RESEARCH PAPER

Volume-dependent effect of perihaematomal oedema on outcome for spontaneous intracerebral haemorrhages

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ABSTRACT

Introduction It is still unknown whether subsequent perihaematomal oedema (PHE) formation further increases the odds of an unfavourable outcome.

Methods Demographic, clinical, radiographic and outcome data were prospectively collected in a single large academic centre. A multiple logistic regression model was then developed to determine the effect of admission oedema volume on outcome.

Results 133 patients were analysed in this study. While there was no significant association between relative PHE volume and discharge outcome (p=0.713), a strong relationship was observed between absolute PHE volume and discharge outcome (p=0.009). In a multivariate model incorporating known predictors of outcome, as well as other factors found to be significant in our univariate analysis, absolute PHE volume remained a significant predictor of poor outcome only in patients with intracerebral haemorrhage (ICH) volumes ≤30 cm^3 (OR 1.123, 95% CI 1.021 to 1.273, p=0.034). An increase in absolute PHE volume of 10 cm^3 in these patients was found to increase the odds of poor outcome on discharge by a factor of 3.19.

Conclusions Our findings suggest that the effect of absolute PHE volume on functional outcome following ICH is dependent on haematoma size, with only patients with smaller haemorrhages exhibiting poorer outcome with worse PHE. Further studies are needed to define the precise role of PHE in driving outcome following ICH.

INTRODUCTION

Intracerebral haemorrhage (ICH) is the second most common and deadliest form of stroke, accounting for 10–15% of all strokes worldwide, with a 1-month mortality rate of nearly 30% and a return to independent function of less than 40% even several years later.[1 2] Several factors, including age, admission Glasgow Coma Scale (GCS) score, haematoma volume, location (supratentorial vs infratentorial), and intraventricular extension, have been demonstrated to predict outcome following ICH. Perihaematomal oedema (PHE) has yet to become a routine marker of ICH severity and injury, or a reliable prognostic indicator. Despite several recent studies, it remains unclear whether oedema formation and volume are independent predictors of unfavourable outcome after ICH.[3–7] Nevertheless, PHE formation is dynamic and continues even after the vast majority of patients have come to medical attention, making it a promising target for potential therapeutic intervention.

While the pathophysiology of PHE formation is still incompletely understood, it is most likely multifactorial, with prior studies implicating hydrostatic pressure and clot retraction in the acute phase, followed by secondary injury from thrombin toxicity, as well as inflammatory and complement cascades, that ultimately result in blood-brain barrier (BBB) breakdown.[8] PHE formation may be deleterious not only through augmentation of the mass effect caused by the initial haematoma, but also by direct toxicity to cerebral tissue via dysregulation of osmotic gradients and facilitation of BBB disruption.[9–11]

The aim of our study was twofold: (1) to assess whether initial PHE formation is independently associated with functional outcome at hospital discharge and (2) to determine the most clinically relevant index of PHE formation (absolute volume vs relative volume) with respect to patient outcome. We hypothesized that the ability of initial PHE formation to predict functional outcome varies with admission ICH volume, which may explain the apparent contradictions in the literature.

METHODS

One hundred and seventy-two consecutive patients with non-traumatic ICH were admitted to the Neurological Intensive Care Unit at Columbia University Medical Center (CUMC) between February 2009 and June 2011 and prospectively enrolled in an institutional review board-approved study, the ICH Outcomes Project (ICHOP). A priori, we excluded 27 patients with arteriovenous malformation-associated ICH from the study, as well as an additional 12 patients who did not receive an admission CT scan, resulting in a final cohort of 133 patients with spontaneous, non-traumatic ICH in our cohort. Demographic (patient age, sex, ethnicity) and clinical variables ((admission) systolic blood pressure (SBP), admission GCS score), diuretic or antihypertensive medication use in the first 24 h of admission were recorded in a prospective fashion as part of our ICHOP protocol. Functional outcome, using the

modified Rankin Scale (mRS) score, and mortality were determined on hospital discharge or postbleed day 14, whichever occurred first. Head CT imaging of each patient was assessed by four of the treating neurointensivists (KL, JC, SM and NB) and the attending neurosurgeon (ESC). Radiographic variables assessed included haematoma location, haematoma boundaries, PHE boundaries and presence of intraventricular extension. The presumed aetiology of each ICH was determined by consensus among the treating neurointensivists during a weekly meeting, based on a combination of demographic/clinical data and radiographic appearance. Admission haematoma and PHE volumes were measured by two authors (RH and AD) blinded to patient outcome using MIPAV software package (V.4.3, National Institutes of Health, Bethesda, Maryland, USA) and independent observer results were averaged. Intraclass correlation coefficients were 0.97 for haematoma volume and 0.88 for PHE volume. The postbleed day of the head CT imaging on admission to CUMC was calculated and included in our analyses.

Functional outcome on hospital discharge was the primary endpoint of this study, which was dichotomised into poor (mRS>3) and good outcome (mRS≤3). We also dichotomised admission haematoma volume to create the variable ICH30, where ICH30+ indicates a patient with a haematoma volume >30 cm^3, while ICH30− indicates a patient with a haematoma volume ≤30 cm^3. A haematoma volume of 30 cm^3 has been shown previously to be an important threshold and is used in several ICH grading scales, including the ICH score.[5 12 13] Recent studies have justified dichotomising haematoma size at this volume given its significant independent association with mortality, similarity to volume stratification in older investigations, and its ease of use.[5 14–16] Independent t test, Wilcoxon rank sum test, Fisher's exact test, χ^2, Pearson's correlation, and Spearman's rank correlation were used to determine univariate associations. Pearson's correlation coefficients from independent samples were compared via Fisher transformation.

Multiple logistic regression was used to determine the effect of admission PHE volume on functional outcome at hospital discharge, adjusted for prior known predictors of outcome following ICH. Two logistic regression models were constructed; the first modelling outcome at discharge as a function of patient age, admission GCS score, admission SBP, admission serum glucose level, admission haematoma volume (as a continuous variable) and location (supratentorial vs infratentorial), presence of intraventricular extension, and admission absolute PHE volume, which was mean-centred for numerical stability. The second model for outcome at discharge utilised these same variables, except that admission haematoma volume was dichotomised at 30 cm^3 (ICH30 variable), as indicated previously, and an interaction variable (absolute PHE volume-ICH30) was added to account for the variability of effect that admission absolute PHE volume was hypothesized to have on discharge outcome as a function of admission haematoma volume. In both logistic regression models, days elapsed from symptom onset to initial CT imaging were included to account for variable timing of admission haematoma and PHE volume measurements. All

Table 1 Admission characteristics of 133 patients with spontaneous, non-traumatic ICH

Factor	Mean±SD, median (IQR), or n (%)
Age (years)	65.49±15.77
Female	53 (39.8)
Ethnicity	
Caucasian	36 (27.1)
African–American	43 (32.3)
Asian	11 (8.3)
Hispanic	42 (31.6)
Other	1 (0.8)
Presumed cause	
Hypertension	94 (70.7)
Amyloid	18 (13.5)
Coagulopathy	2 (1.5)
Antiplatelet	5 (3.8)
Anticoagulant	6 (4.6)
Idiopathic	8 (6.1)
Admission GCS	11 (6–15)
Admission systolic blood pressure (bpm)	180 (151–211)
Admission glucose (mg/dl)	147.73±61.90
Location	
Infratentorial	18 (13.5)
Basal ganglia/thalamic	59 (44.4)
Lobar	56 (42.1)
Admission haematoma volume (cc)	13.43 (4.91–33.52)
Admission oedema volume (cc)	10.41 (4.11–23.74)
Admission relative oedema*	0.98±2.62
Presence of IVH	72 (54.1)
Presence of hydrocephalus	50 (37.6)
Diuretic use in acute period	28 (21.1)
Antihypertensive use in acute period	57 (42.9)
Ventilation	62 (46.6)
Surgical haematoma evacuation	13 (9.8)
Discharge mortality	32 (24.1)
Discharge mRS>3	100 (75.2)
Time from onset to first scan (days)	0 (0–1)

*Relative oedema=oedema volume/haematoma volume.
GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin scale; IVH, intraventricular haemorrhage.

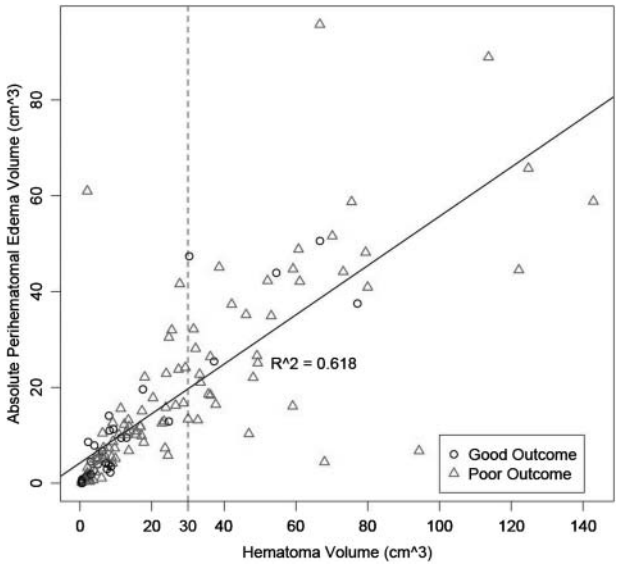

Figure 1 Haematoma volume versus absolute perihaematomal oedema volume by functional outcome at discharge. Both volumes are reported in cm^3. Patients have been dichotomised into good outcome (discharge modified Rankin Scale (mRS)≤3, symbolised by a black circle for each patient), and poor outcome (discharge mRS>3, symbolised by a red triangle for each patient). The line of best fit is represented by the solid diagonal line, while the dashed vertical line represents the intracerebral haemorrhage volume=30 cm^3 demarcation.

statistical analyses were performed using R environment for statistical computing (R Development Core Team, Vienna, Austria, 2008).

All aspects of this study were approved by the institutional review board of CUMC prior to enrolment of human subjects. Informed consent was obtained from all subjects or their authorised surrogates on hospital admission.

RESULTS

Demographic, clinical and radiographic characteristics for the 133 patients with spontaneous, non-traumatic ICH in our cohort are summarised in table 1. The average age was 65.5 years, and 30.8% of patients were women. At hospital discharge, overall mortality was 24.1%, and the incidence of poor functional outcome (mRS>3) was 75.2%. Functional outcome was determined on mean postbleed day 8.5±4.7 in our cohort. Hypertension was the most common aetiology of ICH (70.7%), followed by amyloid angiopathy (13.5%), idiopathic (6.1%), anticoagulant use (4.6%), antiplatelet use (3.8%), and coagulopathy (1.5%). Median admission haematoma volume was 13.43 cm^3, and median admission PHE volume was 10.41 cm^3. There was a strong linear correlation between absolute PHE and haematoma volumes on admission with 0.98 cm^3 of oedema for every cubic centimetre of haematoma (r=0.79, p<0.001) (figure 1). This correlation was not significantly different (p=0.631) when comparing patients with haemorrhages ≤30 cm^3 (r=0.61) with those with haemorrhages >30 cm^3 (r=0.64). There was also a slight negative correlation between ICH volume and relative PHE (ρ=0.12), but this correlation did not reach statistical significance (p=0.152).

Table 2 summarises univariate associations between select demographic, clinical and radiographic variables with functional outcome at discharge in our patient cohort. While there was no significant association between relative PHE (defined as absolute PHE volume/haematoma volume) on admission and outcome (p=0.713), we found a strong relationship between absolute PHE volume and outcome (p=0.002). Furthermore, for patients with small haematoma volumes ≤30 cm^3 (ICH30− group), those with poor outcome had significantly larger absolute PHE volumes than those with good outcome (p=0.003). This observation did not hold true for patients with larger haematoma volumes on admission (ICH30+ group, p=0.724). Patients with poor outcomes tended to have fewer days of elapse from symptom onset to admission head CT than patients with good outcomes (0 vs 1 day, p=0.005) in univariate analysis. This association persisted in our final multivariable model (OR 0.519, 95% CI 0.271 to 0.902, p=0.031); 83.3% of infratentorial haemorrhages were ≤30 cm^3, as opposed to 62.7% of basal ganglia/thalamic haemorrhages, and 73.2% of lobar haemorrhage. None of these proportions were significantly different from each other. In the lobar group, PHE was not significantly associated with outcome for patients with haemorrhage >30 cm^3 (p=0.953), or <30 cm^3 (p=0.110), though the latter relationship approached significance. For both the infratentorial and basal ganglia/thalamic groups, the association of PHE and

Table 2 Characteristics of patients with haematoma volumes ≤30 cm^3 (ICH30+) and >30 cm^3 (ICH30−)

Factor	ICH30−	ICH30+	p Value
Age (years)	64.63±16.22	67.50±14.70	<0.001
Female	37 (39.8)	16 (40.0)	0.865
Admission GCS	61 (52–78)	68.5 (58.75–80.25)	0.276
Admission systolic blood pressure (bpm)	175 (147–205)	183.5 (153.5–218.5)	0.328
Admission glucose (mg/dl)	143.80±65.55	156.88±52.03	0.020
Location			0.193
Infratentorial	15 (16.1)	3 (7.5)	
Basal Ganglia/thalamic	37 (39.8)	22 (55.0)	
Lobar	41 (44.1)	15 (37.5)	
Admission haematoma volume (cc)	9.95±8.27	59.56±28.00	<0.001
Admission oedema volume (cc)	8.70±9.48	36.32±20.06	<0.001
Admission relative oedema	1.13±3.12	0.65±0.30	0.029
Presence of IVH	47 (50.5)	25 (62.5)	0.280
Presence of hydrocephalus	34 (36.6)	16 (40.0)	0.857
Diuretic use in acute period	14 (15.1)	14 (35.0)	0.018
Antihypertensive use in acute period	39 (41.9)	18 (45.0)	0.892
Ventilation	30 (32.3)	32 (80.0)	<0.001
Surgical evacuation of haematoma	6 (6.5)	7 (17.5)	0.061
Discharge mortality	15 (16.1)	17 (42.5)	0.002
Discharge mRS>3	65 (69.9)	35 (87.5)	0.047
Time from onset to first scan (days)	0 (0–1)	0 (0–1)	0.250

GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin scale; IVH, intraventricular haemorrhage.

Table 3 Univariate associations with respect to functional outcome at discharge (data expressed as mean±SD, median (IQR), or n (%)).

Factor	Discharge mRS≤3	Discharge mRS>3	p Value
Age (years)	49.22±14.61	69.23±14.35	<0.001
Female	19 (57.6)	61 (61.0)	0.886
Admission GCS	15 (14–15)	9.5 (5–13)	<0.001
Admission systolic blood pressure (mm Hg)	180 (152–202)	180 (150–211)	0.776
Admission glucose (mg/dl)	138.27±74.62	150.85±57.17	0.382
Infratentorial location	7 (21.2)	11 (11.0)	0.233
Admission haematoma volume (cm^3)	7.19 (2.26–11.41)	17.85 (6.69–37.98)	<0.001
Admission PHE volume (cm^3)	4.11 (1.64–11.25)	12.36 (5.12–26.40)	0.002
ICH30+	40.93±9.94	35.66±21.13	0.377
ICH30−	5.20±5.09	10.20±10.52	0.003
Admission relative oedema*	0.90±0.70	1.02±2.99	0.713
Presence of IVH	12 (36.4)	60 (60.0)	0.031
Presence of hydrocephalus	5 (15.2)	45 (45.0)	0.004
Diuretic use in acute period	1 (3.6)	27 (27.0)	0.003
Antihypertensive use in acute period	12 (36.4)	45 (45.0)	0.505
Time from symptom onset to CT (days)	1 (0–2)	0 (0–1)	0.005

*Relative oedema=oedema volume/haematoma volume.
GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin scale; PHE, perihaematomal oedema; IVH, intraventricular haemorrhage.

outcome for patients with haemorrhages >30 cm^3 was incalculable since all of them had poor outcomes. For patients with haemorrhages ≤30 cm^3, there was a significant association between PHE and outcome in the basal ganglia/thalamic group (p=0.019), but not the infratentorial group (p=0.613).

Our initial logistic regression model took a standard approach to determine the effect of admission PHE volume on functional outcome while controlling for known predictors of outcome as well as additional variables found to be significant in our univariate analysis. This model included age, GCS, absolute PHE volume, ICH volume, infratentorial location, presence of intraventricular haemorrhage (IVH) and days from onset to scan. Absolute PHE volume on admission was not significant in this model, likely due to a high degree of collinearity with haematoma volume. Moreover, this approach did not consider the differential effect of absolute PHE volume on functional outcome between ICH30+ and ICH30− patient groups. To account for this, our second logistic regression model included an absolute PHE volume-ICH30 interaction term (table 3). This model demonstrated a significant independent effect of absolute PHE volume on functional outcome at discharge for patients in the ICH30− group (p=0.034), but not for those in the ICH30+ group (OR 0.967, 95% CI 0.769 to 1.216, p=0.772). After adjusting for other important predictors of functional outcome following ICH, an increase of 1 cm^3 in PHE multiplied the odds of poor outcome by 1.123 (95% CI 1.021 to 1.273) for patients with haematoma volumes ≤30 cm^3 in our cohort. A 10 cm^3 increase in PHE more than tripled the odds of poor outcome in these patients (OR 1.123^{10}=3.190). The absolute PHE-ICH30 interaction variable was also significantly associated with outcome in our final multivariate model (p=0.024), confirming the phenomenon observed in our univariate analysis, namely that absolute PHE had a greater, and significant, effect on outcome among patients with smaller haematomas (ICH30− group) vis-à-vis those with larger haemorrhages (ICH30+ group) (table 4).

DISCUSSION

The effect of PHE on patient outcome following ICH remains incompletely understood. In our study, using data from a prospective database, we observed a strong linear relationship between ICH and PHE volume in the acute period, as well as demonstrating a significant association between absolute PHE volume and functional outcome at discharge for patients with smaller (≤30 cm^3) haemorrhages. The majority of these small haemorrhages are non-operative, and therapies aimed at amelioration of oedema in this population need to be explored.

Table 4 Multiple logistic regression of poor outcome (mRS>3) by admission characteristics

Factor	OR	95% CI for OR		p Value
Age (years)	1.121	1.066	1.199	<0.001
GCS score	0.684	0.541	0.827	<0.001
Absolute PHE volume (cm^3)	1.123	1.021	1.273	0.034
ICH30	0.453	0.042	5.062	0.256
Absolute PHE volume-ICH30 interaction	0.861	0.745	0.975	0.024
Infratentorial location	0.189	0.026	1.253	0.083
Presence of IVH	6.046	1.704	25.607	0.008
Days from onset to scan	0.519	0.271	0.902	0.031

GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin scale; PHE, perihaematomal oedema; IVH, intraventricular haemorrhage.

Additionally, we confirmed known predictors of outcome, such as patient age, admission GCS score, ICH volume, haematoma location and presence of IVH.[5 17 18] Notably, absolute PHE volume on admission head CT and days elapsed from symptom onset to initial imaging were also significant predictors of outcome in our cohort. And while we demonstrate that absolute PHE volume is an independent predictor of functional outcome on discharge, our analysis indicates that the ratio of absolute PHE to haematoma volume (ie, relative PHE) does not significantly affect prognosis. This is likely a result of the high degree of collinearity noted in our cohort between absolute PHE formation and haematoma volume, and is consistent with the conclusion put forth by Staykov *et al*[19] that relative PHE may not be an appropriate variable for investigation in clinical ICH studies. Importantly, our results indicate that the effect of absolute PHE on functional outcome is dependent on ICH volume. In patients with smaller haemorrhages (ICH volume ≤30 cm^3) we noted that a modest increase of 10 cm^3 in PHE more than triples the odds of a poor outcome at discharge, even after controlling for known predictors of outcome following ICH. In other words, smaller haematomas appear to lead to disproportionate increases in the severity of PHE. To our knowledge, this is the first report demonstrating that the influence of PHE on outcome is variably expressed across ICH volumes.

Significant correlations between absolute PHE and ICH volumes have been shown in several recent studies.[19–21] Our study reveals a strong linear association between these two measurements, which continued to hold true even after patients were dichotomised according to haematoma volume or to functional outcome (figure 1). In a recent study that used MRI to assess the natural history of PHE formation following ICH, Venkatasubramanian *et al*[21] argued that a disproportionate amount of PHE forms around smaller haematomas, although notably, no assessment of this effect on patient outcome was performed. Our results, instead, suggest that while the relationship between PHE and haematoma volume may be linear, the effect of PHE volume on patient outcome is not.

While associations have been demonstrated between PHE and haematoma volumes, and between haematoma volume and functional outcome, the relationship linking PHE to functional outcome after ICH is still controversial. Published in the *Lancet* in 2008, the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) is the largest study to date that has assessed the relationship of PHE to outcome following ICH.[22 23] The INTERACT demonstrated that increases in both absolute and relative PHE were significantly associated with increased patient dependency at 90 days posthaemorrhage, after adjustment for patient age, sex and blood pressure treatment group, but not when adjusted for initial haematoma volume. The authors of INTERACT also reported a significant correlation between haematoma and absolute[23] PHE volumes at multiple time points, including on admission, and at 24 and 72 h posthaemorrhage.[23] We observed a similar correlation in our cohort, helping to confirm this finding. The results of more recent studies have suggested that increased absolute PHE is correlated with declines in neurologic status, and is an independent predictor of in-hospital mortality after controlling for admission ICH volume.[19 21]

Multiple factors could explain the differences observed among the aforementioned studies including differences in study design and methodology, the predominant imaging modality used, as well as differences in inclusion criteria and the outcome measure assessed. Based on our results, we posit that absolute PHE volume does not influence outcome equally across

all patients, and that this variability is dependent on admission haematoma volume. This is particularly significant given that patients with smaller ICH volumes are generally expected to have better outcomes, with 30-day mortality ranging from 19% to 44% for patients with haematomas $\leq 30\ cm^3$ haematoma compared with 46% to 91% for those $>30\ cm^3$.[5 14] Qureshi *et al*[15] confirmed that ICH volumes greater than $30\ cm^3$ are associated with significantly higher mortality rates and independently predict early clinical deterioration. Haematoma size is now generally regarded to be the strongest single predictor of mortality and outcome following spontaneous ICH.[24] Together, these data raise an important question, namely, whether focusing novel treatment strategies on patients with small ICH might be more likely to result in a significant clinical effect given that those with larger ICH (ie, $>30\ cm^3$) are possibly too ill for most treatments to have an appreciable impact.

Since ICH patients with smaller haematomas are known to have less profound neurological deficits and better outcome compared with those with larger haemorrhages, increases in absolute PHE and subsequent exacerbation of mass effect may be expected to be more clinically relevant in the former group. While a given absolute amount of PHE formation in a patient with a large ICH may not appreciably alter their grim prognosis, an equal volume of PHE formation in a patient with a small ICH may be the difference between a good (mRS≤3) versus poor (mRS>3) outcome. Another explanation for our results may be that they reflect differences between lobar haemorrhages, which are often secondary to amyloid angiopathy or coagulopathy, and haemorrhages in deep locations, specifically the basal ganglia and thalamus. These regions contain a high density of structures critical to consciousness and motor function that may be more highly susceptible to damage from PHE formation, or at the very least, more likely to result in clinical and functional deterioration following injury. It is intuitive that even small increases in PHE surrounding haemorrhages in these locations could result in extensive damage to critical structures, thereby resulting in worse functional outcome.

In addition to a marker of disease severity, PHE may also be directly toxic to brain parenchyma. The increased effect on outcome of PHE in patients with smaller haemorrhages in our cohort may, in part, be explained by a larger relative amount of perihaematomal inflammation and hypoperfusion. This may be linked to the greater relative mass effect of PHE surrounding smaller haematomas, and the effect of toxic vasoconstrictive substances.[25–27] Disruption of perihaematomal tissue will be less for haemorrhages $\leq 30\ cm^3$ in size compared with larger ICH volumes, holding location and all other factors constant. If neuronal and glial cells in this region are only minimally injured following a small ICH, they may be less tolerant of subsequent PHE formation than cells that have been severely damaged by a large haemorrhage. Our results suggest that there may be a greater potential for neuronal and glial injury from PHE with small haematoma volumes.

There is evidence to suggest that in the context of ICH, PHE forms rapidly upon insult and continues to expand, and can even double in the span of 7–11 days.[19] Existing evidence from animal studies suggests that later developing mechanisms, such as erythrocyte lysis[28] and haemoglobin release[29] contribute to oedema formation. Due to the inherent constraints of its observational nature, this study is restricted to an examination of the effect of the initial acute formation of PHE, and is not equipped to measure the effect of later PHE formation that may come from these or other mechanisms. Future efforts to elucidate the relationship between PHE and outcome should clarify how this continued course of PHE formation within the first 2 weeks from onset is related to outcome. Future studies should also aim to illuminate whether PHE has a longer-term effect on functional outcome.

Our study has a number of limitations, including determining haematoma and PHE volumes on admission CT imaging only. As we previously mentioned, our data is derived from a purely observational database, to which we were not able to dictate a specific imaging protocol, such as that used in the INTERACT, to follow the evolution of PHE at precise time intervals. This is an important limitation since the time course of oedema and its role in affecting outcomes is poorly understood—both the haematoma and PHE may expand after imaging for many of these patients. Additionally, not all admission CT imaging was obtained at the same time from symptom onset in all patients, although we did attempt to adjust for this in our multivariable models. Haematoma and PHE volume measurements were also somewhat limited by the predominant use of CT as the modality of choice for initial admission imaging, compared with MRI, which may have provided more accurate data due to its improved resolution. The differences between PHE and normal brain tissue are subtle on CT, and identification of PHE boundaries may be susceptible to observer error. We attempted to control for interobserver variability in haematoma and PHE volume measurements by averaging readings. Finally, although our cohort of 133 patients is sizeable, it was limited to a single tertiary care centre with a large proportion of patients coming from a single ethnic group reflecting the composition of the local population.

CONCLUSION

The formation of PHE following ICH may simply be a marker of cellular injury that would upgrade an otherwise low-grade event to a more severe insult; however, our results indicate that in patients with small haemorrhages ($\leq 30\ cm^3$), even a modest $10\ cm^3$ increase in PHE volume more than triples the odds of poor functional outcome at discharge. PHE formation may have a deleterious impact on brain parenchyma beyond simply exacerbating mass effect; this may be more apparent with smaller haematoma volumes. Further studies are needed to assess the role of PHE formation in ICH and its impact on patient outcome. Given our results, we encourage subsequent studies to account for the possibility that PHE volume may have a clinical relevance that is dependent on ICH volume. Ultimately, this may guide future therapeutic interventions to maximise potential patient recovery.

Contributors All the authors listed above have been involved in substantial contributions to interpretation of data, conception and design, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. GA, SB, ZLH, BEZ, ESC have been additionally involved in drafting the article, revising acquisition of data, and analysis of data.

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Data sharing statement Upon request, researchers may have access to a limited additional set of data for aggregate research purposes. Please contact the corresponding author.

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