



ORIGINAL RESEARCH

Left Heart Factors in Embolic Stroke of Undetermined Source in a Multiethnic Asian and North African Cohort

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BACKGROUND: Cardiac features diverge in Asians; however, it is not known how these differences relate to embolic stroke of unknown source (ESUS) in Southeast Asian and Eastern Mediterranean regions.

METHODS AND RESULTS: A retrospective analysis of prospectively collected acute ischemic stroke data from 2014 to 2018 was performed. Stroke subtypes were noncardioembolic stroke (large-vessel and small-vessel disease; $n=1348$), cardioembolic stroke ($n=532$), and ESUS ($n=656$). Subtypes were compared by demographic, clinical, and echocardiographic factors. In multivariate logistic regression, patients with ESUS in comparison with noncardioembolic stroke were twice as likely to have left ventricular diastolic dysfunction ($P=0.001$), 3 times the odds of global hypokinesia ($P=0.001$), and >7 times the odds of left ventricular wall motion abnormalities ($P=0.001$). In the second model comparing ESUS with cardioembolic stroke, patients with ESUS were 3 times more likely to have left ventricular wall motion abnormalities ($P=0.001$) and 1.5 times more likely to have left ventricular diastolic dysfunction grade I ($P=0.009$), and 3 times more likely to have left ventricular diastolic dysfunction grades II and III ($P=0.009$), whereas age ($P=0.001$) and left atrial volume index ($P=0.004$) showed an inverse relation with ESUS. ESUS in patients ≥ 61 years old had higher levels of traditional risk factors such as coronary artery disease, but the coronary artery disease was not significantly different in ESUS age groups ($P=0.80$) despite higher left ventricular wall motion abnormalities ($P=0.001$).

CONCLUSIONS: Patients with ESUS and noncardioembolic stroke were younger than patients with cardioembolic stroke. While a third of the patients with ESUS >45 years old had coronary artery disease, it was unrecognized or underreported in the older ESUS age group (≥ 61 years old). In patients with ESUS from Southeast Asia and Eastern Mediterranean regions, left ventricular wall motion abnormalities and left ventricular diastolic dysfunction were related to ESUS.

Key Words: cardiac wall motion abnormalities ■ embolic stroke ■ ESUS ■ left atrial volume index

The Southeast Asian and Eastern Mediterranean regions of the World Health Organization mostly comprise Asian low-income countries. Four Southeast Asian countries (India, Pakistan, Bangladesh, and Sri Lanka) constitute 25% of the world's population and contribute nearly 60% of the global cardiovascular disease burden and up to 40% of global stroke deaths.^{1,2} The stroke-related risk factors relatively specific to Asia include stroke at a younger age, premature atherosclerosis, higher prevalence of intracranial

atherosclerosis, pre-diabetes mellitus (DM), and new-onset DM compared with Whites.²⁻⁴ While coronary artery disease (CAD) has declined in developed countries over the past 40 years, rates have doubled in the South Asian immigrant population.⁵ CAD studies including South Asian immigrants living in Europe and the United States report a higher prevalence, predisposition to, and more extensive CAD at a younger age⁶ and a higher proportional mortality rate compared with non-Hispanic Whites.⁷ The CVDNOR (Cardiovascular

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CLINICAL PERSPECTIVE

What Is New?

- Embolic stroke of undetermined source (ESUS) is an important global public health issue; cardiac features diverge in Asians, and increasing evidence from across the world shows that ESUS risk and clinical profiles differ on the basis of ethnicity.
- Two major studies, the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Dabigatran Etxilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source), reported data on 12 522 ESUS patients with paucity of ESUS from northern Africa, the Middle East and many parts of Asia, representing over one third of the world's population; our study is the first to provide data on ESUS from West Asia, South Asia, and North Africa showing that the burden of ESUS in these areas is greater than other global estimates and that ESUS occurs at a much younger age.
- Our results indicate that cardiac wall motion abnormalities and left ventricular diastolic dysfunction are an important factor in ESUS development in South Asians, implying that underlying cardiac wall motion abnormalities may be a cause of embolism in ESUS; coronary artery disease and myocardial infarction are more common, at a younger age, in these ethnic groups.

What Are the Clinical Implications?

- The risk factor and clinical profiles of patients with ESUS may differ from area to area across the world, influencing the global variations in etiology, occurrence, and outcome of ESUS.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aOR	adjusted odds ratio
CAD	coronary artery disease
CES	cardioembolic stroke
DM	diabetes mellitus
EF	ejection fraction
HF	heart failure
LAVI	left atrial volume index
LVDD	left ventricular diastolic dysfunction
LVWMAs	left ventricular wall motion abnormalities
MI	myocardial infarction
NCES	noncardioembolic stroke

Disease in Norway) project showed that acute myocardial infarction (MI) and stroke rates were highest in South Asians.⁸ Furthermore, in the SHARE (Study of Health Assessment and Risk in Ethnic Groups), South Asian ethnic origin was an independent risk factor for cardiovascular disease.⁹

Embolic stroke of unknown source (ESUS) accounts for 16% to 32% of ischemic strokes.¹⁰ Whereas ESUSs are suspected to be of cardiac origin (particularly covert atrial fibrillation [AF]), South Asian ethnicity is associated with a lower risk of AF despite a higher prevalence of established risk factors.¹¹ This is especially interesting since NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Dabigatran Etxilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) trials with over 13 000 patients did not show the superiority of anticoagulation over aspirin suggesting that undetected paroxysmal AF is not a major cause of recurrent stroke. Recent publications highlight a wide range of potential cardiac embolic sources associated with ESUS, such as atrial fibrosis without AF, left atrial enlargement, unrecognized MI with myocardial scar, left ventricular wall motion abnormalities (LVWMAs), patent foramen ovale, and elevated cardiac troponin levels.^{12–19} Studies have shown that atrial and ventricular features diverge in South Asians compared with the non-South Asians.²⁰ However, there is a paucity of data on how left heart factors relate to ESUS from the 2 aforementioned World Health Organization regions.

The objective of this study, therefore, was to identify left heart factors that are associated with patients with ESUS in a multiethnic Asian and North African cohort from member countries of World Health Organization's Southeast Asian and Eastern Mediterranean regions.

METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Hamad Medical Corporation, Qatar. The study did not require a consent process because of study design (retrospective).

The data were prospectively collected at a tertiary referral center with well-established comprehensive stroke service accredited by Joint Commission International. The stroke service includes acute stroke diagnostic, stroke units, vascular interventional services, vascular neurological surgery, and rehabilitation services. An acute stroke team provides a rapid assessment service 24 hours a day, 7 days a week. The

data that support the findings of this study are available from the corresponding author upon reasonable request.

All patients ≥ 18 years old with acute stroke admitted from January 1, 2014, through December 31, 2018, were included in the study. Exclusion criteria (Figure) consisted of malignancy, hypercoagulable state, incomplete workup, missing data, and ESUS with intracranial or nonstenotic ($< 50\%$) carotid atherosclerotic plaques ipsilateral to the ESUS event. The stroke subtypes were classified according to TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria by stroke neurologists.²¹ Data included age, sex, hypertension, pre-DM and DM (defined according to the American Diabetes Association criteria),²² dyslipidemia, smoking, CAD (defined by a history of MI or typical angina, a positive diagnostic test [stress test, coronary angiography], or appropriate treatment). Admission National Institute of Health Stroke Scale score and CHA₂DS₂-VASc score were also recorded. Vascular imaging included craniocervical magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography. Holter monitoring was performed for at least 24 to 48 hours in patients with nonlacunar stroke within 5 days of symptoms (except for patients with known AF), and 2-dimensional transthoracic echocardiography and additional transesophageal echocardiography (at the discretion of treating physicians) was performed up to 4 days after admission.

Echocardiography

Transthoracic echocardiography was performed according to the American Society of Echocardiography guidelines²³ by specialists blinded to the other variables and independent of the study team. The following atrial and ventricular variables were recorded:

Left atrium and valves: Left atrial volume index (LAVI, expressed as mL/m²), left atrial appendage stasis/spontaneous echo densities, patent foramen ovale/atrial septal aneurysm, mitral and aortic annular calcification, valvular strands, valvular vegetations, and aortic root diameter.

Left ventricle: Left ventricular ejection fraction (EF) as a percentage, LVWMA (scored on a 17-segment model) with wall motion score index also calculated. Left ventricular mass indexed to height^{2.7} to obtain LV mass index LVMI g/m^{2.7}.²⁴ Regional wall thickness with a value of > 0.42 used to indicate abnormal wall thickness.²⁵ Left heart failure (HF) classified according to EF: HF with reduced EF, HF with medium-range EF, or HF with preserved EF²⁶ and left ventricular diastolic dysfunction (LVDD) categorized as mild (grade I), moderate (grade II), and severe (grade III).²⁷

Holter monitoring: Two categories of atrial premature beats were studied: runs of premature atrial contractions defined as atrial premature beat runs of > 20 beats (> 20 consecutive atrial premature beats) and the number of isolated atrial premature beats within 24 hours divided into the following groups: > 0 to < 100 , ≥ 100 to 499, 500 to 999, 1000 to 1499, and ≥ 1500 .²⁸

Statistical Analysis

Descriptive statistics in the form of mean and SD were calculated for all interval variables (eg, age, hemoglobin A_{1c}, LAVI mL/m²), with frequency and percentages calculated for each categorical variable in the study. Data were explored after grouping according to stroke subtype (noncardioembolic strokes [NCES], cardioembolic strokes [CES], and ESUS) and by age (arbitrarily divided into 3 groups, ≤ 45 years old, 46–60 years old, and > 60 years old) for patients with ESUS. One-way ANOVA with post hoc analysis (Bonferroni) were performed for all interval variables, whereas chi-square tests were used to test for associations between categorical variables. Two multivariate logistic regressions were performed: First, ESUS was compared with NCES; and second, ESUS was evaluated in relation to patients with CES. $P < 0.05$ (2-tailed) were considered significant for all statistics. SPSS version 22.0 (SPSS Inc., Chicago, IL) was used for all analysis.

RESULTS

A total of 2536 stroke patients were included in the final analysis after excluding 597 patients that did not meet inclusion criteria (Figure). Within the final cohort, the stroke subtypes were 1348 (53.2%) NCES (large-vessel and small-vessel disease), 532 (21.0%) CES, and 656 (25.8%) ESUS. The baseline demographics, clinical characteristics, and atrial and ventricular factors measured are listed in Table 1. The mean age of patients with ESUS was similar to NCES but significantly younger than CES ($P = 0.001$). For stroke risk factors, there was a higher prevalence of DM in CES, while smoking was more frequent in ESUS ($P = 0.01$) (Table 1).

Stroke Subtypes and Left Atrium

LAVI was largest in CES (30.1 ± 16.5 mL/m²) followed by ESUS (25.6 ± 12.1 mL/m²) and NCES ($P = 0.001$). Mitral valve calcification was observed more often in CES than ESUS and NCES ($P = 0.001$). No difference was seen for patent foramen ovale and atrial septal aneurysm ($P = 0.10$), valvular strands ($P = 0.23$), and

Table 1. Comparison Between Noncardioembolic Strokes, Cardioembolic Strokes, and ESUS

Factors	Noncardioembolic (Large-Vessel and Small-Vessel Disease) (1348/2536) 53.2%	Cardioembolic Stroke (532/2536) 20.9%	ESUS (656/2536) 25.9%	P Value
Age, y	55.6±12.7	60.5±14.1*	56.4±13.7 [†]	0.001
Female, n (%)	232 (17.2)	176 (33.1)	114 (17.4)	0.001
Male, n (%)	1116 (82.8)	355 (66.9)	542 (82.6)	
Diabetes mellitus, n (%)	776 (57.6)	376 (70.7)	369 (56.3)	0.001
Pre-diabetes mellitus, n (%)	278 (20.6)	69 (13)	127 (19.4)	0.001
Hemoglobin A _{1c} %	6.4±1.5	6.4±1.3	6.5±1.5	0.38
Hypertension, n (%)	1082 (80.3)	426 (80.1)	531 (80.9)	0.92
Metabolic syndrome, n (%)	184 (13.6)	76 (14.3)	80 (12.2)	0.53
Smoking, n (%)	166 (12.5)	62 (11.8)	106 (16.6)	0.01
Dyslipidemia, n (%)	951 (70.5)	346 (85)	455 (69.5)	0.06
Coronary artery disease, n (%)	432 (32)	141 (26.5)	200 (30.5)	0.06
LAVI, mL/m ²	23.5±10	30.1±16.5*	25.6±12.1 ^{††}	0.001
PFO/AS aneurysm, n (%)	22 (1.6)	15 (2.8)	8 (1.2)	0.10
Spontaneous echo contrast, n (%)	9 (0.7)	4 (0.8)	8 (1.2)	0.47
Mitral calcification, n (%)	326 (25.1)	186 (36.5)	187 (28.8)	0.001
Aortic sclerosis, n (%)	487 (37.0)	213 (40.6)	248 (38.0)	0.36
Aortic root diameter	3.1±0.5	30±0.6	3.1±0.6 [†]	0.10
EF%	53.5±6.8	50.8±9.2*	49.6±10 ^{††}	0.001
LVWMA, n (%)	91 (7.0)	66 (12.9)	187 (28.7)	0.001
Global hypokinesis, n (%)	42 (3.2)	47 (9.2)	66 (10.1)	0.001
WMSI	1±0.2	1.1±0.2*	1.2±0.3 ^{††}	0.001
LVMI g/m ^{2.7}	37.7±31	35.0±39.5	41.2±36.1 ^{††}	0.01
RWT	0.4±0.5	0.3±0.5*	0.4±0.5	0.09
Heart geometry, n (%)				
Concentric remodeling	156 (13.6)	57 (15.4)	82 (14.2)	0.10
Eccentric LV hypertrophy	126 (11.0)	32 (8.6)	68 (11.8)	
Concentric LV hypertrophy	133 (11.6)	53 (14.3)	72 (12.5)	
LVDD, n (%)				
Grade I	620 (55.6)	201 (45.5)	293 (54.5)	0.001
LVDD Grade II+III	25 (2.2)	15 (3.4)	31 (5.8)	
Congestive heart failure, n (%)				
HFrEF	49 (3.6)	58 (10.9)	86 (13.1)	0.001
HFmrEF	20 (1.5)	21 (3.9)	25 (3.8)	
HFpEF	117 (8.7)	95 (17.9)	58 (8.8)	
Holter, n (%)				
APB run >20 beats	17 (1.3)	12 (2.3)	14 (2.1)	0.19
APB/24 h				0.49
>0 to <100	271 (68.6)	122 (66.3)	133 (67.2)	
≥100 to 499	102 (25.8)	43 (23.4)	48 (24.2)	
500 to 999	4 (1.0)	2 (1.1)	1 (0.5)	
1000 to 1499	1 (0.3)	2 (1.1%)	3 (1.5)	
≥1500	17 (4.3)	15 (8.2)	13 (6.6)	
Admission NIHSS	4.6±4.7	5.3±6.4*	5.7±5.4 [†]	0.001
CHA ₂ DS ₂ VASc	4.1±1.1	4.5±1.2*	4.3±1.2 ^{††}	0.001

APB indicates atrial premature beat; AS, atrial septal aneurysm; EF, ejection fraction; ESUS, embolic stroke of unknown source; HFmrEF, heart failure with medium-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; LVWMA, left ventricular wall motion abnormalities; NIHSS, National Institute of Health Stroke Scale; PFO, patent foramen ovale; RWT, regional wall thickness; and WMSI, wall motion score index.

*Noncardioembolic stroke with cardioembolic.

[†]Cardioembolic stroke with ESUS ($P \leq 0.05$).

^{††}Noncardioembolic stroke with ESUS.

aortic arch atheroma ($P=0.20$) among the 3 stroke groups. Valvular vegetations were reported in 5 patients with CES, and no significant difference in supraventricular arrhythmias was found among the 3 groups (Table 1).

Stroke Subtypes and Left Ventricle

ESUS had the lowest EF ($49.6\pm 10\%$) followed by CES ($50.8\pm 9.2\%$) and NCES ($53.5\pm 6.8\%$) ($P=0.001$). LVWMA were more frequent (28.7% versus 12.9% versus 7.0%) with higher wall motion score index in ESUS compared with CES and NCES ($P=0.001$). LVMI was not different between NCES and CES but significantly higher in ESUS ($P=0.01$) with no divergence noted in heart geometry ($P=0.10$). The percentage of patients with HF with reduced EF was highest in ESUS followed by CES and least in NCES ($P=0.001$). While grade I LVDD was similar in NCES and ESUS but lower in CES, grade II-III LVDD was more common in ESUS alone ($P=0.001$). Admission National Institute of Health Stroke Scale was higher in ESUS compared with other groups, while the $\text{CHA}_2\text{DS}_2\text{VAS}_\text{C}$ scores were higher in CES (Table 1).

In the first multivariate logistic regression (Table 2), patients with ESUS in comparison with patients with NCES were twice as likely to have LVDD (adjusted odds ratio [aOR], 2.15; 95% CI, 1.07–4.31; $P=0.001$), over 3 times the odds of global hypokinesia (aOR, 3.72; 95% CI, 2.0–7.0; $P=0.001$), and more than 7 times the odds of LVWMA (aOR, 7.14; 95% CI, 4.44–10.90; $P=0.001$) after adjustment for age, DM, smoking, mitral calcification, EF, LVMI, and $\text{CHA}_2\text{DS}_2\text{VAS}_\text{C}$ score.

Table 2. Multivariate Logistic Analysis for ESUS in Comparison With Noncardioembolic Stroke

ESUS in Comparison With Noncardioembolic Stroke		
Variable	aOR (95% CI)	P Value
Age	0.988 (0.97–0.99)	0.04
LAVI	1.00 (0.99–1.02)	0.38
EF	1.00 (0.98–1.02)	0.89
LVMI	1.00 (0.99–1.00)	0.19
$\text{CHA}_2\text{DS}_2\text{VAS}_\text{C}$	1.04 (0.90–1.22)	0.53
Diabetes mellitus	0.83 (0.62–1.12)	0.24
Smoking	0.85 (0.58–1.25)	0.42
Mitral calcification	1.26 (0.90–1.77)	0.18
LVDD grade I DD	0.97 (0.96–0.98)	0.073
LVDD grade II+III DD	2.15 (1.07–4.31)	0.001
LVWMA	7.14 (4.44–10.87)	0.001
Global hypokinesia	3.72 (1.98–7)	0.001

aOR indicates adjusted odds ratio; EF, ejection fraction; ESUS, embolic stroke of unknown source; LAVI, left atrial volume; LVDD, left ventricular diastolic dysfunction; LVDD, left ventricular diastolic dysfunction; LVMI, left ventricular mass index; and LVWMA, left ventricular wall motion abnormalities.

Table 3. Multivariate Logistic Analysis for ESUS in Comparison With Cardioembolic Stroke

ESUS in Comparison With Cardioembolic Stroke		
Variable	aOR (95% CI)	P Value
Age	0.98 (0.97–0.99)	0.001
Hypertension	0.81 (0.55–1.19)	0.29
Diabetes mellitus	0.59 (0.42–0.81)	0.001
Dyslipidemia	1.30 (0.93–1.81)	0.12
Smoking	0.92 (0.58–1.45)	0.71
CAD	1.001 (0.72–1.39)	0.99
LAVI	0.98 (0.97–0.99)	0.004
LVDD grade I	1.50 (1.12–2.03)	0.009
LVDD grades II+III	2.90 (1.30–6.32)	0.009
HF _r EF	0.70 (0.43–1.17)	0.18
HF _{mr} EF	0.70 (0.39–1.26)	0.24
HF _p EF	1.12 (0.47–2.65)	0.81
LVMI	1.006 (1.00–1.01)	0.77
LVWMA	3.13 (1.95–5.01)	0.001
Global hypokinesia	1.36 (0.73–2.53)	0.34

aOR indicates adjusted odds ratio; CAD, coronary artery disease; HF_mEF, HF with medium-range ejection fraction; HF_pEF, HF with preserved ejection fraction; HF_rEF, HF with reduced ejection fraction; LAVI, left atrial volume; LVDD, left ventricular diastolic dysfunction; LVMI, left ventricular mass index; and LVWMA, left ventricular wall motion abnormalities.

In the second model (Table 3), patients with ESUS in comparison with patients with CES were 3 times more likely to have LVWMA (aOR, 3.10; 95% CI, 2.06–4.63; $P=0.001$), LVDD grade I (aOR, 1.50; 95% CI, 1.12–2.03; $P=0.009$) and grades II and III (aOR, 2.90; 95% CI, 1.30–6.32; $P=0.009$), whereas age (aOR, 0.98; 95% CI, 0.97–0.99; $P=0.001$), DM (aOR, 0.59; 95% CI, 0.42–0.81; $P=0.001$), and LAVI (aOR, 0.98; 95% CI, 0.97–0.99; $P=0.004$) showed an inverse relation with ESUS after adjusting for age, hypertension, DM, dyslipidemia, smoking, CAD, HF (HF with reduced EF, HF with medium-range EF and HF with preserved EF), LVMI, and global hypokinesia.

ESUS Subgroup Comparison by Age

Univariate analysis was performed according to age categories (≤ 45 , 46–60, and ≥ 61 years old) in patients with ESUS. Patients with ESUS ≥ 61 years old had more DM, hypertension, LAVI, mitral calcification, and LVWMA and higher wall motion score index and $\text{CHA}_2\text{DS}_2\text{VAS}_\text{C}$. Dyslipidemia, smoking, and LVDD were more frequent in the 46 to 60 years age group. LVWMA were observed in 12.2% of the patients ≤ 45 years old. EF showed a decline with increasing age ($P=0.001$). Patent foramen ovale ($P=0.54$) and atrial septal aneurysm ($P=0.13$) were not significantly different among the age groups. LAVI was significantly associated with LVDD grades ($P=0.001$) in reference to age category ≤ 45 (0.21), 46

to 60 ($P=0.03$), and >61 ($P=0.04$). No association was found between LVDD and heart geometry ($P=0.77$) with age ≤ 45 (0.96), 46 to 60 ($P=0.99$), and ≥ 61 ($P=0.44$). CAD was not significantly different in ESUS age groups ($P=0.80$) despite higher LVWMA ($P=0.001$) in the older age groups (Table 4).

DISCUSSION

The present study shows that patients with ESUS were younger in comparison with CES and not NCES, with

higher frequency of LVWMA and LVDD in comparison with NCE and CE strokes. LAVI was higher in patients with CES followed by patients with ESUS and NCES, and it was inversely related to ESUS when compared with CES in multivariate analysis. LVMI was higher in patients with ESUS compared with NCE and CES groups without any significant difference in left ventricular remodeling. Surprisingly, there was no significant difference in the frequency of CAD among the ESUS age groups, despite higher frequency of LVWMA in the older groups.

Table 4. ESUS Subgroup Comparison by Age

Factors	≤ 45 y (139/656)	46 to 60 y (280/656)	≥ 61 y (237/656)	P Value
Female, n (%)	16 (11.5)	28 (10.0)	70 (29.5)	0.001
Male, n (%)	123 (88.5)	252 (90.0)	167 (70.5)	
Diabetes mellitus, n (%)	48 (34.5)	159 (56.8)	162 (68.4)	0.001
Pre-diabetes mellitus, n (%)	37 (26.6)	56 (20.0)	34 (14.3)	0.01
Hemoglobin A _{1c} %	5.9 \pm 1.2	6.6 \pm 1.6*	6.6 \pm 1.5 [†]	0.001
Hypertension, n (%)	102 (73.4)	229 (81.8)	200 (84.4)	0.03
Metabolic syndrome, n (%)	19 (13.7)	32 (11.4)	29 (12.2)	0.80
Smoking, n (%)	15 (11.0)	60 (22.1)	31 (13.5)	0.005
Dyslipidemia, n (%)	85 (61.6)	212 (75.7)	158 (66.7)	0.01
Coronary artery disease, n (%)	45 (32.4)	86 (30.7)	69 (29.1)	0.8
LAVI, mL/m ²	22.7 \pm 9.4	24.3 \pm 11.6	29.3 \pm 13.6 ^{†‡}	0.001
Mitral calcification, n (%)	2 (1.1)	52 (27.8)	133 (71.1)	0.001
Aortic root diameter	3.1 \pm 0.6	3.1 \pm 0.6	3.1 \pm 0.5	0.96
EF%	52.6 \pm 8.4	49.5 \pm 9.8*	48 \pm 10.8 [†]	0.001
LVWMA, n (%)	17 (12.2)	83 (29.6)	87 (36.7)	0.001
Global hypokinesia, n (%)	13 (9.4)	28 (10.0)	25 (10.5)	0.93
WMSI	1.0 \pm 0.2	1.1 \pm 0.4*	1.2 \pm 0.4 [†]	0.001
LVMI g/m ^{2.7}	38.2 \pm 24.2	40.5 \pm 41.8	43.6 \pm 34.5	0.34
RWT	0.36 \pm 0.2	0.37 \pm 0.5	0.42 \pm 0.6	0.58
Heart geometry, n (%)				
Concentric remodeling	16 (13.2)	36 (14.6)	30 (14.3)	0.13
Eccentric LVH	18 (14.9)	20 (8.1)	30 (14.3)	
Concentric LVH	16 (13.2)	39 (15.8)	17 (23.6)	
LVDD, n (%)				
Grade I	45 (15.4)	134 (45.7)	114 (38.9)	0.01
LVDD Grades II+III	5 (16.1)	16 (51.6)	10 (32.3)	
APB/24 h, n (%)				
>0 to <100	29 (65.9)	64 (77.1)	40 (56.3)	0.12
≥ 100 to 499	13 (29.5)	15 (18.1)	20 (28.2)	
500 to 999	0	0	1 (1.4)	
1000 to 1499	1 (2.3)	0	2 (2.8)	
>1500	1 (2.3)	4 (4.8)	8 (11.3)	
CHA ₂ DS ₂ -VAS _C	3.6 \pm 1	4 \pm 0.9*	5.1 \pm 1.1 ^{†‡}	0.001

APB indicates atrial premature beats; EF, ejection fraction; LAVI, left atrial volume index; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; LVWMA, left ventricular wall motion abnormalities; RWT, regional wall thickness; and WMSI, wall motion score index.

* ≤ 45 years with 46 to 50 years.

[†] ≤ 45 years with ≥ 61 years.

[‡]46 to 50 years with ≥ 61 years.

The mean age of our ESUS cohort was 10 years younger compared with the NAVIGATE ESUS and RE-SPECT ESUS, trials with twice the percentage of patients <60 years old, compared with all NAVIGATE ESUS ethnic subgroups.^{29,30} A third of patients with ESUS had CAD, while the frequency of DM, hypertension, and dyslipidemia was higher than reported in the 2 above randomized trials and the ESUS Global Registry.^{10,29,30} Although ESUS subgroups showed no difference in the CAD, higher frequency of LVWMA in older groups point to either unrecognized and or underreported CAD in the older age groups. Of particular concern was the frequency of CAD in patients with ESUS <45 years old (32.4%), 12% having evidence of previous MI (LVWMA), 32% EF <52% and ventricular hypertrophy/remodeling present in 21%. Our data support previously reported MI rates of 23% in patients of South Asian origin under the age of 40.³¹ In the NAVIGATE ESUS trial, 4% of East Asians had CAD, a finding shared by the CVDNOR study, highlighting the ethnic inequalities within Asia and showing that South Asians have the highest risk of acute MI while East Asians have the lowest risk.^{8,29}

LAVI in our cohort was higher in patients with ESUS than patients with NCES but less than patients with CES. When age was taken into consideration, 15% of the patients with ESUS <45 years old had increased LAVI. Recent evidence supports the association between left atrial enlargement and recurrent embolic stroke independent of confounders, including AF.³² The presence of atrial cardiopathy in the Asian ESUS population could serve as a risk-stratifying marker for stroke recurrence. In a subgroup of the NAVIGATE ESUS trial with moderate to severe left atrial enlargement, anticoagulation showed a reduction in stroke recurrence.³³ Whether anticoagulant therapy reduces stroke recurrence in patients with atrial cardiopathy is being tested in the ARCADIA (Atrial Cardiopathy and

Antithrombotic Drugs in Prevention After Cryptogenic Stroke) trial.³⁴

A high burden of supraventricular tachyarrhythmias also indicates an abnormal atrial substrate and is strongly associated with incident AF and increased risk of stroke independent of diagnosed AF³¹ but our data do not support these findings. Patients with ESUS in the current study were younger, with atrial cardiopathy without any significant difference in supraventricular tachyarrhythmias between stroke subtypes (NCES, CES, and ESUS), suggesting that the younger Asian ESUS cohort may have a lower risk of AF.

To our knowledge, there is no data on the implications of left ventricular pathology in patients with ESUS from Asia. The MESA (Multi-Ethnic Study of Atherosclerosis) and LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) studies have reported the association of left ventricular hypertrophy and left ventricular geometry with an increased risk of stroke.³⁵ Our data show higher LVMI in patients with ESUS compared with NCE and CE stroke but the pattern of cardiac remodeling showed no difference. Although LVMI increased with age in ESUS, overall no difference was found in the pattern of remodeling, and it was only concentric left ventricular hypertrophy that increased with age without any association with stroke type. LVMI and cardiac geometry may reflect the severity and chronicity of vascular risk factors, and the regression of LVMI with antihypertension medication may confer protection for ESUS independent of blood pressure reduction.³⁶

LVWMA is another manifestation of left ventricular systolic dysfunction encountered in 5% of patients without known CAD,³⁷ which confers a greater risk for any cardiovascular event including stroke.³⁸ The frequency of LVWMA in our ESUS cohort was 28.7%, in comparison with 4% reported in the ESUS Global Registry.¹⁰ The difference is most likely due to the

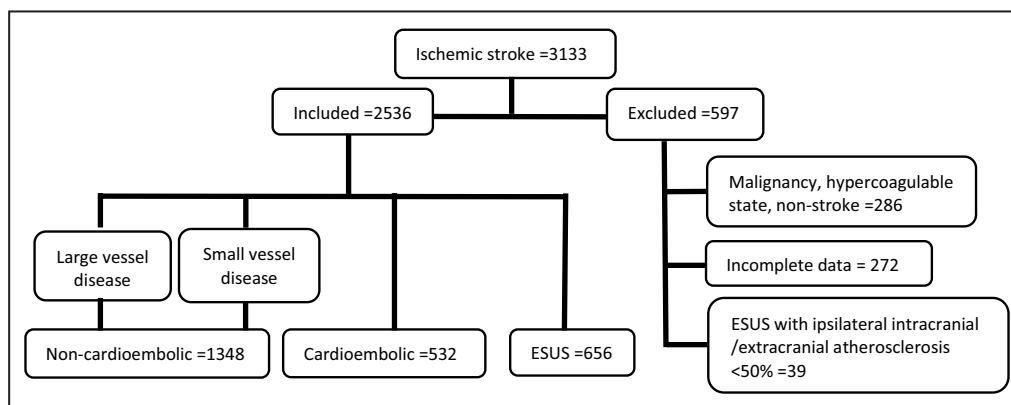


Figure 1. Flowchart with inclusion and exclusion criteria. ESUS indicates embolic stroke of undetermined source.

prevalence of CAD and MI in our younger Asian cohort. Although there is some ambiguity regarding the potential embolic role of LVWMA in stroke,^{14,39} our data show a significant and independent association of LVWMA with ESUS, which remained significant even in the ESUS age subgroups. The current ESUS cohort had lower EF and more HF with reduced EF compared with NCES and CES, and EF decreased further in ESUS according to age subgroups.

The current data show that LVDD was more frequent in patients with ESUS compared with patients with NCES and CES. Consistent with previous publications, we found that LVDD had a significant association with LAVI.⁴⁰ LVDD leads to structural and functional changes of the left atrium, which is a predictor of stroke recurrence and correlates with the new onset of AF. Therefore, LVDD might be a useful marker of atrial myopathy in Asian patients with ESUS and could be helpful in discriminating stroke mechanisms without detected AF.

Multiple studies have reported a higher prevalence of nonstenosing atherosclerotic plaque ipsilateral to ESUS that could be a coexisting potential source of embolism,^{41,42} making it difficult to determine the exact mechanism of stroke. To avoid this, we excluded patients with ESUS with nonstenotic (<50%) intracranial or extracranial vessel atherosclerosis, ipsilateral to the ESUS event. In our data, the minor embolic sources and aortic arch atheroma were not more prevalent in ESUS than NCE and CE strokes. Moreover, the prevalence of extracranial carotid and aortic arch atherosclerotic disease is less in Asians compared with Whites.⁴³ Although prospective studies have shown that mitral annular calcification increases the risk of stroke,⁴⁴ we did not observe such an association despite elevated mitral calcification in ESUS age subgroups (46–60 and ≥61 years old).

Our study has the limitations of a retrospective analysis of prospectively collected data such as collection bias, registration bias, and unregistered confounding factors. Moreover, the number of females was less than males because the expatriate population was mostly men. Despite these limitations, our findings provide the only detailed data from regions where there is a dearth of literature about ESUS.

In conclusion, patients with ESUS from Southeast Asia and Western Mediterranean World Health Organization regions were younger, with a higher frequency of risk factors. The relative mean young age of patients with ESUS was further compounded by the increased incidence of CAD in those <45 years old. The involvement of potential embolic left atrial enlargement and the risk factors for developing AF were present at a much younger age. LVSWMA and LVDD were a significant cardioembolic risk factor in patients with ESUS from Southeast Asia and Eastern Mediterranean regions. Findings from this study could guide future research and clinical practice and

improve outcomes for this at-risk population with the highest stroke mortality.

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Disclosures

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