Embolic Stroke of Undetermined Source in Saudi Arabia: Prevalence, Patient Characteristics, and Outcomes

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Background: Embolic stroke of undetermined source (ESUS) is a newly introduced clinical construct to better characterize cryptogenic stroke. It is associated with considerable morbidity and mortality and a high recurrence rate. It has not previously been investigated in Saudi stroke patients. We aimed to conduct a descriptive analysis of ESUS in Saudi Arabia, including its frequency among patients with acute stroke, characteristics, and outcomes. *Methods*: We reviewed all ischemic stroke patients admitted to the stroke unit at King Abdulaziz Medical City-Riyadh, Saudi Arabia, from February 2016 to July 2018. We applied the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group, which defines ESUS as a radiologically confirmed nonlacunar brain infarct without (a) extracranial or intracranial atherosclerosis causing ≥50% stenosis in arteries supplying the ischemic area, (b) a major-risk cardioembolic source, (c) any other specific cause of stroke. We compared ESUS patients with the other stroke patients. Study was approved by local institutional review board. *Results*: Of the 736 patients admitted with ischemic stroke, 147 (20%) had ESUS. Patients with ESUS had fewer vascular risk factors compared to patients without ESUS. Nearly third were either dead or dependent at discharge. There were no significant differences between ESUS and other types of ischemic strokes in mortality rate and independence at discharge. *Conclusion*: ESUS is common in Saudi stroke patients. Despite of the lack of definite etiology, it is associated with considerable morbidity and mortality.
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Introduction

Ischemic strokes have many vascular etiologies that promote the development of brain thromboembolisms.[1] From a prognostic and therapeutic viewpoint, identifying the main etiology of ischemic stroke is crucial as this could impact the treatment strategy and therefore the short- and long-term outcomes as well as the strategies to prevent recurrence.[2] To categorize cases of ischemic stroke based on their etiology, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system was established. This system categorizes ischemic stroke patients into the following groups: large artery atherosclerosis, cardioembolism, small artery occlusion (lacunar), other determined etiologies, and stroke of undetermined cause (i.e., cryptogenic). Moreover, the TOAST classification system includes 3

circumstances for cryptogenic categorization: incomplete evaluation for cause, negative diagnostic results, or more than or equal to 2 conflicting causes found.[2]

An embolic stroke of undetermined source (ESUS) is a nonlacunar cerebral infarct with no extracranial or intracranial more than or equal to 50% stenosis in arteries supplying the ischemic area, no cardioembolic source, and no other specific causes of stroke. It is a recently proposed clinical entity related to cryptogenic stroke that was put forward by Hart et al. in 2014.[3] It is most likely of embolic origin, emphasizing that most cases of cryptogenic stroke are embolic in origin, from an unidentifiable source that remains undiscovered despite thorough evaluation.[4] ESUS was introduced to provide a more clinically beneficial clinical construct than the ambiguous entity of cryptogenic stroke.[5] ESUS patients may differ from other stroke patients in terms of age, severity, and outcomes. As there is a high probability that cardioembolism is the leading etiology of ESUS, an ESUS diagnosis provides a potential target for secondary prevention strategies.[6-8]

Among ischemic stroke patients, ESUS is common and is associated with different clinical characteristics.[4,9,11,12-14] Despite the high incidence and importance, little is known about ESUS in patients in the Middle East, and in Saudi Arabia in particular. Our aim was to determine the frequency (among patients with acute ischemic strokes) and clinical characteristics of ESUS in Saudi Arabia and to compare ESUS with other types of ischemic stroke.

Materials and Methods

Study Setting and Design

We retrospectively reviewed electronic health records of all patients with acute stroke admitted to the acute stroke unit at King Abdulaziz Medical City-Riyadh (KAMC-R), Saudi Arabia, from February 2016 to July 2018. KAMC-R is an academic and tertiary center with more than one thousand beds that is accredited by Joint Commission International. It provides free-of-charge comprehensive care for acute stroke. The hospital treats an average of 500 stroke patients a year. The stroke unit is divided into 2 levels of care: the hyperacute stroke unit (which provides cardiopulmonary monitoring for the first 72 hours) and the acute stroke unit.

The stroke unit is run by a multidisciplinary team that includes specialized stroke neurologists. The care provided is governed by guidelines on clinical care pathways and best practice. Each acute stroke patient undergoes a workup involving a minimum of routine laboratory tests, computed tomography angiography of the carotid arteries and circle of Willis (or Doppler ultrasound or magnetic resonance angiography in cases involving contraindications), transthoracic echocardiography, and monitoring for 72 hours in the hyperacute stroke unit. Additionally, patients aged less than 50 years with no apparent cause of stroke undergo a full thrombophilia workup, transesophageal echocardiography

(TEE), assessment with a Holter monitor and, occasionally, conventional cerebral angiography and prolonged cardiac rhythm monitoring.

Data Collection

We collected data on demographics, vascular risk factors (Arterial hypertension, diabetes, ischemic heart disease, dyslipidemia, body mass index [BMI], smoking and prior stroke or transient ischemic attack), comorbidities, echocardiography results, vascular imaging results, and laboratory findings, stroke subtype, length of stay (LOS), modified Rankin scale (mRS) score at admission and discharge, National Institutes of Health Stroke Scale (NIHSS) score at admission and discharge, and mortality.

We applied the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group, which defines ESUS as a radiologically confirmed nonlacunar brain infarct without (1) extracranial or intracranial atherosclerosis causing more than or equal to 50% stenosis in arteries supplying the ischemic area, (2) a major-risk cardioembolic source, (3) any other specific cause of stroke.[3] The non-ESUS stroke patients were classified to cardioembolic stroke (CE), large artery atherosclerosis (LAA) and small vessels disease (SVD) according to TOAST classification system.[2] The research team underwent training to apply the criteria. The team members resolved any disputes by discussion and coming to a consensus. For this study, we included all clinically and radiologically confirmed ischemic stroke. We excluded cases involving stroke mimics, cerebral venous thrombosis/venous infarcts, and transient ischemic attacks (defined as a sudden transient neurological deficit with no evidence of cerebral infarct on magnetic resonance images) and stroke due to known causes like vasculitis, moyamoya disease, and arterial dissection. Patients with dementia or terminal illness were also excluded.

Data Analysis

We compared the patients with ESUS (ESUS group) to patients with other types of ischemic stroke (CE, LAA and SVD). The in-hospital mortality, LOS, and independence at discharge (mRS <2) were compared between the 4 groups. Data are presented as mean ± standard deviation (SD) or median for continuous variables, and frequency with a percentage for categorical variables. We used one-way analysis of variance (ANOVA) test for continuous variables and chi square test for association between categorical variables. To compare in-hospital mortality rate and independence at discharge between the 2 groups, multivariate logistic regression was conducted, controlling for age, sex, vascular risk factors, prestroke modified Rankin scale, and stroke severity. All statistical tests were considered significant at $P < 0.05$. Data were analyzed using the statistical program SAS (version 9.4). The study was approved by local institutional review board of King Abdullah International Research Center.

Table 1. *Demographic and baseline clinical characteristics of the patients with ESUS versus those with other types of ischemic strokes** *

Characteristics	ESUS N = 147 (20%)	CE N = 139 (18.8%)	LAA N = 193 (26%)	SVD (N = 257 (35%)	P value *
Age (year)—mean $\pm$ SD	58 $\pm$ 12.3	60 $\pm$ 12.5	60 $\pm$ 12.3	61 $\pm$ 11.9	.11
Female sex—no. (%)	50 (34%)	57 (41%)	64 (33.1%)	72 (28%)	.07
Medical history—no. (%)					
Ischemic heart disease	10 (6.8%)	37 (26.6%)	24 (12.4%)	19 (7.4%)	<.001
Arterial hypertension	93 (63.3%)	107 (76.9%)	134 (69.4%)	177 (68.8%)	.03
Diabetes mellitus	76 (51.7%)	83 (59.7%)	129 (66.8%)	158 (61.5%)	.01
Atrial fibrillation	0 (0%)	52 (37.4%)	0 (0%)	0 (0%)	<.001
Dyslipidemia	36 (24.4%)	41 (30.1%)	59 (30.5%)	90 (35.0%)	.07
BMI mean $\pm$ SD	28 $\pm$ 6.4	29 $\pm$ 5.5	29 $\pm$ 6.9	28 $\pm$ 5.6	.18
History of smoking	23 (15.6%)	23 (16.5%)	32 (16.5%)	34 (13.2%)	.80
Previous stroke/TIA[†]	29 (19.7%)	41 (30.1%)	50 (25.9%)	62 (24.1%)	.23
Stroke onset to arrival (h)					
Median (IQR)	9[22]	8 (29.5)	12.5 (49.5)	10 (23)	.60
Prestroke mRS score[†] <2					
No. (%)	132 (89.8%)	121 (87.0%)	167 (86.5%)	230 (89.4%)	.85
NIHSS-score[‡] at admission—median (IQR)	5 (8)	6 (9)	6 (7)	4 (4)	<.001
t-PA or EVT—no. (%)	9 (6.1%)	18 (12.9%)	17 (8.8%)	9 (3.5%)	.004

BMI, body mass index; CE, cardioembolic; ESUS, embolic stroke of undetermined source; EVT, endovascular treatment; IQR, interquartile range; LAA, large artery atherosclerosis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SVD, small vessels disease, TIA, transient ischemic attack; t-PA, tissue plasminogen activator.

*One-way analysis of variance (ANOVA) test for continuous variables, chi square test for association between categorical variables.

[†]mRS scores range from 0 (no neurologic deficit) to 6 (death).

[‡]NIHSS scores range from 0 (normal function) to 42 (death).

Results

Patient Characteristics

Between February 2016 and July 2018, 736 patients were admitted with acute ischemic stroke. Of these, 147 (20%) met the diagnostic criteria for ESUS. The baseline characteristics of the groups (ESUS versus others) are shown in Table 1. There was no significant difference in age and gender distribution between groups. Patient with ESUS had fewer vascular risk factors compared to other groups. Ischemic heart diseases were observed in 6.8% in ESUS, 26.6% in CE, 12.4% in LAA, and 7.4% in SVD; $P < 0.001$. Arterial hypertension was observed in 63.3% in ESUS, 76.9% in CE, 69.4% in LAA, and 68.8% in SVD; $P < 0.03$. Further, diabetes was reported in in 51.7% in ESUS,

59.7% in CE, 66.8% in LAA and 61.5% in SVD; $P = 0.01$. The rate of receiving intravenous tissue plasminogen activator (t-PA) or endovascular therapy (EVT) was significantly different between groups. The rate was 6.1% in ESUS, 12.9 in CE, 8.8% in LAA, and 3.5% in SVD; $P = 0.004$.

Patient Outcomes

Patient outcomes, comprising in-hospital mortality, independence at discharge, median NIHSS score at discharge, and median LOS, are summarized in Table 2. During hospitalization, 2.04% of ESUS patients died and 64.6 were independent at discharge. The median (interquartile range) NIHSS score at discharge was 2[5] with median LOS 4[8]

Table 2. *Clinical outcomes in patients with ESUS compared to other types of ischemic stroke*

Outcome	ESUS (N = 146)	CE (N = 139)	LAA (N = 193)	SVD (N = 257)
In-hospital mortality—no. (%)	3 (2.04%)	2 (1.44%)	7 (3.63%)	2 (0.78%)
Independence at discharge[†]—no. (%)	95 (64.6)	68 (48.9)	91 (47.2)	177 (68.9)
NIHSS score at discharge[‡]				
Median (IQR)	2 (5)	3 (7)	3 (6)	2 (3)
Median length of stay (IQR)—days	4 (8)	9 (15)	6 (11)	3 (4)

CE, cardioembolic; ESUS, embolic stroke of undetermined source; IQR, interquartile range; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SVD, small vessels disease.

[†]mRS scores < 2 at discharge (scores range from 0 (no neurologic deficit) to 6 (death).

[‡]NIHSS scores range from 0 (normal function) to 42 (death).

Table 3. *Clinical outcomes in patients with ESUS compared with other types of ischemic stroke (unadjusted logistic regression analysis)*

Outcome		Effect size	LCL	UCL	*P* value
In-hospital mortality	Cardioembolic vs ESUS	1.4	0.2	8.6	.69
	LAA vs ESUS	0.5	0.1	2.1	.39
	SVD vs ESUS	2.6	0.4	16.0	.28
Independence at discharge*	Cardioembolic vs ESUS	0.6	0.4	1.0	.10
	LVD vs ESUS	0.6	0.3	0.9	.02
	SVD vs ESUS	1.5	0.9	2.3	.05
NIHSS score at discharge[†]	Cardioembolic vs ESUS	0.6	−0.6	1.9	.33
Median (IQR)	LAA vs ESUS	0.7	−0.4	1.9	.25
	SVD vs ESUS	−1.5	−2.7	−0.4	.006
Median length of stay (IQR)—days	Cardioembolic vs ESUS	6.2	2.2	10.2	.002
	LAA vs ESUS	3.0	−0.6	6.8	.10
	SVD vs ESUS	−4.5	−8.02	−1.0	.01

CE, cardioembolic; ESUS, embolic stroke of undetermined source; IQR, interquartile range; LAA, large artery atherosclerosis; LCL, lower limit of confidence interval; NIHSS, National Institutes of Health Stroke Scale; SVD, small vessels disease; UCI, lower limit of confidence interval.

*Defined as modified Rankin Scale (mRS) score <2 (no or minimal neurological symptoms without disability).

[†]NIHSS scores range from 0 (normal function) to 42 (death).

days. In the nonadjusted logistic regression analyses (Table 3), there were no significant differences between the ESUS and non-ESUS groups in mortality rate. When we compared independence at discharge between groups, patients with LVD were less likely to be independent at discharge compared to ESUS (odds ratio [OR], 0.6, 95% confidence interval [CI], 0.3, 0.9; *P* = 0.02), while there was no statistically significant difference between ESUS and other groups. ESUS patients did not differ in the median NIHSS score at discharge compared to CE and LAA. However, SVD were more likely to have lower NIHSS score at discharge compared to ESUS (OR, −1.5, 95% CI −2.7, −0.4; *P* = 0.006). Further, median LOS was significantly different between the groups. CE patients stayed in hospital for longer period compared to ESUS (OR, 6.2, 95% CI, 2.2, 10,2; *P* = 0.002). Also, SVD patients fewer days in hospital compared to ESUS (OR, −4.5, 95% CI, −8.02, −0,1; *P* = 0.01). No difference noted in LOS between ESUS and LAA. After adjustment for age, sex, vascular risk factors, stroke severity, prestroke mRS and treatment with t-PA or EVT in multivariate regression analyses, there was no significant differences between the ESUS and other groups in mortality rate, independence at discharge, median NIHSS score at discharge, and median LOS except that CE patients spent more days in hospital compared to ESUS (OR, 4.4, 95% CI, 0.5, 8.2; P = 0.02).

Discussion

Among Saudis, our study showed that ESUS occurs in approximately 1 out of every 5 cases of acute stroke (20%). This finding is consistent with the findings of several studies in different parts of the world, as the prevalence of ESUS in ischemic stroke patients ranges from 7% to 42% worldwide.[15] This wide range is likely related to the extent of investigations of the causes of stroke and the variable characteristics of patients included in some of the studies. A study by the ESUS Global Registry Investigators involving 19 countries reported that there was no significant difference in ESUS prevalence across global regions.[16]

Further, our data showed that patients with ESUS were more likely to have fewer vascular risk factors (ischemic heart disease, hypertension, diabetes, and dyslipidemia). Similar findings have been reported previously.[11,17,18] The stroke severity at admission was different between 4 groups. There was no difference between ESUS stroke severity when compared individually with each subtype and the statistically significant difference between groups was mainly driven by mild stroke severity of SVD strokes compared to LAA and CE. The similar severity of stroke in ESUS compared to other types of stroke was reported in previous research.[20] However, several other studies have shown that ESUS may involve milder stroke severity compared to other subtypes.[12,17,19] The overall mortality rate during hospitalization in our cohort (both ESUS and non-ESUS patients) was low (≈2%). This was likely related to the admission criteria set by the hospital, as patients who were aged more than 80 years, had a prestroke mRS score more than 2, or had dementia or a terminal illness prior to stroke onset were ineligible for admission to the stroke unit and were therefore underrepresented in this study. Inclusion of these elderly and more sick patients could have resulted in a considerably higher mortality rate in the non-ESUS group. However, the mortality rate in our ESUS cohort (2.04%) was consistent with the 30-day mortality rate reported by the ESUS Global Registry Investigators and the in-hospital mortality rate reported in Polish ESUS patients.[16,19]

Although the ESUS patients in this study had fewer vascular risk factors, and had no obvious underlying

Table 4. *Clinical outcomes in patients with ESUS compared to other types of ischemic stroke*

Outcome		Adjusted effect size*	LCL	UCL	*P* value
In-hospital mortality	Cardioembolic vs ESUS	0.2	0.01	2.3	.18
	LAA vs ESUS	1.9	0.4	9.8	.40
	SVD vs ESUS	0.9	0.1	7.2	.99
Independence at discharge†	Cardioembolic vs ESUS	1.1	0.6	2.0	.71
	LAA vs ESUS	1.3	0.8	2.3	.26
	SVD vs ESUS	0.6	0.4	1.2	.17
NIHSS score at discharge‡	Cardioembolic vs ESUS	−0.7	−1.9	0.3	.19
Median (IQR)	LAA vs ESUS	0.06	−0.8	0.9	.89
	SVD vs ESUS	−0.6	−1.5	0.2	.14
Median length of stay (IQR)—days	Cardioembolic vs ESUS	4.4	0.5	8.2	.02
	LAA vs ESUS	1.7	−1.8	5.2	.33
	SVD vs ESUS	−3.06	−6.4	0.2	.06

CE, cardioembolic; ESUS, embolic stroke of undetermined source; IQR, interquartile range; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SVD, small vessels disease.

*Regression models included age, sex, vascular risk factors, prestroke mRS, and stroke severity (according to NIHSS at admission).

†Defined as modified Rankin Scale (mRS) score <2 (no or minimal neurological symptoms without disability).

‡NIHSS scores range from 0 (normal function) to 42 (death).

stroke etiology, this entity is not benign. Nearly a third of ESUS patients either died or was discharged with significant neurological deficits (with mRS score ≥2). Additionally, ESUS did not differ from non-ESUS ischemic strokes in terms of mortality rate or lack of independence at discharge. However, this is in contrast to the findings of other studies, which have shown that ESUS may have better outcomes and a lower mortality rate.[10,17]

Out study has some limitations. First, it is a single-center study and the results may not be representative of the whole country. Second, the hospital criteria for admitting stroke patients to the stroke unit (i.e., exclusion of patients aged >80 years and patients with a prestroke mRS score >2, dementia, or a terminal illness) could have introduced selection bias. Third, our cohort was not followed-up beyond discharge. It is known that some ESUS patients may develop atrial fibrillation (AF). For example, 1-year monitoring with an insertable cardiac monitor identified AF in 12.4% of cryptogenic stroke patients aged more than or equal to 40 years.[21] Another study, involving cryptogenic stroke patients aged more than or equal to 55 years, reported that 30-day monitoring with an event recorder revealed AF in 16.1%.[22] Extended cardiac monitoring for 3 years may reveal AF in up to third of ESUS patients.[23] Fourth, the majority of our ESUS patients did not undergo TEE. Although the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group do not include TEE in the mandatory diagnostic workup for ESUS, data suggest that conducting TEE as part of the diagnostic workup for potential ESUS patients may reveal additional findings, alter the diagnosis, and change the management plan of about one in 7 ESUS patients.[24] If all our ESUS cohort had undergone TEE, there is an, albeit small, possibility that some may have been found to have cardioembolic stroke.

Conclusion

ESUS is common in Saudi stroke patients, which is in line with the published data from all over the world.[15] ESUS patients had fewer vascular risk factors, similar in-hospital mortality rate and rate of independence at discharge. This study is the first study to investigate ESUS in Saudi Arabia using the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group. Our findings add to the pool of knowledge on this new entity.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Dr. Al Khathaami was responsible for the study concept, statistical analysis and interpretation, manuscript preparation, and study supervision; Bayan Al Bedah for the statistical analysis; Abdulmajeed Alnosair, Rayan Alrebdi, Shorug Alwayili, and Suleiman Alhamza for the data collection; and Nasser Alotaibi for the revision of the manuscript.

Ethics

The study was approved by the institutional review board of King Abdullah International Research Center.

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