

## The role of left atrial enlargement and age in the prediction of recurrence in embolic strokes of undetermined source

*El papel del crecimiento auricular izquierdo y la edad como predictores de recurrencia en infarto cerebral embólicos de origen indeterminado*

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### Abstract

**Objectives:** Left atrial disease is an independent risk factor for ischemic stroke and can be used to predict atrial fibrillation (AF). We examine whether left atrial enlargement (LAE) could predict stroke recurrence in patients with embolic stroke of undetermined source (ESUS). **Materials and methods:** Sixty-four patients with a confirmed diagnosis of ESUS were followed for a median of 22 months. Clinical data and echocardiogram findings were recorded. The echocardiogram interpretation was performed centrally and blindly. The Brown ESUS – AF score was used to categorize patients into high (human resource planning [HRP]: score > 2) and low-risk patients (non-HRP: score 0-1). Stroke recurrence was the primary outcome. **Results:** The median age was 62 years (range: 22-85 years); and 33 (51.6%) were men. The median initial NIHSS score was three points (range: 0-27). Twelve (18.8%) patients were categorized as HRP. We found a significant tendency toward recurrence among HRP versus non-HRP patients. Three (25%) HRP versus 2 (3.8%) non-HRP experienced recurrence (OR: 8.3 95% CI 1.2-57;  $p=0.042$ ); this association was related to severe atrial dilatation (OR: 14.5 95% CI 0.78-277,  $p = 0.02$ ) and age > 75 years (OR: 12.7 95% CI 1.7-92.2,  $p = 0.03$ ). We found no differences in recurrence in a univariate analysis. **Conclusions:** Patients with severe LAE who are 75 years old or older have a significant tendency to experience stroke recurrence.

**Key words:** Left atrial enlargement. Stroke recurrence. Embolic stroke of undetermined source. Ischemic stroke.

### Resumen

**Objetivos:** La patología atrial izquierda es factor de riesgo independiente para infarto cerebral y puede utilizarse para predecir fibrilación auricular. Examinamos si el crecimiento auricular izquierdo puede predecir recurrencia en pacientes con infarto embólico de origen indeterminado (ESUS). **Materiales y métodos:** Sesenta y cuatro pacientes con diagnóstico confirmado de ESUS fueron seguidos por una mediana de seguimiento de 22 meses. Registramos los datos clínicos y ecocardiográficos.

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La interpretación ecocardiográfica fue centralizada y cegada. La escala de Brown ESUS – AF fue utilizada para categorizar a los pacientes en riesgo alto (HRP puntaje > 2) y bajo riesgo (no-HRP: puntaje 0-1). El descenlace primario fue recurrencia de infarto cerebral. **Resultados:** Mediana de edad fue de 62 años (rango: 22-85 años); 33 (51.6%) fueron hombres. La mediana inicial de la escala de NIHSS fue de 3 puntos (rango de 0 a 27). 12 (18.8%) pacientes fueron de alto riesgo (HRP) y 52 (81.3%) de bajo riesgo (non- HRP). El grupo HRP mostró tendencia significativa hacia mayor recurrencia. Tres (25%) HRP versus 2 (3.8%) no-HRP experimentaron recurrencia (OR: 8.3 IC 95% 1.2-57;  $p = 0.042$ ); esta asociación se relacionó con dilatación auricular severa (OR: 14.5 IC 95% 0.78-277,  $p = 0.02$ ) y edad > 75 años (OR: 12.7 IC 95% 1.7-92.2,  $p = 0.03$ ). En el análisis multivarioado, no encontramos significativas. **Conclusiones:** El crecimiento auricular izquierdo severo y la edad mayor de 75 años mostraron tendencia significativa a recurrencia de infarto cerebral.

**Palabras clave:** Crecimiento auricular izquierdo. Recurrencia. Embolic stroke of undetermined source. Infarto cerebral.

## Introduction

Cryptogenic stroke accounts for approximately 30% of all ischemic strokes<sup>1</sup>. Recently, atrial cardiopathy has been shown to be associated with ischemic stroke, particularly those of embolic subtypes<sup>2,3</sup>.

Several studies suggest that not only atrial fibrillation (AF) but also left atrial diameter and other markers of atrial cardiopathy may be implicated in the pathogenesis of cryptogenic stroke<sup>4</sup>. Left atrial enlargement (LAE) has been shown to be associated with incident AF and incident ischemic stroke risk after adjusting for several confounders, including AF. An analysis of NOMASS<sup>5</sup> showed that moderate to severe LAE is an independent predictor of recurrent stroke risk and is particularly related to embolism (adjusted HR 2.38 95% CI 1.03-7.81). Some studies suggest a mechanistic relationship between LAE and ischemic stroke.

Recently, several scores have been proposed to easily and cost-effectively predict paroxysmal AF on outpatient cardiac monitoring after an Embolic Stroke of Undetermined Source (ESUS)<sup>6,7</sup>. For instance, the Brown ESUS – AF score incorporates moderate – severe LAE and age to assign a score from 0 to 4 with an area under the curve of 0.725 to predict paroxysmal AF<sup>7</sup>. This score still needs to be externally validated.

We sought to examine LAE and age and its relationship with recurrence and AF development in patients with ESUS using the Brown ESUS – AF score.

## Materials and methods

### ESUS cohort

We analyzed data from 64 patients with confirmed diagnoses of ESUS treated in our hospital from November 2015 to March 2018. We used patient data prospectively included in our stroke database. Our registry includes consecutive outpatients with an acute first-ever

confirmed ischemic stroke admitted to the stroke clinic in Mexico City. Every patient in our clinic undergoes a thorough evaluation in search of stroke etiology that comprises brain magnetic resonance imaging (MRI), duplex ultrasound of the neck, transcranial Doppler, and/or computed tomography (CT) angiography of the head and neck arteries, 24-h Holter monitoring, and transthoracic echocardiogram (TE). This study was approved by the local Research and Ethics Committee.

We included patients 18 years old or older with confirmed ischemic stroke by CT or MRI who fulfilled the ESUS criteria<sup>8</sup>. Patients with any identifiable cause of stroke or in whom initial assessments had not been completed were excluded from the study. The diagnosis of ESUS was made according to the ESUS criteria proposed by Hart et al. (1) Ischemic stroke detected by CT or MRI that is not lacunar; (2) absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (3) no major risk cardioembolic source of embolism and; (4) no other specific cause of stroke identified<sup>8</sup>. Every patient underwent a comprehensive clinical investigation in search of stroke etiology, including neuroimaging, either CT or MRI, intracranial and extracranial vessel imaging, TE, and 24-h Holter monitoring.

### Echocardiogram

In all cases, the TE conducted during the index event was evaluated and interpreted by the same certified cardiologist. The left atrial diameter was determined by the auricular area. All measurements were interpreted and recorded on the printed report by the cardiologist using the classification of mild, moderate, or severe LAE according to established parameters<sup>9</sup>.

Patients were categorized into a high (human resource planning [HRP]) or low-risk (non-HRP) group based on their Brown ESUS – AF score (Table 1). Patients were given a score from 0 to 4 according to their

**Table 1.** The Brown embolic stroke of undetermined source – atrial fibrillation score

Variable	Score
Age	
– 18-64 years	0 points
– 65-74 years	+1 points
– $\geq 75$ years	+2 points
Left atrial enlargement	
– Mild	0
– Moderate - severe	+2

age and LAE. The score is composed of two items. The first is age: patients under 64 years of age score 0 points, patients aged 65-74 years score 1 point, and patients over 75 years old score 2 points. The second variable is LAE: patients with mild LAE score 0 points, and patients with moderate-severe LAE score 2 points.

**Table 1** shows how the score is composed.

Patients who scored  $> 2$  were considered HRP. The HRP group was re-evaluated with a new 24-h Holter monitoring in a period of time of 6 months between the first scanning and the second to identify incident AF.

During follow-up, we evaluated stroke recurrence or death. Recurrence was defined as any recurrent stroke occurring during follow-up in any vascular territory, including TIA. Functional outcome was evaluated with the modified ranking scale (mRs); good functional outcome was defined as mRs  $> 2$ .

### Statistical analysis

The statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences, version 23.0, IBM Inc., Armonk, NY). Demographic variables and risk factors for stroke were included in the study. Values for continuous variables were expressed according to their pattern of normality, as evaluated by the Shapiro-Wilk test. Variables that were normally distributed were expressed as the mean and SD, while variables that were not normally distributed were expressed as the median and IQ ranges. Categorical nominal variables were expressed as whole numbers and percentages. Association analysis was performed using Student's t-test or Mann-Whitney Wilcoxon.

A univariate analysis of the independent variables (LAE and age over 65 years) was conducted, with the addition of covariates (sex, hypertension, diabetes, and dyslipidemia), to examine the relationship to appearance

of AF and recurrence using a Chi-Square or Fisher's statistic accordingly, respectively. A multivariate regression analysis was performed in search of further associations with respect to the variables of interest.

### Results

We identified 228 consecutive stroke patients in our clinic's database from November 2015 to March 2018. Sixty-four (28%) were diagnosed with ESUS. Thirty-three (51.6%) were men. The median age was 62 years (range: 22-85 years). Nineteen patients (29.7%) were under 50 years of age. The median initial NIHSS score was 3 points (range: 0-27). Forty patients (77%) had good clinical outcomes (mRs  $\leq 2$ ). There was a significant difference in the number of female patients in the HRP group versus non-HRP group. These patients were followed up for a period of time with a median of 20 months (Range of 4-39 months). **Table 2** describes the baseline characteristics.

Twelve patients (18.8%) were categorized as HRP, while 52 (81.3%) were non-HRP. In the non-HRP group, 34 patients (53%) had a Brown ESUS – AF score of 0, and 18 (28%) had a score of 1. For the HRP group, seven patients (10.9%) scored 3 points, 2 (3.1%) scored 2 points, and 3 patients (4.6%) scored the maximum score of 4 points. **Table 3** shows the complete distribution of the scores.

There were two deaths during follow-up in the HRP group versus 0 in the non-HRP (16.6% vs. 0%,  $p \leq 0.001$ ); one of these deaths was recurrence related, while the other was due to systemic complications of sepsis 18 months after the index event. The remaining ten patients were re-evaluated with a new 24-h Holter monitoring, but we did not document AF in any of these cases.

We found a significant tendency toward recurrence among HRP vs. non-HRP, 3 (25%) versus 2 (3.8%) (OR: 8.3 95% CI 1.2-57,  $p = 0.042$ ). A univariate analysis was performed on the variables that could have been associated with recurrence. No significant difference was found for history of arterial hypertension ( $p = 0.341$ ), diabetes mellitus ( $p = 0.629$ ), tobacco use ( $p = 0.709$ ), ischemic heart disease ( $p = 0.769$ ), or hypercholesterolemia ( $p = 0.454$ ). Looking at the variables of interest, age and LAE, only severe atrial enlargement (OR: 14.5; 95% CI 0.78-277,  $p = 0.02$ ) and age 75 years (OR: 12.7; 95% CI 1.7-92.2,  $p = 0.03$ ) showed an association with recurrence. A multivariate regression was performed, but no association was found.

**Table 2.** Baseline characteristics

Variable	High-risk n = 12 (18.8%)	Low-risk n = 52 (81.3%)	Total n = 64 (100%)	p value
Demographics				
Age				
65	1 (8.3%)	35 (65.4%)	36 (54.7%)	0.001
65-74	2 (16.7%)	18 (34.6%)	20 (31.3%)	0.312
75	9 (75%)	0 (0.0%)	0 (14.5%)	0.000
Female	10 (83.3%)	21 (40.4%)	31 (48%)	0.007
Clinical				
HTN	9 (75%)	32 (61.5%)	41 (64.1%)	0.357
Diabetes Mellitus	2 (16.7%)	17 (33.3%)	19 (30.2%)	0.258
Tobacco	2 (16.7%)	18 (34.6%)	20 (31.3%)	0.427
Dyslipidemia	1 (8.3%)	5 (9.6%)	6 (9.4%)	0.891
Cardiopathy	1 (8.3%)	0 (0.0%)	1 (1.6%)	0.628
Clinical course				
NIHSS (range)	2.5 (0-18)	3.5 (0-27)		0.464
mRs 2 discharge	11 (91.4%)	41 (78.4%)	52 (82.5%)	0.355
mRs 2-3 months	11 (91.4%)	41 (78.4%)	52 (82.5%)	0.355
mRs 2-6 months	11 (91.4%)	43 (79.6%)	54 (85.7%)	0.513

HTN: hypertension; NIHSS: National Institutes of Health Stroke Scale; mRs: modified rankin scale.

**Table 3.** Left atrial enlargement, age, and corresponding brown embolic stroke of undetermined source – atrial fibrillation score

Variable	n (%)	Brown score
Left atrial enlargement		
Absent	46 (72)	+0
Mild	12 (19)	+0
Moderate	4 (6)	+2
Severe	2 (3)	+2
Age (years)		
65	35 (54)	+0
65-74	20 (31)	+1
75	9 (14)	+2

## Discussion

Patients with ESUS represent a heterogeneous group with a high probability of their stroke having a cardiac embolic source and a higher risk of stroke recurrence<sup>3,10</sup>. In a recent population-based study, LAE has been shown to be associated with incident AF and incident ischemic stroke<sup>5,11</sup>. Our findings reinforce the argument that LAE should be considered a risk factor for recurrent ischemic stroke and suggest that left atrial thromboembolism can occur independently of documentation of AF<sup>12</sup>.

The baseline characteristics of our cohort are compatible with those reported in the literature; ESUS patients tend to be younger and have less severe

strokes<sup>3,13,14</sup>. Nevertheless, we observed that women are at higher risk (OR: 7.3 95% CI 1.4-37.1, p = 0.007), a finding that correlates with other prognostic scales such as CHA<sub>2</sub> DS<sub>2</sub> -VASC, in which female sex confers risk of recurrence<sup>15</sup>.

A significant tendency was found between HRP and stroke recurrence compared with non-HRP (OR: 8.3 95% CI 1.2-57, p=0.042); this relationship was conditioned by age > 75 years and severe atrial dilation as demonstrated in the univariate analysis. Although our patients may have presented subclinical AF, the important aspect of our findings is that the risk of recurrence can be predicted with documentation of LAE on a conventional echo. Therefore, we did not find a relation between LAE, age, and AF development, which can be readily explained by our AF monitoring strategy, which was only a 24-h Holter monitor, known to have a low diagnostic yield for paroxysmal AF<sup>2</sup>. Subclinical AF is suggested to play an important role in ESUS pathogenesis, and proper screening for AF in these patients is mandatory<sup>16</sup>. Unfortunately, the reality for most countries in Latin America is that prolonged monitoring, external, or implantable, is very scarce, so searching for better strategies to further select patients who would benefit the most from more strict follow-up protocols is essential. Patients with LAE have been shown to have reduced left atrial contractility, leading to reductions in left atrial volume and kinetic energy. The resultant dysfunctional left atrium leads to atrial thromboembolism.

Furthermore, LAE can promote stasis, endothelial dysfunction, and thrombus formation<sup>17</sup>. In addition, patients with LAE are more likely to have well-known stroke risk factors, which possibly increased their risk of developing stroke.

Our findings suggest that the detection of LAE in patients with ESUS allows the identification of patients at high risk of recurrence in which some pharmacological therapies could be beneficial. In a subanalysis of ESUS NAVIGATE patients with ESUS and enlarged left atrium, there was a lower recurrence rate in the rivaroxaban group, though these results must be taken with caution since they are a positive subgroup in an overall negative trial; however, they show some promising evidence that better-selected ESUS patients may indeed benefit from anticoagulants<sup>18</sup>.

This study was not intended to function as an external validation for the Brown Score since we do not have the option at our center to place our patients on prolonged cardiac monitoring. The score is simple to apply, and it does not require any additional evaluation beyond the standard etiology screening. Better strategies for AF detection that is both feasible and cost effective need to be structured for this group of patients. LAE could be a valuable biomarker to select patients with high risk of stroke recurrence, and further studies need to be performed to fully assess this suggestion. Some limitations of our study must be recognized. First, the small number of patients included is a limitation, considering that this is a selected group of patients with specific ESUS criteria in which no other probable cause of IC was demonstrated. A second limitation is that our sample came from a single neurological center.

## Conclusion

Our findings suggest that patients with severe LAE who are 75 years old or older have a significant tendency to experience stroke recurrence.

## Conflicts of interest

The investigators of this study confirm that there are no conflicts of interest to disclose.

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## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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