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Perihematomal Edema Expansion Rates and Patient Outcomes in Deep and Lobar Intracerebral Hemorrhage

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CONFLICT OF INTEREST

None of the authors has any conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Abstract

Background and Purpose—Perihematomal edema (PHE) expansion rate may predict functional outcome following spontaneous intracerebral hemorrhage (ICH). We hypothesized that the effect of PHE expansion rate on outcome is greater for deep versus lobar ICH.

Methods—Subjects (n=115) were retrospectively identified from a prospective ICH cohort enrolled from 2000–2013. Inclusion criteria were age ≥18 years, spontaneous supratentorial ICH, and known onset time. Exclusion criteria were primary intraventricular hemorrhage (IVH), trauma, subsequent surgery, or warfarin-related ICH. ICH and PHE volumes were measured from CT scans and used to calculate expansion rates. Logistic regression assessed the association between PHE expansion rates and 90-day mortality or poor functional outcome (modified Rankin Scale >2). Odds ratios are per 0.04 mL/h.

Results—PHE expansion rate from baseline to 24 hours (PHE24) was associated with mortality for deep (p=0.03, OR 1.13[1.02–1.26]) and lobar ICH (p=0.02, OR 1.03[1.00–1.06]) in unadjusted regression, and in models adjusted for age (deep: p=0.02, OR 1.15[1.02–1.28]; lobar: p=0.03, OR 1.03[1.00–1.06]), Glasgow Coma Scale (deep: p=0.03, OR 1.13[1.01–1.27]; lobar: p=0.02, OR 1.03[1.01–1.06]), or time to baseline CT (deep: p=0.046, OR 1.12[1.00–1.25]; lobar: p=0.047, OR 1.03[1.00–1.06]). PHE expansion rate from baseline to 72 hours (PHE72) was associated with mRS>2 for deep ICH in models that were unadjusted (p=0.02, OR 4.04[1.25–13.04]) or adjusted for ICH volume (p=0.02, OR 4.3[1.25–14.98]), age (p=0.03, OR 5.4[1.21–24.11]), GCS (p=0.02, OR 4.19[1.2–14.55]), or time to first CT (p=0.03, OR 4.02[1.19–13.56]).

Conclusions—PHE72 was associated with poor functional outcomes after deep ICH, whereas PHE24 was associated with mortality for deep and lobar ICH.

Keywords

Intracerebral Hemorrhage; Biomarker; Cerebral Edema; Function; Mortality; Computed Tomography (CT)

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most common subtype of stroke, constituting 10–15% of the 15 million strokes worldwide each year [1]. Outcomes are often devastating, with a one-month case fatality rate of 40% and with only 20% of patients achieving functional independence [2, 3]. Despite these severe outcomes, there are no effective medical or surgical therapeutic options available [4]. In order to develop novel ICH treatments, it is essential to identify reliable, modifiable predictors of ICH outcome. Doing so will enable the discovery of promising therapies in proof-of-concept pre-phase III studies [5, 6].

Interventions targeting ICH expansion have not shown clinical benefit to date [1], generating interest in targeting additional mechanisms of secondary injury, including perihematomal edema (PHE). Secondary cascades initiated by products of coagulation, clot retraction, and hemoglobin degradation further injure brain parenchyma over a time window more amenable to treatment than primary injury [4, 7]. These same processes increase PHE formation, which may then exacerbate or predict neurological deterioration. However, data on the influence of PHE on patient outcomes are inconsistent and the optimal measures of PHE are still being defined [6–9].

Recent work has demonstrated an accurate and reproducible method for measuring PHE from computed tomography (CT) [10], as well as evidence that PHE expansion rate from admission to 24 or 72 hours post-ICH independently predicts 90-day mortality and functional outcome [11]. The objective of this analysis was to determine whether PHE expansion rate is associated with outcome for both deep and lobar ICH and, if so, whether its effect varies depending on the site of hemorrhage. We hypothesized a larger effect on outcomes in deep ICH because there is literature suggesting worse outcomes in these patients [12, 13]. PHE may partially explain this difference in outcomes if deep brain regions are more susceptible to PHE's contribution to mass effect or to its underlying processes. If PHE expansion is to be used in the future as a diagnostic tool or therapeutic target, it is imperative to have a greater understanding of whether its effects are heterogeneous and influenced by ICH location.

MATERIALS AND METHODS

Subjects

Subjects (n=115) were retrospectively identified from a longitudinal Institutional Review Board-approved prospective cohort study of ICH performed at Massachusetts General Hospital between 2000 and 2013. All subjects or their surrogates gave written informed consent for participation. Clinical data were obtained by interviewing subjects (or their surrogates) and by reviewing hospital records. Blood pressures (Table 1) were obtained at admission. The clinical outcomes, 90-day mortality and 90-day modified Rankin Scale (mRS), were assessed by telephone by trained study staff and supplemented by inspection of the Social Security Death Index. Subjects received routine clinical care and were not recipients of any investigational intervention or treatment protocol.

Inclusion criteria for this study were: 18 years of age, spontaneous supratentorial ICH confirmed on CT, known time of ICH onset, >1 CT scan available, and admission within 36 hours of symptom onset. Exclusion criteria were: infratentorial hemorrhage, primary intraventricular hemorrhage, trauma, warfarin-related ICH, or subsequent surgery or ventriculostomy placement. These exclusion criteria were selected to remove subjects with characteristics that may confound the detection of a meaningful relationship between PHE and outcome. For example, warfarin alters the clotting cascade, and the clotting cascade may contribute to early PHE formation. Decompressive craniectomy can mitigate the damage that PHE expansion inflicts through mass effect and could also alter PHE production [7, 14].

Initially, our cohort included 497 eligible adult subjects diagnosed with primary spontaneous ICH with a known time of onset. We excluded subjects with primary or isolated intraventricular hemorrhage (n=35), infratentorial ICH (n=63), or warfarin-related hemorrhage (n=94). We additionally excluded subjects who underwent craniectomy, hematoma evacuation, or ventriculostomy placement (n=198). In the remaining 139 subjects, 115 had the requisite CT scans to calculate PHE expansion rates: 110 had CT scans available at admission and ~24 hours post-ICH while 58 subjects had CT scans available at admission and ~72 hours post-ICH.

Image Analysis

A single rater (SU) measured ICH, PHE, and IVH volumes on CT scans taken closest to 0, 24, or 72 hours post-ICH onset, utilizing a previously validated measurement protocol. This protocol has excellent interrater and intrarater reliability tested on subjects in this cohort measured by reader SU [10]. Briefly, the rater was blinded to clinical data and used the Region of Interest module in Analyze 11.0 (AnalyzeDirect, Overland Park, KS, USA) to delineate the borders of the hemorrhage and PHE in axial slices. The borders were then refined after examining the lesion in each orthogonal plane with the software's Volume Edit module. PHE measurement also met the criteria that PHE appears more hypodense than the same region contralaterally and is most hypodense adjacent to the hemorrhage. This method has shown excellent interrater and intrarater reliability as well as volume measurements similar to those achieved via magnetic resonance imaging [10, 11]. Expansion rates were calculated by dividing the difference in volume measurements by the elapsed time between serial CT scans and expressed as a continuous variable. ICH locations were determined on admission CT scans by study neurologists who were blinded to clinical data.

Statistical Analysis

Statistical analyses were performed using Statistical Analysis System 9.3 (SAS Institute Inc., Cary, NC, USA). Subjects with ICH in the basal ganglia or thalamus were assigned to the deep ICH group while subjects with ICH in cortical regions were assigned to the lobar ICH group. Logistic regression was used to examine the relationship between PHE expansion rate at 24 and 72 hours and mortality and functional outcome on the modified Rankin Scale in the deep and lobar groups.

To reduce bias from withdrawal of care and other early causes of death, the majority of which occur within the first 72 hours following ICH [9], we examined the relationship

between mortality and the rate of PHE expansion within the first 24 hours. To test the association between PHE expansion and functional outcome, we chose the time point of 72 hours after ICH onset because this is the time point at which the rate of PHE expansion peaks and is likely to have the largest impact on function [7].

Deep and lobar ICH groups were also analyzed in combined, unadjusted models with interaction terms to measure any differences in effect size by ICH location. An mRS>2 was considered a poor functional outcome. Though the sample size was relatively small, we constructed several exploratory bivariable models that adjusted the PHE expansion rates for known predictors of outcome after ICH including Glasgow Coma Scale (GCS) score, age, ICH volume, time to first scan, and ICH expansion (absolute change in ICH volume expressed as a continuous variable). All reported odds ratios are per 0.04 mL/h. Comparisons of demographic and clinical data between the deep and lobar ICH groups were assessed by Student's t-Test for normally distributed continuous variables, Wilcoxon rank-sum test for non-normally distributed continuous variables, or Fisher's exact test for categorical variables. P-values < 0.05 were considered statistically significant.

RESULTS

Of the 497 subjects who presented during the study period with spontaneous ICH, 115 met all inclusion criteria and had the necessary scans to calculate PHE expansion rates. Fifty-nine of these subjects had ICH originating in the basal ganglia and/or thalamus while the remaining 56 subjects had hemorrhage in cortical regions. Clinical and demographic features of these two groups are presented in Table 1. In comparison to the lobar cohort, subjects with deep ICH were younger and hypertensive. The deep cohort additionally had smaller hematomas and larger IVH volumes.

PHE Expansion Rate from Admission to 24 Hours is Associated with Mortality for Deep and Lobar ICH

PHE expansion rate from admission to 24 hours after ICH onset (PHE24) was significantly faster ($P=0.006$) in the Lobar cohort (0.22 mL/h, IQR 0.03–0.90) compared with PHE24 in the deep cohort (0.09 mL/h, IQR –0.02–0.21). In order to determine whether PHE24's effect size varies depending on ICH location when predicting mortality at 90 days, we tested for an interaction between PHE24 and ICH location in an unadjusted logistic regression model. Although the interaction term's p-value was 0.11, we considered this p-value low enough to present stratified analyses of the deep and lobar cohorts as an $\alpha < 0.10$ or 0.20 is commonly used as a cutoff for significance when screening for interactions [15, 16].

Results from the stratified analyses, which consist of several bivariable models that include PHE24 and one known predictor of mortality after ICH [17–21], are presented in Table 2. In bivariable logistic regression models that adjust for age, Glasgow Coma Scale (GCS), or time to first scan, PHE24 was independently associated with 90-day mortality for both deep and lobar ICH. PHE24 was additionally associated with mortality for lobar ICH in models that adjusted for ICH volume or expansion; however, for deep ICH, PHE24 was not a significant predictor of mortality when adjusting for ICH volume ($P=0.08$) or expansion ($P=0.33$). Among all subjects, PHE24 was faster in subjects who died (0.39 mL/h, IQR

0.07–0.95) compared with those who survived (0.09 mL/h, IQR –0.03–0.27; $P=0.004$). The same trend was observed in sub-analyses limited to deep ICH (0.16 mL/h, IQR 0.0001–0.71, died; 0.08 mL/h, IQR –0.03–0.17, survived; $P=0.09$) and to lobar ICH (0.49 mL/h, IQR 0.15–1.91, died; 0.18 mL/h, IQR –0.02–0.61, survived; $P=0.07$).

PHE Expansion Rate from Admission to 72 Hours is Associated with Functional Outcome for Deep ICH

There was no significant difference in the magnitude of the PHE expansion rate from admission to 72 hours post-ICH onset (PHE72) in lobar (0.19 mL/h, IQR 0.02–0.30) versus deep ICH (0.09 mL/h, IQR 0.07–0.14; $P=0.45$). We tested for heterogeneity in PHE72's effect size in an unadjusted logistic regression model and found a significant interaction between PHE72 and ICH location ($P=0.04$). This indicates that PHE72's effect size is different for deep ICH compared to lobar ICH in models predicting functional outcome.

In stratified analyses, presented in Table 3, PHE72 was consistently associated with poor functional outcome for subjects with deep ICH in bivariable logistic regression models that included one additional adjustment variable. This association persisted in bivariable logistic regression models that adjusted for age, hematoma volume, GCS, time to first scan, or ICH expansion. In models that only included lobar ICH subjects, PHE72 was not significantly associated with functional outcome, with or without covariates. In an analysis that included all subjects, PHE72 was faster in those with poor outcomes (0.10 mL/h, IQR 0.07–0.24) compared with in those with good outcomes (0.003 mL/h, IQR –0.02–0.10; $P=0.004$). This was also true in analyses limited to subjects with deep ICH (0.09 mL/h, IQR 0.08–0.14, poor outcome; 0.003 mL/h, IQR –0.01–0.05, good outcome; $P=0.02$) or lobar ICH (0.21 mL/h, IQR 0.05–0.36, poor outcome; 0.01 mL/h, IQR –0.03–0.17, good outcome; $P=0.03$).

DISCUSSION

In this retrospective analysis, we showed that the PHE expansion rate over the first 24 hours following ICH onset (PHE24) was associated with increased mortality within 90-days for both lobar and deep spontaneous supratentorial ICH. The PHE expansion rate over the first 72 hours (PHE72) was associated with poor functional outcome for subjects with ICH located in the thalamus or basal ganglia. These associations persisted in exploratory models that adjusted for known predictors of ICH outcome, with the exception that PHE24 was not a significant predictor of mortality for subjects with deep ICH in models that adjusted for ICH baseline volume or ICH expansion.

The two time periods under investigation in this study were examined in part because they may represent distinct phases of edema formation. In the first 24 hours following ICH onset, PHE arises from serum proteins that leak from the hematoma into the interstitium and establish an osmotic gradient [22]. This gradient is augmented by cytotoxic edema and the downstream activities of thrombin which partially disrupt the blood brain barrier [7, 14]. From 24–72 hours, the release of iron from degraded erythrocytes activates MMP-9, which peaks in expression at about 48 hours post-ICH onset and further degrades the blood brain barrier [6, 7, 23, 24]. The molecular biology of these different phases of PHE progression is still an area of active investigation which may uncover targets for therapeutic intervention.

While PHE continues to accumulate for several weeks, multiple studies have demonstrated that early PHE (72 hours post-ICH) is most indicative of poor outcome [1, 6, 7]. The differences in underlying physiology during these time periods may be relevant to the rational development of therapeutics and biomarkers for ICH outcome such as PHE24 and PHE72.

Although subjects with lobar ICH had faster PHE expansion rates in the first 24 hours, we did not find a significant difference in PHE24's effect on mortality in those with lobar versus deep ICHs. It is possible that in the acute time period, rapid expansion of PHE above a critical threshold rate predisposes patients to subsequent deterioration and death no matter where the ICH is located, as has been described with cutoff IVH volumes [25].

Alternatively, we may have been underpowered to detect an increased effect size in deep ICH compared with lobar ICH, given the direction of effect. For subjects with deep ICH, PHE24 may have not been significantly associated with mortality after adjustment for ICH baseline volume or ICH expansion due to type II error, as in these bivariable models the covariates also fell below the threshold for significance.

In contrast to PHE24, we observed a significantly larger effect size for PHE72 in deep ICH compared with lobar ICH in models that predict poor functional outcome. As described previously, one of the major differences in this later time period compared with the first 24 hours is the pronounced degradation of the blood brain barrier. Subjects with deep ICH presented with higher blood pressures, potentially amplifying the volume of edema fluids traversing the injured blood brain barrier. While the magnitude of PHE72 was not significantly different between the lobar and deep cohorts, it is possible that the edema expansion rate was greater for deep ICH in the 24–72 hour period. In support of this possibility, Vemmos et al. found that patients with elevated blood pressure over the first 24 hours following ICH subsequently had increased PHE formation from days two to five post-onset [26].

Deep structures may also be more susceptible to iron-mediated oxidative stress from degraded hemoglobin and other inflammatory processes which increase during this interval [4, 27, 28]. Additionally, the relative abundance of white matter tracts is greater in lobar regions and cell type-specific differences exist in volume and solute regulation, some of which could represent new pharmacologic targets for ICH [29, 30]. Finally, the ratio of edema to hematoma volume is larger in deep ICH which may increase the relevance of PHE expansion among those with deep ICH.

Presently, no medical or surgical therapies for ICH have been successful in reducing mortality or improving outcomes [4]. Traditional biomarkers, including absolute and relative ICH expansion, have failed to predict outcomes in large clinical studies, which has increased the urgency of developing novel biomarkers for pre-phase III trials [6]. One of the largest studies of ICH ever completed, the INTERACT-2 trial, demonstrated improved functional outcomes in an ordinal analysis with intensive blood pressure management, but found no reduction in absolute or relative hematoma growth [31]. Similarly, the FAST trial found no differences in mortality between their control and treatment groups despite a reduction in

ICH expansion [32]. PHE24 and PHE72 may be attractive new intermediate endpoints to explore for early clinical trials that target secondary injury after ICH.

Prior studies have supported an association between PHE expansion and patient outcomes. Urday et al. found that PHE24 and PHE72 were strong independent predictors of mortality and functional outcome after spontaneous ICH; however, the authors did not account for the relative contribution of different anatomical ICH subtypes in their models [11]. Other groups have studied the effect of relative and absolute PHE expansion with mixed findings. Venkatasubramanian et al. did not find an association between PHE growth from admission to peak volume (average 12 days post-onset) and 90-day functional outcome [23]. In another study, both absolute and relative PHE expansion from baseline to 72 hours were predictors of mortality and functional outcome at 90 days, except when hematoma volume was included in multivariable analyses [8]. Finally, Murthy et al. demonstrated an association between absolute PHE expansion from baseline to 72 hours post-ICH and functional outcome for subjects with ICH in the basal ganglia or with hematoma volumes <30 mL, but did not assess edema expansion in the initial 24 hour interval [33].

This study has several limitations. The small cohort size limited the number of covariates in our analyses and may reduce the external validity of our findings. Despite this limitation, our cohort recapitulates many of the distinguishing demographic and clinical features of deep and lobar ICH reported elsewhere, including hematoma volume, IVH volume, age, and blood pressure [21, 24]. Another limitation is that this study is retrospective and lacks data on other features that might influence PHE expansion such as the use of medical osmotherapy or aggressive lowering of blood pressure. Furthermore, the indications for use of osmotherapy, anti-hypertensives, and other treatments were not standardized which could confound the relationship between edema and outcomes. Because we limited the subjects to those without clinical characteristics that might conceal the effect of PHE24 or PHE72, like those with intratentorial ICH who have a high mortality rate independent of known predictors of ICH outcome [34] and those who underwent surgical intervention, our findings cannot be extrapolated to these groups. Therefore, this study's results may only apply to a subset of ICH patients, potentially those with smaller or less severe ICH. Finally, the precise times and indications for imaging the study subjects were not standardized, possibly biasing the PHE72 cohort to include subjects for whom there was concern for ongoing ICH expansion due to worsening clinical condition. PHE72 may have a larger impact on outcome for these potentially unstable subjects who may have been more susceptible to additional insult compared to those for whom 72-hour imaging was deemed unnecessary.

However, this study also has important strengths. We used an accurate and highly reproducible method for measuring PHE volumes from CT scans that does not depend on magnetic resonance imaging or surrogate measures of PHE volume such as midline shift [10]. Furthermore, this study accounts for the evolving physiology of PHE expansion through the examination of two important and distinct time periods. Finally, the use of a relatively homogenous ICH population is ideal for the selection of a first population in whom to test a novel therapy.

The findings of this study support the need for future investigation of PHE expansion rates in a prospective cohort in which these observations can be independently evaluated. A prospective study would permit the standardization of imaging and the specific recording of adjunct therapies that may affect PHE, such as osmotherapy and blood pressure reduction. With the advent of potential new therapies and strategies that target secondary injury after ICH [7], defining PHE24 and PHE72 as robust and modifiable biomarkers for clinical outcome may aid in the selection of the most promising new therapies and patient populations most likely to benefit from intervention.

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Table 1

Comparison of Deep ICH and Lobar ICH Subjects' Clinical and Demographic Features

	Deep ICH (n=59)	Lobar ICH (n=56)	P Value
Age, median (IQR), y	67.8 (57.1–76.2)	78.4 (72.3–82.7)	<0.001
Male, No. (%)	34 (57.6)	33 (58.9)	1.00
Race, No. (%)			
Caucasian	50 (84.7)	48 (85.7)	1.00
African American	3 (5.1)	5 (8.9)	0.48
Asian	4 (6.8)	1 (1.8)	0.36
Medical History, No. (%)			
Hypertension	50 (84.7)	41 (73.2)	0.17
Diabetes	14 (23.7)	13 (23.2)	1.00
Medication History, No. (%)			
Anti-hypertensive	41 (69.5)	33 (58.9)	0.25
Statin	16 (27.1)	23 (41.1)	0.12
Clinical Features			
Systolic Blood Pressure, mean (SD), mmHg	187.3 (38.2)	174.8 (30.2)	0.03
Diastolic Blood Pressure, mean (SD), mmHg	100.0 (25.0)	89.5 (18.0)	0.006
Body Mass Index, median (IQR)	27.9 (24.2–33.8)	25.5 (22.8–28.9)	0.08
Do Not Resuscitate, No. (%)	15 (25.4)	15 (26.8)	1.00
ICH Baseline Volume, median (IQR), mL	11.3 (6.8–20.4)	36.9 (18.6–65.6)	<0.001
Intraventricular Hemorrhage Baseline Volume, median (IQR), mL	1.4 (0–12.1)	0 (0–0.4)	<0.001
ICH Expansion 24 Hours Post-Onset, median (IQR), mL	0.34 (–0.58–1.71)	0.80 (–1.37–5.30)	0.35
ICH Expansion 72 Hours Post-Onset, median (IQR), mL	–0.07 (–0.87–0.68)	–2.21 (–4.01–4.11)	0.08
Time from Last Seen Well to Admission, median (IQR), h	2.7 (1.3–6.6)	4.7 (2.7–11.9)	0.007
Time from First Known Symptoms to Admission, median (IQR), h	2.3 (1.0–3.0)	3.5 (2.3–5.6)	<0.001
Time from First Known Symptoms to Baseline CT, median (IQR), h	2.9 (1.4–4.7)	5.5 (2.4–7.3)	<0.001
Time from First Known Symptoms to 24-Hour CT, median (IQR), h	22.5 (15.4–27.1)	22.8 (17.6–27.1)	0.45
Time from First Known Symptoms to 72-Hour CT, median (IQR), h	68.6 (64.0–75.8)	65.8 (58.0–75.5)	0.44
Glasgow Coma Scale score, median (IQR)	14 (10–15)	14 (11–15)	0.52
Mortality by 90 days post-ICH, No. (%)	11 (18.6)	19 (33.9)	0.09
Poor Functional Outcome, No. (%)	50 (84.7)	45 (80.4)	0.63

Abbreviations: SD, standard deviation; IQR, interquartile range; ICH, intracerebral hemorrhage

Table 2

PHE24 is Associated with 90-Day Mortality for All ICH

Adjustment Variable	Deep ICH (n=59)		Lobar ICH (n=51)	
	PHE24 Odds Ratio (95% CI)	P Value	PHE24 Odds Ratio (95% CI)	P Value
Unadjusted Model	1.13 (1.02–1.26)	0.03	1.03 (1.0–1.06)	0.02
Age	1.15 (1.02–1.28)	0.02	1.03 (1.0–1.06)	0.02
Baseline Hematoma Volume	1.10 (0.99–1.24)	0.08	1.03 (1.0–1.06)	0.047
Glasgow Coma Scale	1.13 (1.01–1.27)	0.03	1.03 (1.01–1.06)	0.02
Time to First Scan	1.12 (1.0–1.25)	0.046	1.03 (1.0–1.06)	0.047
ICH Expansion 24hrs	1.08 (0.93–1.25)	0.33	1.04 (1.01–1.08)	0.01

Presented odds ratios and p-values measure PHE24's association with 90-day mortality in deep or lobar ICH after adjustment for the predictor in the first column; CI indicates confidence interval, ICH indicates intracerebral hemorrhage, PHE24 indicates perihematoma edema expansion rate from admission to 24 h after ICH onset.

Table 3

PHE72 is Associated with 90-Day Functional Outcome for Deep ICH

Adjustment Variable	Deep ICH (n=32)		Lobar ICH (n=26)	
	PHE72 Odds Ratio (95% CI)	P Value	PHE72 Odds Ratio (95% CI)	P Value
Unadjusted Model	4.04 (1.25–13.04)	0.02	1.17 (0.95–1.44)	0.13
Age	5.39 (1.21–24.11)	0.03	1.2 (0.96–1.51)	0.12
Baseline Hematoma Volume	4.3 (1.25–14.98)	0.02	1.27 (0.95–1.71)	0.11
Glasgow Coma Scale	4.19 (1.2–14.55)	0.02	1.17 (0.95–1.44)	0.15
Time to First Scan	4.02 (1.19–13.56)	0.02	1.18 (0.95–1.46)	0.13
ICH Expansion 72hrs	4.96 (1.24–19.83)	0.02	1.22 (0.96–1.56)	0.11

Presented odds ratios and p-values measure PHE72's association with poor functional outcome (mRS>2) in deep or lobar ICH after adjustment for the predictor in the first column; CI indicates confidence interval, ICH indicates intracerebral hemorrhage, PHE72 indicates perihematoma edema expansion rate from admission to 72 h after ICH onset.