Carotid Stenosis and Inflammation: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to synthesize the current evidence on the association between carotid stenosis and inflammation, encompassing diagnostic biomarkers, imaging modalities, prognostic indicators, and therapeutic interventions. The review utilises 302 studies with 80631 total participants (naïve ΣN). The SCAIL score, a composite metric incorporating carotid plaque inflammation and stenosis severity, is a significant predictor of recurrent stroke and other adverse cardiovascular events, with a median adjusted hazard ratio of 2.4 (range 1.96-4.52). These findings underscore the critical role of inflammation in the pathophysiology and clinical course of carotid stenosis across diverse patient populations. However, the heterogeneity of study designs and variability in inflammatory markers represent the most significant limitation affecting the certainty of these conclusions. A concrete next step for research involves conducting longitudinal intervention trials to evaluate the long-term impact of targeted anti-inflammatory therapies on clinical outcomes in patients with carotid stenosis.

Keywords: Carotid Stenosis; Inflammation; Atherosclerosis; Carotid Plaque; Plaque Instability; Inflammatory Biomarkers; Stroke Risk; Systemic Inflammation; Vulnerable Plaque; Atherothrombosis

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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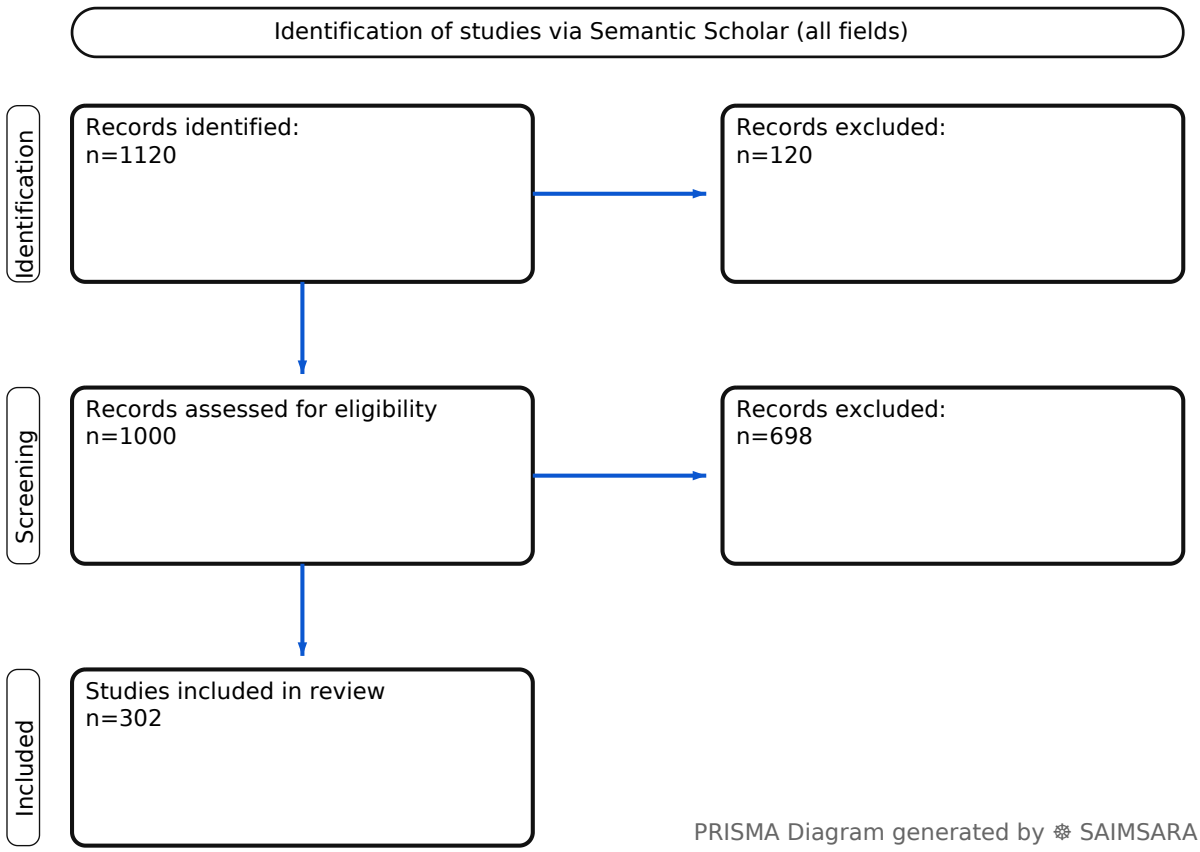
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 302
- Total study participants (naïve ΣN): 80631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Records excluded:
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Included
Studies included in review
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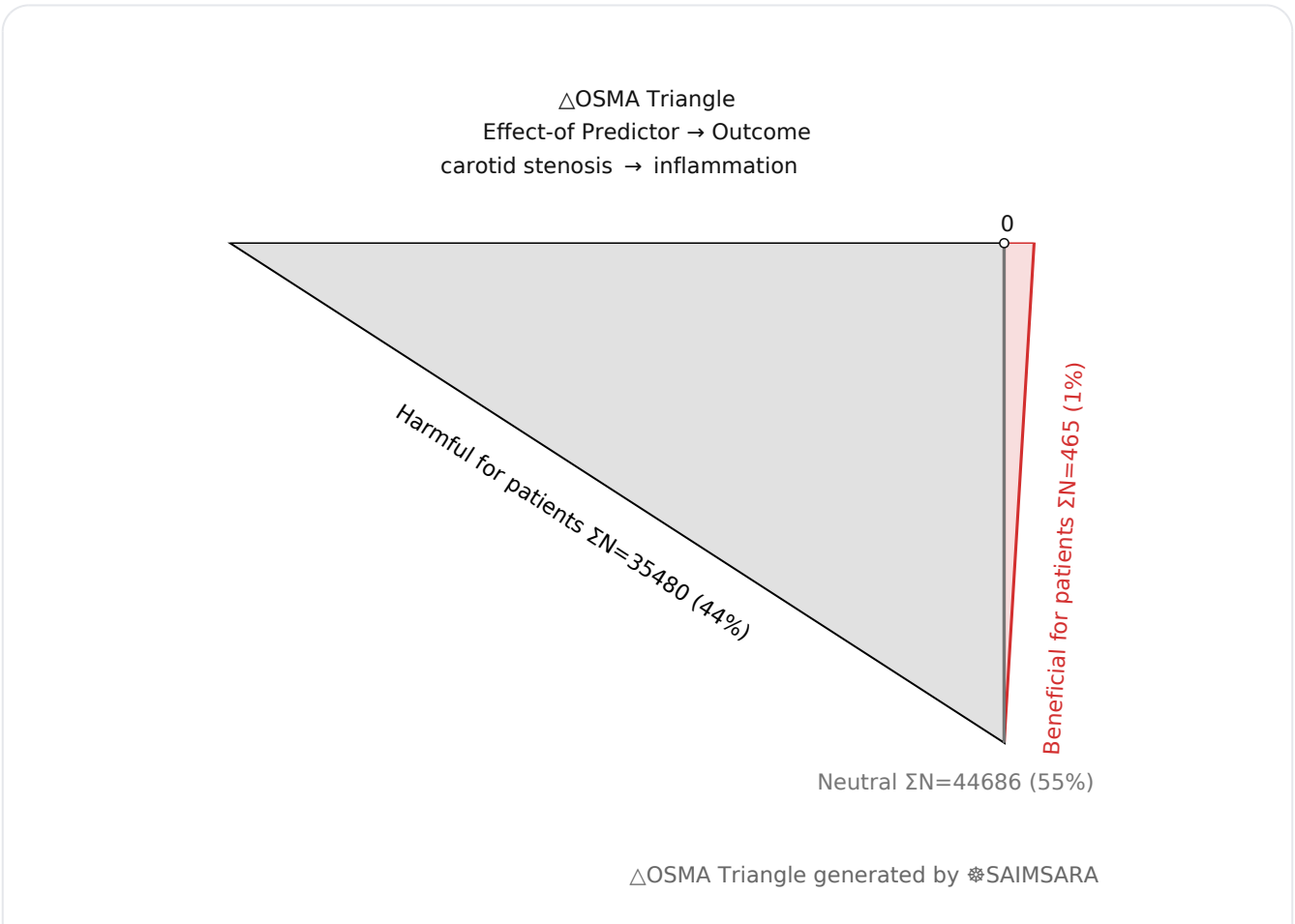
△OSMA Triangle
Effect-of Predictor → Outcome
carotid stenosis → inflammation
0
Harmful for patients ΣN=35480 (44%)
Beneficial for patients ΣN=465 (1%)
Neutral ΣN=44686 (55%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: inflammation Typical timepoints: 90-day, 1-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, healing.

Predictor: carotid stenosis — exposure/predictor. Doses/units seen: 4g, 5g. Routes seen: intravenous. Typical comparator: controls and may be used as a, controls, asymptomatic patients, normoglycemics….

- **1) Beneficial for patients** — inflammation with carotid stenosis — [4], [22], [66], [102], [106], [130], [146], [148], [150], [153], [171], [172], [173], [175], [176], [179], [182], [185], [194], [244], [245], [249], [250], [252], [254], [277], [282], [291], [295], [297] — ΣN=465
- **2) Harmful for patients** — inflammation with carotid stenosis — [1], [2], [3], [5], [8], [10], [11], [12], [13], [15], [17], [19], [20], [24], [25], [51], [52], [54], [55], [56], [57], [58], [59], [60], [61], [62], [68], [69], [71], [75], [86], [100], [101], [104], [105], [108], [109], [111], [112], [113], [116], [117], [119], [120], [122], [123], [124], [125], [126], [127], [134], [139], [145], [147], [149], [151], [152], [154], [155], [156], [157], [158], [160], [161], [162], [164], [165], [166], [168], [169], [170], [178], [183], [186], [187], [188], [189], [190], [191], [192], [193], [195], [196], [198], [226], [227], [228], [229], [230], [231], [232], [233], [235], [236], [237], [239], [240], [242], [243], [246], [247], [248], [251], [253], [255], [260], [264], [265], [270], [271], [274] — ΣN=35480
- **3) No clear effect** — inflammation with carotid stenosis — [6], [7], [9], [14], [16], [18], [21], [23], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [53], [63], [64], [65], [67], [70], [72], [73], [74], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [103], [107], [110], [114], [115], [118], [121], [128], [129], [131], [132], [133], [135], [136], [137], [138], [140], [141], [142], [143], [144], [159], [163], [167], [174], [177], [180], [181], [184], [197], [199], [200], [201], [202], [203], [204], [205], [206], [207], [208], [209], [210], [211], [212], [213], [214], [215], [216], [217], [218], [219], [220], [221], [222], [223], [224], [225], [234], [238], [241], [256], [257], [258], [259], [261], [262], [263], [266], [267], [268], [269], [272], [273], [275], [276], [278], [279], [280], [281], [283], [284], [285], [286], [287], [288], [289], [290], [292], [293], [294], [296], [298], [299], [300], [301], [302] — ΣN=44686

1) Introduction

Carotid artery stenosis (CAS), a common manifestation of atherosclerosis, is a significant risk factor for ischemic stroke and other adverse cardiovascular events. The pathogenesis of atherosclerosis, and by extension CAS, is intrinsically linked to chronic inflammation and oxidative stress within the arterial wall and systemically. Inflammatory processes contribute to plaque formation, progression, and destabilization, leading to conditions such as intraplaque hemorrhage (IPH), fibrous cap rupture, and subsequent thromboembolic events. Understanding the intricate relationship between carotid stenosis and inflammation is crucial for improved risk stratification, early diagnosis, and the development of targeted therapeutic strategies to prevent devastating cerebrovascular outcomes.

2) Aim

This paper aims to synthesize the current evidence on the association between carotid stenosis and inflammation, encompassing diagnostic biomarkers, imaging modalities, prognostic indicators, and therapeutic interventions.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** The included studies predominantly feature observational designs (cohort, cross-sectional, mixed retrospective, and prospective), with fewer randomized controlled trials or purely experimental studies. Many studies do not specify directionality, and sample sizes vary widely, ranging from small case series to large cohorts. This heterogeneity in study design and reporting limits the ability to draw strong causal inferences and suggests a potential for selection bias and confounding in many findings.

4) Results

4.1 Study characteristics

The studies reviewed primarily consisted of cohort (retrospective and prospective), cross-sectional, and mixed designs, with a notable number of experimental studies, particularly using mouse or porcine models. Populations frequently included elderly patients, individuals with diagnosed carotid artery stenosis (both symptomatic and asymptomatic), and those with recent ischemic stroke or transient ischemic attack (TIA). Other populations included patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS), those with comorbidities like diabetes, coronary artery disease, or rheumatoid arthritis, and healthy controls. Follow-up periods, when specified, ranged from 30 days to 5 years, with some studies having median follow-ups of 42 days, 90 days, or 69 months.

4.2 Main numerical result aligned to the query

The Symptomatic Carotid Atheroma Inflammation Lumen stenosis (SCAIL) score, which integrates carotid plaque inflammation and stenosis severity, consistently predicted recurrent stroke and other adverse events. The adjusted hazard ratio (HR) for recurrent stroke or major adverse cardiovascular events (MACE) associated with the SCAIL score ranged from 1.96 to 4.52 [3, 19, 54, 55]. The median adjusted HR for recurrent stroke per 1-point SCAIL increase was 2.4 [3, 19, 54, 55].

4.3 Topic synthesis

- **Plaque Inflammation and Instability:** Carotid plaque inflammation, often assessed by 18F-FDG PET/CT uptake (SUVmax or TBR), is consistently higher in symptomatic patients and correlates with markers of plaque instability such as lipid-rich necrotic core (LRNC), thin fibrous cap, ulceration, and intraplaque hemorrhage (IPH) [6, 7, 40, 47, 61, 69, 77, 101, 104, 108, 120, 123, 127, 170, 174, 213, 216, 231, 234]. Macrophage infiltration is a key component of this inflammation, directly associated with FDG uptake [231].
- **Systemic Inflammatory Biomarkers:** Numerous systemic inflammatory markers are associated with carotid stenosis severity and symptomatology. These include high-sensitivity C-reactive protein (hsCRP) [13, 25, 40, 69, 134, 139, 178, 193, 199, 214, 217, 240, 242, 253, 270], systemic immune inflammation index (SII) [11, 13, 15, 17, 100, 198, 215], neutrophil-to-lymphocyte ratio (NLR) [13, 15, 46, 57, 84, 88, 100, 186, 188, 198, 215, 285], platelet-to-lymphocyte ratio (PLR) [13, 46, 50, 88, 100, 215], and monocyte-to-HDL cholesterol ratio (MHR) [16, 36, 60, 71]. Other markers include IL-6, TNF-α, chemerin, galectin-3, sICAM-1, kynurenine/tryptophan ratio, neopterin, omentin, and matrix metalloproteinases (MMPs) [1, 10, 14, 18, 24, 27, 32, 48, 49, 56, 59, 62, 66, 68, 72, 83, 87, 96, 107, 110, 113, 115, 124, 126, 128, 133, 134, 142, 144, 145, 147, 153, 158, 164, 165, 166, 168, 175, 178, 179, 181, 182, 187, 190, 191, 192, 194, 197, 199, 202, 203, 207, 208, 211, 212, 221, 222, 224, 226, 227, 228, 229, 230, 233, 236, 237, 238, 241, 245, 251, 252, 255, 272, 274, 276, 277, 281, 287, 292, 294, 299].
- **Risk Prediction and Prognosis:** The SCAIL score (median HR 2.4, range 1.96-4.52 for recurrent stroke) [3, 19, 54, 55] and plaque SUVmax (adjusted HR 1.98, 95% CI 1.10–3.56, p = 0.02 per 1–g/mL increase for 5-year recurrent stroke) [55] are robust predictors of stroke recurrence. High levels of PIV, SII, NLR, PLR, MHR, and CRP are also associated with increased risk of adverse events, symptom development, or mortality [2, 11, 13, 15, 28, 46, 60, 71, 100, 134, 145, 149, 190, 191, 198, 201, 203, 210, 213, 217, 232, 240, 242, 243, 253]. Pericarotid fat density (PFD) and perivascular adipose tissue (PVAT) signal intensity are emerging imaging biomarkers for vulnerable plaques and symptomatic disease [29, 82, 95, 97, 109, 117, 149, 196, 208].

- **Advanced Imaging for Inflammation:** 18F-FDG PET/CT and PET/MR are widely used to quantify plaque inflammation (SUVmax, TBR) [6, 7, 12, 40, 47, 61, 63, 69, 70, 76, 77, 101, 103, 120, 122, 123, 156, 174, 213, 231, 232]. Other modalities include contrast-enhanced ultrasound (CEUS) and Superb Microvascular Imaging (SMI) for detecting intraplaque neovascularization and inflammation [64, 65, 143, 216, 225], USPIO-enhanced MRI for assessing inflammation and vascularity [118], and microwave radiometry (MWR) as a promising alternative for inflammation assessment [99, 210].
- **Therapeutic Interventions and Modulators:** Various interventions have shown potential in modulating inflammation and improving outcomes. Statins reduce inflammation and stabilize plaques [73, 106, 133, 239]. Metformin attenuates inflammation and neointimal hyperplasia in diabetic and insulin-resistant models [49, 51, 254]. Novel agents like quercetin [102], honokiol [194], and leonurine [130] have demonstrated anti-inflammatory and plaque-stabilizing effects in animal models. Targeted therapies, including anti-inflammatory nanoparticles [162, 173, 250], NLRP3 inflammasome inhibitors [148, 152, 155], and glucocorticoids [22, 241, 291], are being explored to reduce inflammation and stabilize plaques. Dexmedetomidine improved cognitive recovery post-CEA by reducing cerebral inflammation [66].
- **Comorbidities and Associated Factors:** Several systemic conditions exacerbate carotid stenosis and inflammation. Type 2 diabetes mellitus (T2DM) is associated with higher systemic inflammation, altered lipid profiles, and increased plaque inflammation and embolization risk [32, 45, 49, 51, 126, 139, 140, 141, 195, 200, 214, 233, 236, 279]. Smoking [2] and hypertension [11, 107, 133] are linked to increased inflammation. Rheumatoid arthritis (RA) patients show a higher prevalence of carotid plaque and progressive atherosclerosis with elevated proinflammatory cytokines [195, 230, 266, 299]. Chronic cerebral hypoperfusion induced by bilateral carotid artery stenosis (BCAS) in animal models consistently leads to increased inflammation, glial activation, blood-brain barrier disruption, and cognitive impairment [26, 105, 112, 116, 151, 152, 155, 157, 160, 161, 171, 176, 192, 246, 260, 277]. Genetic variants related to endothelial function and inflammation also increase the risk of carotid atherosclerosis [5, 39, 114, 128, 189, 293].

5) Discussion

5.1 Principal finding

The SCAIL score, a composite metric incorporating carotid plaque inflammation and stenosis severity, is a significant predictor of recurrent stroke and other adverse cardiovascular events, with a median adjusted hazard ratio of 2.4 (range 1.96-4.52) [3, 19, 54, 55].

5.2 Clinical implications

- **Enhanced Risk Stratification:** Integrating plaque inflammation markers (e.g., 18F-FDG PET/CT SUVmax, SCAIL score, PIV, SII, NLR, MHR, CRP, PFD) into clinical assessment can improve the identification of patients at high risk for stroke and other adverse events, even in cases of uncertain benefit from revascularization [3, 6, 7, 19, 21, 54, 55, 61, 70, 82, 95, 149].
- **Personalized Monitoring:** Regular monitoring of systemic inflammatory biomarkers and plaque characteristics via advanced imaging could guide individualized management strategies, including the timing and type of intervention (e.g., medical therapy intensification vs. revascularization) [6, 7, 12, 40, 47, 55, 61, 69, 70, 77, 101, 103, 120, 123, 156, 213, 231].
- **Therapeutic Targets:** The consistent association between inflammation and carotid stenosis progression and instability highlights inflammation as a crucial therapeutic target. Existing therapies like statins and metformin, and emerging agents such as anti-inflammatory nanoparticles, NLRP3 inhibitors, and specific natural compounds, could be leveraged to stabilize plaques and prevent adverse outcomes [49, 66, 73, 93, 102, 106, 130, 133, 148, 150, 152, 155, 162, 171, 173, 176, 182, 185, 194, 220, 221, 239, 241, 245, 250, 252, 254, 291, 295, 297].
- **Comorbidity Management:** Aggressive management of comorbidities like diabetes, rheumatoid arthritis, and other systemic inflammatory conditions is paramount, as these significantly contribute to carotid atherosclerosis and plaque vulnerability [32, 45, 49, 51, 126, 139, 140, 141, 195, 230, 233, 236, 266, 299].

5.3 Research implications / key gaps

- **Standardized Biomarker Validation:** Future research should focus on validating and standardizing panels of inflammatory biomarkers, including their optimal thresholds and temporal dynamics, for consistent clinical application in risk prediction and therapeutic monitoring across diverse populations [11, 13, 15, 16, 17, 21, 28, 46, 60, 71, 100, 134, 149, 198, 199, 201, 240, 243, 253].
- **Longitudinal Intervention Trials:** There is a need for large-scale, prospective randomized controlled trials to evaluate the long-term impact of targeted anti-inflammatory therapies on clinical outcomes in patients with carotid stenosis, particularly in reducing stroke recurrence and MACE [93, 102, 106, 130, 133, 148, 150, 152, 155, 162, 171, 173, 176, 182, 185, 194, 220, 221, 239, 241, 245, 250, 252, 254, 291, 295, 297].
- **Mechanistic Pathway Elucidation:** Further investigation into specific inflammatory pathways (e.g., NLRP3 inflammasome, macrophage phenotypes, specific cytokines and chemokines) and their precise roles in plaque destabilization and cognitive impairment is

warranted to identify novel therapeutic targets [22, 72, 74, 96, 102, 105, 112, 115, 116, 136, 148, 151, 152, 153, 160, 161, 162, 164, 171, 172, 173, 175, 179, 182, 183, 192, 194, 211, 212, 221, 234, 245, 250, 251, 252, 256, 260, 272, 274, 276, 277, 281, 287].

- **Advanced Imaging Accessibility:** Research should focus on developing more accessible, cost-effective, and widely available non-invasive imaging techniques for quantifying plaque inflammation and vulnerability, potentially integrating AI-driven analysis of conventional imaging [6, 7, 12, 40, 47, 61, 63, 64, 65, 69, 70, 76, 77, 78, 80, 82, 95, 97, 99, 101, 103, 109, 118, 120, 121, 122, 123, 137, 143, 149, 154, 156, 174, 208, 213, 216, 223, 225, 231, 232].
- **Multi-Omics and Personalized Medicine:** Future studies should leverage multi-omics data integration (genomics, proteomics, metabolomics) with clinical and imaging data to identify complex molecular signatures associated with carotid plaque instability and symptomatology, paving the way for personalized medicine approaches [5, 21, 39, 81, 110, 114, 128, 184, 189, 218, 224, 235, 238, 243, 247, 251, 256, 281].

5.4 Limitations

- **Heterogeneity of Study Designs** — The diverse range of study designs, from experimental animal models to retrospective human cohorts, limits direct comparability and generalizability of findings.
- **Variability in Inflammatory Markers** — A wide array of inflammatory markers were investigated, often with different methodologies and thresholds, making it challenging to synthesize a unified understanding of inflammation's role.
- **Lack of Standardized Outcomes** — While many studies focused on stroke recurrence or MACE, the definitions and follow-up durations varied, hindering meta-analytic aggregation of outcomes.
- **Limited Causal Inference** — A significant portion of the evidence is observational, making it difficult to establish definitive cause-and-effect relationships between specific inflammatory processes and carotid stenosis outcomes.
- **Focus on Symptomatic Disease** — Many studies preferentially investigated symptomatic carotid stenosis, potentially limiting the understanding of inflammatory processes in asymptomatic, yet vulnerable, plaques.

5.5 Future directions

- **Standardized Biomarker Panels** — Develop and validate consistent panels of inflammatory biomarkers.
- **Longitudinal Intervention Trials** — Conduct trials on anti-inflammatory therapies for carotid stenosis.
- **Advanced Imaging Validation** — Validate accessible imaging techniques for plaque inflammation.
- **Multi-Omics Integration** — Integrate diverse biological data for risk prediction.
- **Targeted Anti-Inflammatory Therapies** — Investigate novel anti-inflammatory drug candidates.

6) Conclusion

The SCAIL score, a composite metric incorporating carotid plaque inflammation and stenosis severity, is a significant predictor of recurrent stroke and other adverse cardiovascular events, with a median adjusted hazard ratio of 2.4 (range 1.96-4.52) [3, 19, 54, 55]. These findings underscore the critical role of inflammation in the pathophysiology and clinical course of carotid stenosis across diverse patient populations. However, the heterogeneity of study designs and variability in inflammatory markers represent the most significant limitation affecting the certainty of these conclusions. A concrete next step for research involves conducting longitudinal intervention trials to evaluate the long-term impact of targeted anti-inflammatory therapies on clinical outcomes in patients with carotid stenosis.

References

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Figure 1. Publication-year distribution of included originals

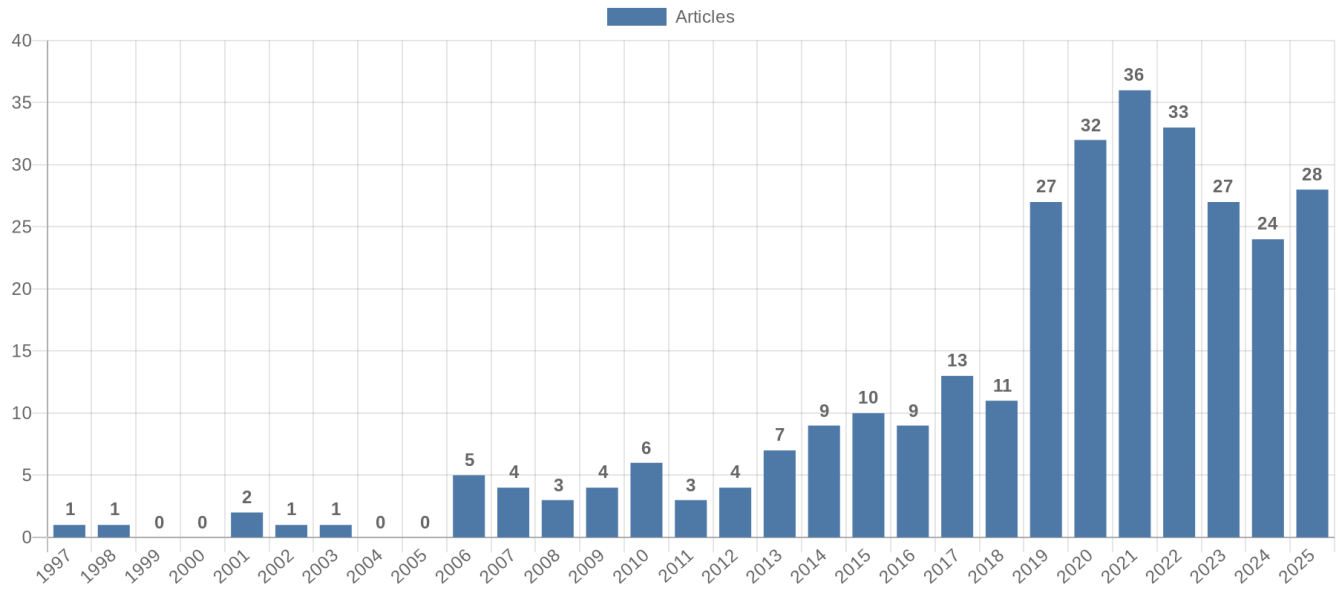

Figure 2. Study-design distribution of included originals

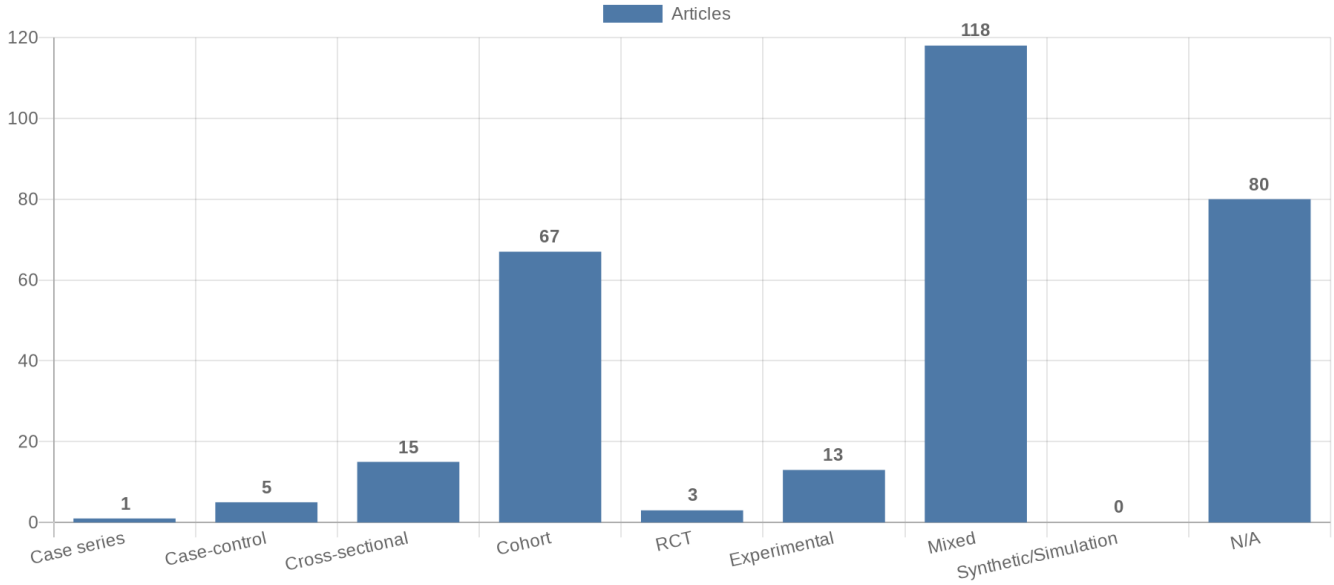

Figure 3. Study-type (directionality) distribution of included originals

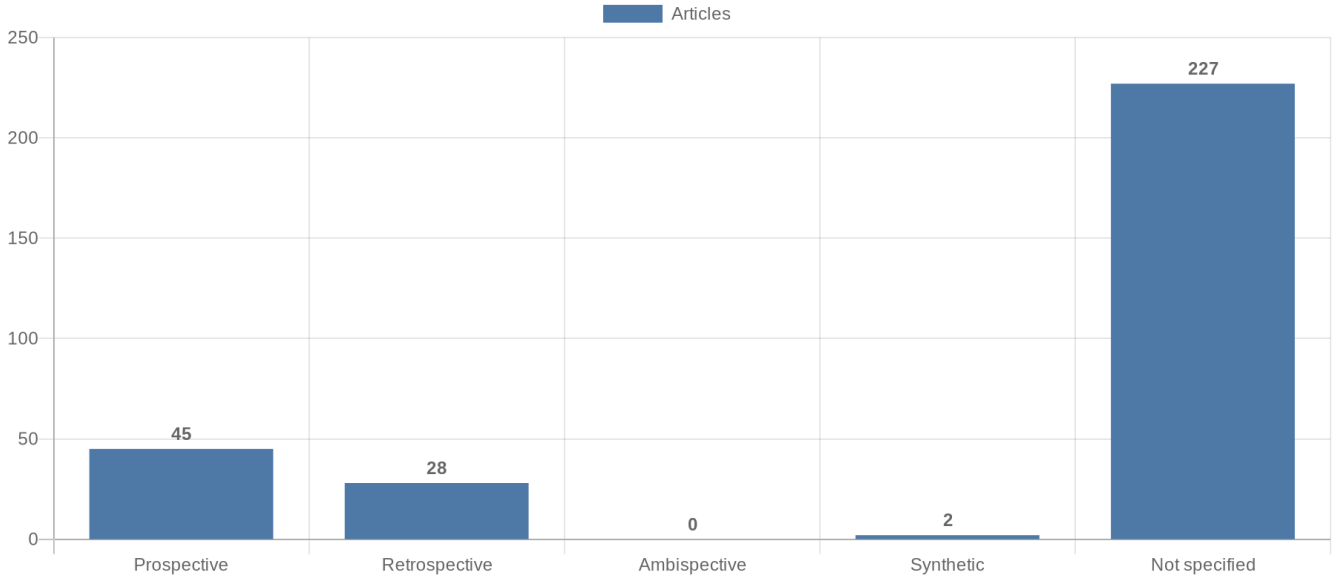

Figure 4. Main extracted research topics

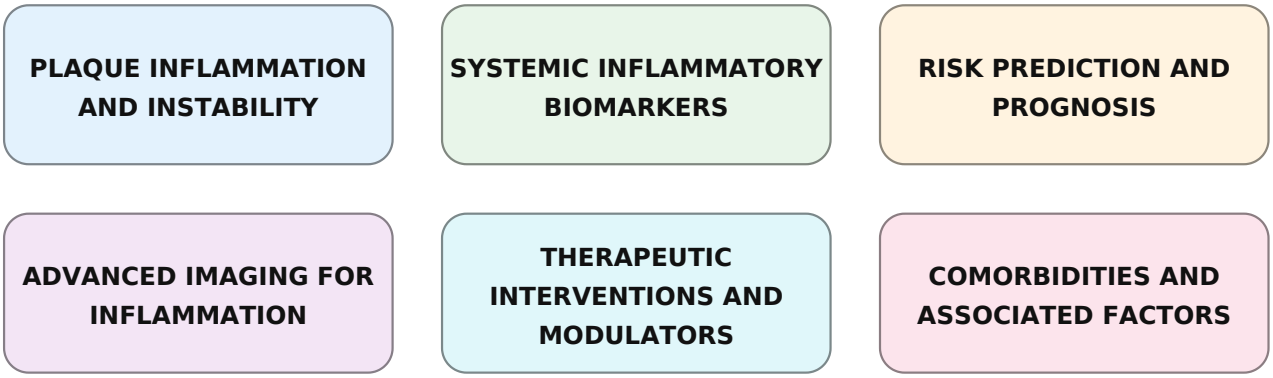

Figure 5. Limitations of current studies (topics)

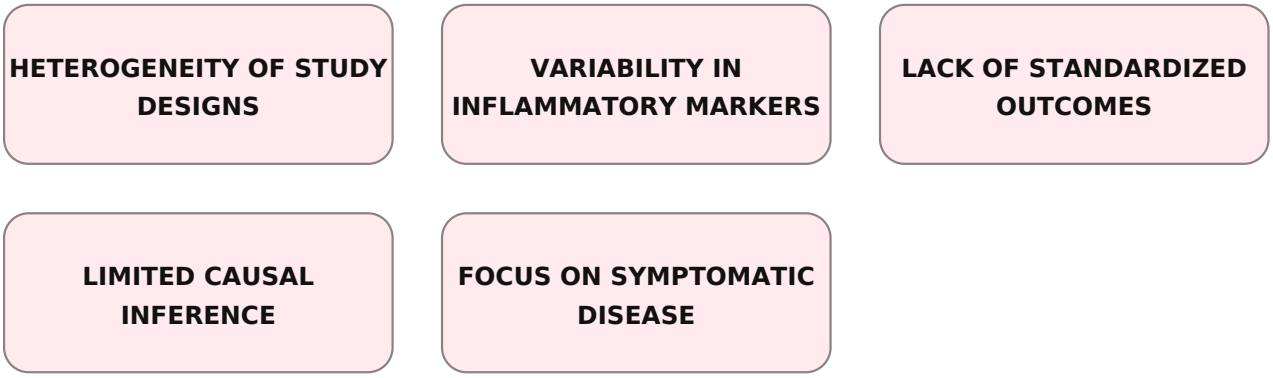

Figure 6. Future research directions (topics)