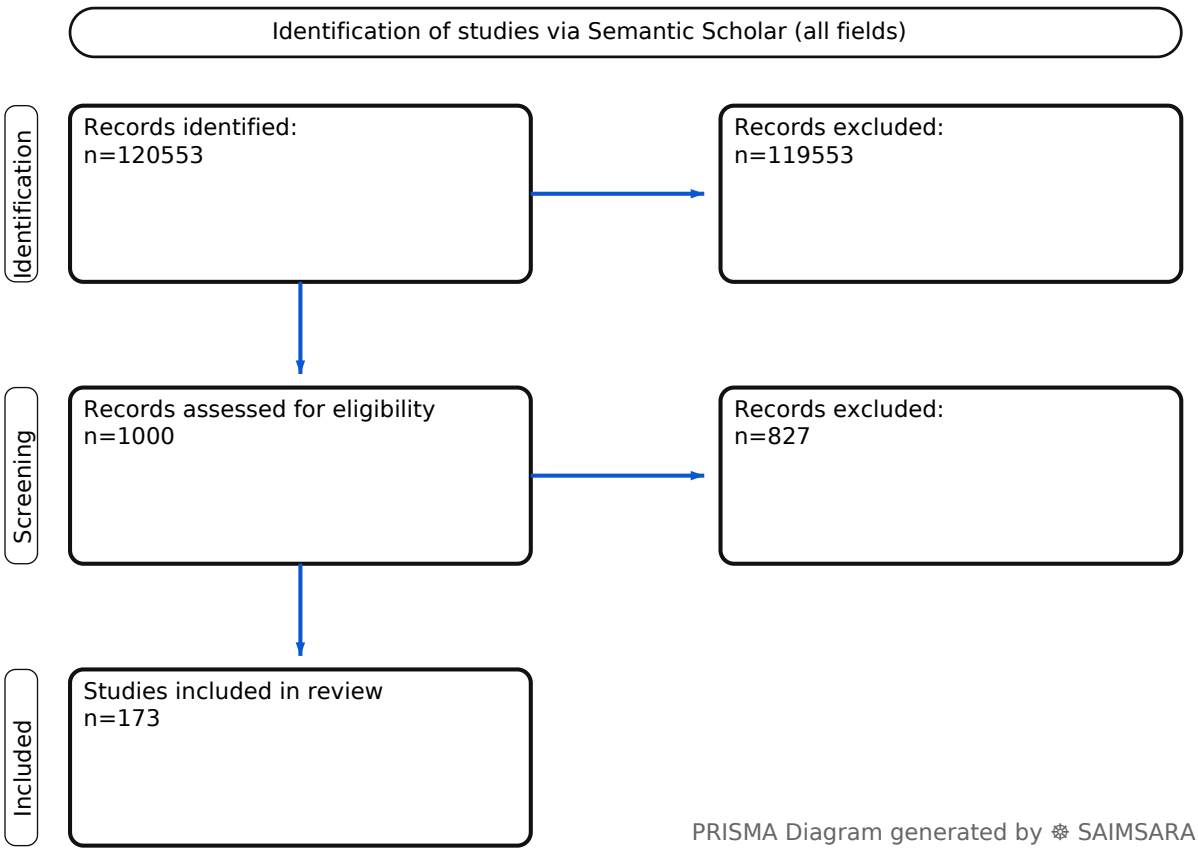
Acute Limb Ischemia and Risk Factors: Systematic Review with ☸SAIMSARA.

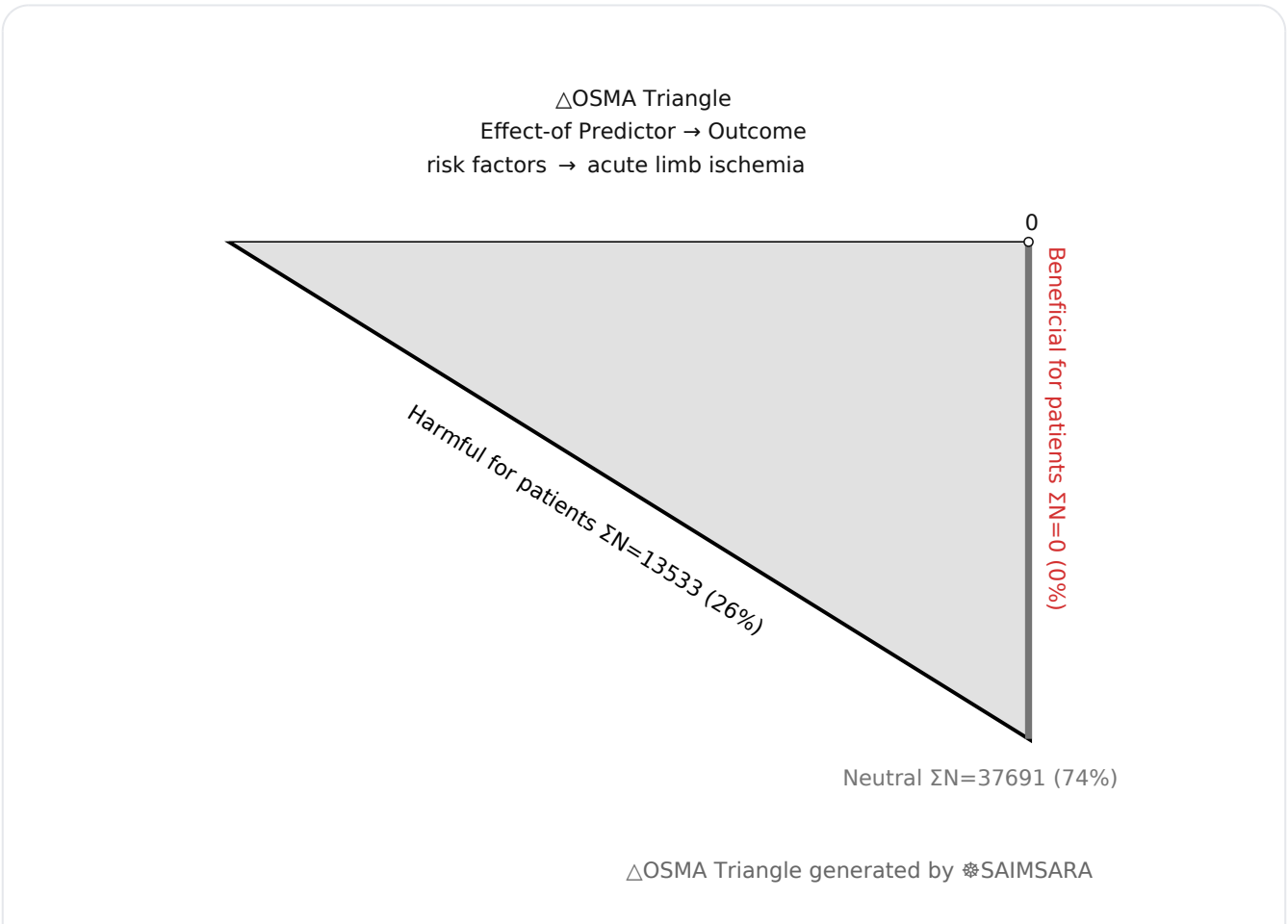
Abstract: The aim of this paper is to systematically review and synthesize the current evidence regarding acute limb ischemia and its associated risk factors, treatment approaches, and patient outcomes. The review utilises 173 studies with 51224 total participants (naïve ΣN). Acute limb ischemia (ALI) is associated with significant morbidity and mortality, with reported amputation rates ranging from 4.1% to 28.9% and mortality rates from 0.3% to 42.1% across various patient cohorts. These findings generally apply to diverse patient populations, including those with peripheral artery disease, COVID-19, and those undergoing complex medical procedures like ECMO. The heterogeneity of study designs and outcome reporting significantly affects the certainty of generalized conclusions. Therefore, timely diagnosis and intervention, coupled with aggressive management of identified risk factors, remain paramount for improving limb salvage and survival in ALI patients.

Keywords: Acute limb ischemia; Risk factors; Peripheral artery disease; COVID-19; Inflammatory biomarkers; Amputation; Mortality; Atrial fibrillation; End-stage renal disease; Extracorporeal membrane oxygenation

Review Stats

- Generated: 2026-02-13 23:00:10 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: 120553
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 173
- Total study participants (naïve ΣN): 51224


Identification of studies via Semantic Scholar (all fields)
Identification
Records identified:
n=120553
Records excluded:
n=119553
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=827
Included
Studies included in review
n=173
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
risk factors → acute limb ischemia
0
Beneficial for patients ΣN=0 (0%)
Harmful for patients ΣN=13533 (26%)
Neutral ΣN=37691 (74%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: acute limb ischemia Typical timepoints: 30-day, peri/post-op. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, admission.

Predictor: risk factors — exposure/predictor. Routes seen: intravenous. Typical comparator: surgical and hybrid treatments, surgical revascularization in, patients treated for chronic, diabetic mice with acute or….

- **1) Beneficial for patients** — acute limb ischemia with risk factors — — — ΣN=0
- **2) Harmful for patients** — acute limb ischemia with risk factors — [1], [4], [5], [6], [9], [11], [15], [30], [31], [36], [37], [38], [39], [42], [45], [50], [55], [57], [59], [101], [109], [111], [122], [134], [136], [137], [138], [139], [141], [142], [143], [148], [149] — ΣN=13533
- **3) No clear effect** — acute limb ischemia with risk factors — [2], [3], [7], [8], [10], [12], [13], [14], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [32], [33], [34], [35], [40], [41], [43], [44], [46], [47], [48], [49], [51], [52], [53], [54], [56], [58], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [102], [103], [104], [105], [106], [107], [108], [110], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [135], [140], [144], [145], [146], [147], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173] — ΣN=37691

1) Introduction

Acute limb ischemia (ALI) represents a critical vascular emergency characterized by a sudden decrease in limb perfusion, threatening limb viability and often associated with high rates of amputation and mortality. The rapid onset and severe consequences necessitate immediate diagnosis and intervention. Understanding the diverse risk factors contributing to ALI, its prognosis, and the efficacy of various treatment modalities is crucial for improving patient outcomes. This paper synthesizes current evidence on the epidemiology, risk factors, management strategies, and prognostic indicators associated with ALI.

2) Aim

The aim of this paper is to systematically review and synthesize the current evidence regarding acute limb ischemia and its associated risk factors, treatment approaches, and 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:** The qualitative assessment of study designs reveals a predominance of retrospective cohort studies and mixed designs, which inherently carry a risk of selection bias and confounding due to their observational nature. While some randomized controlled trials (RCTs) provide higher-quality evidence for interventions, the overall heterogeneity in study design and reporting introduces variability in the certainty of findings.

4) Results

4.1 Study characteristics

The included studies predominantly comprised retrospective cohort designs, mixed methodologies, and case reports, with a smaller number of prospective cohort studies and randomized controlled trials. Sample sizes varied widely, from single case reports to large cohorts exceeding 6,500 patients [8, 112], and follow-up periods ranged from 30 days to several years, with many studies not specifying a follow-up duration.

4.2 Main numerical result aligned to the query

Acute limb ischemia (ALI) is associated with significant morbidity and mortality, with reported amputation rates ranging from 4.1% [59] to 28.9% [55] and mortality rates from 0.3% [34] to 42.1% [134] across various patient cohorts. The median amputation rate reported was 8.8%, and the median mortality rate was 4.9%.

4.3 Topic synthesis

- **Patient Demographics and Comorbidities as Risk Factors:** Age (OR 1.5 [1], OR=1.04 [59]), gender [1], end-stage renal disease (ESRD) (OR 14.92 [1]), heart failure [9], renal disease [9], liver disease [9], chronic kidney disease (HR 2.00 [111]), and diabetes mellitus (adjusted risk ratio 3.01 [137], HR 1.71 [111]) are consistently identified as predictors of poor outcomes. A history of acute myocardial infarction (OR=2.68 [59]), prior peripheral revascularization (HR 4.7 [15], HR 2.18 [111]), baseline atrial fibrillation (HR 1.8 [15]), and peripheral artery disease (PAD) [15, 111, 149] also heighten ALI risk.

- **Inflammatory Biomarkers as Prognostic Indicators:** High preoperative neutrophil-to-lymphocyte ratio (NLR) (OR 9.65 [11], OR 11.09 [4]), platelet-to-lymphocyte ratio (PLR) (OR 8.97 [4]), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), atherosclerosis inflammatory index (AISI) [5], C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [136] are independent predictors of amputation, mortality, and other adverse events.
- **Ischemia Characteristics and Severity:** The degree of ischemia (OR 38.35 [1]), etiology of limb ischemia [1], tibial runoff [1], lower ankle-brachial index (ABI) (HR 1.3 per 0.10 decrease [15], ABI <0.4 HR 4.45 [111]), and occlusion duration exceeding 24 hours (OR 2.6 [55]) are critical determinants of limb salvage and survival.
- **COVID-19 as a Prothrombotic State:** COVID-19 can manifest as arterial thrombosis and ALI [10, 21, 33, 37, 39, 130, 156], with higher systemic inflammatory biomarkers in COVID-19 patients predicting ALI risk, ICU admission, and mortality [5]. Notably, even mild COVID-19 symptoms can be associated with a prothrombotic state [37].
- **Iatrogenic and Procedure-Related Complications:** Failed percutaneous femoral cannulation for venoarterial extracorporeal membrane oxygenation (VA-ECMO) ($p = 0.039$ [109]), larger profile devices for resuscitative endovascular balloon occlusion of the aorta (REBOA) ($p = 0.009$ [101]), and increased vasopressor usage [27] are identified risk factors for ALI. Long femoropopliteal covered nitinol stents are associated with a higher incidence of acute stent thrombosis (HR 6.3 [30]).
- **Substance Use and External Factors:** Cannabis use disorder (OR 1.20 [6]) and cocaine inhalation [42] have been linked to ALI. A case report also highlights ALI following a giant honey bee sting in a patient with pre-existing risk factors [29].
- **Amputation and Mortality Outcomes:** High rates of amputation (median 8.8%, range 4.1-28.9% [3, 44, 55, 57, 59, 84]) and mortality (median 4.9%, range 0.3-42.1% [34, 38, 44, 55, 57, 59, 84, 134]) are common, with specific predictors including age, preoperative hemoglobin, MI history, ischemic ulcers, below-the-knee revascularization [59], and higher calcium scores in the operated limb [148].
- **Timely Intervention is Critical:** Immediate diagnosis, accurate assessment, and urgent intervention are paramount for limb salvage [14, 18], as patient delay is a primary cause of treatment delay [44].
- **Revascularization Modalities:** Endovascular treatment demonstrates significantly better amputation-free survival and lower mortality compared to surgical and hybrid treatments in some contexts [2, 16]. Mechanical debulking (Rotarex) is a safe and effective alternative to thrombolysis [34, 40]. Surgical embolectomy and catheter-directed thrombolysis show comparable in-hospital mortality and amputation risks [9].
- **Pharmacological Management:** Low-dose rivaroxaban plus aspirin reduces ALI after lower extremity revascularization (LER) [8, 112, 128]. Alirocumab reduces peripheral artery

disease (PAD) events, particularly in patients with high lipoprotein(a) [102]. Liposomal prostaglandin E1 (lipo-PGE1) significantly reduces perioperative mortality and major adverse limb events [62]. SGLT2 inhibitors (SGLT2i) are associated with lower risks of lower limb ischemia requiring revascularization or amputation in type 2 diabetes mellitus (T2DM) patients with PAD [162].

- **Adjunctive Therapies and Emerging Treatments:** Delayed fasciotomy is associated with a higher risk of major amputation [23]. Remote ischemic conditioning (RIC) has shown promise in preventing postoperative acute kidney injury after aortic arch replacement [110]. Hypoxia-induced miR-210 stimulates vascular regeneration [20], while overexpression of VEGF-A and FGF4 restores blood flow [49]. A tissue-engineered Human Acellular Vessel (HAV) may be a promising alternative to ePTFE grafts for vascular reconstruction [46].
- **Diagnostic Techniques:** Duplex ultrasound arterial mapping (DUAM) is evaluated as a sole preoperative imaging technique [65], and point-of-care ultrasound (POCUS) can rapidly diagnose arterial occlusions [97].
- **Ischemia-Reperfusion Injury (IRI):** Basic control of reperfusion effectively protects against IRI [54, 77]. Dexamethasone significantly reduces infarct size and muscle damage in tourniquet-induced IRI [73]. Caffeine mitigated lung inflammation induced by lower limb IRI in rats [165].

5) Discussion

5.1 Principal finding

Acute limb ischemia (ALI) is associated with significant morbidity and mortality, with reported amputation rates ranging from 4.1% to 28.9% and mortality rates from 0.3% to 42.1% across various patient cohorts [3, 34, 38, 44, 55, 57, 59, 84, 134].

5.2 Clinical implications

- **Urgent Diagnostic and Therapeutic Pathways:** Given the severe outcomes, clinicians must prioritize immediate diagnosis and urgent intervention for ALI patients, as patient delay is a significant factor in treatment delay [14, 18, 44].
- **Aggressive Risk Factor Management:** Modifiable risk factors such as smoking, hypertension, and diabetes mellitus should be aggressively managed in patients at risk for ALI [137], alongside careful monitoring of inflammatory biomarkers like NLR and PLR as prognostic indicators [4, 5, 11, 50, 136].
- **Consideration of Endovascular First Approach:** Endovascular treatment modalities, including mechanical thrombectomy, may offer better amputation-free survival and lower mortality compared to traditional surgical or hybrid approaches in suitable ALI cases [2, 16,

34, 40].

- **Vigilance for COVID-19 Associated Thrombosis:** Clinicians should maintain a high index of suspicion for ALI as a potential initial manifestation or complication of COVID-19, even in patients with mild symptoms, and consider appropriate anticoagulation strategies [10, 37, 130].
- **Prophylactic Antithrombotic Strategies Post-Revascularization:** For patients with peripheral artery disease undergoing lower extremity revascularization, combination therapy with low-dose rivaroxaban and aspirin significantly reduces the incidence of subsequent ALI and other adverse limb events [8, 112, 128].

5.3 Research implications / key gaps

- **Standardized Risk Stratification Models:** Develop and validate comprehensive, universally applicable risk stratification models for ALI, integrating clinical, imaging, and inflammatory biomarker data [1, 4, 5, 11, 15, 50, 59, 111, 136].
- **Comparative Effectiveness of Revascularization:** Conduct large-scale, prospective randomized controlled trials comparing long-term outcomes of endovascular versus open surgical revascularization for specific ALI etiologies and anatomical patterns [2, 16, 19].
- **Mechanisms of COVID-19 Thrombosis:** Further investigate the precise molecular and immunological mechanisms underlying COVID-19-induced thrombotic ALI to inform targeted preventative and therapeutic interventions [10, 37, 130].
- **Novel Angiogenic and Anti-Inflammatory Therapies:** Explore the clinical translation of promising preclinical therapies, such as microRNA modulators (e.g., miR-210 [20], miR-92a inhibitor [123]), growth factors (VEGF-A, FGF4 [49]), and anti-inflammatory agents (FTY720 [60], dexamethasone [73]), to improve limb salvage and mitigate reperfusion injury.
- **Optimized Remote Ischemic Conditioning:** Investigate optimal protocols (timing, duration, limb choice) and patient populations for remote ischemic conditioning to prevent ALI or reduce ischemia-reperfusion injury in high-risk settings [93, 110, 154].

5.4 Limitations

- **Heterogeneity of Studies** — The included studies exhibit diverse designs (retrospective, mixed, RCT), populations (general ALI, COVID-19, PAD), and outcome measures, limiting direct comparison and meta-analysis.
- **Reporting Inconsistencies** — Many studies lacked explicit reporting of sample sizes, follow-up durations, or detailed statistical metrics, hindering comprehensive quantitative

synthesis.

- **Qualitative Bias Inference** — Bias assessment was qualitatively inferred from study designs rather than a standardized, systematic tool, which may introduce subjective interpretation.
- **Focus on Lower Limb** — A significant portion of the literature focuses on lower limb ischemia, potentially underrepresenting unique risk factors and outcomes for upper limb ALI [27, 48, 61].
- **Lack of Pooled Effect Sizes** — The absence of uniform metrics for risk factors prevented the calculation of pooled effect sizes, necessitating a descriptive summary of individual study findings.

5.5 Future directions

- **Standardized Outcome Reporting** — Standardize reporting of ALI incidence, amputation, and mortality rates across studies.
- **Prospective Registry Development** — Establish large, prospective registries to collect comprehensive data on ALI risk factors, treatments, and long-term outcomes.
- **Biomarker Validation Studies** — Conduct prospective studies to validate inflammatory biomarkers (NLR, PLR) as routine prognostic tools in ALI.
- **Comparative Treatment Trials** — Design RCTs comparing endovascular and surgical revascularization strategies in specific ALI subgroups.
- **COVID-19 Thrombosis Mechanisms** — Investigate the molecular mechanisms underlying COVID-19-associated ALI and evaluate targeted anticoagulant therapies.

6) Conclusion

Acute limb ischemia (ALI) is associated with significant morbidity and mortality, with reported amputation rates ranging from 4.1% to 28.9% and mortality rates from 0.3% to 42.1% across various patient cohorts [3, 34, 38, 44, 55, 57, 59, 84, 134]. These findings generally apply to diverse patient populations, including those with peripheral artery disease, COVID-19, and those undergoing complex medical procedures like ECMO. The heterogeneity of study designs and outcome reporting significantly affects the certainty of generalized conclusions. Therefore, timely diagnosis and intervention, coupled with aggressive management of identified risk factors, remain paramount for improving limb salvage and survival in ALI patients.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

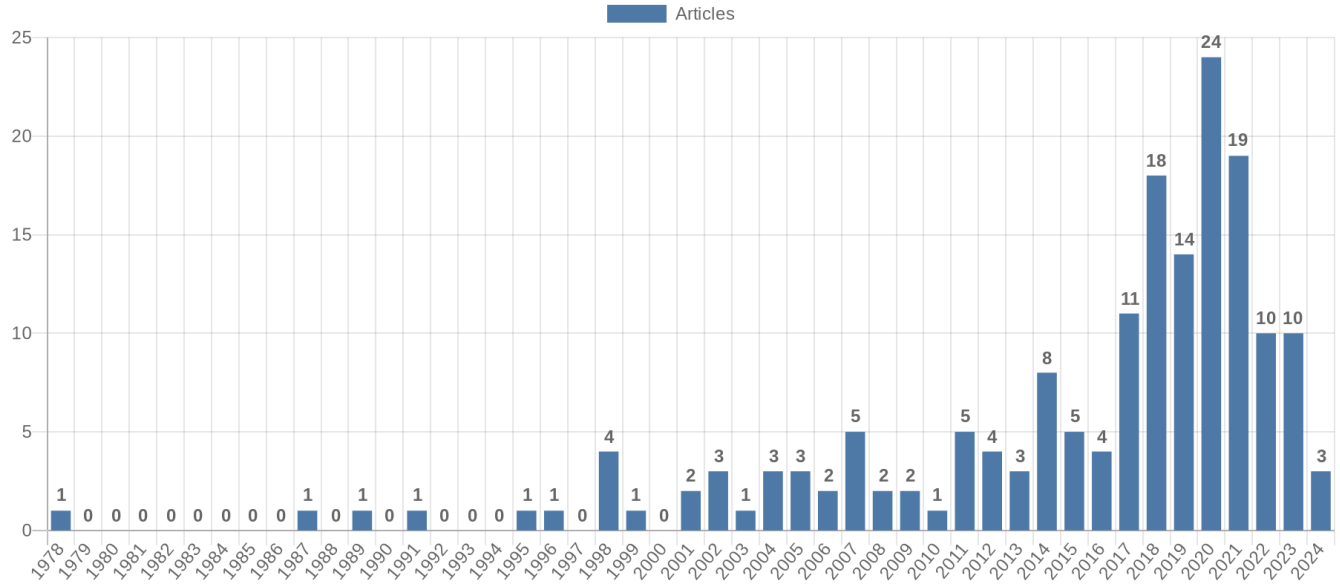


Figure 2. Study-design distribution of included originals

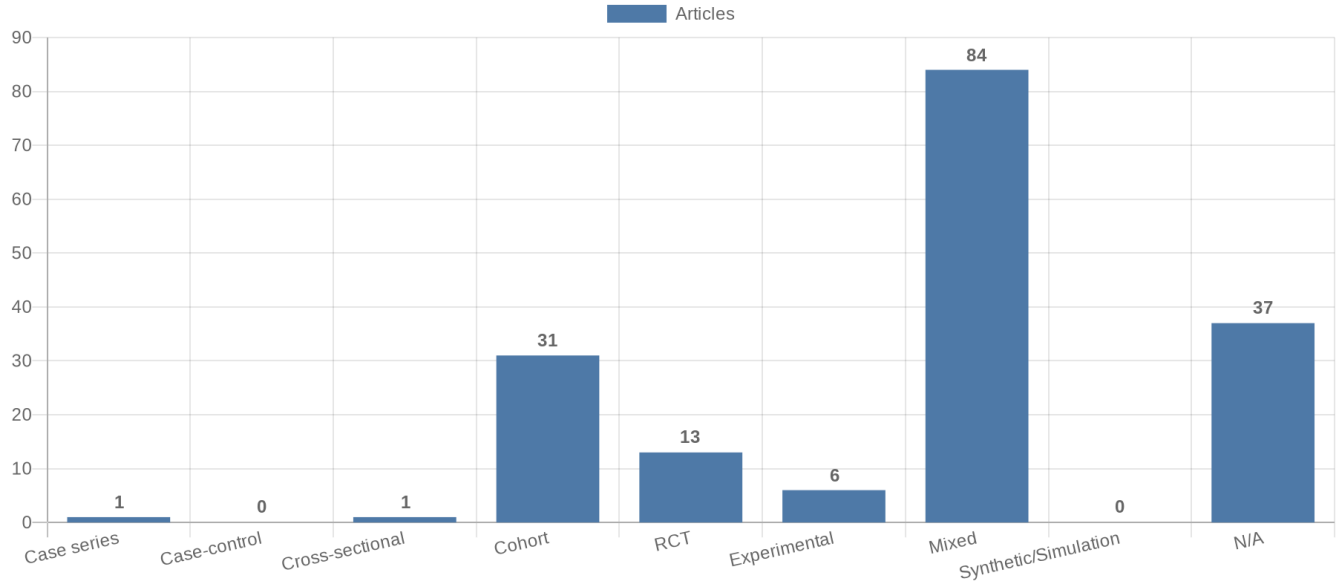


Figure 3. Study-type (directionality) distribution of included originals

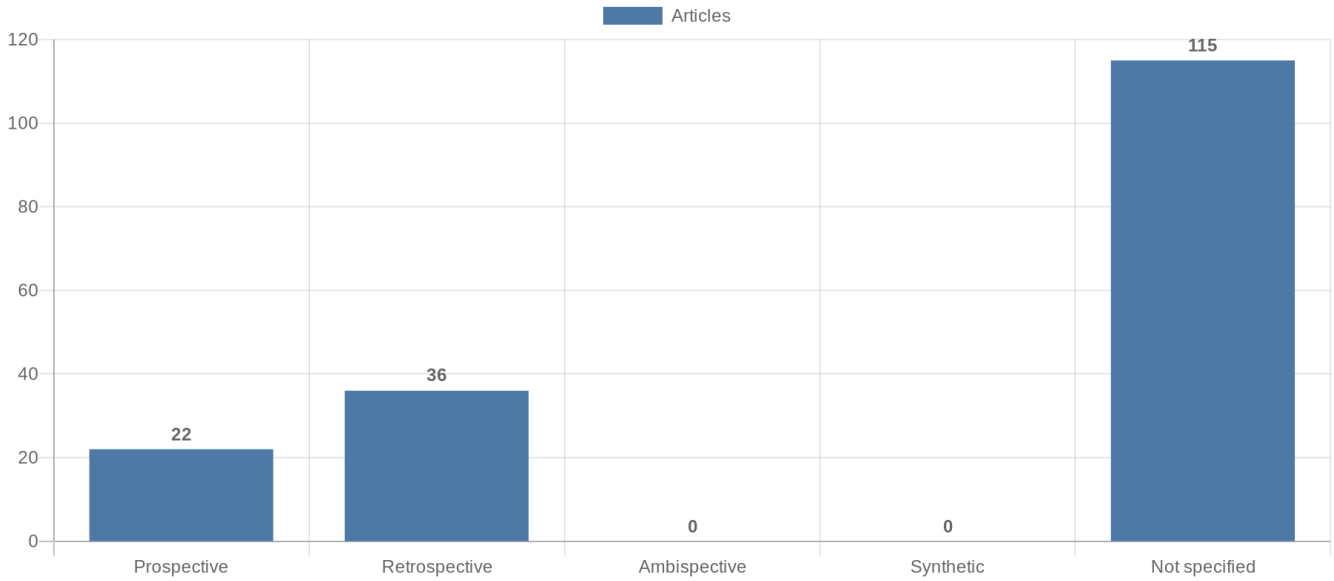


Figure 4. Main extracted research topics

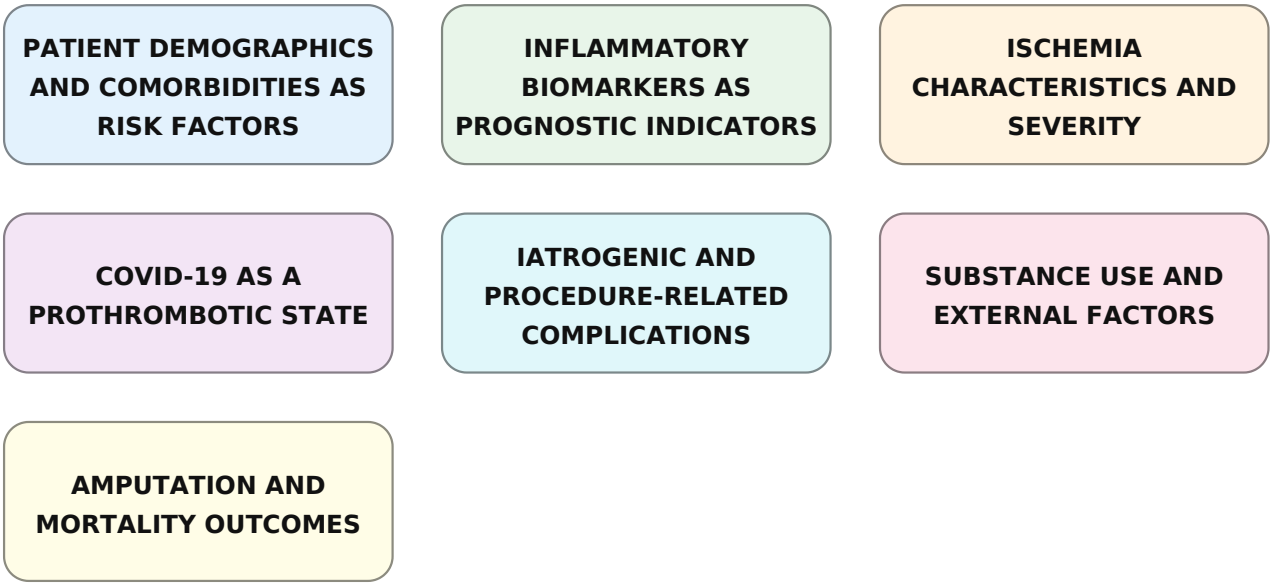


Figure 5. Limitations of current studies (topics)

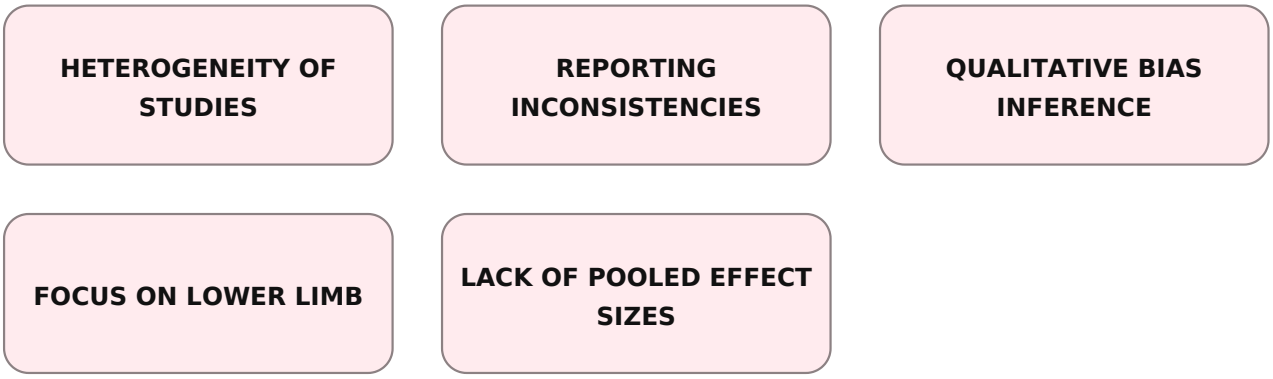


Figure 6. Future research directions (topics)

STANDARDIZED RISK STRATIFICATION MODELS

COMPARATIVE EFFECTIVENESS OF REVASCULARIZATION

MECHANISMS OF COVID-19 THROMBOSIS

NOVEL ANGIOGENIC AND ANTI-INFLAMMATORY THERAPIES

OPTIMIZED REMOTE ISCHEMIC CONDITIONING

STANDARDIZED OUTCOME REPORTING

PROSPECTIVE REGISTRY DEVELOPMENT