Peripheral Artery Disease GLASS: Systematic Review with ☸SAIMSARA.

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Abstract: To synthesize current research on peripheral artery disease, focusing on the utility and implications of the Global Limb Anatomic Staging System (GLASS), and to identify key themes, clinical applications, and future research directions. The review utilises 142 studies with 1759452 total participants (naïve ΣN). The Global Limb Anatomic Staging System (GLASS) consistently demonstrated prognostic value for limb outcomes and survival in peripheral artery disease (PAD) patients. Specifically, higher GLASS stages were associated with worse outcomes, including lower technical success rates, higher amputation and mortality rates at 12 months (p=0.012, p=0.001, p=0.021, p=0.015). This prognostic utility applies broadly to PAD patients, particularly those with chronic limb-threatening ischemia undergoing revascularization. The reliance on heterogeneous study designs and varied outcome reporting represents the single limitation that most affects certainty. A concrete next step is to conduct large-scale prospective randomized controlled trials to validate GLASS-guided treatment algorithms.

Keywords: Peripheral Artery Disease; Global Limb Anatomic Staging System; Chronic Limb-Threatening Ischemia; Endovascular Re

Review Stats

- Generated: 2026-01-30 17:48:35 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)
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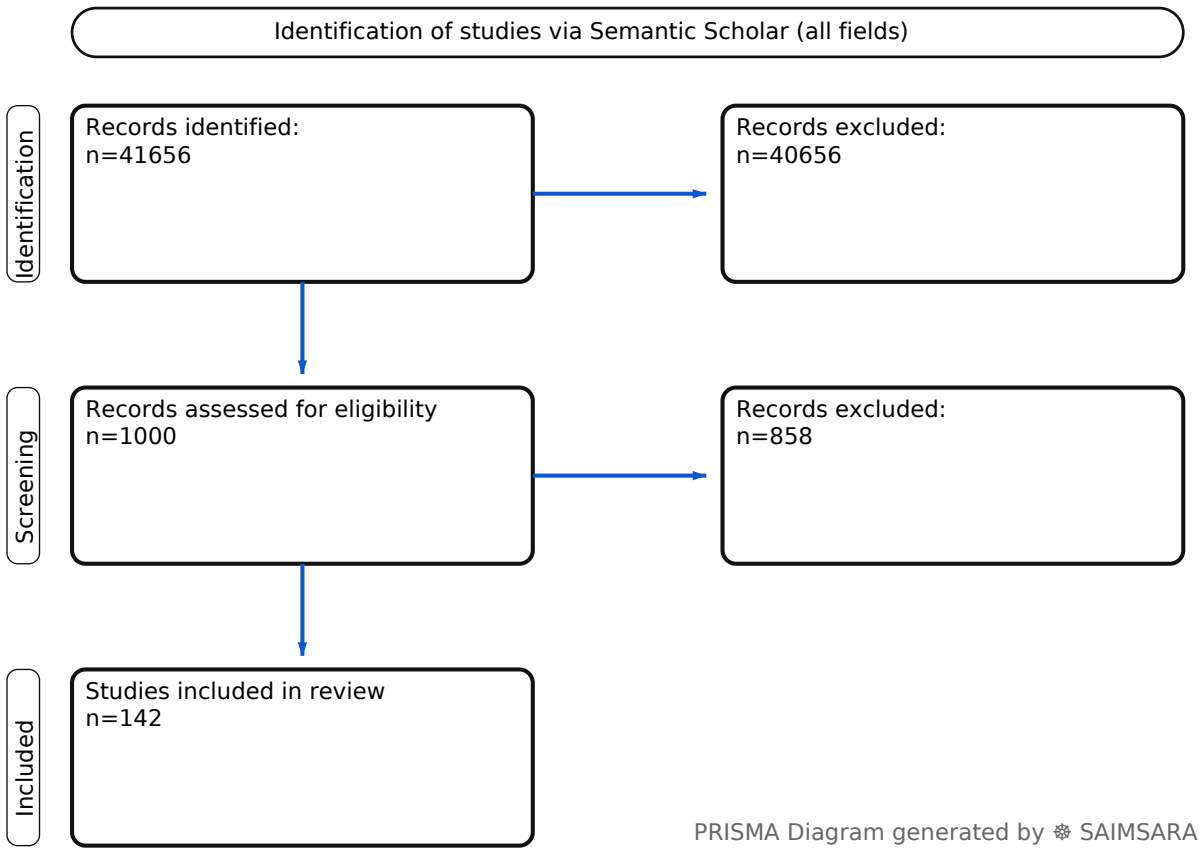
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 142
- Total study participants (naïve ΣN): 1759452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Identification
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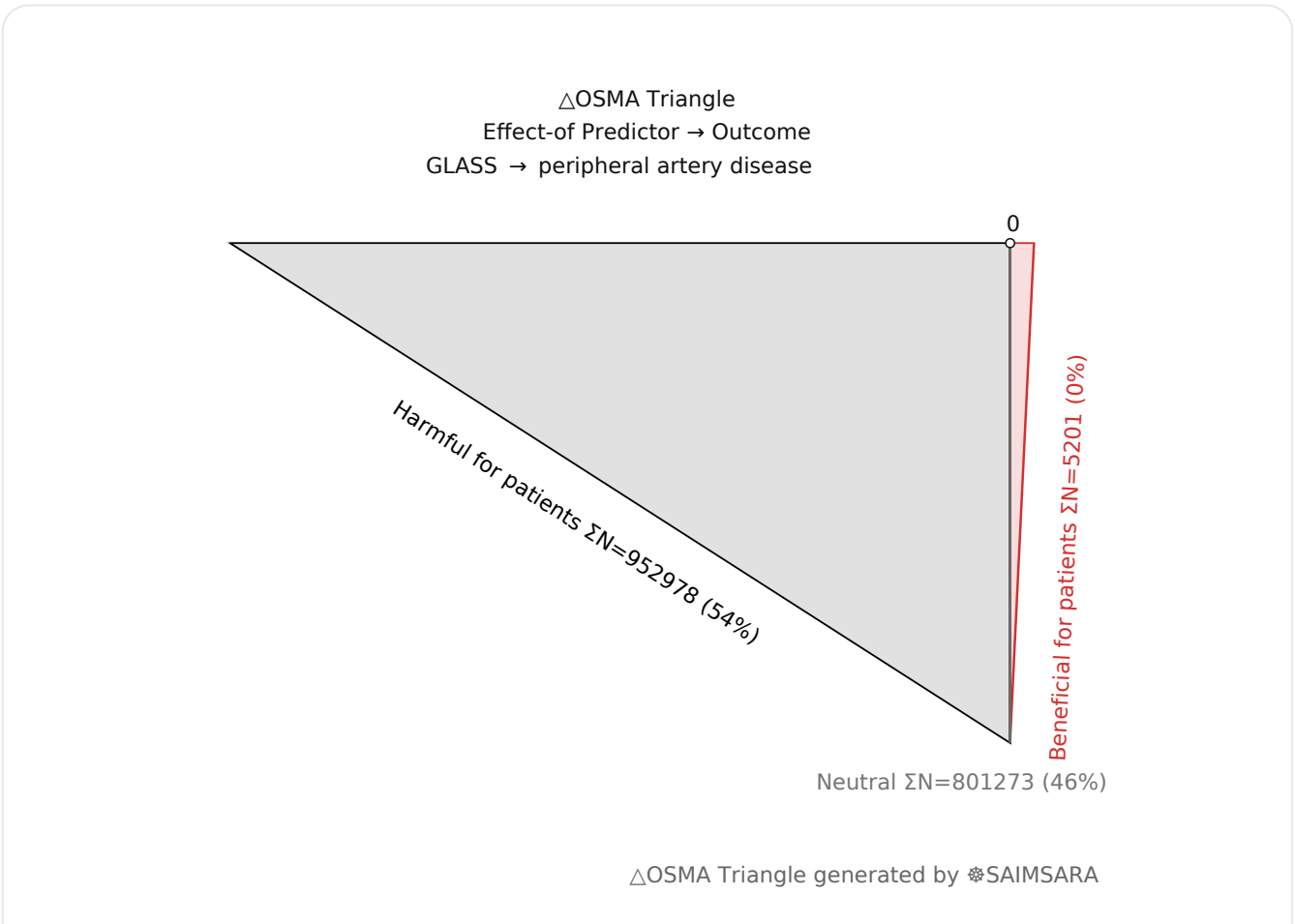
Records excluded:
n=40656
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=858
Included
Studies included in review
n=142
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
GLASS → peripheral artery disease
0
Harmful for patients ΣN=952978 (54%)
Beneficial for patients ΣN=5201 (0%)
Neutral ΣN=801273 (46%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: peripheral artery disease Typical timepoints: peri/post-op, 5-y. Reported metrics: %, CI, p.

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

Predictor: GLASS — procedure/intervention. Routes seen: im, iv, oral. Typical comparator: dual antiplatelet therapy, antiplatelet therapy alone, walking exercise alone, a control group....

- **1) Beneficial for patients** — peripheral artery disease with GLASS — [10], [13], [14], [17], [22], [24], [30], [49], [60], [71], [88], [128], [137] — ΣN=5201
- **2) Harmful for patients** — peripheral artery disease with GLASS — [7], [9], [16], [19], [20], [21], [23], [29], [31], [32], [33], [34], [39], [41], [42], [44], [45], [47], [50], [51], [52], [55], [56], [63], [65], [66], [68], [74], [75], [76], [81], [82], [87], [90], [99], [103], [108], [113], [117], [121], [124], [125], [126], [127], [130], [131], [133], [134], [135], [138] — ΣN=952978
- **3) No clear effect** — peripheral artery disease with GLASS — [1], [2], [3], [4], [5], [6], [8], [11], [12], [15], [18], [25], [26], [27], [28], [35], [36], [37], [38], [40], [43], [46], [48], [53], [54], [57], [58], [59], [61], [62], [64], [67], [69], [70], [72], [73], [77], [78], [79], [80], [83], [84], [85], [86], [89], [91], [92], [93], [94], [95], [96], [97], [98], [100], [101], [102], [104], [105], [106], [107], [109], [110], [111], [112], [114], [115], [116], [118], [119], [120], [122], [123], [129], [132], [136], [139], [140], [141], [142] — ΣN=801273

1) Introduction

Peripheral artery disease (PAD) represents a significant global health challenge, characterized by atherosclerotic occlusion of vessels outside the heart, primarily affecting the lower extremities [102, 106]. Its severe manifestation, chronic limb-threatening ischemia (CLTI), poses a high risk of amputation and mortality [7, 93, 97]. Accurate staging and prognosis are crucial for guiding treatment strategies and improving patient outcomes. The Global Limb Anatomic Staging System (GLASS) has emerged as a key tool for classifying anatomical patterns of PAD and assessing disease severity [6, 8]. This paper systematically reviews the current literature on PAD, with a specific focus on the application, prognostic value, and technological advancements related to the GLASS classification system.

2) Aim

To synthesize current research on peripheral artery disease, focusing on the utility and implications of the Global Limb Anatomic Staging System (GLASS), and to identify key themes, clinical applications, and future research directions.

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 mixed designs are prevalent, potentially introducing selection and recall bias. Non-specified study types and lack of follow-up in some studies further limit certainty and generalizability. Prospective randomized controlled trials are less common, particularly for GLASS-specific outcomes, leading to a higher risk of confounding.

4) Results

4.1 Study characteristics

The included studies predominantly comprised retrospective cohort (e.g., [1, 2, 5, 7, 9, 14, 15, 17, 32, 33, 35, 108]) and mixed-design studies (e.g., [2, 5, 7, 8, 35, 38, 39, 41, 42, 46, 48, 49, 53, 54, 56, 57, 58, 59, 60, 61, 64, 65, 69, 72, 73, 74, 75, 83, 84, 85, 86, 90, 91, 93, 94, 95, 96, 97, 104, 105, 106, 107, 109, 110, 111, 112, 113, 115, 116, 118, 119, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 141, 142]), with a smaller number of prospective cohort studies (e.g., [4, 10, 13, 18, 23, 24, 25, 26, 30, 32, 44, 47, 58, 66, 68, 82, 87, 89, 114, 117, 120, 121, 129, 137]) and randomized controlled trials (RCTs) (e.g., [10, 13, 16, 18, 24, 25, 26, 30, 82, 89, 95, 120, 122]). Populations ranged from general PAD patients to specific subgroups such as those with chronic limb-threatening ischemia (CLTI) [4, 7, 8, 32, 58], femoro-popliteal chronic total occlusions (CTOs) [5], or undergoing endovascular treatment [2, 4, 14, 15, 35]. Follow-up periods varied widely, from 3 months [1] to 12 months [4, 7, 32, 43] and up to 5 years [108, 114, 117, 125].

4.2 Main numerical result aligned to the query

The Global Limb Anatomic Staging System (GLASS) consistently demonstrated prognostic value for limb outcomes and survival in peripheral artery disease (PAD) patients. Specifically, higher GLASS stages were associated with worse outcomes, including lower technical success rates, higher amputation and mortality rates at 12 months ($p=0.012$, $p=0.001$, $p=0.021$, $p=0.015$) [7]. For instance, GLASS III anatomy was linked to worse limb-based patency, limb salvage, amputation-free survival, and overall survival compared to GLASS I at 12 months ($p=0.005$, $p=0.037$, $p=0.021$, $p<0.001$ respectively) [32]. Similarly, GLASS IV lesions were associated with significantly lower patency rates and higher major adverse limb events (MALE) incidence at 24 months ($p=0.002$) [33].

Computer vision and automated machine learning models achieved high accuracy in classifying GLASS grades and predicting limb outcomes, with validation accuracy of 95% and test accuracy of 93% for limb outcome prediction [1], and 100% accuracy in testing for anatomical pattern classification [3].

4.3 Topic synthesis

- **Prognostic Value of GLASS:** Higher GLASS stages (e.g., III, IV) are consistently associated with worse clinical outcomes, including lower technical success rates, increased amputation, higher mortality, reduced patency, and higher major adverse limb events (MALE) [7, 32, 33]. GLASS is a useful prognostic tool for short-term outcomes in CLTI patients undergoing endovascular treatment [4].
- **Automated GLASS Classification and Prediction:** Computer vision and automated machine learning (AutoML) models demonstrate high accuracy in classifying GLASS grades and predicting limb outcomes in PAD patients, outperforming traditional modifiers like IM GLASS [1, 3]. One model achieved 95% validation accuracy and 93% test accuracy for limb outcome prediction [1].
- **Risk Factors and Comorbidities in PAD:** Diabetes [2, 19, 70, 105], smoking [19, 21, 121], microvascular disease [9], dyslipidemia [5, 103], inflammation (e.g., elevated hs-CRP, galectin-3, IL-17A, fibrinogen, oxidized LDL) [23, 38, 56, 58, 72, 83, 84, 115, 117], hyperuricemia [68], and specific genetic variants [21, 80, 88, 131] are identified as significant risk factors or associated conditions for PAD and its progression. PAD itself is a comorbidity for other cardiovascular events [9, 13, 16, 17, 26, 41, 45, 47, 51, 53, 55, 61, 63, 65, 66, 67, 68, 69, 71, 74, 75, 76, 77, 78, 79, 81, 82, 83, 84, 85, 92, 98, 101, 102, 106, 114, 117, 121, 124, 125, 126, 127, 128, 129, 130, 132, 133, 134, 135, 136, 138].
- **Therapeutic Interventions and Outcomes:** Endovascular treatment strategies, including balloon angioplasty and stenting, show territory- and lesion-specific performance [15, 35]. Covered stents in the iliac, interwoven nitinol stents in the SFA, and drug-coated balloons in the popliteal artery exhibit the lowest restenosis rates [15]. Antithrombotic therapies like rivaroxaban plus aspirin [16, 17, 101] and ticagrelor [26] reduce major adverse limb and cardiovascular events, though with increased bleeding risk for rivaroxaban [16]. Vorapaxar also reduces thrombotic events but increases bleeding [82]. Triple antiplatelet therapy (TAPT) may decrease minor amputation risk in diabetic PAD patients but not major adverse limb events [14].
- **Exercise and Lifestyle Modifications:** Supervised exercise therapy (SET) [10, 24, 30, 137] and home exercise programs (HEP) [10] significantly improve walking performance, peak walking time, and 6-minute walk distance in symptomatic PAD patients. Behavioral interventions for weight loss combined with walking exercise are being investigated for

mobility improvement [18].

- **Pathophysiology and Biomarkers:** Impaired mitophagy and electron transport chain complex accumulation in gastrocnemius muscle [11], microRNA-29a suppression of ADAM12 [91], and the role of VSMC HIF in ischemic responses [62] are implicated in PAD pathophysiology. Elevated levels of galectin-3 [23, 117], hs-CRP [23, 58], fibrinogen [38, 58, 83], neopterin [84], endostatin [111, 113], and effector memory T cells [85] are identified as potential biomarkers for PAD severity, progression, and cardiovascular risk.
- **Disparities and Public Health:** Income-related disparities in PAD treatment exist, with lower-income areas showing higher prevalence and pharmacotherapy, while higher-income areas have more outpatient vascular surgery consultations [27]. Barbershop-based screening programs for Black men identified high PAD prevalence and improved awareness with education [22].

5) Discussion

5.1 Principal finding

The Global Limb Anatomic Staging System (GLASS) consistently serves as a critical prognostic tool, with higher stages correlating significantly with worse limb-related outcomes, including increased amputation and mortality rates, as evidenced by studies showing higher stages associated with lower technical success rates, higher amputation and mortality rates at 12 months (p=0.012, p=0.001, p=0.021, p=0.015) [7].

5.2 Clinical implications

- **Risk Stratification:** Clinicians should utilize GLASS staging to accurately stratify PAD patients, as higher stages (e.g., GLASS III/IV) predict poorer limb-based patency, limb salvage, amputation-free survival, and overall survival, guiding more aggressive management or realistic patient counseling [7, 32, 33].
- **Treatment Planning:** The GLASS classification can inform endovascular treatment decisions, with considerations for lesion complexity (e.g., GLASS IV lesions associated with lower patency and higher MALE) and device selection (e.g., balloon angioplasty showing better sustained positive effects than stenting for GLASS III femoropopliteal lesions) [15, 33, 35].
- **Prognostic Monitoring:** GLASS stages, combined with other predictors like neutrophil-to-lymphocyte ratio (NLR) and diabetes, can help identify PAD patients at higher risk of adverse procedural outcomes after endovascular treatment, necessitating closer monitoring [2].
- **Therapeutic Intensification:** Given the augmented risk associated with higher GLASS stages and comorbidities like diabetes and microvascular disease, patients with advanced

PAD may benefit from intensified antithrombotic therapy (e.g., rivaroxaban plus aspirin) to reduce major adverse limb and cardiovascular events, balancing with bleeding risk [9, 16, 17].

- **Lifestyle Interventions:** Supervised exercise therapy and home exercise programs should be strongly recommended for symptomatic PAD patients across GLASS stages to improve walking performance and quality of life, with greater attendance correlating with better outcomes [10, 24, 30, 137].

5.3 Research implications / key gaps

- **Standardized Outcome Metrics:** Future studies should standardize reporting of GLASS-specific outcomes (e.g., amputation-free survival, limb salvage rates) across different stages and timepoints to enable robust meta-analyses and comparative effectiveness research [7, 32, 33].
- **Prospective Validation of AI Models:** While promising, the high accuracy of computer vision and AutoML models for GLASS classification and outcome prediction requires large-scale prospective validation in diverse PAD populations to confirm generalizability and clinical utility [1, 3].
- **Impact of GLASS on Treatment Algorithms:** Research is needed to develop and prospectively evaluate treatment algorithms that explicitly incorporate GLASS staging to optimize revascularization strategies and medical management, comparing outcomes against current guideline-based approaches [2, 4, 6].
- **Biomarker Integration with GLASS:** Investigating the incremental prognostic value of integrating novel biomarkers (e.g., galectin-3, hs-CRP, endostatin, microRNAs) with GLASS staging could refine risk prediction and identify new therapeutic targets [11, 23, 58, 84, 85, 91, 111, 113, 117].
- **Long-term Outcomes Across GLASS Stages:** More long-term prospective studies are needed to understand the natural history and treatment efficacy across different GLASS stages, particularly for outcomes beyond 1-2 years, to inform durable management strategies [4, 32, 33].

5.4 Limitations

- **Heterogeneous Study Designs** — The prevalence of retrospective and mixed-design studies limits the ability to infer causality and introduces potential biases.

- **Varied Outcome Reporting** — Inconsistent reporting of specific numerical outcomes for GLASS across studies hinders direct quantitative comparisons and meta-analysis.
- **Limited Prospective Data** — A scarcity of large-scale prospective randomized controlled trials specifically evaluating GLASS-guided interventions restricts the highest level of evidence.
- **Population Specificity** — Many studies focus on specific patient subgroups (e.g., CLTI, endovascular treatment), which may limit the generalizability of findings to the broader PAD population.
- **Lack of Mechanistic Detail** — While biomarkers are identified, the precise mechanistic links between GLASS stages and specific molecular pathways are not fully elucidated in the current summary.

5.5 Future directions

- **Prospective GLASS Validation** — Conduct large, multicenter prospective cohort studies to validate the prognostic utility of GLASS across diverse PAD populations.
- **RCTs for GLASS-Guided Therapy** — Design randomized controlled trials comparing GLASS-guided treatment strategies against standard care to assess clinical efficacy.
- **AI-Enhanced GLASS Implementation** — Develop and integrate validated AI models for automated GLASS classification into clinical workflows to improve efficiency and consistency.
- **Biomarker-GLASS Integration** — Investigate the additive value of novel biomarkers in conjunction with GLASS to enhance risk stratification and therapeutic targeting.
- **Socioeconomic Disparity Assessment** — Conduct studies to understand and address socioeconomic disparities in PAD diagnosis, treatment, and outcomes across GLASS stages.

6) Conclusion

The Global Limb Anatomic Staging System (GLASS) consistently demonstrated prognostic value for limb outcomes and survival in peripheral artery disease (PAD) patients. Specifically, higher GLASS stages were associated with worse outcomes, including lower technical success rates, higher amputation and mortality rates at 12 months (p=0.012, p=0.001, p=0.021, p=0.015) [7]. This prognostic utility applies broadly to PAD patients, particularly those with chronic limb-threatening ischemia undergoing revascularization. The reliance on heterogeneous study designs and varied outcome reporting represents the single limitation that most affects certainty. A concrete next step is to conduct large-scale prospective randomized controlled trials to validate GLASS-guided treatment algorithms.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

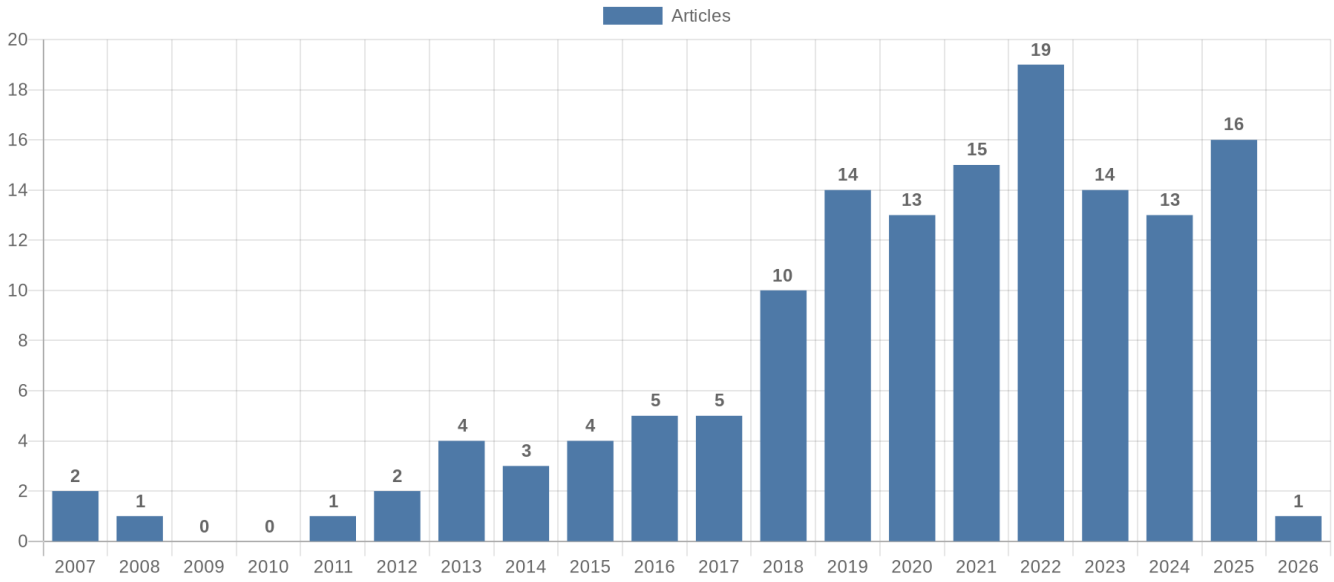


Figure 2. Study-design distribution of included originals

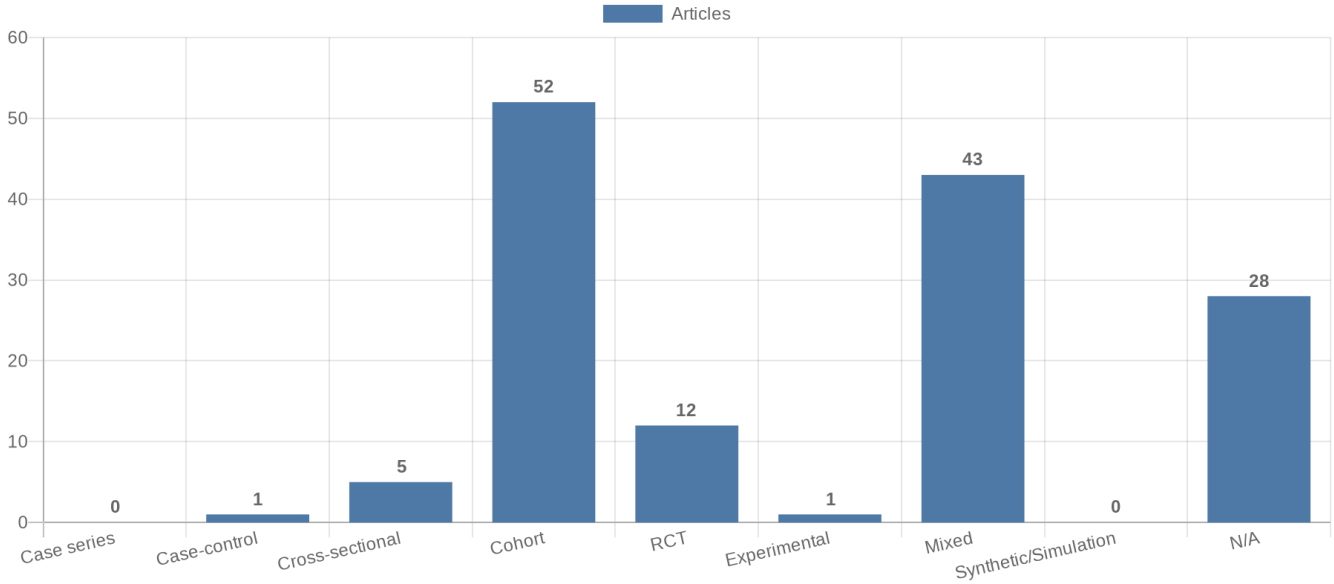


Figure 3. Study-type (directionality) distribution of included originals

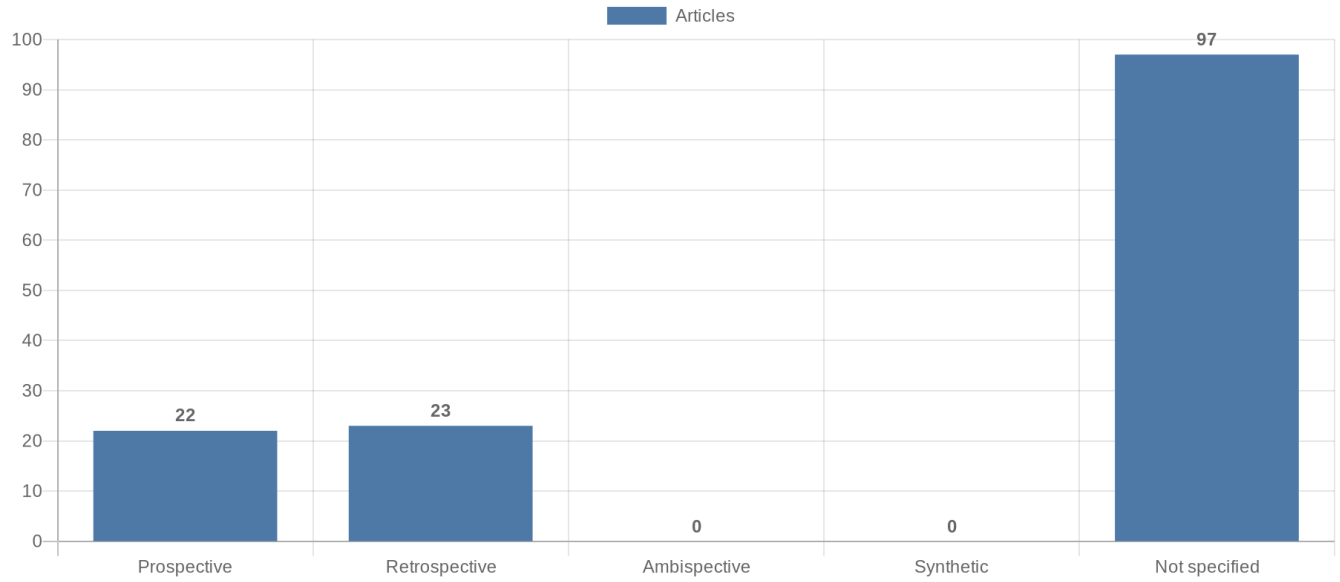


Figure 4. Main extracted research topics

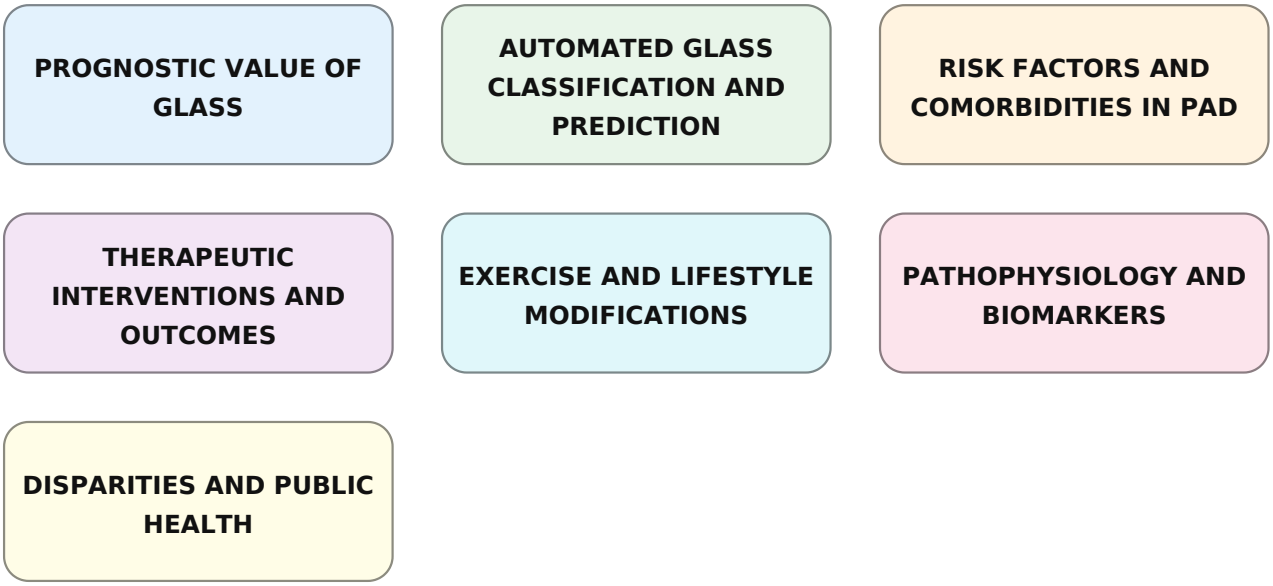


Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)

STANDARDIZED OUTCOME METRICS

PROSPECTIVE VALIDATION OF AI MODELS

IMPACT OF GLASS ON TREATMENT ALGORITHMS

BIOMARKER INTEGRATION WITH GLASS

LONG-TERM OUTCOMES ACROSS GLASS STAGES

PROSPECTIVE GLASS VALIDATION

RCTS FOR GLASS-GUIDED THERAPY