Journal of the Neurological Sciences 401 (2019) 5–11

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Incidence, characteristics and outcomes in patients with embolic stroke of undetermined source: A population-based study

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ARTICLE INFO

Keywords:
Embolic stroke of undetermined source
Cryptogenic stroke
Atrial fibrillation
Anticoagulation
Population-based
Incidence rate
Recurrence
Mortality

ABSTRACT

Embolic stroke of undetermined source (ESUS) represents a subgroup of cryptogenic ischemic stroke (CS) distinguished by high probability of an underlying embolic mechanism. There are scarce population-based data regarding the incidence, characteristics and outcomes of ESUS. Consecutive patients included with first-ever ischemic stroke of undetermined cause in the previously published population-based Evros Stroke Registry were further subdivided into ESUS and non-ESUS CS. Crude and adjusted [according to the European Standard Population (ESP), WHO and Segi population] incidence rates (IR) for ESUS and non-ESUS CS were calculated. Baseline characteristics, admission stroke severity (assessed using NIHSS-score), stroke recurrence and functional outcomes [determined by modified Rankin Scale (mRS) scores], were recorded during the 1-year follow-up period. We identified 21 and 242 cases with ESUS (8% of CS) and non-ESUS CS. The crude and ESP-adjusted IR for ESUS were 17.5 (95%CI: 10–25) and 16.6 (95%CI: 10–24) per 100,000 person-years. Patients with ESUS were younger ($p < .001$) and had lower median admission NIHSS-scores ($p < .001$). Functional outcomes were more favorable in ESUS at 28, 90 and 365 days. ESUS was independently ($p = .033$) associated with lower admission NIHSS-scores (unstandardized linear regression coefficient: -13.34;95%CI: -23.34, −3.35) on multiple linear regression models. ESUS was not related to 1-year stroke recurrence, mortality and functional improvement on multivariable analyses. In conclusion we found that ESUS cases represented 8% of CS patients in this population-based study. Despite the fact that ESUS was independently related to lower admission stroke severity, there was no association of ESUS with long-term outcomes.

Subject terms

Atrial fibrillation
Etiology
Epidemiology
Secondary prevention

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https://doi.org/10.1016/j.jns.2019.04.008
Received 13 February 2019; Received in revised form 28 March 2019; Accepted 5 April 2019
Available online 06 April 2019
0022-510X/

Cardiovascular disease/stroke
Ischemic stroke

1. Introduction

Despite appropriate investigations the cause of ischemic stroke (IS) remains unknown in approximately one third of cases which are defined as cryptogenic [1]. The proportion of unidentified cases varies from 10% to 40% according to the study population and the extension of the investigations performed routinely [2]. Therefore, in young patients the incidence of cryptogenic stroke may be as high as 62.4% [3], whereas in older individuals as low as 20%.

Embolic stroke of undetermined source (ESUS) represents a subgroup of cryptogenic stroke (CS) including non-lacunar infarcts with absence of significant extracranial or intracranial proximal stenosis, or major cardioembolic cause [4]. ESUS is a clinical construct for selection of CS that are distinguished by high probability of an underlying embolic mechanism [4]. Potential unidentified embolic sources include occult paroxysmal atrial fibrillation (AF), patent foramen ovale (PFO), large vessel proximal nonstenotic atherosclerotic plaques, atheromatosis of the aortic arch, coagulopathies (inherited or acquired), migraine, non-bacterial endocarditis, and minor-risk cardioembolic strokes [5]. The ESUS Global Registry study after pooling data from hospital-based registries reported a 16% incidence of ESUS among all IS patients with a mean age at presentation of 62 years that was significantly lower compared to non-ESUS CS patients (mean age 68 years) [6]. Moreover, baseline stroke severity in patients with ESUS is low-to-moderate with median NIHSS scores ranging between 4 and 5 [6,7]. Although the most prevalent diagnosed cause after recurrence or during follow up is atrial fibrillation (AF), even after prolonged heart-rhythm monitoring, AF is eventually detected in < 40% of ESUS [7–9]. On the other hand, non-ESUS CS refer to cases that do not fulfill ESUS criteria; more precisely, those with an incomplete negative investigation, multiple causes of cerebral ischemia, or undetermined non-embolic cases [4,10].

There are scarce population-based data regarding the incidence, baseline characteristics, early and long-term outcomes of ESUS [11], since only hospital-based studies have investigated the natural history of ESUS patients. In view of these considerations, we sought to capitalize on the recently published, large, population-based Evros Stroke Registry (ESR) [12] and compare incidence rates (IR), baseline characteristics and outcomes between ESUS and non-ESUS CS patients at a population-based level.

2. Methods

ESR was a population-based registry established in the Evros prefecture, one of the 51 prefectures of Greece, located in the far northeastern part of Greece between Turkey, Bulgaria and the Aegean Sea as previously described [12]. Data from consecutive patients with first-ever ischemic stroke recorded during a 24-month period (2010 – 2012) in ESR were analyzed and all IS cases were classified according to the TOAST criteria [13]. Patients with IS of undetermined cause (CS) were subsequently divided into two subgroups (ESUS and non-ESUS CS) based on whether they fulfilled or not ESUS criteria [4,14]. The group of non-ESUS CS included CS patients with incomplete negative investigation, multiple causes of cerebral ischemia, or undetermined cause of cerebral ischemia despite the indicated diagnostic work-up [7].

Baseline characteristics, stroke risk factors and admission stroke severity quantified by the National Institutes of Health Stroke Scale (NIHSS) score, were recorded as previously described in ESR and hospital-based studies from our multicenter collaborative group [15,16]. All patients were followed-up for one year. Functional outcomes were assessed using modified Rankin Scale (mRS) score either by visit at the stroke outpatient clinic of Alexandroupolis University Hospital or by structured telephone interview by certified investigators as previously described.[11] All follow-up assessments were performed at 28, 90 and 365 days following stroke onset. The outcome events of interest were death, recurrent stroke and functional improvement determined as 1-point shift in mRS-score. Details about the definitions of these outcome events have been previously published by our group [17,18].

2.1. Statistical analysis

The incidence of strokes is expressed as the number of first-ever corresponding strokes per 100,000 person-years with corresponding 95% confidence intervals (95%CIs). In all analyses 95%CIs were calculated using the normal approximation to the Poisson distribution, as has been previously described [12]. To compare our stroke incidence rates (SIR) with that observed in other studies, we standardized our SI data according to the European Standard Population (ESP) of 2013, WHO standard population of years 2000–2025 and Segi's World standard population for people > 20 years of age, as previously described [12].

Binary variables are presented as percentages, while continuous variables are expressed with their median values and corresponding interquartile ranges (IQRs), while statistical comparisons between the different groups of patients were performed with the Pearson's χ^2 test or Mann-Whitney test, where appropriate. The distribution of the mRS-scores at 28 days, 3 months and 1-year between the two groups was compared with the Cochran-Mantel-Haenszel test [19]. Assuming a binomial distribution in all dichotomous outcome measures of interest, the 95% CI for corresponding proportions were calculated with the adjusted Wald method [20].

Kaplan-Meier curves were generated for both 1-year mortality and 1-year stroke recurrence. To determine further potential predictors of 1-year mortality and 1-year stroke recurrence we used multivariable cox regression models with Firth's penalized likelihood method for rare events [21]. All associations are presented as hazard ratios (HR) with corresponding 95%CI. Also, we used univariable and multivariable ordinal logistic regression models to evaluate associations between baseline characteristics, including CS subtype (ESUS vs. non-ESUS CS), and functional improvement at 1 year. All associations are presented as common odds ratios (cOR) with corresponding 95%CI. Furthermore, we performed univariable and multivariable linear regression analyses to determine independent predictors of admission NIHSS-score. As candidate variables for inclusion in all multivariable models we used all those baseline characteristics, including CS subtype (ESUS vs. non-ESUS CS) that were found to yield a p-value lower than 0.1 ($p < .1$) in the univariable analyses with only that baseline characteristic as predictor. The resulting multivariable models were tested under a two-sided statistical significance hypothesis with a significance level of 0.05. All associations are presented as unstandardized linear regression coefficients (LRC) with corresponding 95%CI. The Stata Statistical Software Release 13 for Windows (College Station, TX, StataCorp LP) and RStudio: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) computer programs were used for all statistical analyses.

2.2. Ethical considerations

The procedures in this investigation were in accordance with the legislation and ethical standards on human experimentation in the Netherlands and in accordance with the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committee of the University Hospital of Alexandroupolis [12].

2.3. Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Table 1
Incidence rates, baseline characteristics and outcomes between ESUS patients and cryptogenic stroke non-ESUS patients.

Variable	ESUS	Non-ESUS	p-Value
	(*n* = 21)	(*n* = 242)	
Incidence rates[a]			
Crude (95% CI)	17.5 (10–25)	202.0 (177–227)	NA
Adjusted (ESP)[b]	16.6 (10–24)	181.4 (159–204)	NA
Adjusted (WHO)[b]	11.6 (7–17)	86.5 (76–97)	NA
Adjusted (Segi)[b]	11.7 (7–17)	77.7 (68–88)	NA
Baseline characteristics			
Age (median, IQR)	68 (61–75)	79 (73–83)	< 0.001
Females (%)	28.6%	46.7%	0.109
Baseline NIHSS-score (median, IQR)	4 (2–8)	8 (6–16)	< 0.001
Hypertension (%)	80.9%	80.4%	0.960
Diabetes (%)	23.8%	26.5%	0.784
Dyslipidemia (%)	76.2%	65.0%	0.300
Smoking (%)	57.1%	18.4%	< 0.001
Coronary artery disease (%)	14.3%	14.1%	0.982
Alcohol (%)	14.3%	9.8%	0.518
Family history (%)	38.1%	32.8%	0.625
Greek ethnicity (%)	95.2%	95.4%	0.964
SBP on admission(median, IQR)	140 (130–160)	150 (130–170)	0.196
DBP on admission (median, IQR)	80 (80–90)	80 (70–90)	0.813
Follow-up outcomes			
28 day mRS (median, IQR)[c]	2 (1–3)	4 (3–6)	< 0.001
3-Month mRS (median, IQR)[c]	1 (0–2)	4 (2–6)	< 0.001
1-Year mRS (median, IQR)[d,e]	1 (0–2)	5 (2–6)	< 0.001
1-Year mortality (%, 95%CI)[f]	0% (0–13.5%)	35.5% (29.8–41.7%)	0.001
1-Year recurrence (%, 95%CI)[f]	0% (0–13.5%)	6.6% (4–10.5%)	0.224

ESUS: embolic strokes of undetermined source, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, 95%CI: 95% confidence interval, NA: not applicable.
[a] Per 100,000 person-years.
[b] Standardized incidence rates for people > 20 years of age according to a. the European Standard Population of 2013, b. The WHO Standard Population of years 2000–2025 and c. the Segi's World standard population.
[c] Not available in 17 patients.
[d] Not available in 23 patients.
[e] Assessed with the Cochran–Mantel–Haenszel test.
[f] Provided with the adjusted Wald method.

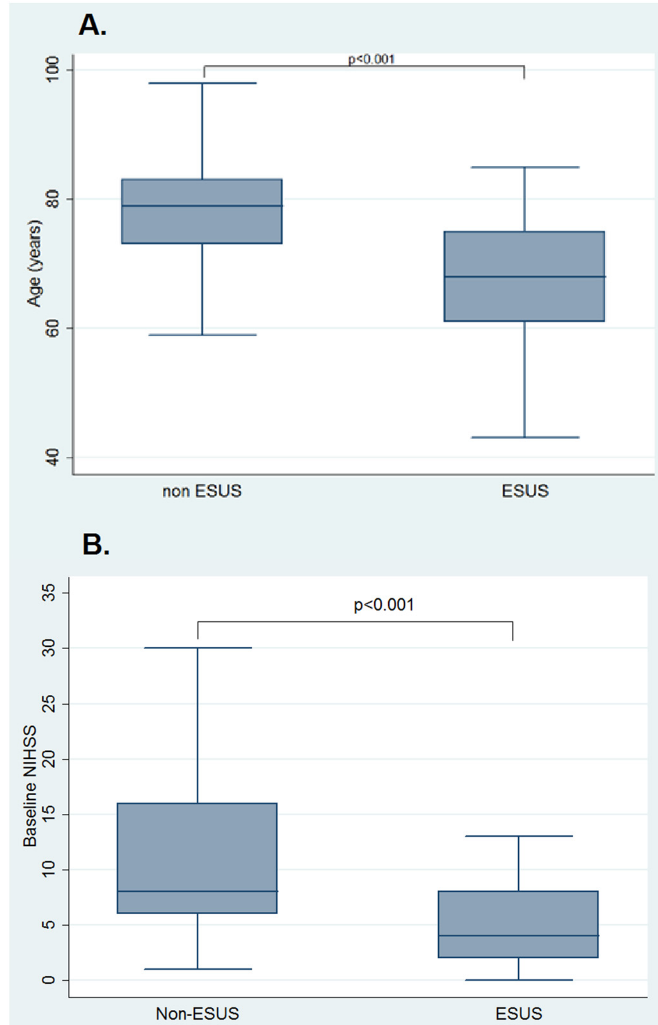

Fig. 1. Whisker plots depicting the distribution of (A) age and (B) admission National Institutes of Health Stroke Scale scores in patients with ESUS (Embolic Stroke of Undetermined Source) and non-ESUS cryptogenic stroke.

3. Results

We identified 263 total patients with first-ever CS Of those, 21 cases fulfilled ESUS diagnostic criteria (8% of patients with CS) [4], while the remaining 242 cases were classified as non-ESUS CS (92% of patients with CS). All ESUS patients received a complete diagnostic work-up, while 58% of the total CS patients received complete diagnostic work-up including vessel imaging, cardiac ultrasound investigation and 24-h Holter monitoring. The IR of ESUS and non-ESUS CS are presented in Table 1. The crude and ESP-adjusted IR for ESUS were 17.5 (95%CI: 10–25) and 16.6 (95%CI: 10–24) per 100,000 person-years, respectively. The WHO- and Segi-adjusted IR for ESUS were 11.6 (95%CI: 7–17) and 11.7 (95%CI: 7–17) per 100,000 person-years, respectively.

Baseline characteristics and stroke risk factors in patients with ESUS and non-ESUS CS are shown in Table 1. Patients with ESUS were younger [median age 68 years (IQR:61–75) vs. 79 years (IQR:73–83); $p < .001$; Fig. 1A] and had lower median admission NIHSS-scores [4 points (IQR:2–8) vs. 8 points (IQR:6–16); $p < .001$; Fig. 1B]. Smoking was more prevalent in ESUS patients (57.1% vs. 18.4%; p < .001). Table 2 depicts the associations of baseline characteristics with admission NIHSS-score on univariable and multivariable linear regression models. Three variables emerged as independent predictors of admission stroke severity. Older age [LRC per 1-year increase: +0.23 (95%CI: +0.13, +0.34), p < .001] and increasing admission diastolic blood pressure levels [LRC per 1 mmHg increase: +0.07 (95%CI: +0.01, +0.13), $p = .031$] were independently related to higher stroke severity, while ESUS was independently ($p = .033$) associated with lower admission NIHSS-scores (LRC: -13.34; 95%CI: −23.34, −3.35).

Table 1 summarizes early and late outcomes in patients with ESUS and non-ESUS CS. Functional outcomes were more favorable in ESUS patients at 28 [median mRS-score: 2 (IQR:1–3) vs. 4 (IQR:3–6); $p < .001$], 90 [median mRS-score: 1 (IQR:0–2) vs. 4 (IQR:2–6); p < .001] and 365 days [median mRS-score: 1 (IQR:0–2) vs. 5 (IQR:2–6); p < .001]. Similarly, 1-year mortality rates were lower in ESUS [0% (95%CI: 0%–13.5%) vs. 35.5% (95%CI: 29.8–41.7%); $p = .001$]. One-year recurrence rates did not differ between the two groups [0% (95% CI: 0%–13.5%) vs. 6.6% (95%CI: 4.0%–10.5%), $p = .224$;].

Tables 3 and 4 depict the associations of baseline characteristics with 1-year stroke mortality and recurrence on univariable and multivariable cox regression analyses respectively using Firth's penalized likelihood method. We used Firth's penalized likelihood method because there were no incidences for ESUS patients and the ordinary estimates and Wald-type confidence intervals from the Cox regression were biased and imprecise, respectively. ESUS was not related to 1-year stroke mortality (HR: 0.25, 95%CI: 0.02–4.36; Fig. 2A) and recurrence (HR: 0.22, 95%CI: 0.01–4.06; Fig. 2B). Increasing age [HR per 1-year

Table 2
Univariable and multivariable linear regression analyses of baseline characteristics with admission National Institutes of Health Stroke Scale score.

Variable	Univariable analysis		Multivariable analysis	
	LRC[a] (95%CI)	p-Value	LRC[a] (95%CI)	p-Value
Age	0.23 (0.14, 0.33)	< 0.001	0.23 (0.13, 0.34)	< 0.001
Female gender	1.99 (0.17, 3.81)	0.032	1.38 (−0.45, 3.20)	0.139
Hypertension	−1.85 (−4.13, 0.43)	0.111	–	–
Diabetes	0.59 (−1.47, 2.65)	0.573	–	–
Dyslipidemia	−1.15 (−3.06, 0.77)	0.239	–	–
Smoking	−3.30 (−5.49, −1.11)	0.003	0.23 (−2.24, 2.70)	0.856
Coronary artery disease	−1.50 (−4.10, 1.09)	0.255	–	–
Alcohol	−1.60 (−4.62, 1.42)	0.297	–	–
Family history of stroke	1.22 (−0.69, 3.13)	0.209	–	–
Greek ethnicity (vs. other)	0.35 (−4.04, 4.73)	0.876	–	–
SBP on admission	0.01 (−0.02, 0.05)	0.343	–	–
DBP on admission	0.06 (−0.01, 0.12)	0.064	0.07 (0.01, 0.13)	0.031
ESUS (vs. non-ESUS CS)	−6.63 (−9.91, −3.36)	< 0.001	−13.34 (−23.34, −3.35)	0.033

ESUS: embolic strokes of undetermined source, CS: cryptogenic stroke, SBP: systolic blood pressure, DBP: diastolic blood pressure.
[a] Unstandardized linear regression coefficient.

increase: 1.07 (95%CI: 1.03–1.11), $p = .001$], increasing admission NIHSS-score [HR per 1-point increase: 1.12 (95%CI: 1.08–1.17), $p < .001$] and history of hypertension [HR: 0.42 (95%CI: 0.21–0.75), $p = .005$] emerged as independent predictors of 1 year mortality in our cohort (Table 3). Multivariable Cox regression analyses identify hypertension (HR = 0.31, 95%CI: 0.11–0.88, $p = .029$; Table 4) as the only independent predictor of 1-year stroke recurrence.

Table 5 shows the associations of baseline characteristics with 1-year functional improvement on univariable and multivariable ordinal logistic regression models. ESUS subtype was not related to 1-year functional improvement (cOR: 1.47, 95%CI: 0.59–3.70) The following variables emerged as independent predictors of 1-year functional improvement: age (cOR: 0.91, 95%CI: 0.87–0.94), baseline NIHSS score (cOR: 0.80, 95%CI: 0.75–0.85), hypertension (cOR: 3.12, 95%CI: 1.28, 7.69) and family history of cardiovascular disease (cOR: 0.51, 95%CI: 0.26–0.93).

4. Discussion

To the best of our knowledge our report is the first population-based study to report crude and adjusted IR in patients with ESUS. We also documented that ESUS patients were younger and more likely to be current smokers compared to cases with non-ESUS CS. ESUS subtype was independently related to lower admission stroke severity after adjustment for multiple confounders including demographics, risk factors and admission blood pressure levels. Finally, despite the fact that in univariable analyses ESUS patients had better early and long-term functional outcomes as well as lower early and long-term mortality rates, ESUS subtype was not related to 1-year stroke mortality, recurrence and functional improvement on multivariable models adjusting for other baseline characteristics.

ESUS subgroup represented 8% and 4% respectively of all CS and IS in our population-based cohort with a corresponding crude IR of 17.5 (95%CI: 10–25) per 100,000 person-years. These findings are at odds with previous hospital-based studies reporting that ESUS represent 9%–25% of all IS and approximately 40% of CS [6,7,22]. These discrepant findings may be attributed to inherent limitations to pursue a detailed diagnostic work-up in CS patients at a population-based level [23], which in turn may lead to under-representation of ESUS patients in our cohort. They may also be partly explained by the substantial inter-observer variability in etiologic stroke subtype classification with CS and ESUS subtypes representing major sources of heterogeneity in this classification across different investigators [22,24]. On the other hand, we reported that ESUS patients are younger and more likely to be current smokers compared to non-ESUS CS. These observations are almost identical to the experience from previous hospital-based registries [5–7,22,25].

ESUS is a subset of CS characterized by a highly probable embolic

Table 3
Associations of baseline characteristics with the risk of 1-year mortality on univariable and multivariable Cox regression models using Firth's penalized likelihood method.

Variable	Univariable analysis		Multivariable analysis	
	HR (95%CI)	p-Value	HR (95%CI)	P-Value
Age	1.10 (1.06, 1.13)	< 0.001	1.07 (1.03, 1.11)	0.001
Female gender	0.88 (0.58, 1.36)	0.583	–	–
Baseline NIHSS-score	1.16 (1.13, 1.20)	< 0.001	1.12 (1.08, 1.17)	< 0.001
Hypertension	0.38 (0.24, 0.60)	< 0.001	0.42 (0.21, 0.75)	0.005
Diabetes	0.75 (0.45, 1.26)	0.273	–	–
Dyslipidemia	0.56 (0.36, 0.86)	0.009	0.75 (0.42, 1.34)	0.383
Smoking	0.65 (0.36, 1.16)	0.148	–	–
Coronary artery disease	1.12 (0.62, 2.00)	0.713	–	–
Alcohol	1.23 (0.62, 2.42)	0.556	–	–
Family history	1.70 (1.01, 2.88)	0.046	1.38 (0.81, 2.34)	0.230
Greek ethnicity	1.82 (0.51, 6.44)	0.355	–	–
SBP on admission	1.00 (0.99, 1.01)	0.355	–	–
DBP on admission	1.00 (0.98, 1.01)	0.782	–	–
ESUS	0.050 (0.01, 0.81)	0.035	0.25 (0.02, 4.36)	0.344

ESUS: embolic strokes of undetermined source, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, CI: confidence interval.

Table 4
Associations of baseline characteristics with the risk of 1-year stroke recurrence on univariable and multivariable Cox regression models using Firth's penalized likelihood method.

Variable	Univariable analysis		Multivariable analysis	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Age	1.04 (0.97, 1.11)	0.237	–	–
Female gender	0.91 (0.34, 2.46)	0.861	–	–
Baseline NIHSS-score	0.96 (0.86, 1.06)	0.440	–	–
Hypertension	0.20 (0.07, 0.54)	0.001	0.31 (0.11, 0.88)	0.029
Diabetes	0.08 (0.01, 1.42)	0.085	0.10 (0.01, 1.92)	0.127
Dyslipidemia	0.33 (0.12, 0.89)	0.028	0.49 (0.17, 1.39)	0.178
Smoking	0.58 (0.15, 2.33)	0.445	–	–
Coronary artery disease	1.02 (0.25, 4.06)	0.981	–	–
Alcohol	1.73 (0.43, 6.91)	0.437	–	–
Family history	1.60 (0.51, 5.04)	0.420	–	–
Greek ethnicity	1.91 (0.10, 34.80)	0.661	–	–
SBP on admission	1.01 (0.99, 1.02)	0.400	–	–
DBP on admission	1.01 (0.97, 1.04)	0.793	–	–
ESUS	0.22 (0.01, 4.06)	0.311	–	–

ESUS: embolic strokes of undetermined source, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, CI: confidence interval.

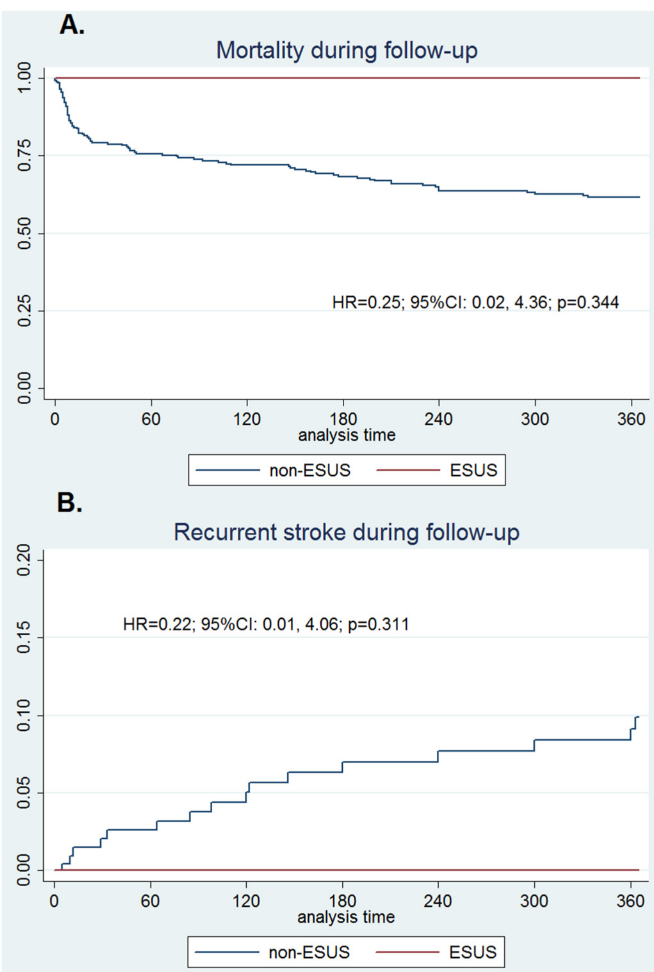

Fig. 2. Kaplan-Meier curves depicting (A) all-cause mortality and (B) recurrent stroke risk during the 1-year follow-up period.

profile, believed foremost being cardioembolic and more specifically due to paroxysmal atrial fibrillation (AF). Both NAVIGATE ESUS and RE-SPECT ESUS trials, which were largely based onto this concept, failed to demonstrate any treatment benefit of rivaroxaban or dabigatran over aspirin for secondary prevention after ESUS [26,27]. The lack of a therapeutic effect of oral anticoagulation questions not only the association of ESUS with AF, but also the concept of ESUS as a separate clinical entity from CS. Indeed, it is argued that apart from embolic sources, additional non-embolic mechanisms may also provoke strokes with ESUS profile, such as transient hypercoagulability states, disturbances in cerebral autoregulation and vasospasm, hemodynamic failure, and in-situ thrombosis [10]. In line with the former considerations and in accordance with previous data [6,7], our study found significantly lower stroke severity at admission in ESUS patients compared to non-ESUS CS. This observation is in line with other hospital-based reports [6,7,22]. It also supports the hypothesis that smaller thrombi that migrate from cardiac, aortic or arterial sources, or even originate in situ may represent the primary cause of ESUS, in contrast to larger emboli formed within the left atrium in individuals with AF [10,28]. This hypothesis is corroborated by recent studies indicating that increased stroke severity [29] and embolic stroke patients [30] were not associated with ESUS subtype among CS patients who experienced recurrent strokes. Thus, it may be argued that AF-related stroke should not be considered as the main underlying mechanism of cerebral ischemia in ESUS.

We documented that ESUS subtype was not related to long-term functional improvement, recurrence and mortality in our population-based cohort. Another population-based report from South London Stroke Register found similar recurrence rates and functional outcomes at 1 or 5 years in patients with ESUS and other IS subtypes on multivariable analyses adjusting for potential confounders [31]. Similarly, the Athens Stroke Registry failed to identify any differences in composite cardiovascular events between ESUS, non-ESUS CS, during a mean follow up of 30.5 ± 24.1 months [32]. These observations lend further support to the assumption that occult AF may not represent the major underlying etiopathogenic mechanism of ESUS given the fact that AF has been established as an independent predictor of long-term mortality and stroke recurrence among stroke survivors [33,34].

Certain limitations of the present report need to be acknowledged. First, the small sample of ESUS patients that we were able to identify increases the likelihood of a type II error, and therefore may have affected the reported associations between ESUS subtype and long-term mortality and stroke recurrence. Nevertheless, we attempted to counterbalance the limited number of events in ESUS subgroup using multivariable cox regression models with Firth's penalized likelihood method for rare events in our analyses. Second, the under-representation of ESUS due to incomplete diagnostic work-up in 42% of total CS patients is another major methodological shortcoming that needs to be taken into account when interpreting our study findings. The high-rate of incomplete diagnostic work up is related to the study design (population-based) and is consistent with other population-based studies evaluating stroke incidence in Greece [35] and Europe [36]. On the other hand, the lack of any available population-based data on the IR of ESUS may partly justify our attempt to retrospectively evaluate the prevalence of ESUS in a contemporary, well-designed population-based registry. Finally, the methodological shortcomings that deserve further attention in the interpretation of our analyses is the missing one-year follow-up in 23 cases (8.7% of all CS) and the lack of data on the detection rate of atrial fibrillation during follow-up.

In conclusion, this population-based study is the first one to report crude and adjusted IR in ESUS patients that represented approximately 8% of our CS cohort. Despite the fact that ESUS subtype was independently related to lower admission stroke severity, there was no association of ESUS with early and long-term outcomes including recurrence, mortality and functional improvement. Given the small number of ESUS patients in our cohort, our findings request

Table 5
Associations of baseline characteristics with the 1-year functional improvement on univariable and multivariable ordinal logistic regression models.

Variable	Univariable analysis		Multivariable analysis	
	cOR (95%CI)	p-Value	cOR (95%CI)	p-Value
Age	0.89 (0.87, 0.92)	< 0.001	0.91 (0.87, 0.94)	< 0.001
Female gender	0.65 (0.41, 1.02)	0.063	0.67 (0.37, 1.19)	0.167
Baseline NIHSS-score	0.78 (0.74, 0.82)	< 0.001	0.80 (0.75, 0.85)	< 0.001
Hypertension	2.56 (1.35, 4.76)	0.004	3.12 (1.28, 7.69)	0.012
Diabetes	1.05 (0.63, 1.75)	0.835	–	–
Dyslipidemia	1.81 (1.12, 2.94)	0.015	1.64 (0.90, 3.03)	0.107
Smoking	2.22 (1.26, 4.00)	0.006	0.57 (0.25, 1.32)	0.186
Coronary artery disease	1.11 (0.57, 2.22)	0.750	–	–
Alcohol	1.02 (0.47, 2.22)	0.951	–	–
Family history	0.46 (0.29, 0.78)	0.004	0.51 (0.26, 0.93)	0.028
Greek ethnicity	0.62 (0.22, 1.69)	0.345	–	–
SBP on admission	1.00 (0.99, 1.01)	0.755	–	–
DBP on admission	0.99 (0.98, 1.01)	0.522	–	–
ESUS	7.14 (3.33, 16.13)	< 0.001	1.47 (0.59, 3.70)	0.399

ESUS: embolic strokes of undetermined source, NIHSS: National Institutes of Health Stroke Scale, SBP: systolic blood pressure, DBP: diastolic blood pressure, cOR: common odds ratio, CI: confidence intervals.

independent confirmation in larger population-based studies.

Funding sources

None.

Compliance with ethical standards - conflicts of interest

All authors declare that they have no conflict of interest.

Author contributions

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Acknowledgments

None.

References

[1] A. Nouh, M. Hussain, T. Mehta, S. Yaghi, Embolic strokes of unknown source and cryptogenic stroke: implications in clinical practice, Front. Neurol. 7 (2016) 37.
[2] H. Tomita, S. Sasaki, J. Hagii, N. Metoki, Covert atrial fibrillation and atrial high-rate episodes as a potential cause of embolic strokes of undetermined source: their detection and possible management strategy, J. Cardiol. 72 (2018) 1–9.
[3] J.M. Ferro, A.R. Massaro, J.L. Mas, Aetiological diagnosis of ischaemic stroke in young adults, Lancet Neurol. 9 (2010) 1085–1096.
[4] R.G. Hart, H.-C. Diener, S.B. Coutts, J.D. Easton, C.B. Granger, M.J. O'Donnell, et al., Cryptogenic Stroke/ESUS International Working Group, Embolic strokes of undetermined source: the case for a new clinical construct, Lancet Neurol. 13 (2014) 429–438.
[5] T. Geisler, A. Mengel, U. Ziemann, S. Poli, Management of Embolic Stroke of Undetermined Source (ESUS), Drugs 78 (2018) 823–831.
[6] K.S. Perera, T. Vanassche, J. Bosch, M. Giruparajah, B. Swaminathan, K.R. Mattina, et al., Embolic strokes of undetermined source: prevalence and patient features in the ESUS GlobalRegistry, Int. J. Stroke 11 (2016) 526–533.
[7] G. Ntaios, V. Papavasileiou, H. Milionis, K. Makaritsis, E. Manios, K. Spengos, et al., Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis, Stroke 46 (2015) 176–181.
[8] D.J. Gladstone, M. Spring, P. Dorian, V. Panzov, K.E. Thorpe, J. Hall, EMBRACE Investigators and Coordinators, et al., Atrial fibrillation in patients with cryptogenic stroke, N. Engl. J. Med. 370 (2014) 2467–2477.

[9] T. Sanna, H.C. Diener, R.S. Passman, V. Di Lazzaro, R.A. Bernstein, C.A. Morillo, CRYSTALAF Investigators, et al., Cryptogenic stroke and underlying atrial fibrillation, N. Engl. J. Med. 370 (2014) 2478–2486.
[10] A.C. Fonseca, J.M. Ferro, Cryptogenic stroke, Eur. J. Neurol. 22 (2015) 618–623.
[11] L. Li, G.S. Yiin, O.C. Geraghty, U.G. Schulz, W. Kuker, Z. Mehta, Rothwell PM, Oxford Vascular Study, Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study, Lancet Neurol. 14 (2015) 903–913.
[12] G. Tsivgoulis, A. Patousi, M. Pikilidou, T. Birbilis, A.H. Katsanos, M. Mantatzis, et al., Stroke incidence and outcomes in northeastern Greece: the Evros stroke registry, Stroke 49 (2018) 288–295.
[13] H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment, Stroke 24 (1993) 35–41.
[14] A.H. Katsanos, R. Bhole, A. Frogoudaki, S. Giannopoulos, N. Goyal, A.R. Vrettou, et al., The value of transesophageal echocardiography for embolic strokes of undetermined source, Neurology 87 (2016) 988–995.
[15] G. Tsivgoulis, C. Bogiatzi, I. Heliopoulos, K. Vadikolias, E. Boutati, S. Tsakaldimi, et al., Low ankle-brachial index predicts early risk of recurrent stroke in patients with acute cerebral ischemia, Atherosclerosis 220 (2012) 407–412.
[16] G. Tsivgoulis, K. Vadikolias, I. Heliopoulos, C. Katsibari, K. Voumvourakis, S. Tsakaldimi, et al., Prevalence of symptomatic intracranial atherosclerosis in Caucasians: a prospective, multicenter, transcranial Doppler study, J. Neuroimaging 24 (2014) 11–17.
[17] A. Safouris, C. Krogias, V.K. Sharma, A.H. Katsanos, S. Faissner, A. Roussopoulou, et al., Statin pretreatment and microembolic signals in large artery atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 1415–1422.
[18] G. Tsivgoulis, A.H. Katsanos, V.K. Sharma, C. Krogias, R. Mikulik, K. Vadikolias, et al., Statin pretreatment is associated with better outcomes in large artery atherosclerotic stroke, Neurology 86 (2016) 1103–1111.
[19] J.L. Saver, J. Gornbein, Treatment effects for which shift or binary analyses are advantageous in acute stroke trials, Neurology 72 (2009) 1310–1315.
[20] J.R. Lewis, J. Sauro, When 100% really Isn't 100%: improving the accuracy of small-sample estimates of completion rates, J Usabil. Stud. 1 (2006) 136–150.
[21] D. Firth, Bias reduction of maximum likelihood estimates, Biometrika 80 (1993) 27–38.
[22] R.G. Hart, L. Catanese, K.S. Perera, G. Ntaios, S.J. Connolly, Embolic stroke of undetermined source: a systematic review and clinical update, Stroke 48 (2017) 867–872.
[23] J.M. Ferro, Ischaemic stroke of undetermined cause, Lancet Neurol. 14 (2015) 871–872.
[24] D.L. Gordon, B.H. Bendixen, H.P. Adams Jr., W. Clarke, L.J. Kappelle, R.F. Woolson, Interphysician agreement in the diagnosis of subtypes of acute ischemic stroke: implications for clinical trials. The TOAST Investigators, Neurology 43 (1993) 1021–1027.
[25] A. Arauz, E. Morelos, J. Colín, J. Roldán, M.A. Barboza, Comparison of functional outcome and stroke recurrence in patients with Embolic Stroke of Undetermined Source (ESUS) vs. Cardioembolic Stroke Patients, PLoS One 11 (2016) e0166091.
[26] R.G. Hart, M. Sharma, H. Mundl, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, et al., NAVIGATE ESUS Investigators, Rivaroxaban for stroke prevention after embolic stroke of undetermined source, N. Engl. J. Med. 378 (2018) 2191–2201.
[27] https://clinicaltrials.gov/ct2/show/NCT02239120.
[28] R.G. Hart, Cardiogenic embolism to the brain, Lancet 339 (1992) 589–594.
[29] G. Ntaios, V. Papavasileiou, G.Y. Lip, H. Milionis, K. Makaritsis, A. Vemmou, et al., Embolic stroke of undetermined source and detection of atrial fibrillation on follow-up: how much causality is there? J. Stroke Cerebrovasc. Dis. 25 (2016) 2975–2980.
[30] I.L. Maier, K. Schregel, A. Karch, M. Weber-Krueger, R.T. Mikolajczyk, R. Stahrenberg, et al., Association between embolic stroke patterns, ESUS etiology, and new diagnosis of atrial fibrillation: a secondary data analysis of the find-AF trial, Stroke Res. Treat. 2017 (2017) 1391843.
[31] W. Muruet, C. Flach, A. Rudd, C. Wolfe, A. Douiri, Embolic strokes of undetermined source in the South London Stroke Register: a population based cohort study, Eur. Stroke J. 3 (2018) 24.
[32] G. Ntaios, V. Papavasileiou, H. Milionis, K. Makaritsis, A. Vemmou, E. Koroboki, et al., Embolic strokes of undetermined source in the Athens stroke registry: an outcome analysis, Stroke 46 (2015) 2087–2093.
[33] C. Marini, F. De Santis, S. Sacco, T. Russo, L. Olivieri, R. Totaro, A. Carolei, Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study, Stroke 36 (2005) 1115–1119.
[34] R. Saxena, S. Lewis, E. Berge, P.A. Sandercock, P.J. Koudstaal, Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial, Stroke 32 (2001) 2333–2337.
[35] K.N. Vemmos, M.L. Bots, P.K. Tsibouris, V.P. Zis, D.E. Grobbee, G.S. Stranjalis, S. Stamatelopoulos, Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry, Stroke 30 (1999) 363–370.
[36] P.L. Kolominsky-Rabas, M. Weber, O. Gefeller, B. Neundoerfer, P.U. Heuschmann, Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study, Stroke 32 (2001) 2735–2740.