Predictors of poor outcome in embolic stroke of undetermined source

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ABSTRACT

الأهداف: معرفة دلالات التنبؤ بالوفاة والعجز عند الخروج من المستشفى.

الطريقة: تم مراجعة ملفات جميع المرضى الذين تم تشخيصهم بالسكتة الدماغية بمدينة الملك عبدالعزيز الطبية، الرياض، المملكة العربية السعودية من شهر فبراير 2016م حتى شهر يوليو 2018م. تم إتباع توصيات المجموعة العالمية للسكتة الدماغية نتيجة انسداد وعائي لسبب مجهول. قارنا المرضى ذوي النتائج السيئة بعد السكتة بالمرضى ذو النتائج المحمودة. تم إستخدام الإنحدار اللوجستي متعدد المتغيرات من أجل تحديد دلالات التنبؤ. شمل نموذج الانحدار الأعمار أكبر من 60 سنة، والجنس، وكتلة الجسم أكثر من 25 كج/م^2، والتدخين، والأمراض المزمنة، والإصابة السابقة بالسكتة الدماغية، ومقياس الإعاقة ما قبل السكتة، ومقياس معاهد الصحة الوطنية للسكتة الدماغية في وقت دخول المستشفى أكثر من 5 ، واستخدام مضادات الصفائح الدموية ومسيلات الدم ما قبل السكته الدماغية.

النتائج: من أصل 147 مريض مطابقين للمعايير، 28.8% كان لديهم نتائج سيئة (وفاة أو اعاقة). دلائل التنبؤ شملت مقياس معاهد الصحة الوطنية للسكته الدماغية أكثر من 5 (النسبة الغريبة 11.1، معاير الثقه كان 95% (4.4–28.2). مقياس الاعاقة ما قبل الجلطه أكثر من 1 (نسبة الاحتمالات=3.7، معاير الثقة 95% (1.14–11.59) ، العمر أكثر من 60 سنة (نسبة الاحتمالات=2.4، معايير الثقة 95% (1.14–5.22).

الخاتمة: نسبة عالية ومهمة من مرضى السكتة الدماغية نتيجة إنسداد وعائي لسبب مجهول توفوا أو أصيبوا بعجز. النتائج السيئة كانت أكثر لدى كبار السن ومن لديهم عجز سابق ومن كانت لدية سكتة شديدة.

Objectives: To identify the clinical predictors of death or disability at discharge.

Methods: We retrospectively reviewed all ischemic stroke patients admitted to the stroke unit of King Abdulaziz Medical City, Riyadh, Saudi Arabia, from February 2016 - July 2018. We applied the Cryptogenic Stroke/ESUS International Working Group Embolic stroke of undetermined source (ESUS) criteria. We compared patients with poor outcomes (death or modified Rankin Scale [mRS] score >2) to those with favorable outcomes. Multivariate logistic regression was used to identify predictors of poor outcome. The regression model included age >60 years, gender, body mass index >25 kg/m^2, smoking history, comorbidities, previous ischemic/transient ischemic attack, pre-stroke mRS score >1, National Institutes of Health Stroke Scale (NIHSS) score at admission >5, pre-stroke antiplatelet use, and thrombolysis treatment.

Results: Out of 147 patients who met the ESUS criteria, 28.8% had poor outcomes. Predictors of poor outcome were NIHSS score >5 (odds ratio [OR] 11.1, 95% confidence interval [CI] 4.4–28.2), pre-stroke mRS score >1 (OR 3.7, 95% CI 1.14–11.59), and age >60 years (OR 2.4, 95% CI 1.14–5.22).

Conclusion: A significant proportion of ESUS patients were dead or disabled at discharge. Poor outcome was more in older patients with pre-stroke functional disability and moderate to severe stroke.

Neurosciences 2019; Vol. 24 (3): 164-167
doi: 10.17712/nsj.2019.3.20190005

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Received 21st January 2019. Accepted 26th March 2019.

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Embolic stroke of undetermined source (ESUS) is a subtype of cryptogenic ischemic stroke in which embolism is the most likely cause of stroke. According to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group, ESUS is defined as a non-lacunar infarct without (a) significant (≥50%) extracranial or intracranial atherosclerosis stenosis in arteries supplying the ischemia area, (b) major-risk cardioembolic source, and (c) any other specific etiology of stroke.[1] Major sources of cardioembolic stroke are permanent or paroxysmal atrial fibrillation, intracardiac thrombus, presence of prosthetic cardiac valve, sustained atrial flutter, atrial myxoma, other cardiac tumors, mitral stenosis, recent myocardial infarction, ejection fraction <30%, valvular vegetation, and infective endocarditis.[1]

In clinical practice, ESUS is common among patients with ischemic stroke (9–25%).[2] It is associated with considerable mortality and morbidity. As many as a third of ESUS patients are either dead or lack independence after the stroke.[3-6] Despite extensive literature on stroke prognosis in general, little is known about the predictors of death and disability in ESUS patients at discharge. Our aim was to identify the clinical predictors of poor outcome (death or disability) at discharge after ESUS.

Methods. ***Study setting and design.*** This is a retrospective chart review of all stroke patients admitted to the acute stroke unit of King Abdulaziz Medical City, Riyadh (KAMC-R), Saudi Arabia, between February 2016 and July 2018. King Abdulaziz Medical City, Riyadh is an academic tertiary center with Joint Commission International accreditation. It has >12,000 beds and nearly 500 stroke admissions annually. For each stroke patient, the minimum assessments involve cardio-pulmonary 72-h monitoring in the stroke unit, routine lab testing, transthoracic echocardiography, and carotid artery and circle of Willis computed tomography angiography (or, if contraindicated, magnetic resonance angiography or Doppler ultrasound). Those aged <50 years with no obvious cause of stroke are also subjected to a thrombophilia workup, Holter monitor assessment, transesophageal echocardiography and, in some cases, prolonged cardiac rhythm monitoring and conventional cerebral angiography.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Data collection. Data on demographics, cardiovascular risk factors (body mass index >25 kg/m^2, history of smoking, previous stroke/transient ischemic attack, and comorbidities such as ischemic heart disease, arterial hypertension, diabetes mellitus, and dyslipidemia), echocardiography, vascular images, laboratory findings, stroke subtype, time from stroke onset to arrival, modified Rankin scale (mRS) score at admission and discharge, National Institute of Health Stroke Scale (NIHSS) score at admission and discharge, and death were obtained from electronic health records. The diagnosis of stroke, stroke subtypes, baseline comorbidities and measurement of stroke outcomes were based on the treating physicians' documentation on electronic health records.

We applied the ESUS criteria proposed by Hart et al[1], which define ESUS as a non-lacunar infarct confirmed by brain images without (a) significant (≥50%) extracranial or intracranial atherosclerosis stenosis in arteries supplying the ischemia area, (b) major-risk cardioembolic source, and (c) any other specific etiology of stroke. Major sources of cardioembolic stroke are permanent or paroxysmal atrial fibrillation, intracardiac thrombus, presence of prosthetic cardiac valve, sustained atrial flutter, atrial myxoma, other cardiac tumors, mitral stenosis, recent myocardial infarction, ejection fraction <30%, valvular vegetation, and infective endocarditis.[1] The research team were trained to apply the criteria. In cases of dispute, the team members discussed the cases individually and any disputes were resolved by consensus.

Data analysis. Patients with ischemic stroke that met the ESUS criteria were included in this study. Poor outcome was defined as death or disability (mRS>2) at discharge. We compared patients who had poor outcomes to those who had favorable outcomes (mRS≤2). Data are presented as mean±standard deviation (SD) for continuous variables, except for NIHSS score and time from stroke onset to arrival, which are presented as median with interquartile range. For categorical variables, data are presented as frequencies with percentages. Student's t-test was used to compare means, and the χ^2 test was used to compare proportions. We examined outcome predictors using multivariate logistic regression. The regression model included age >60 years, sex, body mass index >25 kg/m^2, history of smoking, comorbidities (ischemic heart disease, arterial hypertension, diabetes mellitus, and dyslipidemia), previous ischemic stroke/transient ischemic attack, pre-stroke mRS score >1, NIHSS score at admission >5, pre-stroke antiplatelet use, and treatment with tissue plasminogen activator (t-PA) or endovascular therapy (EVT). All statistical tests

Table 1 - Demographic and clinical characteristics of ESUS patients with poor vs. favorable outcomes.

Characteristic	Favorable outcome n=109	Poor outcome n=38	*P*-value
	n (%)		
Age (year) mean±SD	57.3±12.5	61.4±11.5	0.08
Female gender	36 (33)	14 (37)	0.7
Medical history			
Ischemic heart disease	7 (6.4)	3 (8)	0.72
Arterial hypertension	67 (61.5)	26 (68.4)	0.6
Diabetes mellitus	54 (49.5)	22 (58)	0.45
Dyslipidemia	28 (25.7)	8 (21.0)	0.7
Body mass index mean±SD	28±6.4	28.5±6.5	0.62
History of smoking	19 (17.4)	4 (10.5)	0.44
Previous ischemic stroke/TIA	20 (18.3)	9 (24)	0.5
Pre-stroke antiplatelet use	105 (96.3)	34 (89.4)	0.21
Pre-stroke mRS score* <2	102 (93.5)	30 (79.4)	0.04
NIHSS score† at admission median (IQR)	3.0 (5.00)	11.0 (10.0)	<0.0001
Treatment with t-PA or EVT	5 (5)	4 (10.5)	0.24

ESUS - embolic stroke of undetermined source, EVT - endovascular treatment, IQR - interquartile range, mRS - modified Rankin Scale, NIHSS - National Institutes of Health Stroke Scale, TIA - transient ischemic attack, t-PA - tissue plasminogen activator. *mRS scores range from 0 (no neurologic deficit) to 6 (death). †NIHSS scores range from 0 (normal function) to 42 (death)

were considered significant at $p<0.05$. Data were analyzed using the statistical program Stata (version 15; StataCorp LLC, College Station, TX, USA).

Results. Between February 2016 and July 2018, 147 patients were admitted and met the ESUS criteria. The baseline characteristics of the cohort are shown in **Table 1**. Poor outcome (death or disability at discharge) was observed in 28.8%. Patients with poor outcomes were older but the difference was not statistically significant. There were no difference between-groups in the frequency of cardiovascular risk factors (body mass index >25 kg/m^2, history of smoking, ischemic heart disease, arterial hypertension, diabetes mellitus, dyslipidemia, or previous stroke/transient ischemic attack). Further, there were no significant differences in the rates of pre-stroke antiplatelet use, treatment with t-PA or EVT. However, in comparison to patients with favorable outcomes, those with poor outcomes had more moderate to severe stroke at admission (median NIHSS score, 12.5 vs. 8.0, $p<0.001$) and were more likely to have functional disability prior to stroke (pre-stroke mRS score <2, 79.41% vs. 93.52%, $p=0.04$).

According to the multivariate logistic regression analysis (**Table 2**), predictors of poor outcome were NIHSS score >5 (odds ratio [OR] 11.14, 95% confidence interval [CI] 4.4–28.21), pre-stroke mRS score >1 (OR 3.7, 95% CI 1.14–11.59), and age >60 years (OR 2.4, 95% CI 1.14–5.22). Gender, cardiovascular risk factors, pre-stroke antiplatelet use, and treatment with t-PA or EVT did not predict poor outcome.

Discussion. Several clinical factors influence ischemic stroke outcomes. In previous studies, factors associated with poor outcomes in ischemic stroke patients were older age, female gender, large infarction, severe stroke, high burden of cardiovascular comorbidities, diabetes mellitus, and poor functional status prior to stroke.[7-8] Further, different stroke

Table 2 - Multivariate logistic regression analysis of poor outcome (death or mRS score >2) at discharge.

Characteristic	Odds ratio	95% CI	*P*-value
Age >60 years	2.4	[1.1,5.2]	0.02
Female gender	0.8	[0.4,1.8]	0.7
Body mass index >25 kg/m^2	0.8	[0.35,1.8]	0.6
History of smoking	0.54	[0.17,1.71]	0.30
Ischemic heart disease	1.2	[0.3,5.1]	0.8
Arterial hypertension	1.4	[0.6,3]	0.44
Diabetes mellitus	1.4	[0.7,3]	0.4
Dyslipidemia	0.8	[0.3,2]	0.6
Previous ischemic stroke/TIA	1.4	[0.6,3.3]	0.5
Pre-stroke antiplatelet use	0.3	[0.1,1.4]	0.12
Pre-stroke mRS score (≥2)	4	[1.3,12]	0.01
NIHSS score at admission >5	12	[4.6,29.3]	<0.0001
Treatment with t-PA or EVT	0.4	[0.1,1.6]	0.20

EVT - endovascular treatment, mRS - modified Rankin Scale, NIHSS - National Institutes of Health Stroke Scale, TIA - transient ischemic attack, tPA - tissue plasminogen activator

subtypes may have different outcomes. For example, cardioembolic stroke might be associated with poorer outcomes.[3] Additionally, some reports showed that ESUS might be associated with more favorable outcomes compared to other types of ischemic stroke.[3,5] Our data showed that approximately a quarter (28.8%) of ESUS patients had poor outcomes. However, higher rates (34.5–39.6%) have been reported previously.[3,6] As in other types of stroke, our data showed that stroke severity, older age, and poorer functional status prior to stroke were predictors of outcomes in ESUS patients. These factors have been consistently shown to be associated with poor outcome after stroke in general.[7,8] In ESUS in particular, age was reported to be a strong predictor of stroke recurrence and death.[9] Similar to previous reports, gender was not associated with poor outcome in this study. For example, Ntaios et al showed that gender was not a predictor of stroke recurrence and death in ESUS patients.[9] Arauz et al[3] compared ESUS patients with cardioembolic stroke patients. Using adjusted Cox regression analyses of poor outcome (mRS score 3–6), they found that ischemic cardiomyopathy, antiplatelet use, and anticoagulation treatment were associated with poor outcomes.In contrast, our study indicated that antiplatelet use was not associated with poor outcomes. Despite the scant previous information on the short-term rates of death and disability following ESUS, it is apparent that ESUS is similar to other types of ischemic stroke in terms of risk factors for poor outcomes.

limitations of the study. Our study has several limitations. First, it is a single-center study. The results may not be representative of the whole country or other countries. Second, the small sample size could have introduced type II error (false negatives) because the probability of a type II error increases as the sample size decreases. Third, our cohort was not followed up beyond discharge. It is possible that after long-term follow up, some of our patients may not have had true ESUS. It has been shown that, one in 6 ESUS patients develop atrial fibrillation during 1-year cardiac monitoring.[10,11]

In conclusion, ESUS is not a benign condition. It is associated with significant mortality and morbidity, particularly in older patients with moderate to severe neurological deficits at presentation and poor functional status prior to stroke. This study is the first study to describe predictors of outcomes in ESUS patients 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, and they are particularly relevant for health professional and providers in Saudi Arabia and other Gulf states. Population based studies are needed for further understanding of short-term outcome of this subtype of ischemic stroke.

Acknowledgements. *We would like to thank Maison Al Tarawneh for her help with the study coordination. We would also like to thank Charlesworth author services for English language editing.*

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