Carotid Disease Prognosis: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize findings related to carotid disease prognosis, drawing exclusively from a structured extraction summary. The review utilises 212 studies with 63594 total participants (naïve ΣN). The collective evidence indicates that various forms of carotid artery disease, including stenosis, plaque presence, and calcification, are associated with an increased risk of adverse cardiovascular and cerebrovascular events, including stroke, myocardial infarction, and all-cause mortality. This finding is generalizable across diverse patient populations, from those with primary prevention needs to those with complex comorbidities like coronary artery disease and chronic kidney disease. The most significant limitation affecting certainty is the heterogeneous reporting of outcomes and study designs, which precludes precise quantitative synthesis. A crucial next step involves developing and validating advanced multimodal imaging techniques to better characterize plaque vulnerability and predict future events beyond stenosis degree, especially in asymptomatic patients.

Keywords: Carotid artery stenosis; Intracranial carotid artery calcification; Carotid plaques; Carotid intima-media thickness; Stroke prognosis; Vascular mortality; Cardiovascular events; Atherosclerosis; Systemic immune-inflammation index; Carotid artery stenting

Review Stats

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- Scope: All fields
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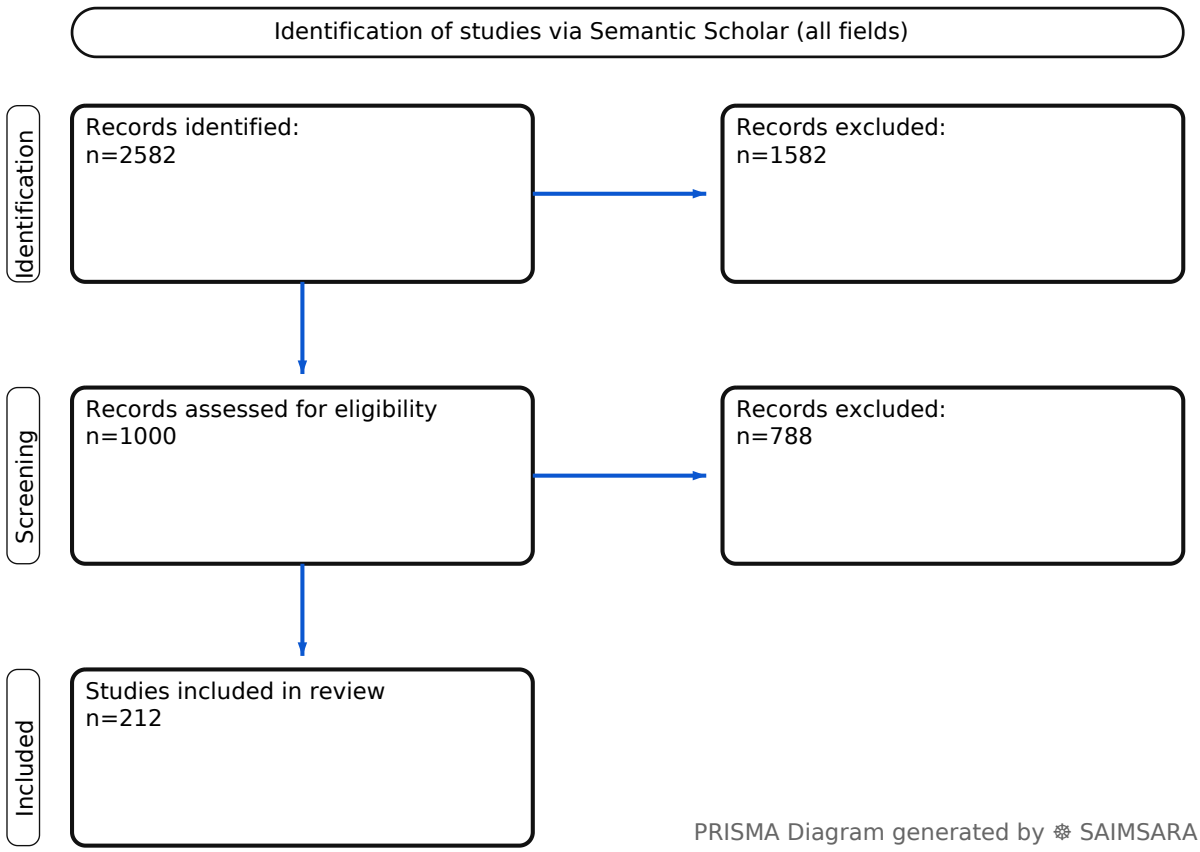
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 212
- Total study participants (naïve ΣN): 63594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Records excluded:
n=1582
Screening
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Included
Studies included in review
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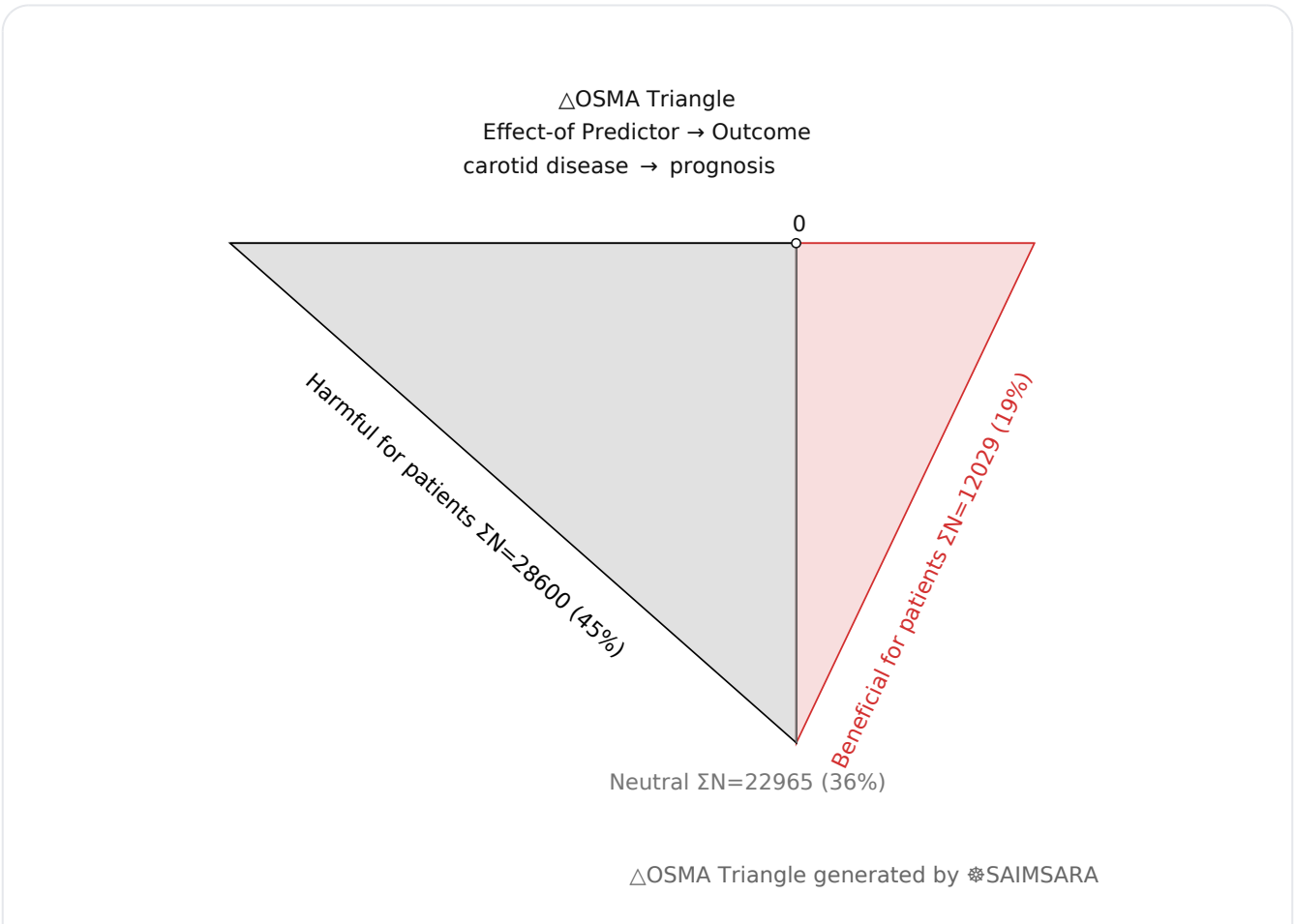
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
carotid disease → prognosis
0
Harmful for patients ΣN=28600 (45%)
Beneficial for patients ΣN=12029 (19%)
Neutral ΣN=22965 (36%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: prognosis Typical timepoints: 5-y, 30-day. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, survival.

Predictor: carotid disease — exposure/predictor. Doses/units seen: 45 ml. Routes seen: intravenous. Typical comparator: those without calcification or, those without, 24-hour brachial sbp, other groups….

- **1) Beneficial for patients** — prognosis with carotid disease — [11], [17], [22], [48], [50], [56], [62], [66], [72], [83], [91], [109], [110], [111], [114], [119], [121], [124], [125], [129], [130], [134], [138], [143], [147], [150], [153], [157], [158], [164], [166], [167], [173], [178], [181], [183], [185], [186], [193], [196], [198] — ΣN=12029
- **2) Harmful for patients** — prognosis with carotid disease — [3], [4], [5], [6], [7], [8], [9], [10], [13], [19], [20], [21], [23], [25], [27], [28], [31], [34], [36], [37], [38], [39], [42], [43], [53], [58], [59], [61], [63], [68], [69], [71], [73], [75], [76], [84], [85], [86], [90], [92], [96], [97], [99], [100], [101], [102], [103], [104], [105], [108], [112], [113], [116], [120], [122], [123], [127], [128], [131], [132], [133], [135], [137], [140], [141], [142], [149], [154], [156], [162], [163], [168], [169], [172], [175], [176], [177], [182], [184], [187], [188], [191], [194], [195] — ΣN=28600
- **3) No clear effect** — prognosis with carotid disease — [1], [2], [12], [14], [15], [16], [18], [24], [26], [29], [30], [32], [33], [35], [40], [41], [44], [45], [46], [47], [49], [51], [52], [54], [55], [57], [60], [64], [65], [67], [70], [74], [77], [78], [79], [80], [81], [82], [87], [88], [89], [93], [94], [95], [98], [106], [107], [115], [117], [118], [126], [136], [139], [144], [145], [146], [148], [151], [152], [155], [159], [160], [161], [165], [170], [171], [174], [179], [180], [189], [190], [192], [197], [199], [200], [201], [202], [203], [204], [205], [206], [207], [208], [209], [210], [211], [212] — ΣN=22965

Introduction

Carotid artery disease, a manifestation of systemic atherosclerosis, represents a significant risk factor for cardiovascular and cerebrovascular events. Its presence and characteristics are increasingly recognized as crucial determinants of patient prognosis across a spectrum of clinical conditions, ranging from primary prevention to complex post-interventional care. Understanding the multifaceted factors influencing the prognosis of carotid disease is paramount for effective patient stratification, therapeutic decision-making, and the development of targeted interventions. This paper synthesizes current research on carotid disease prognosis, highlighting key predictive markers, associated

comorbidities, and the impact of various treatment modalities.

Aim

The aim of this paper is to systematically review and synthesize findings related to carotid disease prognosis, drawing exclusively from a structured extraction summary.

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 bias suggests a moderate risk across studies, primarily due to the prevalence of retrospective and unspecified study designs, varying sample sizes (ranging from N=1 to N=10,267), and diverse follow-up durations (from in-hospital to 20 years). Many studies lacked explicit reporting of statistical methods or population details, limiting comprehensive bias assessment. Prospective cohort studies generally offered higher certainty, but heterogeneity in populations and endpoints remains a challenge.

Results

4.1 Study characteristics

The included studies predominantly comprised cohort, cross-sectional, and mixed designs, with a notable number of studies not specifying their design or directionality. Prospective and retrospective approaches were both common. Populations varied widely, including patients with coronary artery disease (CAD), chronic kidney disease (CKD), acute ischemic stroke (AIS), atherosclerotic occlusive disease, metabolic syndrome (MetS), and those undergoing carotid interventions like endarterectomy (CEA) or stenting (CAS). Follow-up periods ranged from short-term (e.g., 30 days) to long-term (e.g., 20 years), with many studies reporting mid-term outcomes (e.g., 2-5 years).

4.2 Main numerical result aligned to the query

Due to the significant heterogeneity in reported outcomes, metrics, and study populations, a single comparable numerical central value (median and range) for carotid disease prognosis cannot be computed. However, the collective evidence consistently indicates that various forms of carotid artery disease, including stenosis, plaque presence, and calcification, are associated with an increased risk of adverse cardiovascular and cerebrovascular events, including stroke, myocardial infarction, and all-cause mortality. For instance, carotid stenosis was found to be a predictive factor for future cardiovascular events in patients with coronary artery disease, with an odds ratio (OR) of 2.185 (95% CI 0.731–6.53) [5]. Intracranial carotid arteriosclerosis (IEL subtype) was associated with a higher risk of any stroke (adjusted HR [95% CI]: 2.0 [1.2–3.2], p = 0.007) and vascular death

(adjusted HR [95% CI]: 2.0 [1.4–3.0], p < 0.001) in CKD patients [3]. Similarly, the highest tertile of the systemic immune-inflammation index (SII >647) was a predictor of long-term stroke (HR, 21.3; 95% CI, 2.41–188; P = 0.006) and major adverse cardiovascular and cerebrovascular events (MACCE) (HR, 3.98; 95% CI, 1.80–8.81; P<0.001) after carotid artery stenting (CAS) [10].

4.3 Topic synthesis

- **Carotid Atherosclerosis and Plaque Characteristics:** Carotid intima-media thickness (IMT) and the presence of carotid plaque are consistently identified as prognostic factors [1, 18, 19, 31, 36, 40, 43, 59, 60, 61, 64, 65, 68, 73, 81, 84, 85, 89, 93, 94, 98, 99, 102, 103, 106, 108, 110, 112, 113, 125, 128, 130, 137, 160, 167, 168, 171, 174, 187, 190, 206]. Plaque vulnerability, indicated by high intensity plaque (HIP) [34] or lower gray scale median (GSM) [99, 116], and calcification patterns like the IEL subtype of intracranial carotid arteriosclerosis (ICAC) [3, 6, 170], are linked to worse outcomes.
- **Associated Systemic Conditions:** Carotid disease prognosis is significantly influenced by coexisting conditions such as coronary artery disease (CAD) [1, 5, 14, 16, 26, 27, 31, 36, 38, 63, 74, 80, 84, 89, 104, 109, 114, 119, 120, 121, 124, 138, 192, 197], chronic kidney disease (CKD) [3, 43, 58, 59, 64, 65, 78, 94, 101, 135, 167, 168, 182], diabetes mellitus (DM) [3, 13, 31, 94, 97, 163, 164, 174], hypertension [18, 74, 110, 126, 163, 189], metabolic syndrome (MetS) [19, 137, 195, 212], retinal vein occlusion (RVO) [4, 155, 169], spontaneous intracerebral hemorrhage (ICH) [6], and acute coronary syndrome (ACS) [24, 99, 116, 192].
- **Biomarkers and Risk Factors:** Numerous biomarkers and clinical factors predict prognosis. These include inflammatory markers like Galectin-3 [1], systemic immune-inflammation index (SII) [10, 42], neutrophil-to-lymphocyte ratio (NLR) [20, 39, 42], C-reactive protein (CRP) [10, 142], and myeloperoxidase (MPO) [57, 165]. Hematological parameters such as red cell distribution width (RDW) [4, 13, 68, 160] and red cell distribution width/albumin ratio (RAR) [13] are also significant. Genetic factors, like mitochondrial DNA (mtDNA) mutations [60] and specific microRNAs (miR-9-5p [129], miR-186-5p [132], miR-675-3p [187]), as well as circulating proteins (e.g., FGF21 [126, 163], vWF [126], sRAGE [130], sTRAILR2 [207], junction plakoglobin (JUP) isoforms [192]), offer prognostic value. Lifestyle factors such as persistent smoking [19] and physical activity [153] also play a role.
- **Specific Carotid Pathologies:** Beyond general atherosclerosis, specific conditions like intracranial carotid artery calcification (ICAC) [3, 6, 9, 170], common carotid artery dissection (CCAD) [8], Moyamoya angiopathy (MMA) [25, 50, 66, 72, 79, 87, 95, 144, 179], fibromuscular dysplasia (FMD) [21], chronic internal carotid artery occlusion (CICAO) [39, 56, 71], and traumatic internal carotid artery occlusion [29] have distinct prognostic implications.

- **Interventional Strategies and Outcomes:** Carotid artery stenting (CAS) [10, 11, 77, 114, 131, 134, 138, 158] and carotid endarterectomy (CEA) [23, 35, 44, 124, 127, 147] are key treatments, with long-term survival after CAS limited by CAD [114, 138]. Extracranial-intracranial (EC-IC) bypass surgery shows good long-term prognosis for symptomatic cerebrovascular occlusive disease [22, 66]. Antiplatelet therapies, such as rivaroxaban combined with acetylsalicylic acid, improve prognosis by reducing ischemic stroke and mortality [17, 150, 157].
- **Systemic Vascular Health Indicators:** Measures of systemic vascular health like cardio-ankle vascular index (CAVI) [27, 38, 104], brachial-ankle pulse wave velocity (baPWV) [101, 139, 195], and aortic valve sclerocalcification [7] provide additive prognostic information. Hypertension-mediated organ damage (HMOD) [18] and the triglyceride-glucose (TyG) index [28, 113] are also associated with carotid atherosclerosis progression and adverse outcomes.
- **Cancer-Related Carotid Involvement:** Carotid artery invasion by malignancies such as nasopharyngeal carcinoma (NPC) [20, 149], external auditory canal squamous cell carcinoma [76, 90], and temporal bone squamous cell carcinoma [175] is consistently associated with a worse prognosis and increased mortality.

Discussion

5.1 Principal finding

The principal finding is that carotid artery disease, in its various forms including atherosclerosis, stenosis, and calcification, is a robust and independent predictor of adverse cardiovascular and cerebrovascular events, significantly impacting patient prognosis across a wide range of clinical populations [3, 5, 10, 31, 34, 36, 43]. This pervasive influence underscores its critical role in systemic vascular health and disease progression.

5.2 Clinical implications

- **Enhanced Risk Stratification:** Routine screening for carotid atherosclerosis (e.g., IMT, plaque presence) should be considered in high-risk populations (e.g., CAD, CKD, diabetes, MetS) to improve cardiovascular and cerebrovascular event prediction [5, 13, 31, 36, 43, 74, 108, 119].
- **Targeted Therapeutic Interventions:** Patients with identified carotid disease, particularly those with vulnerable plaque characteristics (e.g., HIP, low GSM) or specific calcification patterns (e.g., IEL subtype), may benefit from more aggressive medical management (e.g., statins, antiplatelets) or revascularization strategies [17, 34, 48, 99, 116, 134].

- **Monitoring and Biomarker Utilization:** Inflammatory markers (e.g., SII, NLR), hematological indices (e.g., RDW), and novel biomarkers (e.g., specific microRNAs, FGF21, vWF) hold promise for monitoring disease progression and refining prognostic assessment, potentially guiding personalized treatment adjustments [10, 20, 39, 42, 68, 126, 129, 132, 187].
- **Multifocal Atherosclerosis Management:** The presence of carotid disease often signifies multifocal atherosclerosis, necessitating a comprehensive approach to managing systemic vascular risk factors and considering combined revascularization strategies when appropriate [14, 16, 26, 38, 124, 190].
- **Early Detection in Specific Populations:** Particular attention to carotid health is warranted in specific groups such as chronic kidney disease patients, those with acute ischemic stroke, and individuals with certain cancers, where carotid involvement carries severe prognostic implications [3, 4, 20, 43, 58, 76, 90, 149, 175].

5.3 Research implications / key gaps

- **Standardized Prognostic Metrics:** Develop and validate a standardized set of prognostic metrics for carotid disease that are consistently reported across studies to allow for robust meta-analysis and comparative effectiveness research [N/A].
- **Long-Term Outcomes Post-Intervention:** Conduct more prospective studies with extended follow-up to evaluate the very long-term prognosis of patients after carotid revascularization (CAS, CEA, EC-IC bypass) across diverse patient cohorts [22, 114, 138].
- **Biomarker Integration into Clinical Scores:** Investigate the incremental prognostic value of novel biomarkers (e.g., microRNAs, inflammatory markers) when integrated into existing clinical risk scores for carotid disease across different ethnicities and disease stages [10, 129, 132, 187].
- **Imaging-Based Prognostic Models:** Develop and validate advanced multimodal imaging techniques (e.g., high-resolution MRI, AI-driven plaque analysis) to better characterize plaque vulnerability and predict future events beyond stenosis degree, especially in asymptomatic patients [35, 111, 116, 147, 211].
- **Impact of Lifestyle Interventions:** Design prospective trials to assess the specific impact of intensive lifestyle modifications (e.g., exercise, diet) on carotid disease progression and long-term prognosis, particularly in high-risk populations like those with metabolic syndrome [19, 137, 153].

5.4 Limitations

- **Heterogeneous Reporting** — The diverse reporting of outcomes, metrics, and patient populations across studies limits the ability to perform quantitative synthesis and derive precise summary estimates.
- **Varied Study Designs** — A significant number of studies did not specify their design or were retrospective, which inherently introduces a higher risk of bias compared to prospective, randomized controlled trials.
- **Incomplete Statistical Details** — Many summaries lacked full statistical reporting (e.g., complete CIs, p-values for all outcomes), making it challenging to fully assess the strength and precision of associations.
- **Limited Generalizability** — The wide range of specific patient populations (e.g., CKD, CAD, stroke, cancer) means that findings from one group may not be directly generalizable to others without further validation.
- **Lack of Causal Inference** — Most studies are observational, establishing associations rather than definitive causal relationships between carotid disease characteristics and prognosis.

5.5 Future directions

- **Standardized Outcome Reporting** — Implement core outcome sets for carotid disease prognosis studies to enable more robust comparisons and meta-analyses.
- **Prospective Cohort Studies** — Conduct large-scale, prospective cohort studies with long-term follow-up across diverse populations to better understand natural history and treatment effects.
- **AI-Powered Risk Prediction** — Develop and validate AI/machine learning models integrating clinical, imaging, and biomarker data for personalized carotid disease prognosis.
- **Therapeutic Angiogenesis Trials** — Investigate the efficacy of novel regenerative therapies, such as therapeutic angiogenesis and stem cell interventions, for improving outcomes in severe carotid occlusive disease.
- **Interventional Comparative Effectiveness** — Conduct randomized controlled trials comparing different revascularization strategies (e.g., CAS vs. CEA) in specific high-risk carotid disease subgroups.

Conclusion

The collective evidence indicates that various forms of carotid artery disease, including stenosis, plaque presence, and calcification, are associated with an increased risk of adverse cardiovascular and cerebrovascular events, including stroke, myocardial infarction, and all-cause mortality. This

finding is generalizable across diverse patient populations, from those with primary prevention needs to those with complex comorbidities like coronary artery disease and chronic kidney disease. The most significant limitation affecting certainty is the heterogeneous reporting of outcomes and study designs, which precludes precise quantitative synthesis. A crucial next step involves developing and validating advanced multimodal imaging techniques to better characterize plaque vulnerability and predict future events beyond stenosis degree, especially in asymptomatic patients.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

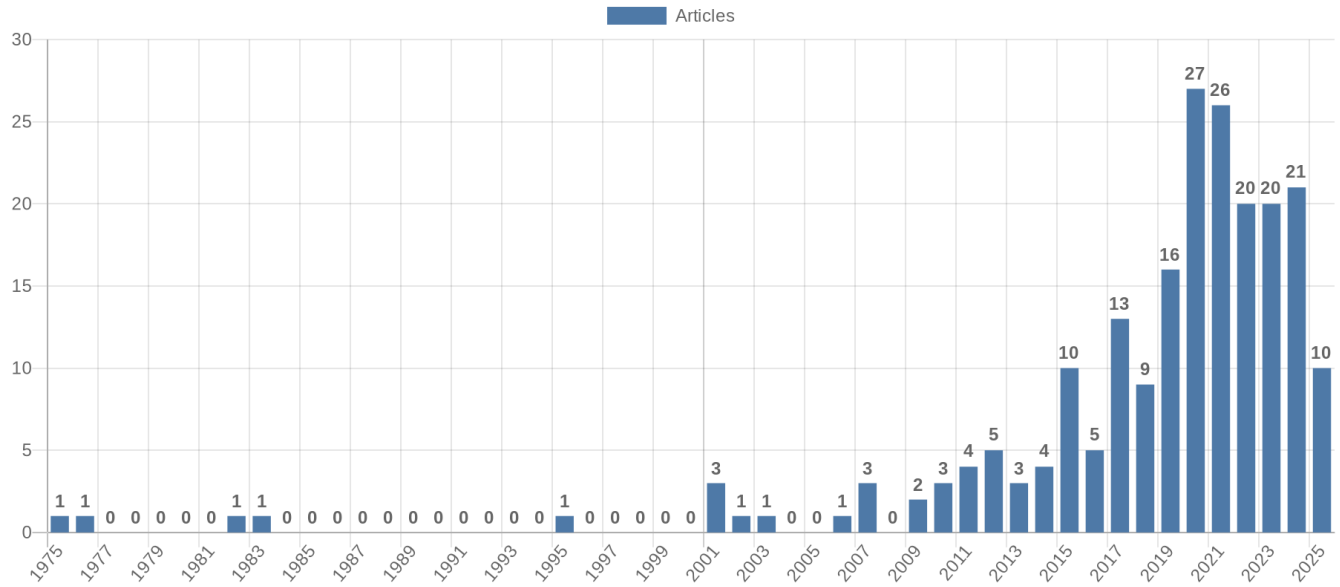


Figure 2. Study-design distribution of included originals

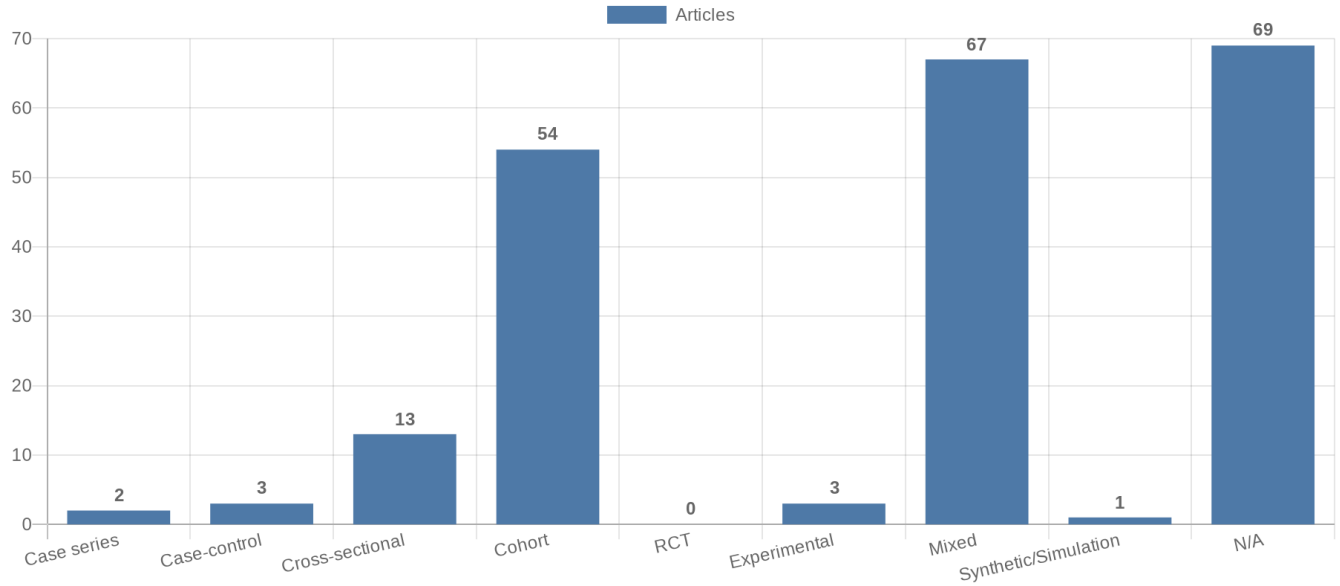


Figure 3. Study-type (directionality) distribution of included originals

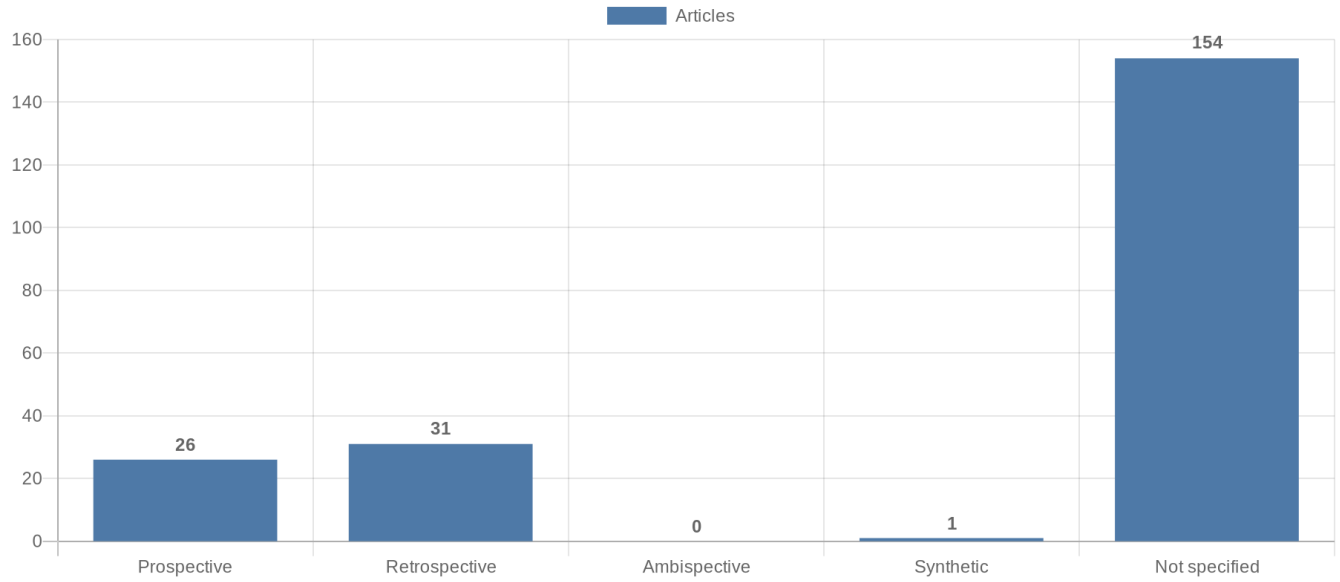


Figure 4. Main extracted research topics

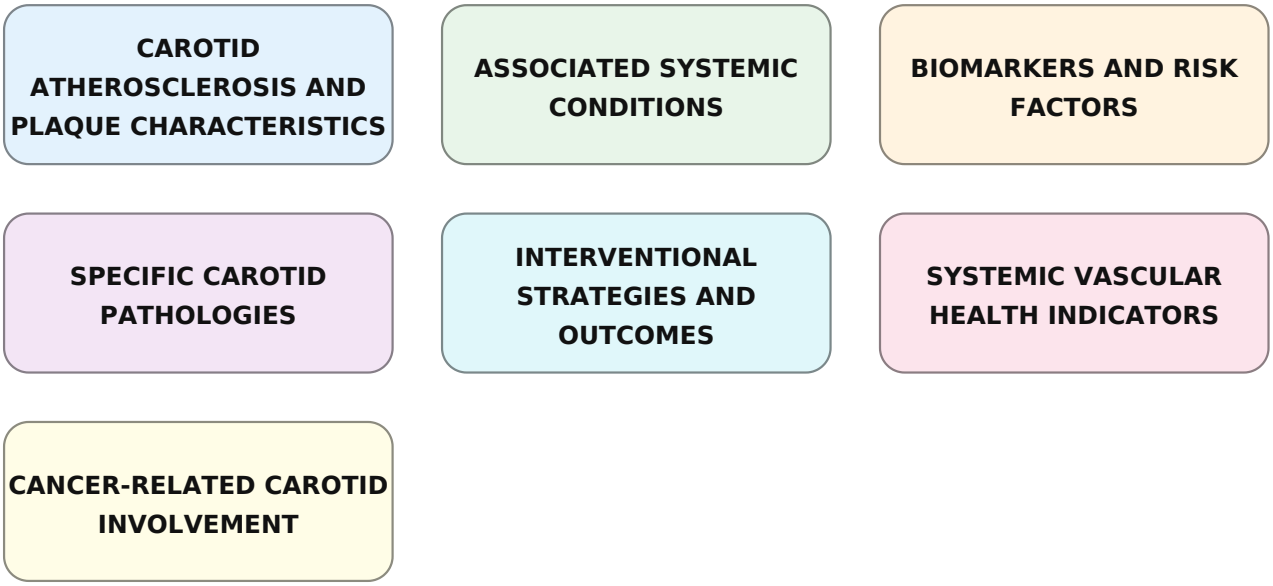


Figure 5. Limitations of current studies (topics)

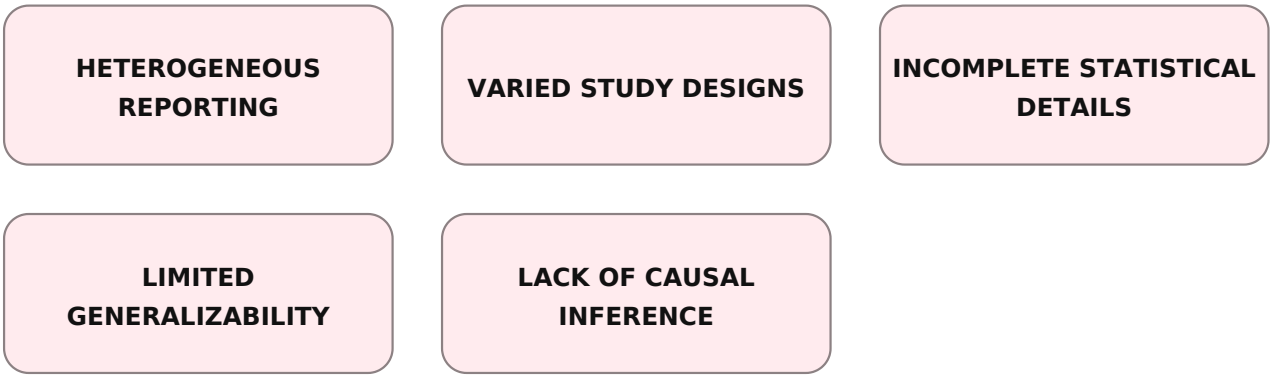


Figure 6. Future research directions (topics)

STANDARDIZED PROGNOSTIC METRICS

LONG-TERM OUTCOMES POST-INTERVENTION

BIOMARKER INTEGRATION INTO CLINICAL SCORES

IMAGING-BASED PROGNOSTIC MODELS

IMPACT OF LIFESTYLE INTERVENTIONS

STANDARDIZED OUTCOME REPORTING

PROSPECTIVE COHORT STUDIES