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ORIGINAL ARTICLE

Asymptomatic parenchymal haemorrhage following endovascular treatment: Impact on functional outcome in patients with acute ischaemic stroke

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Abstract

Background and purpose: In patients with acute ischaemic stroke (AIS), haemorrhagic transformation (HT) following endovascular treatment (EVT) is associated with poor functional outcome. However, the impact of asymptomatic HT, not linked to neurological deterioration in the acute phase, is unknown. We aimed to investigate the impact of asymptomatic PH1 (aPH1) and PH2 (aPH2) subtypes of HT on the functional outcome of patients treated with EVT.

Methods: We conducted a retrospective study of patients with AIS who were consecutively admitted to our comprehensive stroke centre between January 2019 and December 2022, and who underwent EVT. We collected clinical, radiological, and procedural data. HTs were categorized according to the Heidelberg classification. The primary outcome was the shift on the modified Rankin Scale (mRS) at 3 months of follow-up. We performed bivariate and multivariable ordinal regression analyses to test the association between aPH1/aPH2 and the primary outcome.

Results: We included 314 patients (mean age = 72.5 years [SD = 13.6], 171 [54.5%] women). We detected 54 (17.2%) patients with HT; 23 (7.3%) were classified as PH2 (11 asymptomatic) and 17 (5.4%) as PH1 (16 asymptomatic). The adjusted common odds ratio for aPH2 of worsening 1 point on the 3-month mRS was 3.32 (95% confidence interval = 1.16–9.57, $p = 0.026$). No association was observed for aPH1. aPH2 was also independently associated with lower odds of achieving a favourable outcome (mRS = 0–2). Neither aPH1 nor aPH2 was associated with mortality.

Conclusions: In patients with AIS treated with EVT, aPH2 is independently associated with unfavourable functional outcome.

KEYWORDS
endovascular treatment, haemorrhagic transformation, outcome, stroke

INTRODUCTION

Endovascular treatment (EVT) is a highly effective therapy for patients with acute ischaemic stroke (AIS) secondary to intracranial large vessel occlusion [1–3]. Although the proportion of patients who experience a favourable clinical outcome is doubled when they are treated with EVT compared to thrombolysis alone, more than half of the patients present with significant disability at 3 months of follow-up [1]. Therefore, it is anticipated that several complementary therapies and techniques will be explored in the forthcoming years to improve outcome in AIS patients. In this regard, it is crucial to establish reliable indicators of efficacy and safety following EVT.

A lesson learned from the first decade of EVT is that successful recanalization is not a synonym of favourable outcome. A great proportion of patients (32.4%–69.6%) showing an angiographically accomplished result at the end of the procedure still present with unfavourable clinical outcome [4]. This has led to the term *clinically ineffective reperfusion* (CIR). CIR may be due to various phenomenon, including reperfusion injury, haemorrhagic transformation (HT), the no-reflow phenomenon, and periprocedural complications, among others [5].

HT is probably the most feared adverse event following reperfusion therapies. HT is usually categorized according to the European Co-operative Acute Stroke Study-II criteria [6] or the more recently proposed Heidelberg bleeding classification [7]. In both classifications, HT subtype is assigned taking into account radiological features and the impact on neurological symptoms. Despite some variations between these classification systems, the term symptomatic intracranial haemorrhage (sICH) is reserved for HT linked to neurological deterioration. sICH has been related to unfavourable outcome in several studies [8–10].

Traditionally, sICH has been used as the main safety outcome in EVT trials [11–18] and as a key performance indicator in various public health agencies to monitor comprehensive stroke centres. Nevertheless, some recent studies have pointed to a potentially deleterious impact on functional outcome also with asymptomatic intracranial haemorrhage (aICH) following EVT, with conflicting results [19–22]. Whereas a recent analysis of the MR CLEAN-NO IV and MR CLEAN-MED trials [23] concluded that asymptomatic parenchymal haemorrhage type 2 (aPH2) might be associated with poor functional outcome, a later metanalysis failed to confirm an association between any aICH subtype and midterm dependence (modified Rankin Scale [mRS] ≥ 3) [24]. These discrepancies among studies are partly explained by methodological differences. Whereas some studies consider all aICH as a whole exposure variable, others differentiate between aICH subtypes (such as aPH1 or aPH2). Also, whereas some studies use the dichotomization of the mRS as the main outcome variable (significantly increasing the weight of the mortality rate in the category of unfavourable outcome), others use shift analyses to study the probability of worsening 1 point on the mRS score.

In the present study, we aimed to explore whether aICH subtypes aPH1 and aPH2 are associated with functional outcome in patients with AIS treated with EVT. We also aimed to discover whether this association is due to a delay in the initiation of preventive antithrombotic therapies—and thus with early stroke recurrence—or due to a lack of neurological improvement.

METHODS

Study population

We conducted a retrospective study of consecutive adult patients with AIS treated with EVT who were admitted to our comprehensive stroke centre from January 2019 to December 2022. Patients were included according to the following criteria: (i) age ≥ 18 years; (ii) AIS onset within 24 h; (iii) occlusion of the M1, M2, A1, and/or P1 segments, basilar and/or terminal internal carotid artery with or without extracranial occlusion or stenosis, as demonstrated by computed tomographic (CT) angiography; (iv) treatment with any modality of EVT (mechanical thrombectomy, contact aspiration, rescue stenting) plus bridging intravenous alteplase when eligible; and (v) follow-up CT scan within 36 h. We excluded patients with: (i) unavailable information on the mRS score at 3 months and/or (ii) no follow-up CT scan available. The study was approved by the ethics committee of Hospital de la Santa Creu i Sant Pau. Informed consent was waived due to the retrospective design of the study.

We recorded the following variables at admission: (i) demographic information: age and sex; (ii) clinical data: time from symptoms onset or last seen well to admission, previous mRS score, baseline National Institutes of Health Stroke Scale (NIHSS) score, glycaemia, treatment with thrombolysis, and stroke aetiology according to the TOAST criteria [25]; (iii) logistics and metrics: door-to-needle time, door-to-groin puncture time, and groin puncture-to-last angiographic series time; (iv) radiological features: Alberta Stroke Program Early CT Score (ASPECTS) and site of occlusion; and (v) procedural information: modified Thrombolysis in Cerebral Infarction (mTICI) score at the end of the procedure, number of passes, emerging carotid or intracranial stenting, and type of anaesthesia. Successful recanalization was defined as an mTICI score ≥ 2b.

We collected the following variables during the follow-up: NIHSS score at 24 h, ΔNIHSS (calculated as the baseline NIHSS score – the NIHSS score at 24 h), presence of any type of HT on follow-up CT scan, delay between EVT and initiation of antithrombotic preventive therapy, and mRS score at discharge and at 3 months of follow-up after a face-to-face interview by local certified stroke neurologists.

All of the patients were treated according to current recommendations from the American Heart Association/American Stroke Association guidelines on acute stroke management [26]. This includes the presently recommended blood pressure target for patients undergoing EVT (<180/105 mmHg).

Imaging analysis

An expert neuroradiologist (J.P.M.-G.), blinded to the clinical information, reviewed baseline and follow-up CT scans and classified HT

according to the Heidelberg classification as follows: (i) no HT, (ii) PH1 (haematoma within infarcted tissue, occupying <30% without substantive mass effect), (iii) PH2 (haematoma occupying 30% or more of the infarcted tissue, with obvious mass effect), or (iv) other HT (HI1, HI2, remote PH, intraventricular haemorrhage, subarachnoid haemorrhage, and subdural haemorrhage).

Whether PH1 and PH2 provoked changes in the neurological examination was determined by chart review by C.T.-P. and P.C.-R. and subsequently classified as sICH or aICH. We defined sICH following the Heidelberg criteria: any haemorrhage that produces an increase of ≥4 points in the total NIHSS score or ≥2 points in one NIHSS category, or leading to intubation, hemicraniectomy, ventricular drain placement, or other major medical/surgical intervention [7].

Outcomes

The primary outcome was the shift in the mRS score at 3 months of follow-up. The secondary outcomes included the proportion of patients with favourable outcome (defined as an mRS score = 0–2) and mortality at 3 months of follow-up.

Statistical analysis

Continuous variables were reported as mean and SD or median and interquartile range (IQR) if they were not normally distributed, as tested by the Shapiro–Wilk normality test. Categorical variables were expressed as counts and percentages.

First, we described the study population and we compared baseline characteristics according to the study variables (aPH1 and aPH2). We used the Student *t*-test or the Wilcoxon rank-sum test (when a nonparametric test was required) for comparing quantitative variables, and the χ^2-test or the Fisher exact test for comparing categorical variables between groups.

For the primary outcome, we conducted bivariate ordinal regression analyses to explore clinical, radiological (including aPH1 and aPH2), and procedurally related factors associated with the probability of worsening 1 point in mRS score at 3 months. For all the study variables, we calculated the common odds ratio (OR) of worsening 1 point on the mRS with its 95% confidence interval (CI). Thereafter, we performed a multivariable ordinal logistic regression analysis as follows: from an initial model including all variables with $p < 0.1$ in the bivariate analysis, we employed a stepwise backward regression modelling to select variables independently associated with functional outcome. When studying the impact of aPH1 and aPH2 on the primary outcome, patients with sICH were excluded. The final models were adjusted for age, baseline NIHSS, ASPECTS score at admission, number of passes, thrombolysis, successful recanalization, and previous mRS score.

For the secondary outcomes (mRS score = 0–2 at 3 months and mortality), we followed the same approach but using binary logistic regression.

Finally, we performed receiver operating characteristic (ROC) analyses to study the predictive value of sICH, aPH2, and the combination of both for poor outcome by comparing the area under the curve (AUC).

Statistical significance for all the analyses was set at 0.05 (two-sided). All the analyses were performed using Stata v.15.

RESULTS

We initially identified 329 patients who met the inclusion criteria. Fifteen patients were excluded due to lack of critical follow-up information (14 patients had no mRS score available at 3 months and one patient died before a follow-up CT scan could be performed). Thus, we finally studied 314 patients with a mean age of 72.5 years (SD = 13.6), of whom 171 (54.5%) were women. Clinical and radiological characteristics of the patients are detailed in Table 1. Notably, 114 (36.3%) patients received thrombolysis before EVT. Successful recanalization was achieved in the majority of patients (91.7%), and the median of passes was 2 (IQR = 1–3). Other procedurally related variables are also summarized in Table 1.

We identified a total of 54 patients (17.2%) with HT on the follow-up CT scan; 23 (7.3%) of them were PH2 ($n = 11$ asymptomatic), 17 (5.4%) were PH1 ($n = 16$ asymptomatic), and 14 (4.5%) were other types of HT, as previously defined. Of the overall HT, 23 (7.3%) were considered sICH according to Heidelberg criteria; 12 were PH2, and one was PH1.

Table 2 summarizes clinical and early follow-up information associated with both study variables: aPH1 and aPH2. There were no statistically significant differences on baseline characteristics between groups, except for thrombolysis, which was more frequently used in the aPH1 group. Interestingly, both aPH1 and aPH2 led to a delay to the initiation of preventive antithrombotic agents, whereas an increased risk of stroke recurrence during hospitalization was not detected. In addition, patients with aPH2 showed higher NIHSS scores at 24 h and smaller ΔNIHSS compared to patients without this subtype of HT.

At 3 months of follow-up, the median mRS score was 3 (IQR = 1–4). In the bivariate ordinal regression analyses, we found the following factors associated with poorer functional outcome at 3 months: older age, previous mRS score, higher NIHSS score at admission, long groin puncture-to-last angiographic series time, increased number of passes, and the use of general anaesthesia. sICH and aPH2 (after excluding sICH) were also related with poor outcome, but no association was observed in the case of aPH1. In contrast, higher ASPECTS, symptoms onset within 6 h before admission, treatment with thrombolysis, and successful recanalization were all linked to favourable outcome (see Table S1).

Figures 1–3 show the shift analyses of the mRS score at 3 months of follow-up with its unadjusted common OR of worsening 1 point according to the presence of sICH, aPH2, and aPH1. Noteworthily, in the multivariable ordinal regression analysis, after adjusting for age, admission NIHSS, baseline ASPECTS,

TABLE 1 Clinical and radiological characteristics of the patients.

Characteristic	All patients, $n=314$	No aPH, $n=264$[a]	aPH, $n=27$	p[b]
Age, years, mean (SD)	72.5 (13.6)	72.1 (13.9)	74.2 (12.6)	0.448
Sex, female, *n* (%)	151 (54.5)	144 (54.6)	15 (55.6)	0.960
Symptoms onset at <6 h, *n* (%)	219 (69.8)	181 (68.6)	19 (70.4)	0.847
Previous mRS score, md (IQR)	0 (0–2)	0 (0–2)	0 (0–1)	0.380
Admission NIHSS, md (IQR)	16 (10–20)	15 (10–20)	17 (12–21)	0.144
Anterior circulation, *n* (%)	293 (93.3)	246 (93.2)	25 (92.6)	0.908
Intravenous thrombolysis, *n* (%)	114 (36.3)	95 (36.0)	13 (48.2)	0.213
Aetiology, *n* (%)[c]				
Atherothrombotic	61 (19.4)	55 (20.8)	6 (22.2)	0.789
Cardioembolic	141 (44.9)	118 (44.7)	12 (44.4)	
Infrequent	30 (9.6)	26 (9.9)	1 (3.7)	
Unknown	77 (24.5)	62 (23.5)	8 (29.6)	
Two possible aetiologies	5 (1.6)	3 (1.1)	0 (0.0)	
Door-to-needle time, min, md (IQR)	27 (21–34)	27 (21–34)	30 (20–37)	0.850
Door-to-groin puncture time, min, md (IQR)	66 (56–85)	66 (55–84)	73 (60–96)	0.338
Groin puncture-to-last angiographic series time, min, md (IQR)	82 (56–133)	77 (55–127)	94 (65–140)	0.327
Radiological data				
ASPECTS scale, md (IQR)	9 (8–10)	10 (8–10)	9 (8–10)	0.060
Site of occlusion, *n* (%)				
M1	143 (45.5)	124 (47.0)	12 (44.4)	0.410
M2	74 (23.6)	63 (23.9)	7 (25.9)	
TICA	28 (8.9)	22 (8.3)	2 (7.4)	
Tandem	28 (8.9)	19 (7.2)	5 (18.5)	
Extracranial ICA	9 (2.9)	8 (3.03)	0 (0.0)	
ACA	8 (2.5)	6 (2.3)	1 (3.7)	
Basilar	11 (3.5)	10 (3.8)	0 (0.0)	
PCA	13 (4.1)	12 (4.6)	0 (0.0)	
Procedural data				
Successful recanalization, *n* (%)[d]	288 (91.7)	244 (92.4)	24 (88.9)	0.517
Number of passes, md (IQR)	2 (1–3)	2 (1–3)	3 (1–4)	**0.011**
Acute extracranial stenting, *n* (%)	24 (7.6)	21 (8.0)	2 (7.4)	0.920
Acute intracranial stenting, *n* (%)	12 (3.8)	12 (4.6)	0 (0.0)	0.253
Type of anaesthesia, *n* (%)[e]				
General anaesthesia	64 (27.2)	52 (26.8)	7 (29.2)	0.943
Conscious sedation	54 (23.0)	46 (23.7)	6 (25.0)	
Monitored anaesthesia care	117 (49.8)	96 (49.5)	11 (45.8)	

Note: Boldface indicates statistically significant.

Abbreviations: ACA, anterior carotid artery; aPH, asymptomatic parenchymal haemorrhage; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IQR, interquartile range; md, median; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior carotid artery; TICA, terminal internal carotid artery.

[a]Excluding 23 patients with symptomatic intracranial haemorrhage.

[b]Comparison between patients with and without aPH.

[c]According to TOAST criteria.

[d]Modified Thrombolysis in Cerebral Infarction = 2b–3.

[e]Data available for 235 patients.

TABLE 2 Differences on baseline characteristics and early follow-up information according to the presence of aPH2 and aPH1.

	aPH2			aPH1		
Characteristic	**Yes, *n* = 11**	**No, *n* = 280[a]**	***p***	**Yes, *n* = 16**	**No, *n* = 275[a]**	***p***
Age, years, mean (SD)	76.3 (12.5)	72.1 (13.8)	0.326	72.8 (12.9)	72.2 (13.9)	0.884
Sex, female, *n* (%)	9 (81.8)	150 (53.6)	0.119	6 (37.5)	153 (55.6)	0.157
Prior mRS, md (IQR)	0 (0–1)	0 (0–2)	0.362	0 (0–1)	0 (0–2)	0.723
Baseline NIHSS, md IQR	17 (16–22)	15 (10–20)	0.149	15 (12–21)	15 (10–20)	0.516
Anterior LVO, *n* (%)[b]	11 (100)	259 (92.5)	0.346	14 (87.5)	257 (93.5)	0.360
Thrombolysis, *n* (%)	3 (27.3)	105 (37.5)	0.491	10 (62.5)	98 (35.6)	**0.031**
Glycaemia at admission, mg/dL, md (IQR)	134 (−5 to 145)	120 (101–150)	0.731	120 (99–165)	122 (101–149)	0.906
Groin puncture-to-last angiographic series time, min, md (IQR)	91 (53–133)	78 (55–128)	0.599	94 (65–180)	78 (55–128)	0.419
General anaesthesia, *n* (%)[c]	2 (18.2)	57 (27.5)	0.496	5 (38.5)	54 (26.3)	0.340
mTICI ≥ 2b, *n* (%)	10 (90.9)	258 (92.1)	0.882	14 (87.5)	254 (92.4)	0.483
Number of passes, md (IQR)	3 (1–4)	2 (1–3)	0.383	3 (2–5)	2 (1–3)	**0.013**
Emerging carotid stenting, *n* (%)	0 (0.0)	23 (8.2)	0.322	2 (12.5)	21 (7.6)	0.366
NIHSS at 24 h, md (IQR)	18 (13–22)	7 (2–16)	**0.006**	12 (6–22)	7 (2–16)	0.068
ΔNIHSS, md (IQR)[d]	0 (−3 to 9)	6 (1–10)	**0.041**	3 (0–6)	6 (1–10)	0.081
Days from EVT to antithrombotic therapy, md (IQR)	11 (7–12)	2 (1–4)	**<0.001**	3 (1–8)	2 (1–4)	**0.032**
Stroke recurrence during hospitalization, *n* (%)	1 (9.1)	10 (3.6)	0.350	0 (0.0)	11 (4.0)	0.531

Note: Boldface indicates statistically significant.

Abbreviations: aPH, asymptomatic parenchymal haemorrhage; EVT, endovascular treatment; IQR, interquartile rang; LVO, large vessel occlusion; md, median; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale.

[a]Patients (*n* = 23) with symptomatic intracranial haemorrhage were excluded from the analysis.

[b]Versus posterior circulation LVO.

[c]Information available for 218 patients.

[d]ΔNIHSS is calculated as the baseline NIHSS score − the NIHSS score at 24 h.

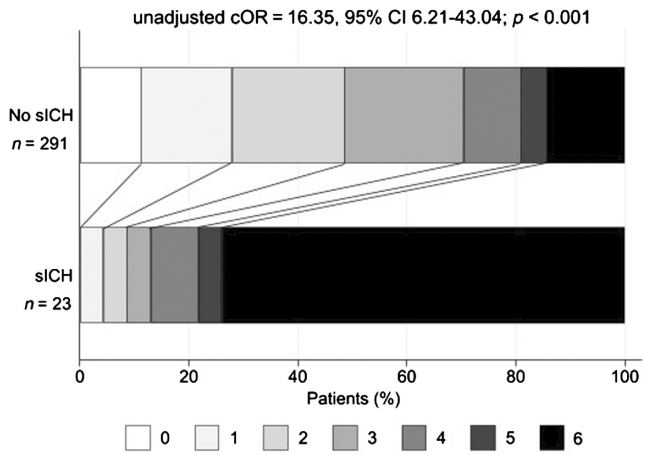

FIGURE 1 Shift analysis on the modified Rankin Scale score at 3 months of follow-up according to symptomatic intracranial haemorrhage (sICH). CI, confidence interval; cOR, common odds ratio.

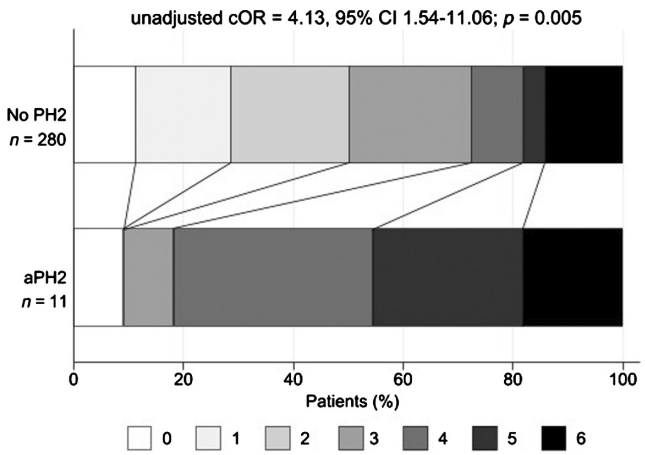

FIGURE 2 Shift analysis of the modified Rankin Scale score at 3 months of follow-up according to asymptomatic parenchymal haemorrhage type 2 (aPH2). CI, confidence interval; cOR, common odds ratio.

thrombolysis, number of passes, successful recanalization, and previous mRS score, aPH2 was independently associated with a worse functional outcome, with a common OR of 3.32 (95% CI = 1.16–9.57, *p* = 0.026; see Table 3).

At 3 months of follow-up, 58 (18.5%) patients had died. In the bivariate logistic regression analysis, sICH was associated with increased mortality. Neither aPH2 nor aPH1 showed a significant association with mortality, as indicated by an OR of 1.41 (95%

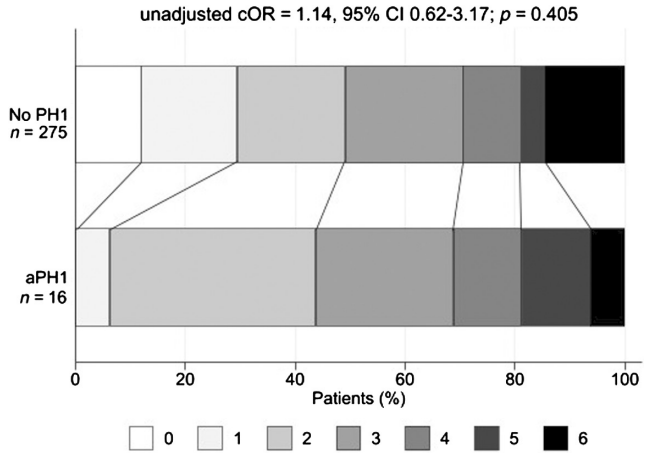

FIGURE 3 Shift analysis of the modified Rankin Scale score at 3 months of follow-up according to asymptomatic parenchymal haemorrhage type 1 (aPH1). CI, confidence interval; cOR, common odds ratio.

TABLE 3 Multivariable ordinal regression analysis of predictors of unfavourable functional outcome at 3 months of follow-up.

Predictor	cOR	95% CI	*p*
aPH2	3.32	1.16–9.57	**0.026**
Age	1.03	1.04–1.04	**0.001**
Admission NIHSS	1.09	1.05–1.13	**<0.001**
ASPECTS scale	0.81	0.68–0.95	**0.011**
Thrombolysis	0.73	0.47–1.14	0.168
Number of passes	1.21	1.07–1.37	**0.003**
Successful recanalization	0.26	0.11–0.59	**0.001**
Previous mRS	1.84	1.45–2.32	**<0.001**

Note: Boldface indicates statistically signifcant.

Abbreviations: aPH2, asymptomatic parenchymal haemorrhage type 2; ASPECTS, Alberta Stroke Program Early CT Score; CI, confidence interval; cOR, common odds ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

CI = 0.29–6.74, $p = 0.670$) and 0.89 (95% CI = 0.19–4.04, $p = 0.876$), respectively (see Table S2).

The proportion of favourable outcome at 3 months of follow-up (defined as mRS score = 0–2) was 9.1% in patients with aPH2, compared to 50.4% in patients without (excluding sICH), which represents a risk ratio of 0.19 (95% CI = 0.03–0.25, $p = 0.013$). No statistically significant differences were found in patients with aPH1 compared to patients without (after excluding sICH and aPH2). In the multivariable logistic regression analysis, presenting an aPH2 was again associated with lower odds of achieving a favourable outcome (OR = 0.11, 95% CI = 0.02–0.98, $p = 0.049$). This OR was adjusted for age, admission NIHSS, baseline ASPECTS, number of passes, successful recanalization, and previous mRS score.

The ROC analysis evaluating the predictive value of sICH for favourable outcome revealed an AUC of 0.55, with a sensitivity of 98.6% and specificity of 12.4%. Upon inclusion of aPH2, the AUC improved to 0.59, with a sensitivity of 97.9% and a specificity of 20.8%. Although modest, this difference was statistically significant, with a *p*-value of 0.001.

DISCUSSION

In patients with AIS who were treated with EVT, we found that aPH2 was associated with worse functional outcome at 3 months of follow-up. Additionally, aPH2 increased the predictive capacity, compared to sICH alone, to determine unfavourable outcome. Our results are relevant in several ways.

First, we found that the presence of a PH2 in the follow-up CT scan of stroke patients treated with EVT was associated with poor functional outcome, regardless of the impact on the neurological deficit during the acute phase. Our results are in line with those recently published by van der Steen et al. [23], and confirm that some subtypes of aICH may also be associated with worse functional outcome. Our findings highlight the need to redefine what is considered symptomatic and asymptomatic. They demonstrate that some radiological subtypes such as PH2 (regardless of symptoms) should be deemed as an additional safety marker alongside sICH in future EVT trials, enhancing the overall safety assessment.

Second, we observed that aPH2 was associated with reduced early neurological recovery, as shown by significantly smaller ΔNIHSS variations at 24 h. This finding may explain in part the association with poorer functional outcome, but the reason behind this observation should be further explored in future studies. One of our hypotheses is related to the underlying pathophysiology of cerebral haemorrhage. In a brain already affected by ischaemic damage, the additional injury caused by the presence of blood could have a summative harmful impact due to mass effect and perihematomal or remote ischaemia (even if it does not result in early neurological deterioration). Moreover, blood has direct deleterious effects that may compromise early neuronal plasticity. These are mediated by several mechanisms, including cytotoxicity, hypermetabolism, excitotoxicity, spreading depression, oxidative stress, and inflammation [27]. In this line, another plausible theory might be that PH2 may hinder the brain's ability to fully utilize its pre-existing functional reserve in the acute/subacute phase of rehabilitation, thereby potentially impeding brain recovery via neuroplasticity processes.

Another hypothesis would be that patients who develop aPH1 or aPH2 may experience a delay in the initiation of antithrombotic therapy, potentially elevating the risk of ischaemic recurrence during hospitalization. Our analysis confirmed that both asymptomatic PH subtypes deferred the start of antithrombotic agents. However, this delay did not contribute to a higher incidence of recurrences in our population.

We also raise the possibility that the reason may lie in the definition we use for sICH, as previously mentioned by a recent article [28]. On the one hand, this definition does not consider the causal

relationship between the haemorrhage and the neurological deterioration, so the prognosis of these patients could be determined by other causes, such as infectious complications, epileptic seizures, drug used during hospitalization, et cetera. On the other hand, the NIHSS may not detect relevant clinical changes that influence functional prognosis, leading us to consider asymptomatic, for example, a motor deterioration in the dominant hand, greater aphasia, or increased gait instability, among others.

Finally, we did not find any association between aPH2 and mortality. Whereas sICH determines high mortality rates, aPH2 serves as a predictor of unfavourable outcome in stroke survivors, as demonstrated by the shift analyses presented in Figures 1 and 2. Hence, we believe that PH2, regardless of whether it is asymptomatic, should be considered as a safety indicator in future EVT trials together with sICH, as both are linked to patient outcomes.

Our study has several limitations that should be acknowledged. First, this study is unicentric and has a retrospective design, which may restrict its external generalizability. Second, the small number of events could have introduced statistical bias and could limit the precision of our findings (there is risk for overadjustment of the multivariable regression models). Additionally, we concede that the lack of data collection on some variables (arterial pressure at admission, platelets and coagulation on baseline blood test, previous antithrombotic treatment, presence of microbleeds, and degree of collateral circulation) may impact the comprehensiveness of our analysis.

In conclusion, in patients with AIS treated with EVT, aPH2 is independently associated with unfavourable functional outcome. Furthermore, combining this subtype of HT with sICH enhances the predictive capacity for poor prognosis compared with sICH alone. These findings suggest that aPH2 could potentially serve as a safety outcome measure alongside sICH in future EVT trials. The identification and monitoring of aPH2 in clinical practice may contribute to improved risk assessment and management strategies in patients undergoing EVT.

AUTHOR CONTRIBUTIONS

Clara Toscano-Prat: Conceptualization; investigation; methodology; formal analysis; writing – original draft; writing – review and editing. **José Pablo Martínez-González:** Investigation; validation. **Marina Guasch-Jiménez:** Validation. **Anna Ramos-Pachón:** Validation. **Joan Martí-Fàbregas:** Validation. **Nerea Blanco-Sanroman:** Validation. **Melissa Fabiola Coronel-Coronel:** Validation. **María Constanza Domine:** Validation. **Alejandro Martínez-Domeño:** Validation. **Luis Prats-Sánchez:** Validation. **Rebeca Marín:** Validation. **Ana Aguilera-Simón:** Validation. **Álvaro Lambea-Gil:** Validation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X
2. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973
3. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442
4. Wang L, Xiong Y. Advances in futile reperfusion following endovascular treatment in acute ischemic stroke due to large vessel occlusion. *Eur Neurol*. 2023;86(2):95-106. doi:10.1159/000528922
5. Nie X, Leng X, Miao Z, Fisher M, Liu L. Clinically ineffective reperfusion after endovascular therapy in acute ischemic stroke. *Stroke*. 2023;54(3):873-881. doi:10.1161/STROKEAHA.122.038466
6. Lees KR. ECASS-II: intravenous alteplase in acute ischaemic stroke. *Lancet*. 1999;353(9146):65-66. doi:10.1016/S0140-6736(05)74846-7
7. von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg bleeding classification. *Stroke*. 2015;46(10):2981-2986. doi:10.1161/STROKEAHA.115.010049
8. van Kranendonk KR, Treurniet KM, Boers AMM, et al. Hemorrhagic transformation is associated with poor functional outcome in patients with acute ischemic stroke due to a large vessel occlusion. *J Neurointerv Surg*. 2019;11(5):464-468. doi:10.1136/neurintsurg-2018-014141
9. Strbian D, Sairanen T, Meretoja A, et al. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology*. 2011;77(4):341-348. doi:10.1212/WNL.0b013e3182267b8c
10. Raychev R, Jahan R, Liebeskind D, et al. Determinants of intracranial hemorrhage occurrence and outcome after Neurothrombectomy therapy: insights from the solitaire FR with intention for thrombectomy randomized trial. *AJNR Am J Neuroradiol*. 2015;36(12):2303-2307. doi:10.3174/ajnr.A4482
11. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587
12. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018. doi:10.1056/NEJMoa1414792
13. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030. doi:10.1056/NEJMoa1414905
14. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061
15. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306. doi:10.1056/NEJMoa1503780
16. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15(11):1138-1147. doi:10.1016/S1474-4422(16)30177-6

17. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the pragmatic Ischaemic stroke thrombectomy evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88(1):38-44. doi:10.1136/jnnp-2016-314117
18. Martins SO, Mont'Alverne F, Rebello LC, et al. Thrombectomy for stroke in the public health care system of Brazil. *N Engl J Med*. 2020;382(24):2316-2326. doi:10.1056/NEJMoa2000120
19. Kent DM, Hinchey J, Price LL, Levine SR, Selker HP. In acute ischemic stroke, are asymptomatic intracranial hemorrhages clinically innocuous? *Stroke*. 2004;35(5):1141-1146. doi:10.1161/01.STR.0000125712.02090.6e
20. Libman R, Kwiakowski T, Lyden P, et al. Asymptomatic hemorrhagic transformation of cerebral infarction does not worsen long-term outcome. *J Stroke Cerebrovasc Dis*. 2005;14(2):50-54. doi:10.1016/j.jstrokecerebrovasdis.2004.11.002
21. Dzialowski I, Pexman JHW, Barber PA, Demchuk AM, Buchan AM, Hill MD. Asymptomatic hemorrhage after thrombolysis may not Be benign. *Stroke*. 2007;38(1):75-79. doi:10.1161/01.STR.0000251644.76546.62
22. Park JH, Ko Y, Kim WJ, et al. Is asymptomatic hemorrhagic transformation really innocuous? *Neurology*. 2012;78(6):421-426. doi:10.1212/WNL.0b013e318245d22c
23. van der Steen W, van der Ende NAM, Luijten SPR, et al. Type of intracranial hemorrhage after endovascular stroke treatment: association with functional outcome. *J Neurointerv Surg*. 2022;15:971-976. doi:10.1136/jnis-2022-019474
24. Tang G, Cao Z, Luo Y, Wu S, Sun X. Prognosis associated with asymptomatic intracranial hemorrhage after acute ischemic stroke: a systematic review and meta-analysis. *J Neurol*. 2022;269(7):3470-3481. doi:10.1007/s00415-022-11046-6
25. Adams HP, Bendixen BH, Kappelle LJ, 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*. 1993;24(1):35-41. doi:10.1161/01.STR.24.1.35
26. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early Management of Patients with Acute Ischemic Stroke: 2019 update to the 2018 guidelines for the early Management of Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211
27. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage. *Stroke*. 2011;42(6):1781-1786. doi:10.1161/STROKEAHA.110.596718
28. Seners P, Wouters A, Maïer B, et al. Role of brain imaging in the prediction of intracerebral hemorrhage following endovascular therapy for acute stroke. *Stroke*. 2023;54:2192-2203. doi:10.1161/STROKEAHA.123.040806

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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