

# Features of Patients Aged 80 Years or Older with Embolic Stroke of Undetermined Source

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*Background:* Embolic stroke of undetermined source has not been thoroughly investigated in older patients. In this study, we investigated the features of this condition in patients greater than or equal to 80 years of age. *Methods:* All patients with acute ischemic stroke in our hospital underwent diffusion-weighted imaging, magnetic resonance angiography, T2-weighted imaging, and fluid-attenuated inversion recovery sequence imaging. Embolic stroke of undetermined source was defined as a radiologically confirmed nonlacunar brain infarct on diffusion-weighted imaging without (1) extracranial or intracranial atherosclerosis causing greater than or equal to 50% luminal stenosis in arteries supplying the ischemic area, (2) major-risk cardioembolic source, and (3) any other specific cause of stroke. We retrospectively identified consecutive patients hospitalized for acute ischemic stroke who met the embolic stroke of undetermined source diagnostic criteria and investigated patients' baseline and diagnostic findings. *Results:* We divided 122 consecutive embolic stroke of undetermined source patients (median age: 73 years; 49 men, 73 women) into 2 groups by age at admission. Patients aged greater than or equal to 80 years had higher D-dimer and brain natriuretic peptide levels, more frequent premature atrial complexes/day in 24-hour Holter electrocardiography, and thicker maximum intima media thickness on ultrasound compared with patients aged less than 80 years ( $P < .05$ , U test). *Conclusions:* Our results suggest that high admission D-dimer and brain natriuretic peptide levels are associated with age of onset in patients with embolic stroke of undetermined source. Patients aged greater than or equal to 80 years tended to have more frequent premature atrial complexes and thicker maximum intima media thickness compared with patients aged less than 80 years.

**Key Words:** Embolic stroke of undetermined source—D-dimer—brain natriuretic peptide—premature atrial complexes—intima media thickness

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## Background

Embolic stroke of undetermined source (ESUS) accounts for approximately one sixth of all cerebral

infarctions.<sup>1,2</sup> ESUS is a recently described condition, not yet thoroughly investigated in older patients; however, most ESUS patients are diagnosed as having embolic stroke. Hart et al defined ESUS as unifying all ESUSs,<sup>3</sup> and underlying etiologies include minor-risk potential cardioembolism, paroxysmal atrial fibrillation (AF) conversion, cancer-associated coagulopathy and embolism, arteriogenic embolism, and paroxysmal embolism.

The diagnosis of ESUS is clinical and based on neurological examination using electrocardiography (ECG), transthoracic echocardiography, transesophageal echocardiography, computed tomography, magnetic resonance (MR) imaging, MR angiography, 3-dimensional computed tomographic angiography, and cerebral angiography.<sup>4</sup> As a new concept, the term, ESUS, provides an operational definition;

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however, diagnosing ESUS remains difficult in some patients. ESUS may be overdiagnosed or misdiagnosed with insufficient examination for the stroke cause.

ESUS has recently attracted increasing attention in all stroke patients, and appears to be common in young stroke patients. In a previous study, ESUS patients were younger and had milder cardiovascular risk factor burdens and generally better long-term outcomes compared with other causes of young-onset stroke.<sup>5</sup> The majority of ESUS cases are considered to be caused by cardioembolism,<sup>6</sup> and the comparable risk of recurrent stroke between ESUS and high-risk sources of cardioembolism might suggest similarities in their pathophysiology. The number of people reaching greater than or equal to 80 years of age is increasing in most populations, worldwide,<sup>7</sup> and although some studies report the features of young patients with ESUS,<sup>8</sup> few reports discuss the features of patients greater than or equal to 80 years of age with ESUS.<sup>9</sup>

The purpose of our retrospective study was to investigate the characteristics of patients greater than or equal to 80 years with ESUS.

## Methods

Plasma D-dimer levels, estimated glomerular filtration rate, brain natriuretic peptide (BNP) levels, and body mass index were measured at admission. Hypertension is defined as systolic blood pressure greater than or equal to 140 mmHg or diastolic blood pressure greater than or equal to 90 mmHg. An individual was diagnosed to have diabetes if the individual's HbA1c value was greater than or equal to 6.5%. Dyslipidemia is defined as a low-density lipoprotein cholesterol level of greater than 140 mg/dL, a high-density lipoprotein cholesterol level of less than 40 mg/dL, or a triglyceride level of greater than 150 mg/dL. Hypertension, diabetes mellitus, dyslipidemia, and ischemic cardiomyopathy were considered present if patients were receiving medical treatment for these diseases at the time of ESUS investigation. All patients underwent brain MR imaging, sonography of the carotid arteries, and echocardiography. MR imaging at admission included diffusion-weighted imaging (DWI), T2-weighted imaging and T2\*-weighted imaging, 3-dimensional time-of-flight MR angiography, and fluid-attenuated inversion recovery imaging. We measured maximum intima media thickness (IMT) with ultrasound in all patients. Maximum IMT of the carotid artery is measured as an indispensable parameter to assess the presence and degree of atherosclerosis. B-mode ultrasound of carotid arteries was performed on commercially available equipment with 7.5 MHz probe. Echocardiography was performed to evaluate ejection fraction and left atrial diameter in patients with ESUS. All patients underwent 12-lead ECG at admission. In patients with sinus rhythm, paroxysmal AF was identified using (1) repeated ECGs during hospital stay, (2) 24-hour Holter

ECG monitoring, and (3) continuous ECG monitoring for 1 week or until discharge in patients where AF was strongly suspected based on clinical presentation and brain imaging findings (e.g., multiterritorial infarcts, strokes presenting with maximum severity at onset, or largely dilated left atrium). AF was defined as an episode of irregular heart rhythm without detectable P waves lasting more than 30 seconds. Premature atrial complexes (PACs) were defined by a coupling interval to the preceding QRS complex of less than 80%. The total number of PACs during the entire recording period was totaled.

ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group<sup>3</sup> as a visualized nonlacunar brain infarct without the following: extracranial or intracranial atherosclerosis causing 50% luminal stenosis in arteries supplying the area of ischemia; major-risk cardioembolic source; and any other specific cause of stroke (e.g., arteritis, dissection, migraine/vasospasm, or drug misuse). Lacunar strokes were defined according to the Trial of Org 10172 in the Acute Stroke Treatment classification.<sup>10</sup>

We investigated abnormal DWI findings in patients who were identified clinically as having ESUS. We also confirmed that lesions were affecting mainly the posterior circulation or anterior circulation.

Stroke severity was assessed by the National Institutes of Health Stroke Scale score on admission.<sup>11</sup>

We retrospectively identified consecutive patients hospitalized for acute ischemic stroke who met the ESUS diagnostic criteria from April 2016 to June 2018, and investigated patients' baseline and diagnostic findings.

## Statistical Analysis

Continuous data are summarized as medians and interquartile ranges, and categorical data as absolute numbers and percentages. Differences between patients greater than or equal to 80 years versus less than 80 years were compared using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. A value of  $P < .05$  was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS Inc., version 17.0 for Windows, Chicago, IL).

## Results

Of the 748 eligible patients, 122 (16.3%) were classified as having ESUS. We retrospectively enrolled these 122 patients (median age: 73 years; 49 men and 73 women; [Table 1](#)), and divided them into 2 groups by age at admission. We found no significant differences between National Institutes of Health Stroke Scale at admission, ejection fraction, left atrial diameter, estimated glomerular filtration rate, or body mass index between groups. Regarding vascular risk factors in ESUS patients greater than or equal to 80 years, hypertension (86.8%), dyslipidemia (68.4%), diabetes (23.7%), and

**Table 1.** Clinical characteristics of patients with ESUS

	Total (N = 122)	Aged ≥80 years (N = 38)	Aged <80 years (N = 84)	P value
Age [years], median (IR)	73 (66.25-84)	84 (81.25-86)	70 (60-74)	<.001*
Sex, male, no [%]	75 [61.4%]	20 [52.6%]	55 [65.5%]	.126
BMI [%], median (IR)	22.81 (20.25-24.5)	21.99 (18.47-24.5)	23.01 (20.85 – 24.45)	.344
Hypertension, no [%]	93 [76.2%]	33 [86.8%]	60 [71.4%]	.082
Dyslipidemia, no [%]	64 [52.5%]	16 [42.1%]	48 [57.1%]	.156
Diabetes mellitus, no [%]	26 [21.3%]	9 [23.7%]	17 [20.2%]	.535
Ischemic heart disease, no [%]	13 [10.7%]	5 [13.2%]	13 [15.5%]	.545
Preadmission CHADS2 score, median (IR)	2 (1-2)	2.5 (1-4)	2 (1-2)	<.001*
Pre-admission mRS score, median (IR)	0 (0-1)	1 (1-2.75)	0 (0-0)	<.001*
NIHSS score, median (IR)	3 (1-7)	4.5 (2-7)	3 (1-7.25)	.147

Abbreviations: BMI, body mass index; ESUS, embolic stroke of undetermined source; IR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

We compared differences between patients aged greater than or equal to 80 years versus less than 80 years using Fisher’s exact test for categorical variables and the Mann-Whitney U test for numerical variables.

\**P* < .05.

ischemic heart disease (10.5%) were not statistically significantly different compared with patients less than 80 years of age (Tables 1 and 2). The incidence of vascular risk factors was not high in either group and did not significantly differ between the groups. The median preadmission CHADS2 and modified Rankin scale scores were 2.5 and 1, respectively, in patients greater than or equal to 80 years and 1 and 0, respectively, in patients less than 80 years (*P* < .001, Mann-Whitney U test) (Table 1). Median D-dimer and BNP levels were 1.6 and 69.95, respectively, in patients greater than or equal to 80 years and .65 and 26.05, respectively, in patients less than 80 years (*P* < .001, Mann-Whitney U test; Table 2); median D-dimer and BNP levels were significantly higher in the greater than or equal to 80 years group. The median number of PACs per day in 24-hour Holter ECGs and the maximum IMT measured by ultrasound were 260.5 and 2.75, respectively, in patients greater than or equal to 80 years and 43 and 2.1, respectively, in patients less than 80 years (*P* < .001, Mann-Whitney U test; Table 2); the number of PACs per day was significantly higher and the maximum IMT thickness was significantly thicker in the

greater than or equal to 80 years group. We found no significant differences in MR imaging for DWI abnormalities between the 2 groups regarding vertebral artery territorial infarction and internal carotid artery infarction.

**Discussion**

In this study, we examined the clinical, radiological, and biochemical characteristics of ESUS in patients aged greater than or equal to 80 years. These patients were more likely to have higher premorbid modified Rankin scale and preadmission CHADS2 scores than those aged less than 80 years. Patients aged greater than or equal to 80 years also had higher D-dimer and BNP levels, more frequent PACs per day in 24-hour Holter ECG monitoring, and thicker maximum IMT by ultrasound compared with those aged less than 80 years.

ESUS is a common cause of stroke and may occur at any age; however, diagnostic criteria and diagnostic examination methods are not standardized.<sup>3,12</sup> In one report, age, but not sex, was a strong predictor of stroke

**Table 2.** Biomarkers, physiological, and radiological features of patients with ESUS

	Total (N = 122)	Aged ≥80 years (N = 38)	Aged <80 years (N = 84)	P value
BNP [years], median (IR)	31.45 (20.3-86.925)	69.95 (32.825-155.475)	26.05 (15.975-56.675)	<.001*
D-dimer [%], median (IR)	.9 (.5-1.675)	1.6 (.925-2.5)	.65 (.5-1.15)	<.001*
eGFR [%], median (IR)	61 (51-74)	59.5 (49.75-72)	62 (51.5-75.5)	.702
LAD [%], median (IR)	32 (27.25-37)	31 (26-37)	32 (28-36.25)	.790
EF [%], median (IR)	72 (66-76)	73.5 (62.25-76)	72 (67-76)	.888
PAC [%], median (IR)	65 (19.25-497.25)	260.5 (63-2544.5)	43 (18-153.25)	<.001*
IMT [%], median (IR)	2.3 (1.6-2.9)	2.75 (2.15-3.7)	2.1 (1.5-2.7)	<.001*
Posterior circulation infarction, no [%]	33 [27.0%]	10 [26.3%]	23 [27.4%]	.544

Abbreviations: BNP, brain natriuretic peptide; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of undetermined source; IMT, intima media thickness; IR, interquartile range; LAD, left atrial diameter; PAC, premature atrial complexes.

We compared differences between patients aged greater than or equal to 80 years versus less than 80 years using Fisher’s exact test for categorical variables and the Mann-Whitney U test for numerical variables.

\**P* < .05.

recurrence and death with ESUS, with an approximately 5-fold higher risk in patients greater than 80 years of age compared with those less than 60 years of age.<sup>9</sup> Age is the single most important risk factor for stroke recurrence and death with ESUS. Therefore, determining the clinical, radiological, and biochemical characteristics of ESUS in patients aged greater than or equal to 80 years may be important to predict prognosis. However, data on ESUS patients greater than 80 years of age are limited. Preadmission CHADS2 scores were associated with onset severity and functional outcomes in acute ischemic stroke with AF, in one study.<sup>13</sup> In another report, elevated cardiac troponin level was more common in patients with ESUS than in those with noncardioembolic strokes.<sup>14</sup> Hawkes et al reported that older age, small-scattered infarcts on initial MR imaging, and high erythrocyte sedimentation rates appeared to identify ESUS patients more likely to be diagnosed with AF during follow-up.<sup>15</sup> In another study, D-dimer level was a predisposing factor for early neurological deterioration in patients with ESUS. Acutely elevated D-dimer levels after stroke onset could suggest a hypercoagulable state secondary to occult malignancy. Schwarzbach et al<sup>16</sup> compared 140 patients with cancer and ischemic stroke with 140 age-matched and sex-matched controls with stroke alone and demonstrated that cancer was associated with a higher prevalence of unidentified stroke (48% versus 27%, respectively;  $P < .001$ ) as well as higher D-dimer levels (6.15  $\mu\text{g}/\text{mL}$  versus 1.39  $\mu\text{g}/\text{mL}$ , respectively). Kim et al showed higher D-dimer levels in patients with cancer and cryptogenic stroke compared with those with cryptogenic stroke without cancer as well as with a control group of patients with cancer without stroke.<sup>16,17</sup> However, specific biomarkers associated with ESUS have not been determined or established.

Recently, atrial cardiomyopathy diagnosed by the presence of one of its serum, imaging, or electrocardiographic biomarkers was reported to be associated with cryptogenic stroke. Atrial cardiomyopathy may constitute a mechanism in ESUS; therefore, anticoagulation therapy might be effective in patients with atrial cardiomyopathy.<sup>18</sup> To improve morbidity and mortality in patients with ESUS, early detection and treatment of AF is necessary. AF detection and treatment is critical not only in the chronic stage as secondary stroke prevention, but also acutely. Guidelines recommend at least 24 hours of ECG monitoring, and long-term ECG monitoring by insertable cardiac monitor (ICM) is an alternative after stroke. ESUS is a recently defined condition; therefore, conversion of paroxysmal AF in ESUS has not yet been thoroughly investigated. The characteristics of AF episodes in cryptogenic stroke patients have recently been explored in carefully selected patient populations. However, the incidence of AF among a large, real-world population of patients with an ICM placed to detect AF following a

cryptogenic stroke has not been systematically investigated.<sup>19</sup> ICMs are used increasingly to diagnose unexplained syncope and for arrhythmia monitoring. The Reveal LINQ (Medtronic, Minneapolis, MN) is a novel miniaturized ICM with improved algorithms and is available in comprehensive stroke centers. The AF-SCREEN international collaboration recommends that longterm and more intensive AF monitoring is required for patients with ESUS.<sup>20</sup>

Antiplatelet therapy is the standard antithrombotic therapy for secondary ischemic stroke prevention worldwide.<sup>2,21</sup> Recurrent stroke risk is higher in ESUS than in noncardioembolic stroke,<sup>22</sup> and current guidelines recommend using antiplatelet agents rather than oral anticoagulation in patients with ESUS unless AF has been demonstrated. However, even under antiplatelet therapy, patients with ESUS have a higher risk of stroke recurrence compared with patients with stroke from other causes. ESUS designates patients with nonlacunar cryptogenic ischemic strokes in whom embolism is the likely stroke mechanism.<sup>23-25</sup> Retrospective methods in available studies limit confidence in stroke recurrence rates but support a substantial (>4% per year) rate of stroke recurrence during mostly antiplatelet therapy.<sup>1</sup> The NAVIGATE ESUS trial compared the efficacy and safety of rivaroxaban, an oral factor Xa inhibitor, versus aspirin for secondary ischemic stroke prevention in ESUS patients.<sup>26</sup> However, the study ended early because of comparable efficacy in treatment arms.<sup>27</sup> Rivaroxaban was not better than aspirin regarding prevention of recurrent stroke after ESUS and was associated with an increased risk of bleeding. There is also no evidence that direct oral anticoagulation is superior to aspirin for secondary ischemic stroke prevention in ESUS. In our study, patients aged greater than or equal to 80 years had more predictive factors for cardiogenic embolism compared with those less than 80 years of age. The incidence of AF is high in elderly patients. So, anticoagulant therapy may be suitable option for older ESUS patients compared with young ESUS patients. In older patients, bleeding is common secondary to anticoagulant and/or antiplatelet therapy compared with younger patients, which is a therapeutic dilemma: secondary stroke prevention in ESUS is necessary to decrease the bleeding risk, especially in older patients. Analyzing data on the prevention of recurrent stroke (efficacy) and minimizing hemorrhagic risks (adverse effects) of antithrombotic management in older patients with ESUS can identify the best medical treatment. However, the ideal medical treatment for patients with ESUS aged greater than or equal to 80 years is undetermined and has not been standardized. It is also unclear whether anticoagulation is more effective than antiplatelet therapy.<sup>28</sup> Clinical trials are ongoing to determine the efficacy of nonvitamin K-antagonist oral anticoagulation in ESUS patients.<sup>25,28</sup>

Our study has several limitations. First, the retrospective design might have introduced selection bias. Second,

we could not assess patients' outcomes after stroke onset. Third, we had no information on factors such as pre-morbid cognitive impairment and socioeconomic status, which might have an impact on stroke onset in older patients. Finally, a larger study population is required to confirm our results.

## Conclusions

These results suggest that high admission D-dimer and BNP levels were associated with onset age in patients with ESUS. Patients with ESUS aged greater than or equal to 80 years tended to have frequent PACs and thicker maximum IMT compared with those aged less than 80 years.

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