Smoking Status Affects the Association Between Hematoma Heterogeneity and Hematoma Expansion

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OBJECTIVE: The purpose of this study was to verify the relationship between hematoma heterogeneity and hematoma expansion and explore any effect modifiers through subgroup analyses.

METHODS: Clinical records of 357 patients with spontaneous cerebral hemorrhage at Shenzhen Second People’s Hospital from March 2016 to October 2018 were included in the study. Hematoma heterogeneity was measured on the first noncontrast computed tomography image according to the Barras scale. Hematoma expansion was defined as an absolute hematoma volume increase of 6 mL, or a 33% increase. We performed univariate and multivariate logistic regression analyses, as well as subgroup analyses, to assess the relationship between the presence of heterogeneity on noncontrast computed tomography and hematoma expansion.

RESULTS: Hematoma expansion occurred in 79 (22.13%) of the 357 patients with intracerebral hemorrhage (ICH). Among the patients with ICH, there were 83 smokers, accounting for 23.24%. The average patient age was 56.21 ± 13.75 years, and 74.51% were male. Compared with the absence of heterogeneity, the risk of hematoma expansion increased by 1.06 times (odds ratio, 2.06; 95% confidence interval, 1.10–3.86). Based on the subgroup analysis, smoking status was found to modify the association between heterogeneity and hematoma expansion; the association was stronger in smokers than in nonsmokers (odds ratio, 10.23; 95% confidence interval, 2.15–48.65).

CONCLUSIONS: Heterogeneity independently predicts hematoma expansion, especially in smoking patients.

INTRODUCTION

Intracerebral hemorrhage (ICH) is the deadliest type of stroke,¹ accounting for about 10%—30% of first strokes,² with a 28-day mortality as high as 26%.³ Most survivors have severe disabilities, and only 20% of survivors can live independently after 6 months.¹ Hematoma expansion can occur in up to one third of patients with ICH, and it is closely related to a poor prognosis.⁴⁵ Many studies have now shown that heterogeneity is an independent predictor of the expansion of substantial bleeding.⁶⁷ Although they have found a connection between the two, these studies have not clarified the differences in this relationship among population subgroups. Therefore, the aim of the present study was to verify whether the heterogeneity of patients with spontaneous ICH is independently related to the expansion of hematomas and to explore whether there are variations among different populations.

METHODS

We conducted a retrospective cohort study. In addition to exploring the relationship between hematoma heterogeneity and hematoma expansion in the general population, we also

Key words
- Hematoma expansion
- Hematoma heterogeneity
- Intracerebral hemorrhage
- Smoking

Abbreviations and Acronyms
CT: Confidence interval
CT: Computed tomography
DBP: Diastolic blood pressure
ICH: Intracerebral hemorrhage
IQR: Interquartile range
OR: Odds ratio

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performed an analysis of effect modifiers. The target independent variable was hematoma heterogeneity observed at baseline, and the dependent variable was hematoma expansion (dichotomous variable: 1, hematoma expansion; 0, no hematoma expansion).

Study Population
We nonselectively and continuously collected clinical records from patients with acute spontaneous ICH from the Department of Radiology, Shenzhen Second People’s Hospital. The data in the database are anonymous to protect the privacy of participants and are stored in the hospital electronic medical record system. Because of the retrospective nature of the cohort, the study did not require informed consent from the participants. Ethics approval was obtained from the agency review board of Shenzhen Second People’s Hospital [approval number 20200422007].

Clinical records of 411 patients admitted from March 2016 to October 2018 were included and assessed for eligibility. Inclusion criteria included patients with spontaneous ICH, older than 18 years, and who had their first noncontrast computed tomography (CT) scan after symptoms and subsequent CT scans within 72 hours. Exclusion criteria included arteriovenous malformations, ruptured intracranial aneurysms, traumatic brain injury, brain tumor hemorrhage, secondary ICH caused by hematologic diseases, severe image artifacts, or bleeding after cerebral infarction. After application of the inclusion and exclusion criteria, 357 records were available for the final data analysis (Figure 1).

Imaging Analysis
We obtained heterogeneity at baseline and recorded it as a categorical variable (1, homogeneity; 2, heterogeneity) (Figure 2). According to the Barras scale, grades $\geq 3$ are considered to show hematoma heterogeneity. The detailed process is described as follows: 2 senior doctors (with $>10$ years’ experience of CT diagnosis), who were unaware of the clinical data and results, independently used RadiAntDICOM Viewer 5.0.1 (Medixant, Poznan, Poland) to assess the appearance of hematoma heterogeneity. The axial section thickness of all CT examination images was 5 mm. The image format was DICOM (Digital Imaging and Communications in Medicine). When the opinions on the hematoma heterogeneity were inconsistent, the 2 doctors discussed and reached a conclusion together.

The final outcome variables (dichotomous variables) were selected based on published guidelines and studies. Hematoma expansion was defined as an intracerebral parenchymal hematoma in which the absolute volume of the hematoma in the follow-up CT examination increased by 6 mL or 33% (compared with the initial CT examination). The calculation method of hematoma volume was as follows: 2 doctors used ITK-SNAP 3.8.0 (Penn Image Computing and Science Laboratory, Philadelphia, Pennsylvania and Scientific Computing and Imaging Institute, Salt Lake City, Utah, USA) to delineate the boundary of brain parenchymal...
hematoma on the axial CT image, calculated the hematoma volume according to the computer-aided plane analysis method (gold standard), and then took the average value.

**Statistical Analysis**

Baseline characteristic variables are summarized as mean ± standard deviation or median and interquartile range (IQR) depending on whether the data were normally distributed or not, respectively. Categorical variables are expressed as percentages. Clinical and imaging variables were compared using the 1-way analysis of variance test (normal distribution), χ² (categorical variables), or Kruskal-Wallis H test (skewed distribution). The intrarater reliability was evaluated using the Cohen κ statistic. We constructed a multivariate logistic regression model to assess the correlation between hematoma heterogeneity and hematoma expansion and calculated the unadjusted and adjusted odds ratios (ORs) for the 95% confidence intervals (CIs). We adjusted the multivariate logistic regression model with P values ≤ 0.1 and

**Table 1. Baseline Characteristics of Patients (N = 357)**

| Hematoma Expansion | No (n = 278) | Yes (n = 79) | P Value |
|--------------------|-------------|-------------|---------|
| Age (years), mean (SD) | 57.00 (13.76) | 53.43 (13.40) | 0.07 |
| Time from symptom onset to baseline computed tomography (hours), median (IQR) | 3.00 (1.50—20.00) | 1.75 (1.00—3.00) | 0.004 |
| Systolic blood pressure (mm Hg), mean (SD) | 174.94 (27.77) | 170.13 (34.82) | 0.23 |
| Diastolic blood pressure (mm Hg), mean (SD) | 102.37 (18.48) | 102.64 (20.25) | 0.92 |
| Glucose (mmol/L), mean (SD) | 7.29 (2.74) | 7.86 (3.24) | 0.14 |
| Baseline intracerebral hemorrhage volume (mL), median (IQR) | 13.53 (5.98—25.80) | 12.93 (5.57—29.19) | 0.56 |
| Heterogeneity, n (%) | 0.004 |
| No | 156 (56.12) | 30 (37.97) |
| Yes | 122 (43.88) | 49 (62.03) |
| Sex, n (%) | 0.001 |
| Male | 196 (70.50) | 70 (88.61%) |
| Female | 82 (29.50) | 9 (11.39%) |
| Hypertension, n (%) | 0.32 |
| No | 35 (12.87) | 13 (17.33) |
| Yes | 237 (87.13) | 62 (82.67) |
| Smoking, n (%) | 0.41 |
| No | 202 (75.22) | 50 (71.43) |
| Yes | 63 (24.78) | 20 (28.57) |
| Alcohol consumption, n (%) | 0.56 |
| No | 214 (80.75) | 57 (83.82) |
| Yes | 51 (19.25) | 11 (16.18) |
| Location, n (%) | 0.09 |
| Deep | 192 (69.06) | 49 (62.03) |
| Lobar | 53 (19.06) | 13 (16.46) |
| Infratentorial | 33 (11.87) | 17 (21.52) |

Statistically significant values are given in bold. Variables are presented as n (%) for nominal data; mean ± standard deviation or median (interquartile range) for continuous data.

**Table 2. Univariate Analysis of Factors for Hematoma Expansion**

| Statistics | Hematoma Expansion | P Value |
|------------|--------------------|---------|
| Heterogeneity | No | 186 (52.10) | Reference |
| Yes | 171 (47.90) | 2.09 (1.25—3.49) | 0.004 |
| Sex | Male | 266 (74.51) | Reference |
| Female | 91 (25.49) | 0.31 (0.15—0.64) | 0.001 |
| Age (years) | 56.21 ± 13.75 | 0.98 (0.96—1.00) | 0.04 |
| Time from symptom onset to baseline computed tomography (hours) | 13.34 ± 21.86 | 0.97 (0.96—0.99) | 0.007 |
| Systolic blood pressure (mm Hg) | 173.94 ± 29.38 | 0.99 (0.99—1.00) | 0.23 |
| Diastolic blood pressure (mm Hg) | 102.42 ± 18.83 | 1.00 (0.99—1.01) | 0.92 |
| Glucose (mmol/L) | 7.42 ± 2.87 | 1.07 (0.98—1.16) | 0.15 |
| Hypertension | No | 48 (13.83) | Reference |
| Yes | 299 (86.17) | 0.70 (0.35—1.41) | 0.32 |
| Smoking | No | 252 (75.22) | Reference |
| Yes | 83 (24.78) | 1.28 (0.71—2.32) | 0.41 |
| Alcohol consumption | No | 271 (81.38) | Reference |
| Yes | 62 (18.62) | 0.81 (0.40—1.65) | 0.56 |
| Baseline intracerebral hemorrhage volume (mL) | 17.88 ± 16.36 | 1.00 (0.99—1.02) | 0.56 |
| Location | Deep | 241 (67.51) | Reference |
| Lobar | 66 (18.49) | 0.96 (0.49—1.90) | 0.91 |
| Infratentorial | 50 (14.01) | 2.02 (1.04—3.92) | 0.04 |

Statistically significant values are given in bold. Variables are presented as n (%) for nominal data; mean ± standard deviation or median (interquartile range) for continuous data.
other classic risk factors for hematoma expansion in the univariate analysis: sex, age, location, time from symptom onset to baseline CT, and baseline ICH volume. Stratified binary logistic regression was used to test the correlation between hematoma heterogeneity and hematoma expansion in the different subgroups and the P value for interaction was recorded. The subgroups were as follows: age-group (<60 years vs. ≥60 years); sex; time from symptom onset to baseline CT group (<12 hours vs. ≥12 hours); baseline ICH volume group (<30 mL vs. ≥30 mL); systolic blood pressure group (<139 mm Hg vs. ≥139 mm Hg); diastolic blood pressure group (<89 mm Hg vs. ≥89 mm Hg); random blood glucose group (<11.1 mmol/L vs. ≥11.1 mmol/L); location; and history of hypertension, smoking, and alcohol consumption.

A 2-tailed P value <0.05 was considered to be statistically significant in all analyses. R software version 3.3.1 (http://www.R-project.org), Empower, version 2.17.8 (www.empowerstats.com; X&Y Solutions Inc., Boston, Massachusetts, USA), and SPSS version 22.0 (IBM Corp., Armonk, New York, USA) were used for all the statistical analyses.

RESULTS

Baseline Characteristics of Selected Patients
The baseline characteristics of the selected patients are shown in Table 1. A total of 357 patients (266 men and 91 women) met the inclusion criteria for spontaneous ICH. The average age of the study participants was 56.21 ± 13.75 years (range, 23–95 years). Hematoma expansion occurred in 79 of the 357 patients with ICH (22.13%). There were 83 smokers among patients with ICH, accounting for 23.24%. The mean baseline hematoma volume was 13.53 mL (IQR, 5.98–25.80 mL). The median time from symptom onset to baseline CT was 3 hours (IQR, 1.5–20 hours). On the hematoma location, 241 cases were in the deep (67.51%), 66 cases in the lobar (18.49%), and 50 cases in the infratentorial (14.01%) locations. Interobserver agreement to assess the presence of hematoma heterogeneity was substantial between the 2 doctors (κ = 0.763).

Table 3. Relationship Between Heterogeneity and Hematoma Expansion in Different Models

| Exposure                  | Crude Model (OR, 95% CI) | Model I (OR, 95% CI) |
|---------------------------|--------------------------|----------------------|
| Heterogeneity             |                          |                      |
| No                        | Reference                | Reference            |
| Yes                       | 2.09 (1.25–3.49) 0.004   | 2.06 (1.10–3.96) 0.02 |

Crude model: no covariates were adjusted. Model I: adjusted for sex, age (years), location, time (hours) from symptom onset to baseline CT group, baseline ICH volume group, systolic blood pressure group, diastolic blood pressure group, random blood glucose group, hypertension, smoking, and alcohol consumption.

Table 4. Effect Size of the Hypodensities on Hematoma Expansion in Prespecified and Exploratory Subgroups

| X = Heterogeneity | N   | Hematoma Expansion | P Value | P for Interaction |
|-------------------|-----|--------------------|---------|------------------|
| Sex               |     |                    |         |                  |
| Male              | 266 | 2.06 (1.05–4.05)    | 0.04    |                  |
| Female            | 91  | 1.81 (0.31–10.61)   | 0.51    |                  |
| Age-group         |     |                    |         |                  |
| <60 years         | 217 | 2.24 (1.04–4.81)    | 0.04    |                  |
| ≥60 years         | 140 | 1.72 (0.54–5.51)    | 0.36    |                  |
| Time from symptom onset to baseline CT |     |                    |         |                  |
| <12 hours         | 246 | 1.96 (0.99–3.89)    | 0.05    |                  |
| ≥12 hours         | 93  | 2.46 (0.48–12.67)   | 0.28    |                  |
| Baseline ICH volume group |     |                    |         |                  |
| <30 mL            | 284 | 1.73 (0.90–3.36)    | 0.10    |                  |
| ≥30 mL            | 73  | 4.14 (0.63–27.40)   | 0.14    |                  |
| Systolic blood pressure group |     |                    |         |                  |
| <139 mm Hg        | 43  | 4.34 (0.83–22.68)   | 0.08    |                  |
| ≥139 mm Hg        | 290 | 1.77 (0.86–3.64)    | 0.12    |                  |
| Diastolic blood pressure group |     |                    |         |                  |
| <89 mm Hg         | 89  | 1.82 (0.51–6.55)    | 0.36    |                  |
| ≥89 mm Hg         | 244 | 2.01 (0.94–4.28)    | 0.07    |                  |
| Hypertension      |     |                    |         |                  |
| No                | 48  | 1.06 (0.20–5.61)    | 0.94    |                  |
| Yes               | 299 | 2.07 (1.03–4.17)    | 0.04    |                  |
| Smoking           |     |                    |         |                  |
| No                | 252 | 1.29 (0.60–2.76)    | 0.51    |                  |
| Yes               | 83  | 10.23 (2.15–48.65)  | 0.004   |                  |
| Alcohol consumption|    |                    |         |                  |
| No                | 271 | 1.58 (0.77–3.25)    | 0.26    |                  |
| Yes               | 62  | 9.37 (1.25–70.01)   | 0.03    |                  |
| Glucose group     |     |                    |         |                  |
| <11.1 mmol/L      | 273 | 2.41 (1.14–5.10)    | 0.02    |                  |
| ≥11.1 mmol/L      | 28  | 0.26 (0.01–4.86)    | 0.36    |                  |
| Location          |     |                    |         |                  |
| Deep              | 241 | 2.81 (1.23–6.46)    | 0.01    |                  |
| Lobar             | 66  | 1.02 (0.20–5.26)    | 0.98    |                  |
| Infratentorial    | 50  | 1.33 (0.32–5.56)    | 0.69    |                  |

Statistically significant values are given in bold. Variables are presented as n (%) for nominal data; mean ± standard deviation or median (interquartile range) for continuous data.
Univariate Analysis
The results of the univariate analysis are shown in Table 2 and indicated that systolic blood pressure, diastolic blood pressure, baseline ICH volume, hypertension, smoking, alcohol consumption, lobar location, and random blood glucose were not associated with hematoma expansion. We also found that sex (OR, 0.97; 95% CI, 0.96–1.00), and the time from onset of symptoms from baseline CT (OR, 0.97; 95% CI, 0.96–0.99) were statistically insignificantly associated with hematoma expansion. In contrast, univariate analysis showed heterogeneity (OR, 2.09; 95% CI, 1.25–3.49 vs. homogeneity) and location: infratentorial (OR, 2.02; 95% CI, 1.04–3.92 vs. deep location) were positively correlated with hematoma expansion.

Results of Unadjusted and Adjusted Analysis
In this study, we constructed 2 models to analyze the independent effects of heterogeneity on hematoma expansion. Table 3 lists the effect sizes. In the unadjusted model (crude model), hematoma heterogeneity increased the risk of hematoma expansion by 1.09 times compared with nonhematoma heterogeneity (OR, 2.09; 95% CI, 1.25–3.49). After adjusting for sex, age, location, time from symptom onset to baseline CT, and baseline ICH volume (model 1), the patients’ risk of hematoma expansion increased by 1.06 times compared with nonhematoma heterogeneity (adjusted OR, 2.06; 95% CI, 1.10–3.86).

Subgroup Analysis
The results of the subgroup analyses are shown in Table 4. Only smoking status was observed to modify the association between hematoma heterogeneity and hematoma expansion (P = 0.02). In nonsmokers, the risk of cerebral hemorrhage expansion in the hematoma heterogeneity group increased by 0.29 times (adjusted OR, 1.29; 95% CI, 0.60–2.76). However, a stronger association between hematoma heterogeneity and hematoma expansion was observed in smokers. In smoking patients, the risk of expansion in the hematoma heterogeneity group increased by 0.23 times (adjusted OR, 10.23; 95% CI, 2.15–48.65). Compared with the significantly different association observed in nonsmokers and current smokers, we did not observe an interaction of age, sex, time from onset of symptoms to baseline CT, baseline ICH volume, systolic blood pressure, diastolic blood pressure, hypertension, alcohol consumption, random blood glucose, and location (P > 0.05).

DISCUSSION
Our research confirmed previous findings that heterogeneity increases the risk of hematoma expansion, but it also found that smoking status could modify the association between hematoma heterogeneity and hematoma expansion. Among smokers, the association between hematoma heterogeneity and hematoma expansion is nearly 10 times stronger than that of nonsmokers. Clinicians are therefore advised to consider the patient’s smoking history when assessing the patient’s risk of increased bleeding and give priority care to these patients.

Barras et al.14 first reported that hematoma heterogeneity independently predicted the expansion of ICH and further studies reported similar findings.6–11 The results of the present study are similar to those previously reported. To the best of our knowledge, other studies have not reported the effect of hematoma heterogeneity in different populations (e.g., by gender, lifestyle habits, and underlying diseases), prompting the subanalyses performed in the present study. As a result, we found that the relationship between hematoma heterogeneity and hematoma expansion was significantly different in smokers, which was a novel finding.

Many studies have confirmed that smoking is positively correlated with the incidence of ICH.16,17 In contrast, the relationship between smoking and hematoma heterogeneity and hematoma expansion is not clear. Smoking can affect the possible mechanism of the relationship between hematoma heterogeneity and hematoma expansion. Tobacco smoke contains hundreds of toxins,20 which can promote the formation of free radicals, which in turn leads to damage and dysfunction of the vascular endothelium. An injury to the arterial wall in smoking patients can cause the rupture of the small arteries of the brain parenchyma.21 Furthermore, coagulation disorder of the small arterial vascular endothelium can lead to a continuous bleeding state, which manifests as an enlarged hematoma on the reexamination of CT. Our results show that smokers with hematoma heterogeneity have a significantly higher risk of hematoma expansion than smokers without hematoma heterogeneity. This finding suggests the need for comprehensive assessment of patients with suspected cerebral hemorrhage by the clinicians as early as possible. In particular, it is necessary to obtain patients’ history of smoking and CT examination results, to focus more closely on smoking patients with hematoma heterogeneity. The condition of the patients with cerebral hemorrhage is often unstable in the first few days of onset, and nearly half the deaths occur within the first 2 days.22 The expansion of hematoma is closely related to the mortality in hemorrhagic stroke.23 Therefore, vital sign monitoring, neurologic assessment, and continuous cardiopulmonary monitoring should be performed routinely and continuously in smoking patients with hematoma heterogeneity. If the condition of such patients deteriorates, clinicians should consider the possibility of the progress of cerebral hemorrhage and arrange CT examinations for the patients in time and evaluate whether surgical intervention is needed. This finding also improves our understanding of the effects of smoking on human health and helps explain the cardiovascular benefits of smoking cessation.

This study has some limitations. First, our research objective focused on patients with spontaneous cerebral hemorrhage. Therefore, the generalizability of the research findings may be limited. Second, because arteriovenous malformations, intracranial aneurysm rupture, brain trauma, brain tumor hemorrhage, secondary cerebral hemorrhage caused by blood system diseases, severe imaging artifacts, or hemorrhage after cerebral infarction were excluded, the results of this study may not be applicable to these patients.
CONCLUSIONS
Our study showed that heterogeneity predicts hematoma expansion independently and the risk of hematoma expansion is significantly increased in smoking patients.

DECLARATION OF COMPETING INTEREST
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Haihua Wei: Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing.
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