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INVITED COMMENTARY

# Commentary: Perihematomal Edema and Clinical Outcome After Intracerebral Hemorrhage; A Systematic Review and Meta-analysis

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Secondary brain injury is a potentially modifiable determinant of functional outcome in patients with spontaneous intracerebral hemorrhage (ICH) [1]. As the common end point for thrombin accumulation, inflammatory mediator influx, and erythrocyte breakdown, perihematomal edema (PHE) is a promising radiographic marker of secondary brain injury. In an attempt to quantify the magnitude of association between PHE and clinical outcome, Marchina et al. [2] performed a systematic review and meta-analysis of studies examining the relationship between PHE volume and functional outcome or mortality in patients with spontaneous ICH.

The authors identified 20 studies, comprising 6633 patients with spontaneous ICH, for inclusion. PHE measurements were collected at heterogeneous time points during the hospital stay, with the majority being at 24 h or 72 h post ictus. In their primary analysis, the authors identified a weak but significant association between PHE and mortality or functional outcome (odds ratio [OR] = 1.05 [confidence interval 1.02–1.08]; $p < 0.01$, per unit increase in PHE). Secondary analyses found a larger effect size for PHE growth (OR = 1.14 [confidence interval 1.04–1.25]; $p < 0.01$, per unit increase in PHE growth) than for PHE volume (OR = 1.04 [confidence interval 1.01–1.07]; $p < 0.01$, per unit increase in PHE volume). Taken together, the findings of their meta-analysis suggested that PHE has a negative impact on functional outcome and mortality after spontaneous ICH and that PHE growth within 72 h after the ictus has the strongest negative impact on outcome. These findings further support PHE as a surrogate marker for future therapeutic strategies seeking to mitigate secondary brain injury after spontaneous ICH [3].

The authors noted that high study heterogeneity was present in their analyses. This is likely a result of the variability in PHE measurement methods, which included manual, semiautomated, ABC/2, and edge-detection methods. Other contributors to the heterogeneity included the timing of PHE measurements (ranging from admission to postictal day 12), PHE quantification metrics (absolute PHE, relative PHE, edema extension distance, and PHE expansion rate), clinical outcome measures (mortality and functional outcome), and timing of clinical outcome measurements (hospital discharge, 30 days, 90 days, and 180 days). The significant heterogeneity had previously limited published meta-analyses to a maximum of three included studies. The current authors expanded their definitions of PHE metrics and outcomes of interest to include these variabilities. However, the resulting high heterogeneity substantially limits the conclusions that can be drawn from the study and underscores the dire need for the standardization of timing of PHE measurements, methods for PHE quantification, and measures of clinical outcome after ICH. This is perhaps the most important finding of the present study and

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a suggested direction for future efforts. This will permit a more accurate analysis of the role of PHE as a surrogate for ICH outcome.

The authors are to be commended for their thorough summary of the literature describing PHE formation after spontaneous ICH and for their inclusion of a large sample size in their meta-analysis. They estimated effect size by summarizing adjusted ORs from the included studies to generate pooled ORs and confidence intervals. They used random effects modeling to account for the high heterogeneity of the included data. Secondary outcome assessments were performed and did not detect significant differences between mortality and functional outcome or between in-hospital and 90-day outcome measures in their associations with PHE. The authors further performed a sensitivity analysis that did not find the removal of any individual study to significantly impact the overall effect size. An additional limitation was the lack of reporting of means and absolute differences among the included studies, which led to pooled ORs of heterogeneous scales. Although the authors attempted to mitigate this weakness by log-transforming their data, it remains a significant limitation to the interpretability of their results. A future study may seek to perform a patient-level meta-analysis of randomized clinical trials data.

In conclusion, this systematic review and meta-analysis found that among published studies to date, PHE growth at 24 or 72 h after the ictus has the strongest negative impact on functional outcome and mortality. Future studies should seek to standardize PHE and clinical outcome measurements in ICH by focusing on PHE growth within this time window.

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**Conflict of interest**
Natasha Ironside has a pending patent for automated intracerebral hemorrhage and perihematomal edema segmentation at the United States Patent and Trademark Office.

## Publisher's Note



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