Original Article

Recurrence of Cryptogenic (ESUS) Strokes in the First Year: Predictors and Outcome—A South Indian Study

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Abstract

Introduction: Around 9–25% of ischemic strokes are embolic stroke of undetermined source (ESUS) with an annual recurrence risk of 4.5–5%. Regarding ESUS, studies from India are limited. Here, we studied the prevalence of cryptogenic ESUS among stroke subtypes, recurrence risk and outcome at 1 year, and their predictors. **Materials and Methods:** We performed a single-center study of ambispective nature. Patients above 18 years of age with a diagnosis of cryptogenic (ESUS) strokes from January 1, 2017, to December 31, 2020 (4 years), with a 1-year follow-up were recruited in our study. All the patients underwent neuroimaging computerised tomography/magnetic resonance tomography (CT/MRI) with angiography, electrocardiogram (ECG), transthoracic echo (TTE), and rhythm monitoring. Functional outcome was measured using the modified Rankin scale with scores 0–2 taken as good outcome. **Results:** We had 234 (11.21% of total ischemic strokes) subjects satisfying the criteria for ESUS over the study period with a mean age of 58.2 ± 12.8 years. 46 patients had a history of stroke/transient ischemic attack (TIA) at admission. 9.4% had a recurrent event at 1 year. The most important neuroimaging predictor of recurrent strokes was multiple embolic followed by superficial watershed pattern. Around 10% had more than one marker of atrial cardiopathy positive. While the risk factors, coronary artery disease (CAD), and neuroimaging pattern showed an association with recurrent events at 1 year on bivariate analysis, only the latter two remained significant on multivariate analysis. **Conclusions:** Our cohort of ESUS had a higher annual recurrence risk than reported before. Though vascular risk factors and ipsilateral vessel abnormalities were more in the recurrent ESUS group, it did not significantly affect the recurrence risk at 1 year. CAD and multiple embolic patterns on imaging showed an association with recurrent strokes, suggesting a possible cardiac substrate in our ESUS population as well.

Keywords: Atrial cardiopathy, cryptogenic strokes, embolic stroke of undetermined source, infarct patterns, recurrent strokes

INTRODUCTION

Among the ischemic stroke subtypes, around 30–40% remain cryptogenic despite exhaustive evaluation, more so in younger patients.[1] Embolic stroke of undetermined source (ESUS) is a clinical construct described by Hart *et al.* to describe cryptogenic strokes of non-lacunar type, which are presumed to be secondary to embolism.[2] ESUS type of cryptogenic strokes ranges from 9 to 25% across studies with an annual recurrence risk of 4.5–5%[2-6], which is higher than other cryptogenic strokes.[7] These strokes are of mild-to-moderate severity and mostly affect younger patients.

Pathological studies of mechanical thrombectomy specimens from ESUS patients have demonstrated smaller thrombi of mixed composition in the majority, indicating a possible proximal cardiac source.[8]

Studies on stroke subtypes and their characteristics from India show some cardinal differences from Western literature, in that cerebrovascular disease occurs at least 1 decade earlier, and we have more rheumatic and congenital cardioembolic sources, especially among young strokes.[9-11] In one of the largest multicenter studies on stroke etiology and risk factors from India, a quarter remained cryptogenic with incompletely evaluated patients constituting around 6–7% even in tertiary care centers.[12] However, studies on ESUS subtype of cryptogenic strokes are limited from our region. Here, we studied the prevalence, 1-year outcome, and recurrence risk of cryptogenic strokes of ESUS pattern from a hospital-based cohort.

MATERIALS AND METHODS

The study was performed at stroke unit, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India. We included all stroke patients above 18 years of age with a final discharge diagnosis of cryptogenic stroke satisfying the criteria for the embolic stroke of undetermined source or ESUS after evaluation.[2] The study design was ambispective, with a retrospective arm of the study recruited from January 2017 till May 2020 and a prospective arm from June 2020 till December 2020. All the follow-ups were completed by December 2021. The selection of study design was based on two facts—the annual number of cryptogenic ESUS strokes attending our center, which is around 45–50, and the minimum sample number required for

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the study being 220 as per the central limit theorem. Informed consent was obtained from all prospectively included patients. For the retrospective arm, clinical and follow-up data were collected from medical records. In those who were missing on follow-up, telephonic follow-up was performed after getting verbal consent. All the patients admitted to the stroke unit underwent etiological evaluation as per the standard protocol including brain imaging computerised tomography/magnetic resonance tomography (CT/MRI) with angiography, 12-lead electrocardiogram (ECG), transthoracic echo (TTE), 24-hour Holter, and blood investigations including vasculitic markers, acquired procoagulant workup, transesophageal echo, and extended (7 days) Holter monitoring (in selected situations). Patients satisfying cryptogenic ESUS criteria after the detailed evaluation, with all the baseline clinical, imaging, and cardiac data available for review, were enrolled in the study. The conduct of the study was approved by the Institutional Ethics Committee (Ref no. SCT/IEC/1564/October2020 dated 30.10.2020).

Clinical and imaging data were collected as per pro forma from medical records. The neuroimaging details were collected by the first author (JG) and verified by the senior author (SES) by reviewing picture archival and communication system (PACS), who were not blinded for the clinical data. Stroke severity was assessed using the National Institute for Health Stroke Scale (NIHSS), and mild, moderate, and severe strokes were defined as per scores $\leq$5, 6–15, and >15, respectively. Discharge and 1-year outcome were assessed during clinic visits or telephonically using a modified Rankin scale with scores 0–2 taken as good outcome. Also, details of any recurrent strokes or any vascular events (acute coronary syndrome/cardiac failure or vascular death) were collected during the review.

Statistical analysis
Data collected were analyzed using SPSS version 28 (SPSS Inc., Illinois, Chicago). Baseline variables were expressed in means and percentages. t-Test was used for testing mean comparison and the Chi-square test for testing association between variables, and *P* values below 0.05 were considered significant and carried forward for multivariate logistic regression analysis. Correlations were made between clinical, cardiac, and imaging parameters with single versus recurrent ESUS.

RESULTS
Of the 2087 screened patients with acute ischemic stroke over 18 years of age, we had 234 patients with a diagnosis of cryptogenic stroke satisfying the criteria for ESUS during the study period (11.21%). 205 of our patients were from the retrospective arm and 29 were from the prospective arm of the study. 1-year completed follow-up data were available in all the patients (158 from medical records and 76 through tele-review). 46 patients had a history of stroke/transient ischemic attack (TIA). The majority had minor strokes (NIHSS $\leq$5) at admission. A comparison of baseline characteristics between single and recurrent ESUS at presentation is given in Table 1, and neuroimaging and cardiac characteristics are given in Table 2.

Recurrent ESUS had a significant association with systemic hypertension (*P* value 0.004), prolonged PR interval (*P* value 0.004), dyslipidemia, coronary artery disease (CAD) (*P* value 0.007), and peripheral occlusive vascular disease (PVOD) (*P* value < 0.001) in bivariate analysis. Among the imaging parameters, superficial watershed infarcts (*P* value 0.020), multiple embolic infarcts (*P* value 0.010), and severe white matter hyperintensities by Fazekas grading (grades 2 and 3) (*P* value 0.013) had an association with recurrent events. Of the parameters that were significant in bivariate analysis (gender, diabetes mellitus, hypertension, CAD, and infarct patterns), multivariate logistic regression analysis showed that CAD and infarct pattern at presentation were predictive of recurrence risk at 1-year follow-up, while none of the risk factors or substenotic ipsilateral vessel disease failed to show an association [Table 3].

In our cohort, 16.3% of patients underwent IV thrombolysis and 8.6% had mechanical thrombectomy. 26 patients (11.3%) had neurological worsening during hospital stay, which had a correlation with terminal branch occlusion (*P* value = 0.019).

At 1-year follow-up, 22 patients had recurrent cerebrovascular events (9.4%), of which 14 (63.63%) were in the same vascular territory. Among the predictors of annual recurrence risk—current smoking, prior history of stroke and neuroimaging pattern of superficial watershed and multiple embolic infarcts showed an association with events on any and ipsilateral recurrent events, while smoking and hypertriglyceridemia showed a significant correlation with events in other arterial territories. However, due to small numbers, none of the parameters were significant in multivariate analysis. 1-year outcome and the ordinal shift in modified rankin scale (MRS) are shown in Figure 1. Over 70% of our cohort had good outcome (MRS 2 or below).

DISCUSSION
ESUS pattern of cryptogenic strokes accounts for 9–25% of all ischemic strokes in the literature,[2] which falls in the range of our hospital series as well.

Most of the studies on ESUS patients in the literature have shown their mean age ranging from 44 to 73 years,[5] which is comparable to our cohort as well. However, our patients
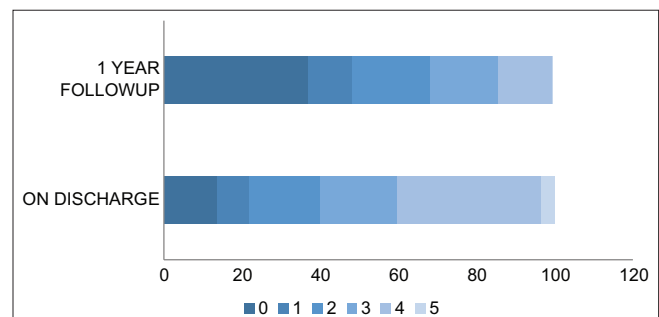
Figure 1: Ordinal shift of MRS at time of discharge and at 1-year follow-up

Table 1: Comparison of clinical characteristics, treatment, and outcome between single and recurrent ESUS strokes (previous strokes/recurrence in 1 year) at baseline

Parameter	Single stroke (n=166)	%	Recurrent stroke (n=68)	%	*P*
Age in years	57.3±13.2 (SD)		60.17±11.7 (SD)		0.11
Gender:male	105	63.25	50	73.5	0.09
Vascular risk factors					
DM	77	46.38	44	64.7	0.007
Systemic hypertension	99	59.7	50	73.5	0.043
Fasting cholesterol	49	29.6	18	26.5	0.648
CAD	19	11.4	20	29.4	0.007
Peripheral vascular disease	1	0.6	10	14.7	0.001
Smoking	37	22.6	20	29.3	0.12
Secondary prevention					
Single antiplatelet	54	32.5	26	38.2	0.12
Dual antiplatelet	112	67.4	40	58.8	0.09
Anticoagulation	-		2	2.94	-
Outcome					
Discharge NIHSS (mean±SD)	4.95±3.2		7.1±5.1		0.011
MRS at 1 year: 0–2	140	84.3%	35	51%	0.001
Recurrences at 1 year	16	9.63%	6	8.82%	0.08

DM: Diabetes mellitus, CAD: Coronary artery disease, NIHSS: National Institute of Health Stroke Severity Scale, MRS: Modified Rankin scale, SD: Standard deviation

Table 2: Comparison between neuroimaging and cardiac parameters in single versus recurrent ESUS patients

Parameter	Single stroke (n=166)	%	Recurrent stroke (n=68)	%	*P*
Neuroimaging					
Territory affected					
Vertebrobasilar	45	27	9	13.3	0.06
Anterior circulation	118	71.1	57	84	0.1
Bilateral	3	1.9	2	2.7	
Infarct pattern					
Superficial watershed	40	23.9	28	41.3	0.02
Internal watershed	36	22	16	24	0.735
Multiple embolic	28	17	22	32	0.01
Ipsilateral substenotic vessel disease					
30–49% stenosis	6	3.51	5	7.7	0.453
<30% stenosis	68	41.02	39	57.7	
Normal vessels	92	55.55	20	30.76	
Chronic infarcts					
Territorial	23	13.8	18	26.7	0.045
Lacunar	47	28.3	18	26.7	
White matter changes in Fazekas grade 2/3	41	24.9	23	34.6	0.013
Cardiac evaluation					
≥2 markers of atrial cardiopathy	17	10.3	9	13.1	0.604
ECG-PTEV1 (mean)	2200		2450		
ECG-atrial ectopics	0		2		0.731
SVT	12		8	3.2	
VPC	9	6.9	6	11.3	
TTE-LA enlargement	8	5.3	2	8.1	0.526
LVEF	63.51	5.1	62.33	2.6	0.364

PTEV1: P terminal force V1 in microvolt/ms, SVT: Supraventricular tachycardia, VPC: Ventricular premature contractions, TTE-LA: Transthoracic echo-Left atrial enlargement, LVEF: Left ventricular ejection fraction

showed a high prevalence of vascular risk factors and coronary disease.[5] This difference can be explained by an early onset of metabolic syndrome in Asians.[11] Like other reported ESUS series, we also observed that the majority had mild–moderate strokes with a reasonably good outcome.[13-15]

Among the risk factors, hypertension, diabetes, CAD, and peripheral vascular disease were found to be significantly higher in recurrent ESUS patients on bivariate analysis. The relationship between risk factors and recurrent strokes has not always been linear. While many authors have consistently

Table 3: Multivariate analysis of association between parameters and recurrent ischemic events at 1-year follow-up of ESUS subjects

Parameter	P	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Gender:male	0.528	0.780	0.360	1.689
DM	0.764	0.891	0.420	1.891
HTN	0.628	0.831	0.394	1.755
CAD	0.012	1.296	1.115	1.762
Infarct pattern				
Multiple embolic infarcts	0.014	2.710	1.227	5.988
Superficial watershed infarcts	0.046	1.515	1.247	2.072

reported a strong relationship between hypertension and stroke recurrence risk across all subtypes, studies on diabetics have yielded mixed results. Diabetes has been found to increase recurrence risk in lacunar and large artery strokes.[16,17] In ESUS series from across the globe, the prevalence of diabetes mellitus (DM) has been low, around a quarter, while hypertension was found in over 60%. A similar association has also been reported by Japanese authors, where DM and hypertension both were significantly associated with recurrence risk.[18]

In our study, over 80% had unilateral anterior circulation strokes. Multiple arterial territory strokes have been reported in 15–42.3% of ESUS series,[13,14] unlike our cohort where it was less than 5%. Very few authors have looked into the association between infarct patterns and recurrent events.[19] While the most common imaging pattern in ESUS is a single embolic infarct, around a quarter had multiple embolic infarcts in a single arterial territory at presentation. We found that the imaging pattern of multiple embolic infarcts and superficial watershed pattern of infarcts were both associated with recurrent strokes in our cohort, which has not been reported previously. One plausible explanation is that patients with this pattern of infarcts are more likely to harbor subclinical ipsilateral vessel atheromas, which may be increasing their risk for ipsilateral events.

Analyzing the chronic infarcts at presentation, we found that chronic lacunar infarcts were found in a quarter of ESUS patients and showed no difference between those with single versus recurrent ischemic events. This may be a marker of chronic vascular burden secondary to risk factors, which were high in our cohort. Overall chronic infarct burden, which is indirectly a reflection of prior vascular insult, was lower in our cohort in comparison with some studies on ESUS, where prior strokes are reported in a higher fraction of subjects.[14,15] White matter hyperintensities of moderate-to-severe grade have also shown an association with recurrent events in other Asian studies,[18] but failed to show significance in our cohort on multivariate analysis.

Nonstenotic carotid and aortic arch plaques have been implicated as a possible embolic source in ESUS patients with a prevalence of 79% and 29%, respectively, reported in the global ESUS registry.[1] Large nonstenotic carotid plaques have been reported in the ipsilateral artery[20] and are more common in ESUS subjects than atrial fibrillation (AF)-related strokes.[21] Though our cohort had a higher prevalence of mild stenosis in the ipsilateral vessel, it did not impact the recurrence risk. The high burden of vascular risk factors and the low number of recurrent events could have made the results negative.

The role of atrial cardiopathy in ESUS is being actively studied, with an aim to predict subjects at a higher risk of atrial fibrillation.[22,23] We found that 46.5% of our subjects had at least one biomarker of atrial cardiopathy on evaluation, the most common being increased P terminal force in V1 (PTEV1) in 39%, followed by prolonged PR interval (17.1%) and atrial arrhythmias Atrial premature contractions (APCs) and supraventricular tachycardia (SVT) (15.5%), while 4.2% had mild left atrial enlargement, which was comparable to other reports on atrial cardiopathy markers in ESUS patients.[22,23] None of the atrial cardiopathy markers showed a significant association with recurrence risk at 1-year follow-up in our study. This could have been due to a low number of recurrent events in our group for comparison, but it needs prospective studies with larger sample numbers for confirmation of the finding.

We found that the presence of CAD had a strong correlation with recurrent events at presentation and 1-year follow-up. Though a low prevalence of CAD below 10% has been reported in many ESUS series,[13,24] its association with recurrence risk has not been reported before. In a study on potential embolic sources in ESUS patients, 36% of subjects had left ventricular (LV) disease, which included regional wall motion abnormalities, LV dysfunction, and recent heart failure.[14] A likely explanation is that CAD patients are more prone to stroke due to multiple mechanisms—atherosclerotic vascular disease in extra- and intracranial circulation, LV disease, and rhythm disturbances—thereby increasing their risk of future stroke.

With the majority having mild-to-moderate strokes, our patients had a good functional outcome at 1 year, comparable to previous reports.[25] A smaller embolism from valvular or arterial sources rather than chambers has been proposed as a mechanism in ESUS, which has been confirmed from thrombectomy specimen studies as well.[26] Some reports suggest that the annual stroke recurrence risk is similar between ESUS and cardioembolic patients.[25] Our cohort had a higher first-year recurrence rate, which showed a significant correlation with coronary disease and infarct pattern, while age, risk factors, and atrial cardiopathy markers failed to show an association.

Our study on ESUS and predictors of 1-year recurrence risk is not without its limitations. Being a tertiary healthcare center, there is an inherent referral bias with minor strokes less often getting admitted for evaluation. The majority of the baseline data were collected from medical records, except imaging data, which were reviewed from PACS. Though the majority of our subjects had MRI available for studying the infarct pattern, a quarter had only CT for image analysis. Vessel imaging mainly

focused on vessel stenosis and presence of nonstenotic plaques, but did not measure the plaque thickness in the carotid or vertebral system. Also, the details of aortic arch plaques were not collected for all subjects due to the nonavailability of arch images in CT angiogram (CTA) or patients having undergone Magnetic resonance (MR) angiography. We did not perform TEE in the majority of our subjects, though a transcranial Doppler with bubble contrast was performed in all young cryptogenic strokes to look for right–left shunt. Though telemetry during admission and 24-hour rhythm monitoring were performed in the majority of the subjects, long-term rhythm monitoring could only be performed in a few patients due to cost factors.

With very few Asian studies on ESUS, ours is the first systematic study on the short-term outcome of ESUS patients from India. All our subjects underwent uniform assessment for stroke etiology with neuroimaging and cardiac evaluation including short-term rhythm monitoring, which adds to the strength of the study. We also got 1-year follow-up of all the recruited subjects, with details on recurrent vascular events.

In conclusion, the prevalence of ESUS was 11.21% with a higher first-year recurrence risk of 9.4% in our cohort. Imaging patterns at baseline and coexistent CAD were strong predictors of recurrent cerebrovascular events in the first year after ESUS, possibly pointing to an underlying cardiogenic source itself in our part of India, which needs to be studied in larger populations. The high prevalence of vascular risk factors and their association with recurrent events at baseline reiterate the importance of risk factor control in this etiological subtype as well.

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Conflicts of interest
There are no conflicts of interest.

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