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The etiologic subtype of intracerebral hemorrhage may influence the risk of significant hematoma expansion

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ABSTRACT

Background: Intracerebral hemorrhage (ICH) growth is an important independent predictor of clinical deterioration and outcome. Little is known about the association between etiology of ICH and occurrence of hematoma expansion (HE). The aim of the present study was to assess whether ICH etiologic subtype may influence the risk of significant HE.

Methods: We conducted an analysis on retrospectively collected data of 424 consecutive patients with ICH, who were admitted to the Verona General Hospital, from March 2011 to December 2014.

Using the SMASH-U (Structural vascular lesions, Medication, Amyloid angiopathy, Systemic disease, Hypertension, or Undetermined) classification, we identified the ICH etiologic subtypes. Outcome measure was significant HE (an absolute increase in ICH volume > 12.5 mL or >50%) within 48 h.

Results: Significant HE occurred in 11/57 (19.3%) Amyloid, 7/14 (50%) Structural, 31/57 (54.4%) Medication, 25/44 (56.8%) in Systemic, 62/139 (44.6%) Hypertensive, and 21/68 (30.9%) Undetermined ICH. Baseline ICH volume (OR 1.011 per mL, 95% CI 1.006–1.017, $p < 0.001$) and onset-to-baseline CT time (OR 0.919 per hour, 95% CI 0.852–0.990, $p = 0.027$) were predictors of significant HE. Compared with Amyloid ICH, ORs for significant HE were higher in patients with Structural ICH (OR 1.430, 95% CI 1.060–1.948, $p = 0.023$), Medication ICH (OR 4.344, 95% CI 1.382–13.653, $p = 0.012$), Systemic ICH (OR 1.796, 95% CI 1.070–3.015, $p = 0.027$), and Hypertensive ICH (OR 3.081, 95% CI 1.426–6.655, $p = 0.004$).

Conclusion: Our study shows that Structural, Medication, Systemic, and Hypertensive ICH were the etiologic subtypes associated with a higher risk of significant HE, compared with Amyloid ICH patients.

1. Background

Intracerebral hemorrhage (ICH) accounts for approximately 15% of all acute strokes and is the deadliest stroke subtype with one-month mortality rates of 40% [1,2]. Initial hematoma volume remains the strongest predictor of 30-day mortality and functional outcome [3]. Nevertheless, approximately 30% of patients continue to bleed and demonstrate significant hematoma expansion during hospitalization, which further aggravates outcome [4–7]. Because of its influence on outcome, identifying patients who have a high risk for HE could influence decision-making in clinical management in stratifying patients for surgery and the design of randomized trials of medical interventions. To date, few predictor of ICH expansion have been identified, including larger ICH volume, earlier presentation after symptom onset, use of oral anticoagulant drugs, and the presence of a spot sign on computed tomography angiography (CTA) [8–16]. Instead, little is known about the association between ICH etiology and occurrence of hematoma expansion (HE). The aim of the present study was to assess whether ICH etiologic subtype may influence the risk of significant HE.

2. Methods

We conducted a study on retrospectively collected data of 627 consecutive patients with ICH, who were admitted to the Emergency Department of Verona General Hospital, from March 2011 to December 2014.

We searched the electronic medical record system to identify all patients who have at discharge diagnosis of ICH (International Classification of Diseases, Ninth Revision (ICD-9) code 431. We included the patients with an available initial CT scan within 12 h after symptoms onset and follow-up CT scan within 48 h after the baseline CT scan. Using the SMASH-U (Structural vascular lesions, Medication, Amyloid angiopathy, Systemic disease, Hypertension, or Undetermined) classification system [17], we identified the etiologic subtypes of ICH. Structural vascular malformation diagnosed at ICH site was confirmed by

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imaging [17]. Systemic or other determined cause for ICH included thrombocytopenia (thrombocyte count < 50 E9/L), liver cirrhosis or known liver disease combined with spontaneously elevated INR or liver enzymes > 3× upper limit of the reference range, or chronic kidney disease stage 5 (glomerular filtration rate < 15 mL/min/1.73 m^2) [17,18]. In the Medication ICH subtype were included the patients who used warfarin with international normalized ratio ≥ 2, new oral anticoagulant within 3 days, full-dose heparin, or thrombolytic agents for non-ischemic stroke [17]. Amyloid ICH was defined as lobar, cortical, or subcortical hemorrhage among individuals aged ≥ 55 years, according to the Boston criteria [17]. Because the sensitivity of the Boston criteria for cerebral amyloid angiopathy (CAA)-related ICH increases when cerebral microbleeds (CMBs) and superficial siderosis detectable with in T2*-weighted MRI are considered [19,20], we included these additional radiological findings, when they were available. Hypertensive ICH was defined as deep or infratentorial hemorrhage with pre-ICH hypertension (mention of pre-ICH elevated blood pressure by patient and/or or medical records together with a left ventricular hypertrophy as a biomarker of hypertension and/or or any pre-ICH use of blood pressure medication) [17]. The identification of etiologic subtypes of ICH was done by discussion, after discussion and consultation among three stroke neurologists. The cases without a consensus for classification were rated as undetermined cause.

Primary outcome measure was significant HE (an absolute growth > 12.5 mL or a relative increase > 50%) [5,7] from initial to control CT scan. Secondary outcome measures were any ICH from initial to control CT scan and in-hospital mortality. ICH volumes were estimated with the standard ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness [21].

We examined differences in continuous variables using the 1-way analysis of variance and the Kruskal–Wallis test in the case of nonnormally distributed data. Differences between proportions were assessed by use of the Fisher exact test or the χ^2 test when appropriate. We reported continuous variables as mean (standard deviation) or median (interquartile range) values. Categorical variables were reported as proportions. We estimated the prognostic effect of ICH subtypes defined according to the SMASH-U classification system, by calculating the odds ratio (OR) with two-sided 95% confidence intervals (CI) for significant HE, establishing statistical significance at two-tailed 0.05 level ($p < 0.05$). We performed an adjusted analysis (logistic regression) of the significant HE using a backward method that included age and sex, known predictors (baseline ICH volume, onset to baseline CT scan time) and all variables with a probability value < 0.10 in univariate analysis. Amyloid ICH was the reference group.

3. Results

Of 627 patients with ICH, 424 entered into the study. Fig. 1 shows the flow diagram of patient inclusion and exclusion. Fifteen patients (3.5%) had Structural ICH (9 cavernomas and 6 arteriovenous malformations), 63 (14.9%) had Medication ICH, 62 (14.6%) had Amyloid ICH, 48 (11.3%) had Systemic ICH, 152 (35.8%) had Hypertensive ICH, and 84 (19.8%) had Undetermined ICH.

Table 1 shows the clinical characteristics of the cohort and the six groups of patients.

There were significant differences among ICH subtypes and outcome measures (Table 2).

Table 3 shows the differences of clinical characteristics between patients with and without significant HE. Of the 8 variables (baseline Barthel Index, onset to baseline CT scan time, ICH volume, lobar ICH,

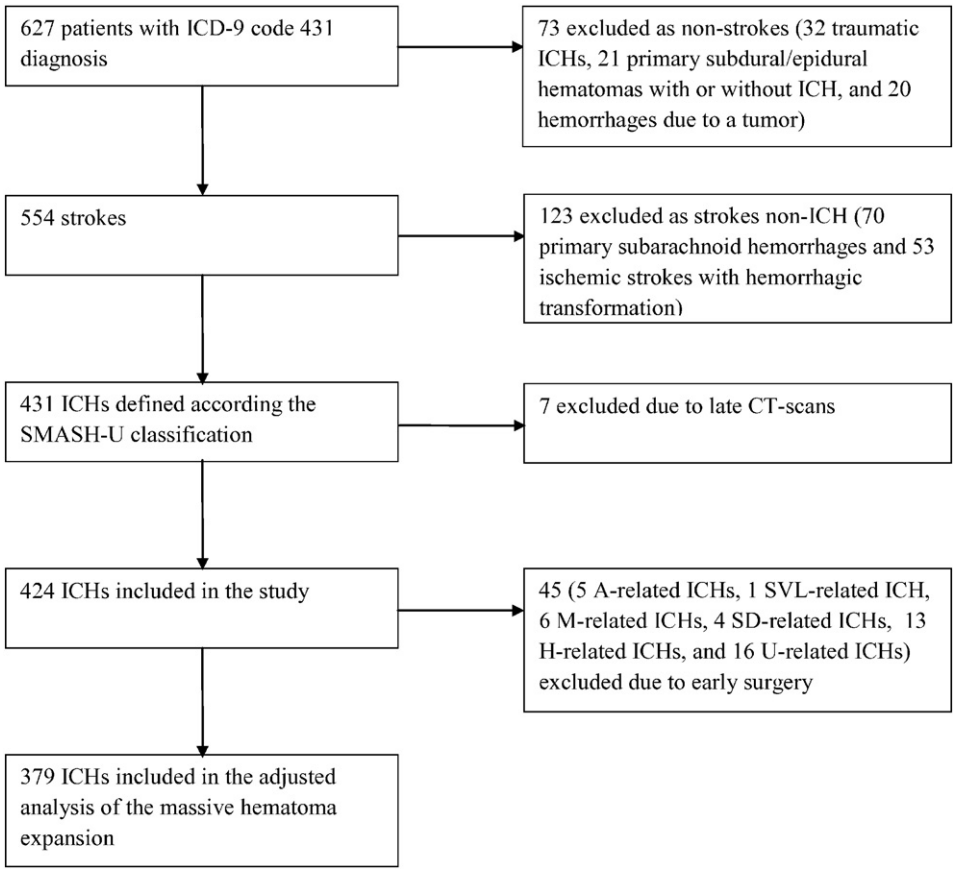

Fig. 1. Flow diagram of patient inclusion and exclusion. Abbreviations: ICD, International Classification of Diseases, Ninth Revision; ICH, Intracerebral hemorrhage; CT, computed tomography; SVL, Structural vascular lesions; M, Medication; A, Amyloid angiopathy; SD, Systemic disease; H, Hypertension; U, Undetermined.