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ORIGINAL RESEARCH

Supracardiac Atherosclerotic Lesions in Embolic Stroke of Undetermined Source: Predicting Stroke Recurrence and Enhancing Secondary Prevention Strategies

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BACKGROUND: Identifying the potential cause of embolic stroke of undetermined source is essential for secondary prevention. We analyzed retrospectively collected real-world data from the South Korean cohort with embolic stroke of undetermined source to examine trends in baseline characteristics, diagnostic practices, and secondary prevention strategies and to identify cardioembolic factors and supracardiac atherosclerotic lesions associated with stroke recurrence.

METHODS: We analyzed 5787 patients from the Real-World Study of Embolic Stroke of Undetermined Source cohort from 19 South Korean stroke centers (2014–2019). Baseline characteristics, diagnostic and secondary prevention trends were evaluated. Factors associated with 1-year stroke recurrence were identified using multivariable Cox regression analysis in 4036 patients with follow-up data.

RESULTS: Over 6 years, vascular risk factors and cardioembolic evaluations significantly increased. Stroke recurrence was strongly associated with intracranial nonrelevant stenosis involving ≥2 vessels (hazard ratio [HR], 2.756, $P<0.001$), paroxysmal atrial fibrillation (HR, 5.590, $P=0.033$), atrial septal aneurysm (HR, 4.741, $P=0.005$), and serum creatinine levels (HR, 1.166, $P=0.008$). In patients without moderate-risk cardioembolic sources, a single intracranial nonrelevant stenosis and complex aortic atheroma were also linked to stroke recurrence.

CONCLUSIONS: Intracranial nonrelevant stenosis and complex aortic atheroma, along with cardioembolic factors like paroxysmal atrial fibrillation and atrial septal aneurysm, are key predictors of stroke recurrence in embolic stroke of undetermined source, especially those without moderate-risk cardioembolic sources. These findings emphasize the need to consider both supracardiac atherosclerotic and cardioembolic mechanisms in embolic stroke of undetermined source and to develop

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tailored secondary prevention strategies for atherosclerotic stroke, particularly in cases with supracardiac atherosclerotic lesions to reduce stroke recurrence.

Key Words: atherosclerosis ■ embolic stroke of undetermined source ■ secondary prevention ■ stroke recurrence

CLINICAL PERSPECTIVE

What Is New?

- Supracardiac atherosclerotic lesions, together with cardioembolic factors, are significant predictors of stroke recurrence in patients with embolic stroke of undetermined source.
- Among supracardiac atherosclerotic lesions, intracranial nonrelevant stenosis and complex aortic atheroma show a particularly strengthened association in patients with embolic stroke of undetermined source without moderate- or high-risk cardioembolic sources.

What Are the Clinical Implications?

- Both supracardiac atherosclerotic and cardioembolic mechanisms should be considered when evaluating and preventing stroke recurrence in patients with embolic stroke of undetermined source, highlighting the need for tailored secondary prevention strategies for those with supracardiac atherosclerotic lesions.

Nonstandard Abbreviations and Acronyms

ESUS	embolic stroke of undetermined source
ILR	implantable loop recorder
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiography

Embolic stroke of undetermined source (ESUS) is defined as the presence of a nonlacunar brain infarct without significant proximal arterial stenosis (stenosis degree ≥50%) or high-risk cardioembolic sources on routine examination.[1] Comprehensive diagnostic evaluations aim to uncover potential causes, such as paroxysmal atrial fibrillation (AF),[2] moderate risk cardioembolic sources,[3] or hypercoagulable disorder.[4] Recent technological advancements, including miniaturized and wireless screening devices, have enhanced the detection of hidden conditions, such as paroxysmal AF.[2] However, despite these improvements in diagnostic methodologies and accessibility, ESUS still accounts for ≈20% of all ischemic strokes.[5]

Recent advances in anticoagulant therapy have significantly influenced the development of secondary prevention strategies for ischemic stroke.[2,6–10] Although several randomized clinical trials of direct oral anticoagulants in ESUS have been conducted, their lack of success highlights the heterogeneity of ESUS, with a substantial proportion attributed to noncardioembolic strokes, such as those caused by nonstenotic atherosclerotic plaques.[6–8,10,11] Innovations in sonography and magnetic resonance imaging have improved the detection of nonstenotic atherosclerotic plaques (<50% stenosis),[11,12] enabling more precise evaluation of both cardioembolic sources and supracardiac atherosclerotic lesions.[12–15] Additionally, high-resolution magnetic resonance imaging has revealed intracranial plaque-enhancing vessels in >50% of patients with ESUS with negative initial workups.[11,16] These findings underscore the critical need for comprehensive screening of supracardiac atherosclerotic lesions along with cardiac evaluation to identify the hidden causes of ESUS.[15] However, the lack of advanced imaging devices in several stroke centers and economic constraints often limit extensive atherosclerotic workups. Assessing atherosclerotic burden as part of a routine stroke evaluation can provide valuable insights, and gathering such evidence is essential to guide effective secondary prevention strategies.[17,18]

To determine appropriate diagnostic evaluation and secondary prevention strategies for patients with ESUS, the cohort with ESUS was analyzed at 19 stroke centers in South Korea over the past 6 years to investigate the trends in baseline characteristics, diagnostic evaluations, and secondary prevention measures, as well as to identify cardioembolic factors and supracardiac atherosclerotic lesions associated with stroke recurrence.

METHODS

Participants

The study population was enrolled from the ROS-ESUS (Real-World Study of Embolic Stroke of Undetermined Sources) cohort. ROS-ESUS is a nationwide retrospective multicenter cohort using real-world data that includes patients with ischemic stroke, including those with only ESUS. The data that support the findings of this study are available from the corresponding author upon reasonable request. We retrospectively enrolled patients from 19 stroke centers in South Korea between

January 2014 and December 2019. The ROS-ESUS cohort included patients aged 20 years or older who experienced a nonlacunar infarction within the past 7 days, with an undetermined cause based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. These cases were identified as either cryptogenic stroke (negative evaluation) or cardioembolism, excluding those classified as having a high cardioembolic risk according to the definition of the TOAST classification.[16] High cardioembolic risk was defined as the presence of ≥1 of the following conditions: left atrial thrombus, left ventricular thrombus, atrial fibrillation, paroxysmal atrial fibrillation, sick sinus syndrome, sustained atrial flutter, recent myocardial infarction, rheumatic valve disease, bioprosthetic heart valve, mechanical heart valve, chronic myocardial infarction with a left ventricular ejection fraction <28%, symptomatic congestive heart failure with left ventricular ejection fraction <30%, dilated cardiomyopathy, nonbacterial thrombotic endocarditis, infective endocarditis, papillary fibroelastoma, or left atrial myxoma. If paroxysmal AF was confirmed during the hospitalization period through 24-hour Holter monitoring, the patient was excluded from the study. ESUS classification was determined by physicians at each institution, and all patients with ESUS were consecutively enrolled in the ROS-ESUS cohort. All registered clinical and imaging information were reinvestigated and rechecked at the core laboratory after anonymization. The requirement for informed consent was waived due to the retrospective nature of the study. This study was approved by the institutional review board of each participating hospital and adhered to the (Strengthening the Reporting of Observational Studies in Epidemiology guidelines for a cohort study.

Examination and Outcomes

Demographic data, risk factors for cardiovascular disease, medication history of prior index stroke, blood laboratory examination results, neurological status including severity, and imaging findings were investigated in all patients. Stroke severity was defined by using the National Institutes of Health Stroke Scale score. Cerebral angiography (either computed tomography angiography or magnetic resonance angiography) was mandatorily performed in all patients. To exclude paroxysmal AF, all the patients underwent a 12-lead electrocardiogram and initial continuous cardiac rhythm monitoring for at least 24 hours upon admission to the acute stroke unit. Routine examination for stroke cause, including laboratory testing, electrocardiography, and cerebral angiography, as well as optional extended evaluations, such as 24-hour Holter monitoring, transthoracic echocardiography (TTE) with/without bubble test, transesophageal echocardiography (TEE) with or without bubble test, implantable loop recorder, and transcranial Doppler with bubble test were performed at the discretion of the treating physicians, and the availability of these evaluations was recorded.

The supracardiac atherosclerotic lesions were evaluated based on intracranial and extracranial nonrelevant stenoses with >50% narrowing, which were not associated with ischemic lesions, as well as complex aortic atheroma characterized by plaque thickness >4 mm, ulceration, and mobile plaques, as identified by TEE and computed tomography angiography.[19]

All patients with ESUS were serially evaluated for the recurrence of ischemic stroke/transient ischemic attack at 3 months and 1 year. During the follow-up period, we monitored the cardiovascular events, all-cause death, and intracranial/extracranial hemorrhage. We defined intracranial hemorrhage as including intraventricular, intracerebral, subarachnoid, subdural, and extradural hemorrhages. Extracranial hemorrhage was defined as the Bleeding Academic Research Consortium type 3 or higher.[20] Cardiovascular events, all-cause death, ischemic stroke, and major intracranial/extracranial hemorrhage were combined as major adverse cardiac and cerebrovascular events.

Statistical Analysis

Continuous variables were expressed as means±SDs and compared using the Pearson correlation coefficient to assess linear trends across years. Categorical variables were summarized as counts and percentages. To evaluate temporal trends in binary categorical variables (eg, presence or absence of comorbidities), the Cochran–Armitage trend test was applied. To account for baseline factors related to the risk of stroke recurrence, a Cox proportional hazards model was used to calculate the hazard ratio (HR), 95% CI, and *P* values. Survival analyses were conducted with Cox proportional hazards models to estimate HRs and 95% CIs. Variables with $P<0.1$ in univariable analysis, along with age and sex, were entered into the multivariable model, and backward elimination was applied for variable selection. Survival analysis was performed using Kaplan–Meier estimates to evaluate the cumulative incidence of stroke recurrence according to number of intracranial nonrelevant stenosis. Differences between survival curves were assessed using the log-rank test. The number of patients at risk at each time point was provided to ensure transparency in follow-up data. All *P* values were calculated using a 2-tailed test. Subgroup analysis was performed in patients with ESUS, excluding those with moderate-risk cardioembolic sources. Subgroup analyses were performed in ESUS patients after excluding moderate-risk cardioembolic sources, and sensitivity analyses were conducted in patients with complete cardiac and vascular evaluations. To address potential informative censoring (≈30% censored before 1 year), survival analyses were repeated

using stabilized inverse probability of censoring weights, estimated from pooled logistic regression models with follow-up time discretized by quantiles and truncated at the 99th percentile. All statistical analyses were performed using SPSS (version 25.0; IBM Corp., Chicago, IL, USA) and the open-source statistical package R version 3.6.3 (R Project for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$.

RESULTS

Baseline Characteristics

Overall, 5787 patients (mean age, 65.9±13.9 years; 39.8% women) were included in the cohort with ESUS, with baseline characteristics and vascular and medium cardioembolic risk factors from 2014 to 2019 summarized in Table 1. During this period, significantly increasing trends were observed in vascular risk factors, including age (64.5 versus 66.8 years, P for trend <0.001), hypertension (56.9% versus 66.2%, P for trend 0.032), diabetes (26.8% versus 32.1%, P for trend 0.053), and hyperlipidemia (30.6% versus 50.2%; P for trend <0.001). Concurrently, the proportion of patients with low risk of paradoxical embolism scores (0–6) rose from 86.1% to 90.2% (P for trend <0.001), reflecting an increase in vascular risk factors, whereas the proportion of patients with high risk of paradoxical embolism scores (7–10) declined (Table 1).

Table 1. Characteristics of the Annual Changes in Patients With ESUS

Y	Total	2014	2015	2016	2017	2018	2019	*P* for trend
Total population with ESUS, n	5787	806	845	890	998	1057	1191	
Age at ESUS, y, mean	65.9 (±13.9)	64.5 (±13.8)	65.1 (±13.9)	66.1 (±13.4)	65.8 (±14.2)	66.5 (±14.1)	66.8 (±13.7)	<0.001
Female sex, n (%)	2305 (39.8%)	322 (40.0%)	344 (40.7%)	360 (40.4%)	372 (37.3%)	448 (42.4%)	459 (38.5%)	0.822
History of comorbidities								
Previous stroke, n (%)	1098 (19%)	158 (19.6%)	172 (20.4%)	159 (17.9%)	185 (18.5%)	188 (17.8%)	236 (19.8%)	0.825
Transient ischemic attack, n (%)	119 (2.1%)	14 (1.7%)	20 (2.4%)	20 (2.2%)	21 (2.1%)	13 (1.2%)	31 (2.6%)	0.881
Coronary heart disease, n (%)	627 (10.8%)	63 (7.8%)	104 (12.3%)	91 (10.2%)	103 (10.3%)	113 (10.7%)	153 (12.8%)	0.191
Hypertension, n (%)	3533 (61.1%)	459 (56.9%)	505 (59.8%)	534 (60.0%)	598 (59.9%)	649 (61.4%)	788 (66.2%)	0.032
Diabetes, n (%)	1706 (29.5%)	216 (26.8%)	214 (25.3%)	271 (30.4%)	284 (28.5%)	339 (32.1%)	382 (32.1%)	0.053
Hyperlipidemia, n (%)	2291 (39.6%)	247 (30.6%)	240 (28.4%)	302 (33.9%)	406 (40.7%)	498 (47.1%)	598 (50.2%)	<0.001
Current smoker, n (%)	1545 (26.7%)	244 (30.3%)	222 (26.3%)	227 (25.5%)	280 (28.1%)	264 (25.0%)	308 (25.9%)	0.686
Peripheral arterial occlusive disease,‡ n (%)	66 (1.1%)	11 (1.4%)	11 (1.3%)	8 (0.9%)	11 (1.1%)	11 (1.0%)	14 (1.2%)	0.810
RoPE score (7–10)	12.3%	13.9%	14.8%	12.1%	13.5%	10.8%	9.8%	<0.001
RoPE score (≤6, %)	87.7%	86.1%	85.2%	87.9%	86.5%	89.2%	90.2%	<0.001
Intracranial nonrelevant stenosis, n (%)								
Stenotic vessel (1 vessel, ≥50%)	991 (17.1%)	113 (14.0%)	150 (17.8%)	120 (13.5%)	189 (18.9%)	210 (19.9%)	209 (17.5%)	0.626
Stenotic vessel (≥2 vessel, ≥50%)	259 (4.5%)	35 (4.3%)	33 (3.9%)	38 (4.3%)	49 (4.9%)	49 (4.6%)	55 (4.6%)	0.536
Extracranial nonrelevant stenosis, n (%)								
Carotid stenosis (1 vessel, ≥50%)	201 (3.5%)	25 (3.1%)	34 (4.0%)	36 (4.0%)	36 (3.6%)	37 (3.5%)	33 (2.8%)	0.156
Carotid stenosis (2 vessel, ≥50%)	38 (0.7%)	5 (0.6%)	3 (0.4%)	3 (0.3%)	9 (0.9%)	10 (0.9%)	8 (0.7%)	0.696
Complex aortic atheroma, n (%)	60 (1.0%)	2 (0.2%)	5 (0.6%)	13 (1.5%)	19 (1.9%)	9 (0.9%)	12 (1.0%)	0.417
Medium cardioembolic risk								0.879
≥1 medium risk, n (%)	1239 (21.4%)	189 (23.4%)	164 (19.4%)	176 (19.8%)	231 (23.1%)	236 (22.3%)	243 (20.4%)	
Mitral valve prolapse, n (%)	6 (0.1%)	1 (0.1%)	3 (0.4%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0.495
Mitral annulus, n (%)	40 (0.7%)	4 (0.5%)	2 (0.2%)	2 (0.2%)	13 (1.3%)	13 (1.2%)	6 (0.5%)	0.381
Left atrial turbulence (smoke), n (%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0.820
Atrial septal aneurysm, n (%)	43 (0.7%)	9 (1.1%)	8 (0.9%)	5 (0.6%)	7 (0.7%)	7 (0.7%)	7 (0.6%)	0.464
Patent foramen ovale, n (%)	1122 (19.4%)	163 (20.2%)	136 (16.1%)	154 (17.3%)	208 (20.8%)	227 (21.5%)	234 (19.6%)	0.786
Congestive heart failure, n (%)	19 (0.3%)	6 (0.7%)	4 (0.5%)	1 (0.1%)	2 (0.2%)	3 (0.3%)	3 (0.3%)	0.358
Hypokinetic left ventricular, n (%)	88 (1.5%)	9 (1.1%)	12 (1.4%)	21 (2.4%)	17 (1.7%)	13 (1.2%)	16 (1.3%)	0.912
Myocardial infarction (>4 wk, <6 mo), n (%)	4 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.1%)	1 (0.1%)	0.527
Systemic embolization, n (%)	4 (0.1%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0.358

ESUS indicates embolic stroke of undetermined source; and RoPE, risk of paradoxical embolism.

Table 2. Differences Over Time for Cardiac Evaluation of ESUS*

Cardiac evaluation	Total	2014	2015	2016	2017	2018	2019	*P* for trend
Transthoracic echocardiogram, n (%)	5178 (89.5%)	685 (85.0%)	743 (87.9%)	800 (89.9%)	917 (91.9%)	971 (91.9%)	1062 (89.2%)	0.048
Transesophageal echocardiogram, n (%)	1624 (28.1%)	312 (38.7%)	223 (26.4%)	229 (25.7%)	262 (26.3%)	260 (24.6%)	338 (28.4%)	0.031
Transcranial Doppler shunt test, n (%)	1775 (30.7%)	145 (18.0%)	193 (22.8%)	250 (28.1%)	312 (31.3%)	414 (39.2%)	461 (38.7%)	<0.001
24-h Holter ECG, n (%)	4427 (76.5%)	538 (66.7%)	579 (68.5%)	676 (76.0%)	793 (79.5%)	864 (81.7%)	977 (82.0%)	<0.001
Implantable loop recorder	93 (1.6%)	2 (0.2%)	4 (0.5%)	3 (0.3%)	14 (1.4%)	10 (0.9%)	60 (5.0%)	<0.001
Pro-brain natriuretic peptide, n (%)	1942 (33.6%)	192 (23.8%)	300 (35.5%)	316 (35.5%)	367 (36.8%)	327 (30.9%)	440 (36.9%)	0.040

ESUS indicates embolic stroke of undetermined source.

Potential Cause of ESUS

An analysis of intra- and extracranial nonrelevant stenoses revealed no significant annual trends based on the number of affected vessels. Intracranial nonrelevant stenosis was identified in 17.1% and 4.5% of patients with 1 and 2 vessels, respectively, whereas extracranial nonrelevant stenosis was present in 3.5% and 0.7% of patients with 1 and 2 vessels, respectively (Table 1). Medium cardioembolic risks were observed in ≈20% of patients annually, without a discernible trend, with patent foramen ovale being the most common factor (Table 1).

Trends of the Diagnostic Evaluation and Secondary Prevention of ESUS

Table 2 shows the changes in the number and percentage of cardiac evaluations over time. From 2014 to 2019, TTE (*P* for trend 0.048) and serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels (*P* for trend 0.040) increased significantly. The rate of transcranial Doppler shunt tests increased from 18% to 38.7% (*P* for trend <0.001), 24-hour Holter monitoring increased from 66.7% to 82.0% (*P* for trend <0.001), and implantable loop recorder (ILR) usage increased from 0.2% to 5.0% (*P* for trend <0.001). Notably, the implementation rate of TEE was unusually high in 2014 at 38.74%; however, a decreasing trend, albeit inconsistent, was observed from 2015 to 2019 (*P* for trend 0.031) (Table 2).

For secondary prevention, the use of warfarin steadily declined from 12.9% to 4.5% (*P* for trend <0.001). According to the CHANCE (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) trial results,[21] antiplatelet therapy during the first 3 weeks included dual therapy, monotherapy, and other regimens (eg, escalation from mono to dual therapy, deescalation from dual to mono therapy, or triple therapy). This approach remained the predominant treatment strategy in >80% of patients. Notably, the use of dual antiplatelet therapy significantly increased from 35.0% to 50.5% (*P* for trend <0.001).

Device patent foramen ovale closure initially decreased from 1.7% to 0.4% between 2014 and 2016 but demonstrated a consistent annual increase from 2.0% to 2.5% starting in 2017 (*P* for trend=0.124) (Table 3).

Factors Associated With Stroke Recurrence in Patients With ESUS

Of the 5787 patients with ESUS included in the study, 4036 were followed up for 1 year post stroke to evaluate the clinical outcomes (Figure 1). The baseline characteristics, risk factors, and blood test results were compared between patients with and without recurrent ischemic stroke during this period (Table 4). The significant factors associated with stroke recurrence included a history of previous stroke (31.7% versus 18.3%, *P*<0.001), intracranial nonrelevant stenosis (21.4% versus 18.7% for 1 vessel; 9.7% versus 4.0% for ≥2 vessels, *P*<0.001), atrial septal aneurysm (2.8% versus 0.6%, *P*=0.006), and higher serum creatinine levels (1.22±1.62 versus 0.99±0.87, *P*=0.001). Cox regression survival analysis identified previous stroke history (HR, 2.013 [95% CI, 1.401–2.891], *P*<0.001), ≥2 intracranial nonrelevant stenosis (HR 2.756 [95% CI 1.534–4.951], *P*<0.001), paroxysmal AF (HR, 5.590 [95% CI, 1.147–27.239], *P*=0.033), atrial septal aneurysm (HR, 4.741 [95% CI, 1.602–14.032], *P*=0.005), and serum creatinine level (HR, 1.166 [95% CI, 1.041–1.306], *P*=0.008) as significant independent predictors of stroke recurrence in multivariate analyses, while extracranial nonrelevant stenosis was significant only in the univariate analysis (Table 4). In the inverse probability of censoring weights-adjusted survival analysis of 5295 patients (including 1259 censored without events), previous stroke (HR, 1.941 [95% CI, 1.352–2.786], *P*<0.001), ≥2 intracranial nonrelevant stenoses (HR, 2.496 [95% CI, 1.414–4.404], *P*=0.002), atrial septal aneurysm (HR,

Table 3. Differences Over Time for Secondary Prevention in Patients With ESUS

Secondary prevention	Total	2014	2015	2016	2017	2018	2019	*P* for trend
Dual antiplatelet, n (%)	2507 (43.3%)	282 (35.0%)	296 (35.0%)	320 (36.0%)	447 (44.8%)	560 (53.0%)	602 (50.5%)	<0.001
Single antiplatelet, n (%)	1459 (25.2%)	249 (30.9%)	245 (29.0%)	249 (28.0%)	246 (24.6%)	218 (20.6%)	252 (21.2%)	<0.001
Other antiplatelet, n (%)	1503 (26.0%)	205 (25.4%)	247 (29.2%)	266 (29.9%)	245 (24.5%)	243 (23.0%)	297 (24.9%)	0.451
Direct oral anticoagulant, n (%)	149 (2.6%)	5 (0.6%)	19 (2.2%)	14 (1.6%)	37 (3.7%)	32 (3.0%)	42 (3.5%)	0.202
Warfarin, n (%)	374 (6.5%)	104 (12.9%)	75 (8.9%)	62 (7.0%)	54 (5.4%)	25 (2.4%)	54 (4.5%)	<0.001
Patent foramen ovale closure, n (%)	105 (1.8%)	14 (1.7%)	10 (1.2%)	4 (0.4%)	20 (2.0%)	28 (2.6%)	30 (2.5%)	0.124

ESUS indicates embolic stroke of undetermined source.

7.976 [95% CI, 2.708–23.486], *P*<0.001), and higher serum creatinine level (HR, 1.143 [95% CI, 1.037–1.259], *P*=0.007) remained significant predictors of stroke recurrence, further supporting the robustness of the primary findings (Table S1).

Cox regression survival analyses were conducted to identify the risk factors associated with major adverse cardiac and cerebrovascular events in patients with ESUS within 1 year. In the multivariate analysis, significant predictors of major adverse cardiac and cerebrovascular events included age at ESUS (HR, 1.012 [95% CI, 1.000–1.023], *P*=0.044), previous stroke history (HR, 1.661 [95% CI, 1.226–2.250], *P*=0.001), ≥2 intracranial nonrelevant stenosis (HR, 2.447 [95% CI, 1.524–3.931], *P*<0.001), atrial septal aneurysm (HR, 3.013 [95% CI, 1.118–8.120], *P*=0.029), hypokinetic left ventricular function (HR, 2.171 [95% CI, 1.011–4.660], *P*=0.047), and serum creatinine level (HR, 1.145 [95% CI, 1.036–1.265], *P*=0.008; Table S2).

Factors Associated With Stroke Recurrence in Patients With ESUS Without Moderate Risk Cardioembolic Sources

For subgroup analysis, patients with ESUS with and without moderate-risk cardioembolic sources were compared. Patients without moderate-risk cardioembolic sources were older (66.74±13.22 versus 61.05±14.26, *P*<0.001), had a higher proportion of women (41.0% versus 35.6%, *P*=0.002), and were more likely to have a history of stroke (19.8% versus 14.7%, *P*=0.004), hypertension (63.3% versus 50.3%, *P*<0.001), and diabetes (31.1% versus 24.4%, *P*<0.001).

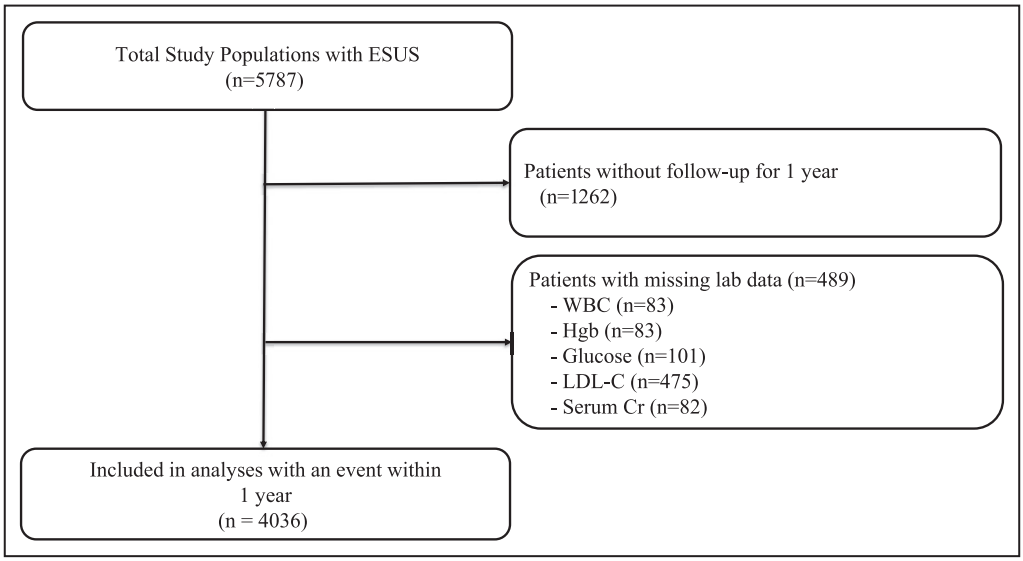

Figure 1. Schematic of the study flow.
Cr indicates creatinine; ESUS, embolic stroke of undetermined source; Hgb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; and WBC, white blood cell.

Table 4. Vascular Risk Factors and Moderate Cardioembolic Risk Factors Associated With Recurrent Stroke Among 4036 Patients With ESUS

Variables	Stroke recurrence (+) (n=145)	Stroke recurrence (–) (n=3891)	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age at ESUS, y	65.9±13.4	65.5±13.6	1.003 (0.991–1.016)	0.577		
Female sex	50 (34.5%)	1562 (40.1%)	0.794 (0.564–1.119)	0.188		
Previous stroke	46 (31.7%)	712 (18.3%)	2.049 (1.444–2.907)	<0.001	2.013 (1.401–2.891)	<0.001
Transient ischemic attack	4 (2.8%)	89 (2.3%)	1.201 (0.444–3.244)	0.718		
Coronary heart disease	20 (13.8%)	411 (10.6%)	1.369 (0.854–2.195)	0.192		
Hypertension	82 (56.6%)	2369 (60.9%)	0.848 (0.611–1.177)	0.325		
Diabetes	49 (33.8%)	1152 (29.6%)	1.228 (0.870–1.732)	0.243		
Hyperlipidemia	57 (39.3%)	1411 (36.3%)	1.125 (0.806–1.570)	0.488		
Current smoker	40 (27.6%)	998 (25.6%)	1.154 (0.788–1.691)	0.462		
Peripheral arterial occlusive disease	1 (0.7%)	45 (1.2%)	0.613 (0.086–4.378)	0.625		
Intracranial nonrelevant stenosis						
Without stenotic vessels			Ref.		Ref	
Stenotic vessel (1 vessel, ≥50%)	31 (21.4%)	728 (18.7%)	1.282 (0.857–1.919)	0.226	1.343 (0.887–2.033)	0.163
Stenotic vessel (≥2 vessels, ≥50%)	14 (9.7%)	157 (4.0%)	2.714 (1.551–4.747)	<0.001	2.756 (1.534–4.951)	<0.001
Extracranial nonrelevant stenosis						
Without stenotic vessels			Ref			
Carotid stenosis (1 vessel, ≥50%)	7 (4.8%)	131 (3.4%)	1.471 (0.688–3.145)	0.319		
Carotid stenosis (2 vessels, ≥50%)	3 (2.1%)	23 (0.6%)	3.496 (1.113–10.975)	0.032		
Complex aortic atheroma, n (%)	4 (2.8%)	44 (1.1%)	2.480 (0.879–6.998)	0.086		
Hidden atrial fibrillation	2 (1.38%)	9 (0.23%)	6.033 (1.292–28.175)	0.022	5.590 (1.147–27.239)	0.033
Medium cardioembolic risk						
≥1 medium risk, n (%)	30 (20.7%)	781 (20.1%)	1.027 (0.690–1.527)	0.896		
Atrial septal aneurysm, n (%)	4 (2.8%)	24 (0.6%)	4.068 (1.506–10.989)	0.006	4.741 (1.602–14.032)	0.005
Patent foramen ovale, n (%)	31 (21.4%)	742 (19.1%)	1.140 (0.766–1.695)	0.519		
Congestive heart failure, n (%)	1 (0.7%)	7 (0.2%)	3.605 (0.504–25.767)	0.201		
Hypokinetic left ventricular, n (%)	3 (2.1%)	53 (1.4%)	1.541 (0.491–4.834)	0.459		
White blood cell	8.14±2.75	8.17±3.42	1.000 (0.953–1.049)	0.995		
Hemoglobin	13.64±2.07	13.70±2.08	0.977 (0.903–1.056)	0.557		
Random glucose	140.85±59.49	140.67±60.16	1.000 (0.997–1.003)	0.917		
Low-density lipoprotein cholesterol	55.10±29.94	57.30±30.79	0.997 (0.992–1.003)	0.355		
Creatinine, mg/dL	1.22±1.62	0.99±0.87	1.183 (1.072–1.306)	0.001	1.166 (1.041–1.306)	0.008

ESUS indicates embolic stroke of undetermined source; and HR, hazard ratio.

Intracranial nonrelevant stenosis was also more prevalent in these patients (19.6% versus 15.7% for 1 vessel, 4.5% versus 3.3% for ≥2 vessels, *P*=0.002). Laboratory tests revealed higher levels of white blood cells (8.23±3.51 versus 7.92±2.90, *P*=0.028), random glucose (141.82±60.07 versus 136.12±60.18, *P*=0.028), low-density lipoprotein cholesterol (58.39±32.04 versus 52.56±24.49, *P*<0.001), and serum creatinine (1±0.92 versus 0.94±0.70, *P*=0.024) in patients without moderate-risk cardioembolic sources (Table S3). Cox regression survival analysis in this group identified female sex (HR, 1.517 95% CI, 1.011–2.275, *P*=0.044), previous stroke history (HR, 2.073, 95% CI, 1.385–3.103, *P*<0.001), 1 intracranial nonrelevant stenosis (HR, 1.612 95% CI, 1.029–2.526, *P*=0.037), ≥2 intracranial nonrelevant stenosis (HR, 3.111 95% CI, 1.638–5.908, *P*<0.001), complex aortic atheroma (HR, 5.589 95% CI, 1.288–17.470, *P*=0.003), paroxysmal AF (HR, 6.368 95% CI, 1.277–31.756, *P*=0.024), and serum creatinine levels (HR, 1.189 95% CI, 1.056–1.338, *P*=0.004) as significant predictors of stroke recurrence (Table S4).

The Kaplan–Meier curves for cumulative stroke recurrence based on the number of intracranial nonrelevant stenoses are shown in Figure 2. A significant difference in relapse rates was observed across all patients with ESUS when analyzed according to the number of intracranial nonrelevant stenoses (*P*=0.001,

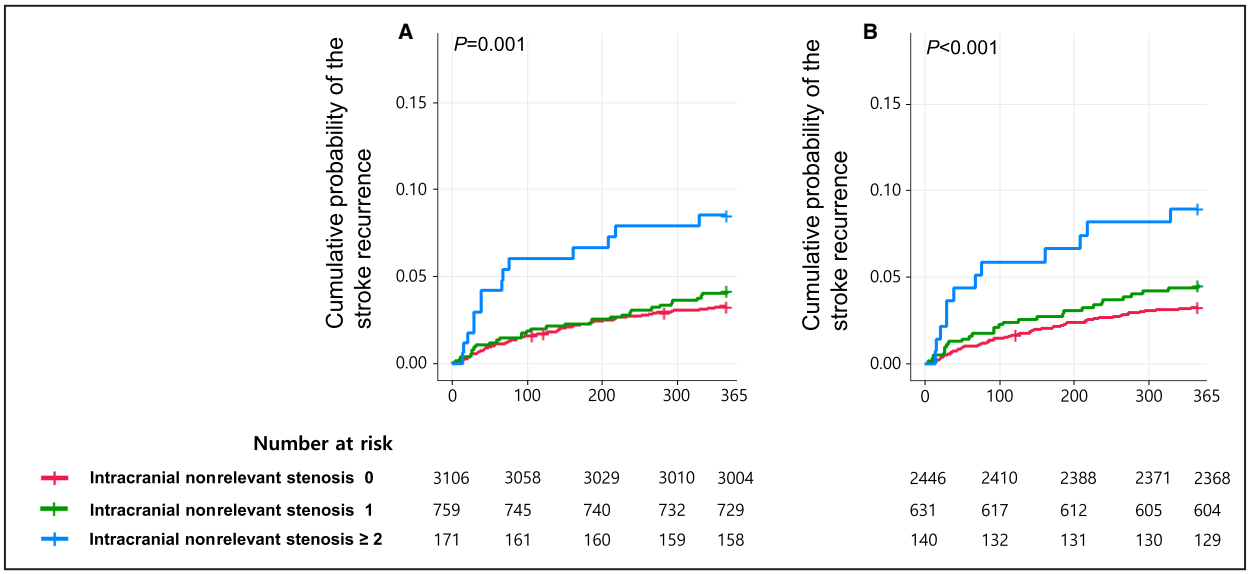

Figure 2. Kaplan–Meier survival curves for stroke recurrence.
A, All patients with ESUS were followed up for 1 year (n=4036; *P*=0.001). **B**, Patients with ESUS without moderate risk cardioembolic sources were followed up for 1 year (n=3225; *P*<0.001). ESUS indicates embolic stroke of undetermined source.

Figure 2A). Among patients with ESUS without moderate-risk cardioembolic sources, a notable difference in relapse rates was evident, even with only 1 intracranial nonrelevant stenosis (*P*<0.001, Figure 2B).

DISCUSSION

In the cohort of 5787 patients with ESUS (mean age, 65.9 years) analyzed from 2014 to 2019, the use of cardiac evaluations, including TTE, transcranial Doppler shunt, 24-hour Holter monitoring, and NT-proBNP, gradually increased over time, except for TEE. Despite an increase from 0.2% to 5.0%, the overall ILR implantation rate remained low (1.6%).

Paroxysmal AF, one of the common causes of ESUS with a high risk of stroke recurrence, has been linked to various diagnostic markers. These include echocardiographic markers such as left atrial size,[22] with recent studies further reinforcing these associations. The data from the present cohort show that TTE is widely used in patients with ESUS to confirm these markers. Additionally, the use of 24-hour Holter monitoring has steadily increased over the years.[23] Advances in technology have led to the development of ILR and recognition of the usefulness of long-term ECG monitoring with ILR for identifying paroxysmal AF, which has resulted in the rate of ILR implantation increasing over the years.[2,24,25] This low use likely reflects real-world limitations including accessibility and cost, and a practice pattern in which ILR was selectively used in patients with suggestive findings, rather than being applied routinely.[22,23,26] Although this may have led to an underestimation of the paroxysmal AF prevalence,[27] recent trials, such as the ARTESIA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation)[28] and NOAH-AFNET 6 (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) trials[29] have suggested that oral anticoagulation in patients with subclinical AF detected by long-term monitoring does not clearly reduce stroke recurrence and may increase bleeding risk. These findings imply that broader ILR use might not universally improve clinical outcomes and underscore the importance of careful patient selection for poststroke rhythm monitoring.

As the cohort aged, the prevalence of vascular risk factors, including hypertension, diabetes, and hyperlipidemia, increased, leading to a higher proportion of patients with low risk of paradoxical embolism scores (0–6). Stroke recurrence was associated not only with cardioembolic factors, such as paroxysmal AF and atrial septal aneurysm, but also with supracardiac atherosclerotic lesions like intracranial nonrelevant stenosis. Among patients with ESUS without moderate-risk cardioembolic sources, the risk of stroke recurrence was significantly higher with increasing numbers of intracranial nonrelevant stenoses, and complex aortic atheroma also emerged as a key predictor.

These findings align with those of previous literature suggesting that nonstenotic plaques, although lacking luminal narrowing, may harbor high-risk features such as ulceration or intraplaque hemorrhage detectable via carotid ultrasonography and high-resolution magnetic resonance imaging.[12,30–32] However, such advanced

imaging remains underused due to cost, limited accessibility, and patient-related constraints. Importantly, this 6-year longitudinal analysis demonstrated that the vascular risk profile of the population with ESUS evolved significantly over time. As vascular risk factors tend to accumulate with age, the overall atherosclerotic burden may increase, potentially resulting in greater plaque vulnerability even in the absence of hemodynamically significant stenosis.[12] Although analysis of the cohort study did not observe a statistically significant interaction between this gradual aging trend and the association between nonrelevant intracranial stenosis and stroke recurrence (Table S5), the ongoing aging of the population may further strengthen this relationship in the future. Therefore, these evolving trends should be taken into account when establishing long-term strategies for secondary stroke prevention in patients with ESUS.

This study had some limitations. First, as a nationwide observational cohort reflecting real-world conditions, this was not a randomized clinical trial, and patients were enrolled retrospectively, introducing a potential selection bias in test administration and drug selection. To mitigate this, patients were recruited consecutively across multiple centers from enrollment initiation. Second, the cohort included only Korean patients, which limits the generalizability of the findings to other ethnicities. Third, because this study relied on real-world data, not all patients underwent 24-hour Holter monitoring, TTE, TEE, or ILR tests, potentially leading to the underdiagnosis of moderate- or high-risk cardioembolic sources. In particular, the low ILR usage, though increasing over time, may have resulted in an underestimation of covert paroxysmal AF. The low ILR usage reflects real-world constraints and selective clinical application. Importantly, recent trials suggest that subclinical AF detected via ILR may not always benefit from anticoagulation,[28,29] questioning the routine use of ILR in all patients with ESUS. Notably, previous studies reported ESUS stroke recurrence rates of 4% to 5%,[33] whereas the recurrence rate in our study was 3.5%, suggesting that the relatively limited use of ILRs did not result in an increased recurrence risk. Nevertheless, the detection of paroxysmal AF in the early phase of stroke remains critically important; therefore, all patients underwent at least 24 hours of continuous ECG monitoring upon admission to the acute stroke unit to ensure a minimum level of screening for paroxysmal AF. Additionally, not all patients in this cohort underwent the same cardiac evaluation, and there was center-to-center variability in the implementation of cardiac assessments across the 19 participating centers (Table S6). Therefore, to evaluate the potential impact of cardiac evaluation on study outcomes, we conducted a sensitivity analysis excluding patients who did not undergo TTE. No substantial differences were observed between the sensitivity analyses and the main analysis, indicating the stability of the results (Table S7). Fourth, we were unable to analyze the effects of medications on stroke recurrence. Although data on medications at admission and discharge were available, the absence of information on changes in antithrombotic agents during the 1-year follow-up period limited this aspect of the analysis. Finally, 1259 patients (approximately 30%) in the present study were lost to follow-up before completing 1 year. The specific reasons for the loss to follow-up were not systematically recorded. Most patient lost to follow-up simply did not return for clinic visits by their own choice. Because patients with unclear reasons for follow-up discontinuation were included, we limited our primary outcome analysis to patients who completed 1-year follow-up. Nonetheless, because differences in the baseline characteristics of patients lost to follow-up may introduce bias, we compared the baseline characteristics between patients with and without 1-year follow-up, and the standardized mean differences are presented in Table S8. Furthermore, we performed additional survival analyses using the inverse probability of censoring weights method, which demonstrated no significant differences from the primary results, confirming the stability of our findings (Table S1).

CONCLUSIONS

In conclusion, although cardiac evaluations are increasingly used to identify potential causes of ESUS, the rise in vascular risk factors driven by an aging population highlights atherosclerosis as a significant cause of ESUS and a key contributor to stroke recurrence. Intracranial nonrelevant stenosis, detectable through routine examinations, is strongly associated with stroke recurrence across all patients with ESUS. This association is particularly pronounced in patients without moderate-risk cardioembolic sources, where the risk of recurrence increases with the number of stenoses. These findings underscore the importance of considering both atherosclerotic and cardioembolic factors in patients with ESUS; implementing targeted secondary prevention strategies for atherosclerotic stroke, especially in cases with supracardiac atherosclerotic lesion could play a vital role in reducing stroke recurrence.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S8

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