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Original Article

All-cause mortality and early cardiovascular complications in relation to lesion location and stroke subtype in haemorrhagic and ischaemic stroke: the Perugia stroke registry

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ABSTRACT

Background: Acute stroke is frequently complicated by new-onset cardiac or thromboembolic events, referred to as Stroke-Heart Syndrome (SHS). The role of stroke subtype and lesion location in determining SHS risk remains underexplored.

Methods: We conducted a retrospective analysis of data from the hospital-based Perugia Stroke Registry (March 2005–September 2019). Patients with acute neurological symptoms were classified as ischaemic stroke (IS) or haemorrhagic stroke (HS) based on neuroimaging. Logistic regression identified predictors of stroke subtype and in-hospital complications. Subgroup analyses compared first-ever versus recurrent strokes, and lesion location (lacunar, non-lacunar anterior, or non-lacunar posterior for IS; typical versus atypical for HS). The primary outcome was a composite of all-cause death, cardiac events and venous thromboembolic events during Stroke Unit stay. Secondary outcomes were each component.

Results: Among 2080 patients (mean age 72.8 ± 12.5 years; 57% male), 1788 (86%) had IS and 292 (14%) HS. During Stroke Unit stay (median 8 days, IQR 5–14), HS patients had higher rates of the composite outcome (26% vs 14%) and all-cause death (21.2% vs 8.8%) than IS. In IS, non-lacunar posterior and anterior strokes were associated with increased risk of composite outcome (OR 1.97, 95%CI 1.10–3.63; OR 1.61, 95%CI 0.96–2.81) and all-cause death (OR 3.35, 95%CI 1.35–9.51; OR 2.90, 95%CI 1.28–7.79) versus lacunar strokes. Among HS, atypical lesions increased risk of composite outcome (OR 2.51, 95%CI 1.24–5.22) and all-cause death (OR 2.80, 95%CI 1.31–6.17).

Conclusions: Lesion location is a key determinant of SHS. Non-lacunar posterior stroke and atypical HS predict higher mortality and cardiovascular complications.

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1. Introduction

Stroke is a major global cause of morbidity and mortality and is frequently complicated by early cardiovascular events, collectively referred to as stroke-heart syndrome (SHS)[1,2]. The SHS encompasses a spectrum of early cardiovascular complications that occur within 30 days of an acute ischaemic stroke, involving either the emergence of new cardiac conditions or the destabilization of pre-existing ones. These include acute myocardial infarction (AMI), heart failure (HF), systolic dysfunction - including Takotsubo cardiomyopathy - arrhythmias (such as atrial fibrillation [AF] and other electrocardiographic abnormalities), and sudden cardiac death[2–5].

In patients with ischaemic stroke (IS), recent large-scale studies have reported SHS incidence rates ranging from 10 % to 20 %, with peak onset within the first 3 to 5 days following the cerebrovascular event[3,6,7]. In a landmark analysis from the Virtual International Stroke Trials Archive (VISTA), SHS occurred in 11.8 % of patients with IS, and when it developed beyond day 10, SHS was associated with a significantly higher 90-day mortality compared to SHS occurring earlier in the post-stroke course[8].

Although most evidence on SHS derives from IS cohorts, similar early cardiac complications also occur in haemorrhagic stroke (HS), with reported incidence rates around 13–15 %[4,9]. While the overall frequency of SHS appears comparable between IS and HS, the distribution of specific manifestations differs, with new-onset AF being less frequently observed in HS[2,4,5]. Such differences could be explained by distinct baseline patient characteristics, including demographic profile, stroke severity, and cardiovascular risk factors, which likely influence the pathophysiological mechanisms underlying SHS.

In addition to cardiac events, venous thromboembolism (VTE) also represents a significant cause of early morbidity and mortality after acute stroke. The risk of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is heightened in the stroke population due to multiple contributing factors such as prolonged immobilization, hemiparesis, systemic inflammation, and endothelial dysfunction[10]. Converging autonomic, inflammatory, neurohumoral, and endothelial alterations after acute brain injury provide a common substrate for arterial and venous events and may influence early mortality, suggesting that early post-stroke complications are facets of the same pathophysiological cascade.

Moreover, some data also suggest that lesion location may influence the incidence and clinical impact of SHS. Anterior circulation infarcts and insular cortex involvement have been linked to arrhythmias and early mortality[11] . Posterior strokes are often considered less severe due to lower National Institutes of Health Stroke Scale (NIHSS), although this underestimates their true impact, as key symptoms like ataxia or impaired consciousness are poorly captured by the scale[12]. While in the context of HS, atypical haemorrhages have been associated with an increased risk of cardiovascular events[13].

Lastly, current literature provides no conclusive data on the incidence or severity of SHS in first stroke versus recurrent strokes. Most available studies include only first-ever stroke[6,7,13] or do not report outcomes stratified by recurrent stroke[2,5].

These gaps limit our understanding of the cumulative burden of SHS and hinders the development of effective strategies for early identification, monitoring, and prevention. For these reasons, we examined clinical features and early outcomes in patients with ischaemic or haemorrhagic stroke admitted to a Stroke Unit, with a specific focus on the incidence of all-cause mortality, early cardiac and thromboembolic events. Additionally, we performed exploratory analyses to assess whether stroke recurrence and lesion location modulate the risk and presentation of SHS, given their potential influence on cardiovascular vulnerability, and the limited available data on these specific dimensions.

2. Methods

2.1. Study design and population

This study is based on data from the Perugia Hospital-Based Stroke Registry (PSR), a retrospective, observational, hospital-based registry that includes consecutive patients admitted to the Stroke Unit of the "Santa Maria della Misericordia University Hospital" (Perugia, Italy). Inclusion in the study did not influence patient management at any stage of in-hospital care. The study was designed as a retrospective exploratory analysis of registry data, with the aim of describing patterns of early in-hospital cardiovascular and thromboembolic complications and identifying data-driven associations across stroke phenotypes. No a priori hypotheses were specified. The study period spanned from March 12, 2005 to September 20, 2019. During this period, the Stroke Unit admitted an average of ~190 patients per year. All patients were evaluated by a board-certified neurologist. Patients were eligible if they were admitted with clinical signs of a focal disturbance of cerebral function and received a radiologically confirmed diagnosis of either IS or HS, based on non-contrast computed tomography (CT) or magnetic resonance imaging (MRI) performed on admission. Patients with subarachnoid haemorrhages, venous sinus occlusion and stroke mimics were excluded. Every patient underwent brain CT scan without contrast in the acute phase and this was repeated 3–7 days from stroke onset. CT scan with contrast was performed only on selected patients. Additional tests, performed in all patients, included: Echo-Power Doppler ultrasonography with frequency spectral analysis (common, external, and internal carotid arteries; vertebral arteries at the intra- vertebral level), 12-lead electrocardiography (ECG), standard blood and urine tests including venous haematocrit and fasting blood cholesterol concentration. Selected patients underwent cerebral magnetic resonance imaging, angio-MR, cerebral angiography (Seldinger technique), two-dimensional echocardiography, and 24-h ECG (Holter) monitoring. In deciding about imaging findings, we used information from CT scan.

2.2. Data collection

The following data were collected: age, sex, hypertension (blood pressure of > 160/90 mmHg at least twice before stroke or already under treatment with antihypertensive drugs), diabetes mellitus (diagnosed previously), cigarette smoking (>10 cigarettes per day or cessation <5 years earlier), family history (stroke and/or heart disease), alcohol abuse (>300 g/week), previous transient ischemic attacks (TIA), dyslipidaemia, obesity, sleep apnoea, depression, AF, peripheral artery disease, admission and discharge date of hospitalization, NIHSS at admission and discharge, pre-hospital therapies, in-hospital therapies, in-hospital complications (all cause of death, AMI, HF, PE, DVT) and laboratory tests. In-hospital deaths were classified as stroke-related or non–stroke-related based on the adjudicated primary cause of death, informed by the clinical course and neuroimaging findings. Stroke subtype (first-ever vs recurrent) was defined based on clinical history. An experienced neuroradiologist determined stroke location, blinded to the clinical subtype of stroke. Lesion location was categorized as follows: for IS i) lacunar, ii) non-lacunar anterior circulation, or III) non-lacunar posterior circulation; for HS: i) typical (deep: basal ganglia, thalamus or cerebellar) or ii) atypical (lobar or brainstem). One experienced neurologist reviewed the medical records of each patient and assigned stroke subtypes on the basis of the TOAST criteria[14]: atherosclerosis (large artery disease), cardioembolic, lacunar (small artery disease), other determined aetiology, undetermined aetiology and multiple possible etiologic. In addition, the Bamford (Oxfordshire Community Stroke Project, OCSP)[15] classification was applied to all cases, categorizing strokes into total anterior circulation infarcts, partial anterior circulation infarcts, lacunar infarcts and posterior circulation infarcts.

In the present study, lesion location was categorized into three groups: non-lacunar anterior IS (including total and partial anterior

circulation infarcts), lacunar stroke, and non-lacunar posterior IS (posterior circulation infarcts). This approach was selected to reflect underlying difference in clinical presentation and to facilitate robust comparisons of lesion-related outcomes across topographically relevant stroke subtypes.

2.3. Outcomes

The primary outcome was the occurrence, during Stroke Unit stay, of a composite endpoint comprising: i) all-cause of death, ii) cardiac events (acute HF and acute coronary syndrome), and III) venous thromboembolic events (PE with or without DVT). Secondary outcomes included the risk of each component of the composite outcome assessed individually.

2.4. Statistical analysis

Categorical variables were presented as frequencies and percentages and compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were reported as mean ± standard deviation (SD) or median with interquartile range (IQR), and compared using the student's *t*-test or the Mann–Whitney U test, depending on data distribution.

We calculated annual incidence rates for adverse in-hospital outcomes (all-cause mortality, cardiac events, and venous thromboembolism). Incidence rates were expressed as the proportion of patients experiencing the first in-hospital event, reported as percentages with 95 % confidence intervals. Comparisons of incidence rates across stroke types (IS vs. HS), stroke recurrence status (first-ever vs. recurrent), and lesion location subgroups were performed using the Poisson test. Person-time was defined as the cumulative duration of hospital stay for each patient, given the short-term nature of the follow-up.

In addition, univariable and multivariable logistic regression analyses were performed to explore associations between clinical characteristics and stroke subtype (IS or HS). Associations were expressed as odds ratios (ORs) with 95 % confidence intervals (CIs). Subsequently, multivariable logistic regression models were then used to explore associations between stroke subtype and early in-hospital adverse outcomes, including all-cause mortality, cardiac events (AMI or HF), VTE (PE with or without DVT), and a composite outcome including any of these events. These models were adjusted for relevant clinical covariates, including age, sex, atrial fibrillation, NIHSS score at admission, diabetes mellitus, dyslipidaemia, obesity, and pre-hospital use of antiplatelet or anticoagulant therapy. To model potential non-linear associations between continuous predictors (age and NIHSS) and the composite outcome, restricted cubic spline functions with 4 knots were incorporated into multivariable logistic regression models. ORs and 95 % Cis were calculated relative to the median values of age and NIHSS, respectively. Predicted OR curves with corresponding confidence intervals were graphically presented.

Sensitivity analyses were performed to further explore whether observed associations varied according to stroke recurrence status and lesion topography. These exploratory analyses were carried out separately within the IS and HS subgroups. Specifically, within each stroke subtype, we compared patients with first-ever versus recurrent strokes in relation to the same predefined outcomes. In parallel, we assessed the influence of lesion location, classifying IS lesions as lacunar, anterior circulation, or posterior circulation, and HS lesions as typical (deep) or atypical (lobar, cerebellar, or brainstem). For each subgroup, outcome incidence was calculated and compared using the χ^2 test, and separate multivariable logistic regression models were used to explore associations within each stratum.

In addition, to account for missing covariate data in the main models, we performed a sensitivity analysis using multiple imputation by chained equations under the assumption that data were missing at random. The imputation model included all variables used in the multivariable regressions and relevant auxiliary predictors of missingness. Twenty imputed datasets were generated and analysed separately, with estimates pooled according to Rubin's rules.

Forest plots were generated to visually represent adjusted odds ratios and 95 % confidence intervals derived from the multivariable models. All statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria)[16], and a two-sided $P < 0.05$ was considered statistically significant.

3. Ethical approval

Ethical approval was waived as this retrospective study collected anonymous data.

4. Results

A total of 2691 patients were initially included in the Perugia Stroke Registry between March 2005 and September 2019. Of these, 611 patients were excluded due to missing data in one or more variables used in the multivariable models (**Flow chart Supplementary Figure 1**). The final cohort comprised 2080 patients, including 1788 with IS (mean age 72 ± 13 years; 43 % female) and 292 with HS (mean age 74 ± 12 years; 43 % female). A comparison of baseline characteristics between included and excluded patients showed minimal differences and is reported in **Supplementary Table 1.**

4.1. Baseline characteristics and group comparison

Patients with HS were older than those with IS (mean age 74 ± 12 vs. 72 ± 13 years, $p = 0.007$), and presented with higher NIHSS (13 ± 8 vs. 9 ± 7, $p < 0.001$). AF was more frequent in patients with IS (30 % vs. 1.7 %, $p < 0.001$), as were diabetes mellitus (25 % vs. 18 %, $p = 0.008$) and dyslipidaemia (34 % vs. 21 %, $p < 0.001$). Regarding baseline treatment, the use of antiplatelet therapy was more common in IS patients (37 % vs. 26 %, $p < 0.001$), whereas anticoagulant therapy was similar between IS and HS patients (13 % vs. 10 %, $p = 0.200$). Additional baseline characteristics are detailed in Table 1.

At univariable analysis, the association of IS with AF, diabetes mellitus, dyslipidaemia, and prior antiplatelet therapy was confirmed, while higher NIHSS scores were associated with HS (**Supplementary Table 2**). To identify independent associations, a multivariable logistic regression model was performed. All variables remained independently associated with stroke subtype, with AF emerging as the strongest predictor of IS (**Supplementary Table 2,** Fig. 1).

Table 1
Baseline characteristics of patients with haemorrhagic and ischaemic stroke.

Characteristic	Haemorrhagic $N = 292$[1]	Ischaemic $N = 1{,}788$[1]	p-value[2]
Age	74 ± 12	72 ± 13	0.007
Male Sex	167 (57 %)	1025 (57 %)	>0.900
Hypertension	234 (80 %)	1349 (75 %)	0.100
Atrial Fibrillation	5 (1.7 %)	538 (30 %)	<0.001
Diabetes Mellitus	52 (18 %)	450 (25 %)	0.008
Dyslipidaemia	61 (21 %)	602 (34 %)	<0.001
Obesity	23 (7.9 %)	163 (9.1 %)	0.600
NIHSS baseline	13 ± 8	9 ± 7	<0.001
NIHSS categories			<0.001
Mild (0–4)	52 (20 %)	592 (33 %)	
Moderate[5–15]	119 (41 %)	863 (48 %)	
Severe (≥16)	115 (39 %)	333 (19 %)	
Antiplatelet	77 (26 %)	660 (37 %)	<0.001
Anticoagulant	37 (13 %)	181 (10 %)	0.200

[1] Mean ± SD; n (%);.
[2] Welch Two Sample *t*-test; Pearson's Chi-squared test.

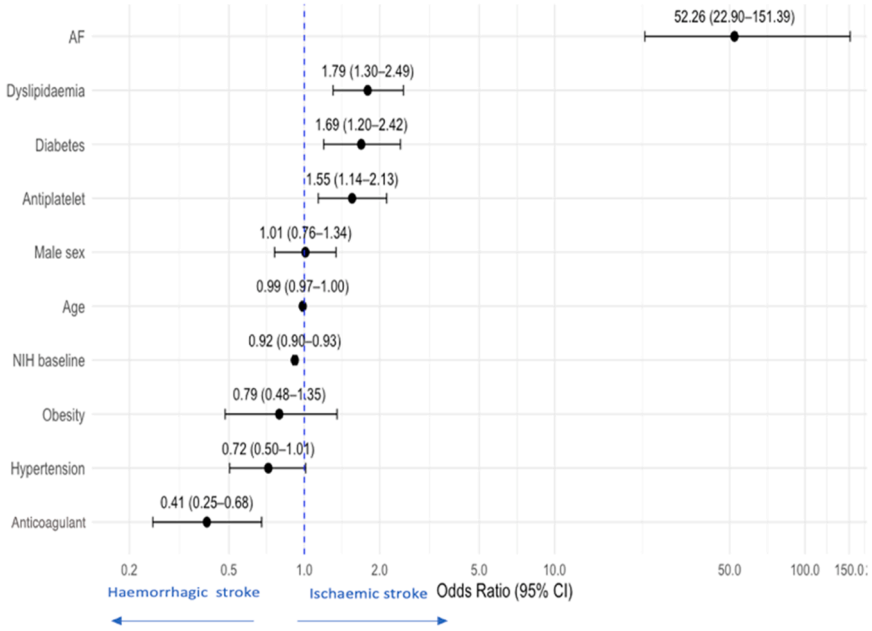

Fig. 1. Forest plot about multivariable logistic regression analysis for factors associated with ischaemic or haemorrhagic events.
Multivariable logistic regression analysis showing odds ratios (ORs, 95 % confidence intervals) for clinical factors associated with ischaemic versus haemorrhagic stroke. Values >1 indicate higher odds of ischaemic stroke; values <1 indicate higher odds of haemorrhagic stroke. All variables are mutually adjusted. AF = atrial fibrillation; NIH = National Institutes of Health Stroke Scale.

4.2. Impact of stroke type on outcome events

HS was associated with a higher incidence of the composite outcome compared with IS (26.0 % vs. 14.0 %, $p < 0.001$). Similarly, all-cause of death was higher in HS (21.2 %) than in IS (8.8 %, $p < 0.001$). No statistically significant differences in HS versus IS were observed for cardiac events (5.1 % vs. 7.1 %, $p = 0.236$) or VTE (1.7 % vs. 1.1 %, $p = 0.588$). Incidence rates, along with univariable and multivariable analyses of clinical outcomes, are reported in Table 2.

In the overall cohort, several clinical and demographic variables were independently associated with early in-hospital adverse events. For the composite outcome, older age (OR 1.03 per year, 95 % CI 1.02–1.05, $p < 0.001$), male sex (OR 1.56, 95 % CI 1.17–2.09, $p = 0.002$), AF (OR 1.49, 95 % CI 1.08–2.06, $p = 0.015$), and higher NIHSS scores at admission (OR 1.16 per point, 95 % CI 1.14–1.18, $p < 0.001$) were all significantly associated with increased risk. Restricted cubic spline analyses demonstrated that the associations of age and NIHSS with the composite outcome were predominantly linear, as illustrated in Fig. 2. Anticoagulant therapy showed an increased risk of the composite outcome (OR 1.52, 95 % CI 0.99–2.30; $p = 0.051$), with an effect size suggesting a possible association, despite not reaching statistical significance. In multivariable-adjusted analysis, no significant differences were found between patients with IS compared to those with HS (OR 0.76, 95 % CI 0.52–1.10, $p = 0.144$).

Regarding all-cause of death, independent predictors included age (OR 1.06, 95 % CI 1.04–1.08, $p < 0.001$), male sex (OR 1.57, 95 % CI 1.11–2.22, $p = 0.011$), NIHSS (OR 1.19 per point, 95 % CI 1.16–1.22, $p < 0.001$), and pre-hospital anticoagulant therapy (OR 2.00, 95 % CI 1.23–3.21, $p = 0.005$). Hypertension was associated with a lower risk of mortality (OR 0.68, 95 % CI 0.47–1.00, $p = 0.048$). In multivariable-adjusted analysis, IS was associated with lower in-hospital mortality compared to HS (OR 0.68, 95 % CI 0.44–1.05; $p = 0.079$), with an effect size suggesting a possible difference, although statistical significance was not reached. Among 219 in-hospital deaths, 146 (66.7 %) were classified as stroke-related and 73 (33.3 %) as non-stroke-related. Patients with stroke-related death presented with higher stroke severity at admission (NIHSS 19 ± 8 vs 15 ± 7; $p < 0.001$) and a higher proportion of HS (34 % vs 16 %; $p = 0.009$), whereas demographic characteristics, vascular risk factors, and pre-admission antithrombotic therapy were broadly comparable between groups (**Supplementary Table 3**).

For cardiac events, AF (OR 2.36, 95 % CI 1.58–3.53, $p < 0.001$), male sex (OR 1.59, 95 % CI 1.10–2.33, $p = 0.015$), and NIHSS (OR 1.09 per

Table 2
Incidence rates and risk of adverse outcomes in haemorrhagic and ischaemic stroke.

	Number of events	In-Hospital Incidence rate (95 % CI)	P-value	Univariable analysis OR (95 % CI)	Multivariable analysis OR (95 % CI)
Composite outcome					
Haemorrhagic Stroke	76	26	< 0.0001	Reference	Reference
Ischaemic Stroke	250	13.9		0.47 [0.35–0.63]	0.76 [0.52–1.10]
All-cause death					
Haemorrhagic Stroke	62	21.2	< 0.0001	Reference	Reference
Ischaemic Stroke	157	8.8		0.36 [0.26–0.50]	0.68 [0.44–1.05]
Cardiac events					
Haemorrhagic Stroke	15	5.1	0.236	Reference	Reference
Ischaemic Stroke	127	7.1		1.44 [0.86–2.60]	1.58 [0.88–3.00]
Thromboembolic events					
Haemorrhagic Stroke	5	1.7	0.588	Reference	Reference
Ischaemic Stroke	20	1.1		0.66 [0.26–2.00]	0.61 [0.19–2.15]

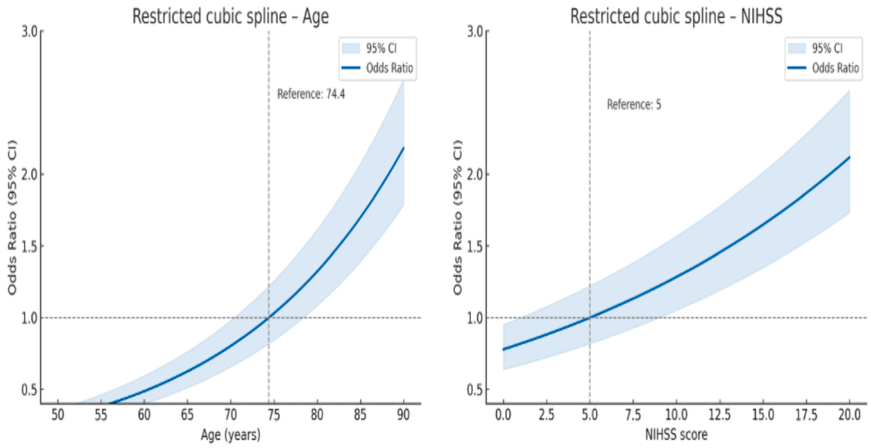

Fig. 2. Restricted cubic spline analyses showing the association of age and NIHSS with the risk of composite outcome.
Restricted cubic spline plots showing the non-linear association of age (left) and baseline NIHSS score (right) with the odds of experiencing a composite in-hospital adverse outcome. Odds Ratios (ORs) are adjusted for all covariates in the multivariable model. The shaded areas represent 95 % confidence intervals. The reference points were set at age 74.4 years and NIHSS score of 5.

point, 95 % CI 1.06–1.11, $p < 0.001$) were independently associated with increased risk. In multivariable-adjusted analysis, IS was associated with a higher risk of cardiac events compared to HS (OR 1.58, 95 % CI 0.88–3.00; $p = 0.145$), suggesting a possible association, although statistical significance was not reached.

For VTE, obesity emerged as the strongest independent predictor (OR 5.82, 95 % CI 2.03–15.39, $p < 0.001$), along with NIHSS score (OR 1.09, 95 % CI 1.03–1.15, $p = 0.001$). No significant differences were observed between stroke types. Complete univariable and multivariable regression results for all outcomes are provided in **Supplementary Table 4**.

4.3. Sensitivity analyses

4.3.1. Ischaemic stroke: first-ever versus recurrent stroke

Among patients with IS, recurrent strokes were associated with a higher incidence of in-hospital mortality compared to first-ever strokes (13.1 % vs. 8.1 %, $p = 0.017$), and showed an increase in the composite outcome rate (18.1 % vs. 13.4 %, $p = 0.053$). No significant differences were observed in the cardiac events (7.6 % vs. 6.8 %, $p = 0.648$) or VTE (1.6 % vs. 0.9 %, $p = 0.390$); full incidences are reported in Table 3.

In multivariable logistic regression analyses, stroke recurrence was not independently associated with increased risk of any adverse outcome. Specifically, composite outcome (OR 1.04; 95 % CI 0.66–1.60, $p = 0.860$), all cause of death (OR 1.13; 95 % CI 0.67–1.86,$p = 0.646$). Although not statistically significant, both associations suggested potentially worse in-hospital outcomes among patients with recurrent IS. Non-significant association was found between recurrence stroke and cardiac events (OR 0.75; 95 % CI 0.40–1.33,$p = 0.350$) or VTE (OR 0.18; 95 % CI 0.01–0.97, $p = 0.110$). Risk estimates for adverse outcomes are summarised, with complete univariable and multivariable regression results available in the corresponding tables (Table 3 **and Supplementary Table 5**).

4.3.2. Ischaemic stroke: non-lacunar anterior, non-lacunar posterior and lacunar stroke

In-hospital outcomes varied significantly according to lesion location. The incidence of the composite outcome was highest in non-lacunar-anterior strokes (19.0 %), followed by non-lacunar posterior (13.6 %) and lacunar infarcts (4.3 %) ($p < 0.001$). Similarly, all-cause of death occurred in 12.6 % of non-lacunar anterior stroke, 8.4 % of non-lacunar posterior stroke, and only 1.3 % of lacunar stroke ($p < 0.001$). Cardiac events were more common in non-lacunar anterior strokes (9.6 %), compared to non-lacunar posterior (5.5 %) and lacunar infarcts (3.2 %) ($p < 0.001$). Full incidence data stratified by lesion location are reported in **Supplementary Table 6**.

In multivariable-adjusted analyses, non-lacunar posterior strokes were independently associated with a significantly increased risk of composite outcome compared to lacunar strokes (OR 1.97; 95 % CI 1.10–3.63, $p = 0.025$). Non-lacunar anterior strokes were associated with a higher risk of the composite outcome (OR 1.61; 95 % CI 0.96–2.81; $p = 0.079$), with an effect size suggesting a possible association. Regarding all-cause mortality, both non-lacunar anterior (OR 2.90; 95 % CI 1.28–7.79, $p = 0.019$) and non-lacunar posterior strokes (OR 3.35; 95 % CI 1.35–9.51, $p = 0–014$) were independently associated with an increased risk. For cardiac events, non-lacunar anterior strokes were associated with increased risk (OR 1.41; 95 % CI 0.77–2.71; $p =$

Table 3
Incidence rates and risk of adverse outcomes according to first-ever vs. recurrent ischaemic stroke.

	Number of events	In-Hospital Incidence rate (95 % CI)	P-value	Univariable analysis OR (95 % CI)	Multivariable analysis OR (95 % CI)
Composite outcome					
Recurrent Stroke	43	18.1	0.053	Reference	Reference
First-ever Stroke	207	13.4		1.45 [0.99–2.07]	1.04 [0.66–1.60]
All-cause death					
Recurrent Stroke	31	13.1	0.017	Reference	Reference
First-ever Stroke	126	8.1		1.76 [1.14–2.66]	1.13 [0.67–1.86]
Cardiac events					
Recurrent Stroke	17	7.2	1.0	Reference	Reference
First-ever Stroke	110	7.1		0.98 [0.55–1.64]	0.75 [0.40–1.33]
Thromboembolic events					
Recurrent Stroke	1	0.4	0.458	Reference	Reference
First-ever Stroke	19	1.2		0.34 [0.02–1.67]	0.18 [0.01–0.97]

0.277), with an effect size suggesting a possible association, although statistical significance was not reached. In contrast, posterior strokes were not significantly associated with cardiac events (OR 1.14; 95 % CI 0.54–2.41; $p = 0.738$). No significant associations were observed between lesion location and venous thromboembolism (Fig. 3). Risk estimates for adverse outcomes are summarised, with complete univariable and multivariable regression results available in the corresponding tables (**Supplementary Table 7**).

4.3.3. Haemorrhagic stroke: first-ever versus recurrent stroke

In the HS subgroup, no significant differences in incidence were observed between first-ever and recurrent strokes for any adverse outcome, full incidence data are available in Table 4**.** In multivariable logistic regression analyses, stroke recurrence was not independently associated with increased risk of any adverse outcome (Table 4). Full univariate and multivariable logistic regression are shown in **Supplementary Table 8.**

4.3.4. Haemorrhagic stroke: atypical versus typical haemorrhagic lesions

Incidence rates of adverse outcomes were higher among patients with atypical haemorrhagic lesions. In particular, the incidence rate of the composite outcome was 32.5 vs 21.2 ($p = 0.041$), and for all-cause death, 28.6 vs 16.7 ($p = 0.024$) in atypical versus typical HS, respectively. No significant differences were observed for cardiac or thromboembolic events; full incidence rates are shown in **Supplementary Table 9**.

In patients with HS, atypical lesion location was significantly associated with worse in-hospital outcomes compared to typical HS. Specifically, atypical lesions were associated with an increased risk of composite outcome (OR 2.51; 95 % CI 1.24–5.22, $p = 0.012$) and all cause of death (OR 2.80; 95 % CI 1.31–6.17, $p = 0.009$), highlighting their prognostic relevance. No significant associations emerged for cardiac events (OR 1.35; 95 % CI 0.39–4.81, $p = 0.630$)(Fig. 4). Full results are shown in **Supplementary Table 10**.

4.3.5. Multiply imputed cohort: impact of stroke type on outcome events

A total of 2691 patients were included in the multiply imputed cohort; baseline characteristics are shown in **Supplementary** Table 11. In multivariable logistic regression models, HS was independently associated with an increased risk of the composite outcome (OR 0.65, 95 % CI 0.44–0.95, $p = 0.02$) and all-cause death (OR 0.54, 95 % CI 0.33–0.86, $p = 0.01$), while no significant association was found with cardiac events (OR 1.60, 95 % CI 0.88–2.90, $p = 0.12$) or VTE (OR 0.70, 95 % CI 0.48–1.01, $p = 0.05$). Full model results are presented in **Supplementary Table 12**.

5. Discussion

In this large, retrospective exploratory cohort study of patients admitted for acute ischaemic or haemorrhagic stroke in Stroke Unit, we observed the following main associations: i) Distinct clinical characteristics of HS and IS; ii) HS showed higher crude incidence rates of the composite outcome and all-cause death compared with IS. Although this association was attenuated after multivariable adjustment in complete-case analyses, it reached statistical significance in sensitivity analyses based on multiple imputation, while IS showed effect estimates suggestive of a possible increased cardiac events; iii) across stroke subtypes, distinct clinical phenotypes were independently associated with the risk of early in-hospital events; iv) among patients with IS, recurrent stroke was associated with higher rates of mortality and composite outcomes compared to first-ever stroke, with effect estimates suggesting a possible increase in the risk of both outcomes; v) lesion location had a significant prognostic impact in IS: both non-lacunar anterior and non-lacunar posterior strokes were associated with increased all cause of death compared to lacunar strokes; non-lacunar posterior strokes also independently predicted the composite outcome and non-lacunar anterior strokes were associated with increased risk of cardiac events, with an effect size suggesting a possible association; vi) in the HS subgroup, atypical haemorrhages were significantly associated with a higher risk of composite outcome and all-cause of death compared to typical haemorrhages.

In this study, patients with IS were more likely to present with a pro-atherosclerotic clinical profile, characterised by older age, diabetes, dyslipidaemia, AF, and prior antiplatelet therapy. In contrast, HS patients had more severe neurological impairment at admission, reflected by higher NIHSS scores. These findings confirm previous studies and highlight the distinct baseline phenotypes between IS and HS, which may contribute to differences in early outcomes[17,18].

In our cohort, patients with HS demonstrated a higher incidence of the composite outcome and all-cause death compared to those with IS. Emerging evidence supports that SHS is not limited to IS. Recent studies, including those from the VISTA-ICH cohort, have confirmed that SHS

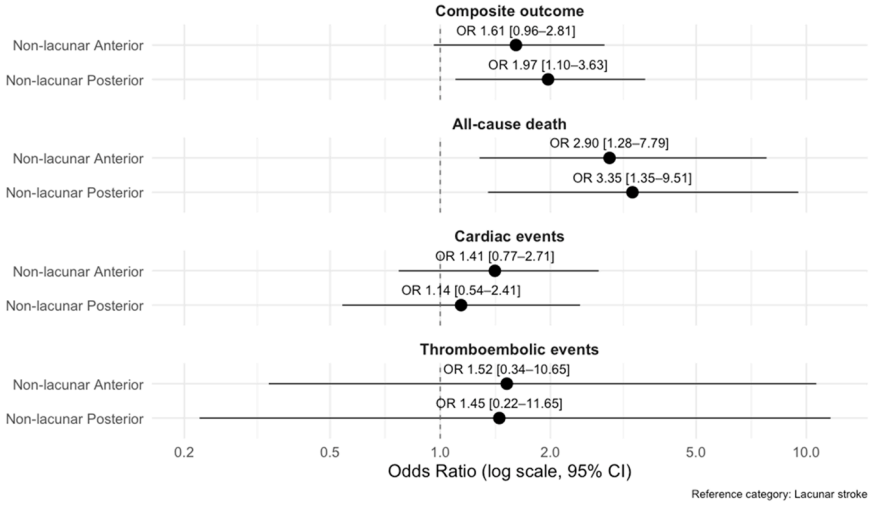

Fig. 3. Forest plot about association between ischaemic stroke lesion location (Non-lacunar Anterior, Non-lacunar Posterior vs Lacunar stroke) and in-hospital outcomes.

Forest plot of multivariable logistic regression showing the association between stroke lesion location (Non-lacunar Anterior and Posterior) and in-hospital adverse outcomes, compared with Lacunar stroke (reference group). Odds Ratios (ORs) are shown on a logarithmic scale with 95 % confidence intervals. Outcomes include composite adverse events, all-cause death, cardiac events, and thromboembolic events.

Table 4
Incidence rates and risk of adverse outcomes according to first-ever vs. recurrent haemorrhagic stroke.

	Number of events	In-Hospital Incidence rate (95 % CI)	P-value	Univariable analysis OR (95 % CI)	Multivariable analysis OR (95 % CI)
Composite outcome					
Recurrent Stroke	11	27.5	1.0	Reference	Reference
First-ever Stroke	65	25.8		0.91 [0.39–1.97]	0.57 [0.20–1.52]
All-cause death					
Recurrent Stroke	8	20	1.0	Reference	Reference
First-ever Stroke	54	21.4		1.02 [0.41–2.27]	0.65 [0.21–1.85]
Cardiac events					
Recurrent Stroke	4	10	0.280	Reference	Reference
First-ever Stroke	11	4.4		1.23 [0.19–4.84]	1.15 [0.16–529.00]
Thromboembolic events					
Recurrent Stroke	0	0	0.795	Reference	Reference
First-ever Stroke	5	1.9		—*	—*

* The limited number of events precluded reliable estimation of odds ratios with corresponding 95 % confidence intervals.

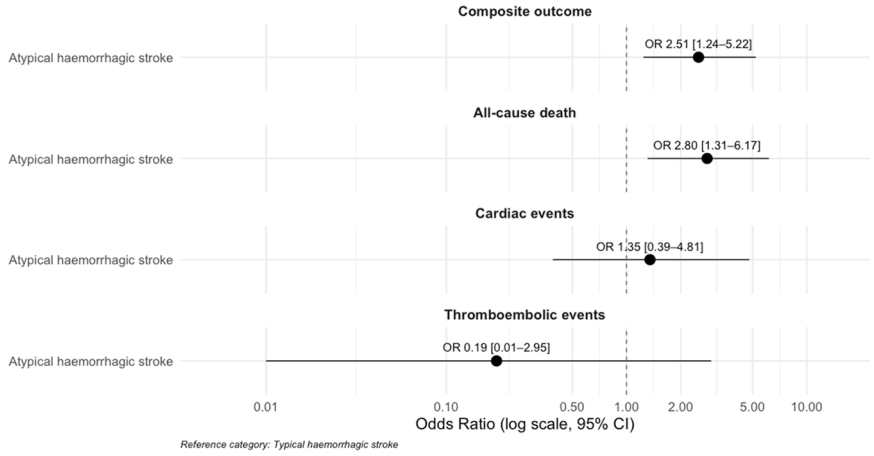

Fig. 4. Forest plot about impact of haemorrhagic stroke location (atypical vs typical) and in-hospital outcomes.
Forest plot from multivariable logistic regression showing the association between atypical haemorrhagic stroke and in-hospital adverse outcomes compared with typical haemorrhagic stroke (reference). Odds Ratios (ORs) and 95 % confidence intervals are displayed on a logarithmic scale for composite outcome, all-cause death, cardiac events, and thromboembolic events.

can occur in up to 15 % of HS patients, contributing independently to increased mortality[4]. Similarly, two recent studies reported that although the overall incidence of SHS is similar in HS and IS, its prognostic implications may be more severe in haemorrhagic cases, potentially due to higher rates of autonomic dysregulation, catecholamine surge, and systemic inflammatory response[2,5]. In addition, neuroanatomical factors also play a critical role in shaping early outcomes in HS. Intraventricular extension of intracerebral haemorrhage has been consistently identified as an independent predictor of poor short-term prognosis and in-hospital mortality, reflecting increased intracranial pressure, hydrocephalus, and secondary brain injury[19].

Interestingly, the incidence of acute cardiac events did not significantly differ between groups. However, we observed a possible, though non-significant, association with higher risk of cardiac events in IS compared to HS. This finding is consistent with growing evidence suggesting under-recognition of SHS in HS. For example, Hoad et al. recently highlighted that cardiac complications following intracerebral haemorrhage are frequently underdiagnosed due to reduced surveillance in patients with severe neurological deficits or those in a sedated state[9]. Our findings underscore the need to expand current post-stroke cardiac monitoring paradigms to better include HS populations. Indeed, stroke subtype is clearly a key prognostic factor. Moreover, our findings demonstrate that baseline clinical phenotype exerts an independent and substantial influence on early in-hospital outcomes.

Among phenotypic variables, age and NIHSS score emerged as the most robust and consistent predictors across all endpoints, in line with extensive evidence confirming their central roles in quantifying stroke severity and forecasting short-term outcomes[14,20,21]. AF was strongly associated with both cardiac events and the composite outcome, reinforcing its relevance not only as a cause of cardioembolic stroke but also as a contributor to SHS through neurocardiac dysregulation and autonomic imbalance[22]. Obesity, often under-recognized in acute stroke settings, showed a clear association with VTE. This likely reflects the synergistic effects of prolonged immobilization, systemic inflammation, and endothelial dysfunction. Our data align with prior studies identifying visceral adiposity as a potent driver of thrombotic risk in hospitalized stroke populations[10]. Anticoagulant therapy was independently associated with increased in-hospital death and VTE. This likely reflects both the elevated baseline risk profile of anticoagulated patients and the inherent challenges in managing anticoagulation in the acute phase—particularly the risks posed by treatment interruption or delayed re-initiation, which may predispose to both thromboembolic and haemorrhagic complications[23,24]. Taken together, these associations highlight the central role of clinical phenotyping at admission in stratifying the early risk of adverse events. The characterization of distinct clinical profiles offers a pragmatic framework to anticipate adverse trajectories and may inform early tailored interventions in routine care.

Among patients with IS, our findings indicate that recurrent stroke was associated with worse in-hospital outcomes, particularly higher rates of all-cause mortality and the composite outcome. Although these associations did not consistently reach statistical significance, the

observed effect estimates may still have clinical relevance. This may reflect the fact that our analysis was focus to early in-hospital complications, which represent only a subset of the total burden of recurrent stroke outcomes. Nonetheless, the observed patterns are consistent with population-based and registry studies reporting higher morbidity and mortality in patients with recurrent ischaemic stroke. Recurrent strokes confer a markedly higher short-term mortality risk. In the South London Stroke Register, recurrence was associated with a twofold increase in early death, independent of comorbidities and stroke severity[25]. Similar findings emerged from the GLORIA-AF registry, where prior stroke—particularly multiple events—was linked to increased risks of death and cardiovascular events[26]. The elevated risk of death following recurrence likely reflects both biological and care-related factors. Recurrent strokes often involve more extensive infarction, reduced collateral reserve, and impaired neuroplasticity. They also frequently occur in older and frailer patients with a higher prevalence of AF, chronic heart failure—all of which contribute to systemic decompensation during the acute phase[27] . Moreover, patients with recurrent stroke may be more vulnerable to early complications such as venous thromboembolism and stroke–heart syndrome (SHS), both of which independently worsen prognosis[22].

A central finding of our study is the prognostic relevance of lesion location in both IS and HS, providing novel evidence that lesion topography exerts a decisive influence on early post-stroke outcomes. In particular, non-lacunar posterior circulation strokes emerged as the most lethal subtype during the acute hospital phase, showing a higher risk of in-hospital death and composite outcome—even after adjusting for stroke severity and clinical covariates. Historically, posterior strokes have been perceived as less severe than anterior strokes, largely due to their lower average NIHSS scores and more subtle or atypical presentations. This discrepancy likely reflects the limitations of the NIHSS, which underrepresents hallmark posterior strokes features such as vertigo, ataxia, dysphagia, diplopia, and impaired consciousness. Consequently, posterior strokes are frequently under-recognized or underestimated during acute triage and prognostic assessments[12]. Mattle HP et al. previously highlighted the diagnostic and therapeutic challenges associated with posterior strokes, particularly in the context of basilar artery occlusion, which is prone to delayed treatment and clinical deterioration[28]. Our study confirms and extends these findings by showing that, among all topographic subtypes, non-lacunar posterior strokes were associated with the highest in-hospital mortality and the strongest independent association with the composite endpoint, highlighting their underestimated clinical burden. In contrast, non-lacunar anterior strokes showed a distinct pattern of risk. While our data confirmed an increased in-hospital mortality in this group, effect estimates also suggested a possible increase in the incidence of acute cardiac events. While the association between insular involvement and cardiac arrhythmias has been described[29,30], evidence directly linking anterior stroke topography with acute myocardial infarction or heart failure remains limited. Our findings support and expand prior evidence by showing that anterior strokes do not merely predispose to ECG abnormalities or transient arrhythmias but are associated with clinically significant cardiac events, reinforcing the concept of a stroke–heart axis that is not only anatomical but topographically specific.

These patterns offer a topographically-informed lens to understand SHS, which has been widely reported in the literature. In a multicentre analysis of over 350,000 stroke patients, reported that SHS affects 20 % of ischaemic strokes and is associated with significantly increased long-term risks of mortality, myocardial infarction, and recurrent stroke[5]. However, that study did not account for lesion location. Our results fill this gap by showing that the nature and severity of SHS may vary according to stroke topography.

Lastly, our findings demonstrate that atypical HS lesions are independently associated with a significantly higher risk of early in-hospital mortality and adverse cardiovascular outcomes compared to typical HS lesions. These results highlight lesion topography as a critical, yet frequently underappreciated, determinant of short-term prognosis in haemorrhagic stroke. Although comparative data remain limited, a recent registry-based study by Mendiola et al. reported higher in-hospital mortality in patients with atypical haemorrhages compared to typical ones, reinforcing the prognostic relevance of haemorrhages location and the need for more granular research into topography-driven outcomes[31].

We observed a non-significant but clinically meaningful association with increased early cardiovascular events in patients with atypical haemorrhages. This may reflect enhanced autonomic dysregulation, particularly in brainstem and posterior fossa lesions, which have been implicated in neurogenic myocardial dysfunction and arrhythmias[22]. As the concept of SHS gains wider acceptance in both ischaemic and haemorrhagic contexts, our findings support the need for heightened cardiovascular surveillance guided by lesion location. Adding to this, recent large-scale analyses have extended our understanding of SHS in HS. A study by Hoad et al. demonstrated that newly diagnosed cardiovascular complications following ICH are not only common (15 %) but are also strongly associated with a significantly higher 5-year risk of major adverse cardiovascular events, including acute myocardial infarction, recurrent stroke, and all-cause mortality[9] . These findings reinforce the notion that early cardiac complications are not incidental but represent a meaningful contributor to long-term outcomes in ICH.

Our results therefore lend further support to emerging calls for phenotype-driven, integrated stroke management approaches, such as the ABC_{stroke} pathway framework, which has been associated with improved outcomes[32–34]. Applying such models in both ischaemic and haemorrhagic populations may allow for earlier identification of high-risk individuals, inform targeted cardiovascular monitoring. Ultimately, this could improve early outcomes through personalised intervention strategies. Future research should build on these findings. Integrating detailed cardiac phenotyping, advanced neuroimaging features, and extended follow-up in prospective multicentre studies may further refine risk stratification and better define the long-term clinical implications of early stroke–heart interactions.

5.1. Limitations

Several limitations should be acknowledged. First, this was a single-centre, retrospective exploratory study that was not supported by an a priori sample size calculation; therefore, it was not formally powered to test predefined hypotheses. Accordingly, all findings should be interpreted as descriptive and hypothesis-generating rather than confirmatory. Second, due to its retrospective design, causal inferences cannot be drawn and residual confounding cannot be excluded. Third, the ascertainment of cardiac complications may have been incomplete, particularly in patients with severe neurological impairment or reduced consciousness, potentially leading to underestimation of their true incidence. In addition, detailed information on specific emboligenic cardiac conditions beyond AF and major cardiac comorbidities was not systematically available, precluding a more granular stratification of cardioembolic mechanisms. Fourth, the absence of post-discharge follow-up represents a significant limitation, as it confined our analysis to early in-hospital outcomes and precluded any insight into the medium and long-term clinical course of these patients. Fifth, exclusion of approximately 600 patients with missing data represents a limitation that may introduce selection bias and reduce statistical power, particularly in subgroup analyses. Sensitivity analyses using multiple imputation by chained equations yielded statistically significant associations, highlighting the impact of missing data and supporting cautious interpretation of both imputed and complete-case results. Finally, the long observational period (2005–2019) may have introduced heterogeneity in clinical management, particularly regarding the increasing use of reperfusion therapies (such as intravenous thrombolysis and mechanical thrombectomy) and the progressive adoption of direct oral anticoagulants. Future multicentre studies with extended follow-up are needed to

validate our findings and assess their long-term clinical implications.

6. Conclusion

Lesion topography and stroke phenotype-encompassing subtype, recurrence status, and baseline clinical context-should no longer be regarded as mere descriptors, but as core prognostic determinants with direct implications for acute management, risk stratification, and multidisciplinary decision-making. Our findings reinforce the need for a shift toward individualized stroke care models that integrate anatomical, clinical, and cardio-neurological dimensions. Future prospective studies are warranted to validate topography-informed prognostic frameworks and to develop coordinated stroke–heart care pathways aimed at improving both early and long-term outcomes in IS and HS cohorts.

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none

Declaration of competing interest

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Caso received honoraria as a member of the speaker bureau of Boehringer Ingelheim, Bayer, and Daiichi Sankyo (all fees were paid to Associazione Ricerca Stroke, Umbria). She received honoraria as consultant or advisory board member of Boehringer Ingelheim, Bayer, Daiichi Sankyo, and Pfizer.

Becattini received honoraria as a member of the speaker bureau of Bristol Meyer Squibb, Daiichi Sankyo, and Bayer.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2026.106822.

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