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Original Article

Exploring the role of left atrial fibrosis and left atrial volume index through cardiac magnetic resonance imaging in embolic stroke of undetermined source: A network meta-analysis

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ABSTRACT

Objectives: Left atrial fibrosis (LAF) and left atrial volume index (LAVI), assessed via cardiac magnetic resonance (CMR), are emerging biomarkers for atrial cardiomyopathy and stroke risk. Their roles in the embolic stroke of undetermined source (ESUS) remain unclear. This study evaluates LAF and LAVI in ESUS and explores whether age modifies these outcomes.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO CRD42024615479), we searched eight databases (inception–October 2024) for studies evaluating LAF or LAVI via CMR in ESUS, compared to atrial fibrillation (AF) without stroke, cardioembolic stroke (CES), non-cardioembolic stroke (NCE), and healthy controls. We performed a Bayesian network meta-analysis to estimate mean differences (MD) with 95 % credible intervals (CrI). Node-splitting tested consistency, and a meta-regression examined the effect of age.

Results: Ten observational studies with 1285 patients (mean age 65.1 ± 12.1 years) were included, demonstrating a generally low risk of bias. ESUS patients had significantly higher LAF than healthy controls (MD 9.86 %, 95 % CrI 3.05 %–16.62 %). No significant LAF differences were found between ESUS and AF without stroke, CES, or NCE. LAVI did not differ significantly between ESUS and any comparator groups. Node-splitting indicated no inconsistencies. Age was not significantly associated with LAF or LAVI.

Conclusion: ESUS patients show increased LAF compared to healthy individuals, suggesting a key role of LAF in ESUS pathogenesis. Nonetheless, the application of CMR-detected LAF as a prognostic biomarker requires prospective validation to confirm its clinical utility in predicting stroke recurrence.

1. Introduction

Stroke remains a critical global health challenge, ranking as the second leading cause of mortality and a significant source of disability.[1] Each year, nearly 800,000 individuals experience a new or recurrent stroke, with approximately 87 % of these events being ischemic.[2] Among ischemic strokes, over 20 % originate from a cardiac source (cardioembolic stroke [CES]), in which embolic material from the heart obstructs cerebral blood flow.[3,4] A particular subset of CES is the embolic stroke of undetermined source (ESUS), a nonlacunar ischemic stroke with no identifiable cause.[5] Despite robust diagnostic tools—including computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography—determining the underlying etiology of ESUS remains challenging.[6] Multiple pathologies, including atrial cardiopathy, covert atrial fibrillation (AF), left ventricular (LV) dysfunction, atherosclerotic plaques, patent foramen ovale, valvular disease, and malignancies, have been implicated in ESUS.[7,8] Among these, atrial cardiopathy—a spectrum of structural and functional abnormalities of the left atrium (LA)—has drawn particular

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List of abbreviations

AF	Atrial fibrillation
CAD	Coronary artery disease
CES	Cardioembolic stroke
CMR	Cardiovascular magnetic resonance
CT	Computed tomography
DM	Diabetes mellitus
ESUS	Embolic stroke of undetermined source
HF	Heart failure
HT	Hypertension
ICCs	Inter-class correlation coefficients
LA	Left atrium
LAF	Left atrium fibrosis
LAVI	Left atrium volume index
LGE	Late-gadolinium enhancement
LV	Left ventricle
MD	Mean differences
MRI	Magnetic resonance imaging
NCE	Non-cardioembolic stroke
NMA	Network meta-analysis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
ROBINS-E	Risk of bias in non-randomized studies of exposure
SUCRA	Surface under the cumulative ranking

interest. The left atrial fibrosis (LAF) and left atrial volume index (LAVI) are two indicators central to LA pathology. They reflect the interplay of atrial remodeling, stasis, endothelial injury, and subsequent thrombus formation.[9]

Although initial assessment of LAF and LAVI often relies on echocardiography, cardiac magnetic resonance (CMR) imaging offers superior spatial resolution and tissue characterization. Specifically, late-gadolinium enhancement (LGE) sequences can detect subtle collagen deposition and fibrotic changes in the LA, which may be vital to understanding ESUS pathophysiology. However, LGE-CMR is not yet universally implemented in stroke protocols due to cost, expertise requirements, and variation in scanning protocols.[10] Elevated LAVI can reflect hemodynamic stress, whereas LAF results from pathologic collagen deposition altering atrial conduction. Both processes are hypothesized to predispose patients to thrombogenesis and ESUS, yet their roles as independent or interrelated markers remain unclear.[11]

In this context, our study systematically evaluates the associations of LAF and LAVI, measured by LGE-CMR, in patients with ESUS compared to those with AF without stroke, CES, noncardioembolic stroke (NCE), and healthy controls. Using a network meta-analysis (NMA), we aim to determine whether these CMR-derived measures may serve as clinically significant biomarkers for ESUS risk stratification. Ultimately, clarifying their clinical utility could inform more refined diagnostic algorithms and better prevention strategies to mitigate the burden of ischemic stroke.

2. Methods

2.1. Protocol registration and reporting guidelines

This NMA was conducted under a pre-specified protocol registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024615479). The methodology follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

2.2. Eligibility criteria

We included observational studies (cohort, cross-sectional, or case–control) that enrolled adults (≥18 years) and LAF or LAVI via CMR in patients with ESUS, compared to AF without stroke, CES, NCE, and healthy controls. Studies were required to report quantitative LAF and/or LAVI measures at the last available follow-up. We excluded studies involving pediatric populations, those published in languages other than English, those including participants with significant structural heart disease unrelated to atrial cardiomyopathy, and those not reporting numerical LAF or LAVI values.

2.3. Data sources and search strategy

A thorough literature search was performed from inception to October 2024 across seven databases: PubMed, EBSCOHost, ScienceDirect, ProQuest, SAGE Journal, Wiley Online Library, Cochrane Library, and Google Scholar. The search strategy combined subject headings and keywords related to "Left Atrial Fibrosis," "Left Atrial Volume Index," "Magnetic Resonance Imaging," and "Atrial Fibrillation" or "Stroke." The complete list of keywords appears in Supplementary Table 1. Reference lists and citations of included articles were manually screened to identify additional relevant studies.

2.4. Study selection and data extraction

All identified records were imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for duplicate removal. Three independent reviewers (SSI, YS, and GF) screened the titles and abstracts for eligibility. Full-text assessments were performed for articles meeting the inclusion criteria, and conference abstracts providing sufficient outcome data were also considered. Any discrepancies were resolved through discussion or consultation with senior authors (AEPS, IP, and VB). Data were extracted using a standardized form. Recorded variables included author/year, study design, participant characteristics (number of participants, mean age, sex distribution, comorbidities such as hypertension [HT], coronary artery disease [CAD], heart failure [HF], diabetes mellitus [DM], smoking status, and CHA_2DS_2-VASc score), LA quantification details imaging details (e.g., type of MRI scanner), and mean ± standard deviation (SD) for LAF and LAVI. In addition, inter-observer agreement data for LAF and LAVI were extracted.

2.5. Risk of bias assessment

Three independent authors (GT, FXR, AS) appraised the risk of bias utilizing the Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E) tool.[13] Seven domains were evaluated: confounding, participant selection, exposure measurement, post-exposure interventions, missing data, outcome measurement, and selective reporting. Each domain was rated as "low," "some concerns," "high," or "very high" risk. Overall judgments were reached by consensus, and unresolved disagreements were referred to senior authors (AEPS, IP, and VB) for final resolution.

2.6. Data synthesis and statistical analysis

All statistical analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria). The NMA employed Bayesian random-effects models—implemented via the gemtc (NMA Using Bayesian Methods, R package version 1.0–2) and BUGSnet (Bayesian Inference Using Gibbs Sampling to conduct NETwork meta-analysis,

version 1.1.2) packages—to assess mean differences (MD) in LAF and LAVI between ESUS and each comparator group (AF without stroke, CES, NCE, and healthy controls).[14–16] A random-effects model was explicitly chosen to account for anticipated heterogeneity across studies, including differences in MRI protocols, study populations, and other methodological variations. Four Markov chain Monte Carlo chains were run for 20,000 iterations each, with the initial 5000 iterations discarded as burn-in, and default diffuse priors were applied for all model parameters. MD with corresponding 95 % credible intervals (CrI) were reported, and consistency between direct and indirect evidence was appraised using node-splitting technique.[17] Publication bias and meta-regression were evaluated when the number of included studies was or more than 10, as recommended for ensuring sufficient power to detect certainty and bias.[18] Rankings were determined by generating the surface under the cumulative ranking (SUCRA) curve and visualized with a litmus rank-o-gram.[19] Sensitivity analyses were performed to evaluate the robustness of the primary findings. Two additional approaches were undertaken: first, by excluding studies at high risk of bias and second, by employing a frequentist random-effects NMA through the netmeta package (NMA using Frequentist Methods, R package version 3.1–1).[20]

3. Results

3.1. Study selection and characteristics

The initial database search yielded 2512 records, of which 1359 were retrieved from PubMed, 291 from EBSCOHost, 287 from ScienceDirect, 251 from ProQuest, 162 from SAGE Journal, 85 from Wiley Online Library, 68 from Cochrane Library, and nine from Google Scholar. After removing duplicates and screening titles and abstracts, 47 full-text articles were screened, with 37 excluded for failing to meet inclusion criteria: 25 due to different study groups for comparison, seven were single-arm studies, and four studies did not use MRI for diagnosis, and one study had a different outcome. Ultimately, 10 studies satisfied all eligibility requirements (Suppl. Fig. 1).[21–30]

These consisted of two cross-sectional, four cohorts, three case–control, and one observational, computational modeling design, totaling 1285 participants (mean age = 65.1 ± 12.1 years; 61.3 % male). The pooled mean values for LAF and LAVI were 16.5 ± 11.7 and 45.7 ± 21.4, respectively. Tables 1 and 2 summarize key demographic information, comorbidities, smoking status, and imaging protocols.[21–30] The clinical parameter showed the mean prevalence of HT (54.2 %), CAD (11.4 %), HF (11.2 %), and DM (11.5 %), smoking (32.4 %), with a mean CHA_2DS_2-VASc score of 1.6 ± 1.4. Most studies employed prolonged ECG or Holter monitoring to exclude AF, thereby minimizing misclassification, as shown in Table 2. Inter-observer reproducibility metrics were available for two studies. Larsen et al. reported intra-class correlation coefficient (ICCs) of 0.966 (inter-observer) and 0.985 (intra--observer) for LAF, while Habibi et al. provided ICCs ranging from 0.88 to 0.96 for various LA metrics including LAVImax and LAVImin.[22,29] For the remaining studies, inter-observer variability was not reported (Suppl. Table 2).[21,23–28,30]

All included studies were evaluated using the ROBINS-E tool. Overall, the methodological quality was deemed acceptable, with four studies classified as having a low risk of bias and six studies as having some concerns regarding bias (Suppl. Fig. 2). One study raised concerns about bias due to confounding, as it lacked information on the confounding factors assessed.[23] Two studies had some concerns regarding bias in the measurement of exposure due to the absence of information on inclusion or exclusion criteria.[22,23] Additionally, seven studies exhibited concerns about bias related to missing data, possibly due to a lack of details on the number of excluded participants and the absence of explicit exclusion criteria.[21–26,28] Lastly, two studies raised concerns about bias in outcome measurement due to the lack of information on outcome standardization in one study and reliance on the Trial of Org 10172 in acute stroke criteria could lead to the misclassification of cardioembolic stroke in the other study.[21,24] No study was excluded solely based on a high risk of bias.

3.2. NMA of LAF

Eight studies (n = 1132 participants) contributed data to the LAF network meta-analysis. The network comprised five groups—ESUS, AF without stroke, CES, NCE, and healthy controls—connected by 10 possible pairwise comparisons, 9 of which had direct data. Five studies were two-arm, and three were multi-arm, forming a single connected network (Suppl. Fig. 3). In the primary Bayesian NMA, three comparisons showed significantly higher LAF relative to healthy controls: CES vs. Control (MD = 14.85 %, 95 % CrI 7.43–22.31), AF without stroke vs. Control (MD = 11.74 %, 95 % CrI 5.59–17.97), and ESUS vs. Control (MD = 9.86 %, 95 % CrI 3.05–16.62). However, no other comparisons reached statistical significance (Table 3). The SUCRA analysis (Supple Table 3; Fig. 1), representing the relative probability of each group attaining the highest rank, demonstrated that CES had the greatest likelihood of being ranked first (94.74), followed by AF without stroke (71.50), ESUS (55.68), NCE (23.03), and healthy controls (5.04). Node-splitting analysis confirmed no statistically significant inconsistencies between direct and indirect comparisons, indicating robust network coherence (Suppl. Fig. 4). No studies were identified as having a high risk of bias; consequently, the only sensitivity analysis performed was a frequentist random-effects NMA, which yielded results broadly consistent with the primary analysis (Suppl. Table 4).

3.3. NMA of LAVI

Seven studies (n = 569 participants) contributed data to the LAVI network meta-analysis. The same five groups—ESUS, AF without stroke, CES, NCE, and healthy controls—were connected by 10 potentials pairwise comparisons, 7 of which had direct data. The network remained fully connected, comprising five two-arm and two multi-arm studies (Suppl. Fig. 3). No significant differences were observed in any pairwise comparisons for LAVI (Table 4).The SUCRA analysis (Supple Table 5; Fig. 2) indicated that CES had the highest ranking probability (92.27), followed by AF without stroke (75.32). ESUS demonstrated an intermediate probability (34.68), ranking above healthy controls (25.50) and NCE (22.23), but below CES and AF without stroke. The node-splitting analysis confirmed the network was coherent, with no statistically significant discrepancies between direct and indirect comparisons (Suppl. Fig. 5). No studies were identified as having a high risk of bias for LAVI; therefore, the only sensitivity analysis performed was a frequentist random-effects NMA, with results broadly consistent with the primary analysis (Suppl. Table 6).

4. Discussion

In this NMA, we found that LAF was significantly higher in patients with ESUS, AF without stroke, and CES than healthy controls. By contrast, no significant differences emerged for the LAVI in any pairwise comparisons. Sensitivity analyses using Bayesian and frequentist approaches confirmed these findings, and node-splitting revealed no appreciable inconsistencies between direct and indirect comparisons.

The elevation of LAF in ESUS relative to healthy controls strongly supports a pathophysiologic role of atrial structural remodeling in patients without overt AF. The presence of LAF increases the risk of clot formation and disrupts the heart's electrical and mechanical functions, leading to stagnant blood flow. This observation aligns with prior evidence suggesting that subclinical atrial cardiopathy may predispose to embolic events, even when conventional markers—such as established AF—are lacking.[31] Although ESUS and AF-without-stroke patients share similar LAF burdens, this does not necessarily imply an identical etiology.[32] Rather, our findings underscore that ESUS likely occupies a

Table 1
Demographic characteristics of included studies.

Study	Design	Database	Follow-up duration (years)	Groups (n)		Age (years)[a]	Male (%)	LAF (mean ± SD)	LAVI (mean ± SD)	MRI scanner	LA segmentation detail (software, manual/ automatic, etc)
Daccarett et al. 2011 [21]	Cross sectional	University of Utah (USA) Klinikum Coburg (Germany)	NA	CES	36	64.0 ± 12.0	36.2	24.4 ± 12.4	NA	Avanto 1.5 T, Siemens Verio 3 T, Siemens	LA borders were manually contoured in Seg3D, and fibrosis was quantified using threshold-based Marrek software. LA enhancement was classified by quartiles: <8.5 %, 8.6–16 %, 16.1–21 %, >21.1 %.
				AF Without Stroke	351	70.0 ± 7.0	66.4	16.2 ± 9.9	NA		
Habibi et al. 2015 [22]	Prospective cohort	John Hopkins University (USA) 2011–2013	0	Control	14	43.0 ± 9.0	71.4	8.9 ± 6.0	36.0 ± 10.0	Avanto, Siemens Aera 1.5 T, Siemens	LA borders manually contoured using QMass 7.2; fibrosis quantified by image intensity ratio (with thresholds ≥0.97 (mild) and ≥1.61 (dense)
				AF Without Stroke	90	61.0 ± 10.0	76.0	31.0 ± 13.8	52.0 ± 15.0		
Johnson et al. 2016 [23]	Prospective cohort	NA	NA	CES	66	72.1 ± 12.2	46.9	17.9 ± 7.2	NA	NA	LA fibrosis was quantified using 3D segmentation software (segmentation type not specified).
				AF Without Stroke	75	71.3 ± 11.4	42.7	15.4 ± 7.8	NA		
Fonseca et al. 2018 [24]	Case-control	Hospital Santa Maria (Portugal) 2014–2017 and Hospital Egas Moniz (Portugal) 2016–2017	0	CES	17	72.7 ± 10.3	41.2	25.0 ± 21.0	61.0 ± 35.0	Achieva 3 T, Philips	LA fibrosis assessed via 3D Slicer with manual adjustment.
				NCE	42	66.2 ± 8.7	73.8	10.5 ± 16.0	37.0 ± 17.0		
				ESUS	52	69.4 ± 9.2	48.1	18.0 ± 16.0	39.5 ± 24.0		
Tandon et al. 2019 [25]	Case-control	University of Washington Comprehensive Stroke Center (USA) Cardiac Arrhythmia Data Repository	NA	Control	10	50.1 ± 16.4	50.0	10.6 ± 5.7	34.6 ± 13.2	Achieva 1.5 T, Philips	LA fibrosis was manually segmented using Corview software with manual border identification and automatic segmentation for consistency; fibrosis quantified as percent LGE after normalization
				AF Without Stroke	10	53.1 ± 12.8	60.0	17.8 ± 4.8	62.5 ± 51.0		
				ESUS	10	50.6 ± 15.7	60.0	16.8 ± 5.7	37.9 ± 12.9		
Bifulco et al. 2021 [26]	Computational modeling	University of Washington (USA) and Klinikum Coburg (Germany) 2016–2019	NA	AF Without Stroke	45	62.0 ± 12.0	67.2	14.2 ± 4.5	57.0 ± 26.0	Ingenia, Philips Avanto, Siemens	LA fibrosis was manually segmented using OsiriX 2.7.5. LA enhancement was classified as mild (<15 % of the LA wall), moderate (15–35 %), or extensive (>35 %).
				ESUS	45	60.0 ± 16.0	56.0	13.6 ± 6.2	60.0 ± 29.0		
Hopman et al. 2021 [27]	Prospective cohort	Amsterdam University Medical Center (Netherlands) 2018–2021	NA	Control	19	58.0 ± 4.0	58.0	NA	37.0 ± 8.0	Avanto, Siemens Sola, Siemens	LA fibrosis quantification was performed semi-automatically
				AF Without Stroke	94	60.0 ± 9.0	64.0	NA	49.0 ± 15.0		

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Database	Follow-up duration (years)	Groups (n)		Age (years)[a]	Male (%)	LAF (mean ± SD)	LAVI (mean ± SD)	MRI scanner	LA segmentation detail (software, manual/ automatic, etc)
											using open software (CE-MRG).
Kühnlein et al. 2021 [28]	Prospective cohort	University of Washington (USA), Klinikum Coburg (Germany), and University of Utah (USA) 2016–2019	1.5 ± 0.5	Control	35	51.0 ± 17.0	65.7	7.9 ± 7.8	NA	Avanto, Siemens	LA fibrosis segmentation was performed manually using Merisight.Inc.
				AF Without Stroke	50	62.0 ± 12.0	67.2	16.6 ± 9.2	NA	Ingenia, Philips	
				CES	50	72.0 ± 10.0	36.0	17.9 ± 11.4	NA		
				ESUS	53	60.0 ± 15.0	57.0	15.0 ± 6.2	NA		
Larsen et al. 2023 [29]	Cross-sectional	Bispebjerg University Hospital (Denmark) and Copenhagen City Heart Study (Denmark) 2019–2021	NA	Control	45	63.6 ± 7.8	58.0	4.7 ± 4.0	36.8 ± 9.3	Magnetom Aera 1.5T, Siemens	LA fibrosis quantification was performed manually using ADAS image post-processing software. LAF was categorized by 10 % increments: mild (0–10 %) moderate (11–20 %), and excessive (>20 %)
				NCE	36	67.3 ± 6.4	75.0	8.4 ± 8.7	36.0 ± 12.4		
Papapostoloua et al. 2023 [30]	Case-control	Australian Stroke Registry (Australia) 2018–2021	1.6 ± 1.3	Control	20	59.3 ± 8.0	90.0	NA	36.0 ± 9.7	Magnetom Prisma 3T, Siemens	Epicardial and endocardial borders were manually traced at end-systole, and strain was computed from both 2- and 4-chamber views using CVI42 software.
				ESUS	20	64.7 ± 12.0	90.0	NA	29.1 ± 10.8		
Summary[b]			**0.8 ± 0.9**		**1.285**	**65.1 ± 12.1**	**61.3**	**16.5 ± 11.7**	**45.7 ± 21.4**		

AF = atrial fibrillation; CES = cardiac embolic stroke; ESUS = embolic stroke of undetermined source; LA = left-atrial; MRI = magnetic resonance imaging; NCE = non-cardioembolic stroke.

[a] Plus-minus values are means ± SD; Parentheses values are median (IQR: Q1 - Q3).

[b] Accounting for only the available data.

continuum of atrial pathology wherein LAF contributes to stroke risk through mechanisms partially distinct from, yet overlapping with, those in patients manifesting overt arrhythmias. Indeed, LAF levels in ESUS appear comparable to those seen in AF or CES, indicating that ESUS may represent part of a broader spectrum of atrial disease rather than a completely separate entity. A previous meta-analysis by Koh et al. also noted elevated LAF in ESUS and AF without stroke. However, that study did not include other stroke subtypes, such as CES and NCE, nor employed an NMA approach.[10]

The lack of significant differences in LAVI across groups is noteworthy. Although LAVI has historically served as a marker of LA remodeling in various stroke etiologies, its inability to discriminate ESUS from other cohorts implies that alterations in atrial volume alone may be insufficient as a robust biomarker.[33] The pooled 95 % CrI for LAVI spans 42 mL/m^2, likely due to substantial variability in standard deviations (4.5–16.2 mL/m^2) and the relatively small sample size (n = 569), which may have limited the ability to detect group differences. Moreover, from a pathophysiological perspective, volume dilation may lag behind micro-fibrotic change, potentially explaining the weaker association between LAVI and thromboembolism. Conversely, LAF—reflecting more subtle tissue remodeling—may be more directly linked to thromboembolic risk. Methodologically, our results highlight the value of CMR imaging for detecting these subclinical abnormalities.[10] CMR, particularly LGE sequences, permits detailed, three-dimensional assessment of the left atrium's tissue composition, which may facilitate earlier identification of patients at elevated stroke risk.[34] Nevertheless, CMR availability remains limited by cost, scanner access, and the specialized training required to interpret and quantify LAF.[35–38] Consequently, CMR often functions more as an advanced imaging modality in complex cases rather than a first-line diagnostic tool.

Our findings should be interpreted cautiously, given several limitations. The small sample size (1285 participants across 10 studies) may constrain the statistical power to detect subtle differences. Some included studies had a moderate risk of bias, often related to missing data, unmeasured confounders, and inconsistent exposure measurement. Moreover, heterogeneity in MRI protocols across studies could influence the measurement of LAF and LAVI. Only two studies, Larsen et al and Habibi et al, reported inter-observer reproducibility for LAF or LAVI, highlighting a lack of consistency metrics across studies. This limits the certainty of pooled estimates.[22,29] Another concern is the potential underdetection of subclinical AF, as even prolonged monitoring may not always capture intermittent arrhythmias. The publication bias and meta-regression analysis could not be performed due to insufficient number of eligible studies, which also limited the assessment

Table 2
Clinical parameters of included studies.

Study	Groups (n)		HT (%)	CAD (%)	HF (%)	DM (%)	Smoking (%)	CHA2DS2-VASc[a]	Diagnostic criteria for excluding AF
Daccarett et al. 2011 [21]	CES	36	66.7	NA	5.5	8.3	NA	3.0 ± 0.6	NA
	AF Without Stroke	351	58.0	NA	10.2	13.4	NA	1.0 ± 0.9	
Habibi et al. 2015 [22]	Control	14	0.0	0.0	0.0	0.0	NA	NA	NA
	AF Without Stroke	90	48.0	12.0	12.0	7.0	NA	NA	
Johnson et al. 2016 [23]	CES	66	NA	NA	NA	NA	NA	NA	NA
	AF Without Stroke	75	NA	NA	NA	NA	NA	NA	
Fonseca et al. 2018 [24]	CES	17	82.4	NA	NA	0.0	NA	3.0 ± 3.0	1. Inpatient continuous ECG monitoring
	NCE	42	81.0	NA	NA	23.8	NA	3.0 ± 2.0	
	ESUS	52	80.8	NA	NA	19.2	NA	3.0 ± 2.0	2. Additional one day Holter monitoring
Tandon et al. 2019 [25]	Control	10	10.0	0.0	0.0	0.0	0.0	0.8 ± 0.6	1. Inpatient telemetry
	AF Without Stroke	10	30.0	0.0	10.0	0.0	10.0	1.2 ± 0.9	2. Additional 30 days of outpatient rhythm monitoring
	ESUS	10	30.0	10.0	10.0	0.0	20.0	1.1 ± 1.0	
Bifulco et al. 2021 [26]	AF Without Stroke	45	61.2	18.4	18.4	12.2	28.0	1.9 ± 0.0	NA
	ESUS	45	68.5	18.4	14.3	20.4	32.0	2.0 ± 0.0	
Hopman et al. 2021 [27]	Control	19	0.0	NA	NA	0.0	NA	NA	NA
	AF Without Stroke	94	32.0	NA	NA	4.0	NA	1.2 ± 1.2	
Kühnlein et al. 2021 [28]	Control	35	18.2	0.0	9.0	0.0	12.0	0.5 ± 1.0	1. Inpatient continuous ECG monitoring
	AF Without Stroke	50	61.2	18.4	18.4	12.2	28.0	1.9 ± 1.4	
	CES	50	74.0	24.0	14.0	22.0	28.0	2.9 ± 1.1	2. Additional 14–30 days of outpatient rhythm monitoring
	ESUS	53	75.0	17.3	13.5	23.1	42.0	2.0 ± 1.4	
Larsen et al. 2023 [29]	Control	45	31.0	0.0	NA	2.0	44.0	1.0 (1.0–2.0)	NA
	NCE	36	69.0	0.0	NA	11.0	61.0	2.0 (1.0–3.0)	
Papapostoloua et al. 2023 [30]	Control	20	0.0	0.0	0.0	0.0	NA	NA	≥ one day of cardiac monitoring
	ESUS	20	55.0	NA	NA	NA	NA	NA	
Summary[b]		**1285**	**54.2**	**11.4**	**11.2**	**11.5**	**32.4**	**1.6 ± 1.4**	

AF = atrial fibrillation; CAD = coronary artery disease; CES = cardiac embolic stroke; DM = diabetes mellitus; ECG = electrocardiogram; ESUS = embolic stroke of undetermined source; HF = heart failure; HT = hypertension; NCE = non-cardioembolic stroke.

[a] Plus-minus values are means ± SD; Parentheses values are median (IQR: Q1 - Q3).

[b] Accounting for only the available data.

Table 3
Pairwise MD for LAF.

Contrast	MD (95 % CrI)	SD	*P*-value
AF without stroke vs CES	3.09 (−2.87, 9.15)	3.07	0.314
AF without stroke vs Control	−11.74 (−17.97, −5.59)	3.16	0.0002
AF without stroke vs ESUS	−1.91 (−7.87, 3.91)	3.01	0.525
AF without stroke vs NCE	−8.37 (−17.71, 0.90)	4.75	0.078
CES vs Control	−14.85 (−22.31, −7.43)	3.80	0.000091
CES vs ESUS	−4.99 (−12.10, 1.90)	3.57	0.162
CES vs NCE	−11.47 (−21.04, −1.90)	4.88	0.019
Control vs ESUS	9.86 (3.05, 16.62)	3.46	0.0044
Control vs NCE	3.37 (−5.35, 12.01)	4.43	0.447
ESUS vs NCE	−6.49 (−15.53, 2.55)	4.61	0.159

AF = atrial fibrillation; CES = cardiac embolic stroke; CrI = credible interval; ESUS = embolic stroke of undetermined source; MD = mean difference; NCE = non-cardioembolic stroke; SD = standard deviation.

of heterogeneity. No retrospective studies were eligible to be included, resulting in restriction of the diversity and limiting the detection of long–term association between LAF-LAVI markers and stroke risk in broader clinical population. Lastly, unreported lifestyle factors and comorbidities may confound associations with atrial biomarkers. Future directions include prospective, longitudinal studies of ESUS patients to gauge whether dynamic changes in LAF or LAVI parallel stroke recurrence or the emergence of overt AF. Standardizing CMR protocols and exploring interventions to reduce LAF could clarify causal mechanisms and inform new therapeutic strategies.

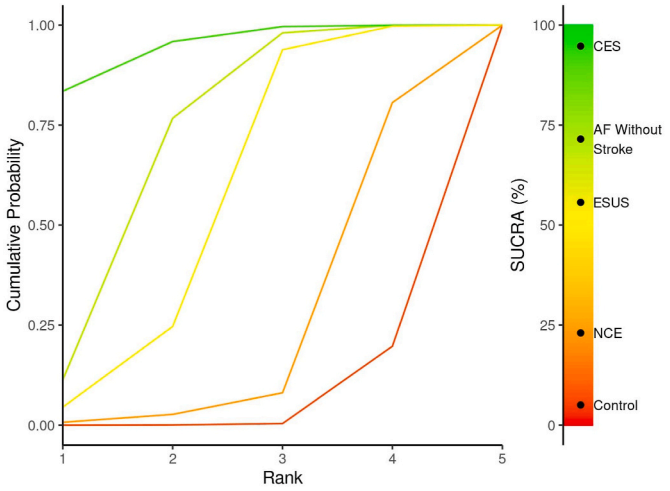

Fig. 1. Litmus rank-o-gram for LAF.

5. Conclusions

This NMA demonstrates a significant elevation of LAF in ESUS relative to healthy controls, mirroring that observed in AF and CES and suggesting a shared atrial pathology across these conditions. By contrast, the LAVI did not differentiate ESUS from other groups, indicating that subtle fibrotic changes—rather than chamber enlargement—may be central to ESUS pathogenesis. While these findings highlight the promise of LAF as a risk marker, the use of CMR-derived LAF for prognostic

Table 4
Pairwise MD for LAVI.

Contrast	MD (95 % CrI)	SD	*p*-value
AF without stroke vs CES	11.42 (−17.23, 39.29)	14.42	0.428
AF without stroke vs Control	−11.45 (−24.52, 0.62)	6.41	0.074
AF without stroke vs ESUS	−10.03 (−24.23, 4.68)	7.38	0.174
AF without stroke vs NCE	−12.41 (−32.26, 6.68)	9.93	0.212
CES vs Control	−22.93 (−49.53, 4.06)	13.67	0.093
CES vs ESUS	−21.38 (−46.29, 4.80)	13.03	0.101
CES vs NCE	−23.80 (−48.93, 1.64)	12.90	0.065
Control vs ESUS	1.43 (−10.36, 14.56)	6.36	0.822
Control vs NCE	−0.98 (−17.25, 15.68)	8.40	0.907
ESUS vs NCE	−2.36 (−19.82, 13.89)	8.60	0.784

AF = atrial fibrillation; CES = cardiac embolic stroke; CrI = credible interval; ESUS = embolic stroke of undetermined source; MD = mean difference; NCE = non-cardioembolic stroke; SD = standard deviation.

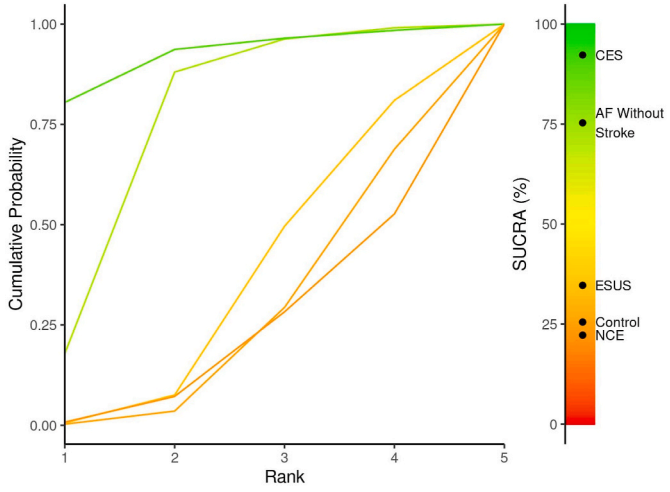

Fig. 2. Litmus rank-o-gram for LAVI.

purposes requires confirmation through prospective studies before being considered for clinical application. Future large-scale prospective studies, including those employing standard echocardiographic measures, are warranted to clarify the clinical significance of LAF in ESUS and refine stroke risk stratification, ultimately aiming to reduce the burden of recurrent stroke.

Data sharing statement

All data, including any derived data supporting the findings, are available from the corresponding author upon reasonable request.

Author contribution

SSI: Conceptualization, data curation, formal analysis, methodology, project administration, visualization, writing – original draft, and writing – review & editing. GT: Investigation, methodology, visualization, writing - original draft, and writing - review and editing. FXR: Formal analysis, investigation, visualization, writing – original draft, and writing - review and editing. YS and AS: Data curation, investigation, writing - original draft, and writing - review and editing. GF: Data curation, investigation, visualization, writing - original draft, and writing - review and editing. AEPS, IP, and VB: Supervision and writing - review and editing.

Declaration of generative AI in scientific writing

This study did not employ any artificial intelligence (AI) tools or methodologies at any stage, including data collection, analysis, visualization, or manuscript preparation. The authors conducted all work presented in this study manually, without the use of AI-based tools or systems.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2025.06.006.

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