Liver Fibrosis and Perihematomal Edema Growth in Primary Intracerebral Hemorrhage

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Abstract

Background/Objectives—Liver disease is associated with altered serum osmolality, increased thrombin generation, and systemic inflammation, all of which may contribute to perihematomal edema (PHE) after intracerebral hemorrhage (ICH). We evaluated the association between a validated liver fibrosis index and PHE growth in a cohort of patients with primary ICH.

Methods—We performed a retrospective cohort study using data from the Virtual International Stroke Trials Archive-ICH. We included adult patients with primary ICH presenting within 6 hours of symptom onset. The exposure of interest was the Fibrosis-4 (FIB-4) score, a validated liver fibrosis index; this was modeled as a continuous variable. The primary outcome was absolute PHE growth over 96 hours. Secondary outcomes were absolute admission and 96-hour PHE volumes. We used multiple linear regression models adjusted for established determinants of PHE. In a secondary analysis, the FIB-4 score was modeled as a categorical variable to compare patients with versus without liver fibrosis.

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1. This manuscript complies with all instruction to authors.

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4. Ethical guidelines were followed. Trials included in the VISTA-ICH cohort were performed with institutional review board and/or regulatory approval, and our analysis was approved by the Weill Cornell Medicine institutional review board.

6. The STROBE checklist for observational research is uploaded along with the manuscript.

Results—Among 354 patients with ICH, 8% had evidence of liver fibrosis based on a validated cut-off. The FIB-4 score was not associated with PHE growth in unadjusted (β, 0.03; 95% CI, −0.01–0.12) or adjusted models (β, 0.04; 95% CI, −0.03–0.13). In a secondary analysis treating FIB-4 as a categorical variable, patients with liver fibrosis did not have greater PHE growth than those without liver fibrosis. FIB-4 score was also not associated with absolute admission or 96-hour absolute PHE volumes.

Conclusions—In a multicenter cohort of patients with primary intracerebral hemorrhage, a liver fibrosis score was not associated with PHE volume or growth.

Keywords

Intracerebral hemorrhage; epidemiology; liver fibrosis; perihematomal edema

Introduction

Medical and surgical interventions targeting hematoma expansion after primary intracerebral hemorrhage (ICH) have shown modest survival benefits with no improvement in major disability.[1,2] There is growing recognition that secondary injury after ICH may be a target to improve patient outcomes.[2,3] A robust surrogate marker for such secondary injury is perihematomal edema (PHE); PHE growth is associated with worse functional outcomes after ICH.[3,4] Changes in local osmotic gradients and an inflammatory response, for example in reaction to thrombin, are among mechanisms implicated in the evolution of PHE.[3] Such aberrations are frequently seen in patients with liver disease, who can have abnormal serum osmolality,[5,6] increased thrombin generation,[7] and systemic inflammation.[8,9] Therefore, it is biologically plausible that liver disease is associated with PHE.

Liver fibrosis, seen in up to 15% of the general population, is an often subclinical manifestation of chronic liver diseases and can be detected using non-invasive tests.[10–12] There is a growing appreciation of the role of subclinical liver fibrosis in human disease.[13,14] We hypothesized that subclinical liver fibrosis – liver fibrosis in a population without overt liver disease – is a potentially unrecognized contributor to PHE in patients with ICH. We evaluated the association between a validated, noninvasive liver fibrosis index and 96-hour PHE growth and absolute PHE volumes in a multicenter cohort of patients with ICH.

Methods

Data Source and Study Design

We performed a retrospective cohort study using data from the Virtual International Stroke Trials Archive ICH (VISTA-ICH).[15] The VISTA-ICH database (www.vistacollaboration.org) houses anonymized, individual patient-level data from completed trials that meet the following requirements: 1) documented entry criteria into a trial with a minimum of 50 randomized patients with ICH; 2) documented consent or waiver of consent from a local ethics board; 3) baseline assessment within 24 hours of ICH; 4) baseline assessment of neurologic deficit at the time of admission; 5) confirmation of ICH by cerebral imaging within 7 days; 6) outcome assessment between 1 and 6 months with a validated stroke scale; and 7) data validation through monitoring.[4] The cohort studied in this

analysis was comprised of patients in the placebo arms of all trials and intervention arms of neutral non-surgical trials. Trials largely excluded patients with overt, advanced liver disease. Trials included in the VISTA-ICH cohort were performed with institutional review board and/or regulatory approval, and our analysis was approved by the Weill Cornell Medicine institutional review board. Per the terms of VISTA-ICH's data use agreement, data used in this analysis cannot be shared directly with other investigators; however, investigators may gain access by submitting a formal application to VISTA-ICH.

Population

We included adult patients with primary ICH who presented within 6 hours of symptom onset. We excluded patients with missing liver chemistries needed to calculate our exposure variable and missing PHE data; only patients with ~96 hour CT scans were included in the study data from VISTA-ICH, so this was available for all patients in our sample. We excluded patients with known overt liver disease to minimize the impact of severe derangements seen in end-stage cirrhosis, and excluded patients with potentially secondary liver chemistry abnormalities due to self-reported alcohol use and use of potentially hepatotoxic medications (valproic acid, amiodarone, methotrexate, and tamoxifen).[16] These exclusions were omitted in a *post hoc* analysis, described below.

Exposures

We calculated the Fibrosis-4 (FIB-4) score for each patient at the time of admission as follows:

$$FIB - 4 = \frac{age\ (years)\ *\ asparate\ aminotransferase\left(\frac{Units}{Liter}\right)}{platelet\ count\left(\frac{10^9}{Liter}\right) * \sqrt{alanine\ aminotransfersae\ (\frac{Units}{Liter})}}$$

The FIB-4 score has been validated to have good accuracy for the non-invasive detection of liver fibrosis across multiple underlying etiologies of liver disease, including nonalcoholic fatty liver disease, hepatitis B, hepatitis C, and alcoholic liver disease.[17–21] Using conservative cut-offs, a FIB-4 score > 3.25 corresponds with a high probability of advanced liver fibrosis, and a score of < 1.45 corresponds to a low probability of liver fibrosis.[21] We chose the FIB-4 score for this analysis because we previously demonstrated that the prevalence of liver fibrosis by this score in VISTA-ICH correlated well with population-based estimates of the prevalence of liver fibrosis.[14]

Outcomes

Our primary outcome was PHE growth, which was defined as the absolute difference between the PHE volume at 96 hours and the PHE volume on admission, calculated from computed tomography scans performed without contrast. We chose this as the primary outcome based on our prior work demonstrating an association between absolute PHE growth and functional outcomes.[4] The PHE volume were calculated using semiautomated planimetry and were read centrally within each specific trial by a panel of radiologists blinded to outcomes.[4,22] This method of PHE assessment has been shown to have a high

inter-rater reliability (correlation coefficient of 0.98).[23] Secondary outcomes were absolute admission PHE volume and 96-hour PHE volume.

Demographics and ICH Characteristics

Demographic and clinical data included age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking, and use of antiplatelet and anticoagulant medication. Clinical markers of ICH severity (Glasgow Coma Scale score, National Institutes of Health Stroke Scale score) were obtained at pre-specified time points. Laboratory data included platelet count and standard liver chemistries. Radiological data were admission hematoma volume, 96-hour hematoma volume, location (lobar, deep, and infratentorial), and intraventricular hemorrhage.

Statistical Analyses

Patient characteristics were described using standard descriptive statistics. Discrete variables are presented as counts (percentages [%]) and continuous variables as means (standard deviation [SD]) or medians (interquartile range [IQR]), as appropriate. Pearson Chi-squared test was used for categorical variables as appropriate; the Student's t test or Wilcoxon rank sum test were used for continuous variables depending on the normality of distribution. Fibrosis indices were treated as continuous variables. We used multiple linear regression models to assess the relationship between the continuous FIB-4 score and absolute PHE growth, which was log transformed, in addition to the secondary outcomes of absolute admission and 96-hours PHE volumes. We *a priori* specified the following universal confounders and potential predictors[3,4,22] of PHE growth, based in part on prior work including in the VISTA-ICH dataset, as model covariates: age, sex, race, antiplatelet use, serum sodium, admission ICH volume, and ICH location. In a secondary analysis, we evaluated the association between a high FIB-4 score consistent with advanced liver fibrosis (>3.25) and PHE growth, as compared to patients with a low FIB-4 score (<1.45) consistent with absent liver fibrosis.

We performed several *post hoc* analyses to evaluate whether our null association findings were consistent across several additional approaches. First, we evaluated the associations between the FIB-4 score and PHE volumes and growth in a sample of all patients, without exclusion for overt liver disease, self-reported alcohol use, or hepatotoxic medications. In this analysis, we restricted models to three covariates. This was done in part to mitigate concerns regarding over-fitted models. In this model, age was excluded because age is already included in the FIB-4 score, and sodium was excluded because it may be a mediator. Second, to address the converse possibility of residual confounding, we added warfarin to existing models. Third, we added an additional outcome measure: relative PHE growth, which was defined as 96-hour PHE volume/admission PHE volume. *Post hoc* analyses adhered to the specification of our primary analysis: the exposure variable (FIB-4) was treated as a continuous variable in these analyses. Last, we separately evaluated univariate associations of AST and ALT with PHE growth and volumes.

Statistical analyses were performed using Stata (version 14.0, College Station, TX). All analyses were two-tailed with the threshold of statistical significance allowing for an alpha error of 0.05.

Results

The VISTA-ICH dataset consisted of 591 patients of whom 354 were eligible for our study (Figure 1). The mean age was 65 years (SD, 12), and 66% were men. Warfarin use was noted in 6% and antiplatelet use in 19% of patients. Based on validated cut-offs, 8.1% had a FIB-4 score consistent with a high probability of advanced liver fibrosis, and 44.1% had a low probability of any liver fibrosis. The median admission ICH volume was 14.8 milliliters (IQR, 7.5–26.3), the median admission PHE volume was 8.6 milliliters (IQR, 4.7–14.3), and the median PHE volume at ~96 hours was 23.3 milliliters (IQR, 11.7–37.2).

In the unadjusted model, FIB-4 score was not associated with PHE growth ($\beta = 0.03$, 95% confidence interval [CI], −0.01–0.12). FIB-4 score was also not associated with PHE growth in models after adjusting for age, sex, race, serum sodium, antiplatelet use, admission ICH volume, and ICH location ($\beta = 0.04$, 95% CI, −0.03–0.13) (Table 2). In a secondary analysis, we evaluated the association between a high FIB-4 score and PHE growth, as compared to patients with a low FIB-4 score. Crude or log transformed PHE expansion volumes did not differ by liver fibrosis group (high probability, indeterminate probability, low probability) (Figure 2). Patients with high FIB-4 scores did not have greater PHE growth than patients with low scores in unadjusted ($\beta = 0.03$, 95% CI, −0.46–0.39) or adjusted models ($\beta = 0.12$, 95% CI, −0.32–0.55) (Table 2).

Secondary outcomes were absolute admission PHE volume and 96-hour PHE volume. FIB-4 score was not associated with admission PHE volume in the unadjusted model or after adjusting for confounders ($\beta = −0.03$, 95% CI, −0.04–0.11) (Table 3). Similarly, there was also no association between FIB-4 and 96-hour PHE volume in any model (Table 3).

Results were consistent across several *post hoc* analyses (Supplemental File). First, FIB-4 was not associated with PHE volume or growth even when including patients with overt liver disease, alcohol use, and use of hepatotoxic medications, and results were consistent in models limited to three covariates (e.g., sex, race, and hematoma volume). Conversely, results were also consistent when adding warfarin to the most adjusted models treating FIB-4 as a continuous variable. Last, the outcome of relative PHE growth was separately examined; an association of FIB-4 with relative PHE growth was not observed. Univariate associations between AST and ALT and PHE parameters were not seen."

Discussion

In a multicenter, retrospective cohort of patients with primary intracerebral hemorrhage, a liver fibrosis score was not associated with PHE volume or increased PHE growth.

Multiple prior studies have demonstrated that chronic liver disease is associated with worse outcomes after ICH.[14,24,25] PHE growth is one determinant of outcomes after ICH,[4,22] and our data provide insufficient evidence to support the hypothesis that liver fibrosis contributes

to worse outcomes through an association with PHE volume or growth. Rather, as we previously demonstrated in the VISTA-ICH cohort, an independent association between liver fibrosis and hematoma volume and growth[14] may underlie the link between liver disease and outcomes after ICH. Other data suggest that non-neurological factors such as susceptibility to infection and liver-related complications are responsible for poor outcomes.[25–27] An improved understanding of mechanistic factors in the association between liver disease and outcomes after ICH may yield novel opportunities for intervention. This is especially the case for liver fibrosis because it is both common and frequently subclinical,[10–12] and its role in cerebrovascular disease is largely unrecognized.

Our null findings must be considered in light of several caveats. First, our focus was to understand the role of subclinical liver fibrosis in PHE volume and growth. The VISTA-ICH cohort was well-suited for this because randomized trials contributing data to VISTA-ICH largely excluded patients with overt, advanced liver disease, and we further excluded the few patients with overt liver disease. Based on our data, there is insufficient evidence of an association between subclinical liver fibrosis and PHE growth; however, our data are not intended to address the impact of end-stage, clinically overt liver disease on PHE. With that said, our results did not meaningfully change with inclusion of patients with overt liver disease and alcohol-use. Second, hematoma volumes were small in VISTA-ICH; patients contributing data to VISTA-ICH trials had clinically and radiographically mild ICH. Because ICH volume is a known determinant of PHE volume and growth,[4] our data do not address the possibility that liver fibrosis is associated with PHE growth in patients with more severe hematomas. Third, while the FIB-4 liver fibrosis score is validated, it is possible that misclassification of liver fibrosis biased our findings towards the null. Specifically, the performance of the FIB-4 score may be suboptimal in unselected patients, e.g., patients without known chronic liver disease who may have a lower pre-test probability of liver fibrosis. However, the concordance of the prevalence of liver fibrosis in VISTA-ICH defined by the FIB-4 with population-based estimates[10–12] partially mitigates this concern. Additionally, in primary analyses, we used the FIB-4 score as a continuous variable in part because the cut-off used to exclude liver fibrosis may vary with age;[28] therefore, the results of our secondary analysis comparing high versus low FIB-4 scores must be interpreted with caution.

Conclusions

In conclusion, there is insufficient evidence of an association between a liver fibrosis score and PHE volume or growth after ICH. Future studies should investigate alternate mechanisms by which liver fibrosis may impact outcomes in ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

APPENDIX

*VISTA-ICH Steering Committee

VISTA-ICH Steering Committee Collaborators: D.F. Hanley (Chair), K. Butcher, S. Davis, B. Gregson, K.R. Lees, P. Lyden, S. Mayer, K. Muir, and T. Steiner.

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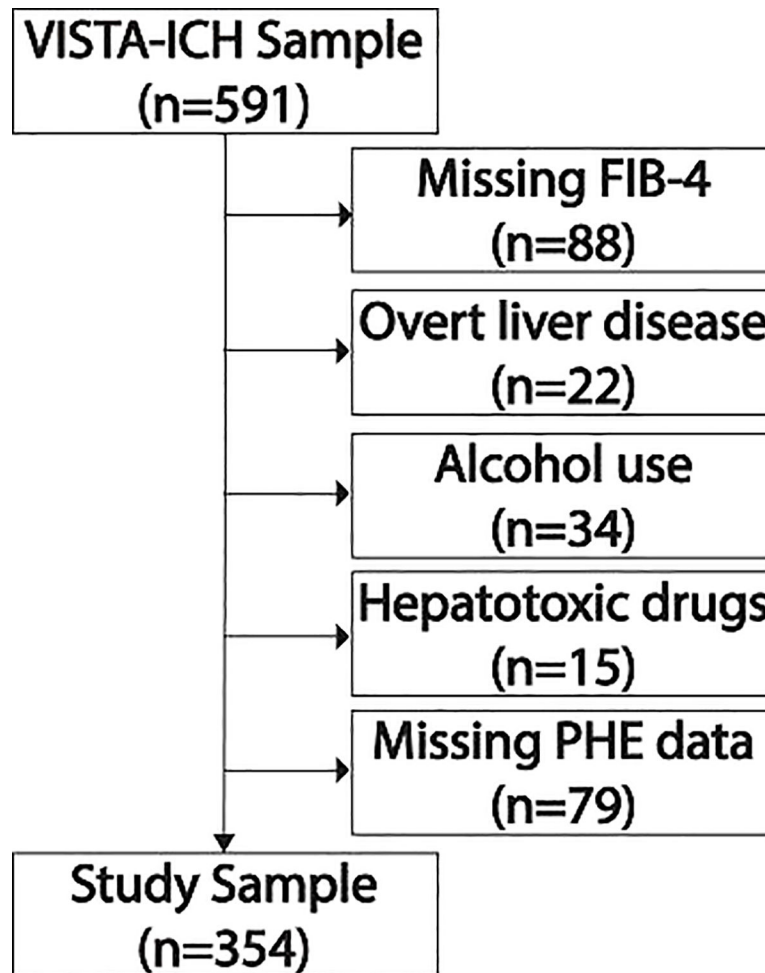
Figure 1.
Patient selection flow diagram.

Patients with missing laboratory data, known overt liver disease, alcohol use, use of potentially hepatotoxic medications, and missing perihematomal edema data were excluded. Some patients had multiple reasons for exclusion. Abbreviations: VISTA-ICH, Virtual International Stroke Trials Archive–Intracerebral Hemorrhage; FIB-4, Fibrosis-4; PHE, perihematomal edema.
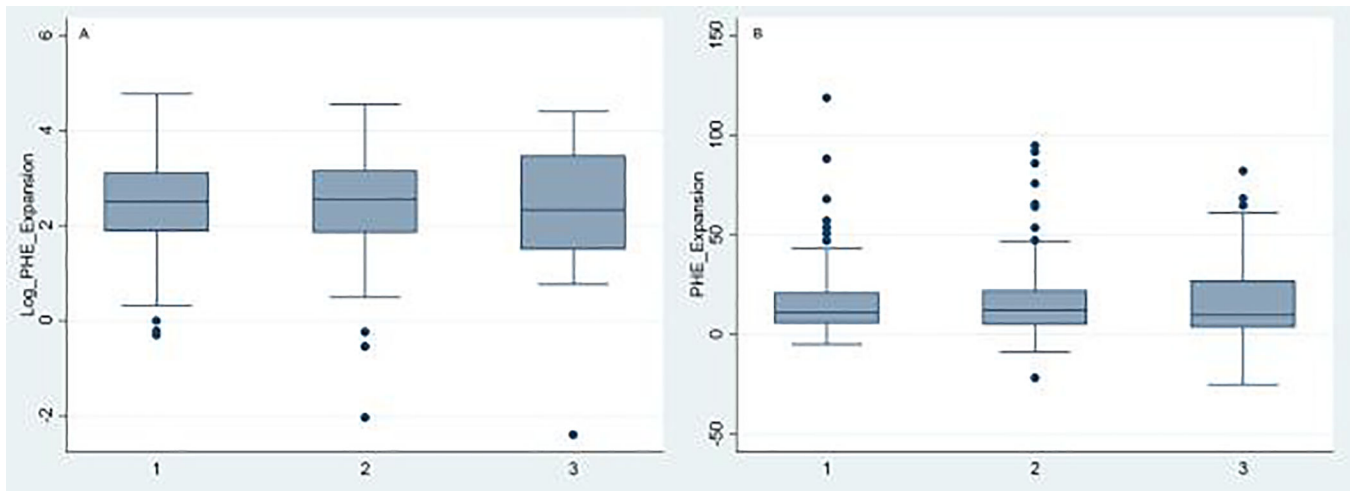
Figure 2.
Box-whisker plot of perihematomal edema volume growth by category of Fibrosis-4 liver fibrosis score.

Log transformed (A) and absolute [milliliters] (B) 96-hour perihematomal edema volume growth, defined as the difference between the 96-hour and admission volumes, categorized by Fibrosis-4 liver fibrosis score category: (1) low probability of liver fibrosis [Fibrosis-4 < 1.45], (2) intermediate probability [Fibrosis-4 1.45–3.25], (3) high probability [Fibrosis-4 > 3.25]. Abbreviations: PHE, perihematomal edema.

Table 1.

Characteristics of Patients with Primary Intracerebral Hemorrhage in VISTA-ICH.

Characteristic[*]	Study Sample (N=354)
Patient Characteristics	
Age, mean (SD), years	64.6 (11.5)
Male sex	232 (66)
Race	
White	291 (82)
Black	16 (5)
Other	47 (13)
Hypertension	293 (83)
Hyperlipidemia	53 (15)
Diabetes mellitus	66 (19)
Atrial fibrillation	28 (8)
Warfarin use	21 (6)
Antiplatelet use	68 (19)
Admission Laboratory Data	
Platelet count[†], $\times 10^3$ per microliter	217 (182–259)
International Normalized Ratio[†]	1.0 (0.9–1.1)
aPTT[†], seconds	24.6 (21.5–29.2)
AST[†], units/liter	23 (2–38)
ALT[†], units/liter	20 (15–29)
Albumin[†], gram/dL	41 (39–44)
Total bilirubin[†], milligram/dL	0.5 (0.3–0.7)
Admission Intracerebral Hemorrhage Data	
Glasgow Coma Scale[†]	15 (14–15)
National Institutes of Health Stroke Scale[†]	13 (9–17)
Intraventricular hemorrhage	107 (30)
Hematoma location	
Lobar	73 (21)
Deep	274 (77)
Infratentorial	7 (2)
Time to admission CT scan[†], hours	1.8 (1.1–2.5)
Hematoma volume at admission[†], mL	14.8 (7.5–26.3)
Perihematoma edema volume at admission[†], mL	8.6 (4.7–14.3)
96-hour Intracerebral Hemorrhage Imaging Data	

Characteristic [*]	Study Sample (N=354)
Time to 96-hour CT scan [†], hours	87.6 (83.2–98.2)
Hematoma volume at 96 hours [†], mL	17.1 (8.2–33.9)
Perihematoma edema volume at 96 hours [†], mL	23.3 (11.7–37.2)

Abbreviations; VISTA-ICH, Virtual International Stroke Trials Archive-Intracerebral Hemorrhage; SD, standard deviation; aPPT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; dl, deciliter; mL, milliliters; μL, microliter.

[*] Data reported as n (%) unless otherwise specified.

[†] Data reported as median (interquartile range).

Table 2.

Association[*] between Fibrosis-4 Liver Fibrosis Score and Perihematomal Edema Growth after Primary Intracerebral Hemorrhage

Primary analysis: Fibrosis-4 score, continuous			
	Beta	95% Confidence Interval	P value
Unadjusted	0.03	−0.01 – 0.12	0.48
Model 2	0.07	−0.01 – 0.18	0.10
Model 3	0.04	−0.04 – 0.12	0.36
Model 4	0.04	−0.03 – 0.13	0.26

Secondary analysis: High Fibrosis-4 versus Low Fibrosis-4[†]			
	Beta	95% Confidence Interval	P value
Unadjusted	0.03	−0.46 – 0.39	0.88
Model 2	0.24	−0.25 – 0.73	0.34
Model 3	0.07	−0.36 – 0.50	0.75
Model 4	0.12	−0.32 – 0.55	0.60

[*] Multiple linear regression was used to model the association between the Fibrosis-4 score and absolute 96-hour perihematomal edema (PHE) growth, which was defined as: absolute difference between 96-hour PHE volume and admission PHE volume. Model 2 was adjusted for age, sex, and race. Model 3 was additionally adjusted for serum sodium, antiplatelet use, and admission hematoma volume. Model 4 was additionally adjusted for intracerebral hemorrhage location (lobar versus deep versus infratentorial). PHE growth was log transformed.

[†] Patients with a high Fibrosis-4 score (>3.25) were compared to patients with a low Fibrosis-4 score (<1.45).

Table 3.

Association [*] between Fibrosis-4 Liver Fibrosis Score and Admission and 96-hour Perihematomal Edema Volumes in Primary Intracerebral Hemorrhage

Admission PHE volume			
	Beta	95% Confidence Interval	P value
Unadjusted	0.03	−0.04–0.11	0.36
Model 2	0.03	−0.05–0.11	0.41
Model 3	−0.03	−0.08–0.02	0.23
Model 4	−0.03	−0.08–0.02	0.28
96-hour PHE volume			
	Beta	95% Confidence Interval	P value
Unadjusted	0.02	−0.06–0.94	0.64
Model 2	0.04	−0.36–0.13	0.28
Model 3	−0.01	−0.07–0.05	0.78
Model 4	−0.002	−0.06–0.06	0.94

[*] Multiple linear regression was used to model the association between the Fibrosis-4 score (continuous measure) and absolute admission and 96-hour perihematomal edema volumes. Model 2 was adjusted for age, sex, and race. Model 3 was additionally adjusted for serum sodium, antiplatelet use, and admission hematoma volume. Model 4 was additionally adjusted for intracerebral hemorrhage location (lobar versus deep versus infratentorial). PHE volumes were log transformed.