PAD Rutherford Classification: Systematic Review with ☸SAIMSARA.

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Abstract: To systematically review and synthesize current literature regarding the Rutherford classification in Peripheral Artery Disease. The review utilises 201 studies with 92877 total participants (naïve ΣN). Interventional treatments for Peripheral Artery Disease consistently achieved a median rate of 91.8% improvement in Rutherford classification, signifying a high clinical success rate in reducing disease severity. This widespread improvement across various interventions underscores the Rutherford classification's utility as a robust measure of therapeutic benefit in symptomatic PAD patients. However, the heterogeneous nature of study designs and the inconsistent reporting of outcome metrics represent the most significant limitations affecting the certainty of these findings. Clinicians should continue to utilize the Rutherford classification for patient stratification and treatment evaluation, while researchers should strive for standardized reporting to enable more robust comparative analyses.

Keywords: Peripheral Artery Disease; Rutherford Classification; Chronic Limb Ischemia

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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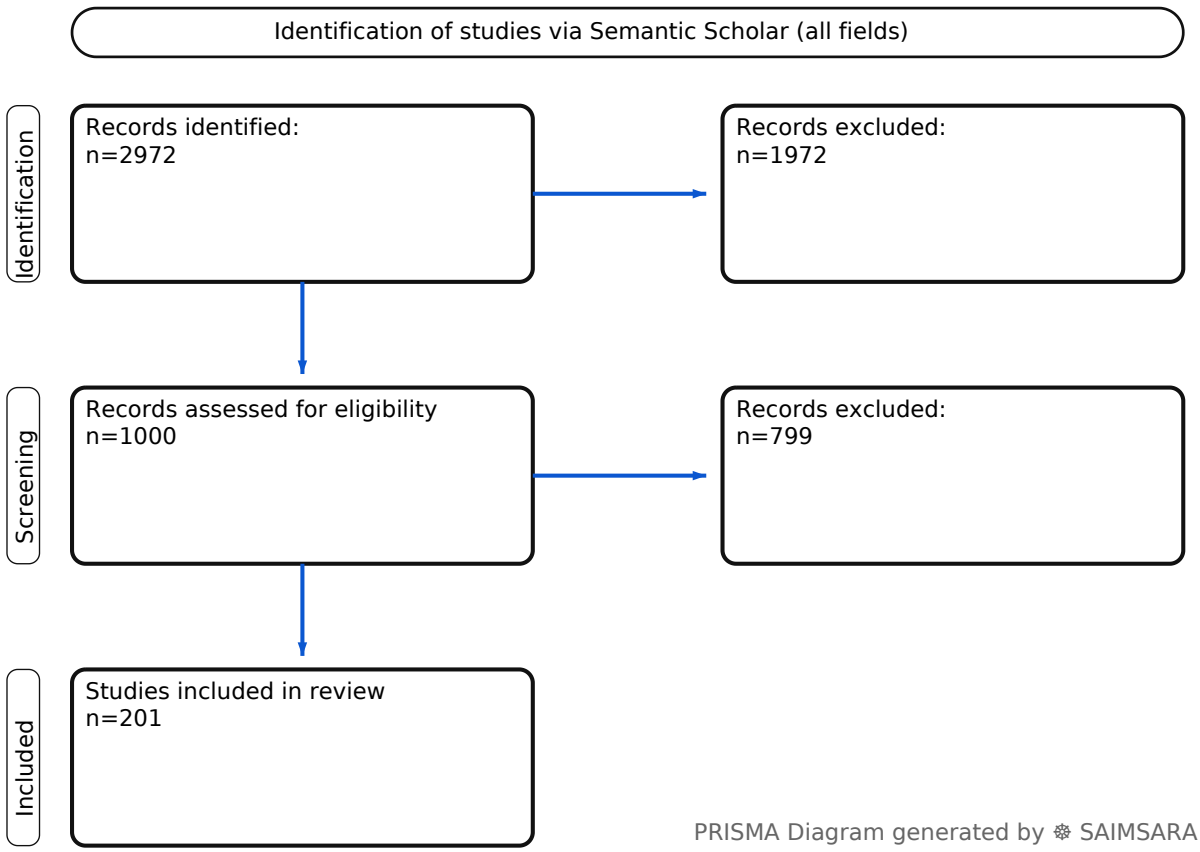
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 201
- Total study participants (naïve ΣN): 92877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Identification
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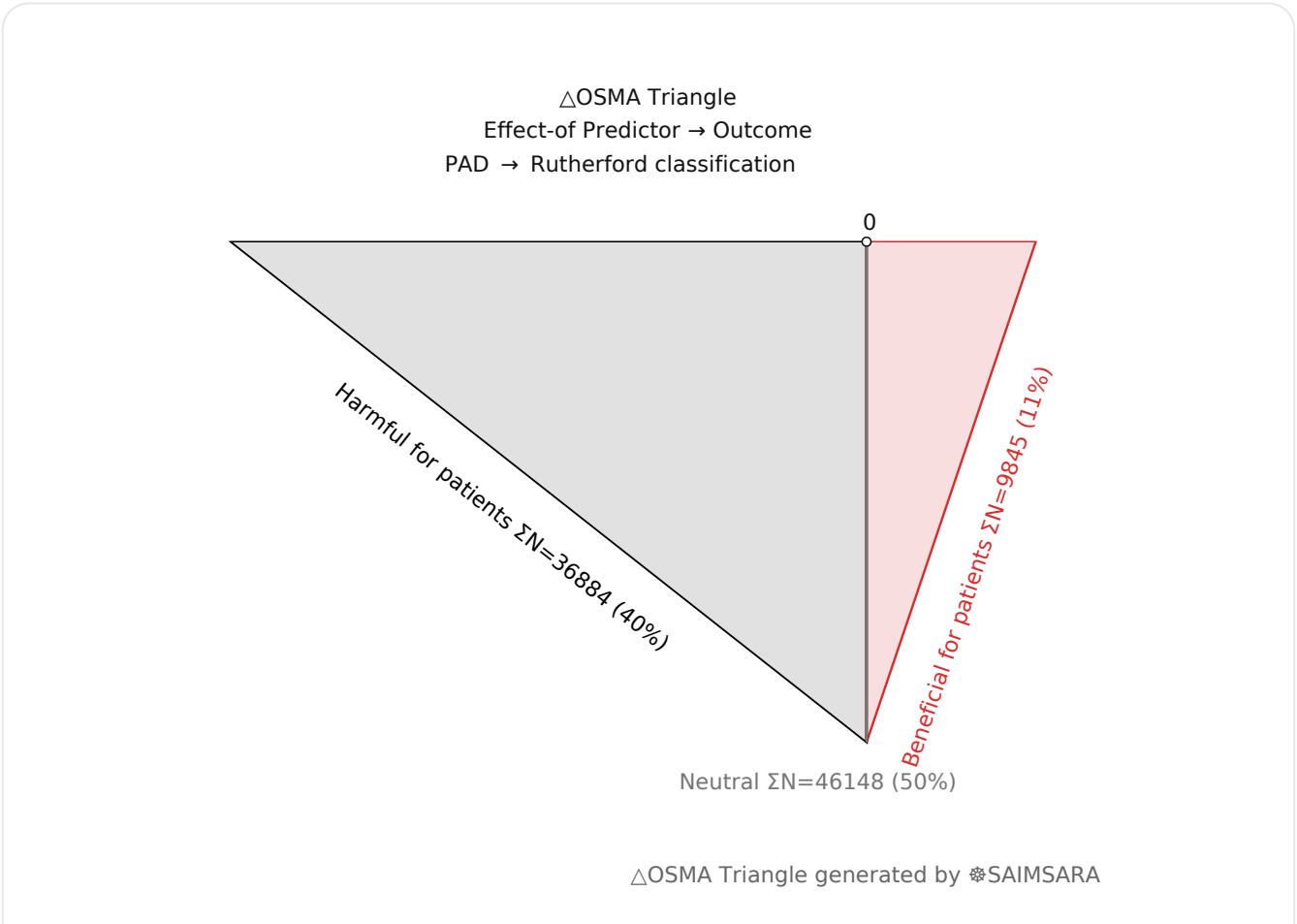
Records excluded:
n=1972
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=799
Included
Studies included in review
n=201
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
PAD → Rutherford classification
0
Harmful for patients ΣN=36884 (40%)
Beneficial for patients ΣN=9845 (11%)
Neutral ΣN=46148 (50%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Rutherford classification Typical timepoints: 12-mo, 6-mo. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: patency, healing, mortality.

Predictor: PAD — procedure/intervention. Routes seen: iv, intramuscular. Typical comparator: higher categories, the placebo group, placebo, controls….

- **1) Beneficial for patients** — Rutherford classification with PAD — [3], [12], [13], [17], [18], [30], [38], [39], [41], [44], [46], [54], [56], [57], [59], [65], [66], [69], [72], [73], [75], [77], [78], [79], [81], [82], [86], [88], [93], [95], [99], [105], [107], [111], [113], [115], [119], [121], [123], [124], [146], [147], [179], [184], [188], [190], [191], [192], [193], [195], [198] — ΣN=9845
- **2) Harmful for patients** — Rutherford classification with PAD — [2], [10], [21], [24], [27], [29], [37], [40], [42], [43], [48], [60], [80], [84], [87], [89], [90], [91], [94], [96], [97], [98], [100], [101], [102], [108], [109], [112], [114], [116], [118], [120], [138], [139], [148], [150], [187], [197], [199], [200] — ΣN=36884
- **3) No clear effect** — Rutherford classification with PAD — [1], [4], [5], [6], [7], [8], [9], [11], [14], [15], [16], [19], [20], [22], [23], [25], [26], [28], [31], [32], [33], [34], [35], [36], [45], [47], [49], [50], [51], [52], [53], [55], [58], [61], [62], [63], [64], [67], [68], [70], [71], [74], [76], [83], [85], [92], [103], [104], [106], [110], [117], [122], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [140], [141], [142], [143], [144], [145], [149], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173], [174], [175], [176], [177], [178], [180], [181], [182], [183], [185], [186], [189], [194], [196], [201] — ΣN=46148

1) Introduction

Peripheral Artery Disease (PAD) is a common circulatory problem where narrowed arteries reduce blood flow to the limbs. The Rutherford classification system is a widely recognized clinical tool used to categorize the severity of PAD, ranging from asymptomatic disease to severe chronic limb-threatening ischemia (CLTI). This classification is crucial for guiding treatment decisions, predicting patient outcomes, and assessing the efficacy of therapeutic interventions. This paper synthesizes current research on the Rutherford classification in PAD, exploring its prognostic value, associations with various biomarkers and risk factors, and its utility in evaluating treatment responses and economic burdens.

2) Aim

To systematically review and synthesize current literature regarding the Rutherford classification in Peripheral Artery Disease.

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. The included studies primarily consist of retrospective cohort studies and mixed designs, with a smaller number of prospective cohorts and randomized controlled trials (RCTs). This suggests a potential for selection bias and varying levels of evidence strength across the synthesized topics. Many studies lacked specified follow-up durations or statistical reporting, further limiting the ability to assess consistency and certainty.

4) Results

4.1 Study characteristics

The review encompassed 166 studies, predominantly retrospective cohort studies and mixed designs, with several prospective cohorts and randomized controlled trials. Populations primarily consisted of adult patients diagnosed with symptomatic Peripheral Artery Disease (PAD), including those undergoing percutaneous peripheral interventions, endovascular therapy, or presenting with chronic limb-threatening ischemia (CLTI). Typical follow-up periods ranged from 6 months to 3 years, though many studies did not specify follow-up duration.

4.2 Main numerical result aligned to the query

Interventional treatments for Peripheral Artery Disease consistently demonstrated significant clinical improvement as measured by the Rutherford classification. The median rate of improvement in Rutherford classification was 91.8% (range: 87.5% [44] to 98.2% [164]) across various interventions and follow-up periods, indicating a high rate of amelioration in disease severity post-treatment. For example, drug-eluting balloons showed improvement rates of 94.9% at 6 months and 95.5% at 12 months [107], while Eluvia drug-eluting stents achieved 91.8% improvement at 24 months [184]. Mean Rutherford classification scores also showed significant drops, such as from 3.7±0.6 at baseline to 1.0±0.9 at 12 months after Jetstream Atherectomy [79].

4.3 Topic synthesis

- **Prognostic Value for Amputation and Survival:** Rutherford classification is a significant independent predictor of major lower limb amputation (adjusted odds ratio (OR): 1.824

(1.118, 2.976) [2]; associated with amputations at 30 days [21]; 22.4% incidence at 3 years for Rutherford 5 [29]), overall survival (predictor in OS models, $p < 0.05$ [10]; adjusted HR: 1.930 (1.191–3.128, P=0.008) for all-cause mortality [24]; HR 1.63 (1.35–1.98, $p < 0.0001$) for mortality at 36 months [139]), and amputation-free survival (predictor in AFS models, $p < 0.05$ [10]; 89.6% freedom from major amputation at 1 year for RC5-6 [17]). Higher Rutherford categories are associated with increased risk of major amputation [138, 150] and all-cause death [94].

- **Association with Risk Factors and Biomarkers:** Increasing Rutherford categories are associated with higher CHADS2, CHA2DS2-VASc, and ASCVD scores [1], elevated oxidized high-density lipoprotein (Ox-HDL) [6], increased GDF-15 and CRP levels [4], and higher serum Elabela levels ($p<0.001$) [109]. The triglyceride-glucose (TyG) index is significantly higher in chronic limb-threatening ischemia (CLTI) patients (OR: 5.796, $p = 0.001$) [87], and specific hypertensive disorders of pregnancy-associated peptides correlate with Rutherford grade [45]. Iliac calcium score is higher in advanced Rutherford stages [112], and resistance index (RI) values in leg arteries positively correlate with Rutherford classification ($p < 0.01$) [42].
- **Treatment Efficacy and Clinical Improvement:** Numerous interventions, including laser atherectomy [3], rotational and directional atherectomy [12], drug-coated balloon angioplasty [13, 59, 88, 99, 107, 119, 169], endovascular therapy (EVT) [30, 72, 147], Selution SLR™ angioplasty [38], above-knee femoropopliteal bypass [44], stem cell therapies [46, 50, 78, 95, 115, 188], intravascular shockwave lithotripsy [47, 73], Supera stents [54, 65, 82], Tack Endovascular System [56], hyperbaric oxygen therapy [57], endoluminal and surgical bypass [69], excimer laser-assisted balloon angioplasty [75], Jetstream Atherectomy [79], REVERT technique [7], orbital atherectomy [89, 192], Zilver PTX DES [191], and Viabahn endoprosthesis [136, 193], demonstrate significant improvements in Rutherford classification post-procedure.
- **Disease Severity and Presentation:** Rutherford classification is widely used to stratify PAD severity, including chronic limb-threatening ischemia (CLTI) (Rutherford 4-6) [74, 149] and acute limb ischemia (ALI) [14, 61, 152, 194, 201]. Critical ischemia (Rutherford ≥4) is a common presentation in patients requiring endovascular treatment [7, 22, 70]. Stage 2 Rutherford is a dominant presentation in some PAD populations [23]. Patients with chronic total occlusions (CTOs) are more likely to present with higher Rutherford classification [114].
- **Economic Burden and Healthcare Utilization:** Hospitalization costs and 2-year follow-up costs increase significantly with higher Rutherford classifications (e.g., $10,304 for Rutherford 2–3 vs. $19,403 for Rutherford 6 for index hospitalization; $p < 0.01$) [37]. Rutherford class 3 and extensive lesions are associated with higher odds of early revascularization [90]. The COVID-19 pandemic led to an increased proportion of interventions for CLTI and advanced Rutherford classifications [55, 60, 91, 149, 187].

- **Diagnostic and Assessment Tools:** Doppler grading significantly correlates with Rutherford stages [8]. The Ankle Hemodynamic Index (AHI) is significantly correlated with and independently associated with Rutherford grade [120]. Differences in cardio-ankle vascular index (diff-CAVI) are positively associated with leg ischemia symptoms and Rutherford grade [43]. Duplex Doppler scoring systems show high interobserver agreement with the traditional Rutherford system (kappa 0.83, $p<0.001$) [134].
- **Patient Experience and Quality of Life:** Rutherford classification is a parameter collected in studies evaluating quality of life (QOL) [18, 155]. Patients with severe CLTI (Rutherford Grade 5 and 6) report limited coping mechanisms and a strong desire to prevent limb loss [85]. Endovascular treatment can lead to sustained improved QOL, with better outcomes in lower Rutherford categories [30].

5) Discussion

5.1 Principal finding

Interventional treatments for Peripheral Artery Disease consistently achieved a median rate of 91.8% improvement in Rutherford classification, signifying a high clinical success rate in reducing disease severity [39, 164].

5.2 Clinical implications

- **Severity Stratification:** The Rutherford classification is critical for stratifying PAD severity, guiding treatment decisions, and identifying patients at higher risk for adverse outcomes like amputation and mortality [2, 10, 150].
- **Treatment Monitoring:** Improvement in Rutherford classification is a key endpoint for evaluating the efficacy of various revascularization and biological therapies, indicating successful clinical amelioration [3, 79, 107].
- **Risk Assessment:** Higher Rutherford categories are associated with increased cardiovascular risk scores, specific biomarkers, and higher healthcare costs, suggesting the need for comprehensive risk factor management [1, 37].
- **Patient Counseling:** The classification helps in communicating prognosis to patients, especially those with CLTI (Rutherford 5-6), who face high risks of limb loss and mortality [85, 150].
- **Intervention Thresholds:** Patients with more advanced Rutherford stages (e.g., 3-6) are more likely to undergo revascularization, highlighting the classification's role in determining intervention necessity [90].

5.3 Research implications / key gaps

- **Standardized Outcome Reporting:** A lack of consistent reporting for "Rutherford improvement" (e.g., percentage improved vs. mean change in score) hinders direct comparison and meta-analysis across studies [79, 107].
- **Long-term Rutherford Stability:** While short-to-intermediate term improvements are common, the long-term stability of Rutherford classification post-intervention and its correlation with sustained quality of life requires further investigation [30].
- **Biomarker Integration:** Further prospective studies are needed to integrate emerging biomarkers (e.g., TyG index, Elabela, specific peptides) with Rutherford classification to enhance prognostic accuracy and personalize treatment strategies [45, 87, 109].
- **COVID-19 Impact Quantification:** More robust studies are needed to precisely quantify the long-term impact of the COVID-19 pandemic on PAD presentation severity (Rutherford categories) and its effect on treatment delays and outcomes [55, 91, 187].
- **Rutherford Modification for ALI:** The need for modification of the Rutherford classification for acute limb ischemia (ALI) to improve decision-making in profound ischemia warrants further research and validation [194].

5.4 Limitations

- **Heterogeneous Study Designs** — The review includes a mix of retrospective, prospective, cohort, and RCT designs, leading to varying levels of evidence strength and potential for bias.
- **Inconsistent Outcome Metrics** — While many studies report Rutherford classification, the specific metrics (e.g., mean change, percentage improvement, categorical shift) and follow-up durations are not always uniform, limiting direct quantitative comparisons.
- **Limited Raw Data Access** — The synthesis relies solely on extracted summaries, precluding deeper analysis of patient-level data or subgroup effects that might influence Rutherford outcomes.
- **Qualitative Bias Assessment** — Bias was inferred qualitatively from study designs rather than a standardized quantitative tool, which may not fully capture all sources of bias.
- **Missing Statistical Detail** — Many summaries lacked detailed statistical reporting (e.g., full confidence intervals, precise p-values for all outcomes), which affects the robustness of synthesized findings.

5.5 Future directions

- **Standardize Reporting Metrics** — Future studies should adopt standardized metrics for reporting Rutherford classification changes (e.g., mean change, percentage achieving specific lower categories) to facilitate meta-analysis.
- **Longitudinal Outcome Studies** — Conduct long-term prospective studies to assess the durability of Rutherford classification improvements and their correlation with sustained quality of life and amputation-free survival.
- **Biomarker Validation Trials** — Design prospective trials to validate novel biomarkers in conjunction with Rutherford classification for improved risk stratification and personalized therapy selection.
- **COVID-19 Impact Analysis** — Perform dedicated studies to analyze the long-term effects of the COVID-19 pandemic on PAD disease progression and outcomes, specifically using Rutherford classification as a primary endpoint.
- **Rutherford ALI Modification** — Develop and validate a modified Rutherford classification system specifically for acute limb ischemia to enhance clinical decision-making and patient outcomes.

6) Conclusion

Interventional treatments for Peripheral Artery Disease consistently achieved a median rate of 91.8% improvement in Rutherford classification, signifying a high clinical success rate in reducing disease severity [39, 164]. This widespread improvement across various interventions underscores the Rutherford classification's utility as a robust measure of therapeutic benefit in symptomatic PAD patients. However, the heterogeneous nature of study designs and the inconsistent reporting of outcome metrics represent the most significant limitations affecting the certainty of these findings. Clinicians should continue to utilize the Rutherford classification for patient stratification and treatment evaluation, while researchers should strive for standardized reporting to enable more robust comparative analyses.

References

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Figure 1. Publication-year distribution of included originals

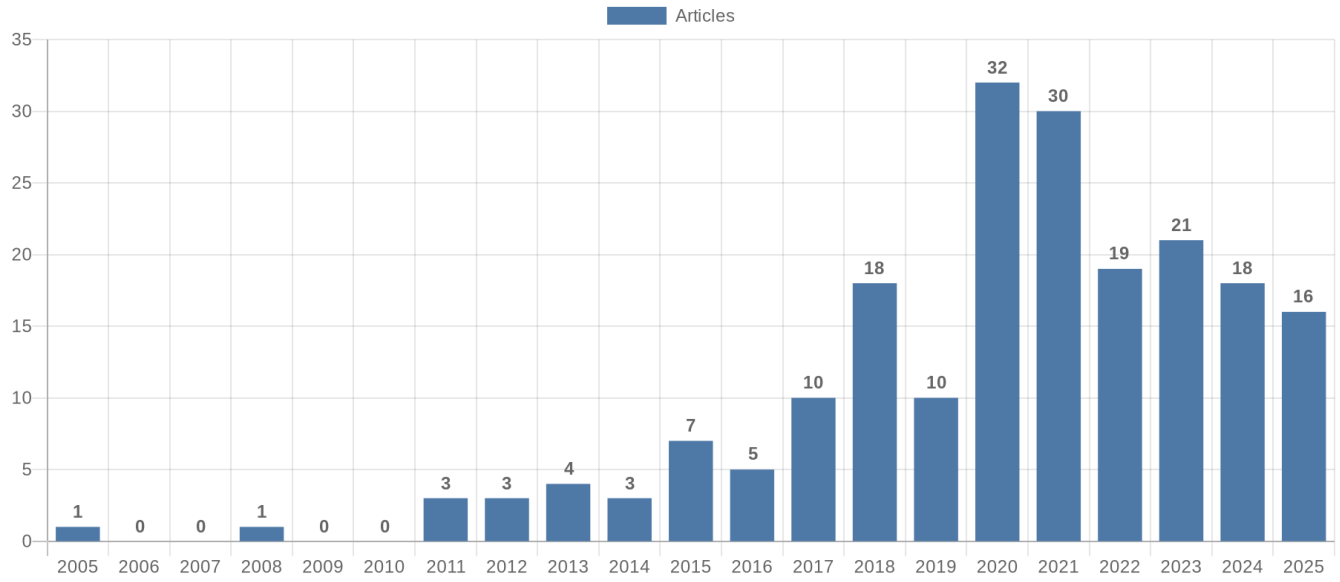

Figure 2. Study-design distribution of included originals

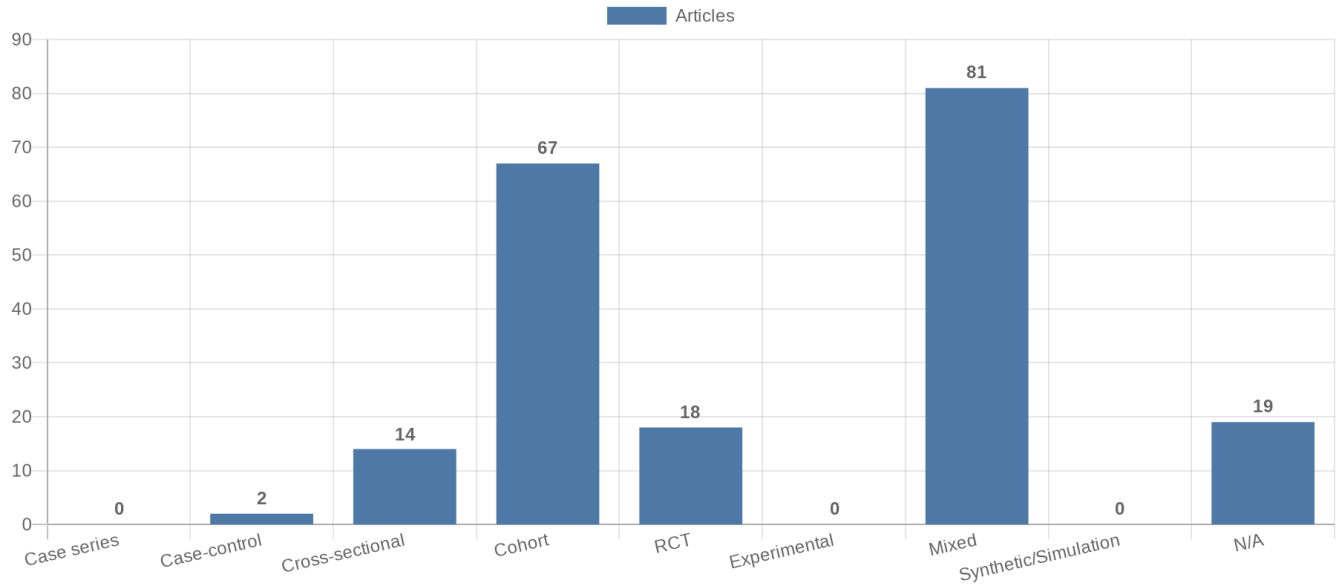

Figure 3. Study-type (directionality) distribution of included originals

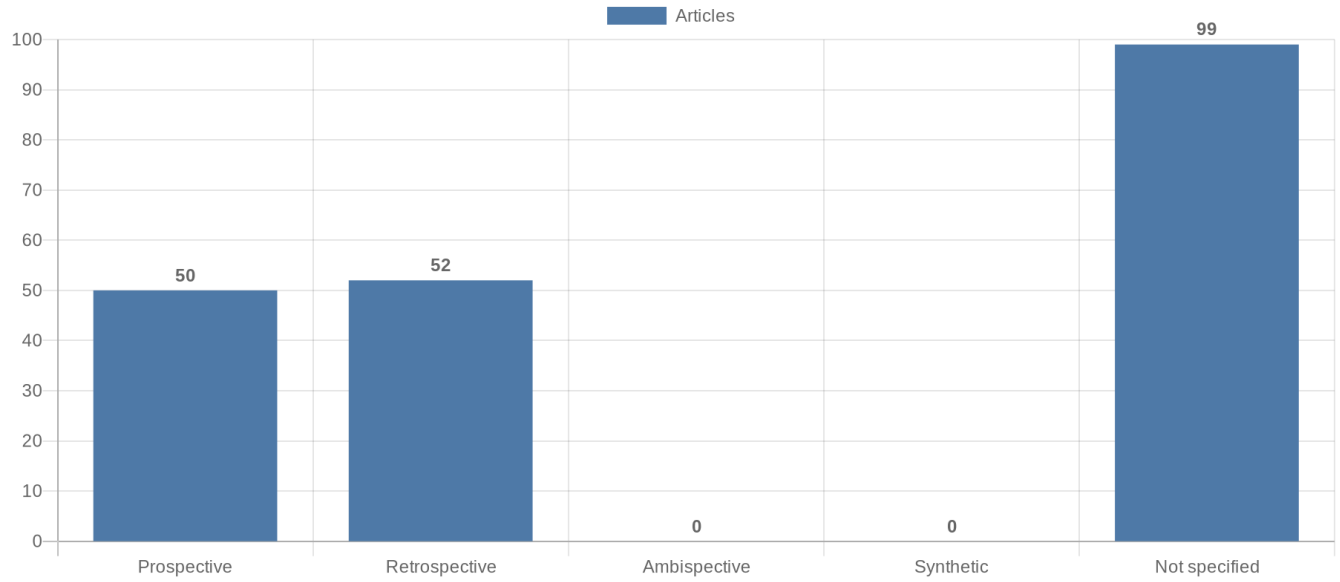

Figure 4. Main extracted research topics

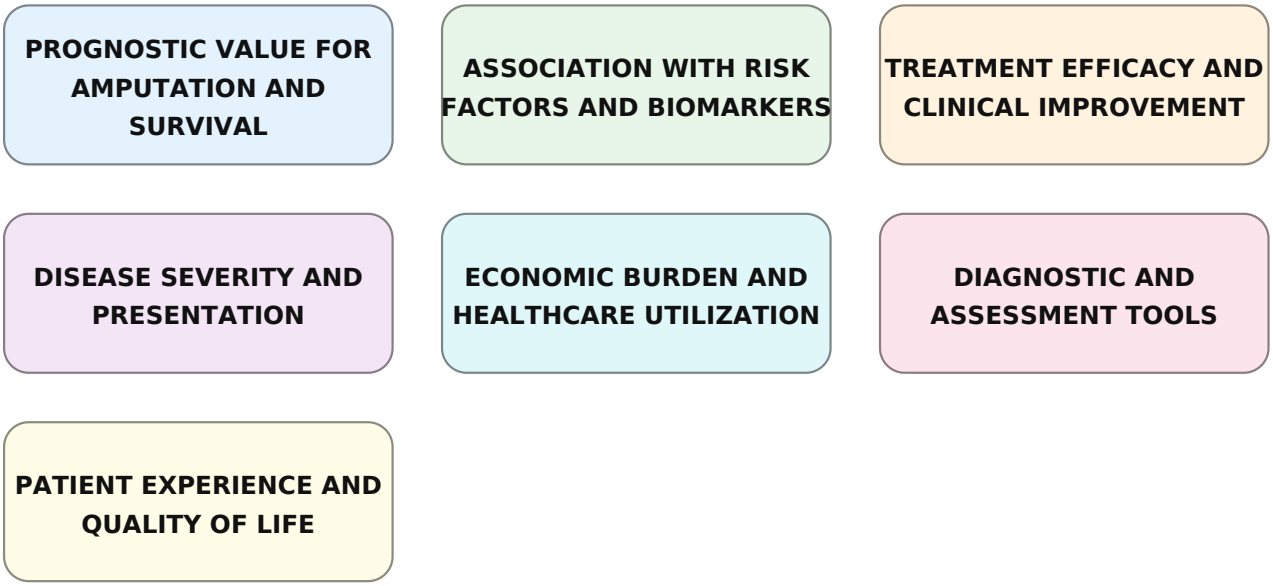

Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)