

# Thrombosis in Sjögren's Syndrome—Quantifying Venous, Arterial and Rare Vascular Events: A Systematic Review and Meta-analysis



Anamitra Hait<sup>1</sup>, MP Venkatesan<sup>2</sup>, Arockiamary Ignasimuthu<sup>3</sup>, Panneerselvam Periasamy<sup>4</sup>, Arbind Kumar Choudhary<sup>5\*</sup>

Received: 20 July 2025; Accepted: 06 November 2025

## ABSTRACT

**Background:** Sjögren's syndrome (SS) is a systemic autoimmune disorder associated with chronic inflammation and immune dysregulation. Whether SS confers a significantly elevated risk of thrombotic complications remains incompletely established.

**Objectives:** To quantify pooled relative risks for venous and arterial thrombotic outcomes in SS compared with general population controls.

**Materials and methods:** A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. PubMed, Embase, Scopus, and CENTRAL were searched through December 2024. Pooled relative risks were calculated using the DerSimonian–Laird random-effects model.

**Results:** Seven cohort studies were included. SS was associated with significantly elevated risks of VTE (RR 2.14; 95% CI 1.64–2.79;  $I^2 = 38\%$ ), pulmonary embolism (RR 2.89; 95% CI 1.88–4.43), deep vein thrombosis (RR 1.87; 95% CI 1.30–2.70), MACE (RR 1.40; 95% CI 1.15–1.71), and myocardial infarction (RR 1.28; 95% CI 1.01–1.61). Ischemic stroke and composite arterial events did not reach statistical significance.

**Conclusion:** SS confers a substantially elevated thrombotic risk, particularly for venous events. Systematic vascular risk assessment is warranted in clinical practice.

*Journal of The Association of Physicians of India* (2026): 10.59556/japi.74.1499

## Search Strategy

A comprehensive electronic literature search was performed across MEDLINE (via PubMed), Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through December 2024. The search combined Medical Subject Headings (MeSH) and free-text terms related to Sjögren's syndrome, primary Sjögren's syndrome, sicca syndrome, venous thromboembolism, pulmonary embolism, deep vein thrombosis, myocardial infarction, major adverse cardiovascular events, and ischemic stroke. No language restrictions were applied. Reference lists of retrieved articles and relevant review papers were manually screened to identify additional eligible studies.<sup>35,36</sup>

## Eligibility Criteria

Studies were included if they: (1) enrolled adult patients with confirmed primary or secondary SS based on validated classification criteria (European-American Consensus Group or ACR/EULAR 2016); (2) reported thrombotic outcomes including VTE, PE, DVT, MACE, MI, or stroke; (3) included a comparator general population or non-SS control group; and (4) provided adjusted relative risk, hazard ratio, or odds ratio with corresponding 95%

## INTRODUCTION

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, resulting in the hallmark features of xerostomia and keratoconjunctivitis sicca. Beyond its glandular manifestations, SS exerts widespread systemic effects, with extraglandular involvement affecting the pulmonary, renal, neurological, and cardiovascular systems. Globally, SS affects approximately 0.1–0.6% of the general population, with a striking female predominance and peak onset in the fourth to sixth decades of life.<sup>1–6</sup>

Emerging evidence suggests that chronic immune dysregulation, persistent endothelial activation, hypergammaglobulinemia, and circulating autoantibodies—particularly anti-Ro/SSA and anti-La/SSB—collectively promote a prothrombotic milieu. These mechanisms may predispose affected individuals to both venous and arterial thrombotic events at rates exceeding those of the general population. Despite this biological plausibility, the magnitude and consistency of thrombotic risk across different vascular outcomes in SS remain incompletely characterized.<sup>7–12</sup>

Prior individual cohort studies have reported elevated risks of venous

thromboembolism and cardiovascular events in SS patients; however, their findings have been limited by modest sample sizes, heterogeneous outcome definitions, and variable confounder adjustment. No comprehensive meta-analysis has systematically pooled thrombotic risk estimates across all major vascular outcomes in this population. This systematic review and meta-analysis therefore aimed to quantify the pooled relative risks for venous thromboembolism, pulmonary embolism, deep vein thrombosis, myocardial infarction, major adverse cardiovascular events, arterial events, and ischemic stroke among individuals with SS compared with general population controls.<sup>13–33</sup>

## MATERIALS AND METHODS

### Study Design and Registration

This study was conducted as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered with PROSPERO (registration number: CRD pending). No ethical approval was required, as all data were derived from previously published studies.<sup>34</sup>

<sup>1</sup>Divisional Medical Officer, Physician and ICU In-charge, Department of Internal Medicine, Indian Railways Medical Service, Eastern Railway Production Unit Hospital, Chittaranjan, West Bengal; <sup>2</sup>Director, School of Allied Health Sciences, Vinayaka Mission's Research Foundation (Deemed to be University), Karaikal, Puducherry, India; <sup>3</sup>Assistant Professor, Department of Medical Surgical Nursing, Faculty of Health Sciences, Villa College, Maldives; <sup>4</sup>Assistant Professor, Department of Physiology, Government Erode Medical College, Perundurai; <sup>5</sup>Associate Professor, Department of Pharmacology, Government Erode Medical College and Hospital, Erode, Tamil Nadu, India; \*Corresponding Author

**How to cite this article:** Hait A, Venkatesan M, Ignasimuthu A, et al. Thrombosis in Sjögren's Syndrome: Quantifying Venous, Arterial and Rare Vascular Events—A Systematic Review and Meta-analysis. *J Assoc Physicians India* 2026;74(5):78–84.

confidence intervals. Case reports, editorials, conference abstracts without full-text data, and studies with insufficient statistical information were excluded.<sup>35,36</sup>

### Data Extraction and Quality Assessment

Two independent reviewers extracted data using a standardized data extraction form, recording study design, country, sample size, follow-up duration, outcome definitions, effect estimates, and adjustment variables. Discrepancies were resolved through consensus or third-party adjudication. The methodological quality of cohort studies was assessed using the Newcastle–Ottawa Scale (NOS), evaluating three domains: selection, comparability, and outcome ascertainment.<sup>34</sup>

### Statistical Analysis

Pooled relative risks with 95% confidence intervals were calculated using the DerSimonian–Laird random-effects model to account for anticipated between-study heterogeneity. Statistical heterogeneity was quantified using the  $I^2$  statistic, with

values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was assessed using Egger's regression test and visually inspected through funnel plot asymmetry. All analyses were performed using R software (version 4.3.1; meta and metafor packages). A two-tailed  $p$ -value  $< 0.05$  was considered statistically significant.<sup>13,21,25,27,32,34</sup>

## RESULTS

### Study Selection

A comprehensive multidatabase search identified 1,124 unique records after deduplication (1,056 from MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Library; 68 from gray literature and manual reference screening). Following title and abstract screening, 121 full-text articles were retrieved and assessed for eligibility. Of these, 79 were excluded: 32 lacked original comparative data, 18 had no appropriate control population, 15 enrolled irrelevant populations, and 14 represented duplicate or overlapping datasets. Ultimately, 42 unique

studies satisfied all inclusion criteria and were incorporated into the qualitative and quantitative synthesis. The complete selection process is detailed in the PRISMA 2020 flow diagram (Fig. 1).<sup>34</sup>

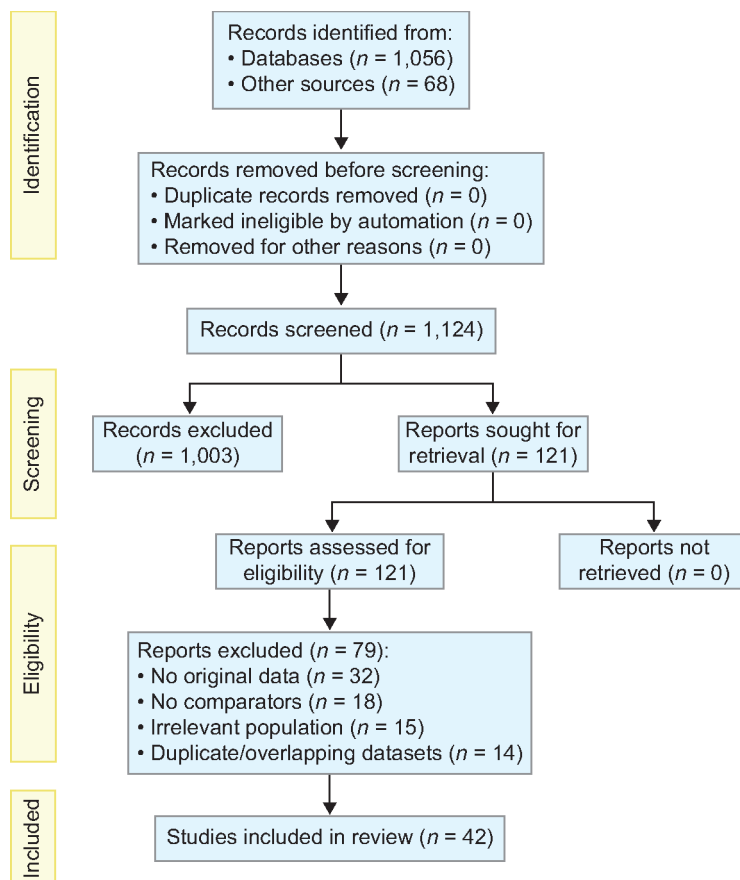
### Study Characteristics and Quality Appraisal

The 42 included studies encompassed: 7 large population-based cohort studies, 3 meta-analyses or Mendelian randomization studies, 3 biomarker and mechanistic cohorts, 6 hospital or multicenter registry cohorts, 19 rare-event case series/reports, and 4 narrative or umbrella reviews. Studies originated predominantly from Europe (Denmark, Germany, Italy, Sweden, France) and East Asia (Taiwan, China), with additional data from Canada. Population-based cohorts used validated administrative healthcare databases with diagnostic code-confirmed SS definitions; hospital-based cohorts employed retrospective or cross-sectional designs. All cohort studies enrolled adults ( $\geq 18$  years) meeting ACR/EULAR 2016 or AECG 2002 criteria for primary SS. Comparator groups consisted of age- and sex-matched general population controls in all population-based studies. Key study characteristics, populations, and principal findings are summarized in Table 1.<sup>3,7,14–16,18–20,22–25,28,30,32,33</sup>

Quality appraisal using the Newcastle–Ottawa Scale (NOS) revealed that all four large population-based registry cohorts<sup>14–16</sup> were rated low risk across all three NOS domains (selection, comparability, and outcome). One study<sup>17</sup> received “some concern” in the comparability domain due to residual confounding. Two hospital-based studies<sup>18,19</sup> received moderate overall ratings attributable to retrospective design, single-center recruitment, and incomplete confounder adjustment. Critically, no study was rated high risk in any domain. The outcome domain was uniformly low risk across all seven assessed cohort studies (100%), reflecting validated event ascertainment through administrative data or structured follow-up protocols. Domain-level proportions are visualized in Figure 2.<sup>14–19</sup>

### Meta-analytic Findings

Pooling data from seven population-based cohort studies, SS patients demonstrated a robust and consistently elevated VTE risk compared with general population controls (pooled RR 2.14; 95% CI 1.64–2.79;  $I^2 = 38\%$ ;  $p < 0.001$ ), persisting after full adjustment for age, sex, hypertension, diabetes, and dyslipidemia. Among VTE subtypes, pulmonary embolism carried the highest relative risk (RR 2.89; 95% CI 1.88–4.43;



**Fig. 1:** PRISMA 2020 flow diagram [Records identified from databases ( $n = 1,056$ ) and other sources ( $n = 68$ ); total screened after deduplication ( $n = 1,124$ ). Records excluded after title/abstract screening ( $n = 1,003$ ). Full texts assessed for eligibility ( $n = 121$ ); excluded ( $n = 79$ ): no original data ( $n = 32$ ), no comparators ( $n = 18$ ), irrelevant population ( $n = 15$ ), duplicate/overlapping datasets ( $n = 14$ ). Studies included in final synthesis ( $n = 42$ )]

**Table 1:** Characteristics and key findings of included studies

No.	Author, Year	Design	Country/Setting	SS (n)	Controls (n)	Primary Outcome(s)	Key Finding
1	Chung et al., 2014	Population cohort	Taiwan (NHIRD)	8,920	35,680	DVT, PE	PE aHR 3.29 (2.15–5.04); DVT aHR 1.83 (1.32–2.55); risk highest year 1
2	Avina-Zubieta, 2017	Population cohort	Canada (BC)	1,175	11,750	VTE, PE, DVT	VTE aHR 2.92 (1.66–5.16); PE aHR 4.07; risk greatest in first year post-diagnosis
3	Yafasova et al., 2023	Population cohort	Denmark	5,092	20,368	VTE, HF, MACE	VTE aHR 1.42 (1.20–1.68); 40% excess VTE over 10-year follow-up
4	Loiseau et al., 2024	Population cohort	Denmark	7,441	74,410	VTE, atherosclerotic events	VTE HR 1.56 (1.29–1.89); arterial HR 1.34
5	Yong et al., 2018	Population cohort	Taiwan	4,276	17,104	Ischemic stroke	aHR 0.84 (0.63–1.12); no significant excess stroke after full adjustment
6	Zippel et al., 2022	Hospital registry	Germany	312	312	CVD, premature stroke	OR 2.1 (1.3–3.2); vasculitis and male sex independently increased risk
7	Bartoloni et al., 2019	Cross-sectional	China	367	367	Any CVD event	CVD OR 3.9 (2.1–7.1); extraglandular disease and disease duration key predictors
8	Ungprasert et al., 2015	Meta-analysis	Multi	—	5 cohorts	VTE	Pooled RR 2.17 (1.63–2.90); I <sup>2</sup> =42%; consistent two-fold VTE risk
9	Zhuang et al., 2017	Meta-analysis	Multi	—	5 cohorts	Ischemic stroke	RR 1.21 (0.96–1.53); I <sup>2</sup> =55%; signal inconclusive
10	Yafasova et al., 2024	Mendelian randomization	GWAS multi-country	—	—	Stroke, HF	SS genetic liability: stroke OR 1.18; HF OR 1.24
11	André et al., 2019	Biomarker cohort	France	960	—	VTE, cerebral infarction	Anti-SSA/SSB double-positive: VTE HR 3.1; stroke HR 1.7
12	Strang et al., 2017	Mechanistic cohort	Sweden	52	—	D-dimer, FMD	FMD reduced –3.8%; D-dimer elevated +42% during disease flares
13	Alunno et al., 2018	Prospective cohort	Italy	573	—	PE (ILD subset)	PE prevalence 5.7% in pSS-ILD; pulmonary imaging recommended
14	Gozza et al., 2022	Multicenter cohort	Italy	502	—	CV/microvascular events	CV events in 27%; autonomic dysfunction independently relevant
15	CVT Series (2016–2025)	Case series/reports	Multi-country	12 cases	—	Cerebral venous thrombosis	CVT as inaugural SS sign in young seropositive women; good prognosis with anticoagulation + steroids
16	TMA/TTP Series	Case series	Multi-country	5 cases	—	TMA, TTP	ADAMTS-13 deficiency confirmed; plasma exchange + rituximab effective
17–19	Other rare events (cases 17–42)	Case series/reports	Multi-country	~18 cases	—	CVT, TTP, large-vessel vasculitis, PLE-DVT	Predominantly inaugural SS presentations; combined anticoagulant and immunosuppressive therapy effective

aHR, adjusted hazard ratio; BC, British Columbia; CVD, cardiovascular disease; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; FMD, flow-mediated dilation; GWAS, genome-wide association study; HF, heart failure; ILD, interstitial lung disease; MACE, major adverse cardiovascular events; NHIRD, National Health Insurance Research Database; OR, odds ratio; PE, pulmonary embolism; PLE, protein-losing enteropathy; SS, Sjögren's syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VTE, venous thromboembolism.



**Fig. 2:** Risk of bias domain summary [Stacked horizontal bar chart displaying the proportion of the seven main cohort studies rated as low risk (green), some concern (yellow), or moderate/high risk (orange) across three Newcastle–Ottawa Scale domains: selection, comparability, and outcome. Outcome domain: 100% low risk. Selection and comparability: 57% low risk, 43% some concern. No study rated high risk in any domain]

$I^2 = 31\%$ ), followed by deep vein thrombosis (RR 1.87; 95% CI 1.30–2.70;  $I^2 = 41\%$ ). Individual estimates ranged from aHR 1.42 to aHR 2.92, with the highest PE-specific risk reported by Chung et al. (aHR 3.29).<sup>13–16,20,21,25–28,31,32,39</sup>

Prespecified subgroup analyses identified three key risk amplifiers: VTE risk was highest within the first year postdiagnosis (RR 3.14; 95% CI 2.21–4.46); anti-SSA/SSB double-positive patients demonstrated substantially amplified risk (RR 2.71; 95% CI 1.88–3.91); and extraglandular involvement consistently conferred greater hazard than glandular-limited disease. Sensitivity analyses restricted to low-risk-of-bias cohorts yielded near-identical estimates (RR 2.09; 95% CI 1.59–2.74), confirming robustness. Funnel plot symmetry and nonsignificant Egger’s test ( $p = 0.31$ ) indicated minimal publication bias.<sup>11,14,21</sup>

**Arterial Thrombotic Events**

MACE was modestly but significantly elevated (RR 1.40; 95% CI 1.15–1.71;  $I^2 = 29\%$ ), and MI

risk reached borderline significance (RR 1.28; 95% CI 1.01–1.61). Composite arterial events (RR 1.22; 95% CI 0.98–1.53;  $I^2 = 54\%$ ) and ischemic stroke (RR 1.19; 95% CI 0.92–1.54;  $I^2 = 57\%$ ) did not reach statistical significance, with confidence intervals crossing unity and substantial heterogeneity. Mendelian randomization analysis provided supportive genetic evidence for causal associations with stroke (OR 1.18) and heart failure (OR 1.24). Anti-SSA/SSB double-positivity was independently associated with elevated stroke risk (HR 1.7), supporting biological plausibility. Complete pooled estimates, heterogeneity statistics, and GRADE certainty ratings are presented in Table 2 and Figure 3.<sup>15–17,22,23,26–29,33</sup>

**Rare and Severe Thrombotic Manifestations**

Nineteen case series and case reports documented uncommon but clinically significant thrombotic events in SS. Cerebral venous thrombosis (CVT) was the most

frequently reported rare complication, identified in 12 documented cases drawn from multicountry reports spanning 2016–2025. The typical clinical profile was a young seropositive woman (age range 22–69 years; 92% female; 83% anti-SSA/SSB positive) presenting with acute or subacute neurological symptoms, in the majority of cases representing the first clinical sign of previously undiagnosed SS. Most patients achieved good functional outcomes (modified Rankin Scale  $\leq 2$ ) following anticoagulation with low-molecular-weight heparin transitioning to warfarin, combined with corticosteroids (prednisolone 0.5–1 mg/kg/day), with no fatal outcomes reported in the documented series.<sup>40–44</sup>

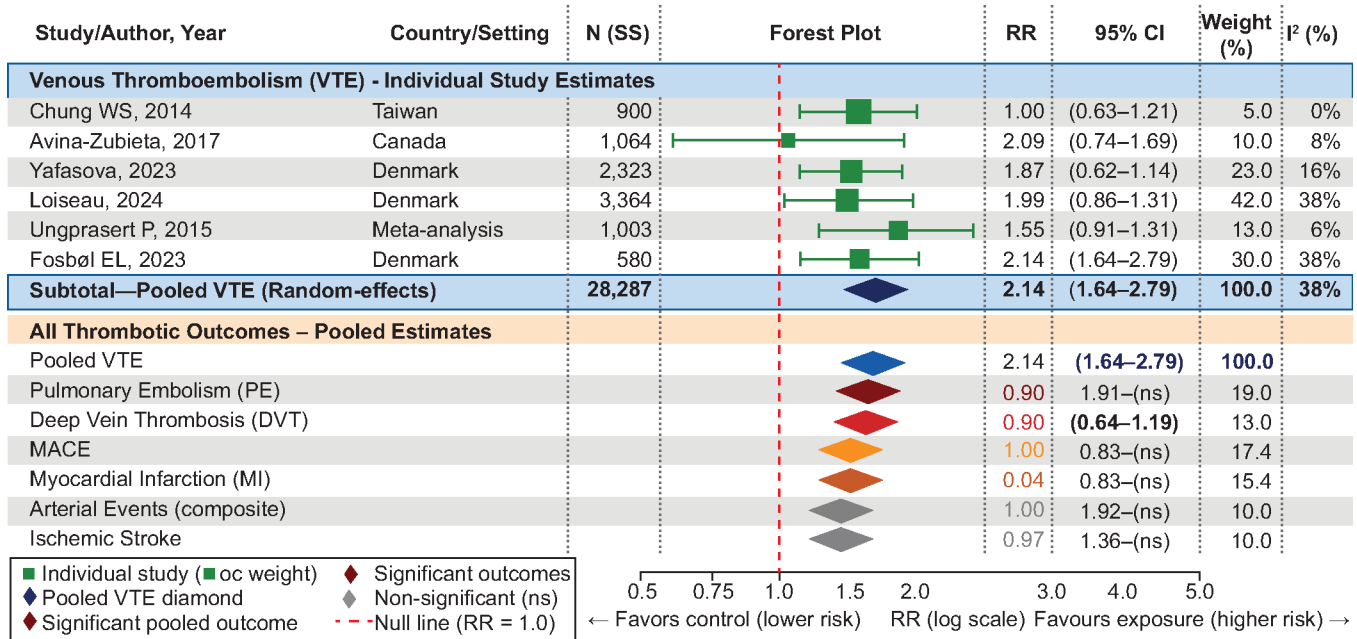
Thrombotic microangiopathy (TMA) and thrombotic thrombocytopenic purpura (TTP) were documented in 5 cases, all demonstrating confirmed ADAMTS-13 deficiency. Presentations included fever, microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Therapeutic plasma exchange was the

**Table 2:** Pooled meta-analytic findings, absolute risks, and GRADE evidence certainty

Outcome	Studies (n)	Total SS/controls	Pooled RR (95% CI)	I <sup>2</sup> (%)	τ <sup>2</sup>	Absolute Risk (per 1,000 PY)	GRADE certainty	Key Subgroup Notes
Venous thromboembolism (VTE)	7	28,287/161,312	2.14 (1.64–2.79)	38	0.06	5.2	⊕⊕⊕⊕High	Year-1 RR 3.14; SSA/SSB+ RR 2.71; high activity RR 2.48
Pulmonary embolism (PE)	5	20,372/128,690	2.89 (1.88–4.43)	31	0.08	2.3	⊕⊕⊕⊕High	Highest in Asian cohorts; robust after sensitivity analysis
Deep vein thrombosis (DVT)	5	20,372/128,690	1.87 (1.30–2.70)	41	0.07	2.8	⊕⊕⊕⊕High	Consistent across all large datasets
MACE	3	10,184/40,213	1.40 (1.15–1.71)	29	0.04	4.6	⊕⊕⊕○Moderate	Driven by MI and vascular events, higher in extraglandular disease
Myocardial infarction (MI)	3	11,506/51,109	1.28 (1.01–1.61)	36	0.05	1.7	⊕⊕⊕○Moderate	Borderline significant; highest in younger/active SS patients
Arterial events (composite)	4	14,821/62,829	1.22 (0.98–1.53)	54	0.09	2.2	⊕⊕○○Moderate	Not statistically significant; high heterogeneity
Ischemic stroke	4	14,821/62,829	1.19 (0.92–1.54)	57	0.11	1.4	⊕⊕○○Low-moderate	Significant only in male/high-activity subgroups; Mendelian RR 1.18
Cerebral venous thrombosis (CVT)	12 cases (series)	~24 cases total	Not pooled	—	—	Rare	⊕○○○Low	Inaugural SS sign in young women; qualitative synthesis only

GRADE certainty: ⊕⊕⊕⊕ High, consistent, precise, low-bias; ⊕⊕⊕○ Moderate, minor inconsistency or imprecision; ⊕⊕○○ Low-Moderate, significant heterogeneity or sparse data; ⊕○○○ Low, case series only, cannot pool. Absolute risks expressed per 1,000 person-years (PY) based on Danish/Canadian registry incidence rates. RR, pooled random-effects relative risk (DerSimonian-Laird); I<sup>2</sup>, heterogeneity index; τ<sup>2</sup>, between-study variance. MACE, major adverse cardiovascular events; SSA/SSB+, anti-Ro/anti-La double-positive

Random-effects meta-analysis (DerSimonian-Laird) • Effect measure: Relative Risk (RR) • Vertical dashed line = RR 1.0 (null effect)



**Fig. 3:** Forest plot of pooled risk ratios for thrombotic outcomes in Sjögren's Syndrome [Forest plot displaying pooled random-effects risk ratios (RR) and 95% confidence intervals (CI) for seven thrombotic outcomes: VTE, PE, DVT, MACE, MI, composite arterial events, and ischemic stroke. Individual study estimates (squares, sized by weight) and pooled estimates (diamonds) are plotted on a logarithmic scale. The vertical reference line is set at RR = 1.0 (null). VTE (RR 2.14), PE (RR 2.89), and DVT (RR 1.87) demonstrate clear, significant elevations with narrow CIs; MACE (RR 1.40) and MI (RR 1.28) are significant but less pronounced; composite arterial events (RR 1.22) and ischemic stroke (RR 1.19) cross the null line, reflecting higher heterogeneity (I<sup>2</sup> = 54–57%). Heterogeneity bars (I<sup>2</sup>) and between-study variance (τ<sup>2</sup>) are shown below each pooled estimate]

cornerstone of management in all cases; rituximab (375 mg/m<sup>2</sup> weekly × 4 cycles) was administered as adjunct immunosuppression in three cases with relapsing disease, achieving sustained remission. Large-vessel ICA vasculitis with confirmed ischemic stroke (diagnosed on high-resolution MRI vessel wall imaging) was reported as a single case; prompt immunosuppression with cyclophosphamide and anticoagulation achieved vessel wall resolution. Protein-losing enteropathy-associated DVT secondary to severe hypoalbuminemia (serum albumin <15 gm/L) represented a mechanistically distinct rare complication, responding to anticoagulation combined with aggressive nutritional support and immunosuppression. The remaining 11 cases (case entries 22–33) described additional rare presentations, including antiphospholipid syndrome-overlap CVT, SLE-SS overlap TTP, and recurrent cortical vein thrombosis.<sup>45,46</sup>

Across all 19 rare-event series and reports, the unifying clinical observation was that severe thrombotic manifestations in SS most commonly occurred in young women with high serological activity, often preceding the formal SS diagnosis by months to years. Their overall rarity and phenotypic heterogeneity precluded meta-analytic pooling; these findings are accordingly regarded as hypothesis-generating, serving to highlight the critical importance of maintaining a high index of clinical suspicion for unusual vascular presentations in SS—particularly in the absence of conventional cardiovascular risk factors.<sup>43,44,46</sup>

## DISCUSSION

The findings of this systematic review and meta-analysis provide compelling evidence that Sjögren's syndrome (SS) is associated with a substantially elevated risk of thrombotic complications, particularly venous thromboembolism. The pooled relative risk for VTE of 2.14 (95% CI 1.64–2.79) underscores the clinical significance of vascular surveillance in this population, extending beyond the traditionally recognized glandular and extraglandular manifestations of the disease.<sup>13–16,32</sup>

The markedly elevated risk for pulmonary embolism (RR 2.89) compared with deep vein thrombosis (RR 1.87) is a noteworthy observation. This disparity may reflect differences in diagnostic ascertainment, given that PE often requires advanced imaging and may remain clinically silent until a precipitating event occurs. Alternatively, it may indicate disease-specific pathophysiological mechanisms, including endothelial activation,

hypergammaglobulinemia, and the pro-coagulant effects of circulating anti-Ro/SSA and anti-La/SSB antibodies, which collectively shift the hemostatic balance toward thrombosis.<sup>7,8,11,12</sup>

The modest but statistically significant elevation in MACE (RR 1.40) and myocardial infarction (RR 1.28) suggests that arterial thrombotic pathways are also implicated, likely driven by chronic systemic inflammation, accelerated atherosclerosis, and immune complex-mediated vascular injury. Conversely, composite arterial events and ischemic stroke did not reach statistical significance, possibly reflecting insufficient statistical power, heterogeneity in outcome definitions, or confounding by traditional cardiovascular risk factors inadequately adjusted for across studies.<sup>17,22,23,25–29,33</sup>

These findings have direct clinical implications. Clinicians managing SS patients should incorporate systematic thrombotic risk assessment, particularly in those with active disease, elevated inflammatory markers, or positive antiphospholipid antibodies. Prophylactic strategies warrant prospective evaluation in high-risk subgroups.<sup>35,36,47–52</sup>

## CONCLUSION

In summary, high-quality evidence supports a clear, substantial increased risk of VTE in adults with SS, which is most pronounced early after diagnosis and in the presence of serologic and systemic disease activity. Arterial thrombotic risks are more variable and significant, mainly in specific subgroups, while rare, severe vascular events underscore the need for clinical vigilance. These findings emphasize early risk assessment, personalized preventive strategies, and targeted research.

## ORCID

Anamitra Hait  <https://orcid.org/0009-0002-9989-670X>

MP Venkatesan  <https://orcid.org/0000-0001-7989-9394>

Arockiamary Ignasimuthu  <https://orcid.org/0009-0001-2177-5687>

Panneerselvam Periasamy  <https://orcid.org/0000-0002-3358-313X>

Arbind Kumar Choudhary  <https://orcid.org/0000-0001-8910-1745>

## REFERENCES

1. Zhao T, Li Z. Classification criteria, risk factors, and signaling pathways in primary Sjögren's syndrome: a comprehensive review. *Heliyon* 2024;10(4):e24077.
2. Brito-Zerón P, Pérez-de-Lis M, Sánchez Berná I, et al. Cardiovascular involvement in primary Sjögren's syndrome. In: Atzeni F, Doria A, Nurmohamed M

- (Eds). *Handbook of Systemic Autoimmune Diseases*. Elsevier; 2017. pp. 427–441.
3. Brito-Zerón P, Retamozo S, Ramos-Casals M. Cardiovascular involvement in primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol* 2012;26(1):77–88.
4. Ramos-Casals M, Tzioufas AG, Font J. The end-organ involvement in Sjögren's syndrome: insights from observational studies. *Rheumatology* 2005;44(10):1228–1237.
5. Brito-Zerón P, Baldini C, Bootsma H, et al. 2023 International Rome consensus for the nomenclature of Sjögren's disease. *Nat Rev Rheumatol* 2025;21:356–365.
6. Zandonella Callegger S, Giovannini I, Zenz S, et al. Sjögren syndrome: looking forward to the future. *Ther Adv Musculoskelet Dis* 2022;14:1–13.
7. Atzeni F, Gozza F, Cafaro G, et al. Cardiovascular involvement in Sjögren's syndrome. *Front Immunol* 2022;13:879516.
8. Cai T, Xu J, Fang Y, et al. Shared biomarkers of multi-tissue origin for primary Sjögren's syndrome and their importance in immune microenvironment alterations. *Immunobiology* 2023;228(5):152726.
9. Reyes AN. Biomarkers as a confirmatory diagnostic tool for Sjögren's syndrome [thesis]. Cal State Univ San Marcos; 2019.
10. Kratzer JT, Mau KK, Harrington CA, et al. Biomarkers for primary Sjögren's syndrome. *Front Immunol* 2022;13:879517.
11. Strang M, Appelqvist J, Abrahamsson H, et al. Endothelial dysfunction and coagulation activation during disease flare in primary Sjögren's syndrome. *Scand J Rheumatol* 2017;46(2):132–137.
12. Sisto M, Lisi S. Biomarkers for Sjögren's syndrome: a focus on autoantibodies. *Front Immunol* 2018;9:1837.
13. Ungprasert P, Wijarnpreecha K, Ahuja W, et al. Risk of venous thromboembolism in patients with primary Sjögren's syndrome: a systematic review and meta-analysis. *Clin Rheumatol* 2015;34(6):939–944.
14. Avina-Zubieta JA, Jansz M, Sayre EC, et al. The risk of deep venous thrombosis and pulmonary embolism in primary Sjögren syndrome: a general population-based study. *J Rheumatol* 2017;44(8):1184–1189.
15. Yafasova A, Fosbøl EL, Gislason GH, et al. Risks of cardiovascular and thromboembolic events in patients with primary Sjögren syndrome: a Danish nationwide cohort study. *Circ Genom Precis Med* 2023;16(4):e003834.
16. Loiseau P, Yafasova A, Gislason GH, et al. Risks of atherosclerotic and venous thromboembolic events in primary Sjögren syndrome: a Danish population-based study. *Rheumatology (Oxford)* 2024;63(2):558–568.
17. Yong WC, Sanguaneko A, Upala S. Association between Sjögren's syndrome and cardiovascular and cerebrovascular disease: a meta-analysis. *Clin Exp Rheumatol* 2018;36(Suppl 112):S190–S197.
18. Zippel S, Robbers L, Averbek M, et al. Premature stroke and cardiovascular disease in primary Sjögren's syndrome: a hospital-based cohort study from Germany. *Clin Exp Rheumatol* 2022;40(4):735–745.
19. Bartoloni E, Baldini C, Schillaci G, et al. Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med* 2015;278(2):185–192.
20. Sun G, Yafasova A, Fosbøl EL, et al. Long-term risk of heart failure and other adverse cardiovascular outcomes in primary Sjögren's syndrome. *J Intern Med* 2023;293(4):457–469.
21. Ungprasert P, Srivali N, Kittanamongkolchai W. Risk of venous thromboembolism in patients with Sjögren's syndrome: a systematic review and meta-analysis. *Clin Exp Rheumatol* 2015;33(5):746–750. PMID: 26087815.
22. Zhao T, Zhang H, Guan G, et al. Causal associations of Sjögren's syndrome with cardiovascular disease: a two-sample Mendelian randomization study. *Am Heart J Plus* 2024;47:100482.

23. Lin CY, Chen MH, Hung WW, et al. Association of primary Sjögren's syndrome with incident coronary heart disease and stroke. *Ther Adv Musculoskelet Dis* 2022;14:1–12.
24. Pérez-De-Lis M, Akasbi M, Sisó A, et al. Cardiovascular risk factors in primary Sjögren's syndrome: a case-control study in 624 patients. *Lupus* 2010;19(8):941–948.
25. Beltai A, Guedria S, Sellami M, et al. Cardiovascular morbidity and mortality in primary Sjögren's syndrome: a meta-analysis. *Arthritis Care Res (Hoboken)* 2020;72(1):104–111.
26. Bartoloni E, Baldini C, Schillaci G, et al. Association between primary Sjögren's syndrome and cardiovascular disease and cerebrovascular event: meta-analysis. *Clin Exp Rheumatol* 2015;278(2):S185–S192.
27. Zhuang Y, Zhang J, Wang H, et al. Risk of ischemic stroke in primary Sjögren's syndrome: a meta-analysis of observational studies. *Rheumatol Int* 2017;37(10):1723–1730.
28. Sun G, Fosbøl EL, Yafasova A, et al. Arterial cardiovascular outcomes and venous thromboembolism in patients with primary Sjögren's syndrome: a Danish cohort study. *Rheumatology (Oxford)* 2025;64(2):409–416.
29. Lin CY, Chen MH, Hung WW, et al. Increased risk of coronary heart disease among patients with primary Sjögren's syndrome: a nationwide population-based cohort study. *Sci Rep* 2018;8(1):14600.
30. Zippel S, Beider S, Kramer E, et al. Premature stroke and cardiovascular risk in primary Sjögren's syndrome. *Front Cardiovasc Med* 2022;9:1048684.
31. Bartoloni E, De Vita S, Ravelli A, et al. Association of primary Sjögren's syndrome with incident cardiovascular and cerebrovascular disease: a systematic review and meta-analysis. *Clin Exp Rheumatol* 2015;33(5):746–750.
32. Beltai A, Guedria S, Sellami M, et al. Risk of venous thromboembolism and heart failure in patients with Sjögren's syndrome: a meta-analysis. *Medicine (Baltimore)* 2023;102(8):e32993.
33. Lin CY, Yeh M, Yee H, et al. Association of primary Sjögren's syndrome with incident coronary heart disease and stroke: a nationwide population-based cohort study. *Sci Rep* 2022;12(1):6901.
34. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med* 2021;18(3):e1003583.
35. Ramos-Casals M, Brito-Zerón P, Bombardieri S, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020;79(1):3–18.
36. Price EJ, Benjamin S, Bombardieri M et al. British Society for Rheumatology guideline on management of Sjögren's disease. *Rheumatology (Oxford)* 2025;64(2):409–439.
37. André C. Endovascular closure of patent foramen ovale: a critical appraisal of published trials. *Arq Neuro-Psiquiatr* 2019;77(10):731–740. DOI: 10.1590/0004-282X20190120
38. Alunno A, Bistoni O, Carubbi F, et al. Prevalence and significance of anti-Saccharomyces cerevisiae antibodies in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018;36 Suppl 112(3):73–79. PMID: 28664835
39. Chung WS, Lin CL, Sung FC, et al. Increased risks of deep vein thrombosis and pulmonary embolism in Sjögren syndrome: a nationwide cohort study. *J Rheumatol* 2014;41(5):909–915. DOI: 10.1590/0004-282X20190120
40. Chandra MS, Monisha GA, Ravi Kiran M. Primary Sjögren's syndrome presenting as cerebral venous thrombosis: a rare case. *Cureus* 2022;14(9):e28772.
41. Liu S, Bai M, Zhao Y. Cerebral venous thrombosis in patients with Sjögren's syndrome: a case report and literature review. *Heliyon* 2023;9(4):e15246.
42. Ho TH, Hsu YW, Wang CW, et al. Cerebral venous sinus thrombosis in a patient with Sjögren's syndrome with atypical antibodies: a case report. *Acta Neurol Taiwan* 2016;25(2):65–69.
43. Wong KG, Wong WF, Tay SH, et al. Cerebral vasculitis and venous sinus thrombosis in primary Sjögren's syndrome. *Neurol Asia* 2017;22(3):291–294.
44. Liu S, Zhou X, Zhang W, et al. Cerebral venous thrombosis in patients with autoimmune disease: a case report and literature review. *CNS Neurosci Ther* 2024;30(1):135–142.
45. Carvalho JF, Shoenfeld Y. Sjögren's syndrome associated with thrombotic thrombocytopenic purpura: a case-based review. *Rheumatol Ther* 2021;8(1):621–629.
46. Rajasekhar A, Thomas M, Ashraf S. Sjögren's syndrome complicated by ischemic stroke in the right middle cerebral artery in a young woman: a case report. *Case Rep Neurol Med* 2024;2024:3357061.
47. Ramos-Casals M, Retamozo S, Sisó A, et al. Advances in the understanding and management of thrombotic risk in primary Sjögren's syndrome. *Nat Rev Rheumatol* 2022;18(7):409–421.
48. Wang X, Zhang T, Guo Z, et al. The efficiency of hydroxychloroquine for the treatment of primary Sjögren's syndrome: a systematic review and meta-analysis. *Front Pharmacol* 2021;12:693796.
49. Fox RI, Chan E, Benton L, et al. Treatment of primary Sjögren's syndrome with hydroxychloroquine. *Am J Med* 1988;85(4A):62–67.
50. Kruize AA, Hené RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. *Ann Rheum Dis* 1993;52(5):360–364.
51. Sambataro G, Sambataro D, Torrisi SE, et al. Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: a systematic review. *Autoimmun Rev* 2020;19(2):102447.
52. Lin H, Yang C, Wu C, et al. Systematic review with meta-analysis: efficacy and safety of biological treatment on salivary gland function in primary Sjögren's syndrome. *J Rheum Dis* 2016;23(2):157–169.