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CLINICAL INVESTIGATION STROKE/NEUROINTERVENTIONS

# Predictors and Prognostic Implications of Hemorrhagic Transformation Following Cerebral Endovascular Thrombectomy in Acute Ischemic Stroke: A Multicenter Analysis

A. Honig[1] · J. Molad[2] · A. Horev[3] · N. Simaan[1] · T. Sacagiu[1] · A. Figolio[1] · J. M. Gomori[4] · H. Hallevi[2] · E. Seyman[2] · O. Rotschild[2] · F. Alguayn[3] · M. J. Star[3] · T. Jonas-Kimchi[5] · U. Sadeh[5] · J. E. Cohen[6] · R. R. Leker[1]

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## Abstract

*Purpose* Hemorrhagic transformation (HT) following cerebral endovascular thrombectomy (EVT) for large vessel occlusion (LVO) in acute ischemic stroke is associated with poor outcome. Recent studies have shown that EVT can be efficacious in imaging-selected patients as late as 6–24 h from onset (late time window; LTW). We sought to determine predictors and prognostic implications of HT following EVT in LTW.

*Methods* Consecutive patients undergoing EVT for LVO were recruited into a prospective multicenter database. HT was divided into petechial hemorrhagic-infarction and parenchymal hematoma (PH) type 1 or 2 defined as confluent hemorrhage covering < or > than 1/3 of the infarct volume, respectively. Multivariate analyses were performed to determine variables associated with HT subtypes.

*Results* Among 611 patients included (mean age 70.5 ± 12.5 years; median NIHSS 16), 115 (18.8%) had HT and 33 of them (5.4%) had PH2. Independent PH2 predictors included failed recanalization (OR 7.0, 95% CI 2.3–21.6), longer time from symptom onset to admission (OR 1.002 per minute 95% CI 1.001–1.003) and hyperlipidemia (OR 3.12; 95%CI 1.12–8.7). HT was not associated with outcome. In contrast, PH2 patients had lower favorable outcome rates (14.3 vs 41.6%, $p = 0.004$) and higher mortality rates (39 vs 17%, $p = 0.001$). Patients who underwent EVT in the late versus early window had similar PH2 rates (4.5 vs 6.7%, $p = 0.27$). In multivariate models, PH2 tripled the odds of both 90-day poor outcome (OR 3.1, 95% CI 1.01–9.5) and 90-day mortality (OR 3.2, 95% CI 1.4–7.3).

*Conclusions* PH2 following EVT is associated with increased mortality and unfavorable outcome rates. Rates of PH2 are not different between LTW patients and those treated < 6 h from symptom onset.

**Keywords** Hemorrhagic transformation · Endovascular thrombectomy · Parenchymal hematoma

✉ A. Honig
Asaf.honig2@gmail.com

[1] Departments of Neurology, Hadassah-Hebrew University Medical Center, P.O. Box 12000, 91120 Jerusalem, Israel

[2] Department of Stroke and Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

[3] Department of Neurology, Soroka- University Medical Center, Beer-Sheva, Israel

[4] Department of Radiology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

[5] Departments of Radiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[6] Departments of Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

## Introduction

Hemorrhagic transformation (HT) following endovascular thrombectomy (EVT) for large vessel occlusion (LVO) in acute ischemic stroke (AIS) is associated with poor outcome [1]. However, data regarding the frequencies and

prognostic impact of HT subtypes following EVT are limited. Furthermore, the large trials exploring the benefits of EVT in late time windows [2, 3] included patients with occlusions in either the internal carotid artery (ICA) or M1 segment of the middle cerebral artery (MCA) or both and excluded other territories such as the basilar, anterior or posterior cerebral arteries (ACA, PCA, respectively) [4]. DEFUSE-3 [2] and DAWN [3] showed the benefit of EVT in the late window for patients selected based on perfusion imaging (6–16 h and 6–24 h from symptom onset, respectively) on 90-day functional outcome. Given the rising popularity of EVT in these territories and especially in patients with medium vessel occlusions (MeVO) [5], we have included them in our cohort. As recent guidelines allow EVT for LVO in imaging-based selected AIS in the late (6–24 h from onset) time windows, we sought to determine predictors and prognostic implications of HT following EVT in these different time frames.

## Methods

All consecutive patients undergoing EVT for LVO in three participating academic centers were recruited into a prospective ongoing database. The data were pooled and retrospectively analyzed per prespecified protocol. The study was approved by the institutional review boards of the participating centers with a waiver of informed consent.

The current study included patients who experienced an acute ischemic stroke with LVO or MeVO proven on vascular imaging. Unless there was a contraindication, the preferred vascular imaging upon arrival was CT Angiography (CTA) from the arch of the aorta to the vertex of head. CTA included two phases, arterial and venous, in order to detect either cerebral venous thrombosis or arteriovenous malformations and to determine early and delayed collateral filling. Whenever using iodine contrast was contraindicated (chronic renal failure, Iodine contrast allergy, pregnancy), a Magnetic Resonance Angiography (MRA) was performed with additional Flair, DWI, SWI and Perfusion imaging sequences. Patients with ICA, M1 and M2 MCA, tandem occlusions, basilar, A1 and A2 ACA, and P1 PCA occlusions on digital subtraction angiography (DSA) were included.

Patients presenting in the early time window (< 6 h from onset or last seen normal) were chosen for EVT based on Alberta Stroke Program Early CT Score (ASPECTS) of 6 and above and favorable collateral scores (4–5) while perfusion imaging was not mandatory. The ASPECTS is a quantitate score that measures the extent of early ischemic changes in anterior circulation hyperacute ischemic stroke. The maximal ASPECTS score is 10 and one point is deducted for each of the ten MCA territory zones whenever it shows hypodensity. However, in the late time window (> 6 h and < 24 h from last seen normal) we have applied radiological selection criteria similar to those used in the DEFUSE-3 trial using perfusion CT or MRI studies (supplemental material) [2]. Patients with either missing or controversial details regarding time of symptom onset or last seen normal were excluded from the analysis comparing early versus delayed patient groups.

All included patients underwent EVT with device use at the discretion of the treating endovascular specialist. Patients that underwent bridging intravenous tPA thrombolysis (IV-tPA) prior to EVT were included. All patients were treated with similar institutional protocols including intensive care unit admissions post-procedure. All patients underwent either CTA or MRA upon Emergency Room (ER) admission and a repeated non-contrast head CT (NCCT) 24 h post-procedure prior to initiating antiplatelet or anticoagulation treatment. Following carotid stent insertion patients were treated with dual antiplatelet therapy of Aspirin and Clopidogrel prior to the repeated NCCT. Carotid stents were inserted during the EVT procedure at the discretion of the treating physicians.

We collected demographic and vascular risk factors. Neurological deficits were measured using the National Institutes of Health Stroke Scale (NIHSS) at admission and discharge [6]. Stroke etiology was classified with the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification [7]. We also assessed time metrics and imaging variables including ASPECTS [8] before and after treatment. Collateral status was assessed according to the ASPECTS collateral grading scale on the admission CTA [9]. Good collaterals were defined as having score of 4–5.

Data on procedural variables including the modified thrombolysis in cerebral infarction (mTICI) score [10] at the end of the procedure and the number of passes needed to achieve the best possible recanalization were also studied. mTICI2b-3 was considered as successful target vessel recanalization.

We used post-EVT NCCT data to classify HT according to the ECASS-2 criteria [11] into petechial hemorrhagic-infarction (HI) and parenchymal hematoma (PH) type 1 or 2 defined as confluent hemorrhage covering < or > than 1/3 of the infarct volume, respectively [12]. Imaging studies were reviewed by experienced stroke neurologists and neuroradiologists blinded to the clinical scenario and degree of HT was adjudicated by discussion and agreement. Nine experts read the imaging (three on each site) with an interobserver agreement that was almost perfect for the presence of HT (Cohen's κ 0.93, 95% CI 0.9–0.96) and strong for the presence of PH2 (Cohen's κ 0.85, 95% CI 0.78–0.92). Symptomatic intracerebral hemorrhage (sICH) was defined as any apparent extravascular blood in the brain or within the cranium that was associated with

clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurological deterioration [13].

Functional outcome was assessed with the modified Rankin scale (mRS) [14] prior to stroke, upon discharge and 90 days from stroke. Good functional outcome was defined as either an mRS $\leq 2$ for patients with baseline mRS $\leq 2$ or mRS 3 in patients that had mRS 3 on admission. 90-day mortality was used as a secondary outcome parameter.

### Statistical Analysis

Statistical analysis was performed using the SPSS 25 (IBM USA). $P < 0.05$ was considered significant. The $x^2$ test was used to explore the link between qualitative variables. The student's $t$ test was used to compare quantitative variables. The Mann–Whitney $U$ test was used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Included in the multivariate models were age, sex and predictors who were found significant in the univariate analysis.

## Results

The study included 611 consecutive patients with either LVO or MeVO that underwent EVT (mean age 70.6 ± 13.8, 50.4% males). The baseline characteristics of the study population are presented in Table 1S. 560 patients underwent EVT in the anterior circulation (Carotid, MCA, ACA) and 51 in the posterior circulation (Basilar, Vertebral and PCA arteries). All patients had follow-up NCCT obtained 24 h after EVT and HT was detected in 115 (18.8%, Table 2S). Smoking (35 vs 25%, $p = 0.025$) and chronic renal failure (11 vs 6%, $p = 0.035$) were more common in patients with HT but other baseline characteristics did not differ.

PH2 was identified in 33 patients (Table 1). Patients with PH2 presented later from symptom onset (315 ± 461 vs 175 ± 218 min, $p = 0.003$), more commonly had hyperlipidemia (64 vs. 46% $p = 0.047$) and less commonly achieved favorable recanalization (69 vs 87%, $p = 0.004$). Patients with PH2 showed less neurological improvement at 24 h following EVT [delta NIHSS 2 (0–7) vs 7 (2–13), $p = 0.013$]. There was a tendency toward higher number of passes in patients that ultimately developed PH2, but the difference did not reach statistical significance [2 (1–4) vs 2 (1–3), $p = 0.07$].

Multivariate analysis (Table 2) showed that failure to achieve TICI2b-3 (OR 6.98; 95% CI 2.26–21.56,

**Table 1** Characteristics of patients with and without PH2

| Characteristics | PH2 $N = 33$ | No PH2 $N = 578$ | $P$ |
|---|---|---|---|
| Age ± SD | 72.42 ± 10.16 | 70.39 ± 13.90 | 0.056 |
| Male (%) | 20 (61) | 288 (49) | 0.207 |
| Hypertension (%) | 22 (67) | 399 (68) | 0.842 |
| Diabetes (%) | 13 (39) | 193 (33) | 0.452 |
| Hyperlipidemia (%) | 21 (64) | 268 (46) | **0.047** |
| Smoking (%) | 10 (30) | 155 (27) | 0.639 |
| Atrial fibrillation (%) | 17 (52) | 251 (43) | 0.336 |
| Ischemic heart disease (%) | 12 (36) | 203 (34) | 0.851 |
| Valvular disease (%) | 0 (0) | 43 (9) | 0.095 |
| Congestive heart failure (%) | 2 (9) | 44 (10) | 0.980 |
| Chronic renal failure (%) | 0 (0) | 39 (7) | 0.125 |
| Prior stroke (%) | 5 (15) | 78 (13) | 0.769 |
| Statins (%) | 11 (34) | 171 (32) | 0.804 |
| Antiplatelets (%) | 9 (32) | 132 (28) | 0.675 |
| Coumadin (%) | 1 (3) | 50 (9) | 0.260 |
| NOACs (%) | 3 (9) | 62 (11) | 0.776 |
| IV-tPA (%) | 6 (21) | 161 (34) | 0.165 |
| Vessel lesion (%) | | | 0.963 |
| ICA | 9 (28) | 173 (30) | |
| M1 MCA | 19 (59) | 299 (52) | |
| M2 MCA | 2 (6) | 56 (10) | |
| ACA | 0 (0) | 3 (0.5) | |
| Vertebral | 0 (0) | 2 (0.3) | |
| Basilar | 2 (6) | 40 (7) | |
| PCA | 0 (0) | 7 (1) | |
| Anterior circulation (%) | 31 (94) | 529 (92) | 0.238 |
| Posterior circulation (%) | 2 (6) | 49 (8) | |
| Tandem lesion | 3 (9) | 82 (14) | 0.416 |
| TOAST (%) | | | 0.796 |
| Cardioembolism | 21 (66) | 347 (60) | |
| Large-artery atherosclerosis | 6 (19) | 128 (22) | |
| Other determined etiology | 3 (9) | 19 (3) | |
| Undetermined | 3 (9) | 82 (14) | |
| Carotid stent | 8 (24) | 91 (16) | 0.187 |
| TICI 2b-3 (%) | 22 (69) | 502 (87) | **0.004** |
| Collaterals ## (SD) | 3.17 (1.31) | 3.53 (1.24) | 0.178 |
| Good collateral score (%) | 2/19 (10.5) | 65/262 (24.8) | 0.158 |
| Symptom onset to door in minutes (SD) | 315 (461) | 175 (218) | **0.003** |
| Door to imaging in minutes (SD) | 28 (16) | 34 (51) | 0.554 |
| Symptom onset to groin puncture in minutes (SD) | 395 (452) | 319 (267) | 0.157 |

**Table 1** continued

| Characteristics | PH2 $N = 33$ | No PH2 $N = 578$ | $P$ |
|---|---|---|---|
| Number of passes (IQR) | 2 (1–4) | 2 (1–3) | 0.072 |
| NIHSS on admission median (IQR) | 17 (12–22) | 16 (11–20) | 0.117 |
| NIHSS on discharge median (IQR) | 10 (3–18) | 5 (2–10) | **0.004** |
| †Delta NIHSS median (IQR) | 2 (0–7) | 7 (2–13) | **0.013** |
| ASPECTS on admission (SD) | 9 (2) | 9 (1) | 0.415 |
| †ASPECTS post (SD) | 5 (3) | 7 (3) | **0.003** |
| MRS before stroke median (IQR) | 0 (0–1) | 0 (0–2) | 0.165 |
| MRS discharge median (IQR) | 5 (4–6) | 4 (2–5) | **< 0.001** |
| MRS 90 median (IQR) | 3 (4–6) | 3 (2–5) | **< 0.001** |
| mRS ≤ 2 on discharge (%) | 3 (9) | 177 (30.6) | **0.01** |
| ‡ mRS ≤ 2 on day 90 (%) | 4/28 (14.3) | 177/471 (37.6) | **0.012** |
| §Good functional outcome (%) | 4/28 (14.3) | 196/471 (41.6) | **0.004** |
| 90-day mortality (%) | 13 (39) | 97 (17) | **0.001** |

Bold values are statistically significant ($p < 0.05$)

† Per assessment on 24 h post-procedure

‡Analysis was performed without one center due to incomplete follow-up data

§ Either mRS ≤ 2 or mRS 3 before stroke who remained mRS 3 on day 90

**Table 2** Multivariate analysis for predictors of PH2

| | OR | 95% CI | | $P$ |
|---|---|---|---|---|
| Age (per year) | 1.01 | 0.97 | 1.05 | 0.563 |
| Sex (female) | 0.67 | 0.23 | 1.92 | 0.457 |
| Hyperlipidemia | 3.12 | 1.12 | 8.7 | **0.029** |
| Number of passes | 1.06 | 0.9 | 1.25 | 0.47 |
| Failure to achieve TICI 2B-3 | 6.984 | 2.263 | 21.558 | **0.001** |
| Symptom to door (per minute) | 1.002 | 1.001 | 1.003 | **0.007** |

Bold values are statistically significant ($p < 0.05$)

$p = 0.001$), longer duration from symptom onset to ER arrival (OR 1.002 per minute, 95% CI 1.001–1.003, $p = 0.007$) and hyperlipidemia (OR 3.12; 95%CI 1.12–8.7, p = 0.029) remained significant predictors of PH2 development.

sICH was diagnosed in 16 patients (2.6%) and all had PH2 (Tables 3S, 4S). In comparison to patients without sICH (Table 3S) patients with sICH less often had 90-day good functional outcome (6 vs 44%, $p = 0.005$) and more often increased 90-day mortality (44 vs 17%, $p = 0.006$). Due to the small number of patients with sICH, we focused all statistical analyses on PH2.

We next evaluated whether treatment in later time windows (6–24 h from symptom onset) affects likelihoods of HT and PH2 development (Table 3). Accurate time of onset was available for 536 patients (87.7% of patients). Early-window patients (0–6 h from symptom onset) presented with higher median NIHSS [17 (12–21) vs 15 (10–18), $p < 0.001$], more often had cardioembolic stroke (60 vs 43%, $p = 0.0004$) and more commonly received IV-tPA (44 vs. 28%, $p = 0.0003$). In contrast, in late-window patients, LVO was more commonly attributed to atherosclerotic disease (24 vs 45.3%, $p < 0.0001$) and they more often had favorable collaterals (53.3 vs 35.1%, $p = 0.005$). However, rates of successful recanalization, HT, total PH (PH1 and PH2), PH2 and sICH were similar.

Early-window patients improved to greater extent from baseline to 24 h post-EVT [median delta NIHSS 9 (3–11) vs 7 (1–11), $p = 0.001$] but the absolute discharge NIHSS and rates of good functional outcome and survival were similar (Table 3).

Fifty-one patients (8.3%) underwent an EVT in the posterior circulation. Rates of PH2 were similar between the anterior and posterior circulation LVO (5.5 vs. 3.9%, $p = 0.24$).

Rates of PH2 among LVO strokes (ICA, M1-MCA and basilar arteries; 30/542—5.5%) were similar to MeVO strokes (M2-MCA, A1-ACA, P1-PCA, Vertebral arteries; 2/69—2.9%) ($p = 0.35$).

Finally, we examined the association of PH2 with outcome at discharge and at 90 days post-EVT. On univariate analysis, patients that experienced a PH2 were discharged with higher median NIHSS [10 (3–18) vs 5 (2–10), $p = 0.004$], had lower rates of favorable outcomes on discharge (9 vs 31%, $p = 0.01$) and had higher median mRS upon discharge [5 (4–6) vs 4 (2–5), $p < 0.0001$].

Similar analyses performed at 90 days post-stoke were completed in 499 patients only since data regarding mRS 90 were missing in one center. However, baseline criteria including stroke severity and etiology, and discharge outcomes were similar between patients with and without 90-day mRS scores. On day-90, PH2 patients had lower rates of favorable functional outcome (14.3 vs 41.8%, $p = 0.004$) and higher mortality rates (39 vs 17%, $p = 0.001$). On multivariate analysis (Table 4), PH2 remained an independent predictor of poor functional outcome (OR 3.1, 95% CI 1.01–9.5, $p = 0.048$) as were stroke severity, failure to achieve successful target vessel recanalization and age.

Mortality data were available for all 611 patients. On multivariate analysis (Table 5), PH2 was associated with mortality (OR 3.2, 95% CI 1.4–7.3, $p = 0.005$) as were failure to achieve TICI 2b-3 (OR 2.72, 95% CI 1.5–4.8, $p = 0.001$) and higher admission mRS (OR 1.46, 95% CI 1.22–1.74, $p < 0.001$).

**Table 3** Patient's characteristics for EVT before and after 6 h from symptom onset

| | < 6 h *N* = 357 | > 6 h *N* = 179 | *p* |
|---|---|---|---|
| Age ± SD | 71.44 ± 13.8 | 70.58 ± 13.22 | 0.487 |
| Male (%) | 174 (49) | 88 (49) | 0.926 |
| Hypertension (%) | 232 (65) | 129 (72.5) | 0.082 |
| DM (%) | 109 (30.5) | 64 (36) | 0.223 |
| Hyperlipidemia (%) | 160 (45) | 93 (52) | 0.119 |
| Smoking (%) | 94 (26.3) | 41 (23) | 0.408 |
| IHD (%) | 132 (37) | 59 (33) | 0.36 |
| CHF (%) | 27/237 (11.4) | 16/162 (9.9) | 0.632 |
| CRF (%) | 24 (6.7) | 9 (5) | 0.441 |
| Previous stroke (%) | 53 (15) | 21 (11.7) | 0.324 |
| Statins (%) | 109 (30.7) | 63 (35.3) | 0.3 |
| Antiplatelet % | 87 (24.4) | 50 (28) | 0.286 |
| Coumadin (%) | 38 (10.6) | 10 (5.6) | 0.055 |
| NOAC (%) | 44 (12) | 19 (10.6) | 0.54 |
| Anticoagulation | 82 (23) | 29 (16) | 0.07 |
| IV-tPA (%) | 157 (44) | 50 (28) | **0.0003** |
| AF (%) | 178 (50) | 71 (40) | **0.026** |
| Valvular dis (%) | 35 (10) | 7 (4) | **0.025** |
| Cardioembolic (%) | 213 (60) | 78 (43.6) | **0.0004** |
| Atherosclerosis (%) | 75 (24.1) | 62 (45.3) | **0.000** |
| Tandem (%) | 44 (12) | 29 (16) | 0.23 |
| Good collaterals (%) | 66 (35.1) | 24 (53.3) | **0.005** |
| Number of passes median (IQR) | 2 (1–3) | 2 (1–3) | 0.415 |
| First pass (%) | 121 (48.4) | 32 (34.8) | **0.025** |
| TICI2b3 | 301 (84.3) | 151 (84.3) | 0.98 |
| NIHSS admission median (IQR) | 17 (12–21) | 15 (10–18) | **0.000** |
| †NIHSS delta median (IQR) | 9 (3–14) | 7 (1–11) | **0.001** |
| NIHSS discharge median (IQR) | 5 (2–10) | 5 (2–10) | 0.403 |
| ASPECT admission (SD) | 8.8 (1.3) | 8.8 (1.2) | 0.357 |
| †ASPECT post (SD) | 6.8 (2.9) | 7.3 (2.4) | 0.204 |
| HT (%) | 66 (18.5) | 28 (15.6) | 0.454 |
| PH total-PH1 and PH2 (%) | 50 (14) | 30 (16.8) | 0.4 |
| PH2 (%) | 16 (4.5) | 12 (6.7) | 0.268 |
| Symptomatic ICH (%) | 11 (3) | 2 (1) | 0.167 |
| mRS discharge median (IQR) | 4 (2–5) | 4 (3–5) | 0.162 |
| ‡mRS 90 median (IQR) | 3 (2–5) | 3 (2–5) | 0.835 |
| 90-day survival (%) | 297/355 (83.7) | 143/177 (80.8) | 0.409 |
| §90-day Good Functional Outcome (%) | 195/323 (60.4) | 75/118 (63.5) | 0.543 |

Bold values are statistically significant ($p < 0.05$)

†Per assessment on 24 h post-procedure

‡Analysis was performed without one center (*n*-112) due to incomplete follow-up data

§ Either mRS ≤ 2 or mRS 3 before stroke who remained mRS 3 on day 90

## Discussion

The main findings of the current study are that PH2 type of HT is not rare after EVT and is associated with poor outcome. We also show that the rates of HT and PH2 were similar between early- and late-window-treated patients and between LVO and MeVO patients.

PH2 was detected in 5.5% of our patients and was associated with lower rates of favorable functional outcomes at discharge and at 90 days and higher mortality rates at 90-day. These findings are not surprising and corroborate previous publications [1, 15]. However, our findings are novel for showing the safety of EVT procedures in MeVO patients with distal M1 and M2 MCA segments and

**Table 4** Multivariate analysis for predictors of 90-day poor functional outcome

| | OR | 95% CI | | *P* |
|---|---|---|---|---|
| Age (per year) | 1.032 | 1.016 | 1.047 | **0.0001** |
| Sex (male) | 1.002 | 0.67 | 1.5 | 0.99 |
| PH2 | 3.1 | 1.01 | 9.54 | **0.048** |
| Admission NIHSS (per unit) | 1.06 | 1.03 | 1.1 | **0.0001** |
| Failure to achieve TICI 2B-3 | 9 | 3.9 | 20.8 | **0.0001** |

Bold values are statistically significant ($p < 0.05$)

**Table 5** Multivariate analysis for predictors of 90-day mortality

| | OR | 95% CI | | *P* |
|---|---|---|---|---|
| Age (per year) | 1.034 | 1.013 | 1.056 | **0.001** |
| Sex (male) | 1.064 | 0.658 | 1.721 | 0.8 |
| PH2 | 3.226 | 1.442 | 7.353 | **0.005** |
| Admission NIHSS (per unit) | 1.037 | 0.999 | 1.077 | 0.055 |
| Failure to achieve TICI 2B-3 | 2.72 | 1.545 | 4.784 | **0.001** |
| Admission mRS (per unit) | 1.46 | 1.225 | 1.74 | **< 0.001** |

Bold values are statistically significant ($p < 0.05$)

PCA ACA and vertebral occlusions that were all excluded from the late-window clinical trials [2, 3]. This finding is reassuring and provides further evidence as to the generalizability of randomized study data. These findings can be attributable to the meticulous selection process of patients beyond 6 h in the current cohort. Patients were chosen for EVT based on good ASPECT score, favorable collateral scores and perfusion CT or MRI studies showing a small core and large penumbra.

Interestingly, our study indicates that the most common underlying etiology of patients in the delayed window was mainly atherosclerotic while in the patients treated in the early time window the leading etiology was cardioembolic. This may imply that patients with chronic atherosclerotic disease have built more collaterals during the years and perhaps their better collateral score represents a marker of ischemic preconditioning which may be responsible for the low rates of HT in this subpopulation. Another plausible explanation to the similar rates of HT and PH2 in the early and late time windows is the similar rate of successful target vessel recanalization which appears to be a prominent determinant of PH2 occurrence.

Additionally, our study did not show that the specific vessel responsible for the LVO correlated with the chances for sustaining a PH2. Specifically, patients had similar rates of PH2 following EVT in either the anterior versus posterior circulation or in LVO versus MeVO. However, given the small number of posterior circulation patients included, our results should be interpreted with caution and further large-scale studies should examine this aspect.

The three variables independently associated with PH2 were failure to achieve target vessel recanalization, longer duration from symptom onset to arrival at the emergency department and hyperlipidemia. Our results show that failure to achieve TICI2b-3 is an independent predictor for PH2 while the method to achieve recanalization is not significant predictors of PH2. The significance of successful recanalization in reducing rates of PH2 has been previously described. [16, 17].

Not surprisingly, similar to previous reports, longer time from symptom onset to ER admission [15, 18] was independently associated with PH2 on multivariate analysis.

In the current study, the interval from symptom onset to door was the time epoch with the greatest impact on the chances of developing a PH2. We can postulate that symptoms may have started earlier than reported in some patients or that time from door to intervention has less impact as the patient is receiving treatment such as IV-tPA or intravenous fluids during the door to intervention.

Hyperlipidemia was independently associated with PH2 on univariate and multivariate analysis. This finding contrasts with those seen in a previous study [16] and further research is needed to elucidate the effect of hyperlipidemia in EVT-treated patients. Perhaps in patients with hyperlipidemia, the cerebral vasculature is more impaired due to extensive atherosclerosis, consequently leading to more extensive BBB breakdown and eventually HT. Alternatively, early statin administration may have been associated with HT. In the SPARCL study, patients who received early high dose statin showed more events of intracerebral hemorrhage [19]. Regretfully, we do not have full data of early statin administration in our study.

Similar to previous publications, our findings did not show that the number of passes [20] or bridging with IV-tPA [21] resulted in higher rates of HT or PH2. Of note, one previous study found an association between bridging with IV-tPA and HT at 24-hour [18] but no association was specifically shown with PH2. Recent publications found that more than three retrieval attempts were independently associated with an increased risk for sICH [22] and parenchymal hematoma [23]. However, the latter study found that association only when stent-retrievers were used and not with contact aspiration and these data were not available for the current analysis.

When we tried to analyze our data according to whether or not patients had a sICH we found that only a relatively small number of patients (2.6%) had indeed had a sICH precluding us from performing a thorough statistical evaluation. Thus, given the small number of sICH patients included in our study, our multivariate analysis for predictors of sICH (Table 4S) should be interpreted with caution.

The main strengths of the study are that it involved non-selective, prospective recruitment of patients offering comprehensive real-world data regarding rates of HT and its all-inclusive nature with LVO and MeVO involving different vascular territories and different treatment windows included. Moreover, the study offers real-world data of all perfusion-guided eligible EVT patients without being subjected to clinical trial selection criteria.

The study has several limitations. The protocols used at each of the prospective registries were slightly different allowing us analysis of comparable data only. Therefore, we cannot exclude selection bias and our results should be interpreted with caution. Also, not all the patients had complete data sets and as a result mRS-90 was not available in one of the centers. However, all baseline criteria and treatment allocations were similar to the patients with complete data sets. Furthermore, our study did not include a control group of similar patients not treated with EVT thereby potentially introducing further selection bias. Another limitation was the lack of a centralized core imaging facility although experienced stroke neurologists determined HT subtypes and sICH presence.

In conclusion, PH2-HT is not uncommon after EVT and is associated with increased mortality and unfavorable outcome rates. Our study suggests that the two most significant predictors of PH2 were failure to achieve TICI2b-3 and longer duration from symptom onset to ER arrival. Reassuringly, rates of PH2 are not different between patients treated in the early and late windows or between those with LVO or MeVO involving the anterior or posterior circulation.

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**Declarations**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Consent for Publication** For this type of study, consent for publication is not required.

**Informed Consent** For this type of study (retrospective), formal consent is not required.

## References

1. 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 Neurointervent Surg. 2019;11(5):464–8.
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):708–18.
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.
4. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. Stroke. 2018;49(3):e46–110.
5. Saver JL, Chapot R, Agid R, et al. Thrombectomy for distal, medium vessel occlusions: a consensus statement on present knowledge and promising directions. Stroke. 2020;51(9):2872–84.
6. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20(7):864–70.
7. Adams HP Jr, 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.
8. Hill MD, Demchuk AM, Goyal M, et al. Alberta Stroke Program early computed tomography score to select patients for endovascular treatment: interventional management of stroke (IMS)-III Trial. Stroke. 2014;45(2):444–9.
9. Menon BK, d'Esterre CD, Qazi EM, et al. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. Radiology. 2015;275(2):510–20.
10. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. Stroke. 2003;34(8):e109-137.
11. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study investigators. Lancet. 1998;352(9136):1245–51.
12. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274(13):1017–25.
13. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359(13):1317–29.
14. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. prognosis. Scott Med J. 1957;2(5):200–15.
15. Kaesmacher J, Kaesmacher M, Maegerlein C, et al. Hemorrhagic transformations after thrombectomy: risk factors and clinical relevance. Cerebrovasc Dis. 2017;43(5–6):294–304.
16. Lee YB, Yoon W, Lee YY, et al. Predictors and impact of hemorrhagic transformations after endovascular thrombectomy in patients with acute large vessel occlusions. J Neurointervent Surg. 2019;11(5):469–73.
17. Desai SM, Tonetti DA, Morrison AA, et al. Relationship between reperfusion and intracranial hemorrhage after thrombectomy. J Neurointervent Surg. 2020;12(5):448–53.
18. Nogueira RG, Gupta R, Jovin TG, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointervent Surg. 2015;7(1):16–21.
19. Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the stroke prevention by aggressive reduction in cholesterol levels study. Neurology. 2008;70(24 Pt 2):2364–70.
20. Hassan AE, Kotta H, Shariff U, Preston L, Tekle W, Qureshi A. There is no association between the number of stent retriever

passes and the incidence of hemorrhagic transformation for patients undergoing mechanical thrombectomy. Front Neurol. 2019;10:818.
21. Casetta I, Pracucci G, Saletti A, et al. Combined intravenous and endovascular treatment versus primary mechanical thrombectomy. The Italian registry of endovascular treatment in acute stroke. Int J Stroke Off J Int Stroke Soc. 2019;14(9):898–907.
22. Maros ME, Brekenfeld C, Broocks G, et al. Number of retrieval attempts rather than procedure time is associated with risk of symptomatic intracranial hemorrhage. Stroke. 2021;52(5): 1580–8.
23. Bourcier R, Saleme S, Labreuche J, et al. More than three passes of stent retriever is an independent predictor of parenchymal hematoma in acute ischemic stroke. J Neurointerv Surg. 2019;11(7):625–9.