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META-ANALYSIS

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Altered left atrial metrics in patients with cryptogenic stroke: A systematic review and meta-analysis

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Abstract

Background: There is no defined cause for cryptogenic stroke/embolic stroke of undetermined source (CS-ESUS). As atrial fibrillation (AF) develops in a significant proportion of these patients, it has been suggested that left atrial (LA) myopathy may predispose to CS-ESUS. We investigated alterations in echocardiographic measures of LA size and function in patients with CS-ESUS.

Methods: A systematic literature review and meta-analysis was performed. PubMed, EMBASE, Cochrane Library, Web of Science and SCOPUS were searched for articles published between 1 January 1990 and 10 February 2023. All observational studies of adult CS-ESUS patients with LA volume or function measurements performed by transthoracic echocardiogram were included. Individual random effects meta-analyses were performed on LA measurements in the CS-ESUS patients using subgroup analysis of comparator groups.

Results: We included 29 articles with 3927 CS-ESUS patients. Analysis of weighted mean differences showed CS-ESUS patients had altered LA structure and function parameters, with a larger maximum indexed LA volume, reduced LA emptying fraction and/or LA reservoir strain, compared to healthy controls and noncardioembolic stroke patients. Conversely, CS-ESUS patients had a smaller left atrium with better function, compared to cardioembolic stroke patients and CS-ESUS patients who subsequently developed atrial fibrillation.

Conclusions: LA volume and function are altered in CS-ESUS patients compared to healthy controls and other stroke aetiologies. An underlying atrial myopathy in a subset of CS-ESUS patients may be involved in both thrombogenesis and dysrhythmia (specifically AF). While LA functional assessment is not currently recommended following stroke, it may offer an opportunity for recurrent stroke risk stratification.

KEYWORDS

echocardiography, heart atria, ischaemic stroke, meta-analysis

PROSPERO registration number: CRD42023391770.

1 | BACKGROUND

Early classification of ischaemic stroke by the Trial of Org 10,172 defined 'cryptogenic stroke' as an ischaemic stroke of undetermined source or incomplete diagnostic work up.[1] Embolic stroke of undetermined source (ESUS) has since been identified as a subset of cryptogenic stroke with minimum diagnostic criteria defined by a nonlacunar, ischaemic stroke with no identifiable source.[2] Ischaemic strokes with undetermined aetiology (45%) are composed of ESUS (43%) with the remainder (2%) cryptogenic (CS) due to incomplete work up.[3] While CS and ESUS are not synonyms, the classification system used in clinical practice (TOAST or ESUS), and the extent of nonembolic exclusion in post-stroke assessment, has seen the terms used interchangeably in the published literature.[1,2] Stroke of undetermined source (CS-ESUS) has a high rate of recurrence.[2] An improved aetiologic understanding and definition of subtypes is required to improve patient risk stratification and secondary prevention of recurrent stroke.[2]

AF demonstrates a threefold to fivefold independent risk of cardioembolic stroke[4] and undetected paroxysmal atrial fibrillation (AF) is a potential cause of CS-ESUS.[2] An alternate cause of CS-ESUS is an underlying atrial cardiomyopathy (ACM), with associated structural and functional left atrial (LA) changes, that promotes both thrombogenicity and future AF development.[2] LA dilatation is an independent predictor of ischaemic stroke in patients in sinus rhythm,[5] while LA function evaluated by strain and LA volume have been reported to be altered in CS-ESUS patients.[6,7]

A previous systematic review of markers of ACM reported electrocardiographic, biomarker and LA volume changes in ESUS patients, but did not examine LA function.[8] In this study, we evaluated LA volume and function through a pooled meta-analysis in CS-ESUS patients, to examine its utility for patient risk stratification.[8]

2 | METHODS

The study design and reporting were performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[9] The study protocol is registered in the International Prospective Register of Systematic Reviews database (PROSPERO registration number: CRD42023391770, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023391770). Two authors (AC—senior sonographer and PhD candidate, and AF—Cardiologist and PhD candidate) were involved in all stages of literature search, screening and data extraction.

2.1 | Literature search

PubMed, EMBASE, Cochrane Library, Web of Science and SCOPUS were searched for articles published between 1 January 1990 and 10 February 2023. We required articles to conform to the PICO question: In CS-ESUS patients (P), do transthoracic echocardiogram (TTE) measurements (E) when compared with other patient populations (C) demonstrate differences in volume and/or function (O)? Combinations of the following subject headings and keywords were used across all databases: 'cryptogenic stroke/ESUS', 'atrial volume/atrial function/atrial cardiomyopathy' and 'strain/speckle tracking' with the complete string search formula displayed in Figure S1. Both authors adhered to the same search formula and selection criteria.

We included studies that (1) were published in English peer-reviewed journals, (2) had a minimum of 30 adult participants (≥18 years old), (3) defined CS or ESUS according to TOAST criteria[1,10] and (4) had observational LA volume or function measurements performed by transthoracic echocardiogram (TTE).

Exclusion criteria included: (1) Reviews, case reports, opinions, clinical trials and unpublished abstracts, (2) paediatric or animal studies, (3) studies that did not define stroke subtype and (4) studies that reported LA diameter only.

2.2 | Study selection

Articles were uploaded to Covidence[11] for streamlined screening and data extraction. Initial search and title/abstract screening was conducted simultaneously and independently with duplicate articles and those not meeting inclusion criteria excluded from analysis. Articles considered potentially relevant underwent subsequent full-length review. An additional search of retrieved article reference lists and abstracts was performed to identify potentially relevant publications. Studies using the same patient cohort were identified with the most recent study and/or most relevant LA metrics identified for extraction to prevent double counting. The author conflict in article inclusion/exclusion was automatically highlighted by covidence with disagreements resolved through discussion and consensus, for complete inter-rater agreement.

Quality assessment was performed using the Newcastle–Ottawa quality assessment Scale (NOS) for cohort studies with modification for case–control and cross sectional studies. Study quality was considered high if NOS score was ≥7 stars, fair quality if 5–6 stars and poor quality if <4 stars.

2.3 | Data extraction

Data extraction was performed by one author (AC) and with comprehensive review by second author (AF). Disagreements were resolved through discussion and consensus with complete agreement.

Studies were included for extraction when individual LA volume and function measurements were present in more than three studies, with independent meta-analysis for each separate measurement. Data extraction was performed using predefined search fields within an MS Excel extraction form. The extraction template was pilot tested for completeness and accuracy. For eligible studies, the following continuous metrics were extracted: minimum LA volume indexed to body surface area (LAVImin); maximum LA volume indexed to body surface area (LAVImax); LA emptying fraction (LAEF); LA reservoir strain (LASr, %); LA contractile strain (LASct, %); LA conduit strain (LAScd, %); LA systolic strain rate (LA-SSR); LA early diastolic strain rate (LA-ESR); and LA late diastolic strain rate (LA-ASR).

Raw data was transformed for data analysis where necessary, including median conversion and subgroup combination, according to current recommendations.[12,13] As data were observational, further investigation of interventions or outcomes, including missing data, was not required.

For each eligible study, the following data were extracted:

1. Study details: First author, year of publication, study design and comparator groups.
2. Sociodemographics: Patient age, gender, BSA/BMI and number of subjects.
3. Technical components: TTE vendors/probes, software for LA analysis and imaging views used.
4. LA volume and function measurements performed by TTE, expressed as mean ± standard deviation.

2.4 | Data analysis

Separate random-effects meta-analysis was performed on each measurement using IBM SPSS® software (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp). Subgroup analysis was performed with comparator groups, as all studies examined CS-ESUS patients compared to one or more of following groups (1) healthy controls (HC) in sinus rhythm, (2) cardioembolic stroke (CES) patients, (3) noncardioembolic stroke (NCES) patients and (4) cryptogenic/ESUS cohort patients who subsequently developed AF within 12 months (CS-AF). According to TOAST criteria, NCES includes large artery atherosclerosis, small artery atherosclerosis and other defined cause.[1] For continuous outcome meta-analyses, a restricted maximum-likelihood estimator (REML) model was used to estimate between study variance, with a Knapp-Hartung adjustment. Results are presented as unstandardized weighted mean difference with 95% confidence interval (CI), and displayed with forest plots. A $p < .05$ was considered significant. We explored heterogeneity among studies using I^2 statistic and examined publication bias with visual assessment of funnel plots. Additional exploration of heterogeneity included assessment of subgroup variation, meta-regression of known confounder age and both visual and sensitivity assessment of outlier studies.

3 | RESULTS

3.1 | Search results

A flow chart of article selection is demonstrated in Figure 1. We initially identified 6897 articles, with 4292 excluded as duplicates and 2402 excluded as nonrelevant based on title and abstract screening. Full text was examined in 200 articles, with 29 fulfilling inclusion criteria for data analysis.[6,7,14–40]

All studies were observational, with nine case–control, two cross sectional and 18 cohort study designs (Table 1). CS-ESUS patients were compared to healthy controls in sinus rhythm (12 studies), cardioembolic stroke (CES) or noncardioembolic stroke (NCES) patients (seven studies) and CS-ESUS patients who subsequently developed AF (CS-AF) (15 studies). A total of 3927 CS-ESUS patients were included with a weighted mean age of 63 years (58% male). From 29 studies, only 10 were considered large (i.e. >100 CS-ESUS patients), with only five examining LA strain parameters.

Quality assessment was performed on all included studies using the NOS risk of bias with 23 studies receiving a score of ≥7 (high quality) and six studies with scores of 5–6, (fair quality) (Figure 2). Highest risk of bias was observed in the 'comparability' domain with limited control for confounders in 15/29 studies. 'Outcome' domain demonstrated limitation primarily in performance of independent or blinded assessment with 11/29 studies risk of bias. 'Selection' domain had the lowest risk of bias with 5/29 studies unclear on control selection in case–control studies.

No publication bias was detected, with funnel plot observation (Figure S2), and statistical testing (Egger's regression) demonstrating $p > .5$ for all metrics.

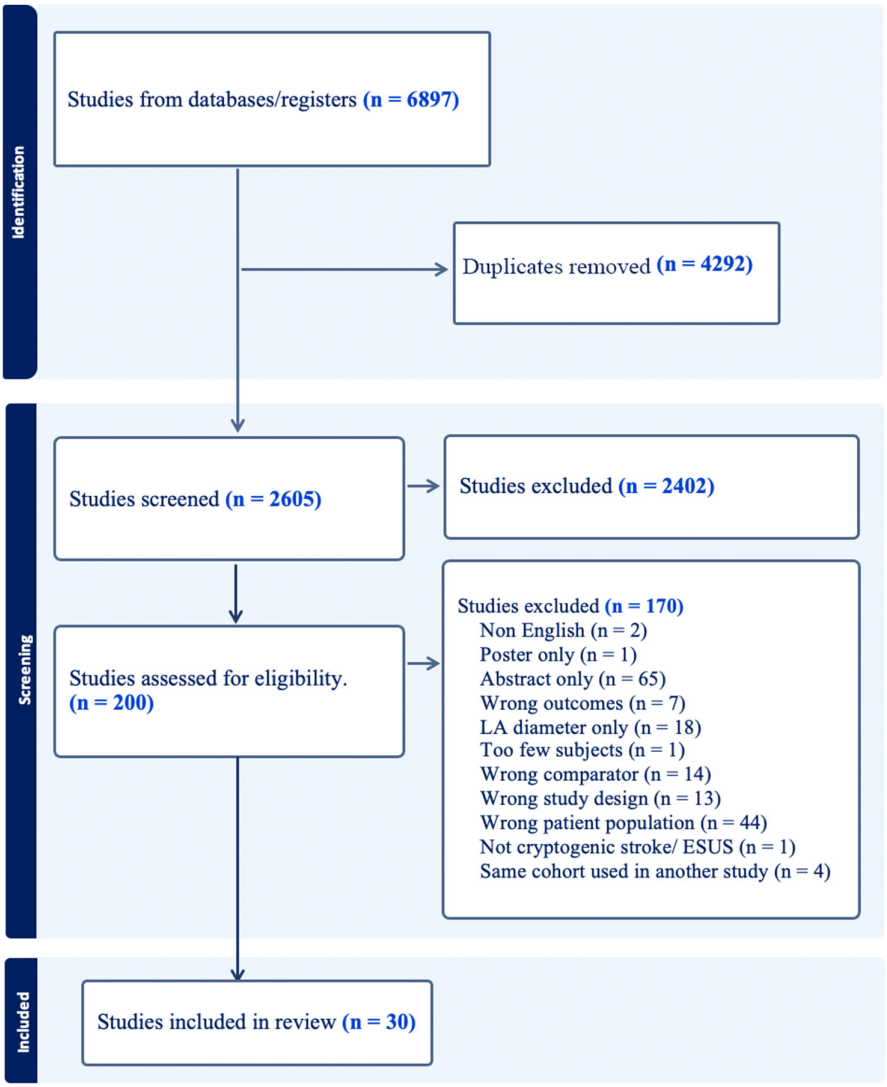


FIGURE 1 PRISMA flow diagram.

3.2 | Study characteristics

TTE was performed with Philips Medical Ultrasound systems in eight studies, General Electric Medical Systems in nine studies, Aloka Alpha in one study and the ultrasound vendor was not disclosed in 11 studies. Offline measurements were performed with Philips Medical System, TomTec Imaging Systems, General Electric Healthcare and GE Vingmed or Siemens Ultrasound Solutions.

Of 15 studies including CS-AF patients, methods for AF detection included in-hospital telemetry (72 h), outpatient Holter-monitors (up to 28 days), electronic medical record searches (up to 5 years) and implantable cardiac devices. AF detection varied from 7.6% to 49%, with higher detection in studies including acute hospital monitoring. Of large studies (>100 patients), AF was detected in 7.6%–21%, which included long-term implantable cardiac monitoring.

LA volumetric measurements included LAVImax (27 studies), LAVImin (seven studies), and LAEF (12 studies). The majority of measurements were performed by biplane analysis (16 studies) from apical four- and two-chamber views using either area-length method or modified Simpsons method. Two studies used four-chamber volume only, three studies employed 3D/4D volumetric analysis and six studies did not define the method used. LAVImax was an independent predictor of AF in 4/15 studies with CS-AF patients.

LA strain measurements reported included reservoir strain (LASr) (17 studies), contractile strain (LASct) (11 studies), conduit strain (LAScd) (seven studies), systolic strain rate (LA-SSR) (six studies), early diastolic strain rate (LA-ESR) (four studies) and late diastolic strain rate (LA-ASR) (four studies). The majority of studies reported R-R gating (13 studies), one reported P-P gating and three studies did not define gating. Eleven studies reported LA strain as an average of four- and two-chamber

TABLE 1 Characteristics of selected studies.

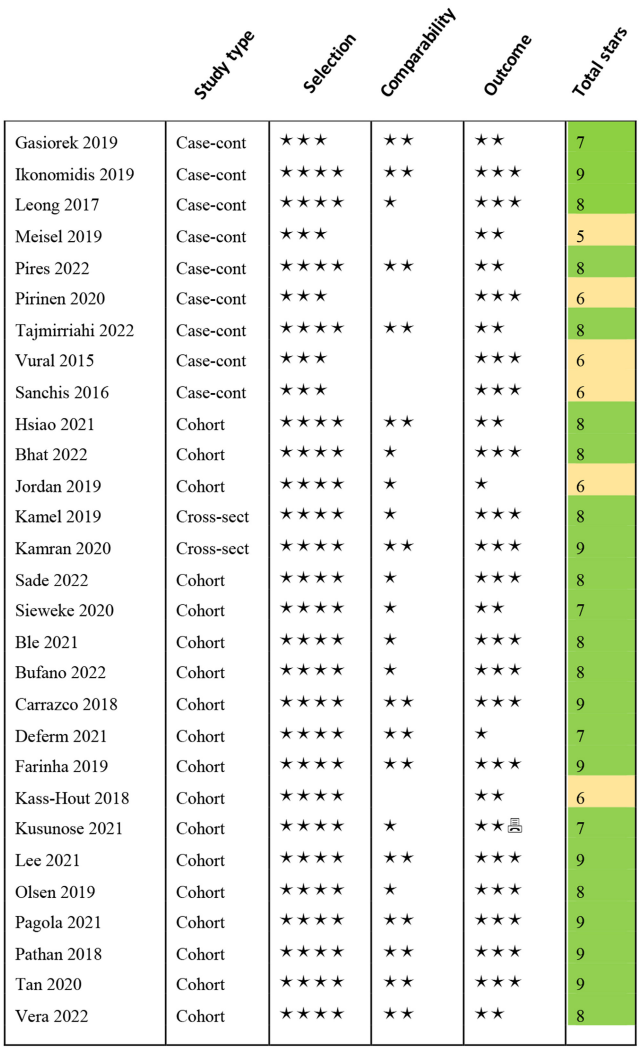
Author	Year/country	Sample size	Comparator groups	Age (years)	Male (%)	Platform	2D/3D	Views (apical)	Gating	Software	Volumes and volumetric function	Strain parameters
Hsiao	2021/Taiwan	49	CES, NCES, HC	66	76		2D	4/2 A-L			LAVImax/min LAEF	
Sanchis	2016/Spain	50	CES, NCES, HC	67	46	Phillips iE33	2D	Four volume four strain	R-R	Philips QLab v7.1	LAEF	LASr, LASSR LAESR, LAASR
Bhat	2022/Australia	291	CES, NCES	63	54	Phillips EPIQ and E95 (GE)	2D	4/2 (A-L) volume 4/2 strain	R-R	Arena v 4.6, TomTec	LAVImax LAEF	LASr, LASct LAScd
Jordan	2019/USA	412	CES, NCES, CS-AF	68	52		2D	4/2 (BS) volume			LAVImax	
Kamel	2019/USA	531	CES, NCES	70	46		2D			Philips Xcelera	LAVImax	
Kamran	2020/Qatar	656	CES, NCES	56	83		2D				LAVImax	
Sieweke	2020/Germany	56	CES, NCES, CS-AF, HC	65	66	Philips Epic 7	2D	4/2 strain		Philips QLab v7.0		LASr, LASSR LAESR, LAASR
Gasiorek	2019/Poland	65	HC	54	42	Aloka Alpha 10	2D				LAVImax	
Ikonomidis	2019/Greece	90	HC	50	54	GE Vivid 7	2D	4/2 (BS) volume 4/2 strain	R-R	GE Echopac	LAVImax	LASr
Leong	2017/Australia	341	HC	59	53	GE Vivid 7 or E9	2D	4/2 (BS) volume 4/2 strain	R-R	GE Vingmed V111.0.0	LAVImax	LASr
Meisel	2019/USA	18	HC	58	56	GE Vivid E9	2D & 3D	4/2 (BS) volume		GE EchoPac	LAVImax/min LAEF	
Pires	2022/Portugal	31	HC	50	52	GE Vivid E95	2D & 3D	3D volume 4/2 strain	R-R	GE EchoPac	LAVImax/min LAEF	LASr, LASct LAScd
Pirinen	2020/Finland	30	HC	43	50	GE Vivid E9	2D & 3D	4D volume 4/2 strain	P-P	GE EchoPac v 113	LAVImax/min LAEF	LASr, LASct LASSR (no timing)
Tajmirriahi	2022/Iran	82	HC	60	55		2D	4/2 (A-L) volume			LAVImax LAEF	
Vural	2015/Turkey	40	HC	42	50	Philips iE33	2D	4/2 strain		Philips QLAB v. 6.0	LAVImax	LASr, LAESR, LAASR
Sade	2022/Turkey	58	HC, CS-AF, NCES	70	64	GE Vivid E9 or E95	2D & 3D	3D volume 4/2 strain	R-R	GE EchoPac v 203	LAVImax/min LAEF	LASr, LASct
Ble	2021/Spain	38	CS-AF	73	61	GE Vivid E9	2D	4/2 volume 4 strain	R-R	GE Q-analysis	LAVImax LAEF	LASr, LASct
Bufano	2022/Italy	49	CS-AF	66	59	Phillips Affinity 50c	2D	4/2 (BS) volume 4 strain	R-R	Siemans Syngo VVI Longitudinal	LAVImax LAEF	LASr, LASct LAScd
Carrazco	2018/USA	69	CS-AF	63	52						LAVImax	
Deferm	2021/USA	163	CS-AF	64	55	Philips EPIQ 7 or IE33	2D	4/2 (BS) volume 4 strain	R-R	Siemens Syngo and TomTec	LAVImax LAEF	LASr, LASSR LAESR, LAASR

(Continues)

TABLE 1 (Continued)

Author	Year/country	Sample size	Comparator groups	Age (years)	Male (%)	Platform	2D/3D	Views (apical)	Gating	Software	Volumes and volumetric function	Strain parameters
Farinha	2019/Portugal	66	CS-AF	53	61	GE Vivid 7					LAVImax	
Kass-Hout	2018/USA	82	CS-AF	69	52						LAVImax	
Kusunose	2021/Japan	75	CS-AF	73	64		2D	4/2 volume 4/2 strain	R-R	EchoInsight, Epsilon	LAVImax	LASr, LASct LAScd
Lee	2021/Korea	116	CS-AF	63	65		2D	4/2 (BS) volume			LAVImax	
Olsen	2019/Denmark	43	CS-AF	50	60	Phillips iE33	2D	4/2(A-L) volume 4/2 strain	R-R	Xcelra, Epsilon EchoInsight	LAVImax/min	LASr, LASct LAScd, LASSR LAESR, LAASR
Pagola	2021/Spain	199	CS-AF	74	48	GE Vivid-I	2D	4 volume 4 strain		GE EchoPAC	LAVImax	LASr LASct
Pathan	2018/Australia	477	CS-AF	65	57		2D	4/2 volume 4/2 strain	R-R		LAVImax	LASr, LASct LAScd
Tan	2020/ Singapore	171	CS-AF	63	73		2D	4/2 (BS) volume			LAVImax	
Vera	2022/Spain	56	CS-AF	77	45	Philips Vivid 7	2D	4/2 volume 3D volume 4 strain	R-R	Philips Dynamic	LAVImax (2D and 3D) LAEF	LASr, LASct LAScd

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; A-L, area-length; BS, Simpson's biplane; CES, cardioembolic stroke; CS-AF, cryptogenic patients with atrial fibrillation; HC, healthy controls; LAASR, left atrial late diastolic strain rate; LAEF, left atrial emptying fraction; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASER, left atrial early diastolic strain rate; LASr, left atrial reservoir strain; LASSR, left atrial systolic strain rate; LAVImax, maximum indexed left atrial volume; LAVImin, minimum indexed left atrial volume; NCES, noncardioembolic stroke.



	Study type	Selection	Comparability	Outcome	Total stars
Gasiorek 2019	Case-cont	★★★	★★	★★	7
Ikonomidis 2019	Case-cont	★★★★	★★	★★★	9
Leong 2017	Case-cont	★★★★	★	★★★	8
Meisel 2019	Case-cont	★★★		★★	5
Pires 2022	Case-cont	★★★★	★★	★★	8
Pirinen 2020	Case-cont	★★★		★★★	6
Tajmirriahi 2022	Case-cont	★★★★	★★	★★	8
Vural 2015	Case-cont	★★★		★★★	6
Sanchis 2016	Case-cont	★★★		★★★	6
Hsiao 2021	Cohort	★★★★	★★	★★	8
Bhat 2022	Cohort	★★★★	★	★★★	8
Jordan 2019	Cohort	★★★★	★	★	6
Kamel 2019	Cross-sect	★★★★	★	★★★	8
Kamran 2020	Cross-sect	★★★★	★★	★★★	9
Sade 2022	Cohort	★★★★	★	★★★	8
Sieweke 2020	Cohort	★★★★	★	★★	7
Ble 2021	Cohort	★★★★	★	★★★	8
Bufano 2022	Cohort	★★★★	★	★★★	8
Carrazco 2018	Cohort	★★★★	★★	★★★	9
Deferm 2021	Cohort	★★★★	★★	★	7
Farinha 2019	Cohort	★★★★	★★	★★★	9
Kass-Hout 2018	Cohort	★★★★		★★	6
Kusunose 2021	Cohort	★★★★	★	★★	7
Lee 2021	Cohort	★★★★	★★	★★★	9
Olsen 2019	Cohort	★★★★	★	★★★	8
Pagola 2021	Cohort	★★★★	★★	★★★	9
Pathan 2018	Cohort	★★★★	★★	★★★	9
Tan 2020	Cohort	★★★★	★★	★★★	9
Vera 2022	Cohort	★★★★	★★	★★	8

FIGURE 2 Newcastle–Ottawa scale quality assessment for risk of bias.

measurements while six studies performed measurements in only four-chamber view. Strain (LASr/LASct) were independent predictors of AF in 9/15 studies with CS-AF patients, with six demonstrating predictive value over LA volume.

3.3 | Data analysis

3.3.1 | CS-ESUS versus healthy controls

Healthy controls demonstrated significantly smaller LAVImax compared to CS-ESUS patients (Figure 3B, Table 2). Altered function parameters included higher LAEF (Figure 3C) and LASr (Figure 3D) in healthy controls compared to CS-ESUS patients. No difference was observed in LAVImin, LASct, LA-ESR and LA-ASR (Table 2), although study numbers were limited. Insufficient study numbers were available for analysis of LA-SSR.

3.3.2 | CS-ESUS versus NCES patients

Compared to CS-ESUS patients, NCES patients also demonstrated smaller LAVImax (Figure 3B) and higher LAEF (Figure 3C and Table 2). There was no difference in LASr between CS-ESUS and NCES patients (Figure 3D). Insufficient study numbers were available for analysis of LAVImin, LASct, LA-SSR, LA-ESR and LA-ASR compared to NCES patients.

3.3.3 | CS-ESUS versus CES patients

Compared to CS-ESUS patients, CES patients demonstrated an increased LAVImax in CES patients and a decrease in both LAEF and LASr (Figure 4A–C and Table 3). Insufficient study numbers were available for analysis of LAVImin, LASct, LAScd, LA-SSR, LA-ESR and LA-ASR versus CES patients.

3.3.4 | CS-ESUS versus CS-AF patients

Differences were also observed between CS-ESUS and CS-AF patients, with measurements performed prior to AF onset. Compared to CS-ESUS, CS-AF patients demonstrated larger LAVImax and reduced LAEF, LASr, LASct, LA-SSR and LA-ESR (Figure 4A–E and Table 3). There were insufficient studies for analysis of LAVImin.

3.4 | Heterogeneity

We found heterogeneity across all LA metrics analysed ($I^2 > 70\%$) without significant improvement using individual comparator subgroup meta-analysis. We examined a number of covariates for influence, however acknowledging that characteristics presented at study level may induce aggregation bias.[13] While a minimum of 10 studies per covariate is the Cochrane recommendation for unbiased meta-regression, a recent study indicates as little as two studies may provide valid results.[13,41] Hence, we applied a meta-regression model with maximum likelihood estimator, and a Knapp-Hartung adjustment of standard error for small sample sizes. Scatterplot observation determined trends of mean weighted metrics (LAVImax, LAEF and LASr) when controlled for age, a known contributor to LA volume and strain changes (Figure 5).[42]

Heterogeneity was reduced for most LA metrics after controlling for age, with all variability accounted for in the CES subgroup analysis (.90 mL/m^2 increase in mean difference per year, $p = .002$ [95% CI .61–1.19], $R^2 = 100\%$, I^2 0%). Age also significantly influenced

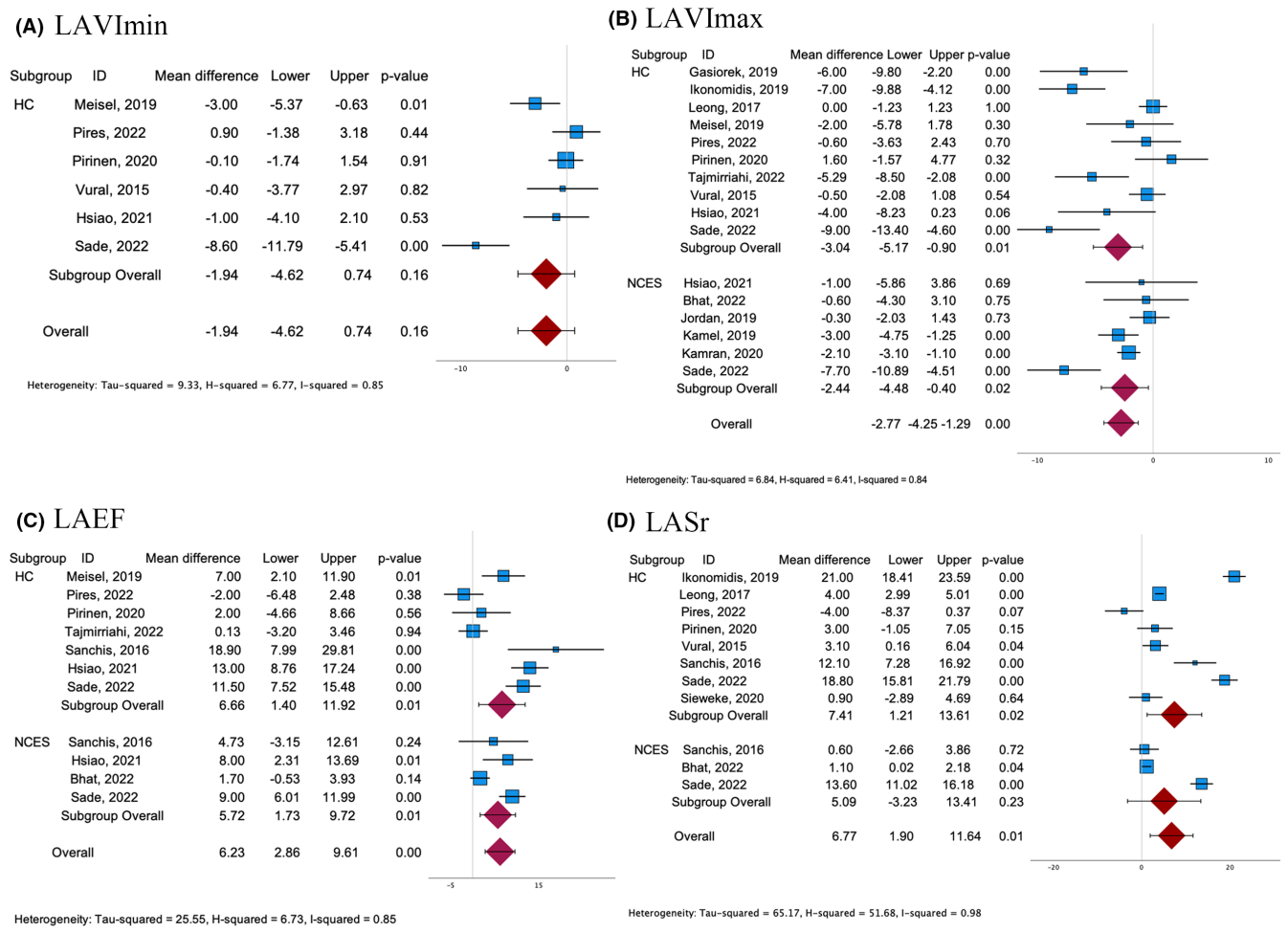


FIGURE 3 Forest plots demonstrating weighted mean difference and 95% confidence interval between CS-ESUS patients and HC/NCES subgroups from studies assessing LA metrics: (A) LAVImin (mL/m^2), (B) LAVImax (mL/m^2), (C) LAEF (%) and (D) LASr (%). CS-ESUS, cryptogenic stroke/embolic stroke of undetermined source; HC, healthy controls; LAEF, left atrial emptying fraction; LASr, left atrial reservoir strain; LAVImax, maximum indexed left atrial volume; LAVImin, minimum indexed left atrial volume; NCES, noncardioembolic stroke.

TABLE 2 Comparison of weighted mean difference of LA parameters between CS-ESUS patients and healthy controls/NCES patients.

	Healthy controls				NCES patients			
	n	WMD	95% CI	*p*-Value	*n*	WMD	95% CI	*p*-Value
LAVImin	6	−1.94	−4.62, .74	.16				
LAVImax	10	−3.04	−5.17, −.90	.01	6	−2.44	−4.48 to −.40	.02
LAEF	7	6.66	1.40, 11.92	.01	4	5.72	1.73 to 9.72	.01
LASr	8	7.41	1.21, 13.61	.02	3	5.09	−3.23 to 13.41	.23
LASct	3	2.32	−1.86, 6.5	.28				
LA-ESR	3	.17	−.48, .81	.61				
LA-ASR	3	.42	−.22, 1.06	.20				

Abbreviations: 95% CI, 95% confidence interval; LAASR, left atrial late diastolic strain rate; LAEF, left atrial emptying fraction; LASct, left atrial contractile strain; LASER, left atrial early diastolic strain rate; LASr, left atrial reservoir strain; LAVImax, maximum indexed left atrial volume; LAVImin, minimum indexed left atrial volume; *n*, number of studies; NCES, noncardioembolic stroke; WMD, weighted mean difference.

LAEF in the CS-ESUS subgroup (.6% increase in mean difference per year, $p = .04$ [95% CI .03–1.18], $R^2 = 70\%$), and NCES subgroup analyses (1% increase in mean difference per year, $p = .043$ [95% CI .8–2.04], $R^2 = 100\%$). As remaining heterogeneity remained high, we observed meta-regression bubble plots for

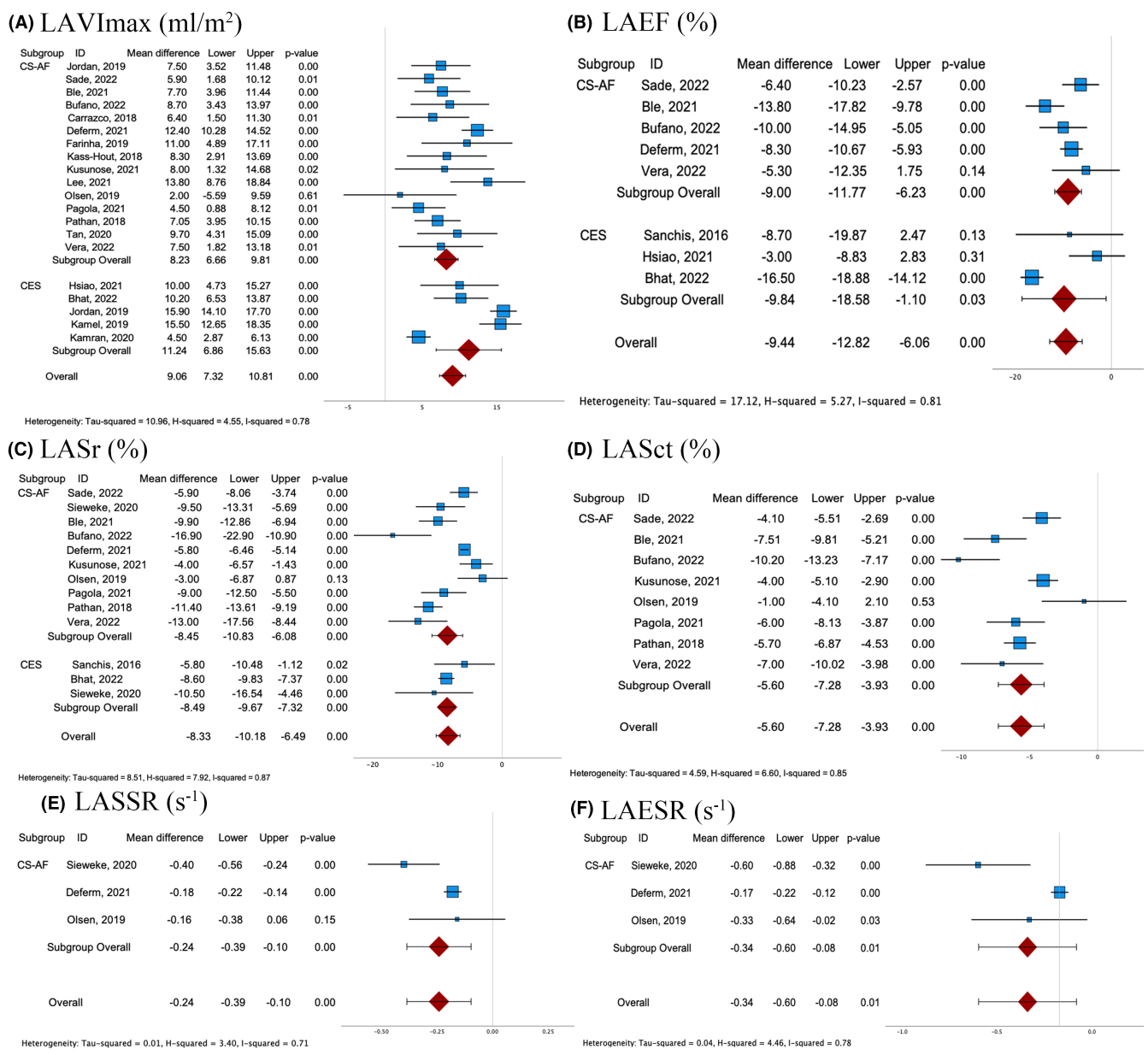


FIGURE 4 Forest plots demonstrating weighted mean difference and 95% confidence interval between CS-ESUS patients and CS-AF/CES subgroups from studies assessing LA metrics: (A) LAVImax (mL/m^2), (B) LAEF (%), (C) LASr (%), (D) LASct (%), (E) LASSR (s^{-1}) and (F) LAESR (s^{-1}). Forest plots demonstrate. CES, cardioembolic stroke; CS-AF, cryptogenic stroke with atrial fibrillation; CS-ESUS, cryptogenic stroke/embolic stroke of undetermined source; LAEF, left atrial emptying fraction; LAESR, left atrial early diastolic strain rate; LASr, left atrial reservoir strain; LASSR, left atrial systolic strain rate; LAVImax, maximum indexed left atrial volume.

visible outlier studies, and also performed a rigorous exclusion protocol by sequentially leaving out one or more studies from each analysis, in order to identify influential studies for potential sources of variation (Table 4).[6,16,21–23,26,28,30,32,34,35,37,39] Following outlier omission, variability was significantly reduced for all LA metrics, after controlling for age ($I^2 < 40\%$ for all variables). Due to the number of outlier studies, potential for pooled effect bias/distortion, reduction in generalizability following exclusion and lack of single obvious cause of outlier status,[13] we maintained these studies within the analysis and performed a thorough exploration for sources of discrepancy.

4 | DISCUSSION

This is the first systematic review and meta-analysis demonstrating significant alterations in both LA volume and function parameters in CS-ESUS patients compared to healthy controls and other stroke subtypes. We demonstrate alterations in LA parameters between groups,

TABLE 3 Comparison of weighted mean difference of LA parameters between CS-ESUS patients and CS-AF/CES patients.

	CS-AF				CES			
	n	WMD	95% CI	*p*-Value	*n*	WMD	95% CI	*p*-Value
LAVImax	15	8.23	6.66, 9.81	<.001	5	11.24	6.86 to 15.63	<.001
LAEF	5	−9.00	−11.77, −6.23	<.001	3	−9.84	−18.58 to −1.1	.027
LASr	10	−8.45	−10.83, −6.08	<.001	3	−8.50	−9.67 to −7.32	<.001
LASct	8	−5.60	−7.28, −3.93	<.001				
LAScd	5	−1.72	−6.32, 2.89	.46				
LA-SSR	3	−.24	−.39, −.10	.001				
LA-ESR	3	−.34	−.60, −.08	.01				
LA-ASR	3	−.39	−.89, .11	.13				

Abbreviations: 95% CI, 95% confidence interval; CES, cardioembolic stroke; CS-AF, cryptogenic stroke with atrial fibrillation; LAASR, left atrial late diastolic strain rate; LAEF, left atrial emptying fraction; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASER, left atrial early diastolic strain rate; LASr, left atrial reservoir strain; LASSR, left atrial systolic strain rate; LAVImax, indexed maximum left atrial volume; LAVImin, indexed minimum left atrial volume; *n*, number of studies; WMD, weighted mean difference.

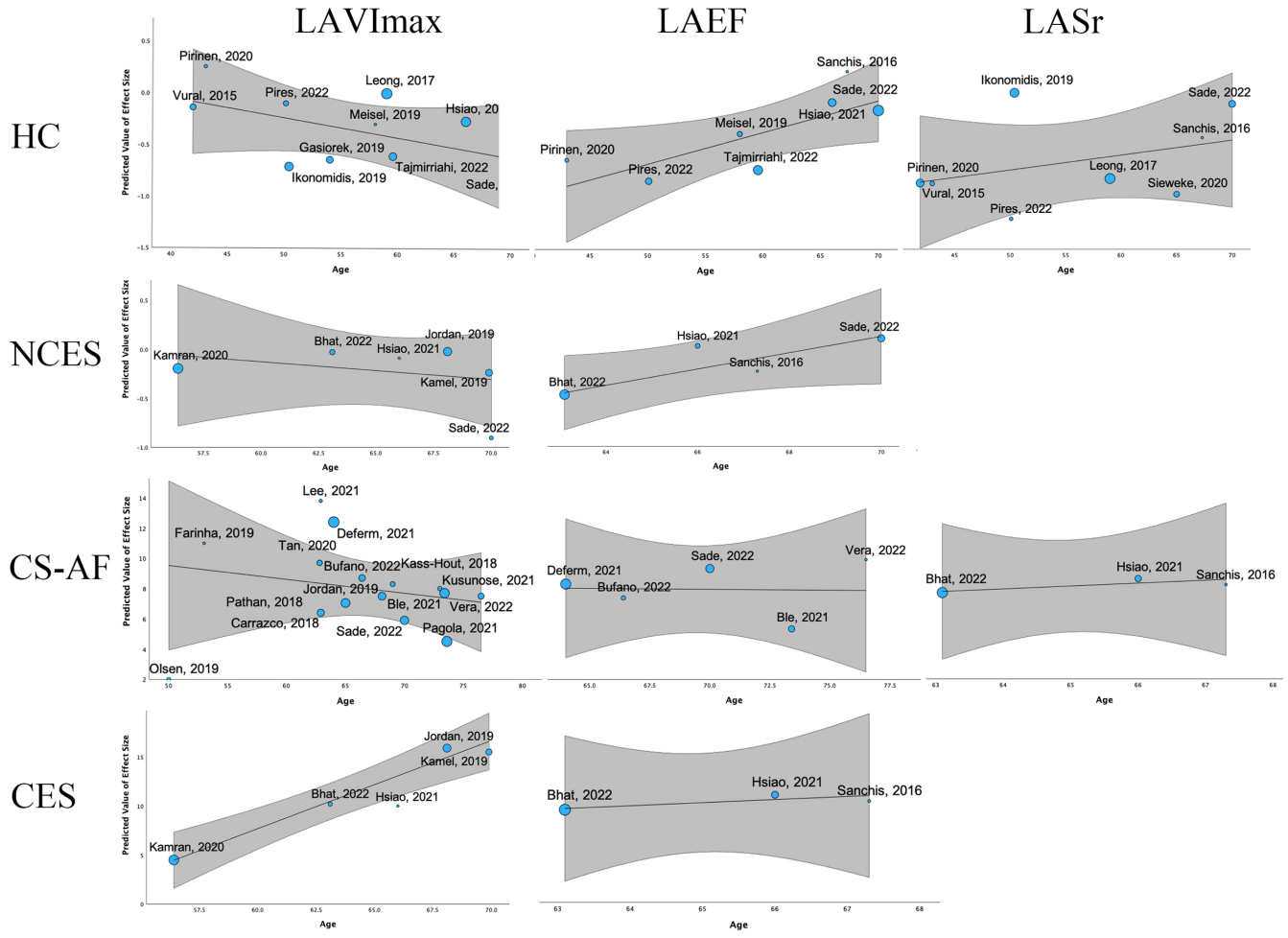


FIGURE 5 Association between LA metrics and participant age. The weighted mean difference of each metric (by subgroup) was modelled against participant age using a linear trend with a random-effects meta-regression model. The central black line represents the weighted regression line. The shaded grey area shows the 95% confidence interval. The blue circles indicate the mean difference of each study with the circle size representing study weight. CS-AF, cryptogenic stroke with atrial fibrillation; CS-ESUS, cryptogenic stroke/embolic stroke of undetermined source; HC, healthy controls; LAEF, left atrial emptying fraction; LASr, left atrial reservoir strain; LAVImax, maximum indexed left atrial volume; NCES, noncardioembolic stroke.

TABLE 4 Exploration of heterogeneity in meta-analysis assessment of left atrial metrics (1) following initial analysis, (2) following meta-regression with age covariate and (3) after removal of study outliers demonstrated with meta-regression.

	1. Heterogeneity with initial meta-analysis				2. Heterogeneity after controlling for age				3. Heterogeneity after controlling for age and excluding outlier studies					
	I^2	T^2	Q	p-Value	I^2	T^2	Q	p-Value	I^2	T^2	Q	p-Value	Final R^2	Significant outliers
LAVImin														
HC		9.3	28.1	<.001	67	3.19	18.4	.001	27	.98	6.9	.08	94.5	Hsaio
LAVImax	85													
HC	84	9.2	48.7	<.001	73	5.34	44.3	<.001	.1	.004	8.0	.24	99.9	Ikonomidis, Leong
NCES	61	3.2	17.9	<.001	64	3.0	17.5	.002	0	.001	8.9	.03	100	Jordan
CS-AF	47	4.2	28.9	.01	38	2.9	24.9	.02	26	1.6	16.1	.19	54	Olsen
CES	93	22.4	98.7	<.001	0	0	2.9	.4					100	
LAEF														
HC	88	42.3	48.7	<.001	69.9	12.4	22.7	<.001	16	1.05	6.32	.01	96.2	Tajmahiri, Sanchis
NCES	75	11.27	16.2	<.001	0	0	1.4	.50					100	
CS-AF	57	5.35	8.8	.07	36.9	2.91	8.4	.04	18	.98	5.2	.08	70	Vera
CES	85	47.91	18.7	<.001	0	0	2.7	.1					100	
LASr														
HC	98	77	252	<.001	97	58.1	247	<.001	0	0	2.6	.27	100	Ikonomidis, Pires, Sade
CS-AF	89	11.8	59	<.001	84	8.4	51	<.001	0	0	8.8	.11	100	Kusunose, Bufano, Pathan
CES	0	.01	1.73	.42	0	0	.93	.34					100	

Abbreviations: CES, cardioembolic stroke; CS-AF, cryptogenic stroke with atrial fibrillation; HC, healthy controls; LAEF, left atrial emptying fraction; LASr, left atrial reservoir strain; LAVImax, indexed maximum left atrial volume; LAVImin, indexed minimum left atrial volume; NCES, noncardioembolic stroke.

with CS-ESUS patients having larger LAVImax with reduced function compared to healthy controls and NCES patients. In contrast, CS-ESUS patients had smaller LA volume with better function when compared to CES and CS-AF patients. This finding suggests a potential role for CE-ESUS stroke subtype stratification using echocardiography, a readily available and relatively inexpensive investigation that is normally performed in stroke patients.

CS-ESUS was previously considered a posited consequence of subclinical AF[43]; however, large cohort studies presented here demonstrate AF in only 7.6%–21% of CS-ESUS patients.[6,18,23,27,31,38] LA dilatation has been demonstrated to be an independent predictor of AF in CS-ESUS patients,[15,23,38,39] although recent findings suggest alterations of LA function (LA strain) precede LA dilatation.[44] Notably, LA strain has predictive value over LA volume in identification of the CS-ESUS patient subset who develop AF,[16,18,26,30,34] with incremental validity.[6] Additionally, reduced LA strain had predictive value for recurrent stroke in CS-ESUS patients albeit in a single-centre study of modest size.[14] Our findings demonstrate CS-AF patients have altered LA volume and function resembling CES patients, highlighting a unique subtype of CS-ESUS patients prone to AF development that may benefit from extended rhythm monitoring and treatment adjustment.

There is increasing evidence which suggests that development of AF is preceded by an underlying ACM with increased thromboembolic risk, irrespective of AF development.[2] Expert consensus from the European Heart Rhythm Association, the Heart Rhythm Society, the Asian Pacific Heart Rhythm Society and Sociedad Latino Americana de Estimulacion Cardiaca y Electrofisiologia EHRAS have defined four classes which are influenced by pathological and genetic feedback. Classes I–IV are defined by histological changes and include: (I) cardiomyocyte hypertrophy observed with lone AF and with genetic diseases; (II) interstitial fibrotic changes consequential to ageing and smoking; (III) combination cardiomyocyte and fibrotic changes observed with cardiac pathologies of heart failure and valvular disease; and (IV) neutrophilic myocarditis secondary to infiltrative disease such as amyloidosis.[45] Fibrosis, in particular (Classes II and III), is a substrate for both AF development and thrombogenesis through disruption of LA electrical and mechanical properties.[46] Reduced LA functional metrics of LAEF, LASr, LAScd and LASct have been associated with increased LA fibrosis.[47] Our findings of increased LA volume and reduced LA function in CS-ESUS patients compared to healthy controls (LAVImax/LASr) and NCES patients (LAVImax/LAEF) suggest a underlying ACM in a proportion of CS-ESUS patients, with further distinction in CS-ESUS patients who subsequently develop AF.

Annually, over 13 million new stroke cases are reported worldwide, with the majority (84%) being ischaemic strokes.[48] Ischaemic stroke classification into current subtypes of large artery atherosclerosis, small artery atherosclerosis (lacunar), cardioembolic, other defined cause and cryptogenic (undetermined cause or incomplete evaluation), help guide early treatment and secondary prevention of stroke.[1] CES accounts for ~41% of all ischaemic strokes and typically has worse prognosis than other stroke subtypes, with anticoagulation recommended for secondary stroke prevention in patients demonstrating AF.[3,49] In contrast, secondary prevention in CS-ESUS patients remains a challenge due to lack of clarity of its pathogenesis and failure of classification of subtypes, amplified by a high recurrence rate.[2] Current recommendations for post-stroke imaging include a comprehensive TTE with assessment of LAVImax.[9] While LA strain has demonstrated predictive value for both AF and recurrent stroke in CS-ESUS patients, measurements of LA function are currently not recommended.

Our meta-analysis has demonstrated key findings: First, the improved LA volume and function metrics observed with CS-ESUS patients with sinus rhythm maintained compared to CS-AF patients, reveals CS-AF patients are a distinct subset of CS-ESUS patients, with LA parameters resembling CES patients. This would suggest that further subtypes are needed to be characterized within the currently held fairly broad definition for CE-ESUS. Second, LA enlargement and impaired function in CS-ESUS patients compared to healthy controls and NCE stroke patients, independent of AF, strongly suggests an underlying ACM. These findings present the opportunity for further risk stratification of CS-ESUS patients, with the subset of likely CS-AF patients targeted for anticoagulation. Our findings suggest the need for prospective studies of LA strain assessment, to assess its potential utility for standardization of stoke subtypes.

4.1 | Limitations

This study has some limitations. Correction for multiple comparisons was considered as a number of studies included multiple LA measurement outcomes. Multiplicity correction was not applied, however, as (1) each outcome variable was analysed in a separate meta-analysis with unique conclusion (2) studies varied in the number of reported outcome variables, including 9/29 studies with only one outcome variable and (3) multiplicity correction occasions a reduction in statistical power[50]— a consequence we determined objectionable in this study.

As previously mentioned, heterogeneity was high which was expected due to the observational nature of all

studies and subsequent clinical and methodological diversity. Improvement in heterogeneity was observed after controlling for age, which is an expected influential covariate.[42] Complete resolution of variation was observed in individual meta-analysis studies of CES subgroup (all LA metrics) and NCES subgroup (LAEF) after controlling for age; however, heterogeneity remained in some meta-analyses. We therefore examined meta-regression bubble plots and performed an exclusion analysis to identify outlier studies for sources of influence. A number of studies were identified over all meta-analysis studies, with resolution of heterogeneity observed following their exclusion.[6,16,21–23,26,28,30,32,34,35,37,39] Notably, the majority of outlier studies were observed in studies comparing CS-ESUS to HC, indicating probable unidentified clinical covariates in patients compared with healthy participants. In addition, meta-analysis examining the advanced measurement of LASr had a number of outlier studies which may indicate technical limitations. There are currently no standardized guidelines for a single technique of performing LA strain, with methodological variation in views, gating and tracing of the LA roof. In addition, a recently published meta-analysis of LA strain in healthy participants observed similarly high levels of heterogeneity, with comprehensive examination of potential covariates including sample size, BSA, heart rate, methodological approach, region-of-interest width and operator experience.[51] In our study, the majority of studies examining LA volume (16/29) used current or earlier (4/29) recommendations for LA volume[52,53] with the remainder (9/29) not defining specific standards used. For all outlier studies, we surmise body habitus played a role; however, BMI was only available in 12/29 studies and BSA in 8/29 which prevented additional meta-regression.[54,55] No specific trends were detected from study location; however, participant ethnicity was also likely influential, as previously demonstrated with international comparison of left atrial size and function.[42] Some variation in study design was observed as two studies demonstrated lower risk-of-bias score,[23,35] and five studies began patient enrolment in 2010 or earlier,[6,21,28,30,35] which we conject may have played a role in image acquisition and analysis due to earlier ultrasound systems and older TTE guidelines. Importantly, five outlier studies enrolled ≤31 participants in comparator groups[16,30,32,35,39] while only 10 studies were considered large scale (>100 participants), thereby reducing the power, precision and generalizability of results. While initial heterogeneity was high, after controlling for age and excluding outlier studies, residual heterogeneity of <40% for all metrics indicates our overall findings of differences between CS-ESUS patients and comparator subgroups are robust; however, we do advise caution at this stage in regard to clinical application of measurements.

Another limitation was the absence of extended diagnostic testing, as the majority of studies did not include transoesophageal echocardiogram to exclude patent foramen ovale (PFO), or pathology results of troponin,[56] brain natriuretic peptide (BNP) or N-Terminal pro-brain natriuretic peptide (NT-proBNP)[57] for improved discernment of patients as CS-ESUS or CES. Nevertheless, the significant differences in LA metrics we observed between these two subgroups demonstrates the overall precision and robustness of the meta-analysis, overriding intra-study error.

While we have demonstrated differences in echocardiographic LA metrics according to current stroke subtype classification, it suggests that CE-ESUS may require additional subtype characterization rather than the fairly broad current definition. We recommend future prospective examination of LA volume and function (including strain analysis), with standardization and refinement of acquisition and measurement techniques in order to define measurement limits. Future studies should include a large sample size for improvement in robustness and generalizability. We also suggest inclusion of additional diagnostic criteria of TOE/PFO, and pathology markers Troponin and NT-proBNP to improve stroke subtype classification prior to application in clinical practice.

5 | CONCLUSION

Our study demonstrates alterations in LA volume and function parameters in CS-ESUS patients that are indicative of an associated atrial myopathy. Additionally, the CS-ESUS subtype that subsequently develop AF (CS-AF), has greater alterations in LA parameters, suggesting the need to define CE-ESUS subtypes. TTE offers an affordable and easily available modality for assessment of LA parameters and is performed routinely in almost all stroke patients, however without assessment of LA function. Routine measures of LA volume and function should be considered for ischaemic stroke risk stratification. Future prospective studies are required with stringent covariate controls to validate the clinical utility of LA volume and function parameters, and to define cut offs for patient classification and risk stratification.

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CONFLICT OF INTEREST STATEMENT

None.

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