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Review

Prognostic Role of Perihematomal Edema in Intracerebral Hemorrhage: A Systematic Review

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ABSTRACT

Although several studies have suggested perihematomal edema (PHE) is associated with prognosis in intracerebral hemorrhage (ICH), the results are different in other studies. The purpose of this study was to evaluate the prognostic role of PHE in ICH. According to PRISMA guidelines, a systematic literature search of PubMed, EMBASE, SCOPUS, Web of Science and Cochrane Library was performed. Published clinical studies reporting association between PHE and prognosis in ICH were included. Data were extracted including sample size, patient characteristics, PHE measures, outcome measures and follow-up. A total of 21 studies were included with 6 prospective studies and 15 retrospective studies. PHE measures included perihematomal edema absolute volume (PHEAV), relative perihematomal edema volume (rPHE), perihematomal edema absolute volume growth (PHEAV growth), perihematomal edema expansion rate (PHEER), relative perihematomal edema growth (relative PHE growth), cytotoxic edema (CE) and perihematomal edema absolute area (PHEAA). The association of PHEAV/ rPHE /PHEAV growth and outcome are conflicting in different studies. Meta-analysis showed 72h PHEER at 72 hours was significantly associated with poor clinical outcome at 90 days (OR=1.54, 95%CI 1.04-2.22, p<0.001). This study suggests the measures and time points for PHE and outcome are various in previous studies. The prognostic values of PHEAV, rPHE, PHEAV growth and other measures are still controversial. PHEER is likely a prognostic predictor for ICH. Further studies with larger sample size, more accurate measures and more time points are needed to investigate the prognostic role of PHE in ICH and the optimal PHE measure to predict outcome in ICH.

KEYWORDS: Perihematomal edema, Intracerebral hemorrhage, Prognosis

INTRODUCTION

Intracerebral hemorrhage (ICH) is a severe type of stroke and accounts for about 10-15% of all strokes (43). Patients with ICH have high risk of severe disability or death (20). Cerebral injury secondary to ICH includes several complex mechanisms. Direct destruction and mass effect of hematoma bring primary injury to brain tissue at the beginning of ICH (13). Hematoma expansion further aggravates the primary injury (26). Inflammation, thrombin activation and erythrocyte lysis caused by primary injury lead to breakdown of brain blood barrier (BBB) and swelling of brain cells, which results in formation of perihematomal edema (PHE)(50). Thrombin formation induces BBB disruption and parenchymal cell death, which induces PHE formation in ICH (17). After erythrocyte lysis and hemoglobin release, AQP4 upregulation affected by the increased iron concentration has an important role in PHE (28). Complement activation rapidly induces downstream pathways of cerebral injury, which is correlated to formation of PHE (7). PHE can cause mass effect, which brings further cerebral injury (29). PHE is related to many factors, such as initial ICH volume, genetic variation, blood pressure, hyperglycemia and body temperature (42). PHE has been considered as an important target for treatment of ICH (16). New approaches aimed at PHE are hoped to improve prognosis of ICH patients (5,9,33). Although many previous

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studies have suggested PHE may be associated with clinical outcome in ICH, the PHE measures are various and the results are conflicting (2,8,11,46,47). Thus, we conducted this systematic review to evaluate the prognostic role of PHE in ICH.

MATERIAL and METHODS

Search Strategy

A prespecified protocol following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was followed. Two researchers (Zhiyuan YU & Lu MA) independently searched literature in the PubMed (1958 to present), EMBASE (1980 to present), SCOPUS (1966 to present), Web of Science (1970 to present) and Cochrane Library on July 20, 2016. Our search strategy was combined by key words as following: "intracerebral hemorrhage" or "cerebral hemorrhage" or "intracerebral haemorrhage" or "cerebral haemorrhage" or "brain haemorrhage" or "brain haemorrhage" or "hemorrhagic stroke" or "haemorrhagic stroke" or "ICH" and "perihaematomal edema" or "perihaematomal oedema" or "perihematomal edema" or "perihematomal oedema" or "perihemorrhagic edema" or "perihaemorrhagic oedema" or "perihaemorrhagic edema" or "perihemorrhagic oedema" or "PHE" or "PHO" and "outcome" or "prognosis"or "predictor"or "mortality" or "death" or "disability" or "dependence" or "deterioration". MeSH terms were also adapted according to different indexing for each database. References of selected publications were also searched for potential literature. No language restrictions were set in our strategy.

Study Selection

The eligibility criteria for this systematic review were defined as following:

1. Published clinical studies in adult human beings
2. Sample size ≥ 20 patients
3. ICH diagnosed by computed tomography (CT) or Magnetic Resonance Imaging (MRI)
4. Evaluating the association between PHE and prognosis in ICH
5. Providing detailed method to evaluate PHE and prognosis
6. Providing credible data for PHE and prognosis.

Titles and abstracts of all included literature were screened by two reviewers independently. Full-text articles were obtained if studies were considered as potentially related to the association between PHE and prognosis by at least one reviewer. Full-text articles were screened by both reviewers for inclusion. If disagreement occurred, it would be resolved by the help of a third reviewer. Quality of study and risk of bias were evaluated by two reviewers (34).

Data Extraction

All relevant data were extracted by two reviewers independently with a standardized data abstraction form. All data were checked by the third reviewer for accuracy. Any possible disagreement of data was solved by consensus of three reviewers. If different publications described the same group of patients, all publications were reviewed and the most representative one would be included. The following data were collected from each study: author, publication year, study design, sample size, study duration, inclusion/exclusion criteria, patient characteristics, PHE measures, outcome measures and follow-up.

Statistical Analysis

Because of the various measures for PHE and prognosis, we carefully considered if the meta-analysis was feasible. We decided if the meta-analysis was appropriate for each measure of PHE and prognosis by consensus. The evaluation of feasibility for meta-analysis was based on the methodology for meta-analysis of observational studies (10). If the meta-analysis was not appropriate to evaluate the association, we used the descriptive way to describe the results.

Our analyses focused on the association between PHE and outcome in ICH. All measures for PHE in included studies were analyzed. Only studies reporting odds ratios (OR) and 95% confidence intervals (CIs) for the effect of a defined increment were included in meta-analysis (10). If adjusted ORs for confounding factors in multivariable analyses were available, we used the adjusted OR and 95% CI in the meta-analysis. Pooled ORs, 95%CIs, p values and Higgins I^2 were calculated. If I^2>50%, we considered substantial heterogeneity existed between results of included studies. When no substantial heterogeneity existed, we used Woolf's method based on the fixed-effects model to calculate the pooled estimate; otherwise, we used the Der Simonian and Laird method based on the random-effects model (12). All statistical analysis was performed using STATA version 12.0 software (StataCorp., College Station, TX). If $p<0.05$, it was considered as statistical significance.

RESULTS

A total of 21studies between 1999 and 2016 were included from 805 original citations in 5 databases (Figure 1). Although data resource of Arima's and Yang's studies (2,47) were both from INTERACT studies, the measures for PHE were different, so both of them were included. In these 21 studies, 6 (3,11,19,21,39,45) were prospective studies and 15 (1,2,8,18,23,27,30-32,35,36,40,46,47,52) were retrospective studies. Sample size ranged from 21 to 1310 patients. Sixteen studies (1-3,8,11,18,21,23,27,30,31,35,40,46,47,52) assessed PHE with CT scan, 3 studies (19,39,45) used MRI and 2 (32,36) studies had CT or MRI results to evaluate PHE (Table I).

Measures for PHE were various in 21 included studies. Perihematomal edema absolute volume (PHEAV) was accessed in 16 studies (1,3,8,11,18,19,21,23,27,30-32,35,39,40,46), relative perihematomal edema volume (rPHE) was evaluated in 8 studies (1,8,11,23,35,36,45,46), 7 studies (2,23,35,45-47,52) used perihematomal edema absolute volume growth (PHEAV growth), 2 studies (23,40) adopted perihematomal edema expansion rate (PHEER), relative perihematomal edema growth (relative PHE growth) was used in 2 studies (2,45), 2 studies

Table I: Included Studies Evaluating Association Between PHE and Outcome in ICH

Study	n	Study Design	Study Duration	Neuro-imaging	PHE Measures	Outcome Measures
Appelboom (2013) [1]	133	Retrospective Study	Feb. 2009-Jun. 2011	CT	PHEAV & rPHE	Functional Outcome
Arima (2009) [2]	270	Retrospective Study	Nov. 2005-Apr. 2007	CT	PHEAV Growth & relative PHE Growth	Functional Outcome & Death
Bakhshayesh (2014) [3]	98	Prospective Study	Jan. 2010-Jan. 2011	CT	PHEAV	Death
Gebel (2002) [8]	103	Retrospective Study	1989-1994	CT	PHEAV & rPHE	Functional Outcome
Gupta (2014) [11]	44	Prospective Study	Oct. 2010-Aug. 2012	CT	PHEAV & rPHE	Functional Outcome
Levine (2007) [18]	98	Retrospective Study	Oct. 1998-Jun. 2004	CT	PHEAV	Death
Li (2013) [19]	21	Prospective Study	Not Mentioned	MRI	PHEAV & CE	Functional Outcome
McCarron (1999) [21]	192	Prospective Study	Not Mentioned	CT	PHEAV	Death
Murthy (2016) [23]	596	Retrospective Study	Not Mentioned	CT	PHEAV & rPHE & PHEAV Growth & PHEER	Functional Outcome & Death
Ozdinc (2016) [27]	106	Retrospective Study	Jan. 2012-Feb. 2015	CT	PHEAV & PHEAA	Death
Rodriguez-Luna (2016) [30]	322	Retrospective Study	Jun. 2006-Sep. 2010	CT	PHEAV	Functional Outcome & END
Sansing (2003) [31]	80	Retrospective Study	Jan. 1996-Dec. 1996	CT	PHEAV	Discharge Disposition
Sansing (2011) [32]	287	Retrospective Study	Not Mentioned	CT/ MRI	PHEAV	Functional Outcome
Staykov (2011) [35]	219	Retrospective Study	Jan. 2006-Dec. 2009	CT	PHEAV&rPHE& PHEAV Growth	Death
Sykora (2009) [36]	38	Retrospective Study	Oct. 2006-Dec. 2007	CT/ MRI	rPHE	END
Tsai (2011) [39]	56	Prospective Study	Not Mentioned	MRI	PHEAV & CE	Functional Outcome
Urday (2016) [40]	139	Retrospective Study	2000-2013	CT	PHEAV & PHEER	Functional Outcome & Death
Venkatasubramanian (2011) [45]	27	Prospective Study	Not Mentioned	MRI	rPHE & PHEAV Growth & relative PHE Growth	Functional Outcome & Death
Volbers (2016) [46]	220	Retrospective Study	Jan. 2006-Feb. 2010	CT	PHEAV & rPHE & PHEAV Growth	Functional Outcome
Yang (2015) [47]	1310	Retrospective Study	Nov. 2005-Aug. 2012	CT	PHEAV Growth	Functional Outcome & Death
Zubkov (2008) [52]	88	Retrospective Study	Jan. 1997-Dec. 2005	CT	PHEAV Growth	Functional Outcome & Death

PHE: *Perihematomal edema,* ***CT:*** *Computed tomography,* ***MRI:*** *Magnetic resonance imaging,* ***PHEAV:*** *Perihematomal edema absolute volume,* ***rPHE:*** *Relative perihematomal edema volume,* ***PHEAV growth:*** *Perihematomal edema absolute volume growth,* ***PHEER:*** *Perihematomal edema expansion rate,* ***relative PHE growth:*** *Relative perihematomal edema growth,* ***CE:*** *Cytotoxic edema,* ***PHEAA:*** *Perihematomal edema absolute area,* ***END:*** *Early neurological deterioration.*

Figure 1: Study selection.

(19,39) accessed cytotoxic edema (CE) and perihematomal edema absolute area (PHEAA) was evaluated in 1 study (27). PHE measures had different time points in these studies (Table II).

In 21 included studies, 14 studies (1,2,8,11,19,23,30,32,39, 40,45-47,52) evaluated functional outcome. Modified Rankin Scale (mRS) was used in all these 14 studies. Barther Index (BI) was adopted in 2 studies (8,45). Death was accessed in 11 studies (2,3,18,21,23,27,35,40,45,47,52). Early neurological deterioration (END) was evaluated in 2 studies (30,36). Discharge disposition was used in 1 study (31). There were also various time points for outcome assessment (Table III).

PHEAV and Outcome in ICH

A total of 8 studies (1,8,11,23,30,32,39,46) discussed the association between baseline PHEAV and functional outcome in ICH. Because of insufficient studies with consistent outcome measure, a meta-analysis was not performed. In Appelboom's study, PHEAV was showed to be a significant predictor of short-term poor outcome (mRS>3) in ICH patients, especially in those with smaller ICH (≤30 cm^3) (1). Volbers et al. showed baseline PHEAV was significantly higher in those with poor outcome (mRS>3) at discharge (46). Rodriguez-Luna et al. found baseline PHEAV was higher in patients with a poor 90-day outcome (mRS≥3) (30). In Sansing's study, baseline PHEAV was found to be independently associated with worse clinical outcome (32). However, other 4 studies (8,11,23,39) did not show a significant association between baseline PHEAV and functional outcome.

The association between PHEAV at 72 hours (72h)/3 days(3d) and functional outcome was evaluated in 3 studies (19,23,40). Li's study showed 3d PHEAV was significantly larger in patients with unfavorable 90-day clinical outcome (mRS 4-6) (19). Murthy et al. found 72h PHEAV was significantly associated with poor outcome (mRS 3-6) at 90 days in multivariate analysis (23). In Urday's study, no significant association was found between 72h PHEAV and poor functional outcome (mRS>2) at 90 days (40). Meta-analysis of Murthy's and Urday's studies showed a significant association between 72h PHEAV and poor functional outcome at 90 days (OR=1.02, 95%CI 1.00-1.03, p=0.007) (Figure 2).

Six studies (3,18,21,23,27,35) evaluated the association between baseline PHEAV and mortality in ICH. Bakhshayesh's study suggested baseline PHEAV could predict the risk of in-hospital mortality (3). McCarron et al. found non-survivors had larger edema volumes (21). In Staykov's study, initial PHEAV was found to be significantly associated with in-hospital mortality (35). Ozdinc's study showed baseline PHEAV was significantly higher in non-survivors at 30 days (27). Baseline PHEAV was found to be a significant predictor for 90-day mortality in Warfarin-related ICH in Levine's study (18). However, Murthy's study showed baseline PHEAV was not significantly associated with mortality at 90 days (23). Meta-analysis of Levine's and Murthy's studies did not find a significant association between baseline PHEAV and mortality at 90 days (OR=0.71, 95%CI 0.29-1.72, p=0.446) (Figure 3). The association between 72h PHEAV and 90-day mortality was assessed in 2 studies (23,40). In Murthy's study, there was no significant association between 72h PHEAV and 90-day mortality (23). Urday's study showed 72h PHEAV was significantly associated with 90-day mortality in unadjusted analysis but insignificantly in adjusted analysis (40). Meta-analysis did not suggest significant association between 72h PHEAV and 90-day mortality (OR=1.02, 95%CI 0.99-1.04, p=0.180) (Figure 4).

Rodriguez-Luna's study found baseline PHEAV was higher in patients with END (30). Sansing et al. suggested baseline PHEAV was correlated with poor discharge disposition (31).

Table II: Time Points of PHE Measures in 21 Included Studies

Study	PHEAV	PHEAA	rPHE	PHEAV Growth	PHEER	rPHE Growth	CE
Appelboom (2013)	Baseline	/	Baseline	/	/	/	/
Arima (2009)	/	/	/	72h	/	72h	/
Bakhshayesh (2014)	Baseline	/	/	/	/	/	/
Gebel (2002)	Baseline	/	Baseline	/	/	/	/
Gupta (2014)	Baseline	/	Baseline	/	/	/	/
Levine (2007)	Baseline	/	/	/	/	/	/
Li (2013)	3d	/	/	/	/	/	3d
McCarron (1999)	Baseline	/	/	/	/	/	/
Murthy (2016)	Baseline & 72h	/	Baseline	72h	72h	/	/
Ozdinc (2016)	Baseline	Baseline	/	/	/	/	/
Rodriguez-Luna (2016)	Baseline	/	/	/	/	/	/
Sansing (2003)	Baseline	/	/	/	/	/	/
Sansing (2011)	Baseline	/	/	/	/	/	/
Staykov (2011)	Baseline	/	3d	3d	/	/	/
Sykora (2009)	/	/	72h	/	/	/	/
Tsai (2011)	Baseline	/	/	/	/	/	Baseline
Urday (2016)	72h	/	/	/	24h&72h	/	/
Venkatasubramanian (2011)	/	/	Peak	Peak	/	Peak	/
Volbers (2016)	Baseline & Peak	/	Peak	48h&Peak	/	/	/
Yang (2015)	/	/	/	24h	/	/	/
Zubkov (2008)	/	/	/	Peak	/	/	/

PHE: *Perihematomal edema,* ***PHEAV:*** *Perihematomal edema absolute volume,* ***rPHE:*** *Relative perihematomal edema volume,* ***PHEAV growth:*** *perihematomal edema absolute volume growth,* ***PHEER:*** *Perihematomal edema expansion rate,* ***relative PHE growth:*** *Relative perihematomal edema growth,* ***CE:*** *Cytotoxic edema,* ***PHEAA:*** *Perihematomal edema absolute area.*

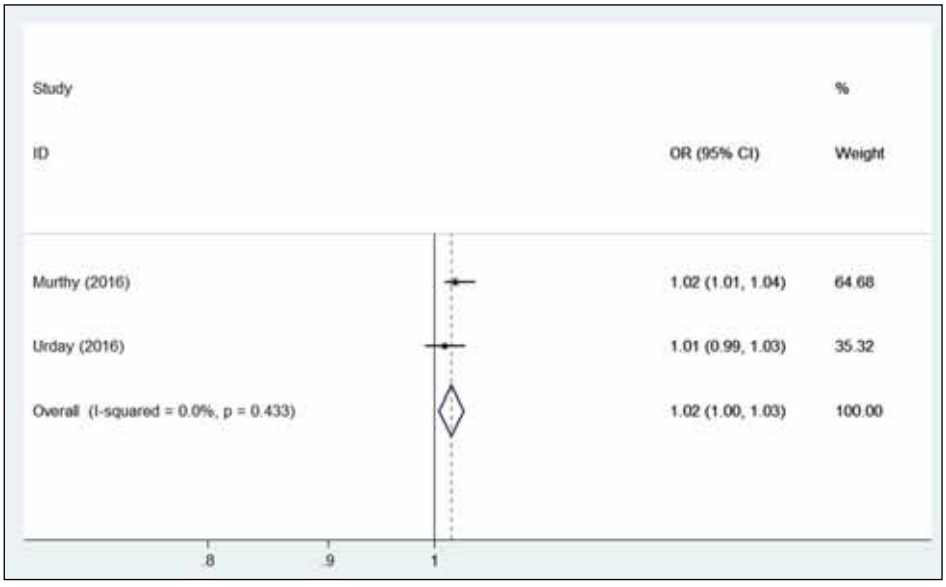

Figure 2: Meta-analysis of studies reporting an association between 72h PHEAV and poor 90-day outcome.

Table III: Outcome Measures in 21 Included Studies

Study	Outcome 1	Unit	Follow-up time	Outcome 2	Unit	Follow-up time
Appelboom (2013)	Poor functional outcome	mRS(4-6)	Discharge/ 14 days	/	/	/
Arima (2009)	Poor functional outcome	mRS(3-6)	90 days	Death	Dead or alive	90 days
Bakhshayesh (2014)	Death	Dead or alive	Discharge	/	/	/
Gebel (2002)	Poor functional outcome	mRS(3-6)	12 weeks	Poor functional outcome	BI<80	12 weeks
Gupta (2014)	Poor functional outcome	mRS(3-6)	12 weeks	/	/	/
Levine (2007)	Death	Dead or alive	90 days	/	/	/
Li (2013)	Poor functional outcome	mRS(4-6)	90 days	/	/	/
McCarron (1999)	Death	Dead or alive	In-hospital	/	/	/
Murthy (2016)	Poor functional outcome	mRS(3-6)	90 days	Death	Dead or alive	90 days
Ozdinc (2016)	Death	Dead or alive	30 days	/	/	/
Rodriguez-Luna (2016)	Poor functional outcome	mRS(3-6)	90 days	END	NIHSS increase>4 or Death	24h
Sansing (2003)	Discharge Disposition	Good or poor	Discharge	/	/	/
Sansing (2011)	Poor functional outcome	mRS	90 days	/	/	/
Staykov (2011)	Death	Dead or alive	In-hospital	/	/	/
Sykora (2009)	END	NIHSS increase>4 or death	72h	/	/	/
Tsai (2011)	Poor functional outcome	mRS(3-6)	6 months	/	/	/
Urday (2016)	Poor functional outcome	mRS(3-6)	90 days	Death	Dead or alive	90 days
Venkatasubramanian (2011)	Functional outcome	mRS; NIHSS; eGOS; BI	3 months	Death	Dead or alive	3 months/6 months
Volbers (2016)	Poor functional outcome	mRS(4-6)	Discharge	/	/	/
Yang (2015)	Poor functional outcome	mRS(3-6)	90 days	Death	Dead or alive	90 days
Zubkov (2008)	Poor functional outcome	mRS(3-6)	Discharge/ 1 year	Death	Dead or alive	7 days

mRS: *Modified Rankin scale,* ***BI:*** *Barther Index,* ***NIHSS:*** *National Institute of Health stroke scale,* ***eGOS:*** *Extended Glasgow outcome scale.*

rPHE and Outcome in ICH

Association between baseline rPHE and functional outcome was assessed in 4 studies (1,8,11,23). Appelboom's study did not show a significant association between baseline rPHE and functional outcome at discharge (1). Increased baseline rPHE was found to be significantly associated with decreased probability of poor 12-week functional outcome (mRS>2) in Gebel's study (8). Gupta et al. suggested baseline rPHE was significantly associated with functional outcome (MRS≥3) at 3 months (11). However, no significant association between baseline rPHE and 90-day functional outcome (mRS3-6) was found in Murthy's study (23). Meta-analysis did not find a significant association between baseline rPHE and functional outcome at 90 days/12 weeks (OR=0.10, 95%CI 0.01-1.91, p=0.127) (Figure 5).

Two studies (45,46) evaluated the association between peak rPHE and functional outcome and did not find significant association. Volber's study did not show a significant association between 48h rPHE and functional outcome (46). Association between rPHE and mortality was discussed in 3 studies (23,35,45) and no significant association was identified. 72h rPHE was found to be significantly associated with END in Sykora's study (36).

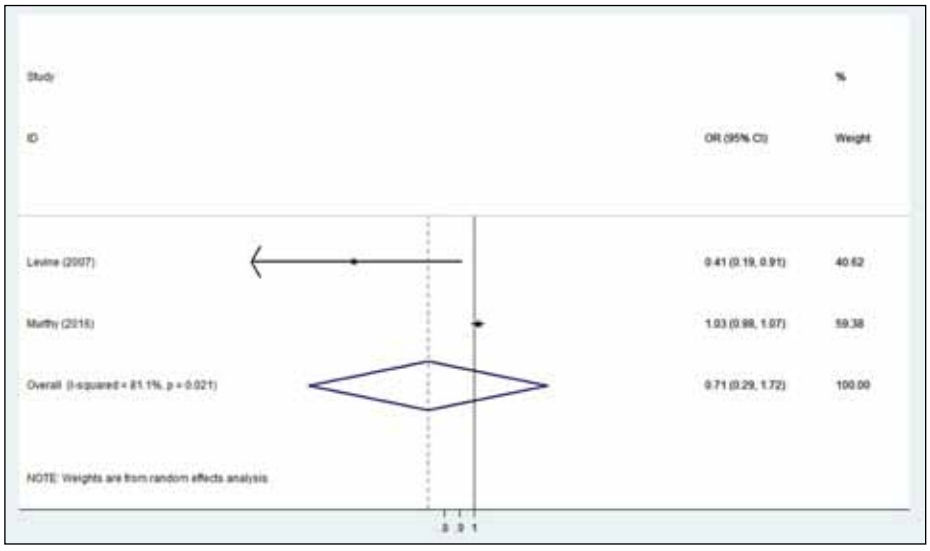

Figure 3: Meta-analysis of studies reporting an association between baseline PHEAV and 90-day mortality**.**

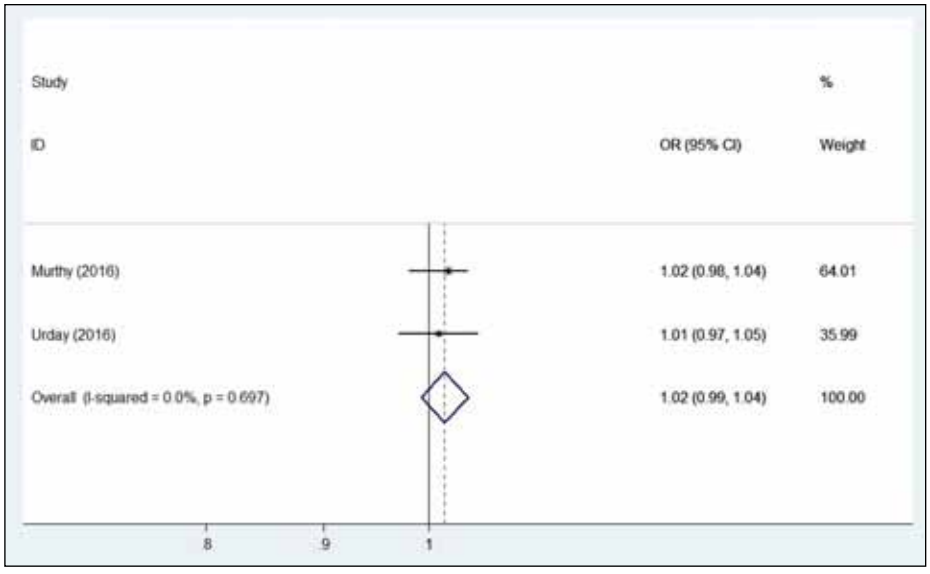

Figure 4: Meta-analysis of studies reporting an association between 72h PHEAV and 90-day mortality.

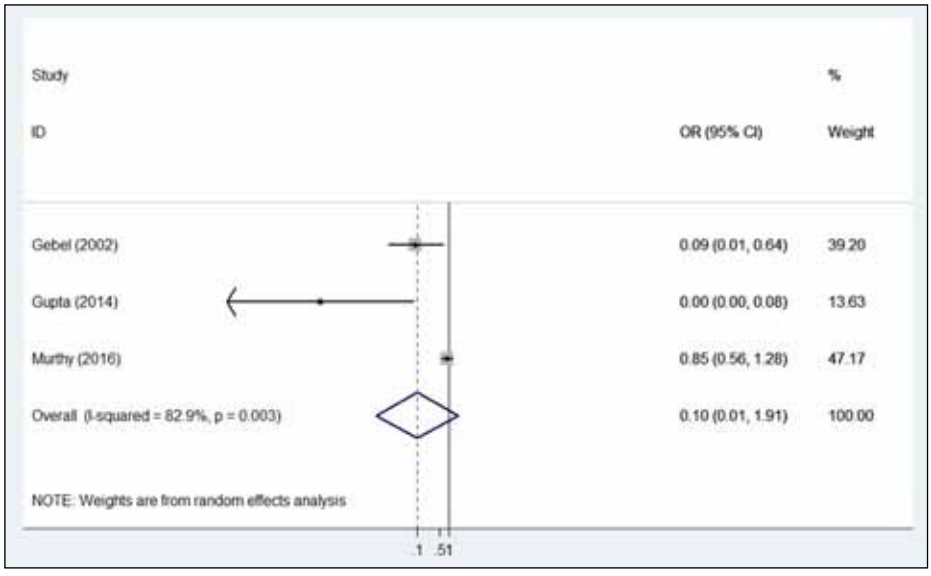

Figure 5: Meta-analysis of studies reporting an association between baseline rPHE and poor 90-day outcome.

PHEAV Growth and Outcome in ICH

A total of 6 studies (2,23,45-47,52) discussed the association between PHEAV growth and functional outcome in ICH. Volbers et al. found higher PHEAV growth between day 1 and day 2–3 in patients with poor outcome at discharge (46). Yang's study suggested 24h PHEAV growth has significant association with poor outcome (mRS3-6)(47). No significant association between PHEAV growth and functional outcome was found in Venkatasubramanian's and Zubkov's studies (45,52). Arima's study suggested 72h PHEAV growth was associated with poor functional outcome significantly in univariate analysis, but insignificant after adjustment of age, sex, randomized treatment, and log of baseline hematoma volume (2). A significant association between 72h PHEAV growth and poor functional outcome (mRS 3-6) at 90 days was found in Murthy's study (23). Meta-analysis of Arima's and Murthy's study did not show a significant association between 72h PHEAV growth and 90-day poor functional outcome (OR=1.35, 95%CI 0.81-2.26, p=0.255) (Figure 6).

Association between PHEAV growth and mortality was assessed in 5 studies (2,23,35,47,52). PHEAV growth between Day 1 and Day 3 was found to be associated with in-hospital mortality significantly in Staykov's study (35). Murthy's study showed a significant association between 72h PHEAV growth and 90-day mortality (23). In Arima's study, 72h PHEAV growth was associated with 90-day mortality significantly in univariate analysis, but insignificantly after adjustment (2). No significant association between PHEAV growth and mortality was found in Yang's and Zubkov's studies (47,52).

PHEER and Outcome in ICH

Association between PHEER and outcome in ICH was evaluated in 2 studies (23,40). Urday's study suggested 24h PHEER was significantly associated with worse mRS score and 72h PHEER was significantly associated with poor functional outcome (mRS 3-6) at 90 days (40). In Murthy's study, 72h PHEER was found to be significantly associated with poor functional outcome (mRS 3-6) and 90-day mortality (23). Meta-analysis showed the significant association between 72h PHEER and poor functional outcome (mRS 3-6) at 90 days (OR=1.62, 95%CI 1.27-2.06, p<0.001) (Figure 7).

Other PHE Measures and Outcome in ICH

Ozdinc's study showed perihematomal edema absolute area (PHEAA) was a simple value and an independent predictor for 30-day mortality (27). In Arima's study, 72h relative PHE growth was associated with poor functional outcome at 90 days significantly in univariate analysis but insignificantly after adjustment, and 72h relative PHE growth was not associated with 90-day mortality (2). No significant association was found between relative PHE growth (baseline to peak) and poor outcome at 3 months in Venkatasubramanian's study (45). Li's study suggested patients with CE at Day 3 tended to have poor outcome at 90 days (19). In Tsai's study, CE was found to be significantly associated with poor clinical outcome at 6 months (39).

■ DISCUSSION

Most ICH patients have PHE during the course of the disease, which increases the mass effect (38). Early PHE starts after ictus of ICH and peaks at 4-5 days, which is mainly caused by vasogenic effect of pro-osmotic substances from the hematoma; delayed PHE lasts for about 2-4 weeks, which is affected by both vasogenic and cytotoxic effects (4). PHE increases significantly during first 24 hours after ictus of ICH (37). PHE is influenced by many factors, such as hematoma volume, hematoma expansion, intraventricular hemorrhage, hypertension and diabetes (15). Hematoma volume is correlative to PHE (22). It is reported that the association between hematoma volume and PHE increases in large hematomas and decreases in small hematomas over time (44,48,51). Ambient temperature has association with PHE volume in acute spontaneous ICH (49). PHE development in ICH is higher in diabetic patients (14). It is reported that statin use prior to ICH is related to decreased PHE (24). As more and more studies suggest PHE may be associated with outcome in ICH, new methods are developed to reduce PHE (16,48). However, although several studies suggest PHE is a prognostic factor for ICH, some other studies have different results. Moreover, different studies have different measures for PHE and the best measure for PHE is still uncertain. We performed this systematic review and meta-analysis to evaluate the prognostic value of different measures for PHE. Finally, a total of 21 studies were included in this systematic review and meta-analysis.

Most of the studies (16/21, 76.19%) evaluated PHE with CT scan. It is more difficult to measure PHE with CT scan because the boundaries of PHE become unclear during the course of ICH (45). It is also challenging to distinguish PHE from normal tissue and infarction which presents as perihematomal hypodensity (6). An approach based on a quantitative edge-detection algorithm was developed to improve the accuracy of PHE measurement based on CT scan (41). MRI is another neuroimaging method to determine PHE after ICH. Three (14.29%) studies determined PHE with MRI and 2 (9.52%) studies assessed PHE with results of CT or MRI. MRI can suggest significant perfusion delay and facilitated diffusion admixed with restricted diffusion in the region of PHE (25). ADC can suggest the existence of cytotoxic and vasogenic edema (39). Further studies should measure PHE accurately with both CT and MRI.

PHEAV is the most frequent measure for PHE (16/21, 76.19%). The time points in these studies are different and baseline PHEAV is assessed most frequently (14/16, 87.50%). Although 4 studies (1,30,32,46) showed baseline PHEAV was significantly associated with functional outcome, other 4 studies (8,11,23,39) did not have the same results. In 3 studies (19,23,40) evaluating association between 72h PHEAV and functional outcome, 2 studies (19,23) showed 72h PHEAV was significantly associated with functional outcome, while another study (40) did not. Meta-analysis of Murthy's and Urday's studies (23,40) found a significant association between 72h PHEAV and functional outcome at 90 days. In 6 studies assessing the association between baseline PHEAV

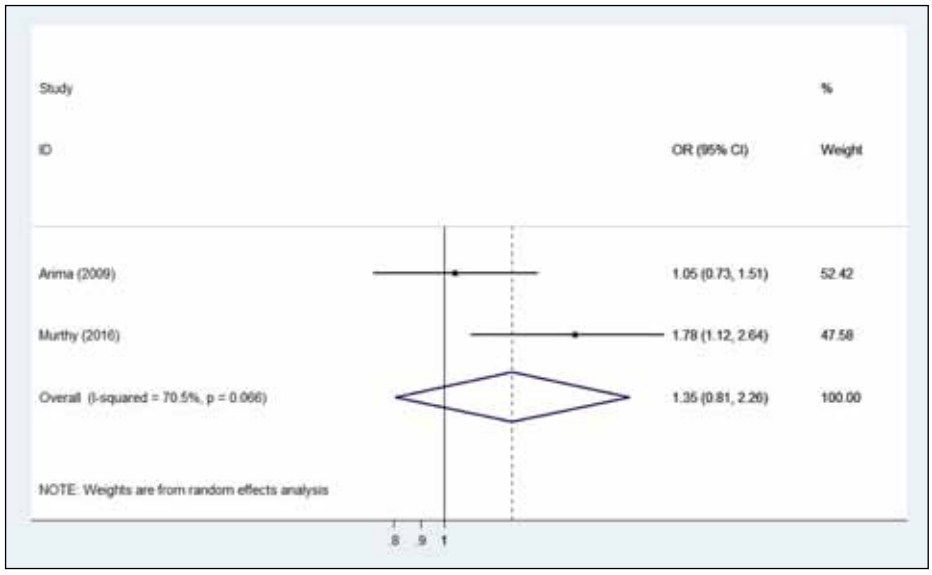

Figure 6: Meta-analysis of studies reporting an association between 72h PHEAV growth and poor 90-day outcome.

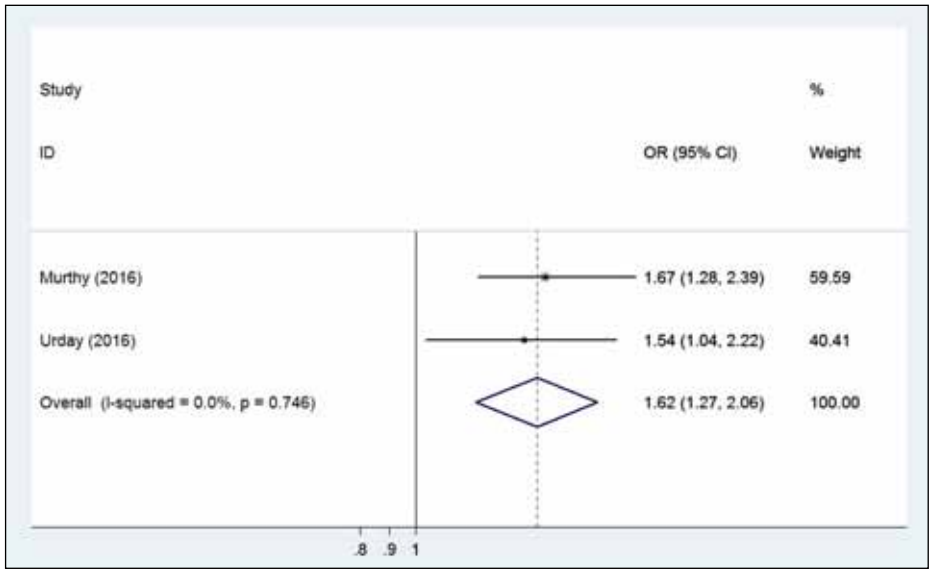

Figure 7: Meta-analysis of studies reporting an association between 72h PHEER and poor 90-day outcome.

and mortality in ICH, 5 studies (3,18,21,27,35) find the baseline PHEAV was significantly associated with mortality, but Murthy's study (23) and meta-analysis of Levine's and Murthy's studies (18,23) did not show the significant association. In 2 studies evaluating association between 72h PHEAV and 90-day mortality, both results of 2 studies and meta-analysis suggest no significant association. It seems that PHEAV may have prognostic value for ICH patients PHEAV. However, the exact association needs more studies to confirm.

rPHE is defined as PHEAV divided by hematoma volume (8). A total of 8 (38.10%) studies evaluate the prognostic role of rPHE in ICH. In 4 studies (1,8,11,23) discussing association between baseline rPHE and functional outcome, 2 studies (8,11) suggest significant association, while other 2 studies (1,23) and meta-analysis of 3 studies (8,11,23) did not. No significant association between Peak/48h rPHE and functional outcome was found (45,46). No significant association between rPHE and mortality was showed (23,35,45). One study showed 72h rPHE was significantly associated with END (36). Further studies are needed to determine the association between rPHE and outcome in ICH.

In all 6 studies (2,23,45-47,52) evaluating association between PHEAV growth and functional outcome, 3 studies (23,46,47) suggested significant association, 2 studies (45,52) showed no significant association and 1 study (2) had different results before and after adjustment. Meta-analysis of 2 studies (2,23) did not show significant association between 72h PHEAV growth and 90-day poor functional outcome. 5 studies (2,23,35,47,52) assessing the association between PHEAV growth and mortality in ICH. A significant association was found in 2 studies (23,35), while 2 studies (47,52) did not show a significant association. Different results were showed before and after adjustment in 1 study (2). The prognostic value of PHEAV growth in ICH is still uncertain.

PHEER is defined as (PHE at time point−PHE at baseline)/(time to time point CT scan−time to baseline CT scan, hours) and unit is mL/hour (23). The prognostic value of PHEER in ICH was discussed in 2 studies. 24h PHEER was found to be associated with significantly worse mRS (40). The results of 2 studies (23,40) and meta-analysis suggested significant association between 72h PHEER and poor functional outcome at 90 days. 72h PHEER was also found to be associated with 90-day mortality significantly (23). PHEER seems to be an important predictor for outcome in ICH. Further studies are necessary to prove the prognostic role of PHEER in ICH.

Some other measures for PHE were also evaluated in included studies. PHEAA seems to be a predictor for outcome in ICH (27), but more studies are needed to confirm. Relative PHE growth was not found to be associated with the outcome in ICH (2,45). CE determined by MRI was found to be potential prognostic factor in ICH (19,39), but its prognostic value should be examined in more studies.

During the first 24 hours, PHE increases greatly (40). The rapid growth of PHE remains during next 48 hours and PHE has its peak volume at the average of 12 days (45). PHE has mass effects leading high intracranial pressure and even herniation, which may influence the clinical outcome in ICH (46). Moreover, the factors involved in PHE development represent several devastating processes for brain, such as thrombin formation, erythrocyte lysis, hemoglobin toxicity and complement activation (50). Thus, PHE is considered to be associated with outcome, but the best measure for PHE to predict prognosis in ICH is still unclear (42). Some studies suggest PHEAV, rPHE and PHEAV growth are associated with outcome (1,8,47), and PHEER seems to be an important predictor for outcome in ICH patients (23,40). However, due to the complicated mechanism and process of PHE, further studies need more accurate PHE measures with more time points to investigate the prognostic value of PHE and the best PHE measure to predict outcome in ICH.

This systematic review has several limitations. First, different measures and time points for PHE and outcome were adapted in included studies, only studies with same measure, same time point and adjusted ORs were included in meta-analysis. Thus, the statistical power of meta-analysis was limited. Moreover, the meta-analysis was performed based on adjusted ORs instead of original data. Furthermore, the factors for adjustment in different studies were various, which brought confounders to the results.

CONCLUSION

This systematic review suggests that current evidence about prognostic role of PHE in ICH has high heterogeneity. The measures and time points for PHE and outcome are various. The prognostic values of PHEAV, rPHE, PHEAV growth and other measures are still controversial. PHEER seems to be a prognostic predictor for ICH. Further studies with larger sample size, more accurate measures and more time points are needed to investigate the prognostic role of PHE in ICH and the best PHE measure to predict outcome in ICH.

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