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Prognostic Burden of Hemorrhagic Transformation in Acute Ischemic Stroke: A Brief Report from the Real Life

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Abstract

Introduction: Hemorrhagic Transformation (HT) represents one of the main complications of acute ischemic stroke, affecting its management and prognosis. Few data exists on prognosis of HT in the real world. Aim of this study was to evaluate the prognostic impact of HT in a real world cohort of patients hospitalized for acute ischemic stroke.

Methods: We retrospectively analyzed the clinical data of patients with acute ischemic stroke consecutively admitted to our Stroke Unit. Patients with HT were compared with those without HT. Modified Rankin Scale (mRS) at hospital discharge and at 90 days were the study outcomes. Poor prognosis was defined as mRS≥4. A multivariate logistic regression analysis was performed to identify independent predictors of outcomes.

Results: The study population consisted of 564 patients with mean age 77.5±11.8 years. Fifty-two patients (9.2%) showed HT on brain CT. Length of hospitalization, in-hospital mortality, median mRS at discharge, percentage of patients with mRS≥4 at discharge, percentage of HT patients discharged without secondary antiplatelet or anticoagulant prophylaxis and median 90-day mRS were significantly higher in patients with HT than in those without. The presence of HT was predictive of mRS≥4 at discharge and at 90 days (AUC 0.720 and 0.776, respectively). The presence of HT was an independent predictor of poor outcome, increasing the risk by about four times both at discharge (OR 3.64, 95% 1.46-9.06) and at 90 days (OR 4.26, 95% 1.07-16.88).

Conclusions: HT is associated with a poor outcome in terms of mortality and severe residual disability both in the acute phase and at 90 days.

Introduction

Hemorrhagic transformation (HT) is the most feared complication in the hyperacute phase of ischemic stroke, with an incidence of about 5-10% of cases [1,2]. HT can be symptomatic being associated with neurological worsening often leading to coma and death, or more frequently asymptomatic, without significant neurological deterioration [3]. HT has been classified in petechial (type I, isolated petechiae and type II, confluent petechiae) and parenchimal (type I, hematoma less than 30%

of ischemic lesion and type II, hematoma major than 30% of ischemic lesion with mass effect). Clinical studies showed that only parenchymal HT, occurring in 3% of ischemic strokes, is associated with a poor outcome [2,4]; on the contrary, petechial HT, occurring in about 5.5% of patients, does not seem to have a negative effect on ischemic stroke [2]. Few data exist about the relationship between stroke patients with HT and short and long term prognosis in real life, therefore the aim of this study was to provide evidence on this topic.

Methods

We retrospectively analyzed clinical data of patients with acute ischemic stroke consecutively admitted to our Stroke Unit along a period two years long. For all patients demographic characteristics (age, sex), pre-stroke modified Rankin Scale (mRS), cardiovascular risk factors, clinical severity using National Institute of Stroke Scale (NIHSS), acute revascularization by systemic thrombolysis and/or mechanical thrombectomy, the site and number of the brain ischemic lesion(s), the presence of large vessel occlusion on CT angiography, the presence of HT on computer tomography (CT) scan after 24-48 hours from baseline, antithrombotic therapy before stroke, etiopathogenetic stroke subtype, secondary antithrombotic prophylaxis at discharge, in-hospital and 90-day mortality, and modified Rankin Scale (mRS) at discharge and at 90 days were analyzed. HT was defined symptomatic when associated to neurological worsening determining an increase of ≥ 4 points at NIHSS. Patients with HT were compared with those without HT. mRS at hospital discharge and at 90 days were the study outcomes. Poor prognosis was defined as mRS≥4.

Statistical analysis: Continuous variables were reported as mean ± standard deviation (SD) or as median and interquartile range (IQR) as appropriate. Categorical variables were analyzed using the χ2 test and Fisher's exact test when appropriate. Univariate and multivariate logistic regression analyses were used to identify predictors of outcome; odds ratio (OR) and their 95th percentile confidence intervals (CI) were reported. A p value of <0.05 was considered statistically significant. All analyses were performed using MEDCALC statistical software (MedCalc Software Ltd, Acacialaan 22, B-8400 Ostend, Belgium).

Results

Five hundred and sixty-four patients (51.5% females) with mean age 77.5±11.8 years were the study population. Median pre-event mRS was 0 (IQR 0-0). Stroke subtypes were aterothrombotic: 10.8%, lacunar 23.9%, cardioembolic 30.6%, embolic of undetermined source (ESUS) 15.3%, undefined or other 19.1%. Fifty-two patients (9.2%) showed HT on brain CT performed 24-48 hours after baseline. In 28 patients (4.9%) HT was symptomatic. In patients with HT, history of previous transient ischemic attack (TIA)/stroke, known atrial fibrillation and heart failure were significantly more frequent than in patients without HT (Table 1).

No difference was found in NIHSS upon arrival between the two subgroups of patients, while at Stroke Unit admission median NIHSS was significantly higher in HT patients compared with those without [8(3-11) vs 3(1-5.25), p=0.0001]. Among patients with HT there was a higher percentage of cardioembolic strokes (59.6% vs 27.7%, p=0.0001) and of large vessel occlusion on CT

angiography (44.2% vs 11.3%, p=0.0001) compared to patients without HT. The percentage of patients who underwent systemic thrombolysis, mechanical thrombectomy, or both was higher in patients with HT than in those without (Table 2).

Patients with HT had significantly higher length of hospitalization (LOS), in-hospital mortality, median mRS at discharge and at 90 days and higher percentage of mRS≥4 at discharge than patients without HT. HT patients were more frequently discharged without secondary antiplatelet or anticoagulant prophylaxis than those without (Table 3). The percentage of patients who died or with severe residual disability (mRS≥4) at discharge was significantly higher in patients with symptomatic HT than in those with asymptomatic HT (92.8% versus 45.8%, respectively, p=0.0028). In-hospital mortality was 17.8% in patients with symptomatic HT versus 12.5% in those with asymptomatic HT (p=0.7109).

The presence of HT was predictive of a negative outcome (mRS≥4 at discharge and at 90 days) with a good performance (AUC 0.720 and 0.776, respectively) (Figures 1a and 1b).

At multivariate analysis, the presence of HT was an independent predictor of negative outcome (mRS≥4), increasing the risk approximately four times both at discharge (OR 3.64, 95% CI 1.46-9.06) and at 90 days (OR 4.26, 95% CI 1.07-16.88). Dementia, creatinine clearance <50 ml/min, NIHSS≥8 at Stroke Unit admission, and increase of ≥4 points on NIHSS from emergency department arrival to Stroke Unit admission were additional predictive variables of negative outcome at discharge. Dementia and a NIHSS≥8 at Stroke Unit admission were also predictive variables of negative outcome at 90 days (Tables 4 and table 5).

Table 1: Cardiovascular risk factors and antithrombotic therapy of patients with and without hemorrhagic transformation.

	HT	no HT	p
Number, %	52(9.2)	512(90.8)	
Sex, n(%)	25(48)	266(51.9)	0.66
Mean age ± SD, years	75.9±15.5	77.7±11.4	
Arterial hypertension, n(%)	42(80.7)	353(68.9)	0.08
Diabetes mellitus, n(%)	12(23.0)	143(29.8)	0.51
Previous TIA/stroke, n(%)	19(36.5)	111(21.6)	0.023
Carotid stenosis >50%/previous TEA, n(%)	2(3.8)	25(4.8)	1
Known atrial fibrillation, n(%)	17(32.6)	98(19.1)	0.029
Ischemic heart disease, n(%)	6(11.5)	62(12.1)	1
Heart failure, n(%)	8(15.3)	30(5.8)	0.016
Renal failure (CrCl<50 ml/min), n(%)	10(19.2)	93(18.1)	0.47
Dementia, n(%)	7(13.4)	53(10.3)	0.75
Previous antiplatelet therapy, n(%)	17(32.6)	158(30.8)	0.26
Previous anticoagulant therapy, n(%)	9(17.3)	60(11.7)	0.35
DOAC, n(%)	5(9.6)	30(5.8)	0.54
VKA, n(%)	4(7.7)	30(5.8)	

HT: Hemorrhagic Transformation; SD: Standard Deviation; TIA: Transient Ischemic Attack; TEA: Thromboendoarteriectomy; Crcl: Creatinine Clearance; DOAC: Direct Oral Anticoagulant; VKA; Vitamin K Antagonist.

Table 2: Clinical and neuroradiological characteristics in patients with and without hemorrhagic transformation.

	HT	no HT	p
NIHSS at ED arrival (median, IQR)	3(0-5)	3(2-7)	ns
NIHSS at SU admission (median, IQR)	8(3-11)	3(1-5.25)	0.0001
GCS at ED arrival (median, IQR)	15(15-15)	15(15-15)	ns
Cardioembolic etiology, n(%)	31(59.6)	142(27.7)	0.0001
Large vessel occlusion, n(%)	23(44.2)	58(11.3)	0.0001
Systemic thrombolysis and/or			
Mechanical thrombectomy, n(%)	17(32.6)	72(14.0)	0.0012
Bilateral ischemic lesions, n(%)	2(0.3)	20(0.3)	1
Posterior circulation ischemic lesion, n(%)	7(1.3)	119(2.3)	0.11

HT: Hemorrhagic Transformation; NIHSS: National Institutes Of Health Stroke Scale; ER: Emergency Department; IQR: Interquartile Range; SU: Stroke Unit; GCS: Glasgow Coma Scale; BP: Blood Pressure; SD: Standard Deviation.

Table 3: Outcome at discharge and at 90 days in patients with and without hemorrhagic transformation.

	HT	no HT	p
No secondary antithrombotic prophylaxis at discharge, n(%)	17/44(38.6)	59/490(12)	0.0001
In-hospital mortality, n(%)	8(15.3)	22(4.2)	0.0036
Length of stay, days (median, IQR)	10.2±5.9	7.5±4.2	0.0001
mRS alla dimissione (median, IQR)	4(3-5)	3(1-4)	0.0001
mRS ≥ 4 at discharge, n(%)	38(73)	192(37.5)	0.0001
90-day mRS (median, IQR)	4(3-5)	2(1-3)	0.0001

HT: Hemorrhagic Transformation; IQR: Interquartile Range; mRS: odified Rankin scale.

Table 4: Variables predictive of negative outcome (mRS≥4) at discharge.

Variable	OR	95% CI
Systemic thrombolysis and/or	4.2615	1.0757-16.8820
mechanical thrombectomy	0.4167	0.2081 - 0.8345
HT at 24/48 hours	3.6439	1.4648-9.0643
Posterior circulation stroke	1.5195	0.9023-2.5589
Bilateral stroke	0.8582	0.3078-2.3928
Female sex	1.1754	0.7560-1.8277
Large vessel occlusion	1.5422	0.8389-2.8353
NIHSS ≥ 8 at ED arrival	0.5900	0.3320-1.0482
NIHSS ≥ 8 at SU admission	4.5742	2.0855-10.0329
CrCl ≤ 50 ml/min	2.3656	1.3681-4.0903
Increase of NIHSS ≥ 4 between ED arrival	0.8825	0.5567-1.3988
and SU admission	2.4046	1.0998-5.2575
Age ≥ 75 years	0.8825	0.5567-1.3988
Dementia	3.3167	1.5725-6.9953
Diabetes mellitus	1.1175	0.6803-1.8358
Arterial hypertension	1.2532	0.7762-2.0232
Ischemic heart disease	1.1043	0.5559-2.1937
Known or newly diagnosed atrial fibrillation	1.2300	0.7798-1.9400
Platelets ≤ 150.000	0.8338	0.4283-1.6230
PreviousTIA/stroke	1.3161	0.7794-2.2226
Cortical and/or cortical/subcortical stroke	1.1319	0.7174-1.7861

mRS: modified Rankin scale; OR: Odds Ratio; CI: Confidence Interval; HT: Hemorrhagic Transformation; NIHSS: National Institutes of Health Stroke Scale; ED: Emergency Department; SU: Stroke Unit; CrCl: Creatinine Clearance; TIA: Transient Ischemic Attack.

Table 5: Variables predictive of negative outcome (mRS≥4) at 90 days.

Variable	OR	95% CI
HT at 24/48 hours	4.2615	1.0757-16.8820
Systemic thrombolysis and/or	3.6439	1.4648-9.0643
mechanical thrombectomy	0.9209	0.2961-2.8637
Posterior circulation stroke	0.4755	0.1818-1.2433
Bilateral stroke	2.1350	0.4669-9.7624
Female sex	1.3163	0.6078-2.8510
Large vessel occlusion	0.4593	0.1277-1.6522
NIHSS ≥ 8 at ED	1.2198	0.4481-3.3203
NIHSS ≥ 8 at SU admission	24.7589	6.4885-94.4750
CrCl ≤ 50 ml/min	0.6263	0.1894-2.0718
Increase of NIHSS ≥ 4 between ED arrival and	0.8825	0.5567-1.3988
SU admission	0.7661	0.2018-2.9080
Age ≥ 75 years	0.5251	0.2302-1.1981
Dementia	22.8875	4.7970-109.1999
Diabetes mellitus	1.2389	0.5025-3.0543
Arterial hypertension	0.9873	0.4166-2.3398
Ischemic heart disease	1.5027	0.4496-5.0227
Known or newly diagnosed atrial fibrillation	1.9461	0.8864-4.2725
Platelets ≤ 150.000	3.0167	0.9913-9.1806
Pregvious TIA/stroke	1.6293	0.6532-4.0641
Cortical and/or cortical/subcortical stroke	0.4604	0.1930-1.0985

mRS: modified Rankin scale; OR: Odds Ratio; CI: Confidence Interval; HT: Hemorrhagic Transformation; NIHSS: National Institutes of Health Stroke Scale; ED: Emergency Department; SU: Stroke Unit; CrCl: Creatinine Clearance; TIA: Transient Ischemic Attack.

Discussion

Despite HT is a well recognized entity in stroke medicine, it remains a poorly defined issue with many aspects of uncertainty. HT may influence the clinical course and prognosis of stroke. The interest on HT has grown in recent years, due to the widespread of systemic thrombolysis and/or mechanical thrombectomy. Our study showed that HT influences outcome and management of patients with acute ischemic stroke, representing an independent risk factor for poor prognosis, both in the short and long term. In our study HT was associated with a
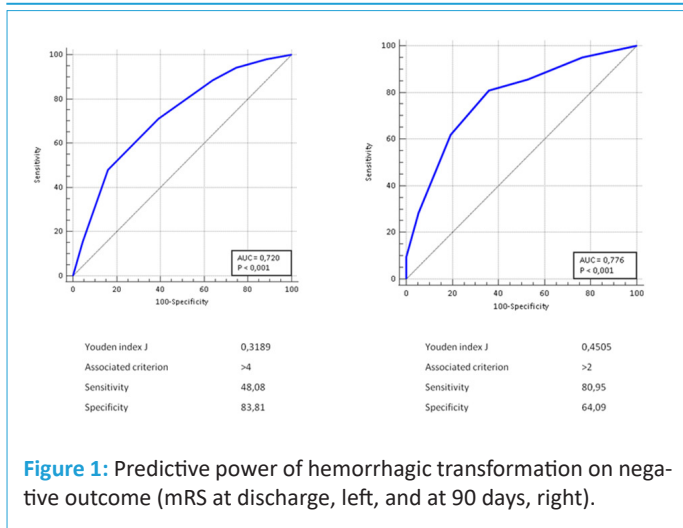
Figure 1: Predictive power of hemorrhagic transformation on negative outcome (mRS at discharge, left, and at 90 days, right).

significantly longer LOS and a significantly lower percentage of patients discharged on secondary antithrombotic prophylaxis. Furthermore, our study highlighted a significant difference in the composite outcome in-hospital mortality/severe residual disability at discharge between patients with symptomatic and non-symptomatic HT. Although higher in percentage, the in-hospital mortality of patients with symptomatic HT was not significantly higher compared to non-symptomatic HT.

The association between HT and negative prognosis was already known in the literature. Paciaroni M et al. showed a fifteen-time higher risk of mortality or severe disability in patients with parenchymal HT compared with patients without HT [2]. More recently, similar results were reported by D'Amelio M et al. showing an association between parenchymal HT and in-hospital and three-month mortality [5], and Andrade JBC et al. who found that the presence of HT is associated with mortality, prolonged LOS, severe disability at discharge, risk of pneumonia and seizures, and that asymptomatic HT is associated with a more than five-fold risk of mRS≥4 at discharge [6]. Similar results were reported by Van Kranendonk KR et al. who found an association between HT and negative outcome, showing no significant differences in prognosis between patients with confluent petechial HT and those with parenchymal HT [7]. Gill D et al. showed that the development of post-thrombolysis parenchymal HT is associated with the absence of improvement or even neurological worsening (average increase of 7 points on NIHSS), in contrast to patients without HT, who show an improvement of post-thrombolysis NIHSS score in the large majority of cases [8]. In a study by Ge WQ et al. the NIHSS score 2 hours after thrombolysis and the presence of atrial fibrillation were risk factors for HT [9]. In our study NIHSS score ≥ 8 at Stroke Unit admission was an independent risk factor for poor in-hospital and 90-day outcome. Moreover, our study showed that an increase of more than 4 points of NIHSS from emergency department to Stroke Unit admission was also an independent risk factors for negative in-hospital outcome.

The management of antithrombotic secondary prophylaxis in patients with HT is controversial. While parenchymal HT, especially type II, should be considered as an intraparenchymal hemorrhage and managed accordingly, the management of petechial HT is more uncertain. Indeed, there are very few literature studies focusing attention on this topic. In the randomized controlled trial Tinzaparin in Acute Ischemic Stroke, asymptomatic petechial HT was found in approximately 30-35% of patients, with no significant differences between the aspirin arm and the medium and high dose tinzaparin arms, and no

differences in terms of outcome between the three groups [10]. In another study by Kim JT et al. the introduction of secondary antithrombotic prophylaxis did not negatively affect the prognosis of patients with petechial HT [11]. However, the fear of further neurological deterioration represents the main reason for the delayed introduction of secondary antithrombotic prophylaxis in patients with HT. In the RAF and RAF-DOAC studies on more than 2000 patients with atrial fibrillation-related cardioembolic stroke, the incidence of HT was 11% (7.9% petechial, 3.1% parenchymal), and the presence of HT was associated with significantly higher mortality and disability [12]. The timing of initiation of secondary anticoagulant prophylaxis was on average twice longer in patients with HT than in those without HT (23.3 vs 11.6 days, respectively); however, the incidence of embolic recurrences at 90 days was comparable between the two groups (4.6% vs 4.9%, respectively) [12]. Our study showed similar results for patients with atrial fibrillation-related ischemic stroke. The most recent AHA/ASA guidelines, based on very limited available evidence, suggest the possibility of starting or continuing antithrombotic secondary prophylaxis in HT patients with a grade of recommendation IIb, weighing the clinical presentation and indications [13].

We recognized that our study has limitations mainly due to the retrospective and single center design. Despite these limitations, we think that it could add information about the topic.

Conclusion

HT represents the most feared complication of hyperacute phase of ischemic stroke being associated with higher mortality and residual disability. Our real life study confirms that HT is associated with a poor outcome in terms of mortality and severe residual disability, both in the acute phase and at 90 days and that HT represents an independent risk factor of poor outcome. Strategies aimed to reduce the incidence of HT and make an early diagnosis are warranted.

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