PAD Fontaine Classification: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review the current scientific literature, leveraging a multilayer AI research agent, to synthesize findings related to the Fontaine classification in the context of PAD, encompassing its utility in diagnosis, prognosis, and treatment evaluation. The review utilises 139 studies with 683465 total participants (naïve ΣN). The Fontaine classification is consistently used across studies as a primary metric for assessing PAD severity and evaluating treatment efficacy, though no single comparable numerical outcome (e.g., a pooled success rate or odds ratio) is reported across multiple studies to allow for a central value calculation. This classification remains indispensable for guiding clinical decisions, stratifying patient risk, and assessing the impact of various interventions on disease progression and patient quality of life. The heterogeneity of study designs and outcome reporting across the literature most significantly affects the certainty of synthesized findings. To advance PAD management, future research should prioritize standardized outcome reporting and the development of AI-driven predictive models that integrate Fontaine stages with comprehensive patient data.

Keywords: Peripheral Artery Disease; Fontaine Classification; Disease Staging

Review Stats

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- 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)
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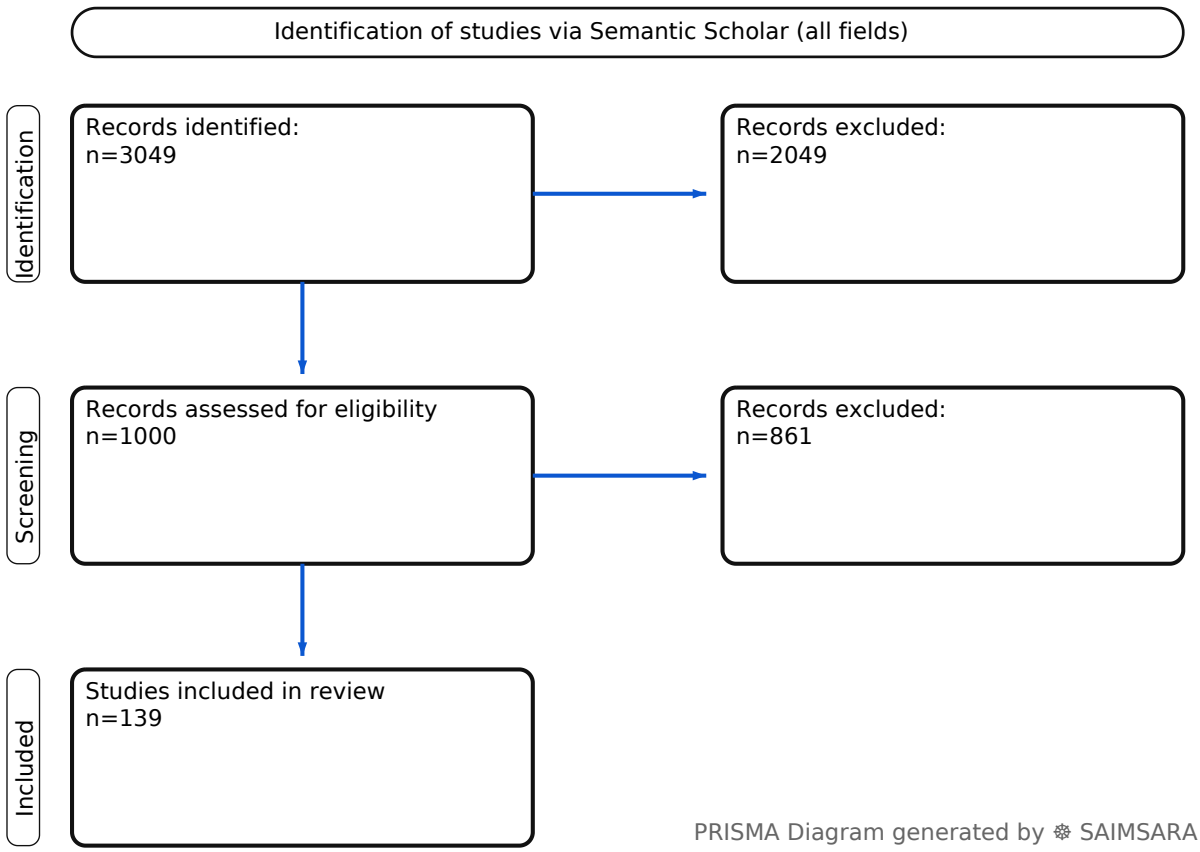
- Included original Abstracts/Papers: 139
- Total study participants (naïve ΣN): 683465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Records excluded:
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Screening
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Records excluded:
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Included
Studies included in review
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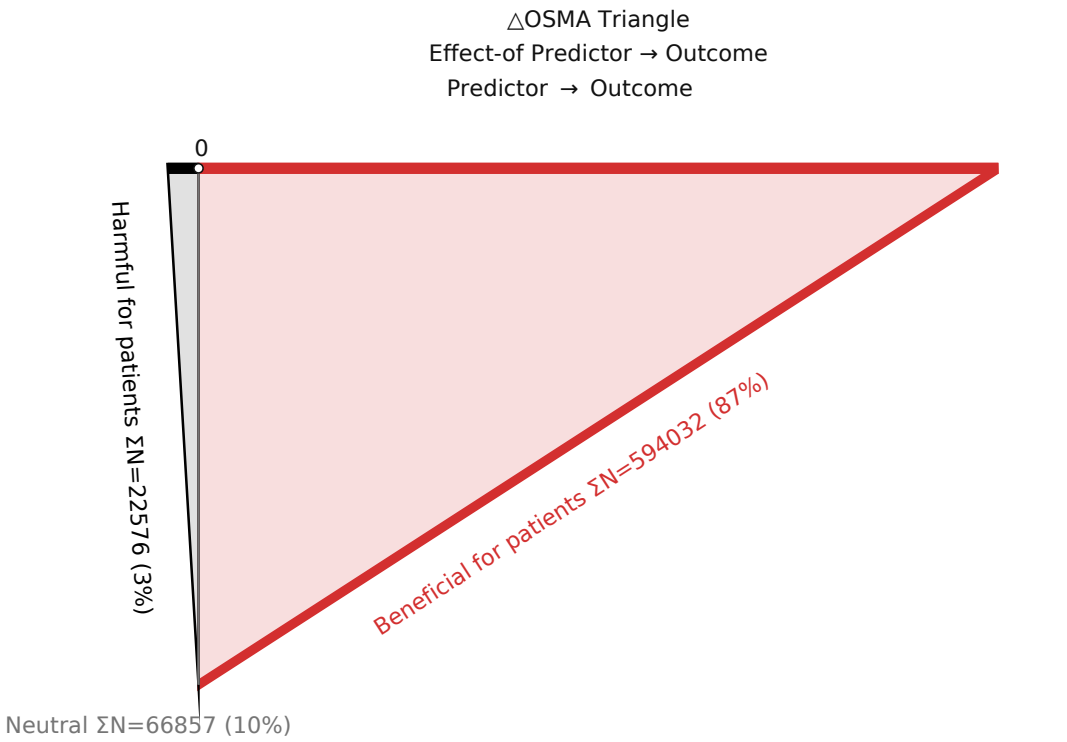
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
Predictor → Outcome
0
Harmful for patients ΣN=22576 (3%)
Beneficial for patients ΣN=594032 (87%)
Neutral ΣN=66857 (10%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*
Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar
Outcome: Outcome Typical timepoints: peri/post-op, 2-y. Reported metrics: %, CI, p.
Common endpoints: Common endpoints: mortality, admission, qol.
Predictor: Predictor — exposure/predictor. Routes seen: iv, intramuscular, oral. Typical comparator: control, severe pad, class iv and non-pad patients, those without wound occurrence….

- **1) Beneficial for patients** — Outcome with Predictor — [31], [42], [43], [45], [48], [49], [59], [65], [67], [70], [72], [73], [74], [76], [86], [90], [91], [92], [93], [95], [99], [100], [128], [132], [135], [136], [139] — ΣN=594032
- **2) Harmful for patients** — Outcome with Predictor — [33], [36], [38], [39], [40], [47], [50], [52], [54], [55], [56], [57], [58], [60], [61], [62], [63], [64], [69], [71], [75], [78], [81], [82], [87], [88], [96], [98], [131], [134], [138] — ΣN=22576
- **3) No clear effect** — Outcome with Predictor — [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [32], [34], [35], [37], [41], [44], [46], [51], [53], [66], [68], [77], [79], [80], [83], [84], [85], [89], [94], [97], [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], [129], [130], [133], [137] — ΣN=66857

1) Introduction

Peripheral artery disease (PAD) is a prevalent circulatory condition characterized by narrowed arteries that reduce blood flow to the limbs, most commonly the legs. The Fontaine classification, originally developed by René Fontaine, provides a standardized system for categorizing the severity of PAD based on clinical symptoms, ranging from asymptomatic disease to critical limb ischemia (CLI) with tissue loss [130, 32]. This classification is widely utilized in clinical practice for diagnosis, guiding treatment decisions, and assessing prognosis across various patient populations, including those with comorbidities like diabetes mellitus and hypertension. Its application spans from evaluating novel therapeutic interventions to identifying risk factors and predicting adverse outcomes.

2) Aim

The aim of this paper is to systematically review the current scientific literature, leveraging a multilayer AI research agent, to synthesize findings related to the Fontaine classification in the

context of PAD, encompassing its utility in diagnosis, prognosis, and treatment evaluation.

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 inference of bias suggests a mix of study designs, including retrospective cohorts, cross-sectional studies, and randomized controlled trials (RCTs). While RCTs offer higher evidence levels for interventions, many studies are observational, which may introduce selection bias or confounding. Small sample sizes in some interventional studies [1, 3, 20] limit generalizability, while larger cohort studies [2, 10, 13] provide broader population insights. The "not specified" directionality in many abstracts further limits the ability to fully assess methodological rigor.

4) Results

4.1 Study characteristics:

The extracted literature comprises a diverse range of study designs, including mixed-method studies, cohort studies (both retrospective and prospective), randomized controlled trials (RCTs), and cross-sectional analyses. Populations predominantly include patients with lower extremity peripheral artery disease (PAD), often stratified by specific Fontaine classification stages, and frequently coexisting with conditions such as diabetes mellitus (T2DM), hypertension (HTN), and coronary artery disease (CAD). Follow-up periods varied significantly, from short-term (1 month [3], 3 weeks [34], 6 months [1, 2, 11, 17, 19, 59]) to intermediate (1 year [20, 42, 73], 2 years [4, 36, 93, 121]) and long-term (5 years [89], 7 years [119], 18.8 years [38], 17.4 years [52]).

4.2 Main numerical result aligned to the query:

The Fontaine classification is consistently used across studies as a primary metric for assessing PAD severity and evaluating treatment efficacy, though no single comparable numerical outcome (e.g., a pooled success rate or odds ratio) is reported across multiple studies to allow for a central value calculation. Instead, various interventions demonstrate significant improvements in Fontaine stages or related clinical parameters. For instance, Lumbar sympathetic blockade (LSB) led to regressed Fontaine Classification Stages [1], and rotational atherothrombectomy significantly improved postoperative Rutherford and Fontaine classifications ($p<0.001$) [42]. Cilostazol treatment significantly improved PAD symptoms classified by Fontaine classification [43], and iliac artery stenting improved Fontaine classifications from stages IIa-IV to I-IV, with 88% ischemic symptom improvement [132].

4.3 Topic synthesis:

- **Therapeutic Efficacy and Fontaine Stages:** Interventions like Lumbar sympathetic blockade (LSB) [1], Noclaud® [2], high TENS and graded exercises [3], Taurisolo® [7], pl-VEGF165 gene transfer [11], pulsed electromagnetic field (PEMF) therapy [31], rotational atherothrombectomy [42], cilostazol [43, 76], exercise therapy [45, 70, 90, 100], mobile interventions (TrackPAD) [59, 107], spinal cord stimulation (SCS) [73], and granulocyte colony-stimulating factor-mobilized cell transplantation [74] all showed significant improvements in Fontaine stages or associated symptoms (e.g., walking distance, pain reduction) in PAD patients.
- **Biomarkers and Disease Severity:** Several biomarkers correlate with Fontaine classification severity, including C-reactive protein (CRP) and Growth Differentiation Factor 15 (GDF-15) for lower-extremity ulcers [5], Cyr61 levels in T2DM [14], Desmosines for elastin degradation [15], Thrombospondin-4 (TSP-4) [16], Omentin-1 serum levels in diabetic PAD patients [56], plasma HSPB1 levels in arteriosclerosis obliterans (ASO) [57], Lipoprotein(a) (Lp[a]) [55], and VASCULAR-2 levels [120].
- **Diagnostic and Prognostic Tools:** Novel methods like waveshape-based method (RMSD) combined with ABI [6], digital pulse oximetry [22], laser speckle measurement [28], deep learning-based photoplethysmography (PPG) [29], retinal and choriocapillaris perfusion parameters [30], AI-PAD score [68], regional tissue oxygenation saturation (rSO2) [75], perfusion index (PI) [96], and laser Doppler flowmetry (LDF) [105] show utility in classifying PAD Fontaine stages or identifying early-stage disease. The Fontaine IV classification is a strong risk factor for vascular events [121] and a predictive factor for significant asymptomatic carotid artery stenosis (ACAS) [111].
- **Comorbidities and Risk Factors:** Diabetes mellitus (T2DM) is frequently associated with PAD severity across Fontaine stages [8, 9, 14, 20, 23, 24, 40, 46, 47, 56, 69, 101, 103, 113, 122]. Hypertension [10, 13], elevated blood pressure in young adults [38], inflammatory bowel disease (IBD) [114], chronic venous insufficiency (CVI) [87], and chronic obstructive pulmonary disease (COPD) [123, 138] are also linked to PAD or its progression. Malnutrition increases with advancing Fontaine class [58].
- **Impact on Quality of Life and Function:** PAD severity, as measured by Fontaine stages, is strongly associated with decreased quality of life (QoL) [21, 54, 131], physical functioning [8, 49, 65, 76], and increased depressive symptoms [21]. Supervised exercise training significantly improves pain-free and maximal walking distances in Fontaine stage II PAD patients [70, 90].
- **Advanced Imaging and AI in Classification:** Advanced imaging techniques like run-off computed tomography angiography (CTA) [104] and magnetic resonance angiography (MRA) [83] are used for PAD assessment. Machine learning and deep learning methods show

high accuracy for detecting and classifying PAD [28, 29, 86, 91], with deep neural networks analyzing thermal patterns in Fontaine stage IIa-IIb patients [44].

- **Predictors of Adverse Outcomes:** Rutherford classification, often used alongside Fontaine, predicts major amputation [39] and PAD-related healthcare costs [36]. Neutrophil-lymphocyte ratio (NLR) and systemic inflammation index (SII) predict poor outcomes in critical limb ischemia (Leriche-Fontaine stage III) [64]. Fontaine stages are included as a common factor for Major Adverse Limb Events (MALE) in predictive models [51]. In-hospital mortality increases with Fontaine stages [12].

5) Discussion

5.1 Principal finding:

The Fontaine classification is a fundamental and widely utilized tool for stratifying peripheral artery disease (PAD) severity, consistently demonstrating its utility in guiding therapeutic interventions, correlating with various biomarkers, and predicting clinical outcomes across the spectrum of the disease [1, 42, 43, 132].

5.2 Clinical implications:

- **Treatment Guidance:** The Fontaine classification helps clinicians select appropriate interventions, from conservative management for early stages (e.g., exercise for stage II [70, 90]) to revascularization for advanced stages (e.g., endovascular treatment for stage II [23], rotational atherothrombectomy for total SFA occlusion [42], or SCS for CLTI in stages III/IV [73]).
- **Risk Stratification:** Higher Fontaine stages are associated with increased risks of major adverse limb events (MALE) [51], major amputations [71, 72], in-hospital mortality [12], and critical limb ischemia (CLI) [10, 13, 96], enabling clinicians to identify high-risk patients for intensive monitoring and aggressive management.
- **Prognostic Assessment:** The classification aids in predicting patient quality of life [21, 54, 131] and functional capacity [8, 49, 65, 76], allowing for more informed patient counseling and goal setting.
- **Biomarker Interpretation:** Understanding the correlation between Fontaine stages and various biomarkers (e.g., CRP, GDF-15 [5], Omentin-1 [56], Lp[a] [55]) can enhance diagnostic precision and potentially guide targeted therapies.
- **Comorbidity Management:** The strong association between Fontaine stages and comorbidities like diabetes [8, 9, 14, 20, 23, 24, 40, 46, 47, 56, 69, 101, 103, 113, 122] and hypertension [10, 13] underscores the need for integrated care and aggressive risk factor control.

5.3 Research implications / key gaps:

- **Standardized Outcome Metrics:** Future RCTs should aim for more standardized reporting of Fontaine classification changes as primary or secondary endpoints to enable robust meta-analysis of treatment effects [e.g., 2, 3, 7].
- **Early Stage Biomarkers:** Research is needed to identify and validate biomarkers that can predict progression from asymptomatic (Fontaine I) or mild claudication (Fontaine IIa) to more severe stages before overt clinical deterioration [e.g., 5, 14, 15, 16].
- **AI-Driven Predictive Models:** Further development and validation of AI/machine learning models that integrate Fontaine classification with other clinical, imaging, and biomarker data to predict individual patient trajectories and treatment responses are warranted [e.g., 28, 29, 44, 68, 86].
- **Longitudinal QoL Data:** More prospective studies are required to track long-term changes in quality of life and functional status across different Fontaine stages, particularly in response to various interventions, to better understand patient-centered outcomes [e.g., 21, 54, 131].
- **Comorbidity-Specific Interventions:** Studies should investigate the differential efficacy of PAD treatments across Fontaine stages in specific high-risk populations, such as diabetic patients with foot ulcers [9, 43] or those with coexisting inflammatory conditions [114].

5.4 Limitations:

- **Heterogeneity of Study Designs** — The included studies encompass a wide array of designs, from RCTs to retrospective cohorts, limiting direct comparability and meta-analysis.
- **Variability in Outcome Reporting** — Diverse metrics for assessing PAD severity and treatment efficacy, beyond simple Fontaine stage changes, make it challenging to synthesize a single, comparable numerical result.
- **Lack of Standardized Follow-up** — Follow-up durations vary significantly across studies, hindering a consistent understanding of long-term effects of interventions or disease progression.
- **Qualitative Assessment of Bias** — The qualitative inference of bias, due to limited detail in some structured summaries, prevents a comprehensive quantitative assessment of study quality.
- **Focus on Symptomatic Stages** — A significant portion of the literature focuses on symptomatic Fontaine stages (II-IV), potentially underrepresenting research on asymptomatic PAD (stage I).

5.5 Future directions:

- **Standardize Reporting Outcomes** — Implement common data elements for Fontaine classification changes in PAD trials.
- **Validate AI Predictive Models** — Develop and test AI models that integrate Fontaine stages with multi-modal data.
- **Longitudinal Biomarker Studies** — Track novel biomarkers across Fontaine stages to predict progression.
- **Patient-Reported Outcome Measures** — Incorporate patient-reported outcomes alongside Fontaine classification in clinical trials.
- **Targeted Comorbidity Trials** — Evaluate PAD interventions in specific high-risk populations across Fontaine stages.

6) Conclusion

The Fontaine classification is consistently used across studies as a primary metric for assessing PAD severity and evaluating treatment efficacy, though no single comparable numerical outcome (e.g., a pooled success rate or odds ratio) is reported across multiple studies to allow for a central value calculation. This classification remains indispensable for guiding clinical decisions, stratifying patient risk, and assessing the impact of various interventions on disease progression and patient quality of life. The heterogeneity of study designs and outcome reporting across the literature most significantly affects the certainty of synthesized findings. To advance PAD management, future research should prioritize standardized outcome reporting and the development of AI-driven predictive models that integrate Fontaine stages with comprehensive patient data.

References

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Figure 1. Publication-year distribution of included originals

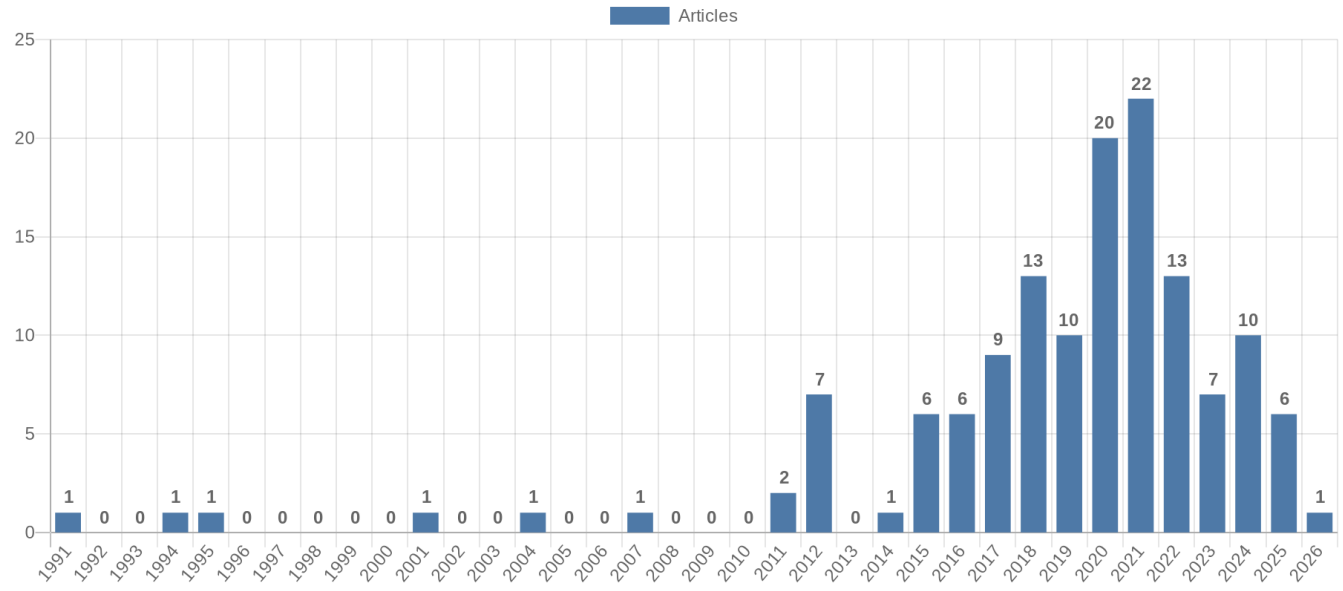

Figure 2. Study-design distribution of included originals

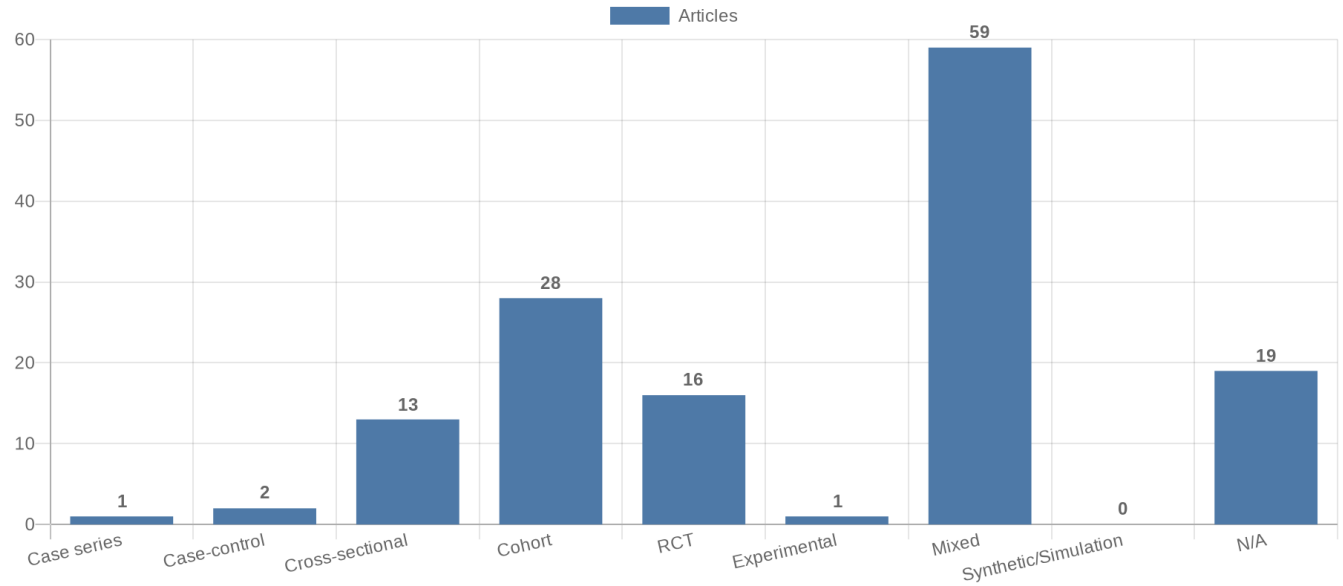

Figure 3. Study-type (directionality) distribution of included originals

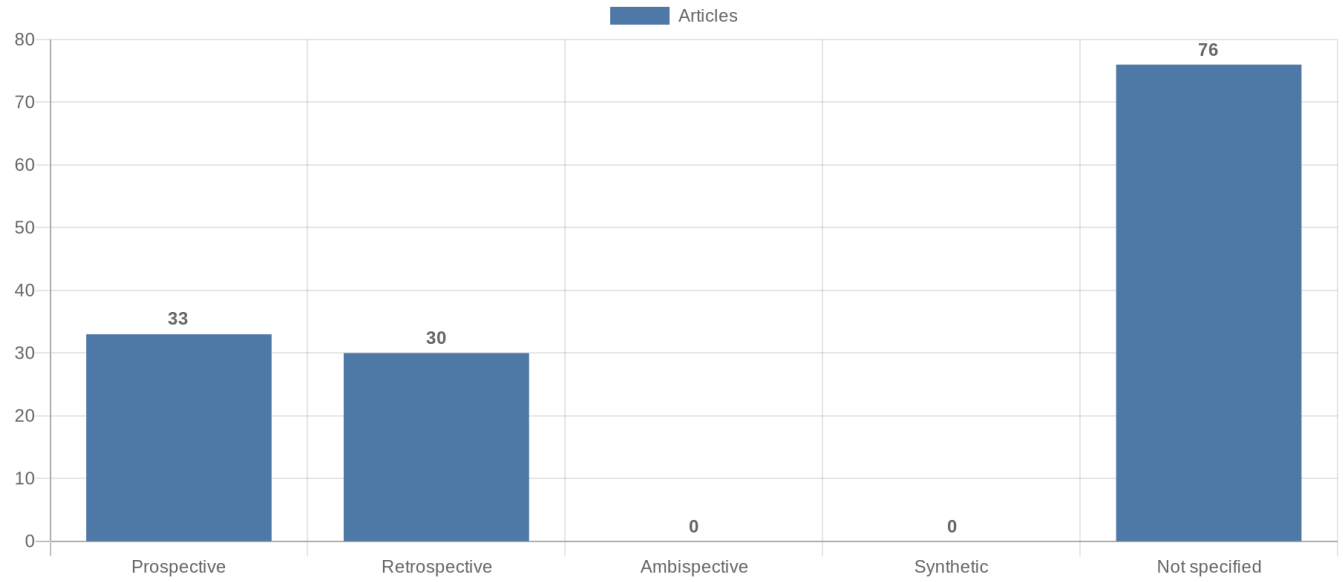

Figure 4. Main extracted research topics

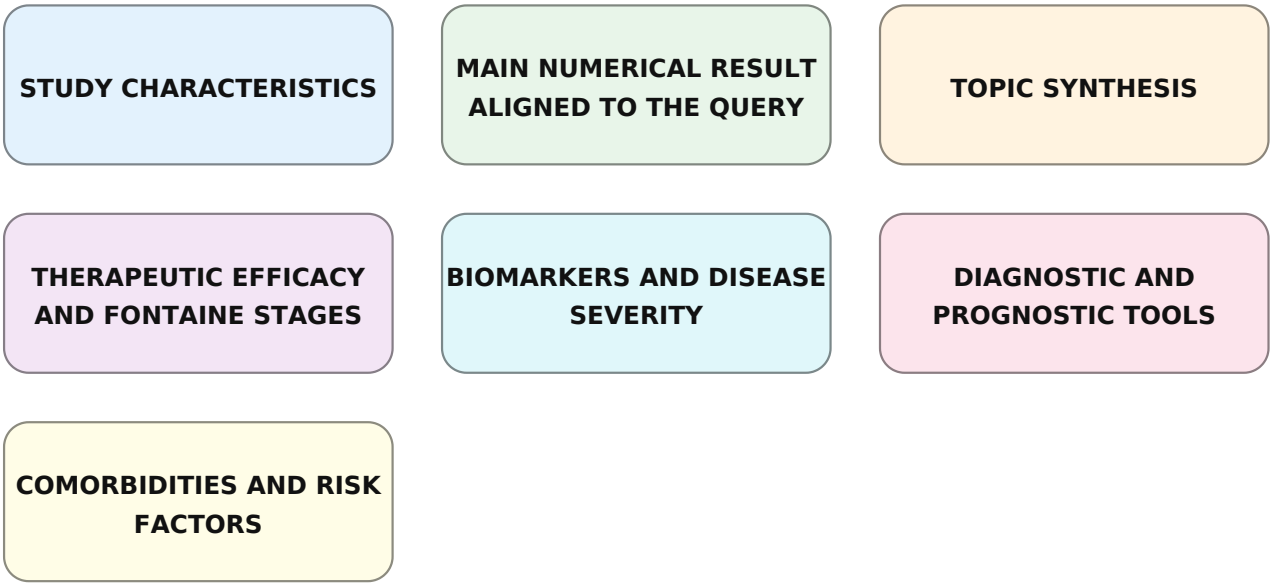

Figure 5. Limitations of current studies (topics)

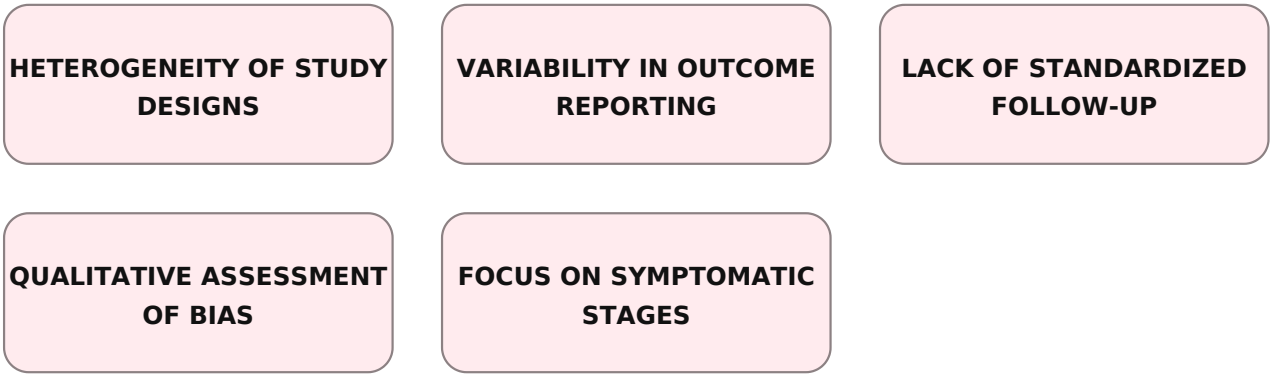

Figure 6. Future research directions (topics)