based therapies, and spinal cord stimulation offer promising limb salvage and pain relief, necessitating their consideration in multidisciplinary care pathways [4, 24, 75, 80, 84, 86, 189, 222].
- **Prognostic Tool Integration:** Routine use of prognostic tools such as WIfI and GLASS classifications, along with assessment of frailty and nutritional status (e.g., CONUT, GNRI), is

crucial for accurate risk stratification and guiding individualized treatment plans [13, 76, 123, 129, 133, 151, 157, 197, 220, 285, 370, 447].

- **Addressing Health Disparities:** Clinical pathways should actively identify and address socioeconomic and racial disparities in CLTI care, particularly for Black and Hispanic patients and those in rural areas, who experience worse outcomes and higher amputation rates [23, 82, 85, 141, 409, 417].
- **Inflammation as a Therapeutic Target:** Elevated inflammatory markers are consistently linked to poor outcomes; therefore, anti-inflammatory strategies and monitoring of inflammatory biomarkers may offer additional therapeutic avenues or prognostic insights [8, 16, 43, 49, 190, 218, 224, 339, 424, 437, 439, 455].

5.3 Research implications / key gaps

- **Comparative Effectiveness of Novel Therapies:** Future RCTs are needed to directly compare the long-term efficacy and safety of emerging treatments for no-option CLTI (e.g., cell-based therapies, deep venous arterialization, spinal cord stimulation) against standard conservative care [4, 24, 75, 80, 84, 86, 116, 189, 198, 222].
- **Standardization of Biomarker Panels:** Research should focus on developing and validating standardized panels of inflammatory and metabolic biomarkers for early diagnosis, risk stratification, and monitoring treatment response in CLTI patients, including those with diabetes [8, 49, 200, 218, 224, 229, 234, 424, 432, 437, 439, 444, 455].
- **Impact of Multidisciplinary Care Models:** Prospective studies are needed to evaluate the long-term impact of integrated multidisciplinary team approaches on limb salvage, quality of life, and mortality, particularly in complex CLTI populations [73, 112, 238].
- **Optimizing Wound Healing Strategies:** Further research is required to identify optimal wound care protocols, including the role of advanced dressings, NPWTi-d, and targeted antibiotic strategies, especially in the context of antimicrobial resistance in CLTI-associated infections [44, 59, 65, 165, 419].
- **Long-term Outcomes of Inframalleolar Interventions:** More robust, long-term data from RCTs are needed to clarify the optimal revascularization strategies (e.g., plain balloon angioplasty, drug-coated balloons, stents) for inframalleolar lesions, considering their impact on wound healing, patency, and limb salvage [5, 39, 57, 158, 225, 227, 250, 297, 346, 364, 386, 391, 398, 403, 426, 461, 469, 470, 487, 489, 499, 506].

5.4 Limitations

- **Study Design Heterogeneity** — The included studies vary significantly in design, with a large proportion being retrospective cohorts, which limits the ability to draw definitive conclusions.
- **Outcome Reporting Variability** — Different studies report diverse primary and secondary endpoints, making direct comparisons and quantitative synthesis challenging.
- **Population Specificity** — Many studies focus on specific subgroups (e.g., diabetic, no-option CLTI), limiting generalizability to the broader CLTI population.
- **Lack of Direct Comparisons** — For many interventions, head-to-head comparisons or large-scale randomized controlled trials are scarce, particularly for novel therapies.
- **Variable Follow-up Duration** — Follow-up periods range from 30 days to several years, impacting the assessment of long-term efficacy and safety.

5.5 Future directions

- **Standardized Outcome Reporting** — Implement core outcome sets for CLTI research.
- **Large-Scale RCTs** — Conduct large, multicenter randomized controlled trials for novel therapies.
- **Real-World Data Registries** — Expand and utilize national/international CLTI registries.
- **Biomarker-Guided Therapies** — Develop trials testing biomarker-driven treatment algorithms.
- **Health Equity Interventions** — Design and evaluate interventions to reduce disparities.

6) Conclusion

The 1-year amputation-free survival (AFS) rate in patients with chronic limb-threatening ischemia (CLTI) ranged from 37% [3] to 91.5% [73], underscoring the severe and varied prognosis of this condition. While surgical and endovascular revascularization remain cornerstones of therapy, novel interventions for "no-option" CLTI and improved prognostic tools are continually emerging, offering hope for improved limb salvage and patient outcomes across diverse populations. The heterogeneity in study designs and outcome reporting represents a significant limitation, affecting the certainty of current evidence. Clinicians should integrate prognostic tools like WIfI and GLASS classifications to guide personalized treatment strategies, while future research should prioritize large-scale randomized controlled trials to establish the comparative effectiveness of novel therapies.

References

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Figure 1. Publication-year distribution of included originals

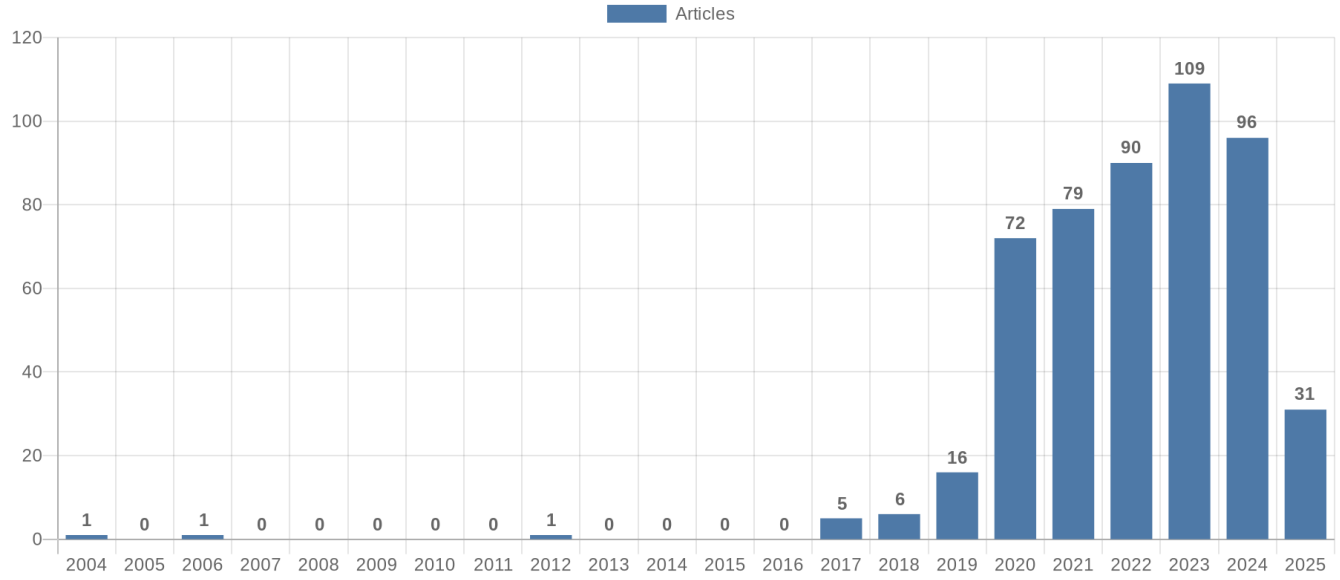

Figure 2. Study-design distribution of included originals

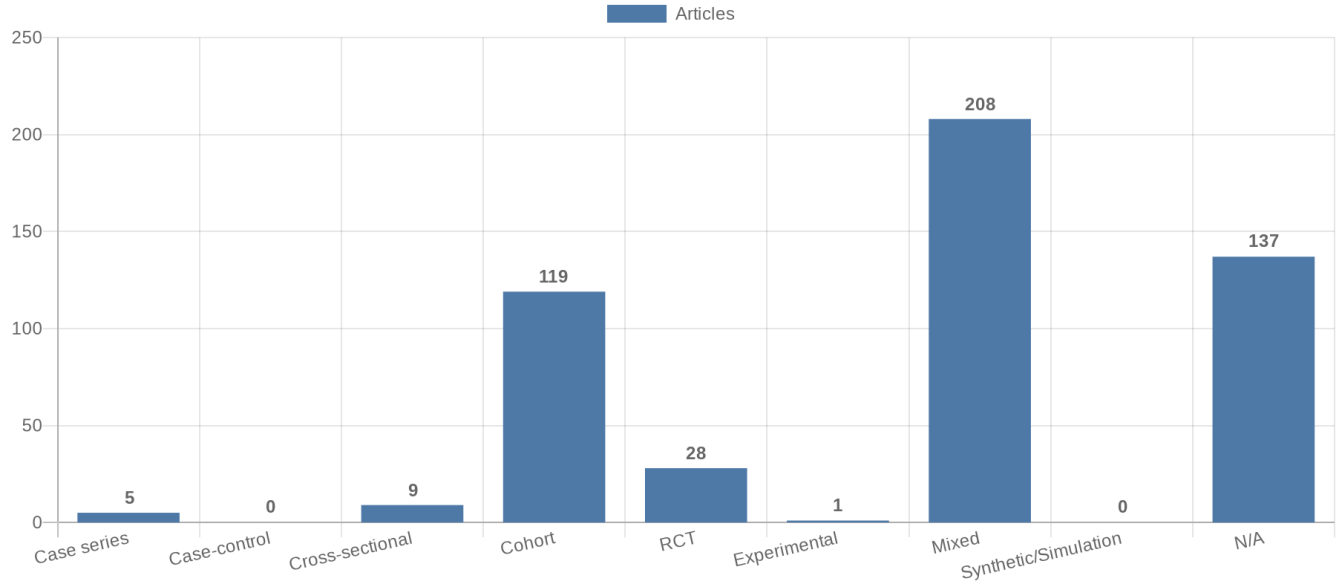

Figure 3. Study-type (directionality) distribution of included originals

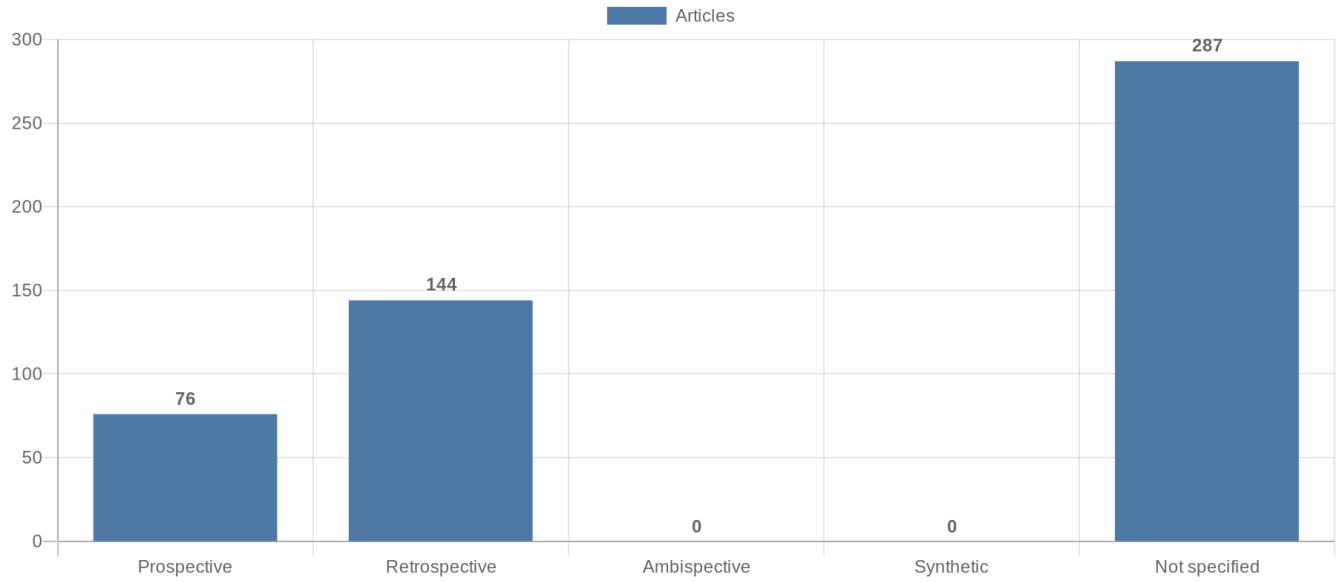

Figure 4. Main extracted research topics

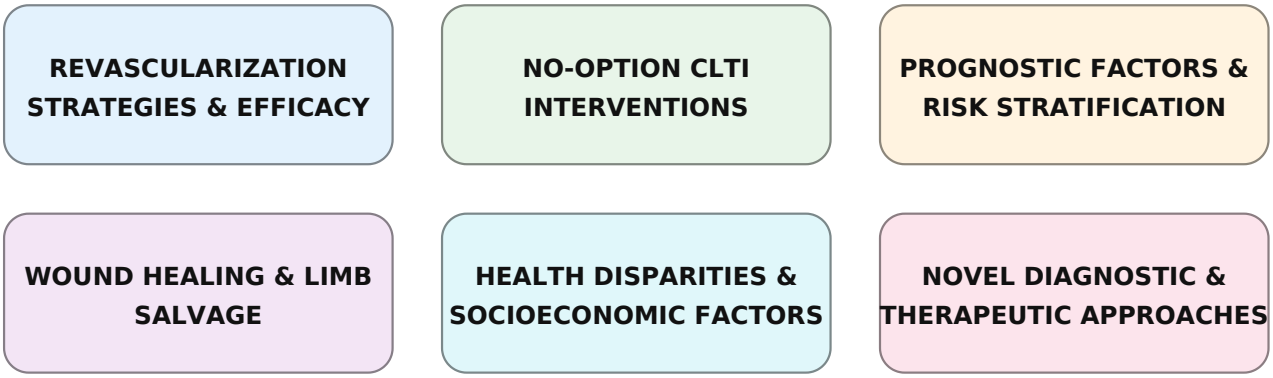

Figure 5. Limitations of current studies (topics)

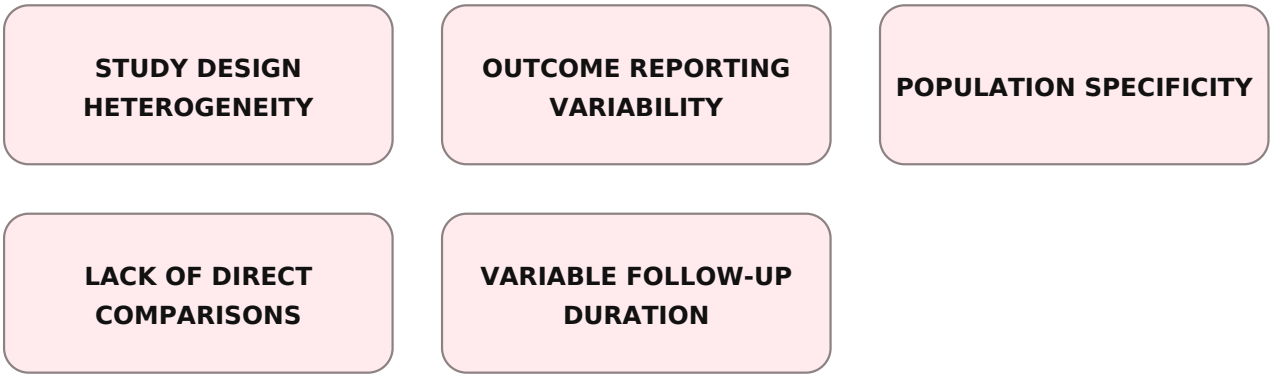

Figure 6. Future research directions (topics)

COMPARATIVE EFFECTIVENESS OF NOVEL THERAPIES

STANDARDIZATION OF BIOMARKER PANELS

IMPACT OF MULTIDISCIPLINARY CARE MODELS

OPTIMIZING WOUND HEALING STRATEGIES

LONG-TERM OUTCOMES OF INFRAMALLEOLAR INTERVENTIONS

STANDARDIZED OUTCOME REPORTING

LARGE-SCALE RCTS