



Hurford, R., Vail, A., Heal, C., Ziai, W. C., Dawson, J. , Murthy, S. B., Wang, X., Anderson, C. S., Hanley, D. F. and Parry-Jones, A. R. (2019) Oedema extension distance in intracerebral haemorrhage: Association with baseline characteristics and long-term outcome. *European Stroke Journal* (doi:[10.1177/2396987319848203](https://doi.org/10.1177/2396987319848203))

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/188025/>

Deposited on: 12 June 2019

Enlighten – Research publications by members of the University of Glasgow

<http://eprints.gla.ac.uk>

## **Oedema extension distance in intracerebral haemorrhage: association with baseline characteristics and long-term outcome**

Robert Hurford, MRCP<sup>1</sup>; Andy Vail, MSc<sup>2</sup>; Calvin Heal, MSc<sup>2</sup>; Wendy C. Ziai, MD, MPH<sup>3</sup>; Jesse Dawson, MD<sup>4</sup>; Santosh B. Murthy MD, MPH<sup>5</sup>; Xia Wang, MMed, PhD<sup>6</sup>, Craig S. Anderson, MD, PhD<sup>6</sup>; Daniel F. Hanley, MD<sup>7</sup>, Adrian R. Parry-Jones, PhD, MRCP<sup>2</sup>, on behalf of the VISTA-ICH Collaborators\*.

<sup>1</sup>Nuffield Department of Clinical Neurosciences, University of Oxford, Level 6 West Wing, John Radcliffe Hospital, Oxford, UK; <sup>2</sup>School of Medical Sciences, The University of Manchester, Manchester Academic Health Sciences Centre, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK; <sup>3</sup>Department of Neurology, Johns Hopkins University, Baltimore, MD, USA; <sup>4</sup>Institute of Cardiovascular and Medical Sciences, Queen Elizabeth University Hospital, University of Glasgow, Glasgow, UK; <sup>5</sup>Division of Stroke and Neurocritical Care, Department of Neurology, Weill Cornell Medicine, New York, NY, USA; <sup>6</sup>The George Institute for Global Health, Faculty of Medicine, UNSW, Sydney, New South Wales, Australia; <sup>7</sup>Division of Brain Injury Outcomes, Johns Hopkins University, Baltimore, MD, USA.

### **Corresponding author:**

Dr. Adrian R. Parry-Jones

Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, UK

E-mail: [adrian.parry-jones@manchester.ac.uk](mailto:adrian.parry-jones@manchester.ac.uk)

Tel: +44 161 2064458; Fax: +44 161 7076534

**Key words:** intracerebral haemorrhage, oedema, inflammation, surrogate markers.

**Word Count:** 3,910 (Max 4,500)

**Abstract:**

**Introduction:** Oedema extension distance (EED) is a derived parameter that may reduce sample size requirements to demonstrate reduction in perihematoma oedema in early-phase acute intracerebral haemorrhage (ICH) trials. We aimed to identify baseline predictors of EED and its association with clinical outcomes.

**Patients and methods:** Using VISTA-ICH, INTERACT1 and MISTIE-II datasets, we calculated EED at baseline and at 72 hours measured using computed tomography. Using linear regression, we tested for associations between baseline characteristics and EED at 72 h. Ordinal regression (underlying assumptions validated) was used to test for associations between EED at baseline, 72h and EED change between baseline and 72 h, and modified Rankin scale (mRS) scores at 90 days, adjusted for baseline and 72 h prognostic factors.

**Results:** There were 1,028 ICH cases with outcome data for analyses. Mean (standard deviation, SD) EED at 72 h was 0.54 (0.26) cm, and mean EED difference from baseline (EED<sub>72-0</sub>) was 0.24 (0.18) cm. EED at 72 h was greater with increasing baseline haematoma volume and baseline EED. Increasing age, lobar haemorrhage and IVH were independently associated with EED<sub>72-0</sub>. In multifactorial ordinal regression analysis, EED<sub>72-0</sub> was associated with worse mRS scores at 90 days (OR 1.96, 95% confidence interval (CI) 1.00 to 3.82).

**Conclusions:** Increase in EED over 72 h is independently associated with decreasing functional outcome at 90 days. EED may be a useful surrogate outcome measure in early phase trials of anti-oedema or anti-inflammatory treatments in ICH.

## Introduction

Perihaematoma oedema (PHE) develops rapidly and increases over several days following acute spontaneous intracerebral haemorrhage (ICH) and is proposed to reach maximal volume by two weeks(1). The additional mass effect of PHE contributes to early neurological deterioration and poor outcome(2,3). In addition, PHE may be a marker of secondary injury and a potential therapeutic target in ICH(4). A key-mediator of PHE is the innate immune response within the brain, characterised by the activation of resident microglia by damage-associated molecular patterns, infiltration of peripheral immune cells, and the production of inflammatory mediators(5). These inflammatory mechanisms orchestrate tissue damage and blood–brain barrier breakdown, playing a key role in the development of PHE(6).

PHE has been widely used as the main outcome measure in pre-clinical ICH studies targeting secondary injury and can be efficiently and reliably measured in both the experimental and clinical settings(7–9). We have recently described a novel parameter, the oedema extension distance (EED), which has been employed by other groups(10,11). It is relatively less dependent on haematoma volume and may reduce the sample size required in proof-of-concept trials by around 75% when compared to absolute or relative PHE volume(12). Understanding the baseline determinants of EED and its association with clinical outcomes is required to establish the utility of EED as a surrogate outcome measure in ICH clinical trials.

In this study, we aimed to evaluate the EED in a large sample of ICH patients (taken from the Virtual International Stroke Trials Archive [VISTA](13), the first Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial [INTERACT1](14), and the Minimally Invasive Surgery and rtPA for Intracerebral Hemorrhage Evacuation II [MISTIE II] trial(15)), to test for associations between EED, baseline clinical characteristics and clinical outcome.

## Patients and methods

We conducted a retrospective analysis of prospectively collected data from three sources: VISTA(13), INTERACT1(14) and MISTIE-II(15). Patients aged  $\geq 18$  years old with a supratentorial ICH were eligible for inclusion in our study. Those with high premorbid disability were excluded from the trials from which the datasets are derived. Ethical approval was not required for the re-use of these existing, anonymised clinical trial datasets.

Variables included baseline clinical characteristics (age, sex, hypertension, smoking, diabetes mellitus, hypercholesterolaemia, atrial fibrillation, past history of stroke or transient ischaemic attack [TIA], smoking status, baseline blood pressure, and neurological impairment based on scores on the National Institutes of Health Stroke Scale [NIHSS]), medication at baseline (antiplatelet agent[s], anticoagulants, and lipid lowering/statin use), imaging parameters (baseline and 72 hour haematoma and oedema volumes, haematoma location, presence of intraventricular haemorrhage [IVH]) and outcome data at 90 days.

All datasets used equivalent techniques to calculate PHE. As described in Yang *et al* (16), PHE volumes were calculated independently by two trained neurologists, blind to clinical data, treatment, and date and sequence of scan, using computer-assisted multi-slice planimetric and voxel threshold techniques. A semi-automated threshold-based approach (range 5-33 Hounsfield Units) was applied with adjustment to identify regions of PHE to estimate volumes ( $\text{cm}^3$ ) from slice thickness separate to boundaries of blood. Inter-reader reliability was tested with re-analysis after 30% and 60% of the scans were read by both readers to assess for drift(16).

The EED was calculated from the haematoma and PHE volumes, as outlined elsewhere(12) (*Figure 1*) at baseline ( $\text{EED}_0$ ) and 72 h ( $\text{EED}_{72}$ ), and these were used to calculate change from

baseline to 72 h (EED<sub>72-0</sub>). The relationship between PHE volume and EED is described by the equation below:

$$PHE \text{ volume} = \frac{4}{3}\pi(3r_h^2r_{eed} + 3r_h r_{eed}^2 + r_{eed}^3)$$

Where  $r_h$  is the radius of the haematoma and  $r_{eed}$  is the EED.

### *Statistical methodology*

Summary statistics were used to inform sample size calculations for trials with EED as an endpoint. Pearson correlation coefficients were used to test for correlations between perihæmatomal oedema and EED with haematoma volumes at baseline and 72 hours with visual representation using box plots, **a comparison of correlation coefficients drawn from the same sample was performed**. Multifactorial linear regression was used to test for associations between EED<sub>72-0</sub> and baseline clinical and imaging characteristics. Ordinal regression models were used to determine independent associations of EED and outcome (90-day mRS scores), with EED<sub>0</sub>, EED<sub>72</sub>, and EED<sub>72-0</sub> considered in separate models. Backward elimination was used to select the final model for linear and ordinal regression, with variables being removed manually after inspection of model fit. A Cox regression model was also used to examine mortality over 90 days. Data are reported with odds ratios (OR) or hazard ratios (HR), as appropriate, with 95% confidence intervals (CI). A sensitivity analysis excluding those patients with acute neurosurgical intervention was performed. All analyses were undertaken using Stata Statistical Software: Release 14 (StataCorp 2015).

## Results

Of a total of 1,373 ICH patients in the pooled dataset (286 INTERACT1, 987 VISTA and 100 MISTIE-II); 50 were excluded due to infratentorial ICH, 71 as their 72 h follow-up scan was performed <48 hours or >96 hours from ictus and 224 due to incomplete data (see *Supplemental Figure I* for details). Thus, 1,028 ICH patients comprised the final study population. *Table 1* shows that patients in the MISTIE-II dataset had larger haematoma and oedema volumes, a higher proportion of vascular risk factors (hypertension and hypercholesterolaemia), and a higher proportion of lobar ICH and IVH than those in the other datasets.

Overall, mean (SD) EED<sub>0</sub> and EED<sub>72</sub> were 0.30 cm (0.14) and 0.54 cm (0.26), respectively, and mean EED<sub>72-0</sub> was 0.24 cm (0.18). The relationship between EED<sub>0</sub> and EED<sub>72</sub> is demonstrated by scatterplot in *Supplemental Figure II*. *Table 2* indicates the sample sizes required to detect reductions in the various PHE volume parameters. For example, to detect a 10% effect size with 90% power, 3179, 2673 and 1182 ICH patients are needed for the different endpoints of difference from baseline to 72 hours in PHE volume, relative PHE volume, and EED, respectively. At median values for haematoma volume and EED, a given percentage reduction in EED is expected to give rise to a similar reduction in PHE volume using the model described in *Figure 1*.

*Figure 2* demonstrates a positive correlation between (a) baseline ( $r= 0.78$ ;  $p< 0.001$ ) and (b) 72 h PHE and haematoma volumes ( $r= 0.80$ ;  $p<0.001$ ), confirming that PHE volume is strongly influenced by haematoma size. In contrast, EED is much less strongly correlated with haematoma volume at baseline ( $r= 0.35$ ;  $p<0.001$ ) and 72 hours ( $r= 0.30$ ;  $p< 0.001$ ). A comparison of the respective correlation coefficients demonstrated significant difference at both baseline and 72 hours ( $p <0.001$ ). *Table 3* shows results of a multivariable linear regression model used to identify factors associated with EED<sub>72-0</sub>. Larger baseline haematoma volume was associated with higher EED<sub>72-0</sub> ( $p <0.001$ ), whereas increasing age ( $p <0.001$ ),



lobar location [vs. deep] ( $p = 0.018$ ), and presence of IVH [vs. not] ( $p = 0.003$ ) were associated with lower EED<sub>72-0</sub>. *Table 4* shows the results of ordinal regression analysis; larger EED<sub>72-0</sub> (OR 1.96, 95% CI 1.00 to 3.82), presence of IVH, diabetes mellitus, prior use of antiplatelets and anticoagulation and 72 hour haematoma volume were independently associated with a poor 90 day outcome (mRS score 3-6). Lobar haemorrhage location and male sex were predictive of a good 90 day outcome (mRS score 0-2). At 90 days 128 (12.5%) patients had died. EED<sub>72-0</sub> was not associated with death by 90 days (HR 2.21, 95% CI 0.90 to 5.47) (*Supplementary Table I*).

Of the 1,028 patients, 82 (8.0%) underwent acute neurosurgical intervention (41 VISTA and 41 MISIE-II). Of the 41 VISTA patients, 26 (63.4%) underwent ventricular drainage, 2 (4.9%) underwent haematoma evacuation, 5 (12.2%) had craniotomies and in 8 (19.5%), the procedure details were unavailable. The MISTIE-II patients who had undergone neurosurgical intervention were in the minimally invasive surgery treatment arm of the trial. A multivariable ordinal regression sensitivity analysis was performed excluding patients that underwent acute neurosurgery and larger EED<sub>72-0</sub> was associated with 90 day outcome (OR 1.95, 95% CI 0.97-3.92) with a similar OR point estimate, but it was no longer statistically significant ( $p=0.06$ ) (*Supplementary Table II*).

## Discussion

Our analysis of a large dataset of over 1,000 ICH patients has shown that  $EED_{72-0}$ , as a derived parameter, can markedly reduce the sample size required in early-phase ICH clinical trials targeting PHE, as compared with conventional measures of absolute or relative PHE volumes. We show that higher  $EED_{72-0}$  is associated with higher baseline haematoma volume, while a lower  $EED_{72-0}$  was associated with advancing age, lobar location and IVH. Furthermore,  $EED_{72-0}$  was independently associated with a worse 90-day outcome, as measured by mRS.

As haematoma and PHE volumes are closely correlated, PHE is highly variable and necessitates large sample sizes for clinical trials with oedema as an outcome measure. Relative PHE volume has been considered as a means of reducing the variability introduced by the correlation between haematoma and oedema volumes, but is typically disproportionately large for smaller haematoma volumes, and thus an unsuitable parameter for clinical trials(8). PHE is strongly influenced by the intensity of the parenchymal inflammatory response, which diffuses in a linear fashion from the haematoma border. Conversely, EED is relatively less dependent on haematoma volume and likely to be more representative of the pathophysiological processes related to PHE than total PHE volume(17).

In performing a sensitivity analysis by excluding patients with acute neurosurgical intervention, the  $p$ -value for the association between  $EED_{72-0}$  and 90-day mRS increased from 0.049 to 0.06. The majority of neurosurgical patients in VISTA had ventricular drainage only (26/ 41; 63.4%), which would not be expected to significantly alter the PHE. Patients in MISTIE were randomized to either undergo tPA-augmented minimally invasive surgery to evacuate the haematoma or standard medical care. Our analysis demonstrates a clear correlation between haematoma volume and PHE volume, suggesting that a surgical reduction in haematoma volume will also reduce PHE volume, which was confirmed in MISTIE-II(9). However, given that EED is relatively less dependent on haematoma volume (unlike PHE

volume) we would not expect EED to be reduced in patients undergoing haematoma evacuation, relative to non-surgical patients. Further analysis of our dataset confirms this, with no difference in EED<sub>72-0</sub> between surgical and non-surgical patients, either in the whole combined dataset (surgical mean EED<sub>72-0</sub> 0.24cm [SD 0.20cm] vs. non-surgical mean EED<sub>72-0</sub> 0.24cm [0.18cm]; T-test p= 0.86) or within the MISTIE II dataset alone (surgical 0.16cm [0.16cm] vs. non-surgical 0.14cm [0.10cm]; p= 0.44). The slight increase in the p-value from 0.049 to 0.06 on excluding surgical cases is thus likely to be related to reduced power (a type II statistical error), rather than heterogeneity in the association between EED<sub>72-0</sub> and 90-day mRS by whether or not neurosurgery was performed.

We have identified larger haematoma volume as predictors of EED<sub>72-0</sub>. Older age, lobar (vs. deep) haemorrhage location and IVH were predictors of smaller EED<sub>72-0</sub>. Older age is an independent predictor of poor outcome after ICH and is used in clinical grading scales(18). However, this might be due to any number of pathophysiological mechanisms, such as impaired coagulation cascade, inflammatory or astrocyte responses, cerebral atrophy or reduced functional reserve. A study of experimentally induced ICH found worse neurological outcome and larger PHE volumes in 18 month compared to 3 month old rats(19). However, a retrospective analysis of 219 consecutive ICH patients assessed with sequential CT failed to find any association of PHE volume and age(20). Older age emerged as a predictor of a smaller EED<sub>72</sub> in our study involving a much larger ICH cohort, which may suggest that older people have impaired, or delayed, inflammatory response in ICH(21).

We found that lobar location of ICH was predictive of smaller EED<sub>72-0</sub>. The existing literature is conflicted in regards to haematoma location and PHE volume(22–24), which may be due to confounding and chance related to study design and sample size, as well as the inclusion of larger haematomas which may not be easily classified as deep or lobar. Moreover, no previous study has used EED as a measure of PHE which is relatively less dependent on haematoma

size and likely to provide a more reliable assessment of the association between ICH location and oedema by adjusting for haematoma volume. The capacity for water to diffuse through brain tissue can be driven by any change in the microstructure which alters diffusivity such as mechanical compression, membrane damage, inflammation, and shifts in water content in either the intra- or extra-cellular space. A potential biological explanation for higher EED in deep ICH is that deep haematomas are typically adjacent to densely packed white matter tracts. Myelin is a major diffusion barrier to water, a property that is exploited in diffusion tractography. This may preferentially facilitate the movement of water along the direction of white matter tracts, allowing greater propagation of oedema than might be seen with a lobar haemorrhage surrounded by gray matter. Further studies using diffusion tensor MRI may help to test this hypothesis further. Finally, although  $EED_{72-0}$  was not statistically associated with mortality, it had a large HR in the model and requires confirmation in a larger dataset.

The presence of baseline IVH was also associated with a lower  $EED_{72-0}$ . Although there is no clear explanation for this association, it may be that IVH leads to higher intraventricular pressure which may be transmitted to the brain parenchyma, reducing the production of perihæmatomal oedema. Secondly, the presence of blood adjacent to the ventricular ependyma may alter the biological processes in the underlying brain parenchyma such that less oedema is generated over the first 72 h. For example, the inflammatory response may progress more quickly in the intraventricular space and ‘anti-inflammatory’ cytokines (e.g. interleukin-1 receptor antagonist, transforming growth factor beta) associated with repair and recovery may be generated earlier, influencing the brain parenchyma adjacent to the ventricle. Further work in experimental models is needed to test these hypotheses.

Although our study was strengthened by having a large, ethnically diverse (60% Caucasian, 34% Asian) sample with robust measures of PHE, we acknowledge several limitations that includes the development of the EED parameter, which required the assumption of an ellipsoid-

shaped haematoma and oedema, which is present in only 70% of patients(4). Peak PHE volume may have an independent effect on outcome in ICH(25), but we were unable to assess this in our cohort. Furthermore, our sample size was still small for examination of modest, but still clinically important, associations relevant to the serious disease of ICH. Finally, our cohort was younger and with a greater proportion of lobar ICH compared to population based studies(26), this may limit our study's representativeness.

## **Conclusion**

We have previously shown that the use of EED as the outcome measure for PHE in clinical trials markedly reduces the sample size required. We have now confirmed this in a much larger dataset and demonstrated that EED<sub>72-0</sub> is significantly associated with mRS at 90 days. Although validation in prospective studies is desired, our study strengthens the case for the use of EED<sub>72-0</sub> as a surrogate outcome measure for early phase clinical trials of anti-oedema treatments in ICH.

## **Acknowledgements**

Study concept and design: RH, AV, CH and APJ. Acquisition of data: RH, APJ, WZ, JD, SM, XW, CA and DH. Analysis and interpretation of data: RH, AV, CH and APJ. Drafting of the manuscript: RH and APJ. Critical revision of the manuscript for important intellectual content: CH, WZ, JD, SM, XW, CA and DH. Statistical analysis: RH, AV and CH. Study supervision: APJ.

*\*VISTA-ICH Steering Committee:* Daniel F. Hanley (Chair), Kenneth S. Butcher, Stephen Davis, Barbara Gregson, Kennedy R. Lees, Patrick Lyden, Stephan Mayer, Keith Muir and Thorsten Steiner.

## **Sources of funding**

RH is supported by an Association of British Neurologists' Clinical Research Training fellowship. APJ is supported by a National Institute for Health Research Clinician Scientist Award.

## **Disclosures**

None.

## References

1. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol.* England; 2012 Jan;11(1):101–18.
2. Zazulia AR, Diringner MN, Derdeyn CP, Powers WJ. Progression of mass effect after intracerebral hemorrhage. *Stroke.* UNITED STATES; 1999 Jun;30(6):1167–73.
3. Appelboom G, Bruce SS, Hickman ZL, Zacharia BE, Carpenter AM, Vaughan KA, et al. Volume-dependent effect of perihematoma oedema on outcome for spontaneous intracerebral haemorrhages. *J Neurol Neurosurg Psychiatry.* England; 2013 May;84(5):488–93.
4. Wang J, Dore S. Inflammation after intracerebral hemorrhage. *J Cereb Blood Flow Metab.* United States; 2007 May;27(5):894–908.
5. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol.* England; 2012 Aug;11(8):720–31.
6. Keep RF, Xiang J, Ennis SR, Andjelkovic A, Hua Y, Xi G, et al. Blood-brain barrier function in intracerebral hemorrhage. *Acta Neurochir Suppl.* Austria; 2008;105:73–7.
7. Frantzijs J, Sena ES, Macleod MR, Al-Shahi Salman R. Treatment of intracerebral hemorrhage in animal models: meta-analysis. *Ann Neurol.* United States; 2011 Feb;69(2):389–99.
8. Volbers B, Staykov D, Wagner I, Dorfler A, Saake M, Schwab S, et al. Semi-automatic volumetric assessment of perihemorrhagic edema with computed tomography. *Eur J Neurol.* England; 2011 Nov;18(11):1323–8.
9. Mould WA, Carhuapoma JR, Muschelli J, Lane K, Morgan TC, McBee NA, et al. Minimally invasive surgery plus recombinant tissue-type plasminogen activator for

- intracerebral hemorrhage evacuation decreases perihematomal edema. *Stroke*. United States; 2013 Mar;44(3):627–34.
10. Wu TY, Putaala J, Sharma G, Strbian D, Tatlisumak T, Davis SM, et al. Persistent Hyperglycemia Is Associated With Increased Mortality After Intracerebral Hemorrhage. *J Am Heart Assoc*. England; 2017 Aug;6(8).
  11. Wu TY, Sharma G, Strbian D, Putaala J, Desmond PM, Tatlisumak T, et al. Natural History of Perihematomal Edema and Impact on Outcome After Intracerebral Hemorrhage. *Stroke*. United States; 2017 Apr;48(4):873–9.
  12. Parry-Jones AR, Wang X, Sato S, Mould WA, Vail A, Anderson CS, et al. Edema Extension Distance: Outcome Measure for Phase II Clinical Trials Targeting Edema After Intracerebral Hemorrhage. *Stroke*. 2015 Jun;46(6):e137–40.
  13. Ali M, Bath P, Brady M, Davis S, Diener H-C, Donnan G, et al. Development, expansion, and use of a stroke clinical trials resource for novel exploratory analyses. *Int J Stroke*. United States; 2012 Feb;7(2):133–8.
  14. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. England; 2008 May;7(5):391–9.
  15. Hanley DF, Thompson RE, Muschelli J, Rosenblum M, McBee N, Lane K, et al. Safety and efficacy of minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation (MISTIE): a randomised, controlled, open-label, phase 2 trial. *Lancet Neurol*. England; 2016 Nov;15(12):1228–37.
  16. Yang J, Arima H, Wu G, Heeley E, Delcourt C, Zhou J, et al. Prognostic significance of perihematomal edema in acute intracerebral hemorrhage: pooled analysis from the intensive blood pressure reduction in acute cerebral hemorrhage trial studies. *Stroke*.



- United States; 2015 Apr;46(4):1009–13.
17. Parry-Jones AR, Wang X, Sato S, Mould WA, Vail A, Anderson CS, et al. Edema Extension Distance: Outcome Measure for Phase II Clinical Trials Targeting Edema After Intracerebral Hemorrhage. *Stroke*. United States; 2015 Jun;46(6):e137-40.
  18. Rost NS, Smith EE, Chang Y, Snider RW, Chanderraj R, Schwab K, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. *Stroke*. United States; 2008 Aug;39(8):2304–9.
  19. Gong Y, Hua Y, Keep RF, Hoff JT, Xi G. Intracerebral hemorrhage: effects of aging on brain edema and neurological deficits. *Stroke*. United States; 2004 Nov;35(11):2571–5.
  20. Staykov D, Wagner I, Volbers B, Hauer E-M, Doerfler A, Schwab S, et al. Natural course of perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. United States; 2011 Sep;42(9):2625–9.
  21. Sieber MW, Claus RA, Witte OW, Frahm C. Attenuated inflammatory response in aged mice brains following stroke. *PLoS One*. United States; 2011;6(10):e26288.
  22. McCarron MO, McCarron P, Alberts MJ. Location characteristics of early perihematoma edema. *J Neurol Neurosurg Psychiatry*. England; 2006 Mar;77(3):378–80.
  23. Arima H, Wang JG, Huang Y, Heeley E, Skulina C, Parsons MW, et al. Significance of perihematoma edema in acute intracerebral hemorrhage: the INTERACT trial. *Neurology*. United States; 2009 Dec;73(23):1963–8.
  24. Gebel JMJ, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al. Natural history of perihematoma edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke*. United States; 2002 Nov;33(11):2631–5.

25. Volbers B, Giede-Jeppe A, Gerner ST, Sembill JA, Kuramatsu JB, Lang S, et al. Peak perihemorrhagic edema correlates with functional outcome in intracerebral hemorrhage. *Neurology*. United States; 2018 Mar;90(12):e1005–12.
26. Samarasekera N, Fonville A, Lerpiniere C, Farrall AJ, Wardlaw JM, White PM, et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome: population-based study. *Stroke*. United States; 2015 Feb;46(2):361–8.

## Tables and Figures

**Figure 1:** Example of a CT scan demonstrating delineation of the region of perihematoma oedema (PHE) (outlined in green) and ICH (outlined in red). The EED is the difference between the radius ( $r_e$ ) of a sphere (shown in green) equal to the combined volume of PHE and ICH and the radius of a sphere (shown in red) equal to the volume of the ICH alone ( $r_h$ ) (12).

**Figure 2:** Box plots showing the relationship between oedema volume and haematoma volume, at baseline (A:  $r= 0.78$ ,  $p< 0.001$ ) and 72 hours (B:  $r= 0.80$ ,  $p<0.001$ ) and oedema extension distance and haematoma volume, at baseline (C:  $r= 0.35$ ,  $p< 0.001$ ) and 72 hours (D:  $r= 0.30$ ,  $p<0.001$ ).

**Table 1:** Population baseline characteristics. *SD= standard deviation, TIA= transient ischaemic attack, SBP= systolic blood pressure, NIHSS= National Institute of Health Stroke Score, IVH= intraventricular haemorrhage.*

	Total N= 1028	Cohort			p-value
		VISTA N= 725	INTERACT1 N= 241	MISTIE-II N= 62	
Mean age (SD)	64.7 (12.1)	65.6 (12.1)	62.7 (12.3)	62.5 (10.9)	0.002
Male (%)	656 (63.8)	466 (64.3)	151 (62.7)	39 (62.9)	0.89
Hypertension (%)	843 (82.0)	610 (84.1)	178 (73.9)	55 (88.7)	0.001
Diabetes mellitus (%)	170 (16.5)	132 (18.2)	22 (9.1)	16 (25.8)	<0.001
Previous anticoagulation (%)	10 (1.0)	-	3 (1.2)	7 (11.3)	<0.001
Mean baseline SBP mmHg (SD)	173.0 (37.0)	173.0 (39.0)	178.5 (30.0)	143.5 (30.0)*	<0.001
Median baseline NIHSS (IQR)	13.0 (9.0)	13.0 (8.0)	10.0 (10.0)	19.5 (7.0)*	<0.001
Median baseline haematoma volume cm <sup>3</sup> (IQR)	13.7 (19.8)	14.6 (19.1)	9.5 (12.4)	39.0 (24.0)	<0.001
Median 72h haematoma volume cm <sup>3</sup> (IQR)	15.0 (22.9)	17.1 (25.8)	9.9 (12.6)	19.6 (30.3)	<0.001
Median baseline oedema volume cm <sup>3</sup> (IQR)	9.2 (12.9)	8.9 (12.3)	7.5 (9.1)	27.1 (20.8)	<0.001
Median 72h oedema volume cm <sup>3</sup> (IQR)	21.8 (27.8)	23.5 (30.9)	15.3 (21.4)	30.0 (16.4)	<0.001
Presence of IVH at baseline (%)	320 (31.1)	225 (31.0)	60 (24.9)	35 (56.5)	0.11
Index haematoma location (%)					
Supratentorial lobar	159 (15.5)	113 (15.6)	22 (9.1)	24 (38.7)	<0.001
Supratentorial deep	869 (84.5)	612 (84.4)	219 (90.9)	38 (61.3)	

\*Recordings at randomization.

**Table 2:** Clinical trial sample size calculations using PHE as the primary outcome. Number of patients required in each arm of a clinical trial with difference in PHE between baseline and 72 hours as the primary outcome, assuming  $\alpha = 0.05$  and either 80% or 90% power to detect a range of reductions in each measure. Calculations based on data from the conservative arms of VISTA, INTERACT1 and MISTIE-II. Mean (SD) for each measure were PHE volume (72-0), 15.27 ml (18.78 ml); relative PHE (72-0), 0.86 ml (0.97 ml); EED<sub>72-0</sub>, 0.24 cm (0.18 cm). PHE= perihæmatomal oedema, EED= oedema extension distance.

Reduction in measure (%)	80% power			90% power		
	PHE Vol (72-0)	Relative PHE (72-0)	EED <sub>72-0</sub>	PHE Vol (72-0)	Relative PHE (72-0)	EED <sub>72-0</sub>
5	9485	7988	3532	12698	10694	4728
10	2374	1997	883	3179	2673	1182
15	1056	888	392	1413	1188	525
20	594	499	221	795	668	296
25	380	320	141	508	428	189
30	264	222	98	353	297	131
35	194	163	72	260	218	96
40	148	125	55	199	167	74

**Table 3:** Table describing baseline factors associated with (square root)  $EED_{72-0}$ . *EED*= oedema extension distance, *IVH*= intraventricular haemorrhage.

<b>Predictor variable</b>	<b>Coefficient</b>	<b>P value</b>	<b>Lower 95% CI</b>	<b>Upper 95% CI</b>
Age	-0.001	<0.001	-0.001	<-0.001
Lobar haemorrhage (vs. deep haemorrhage)	-0.018	0.018	-0.033	-0.003
Baseline haematoma volume	0.001	<0.001	<0.001	0.001
Presence of baseline IVH (vs. not)	-0.016	0.003	-0.027	-0.006

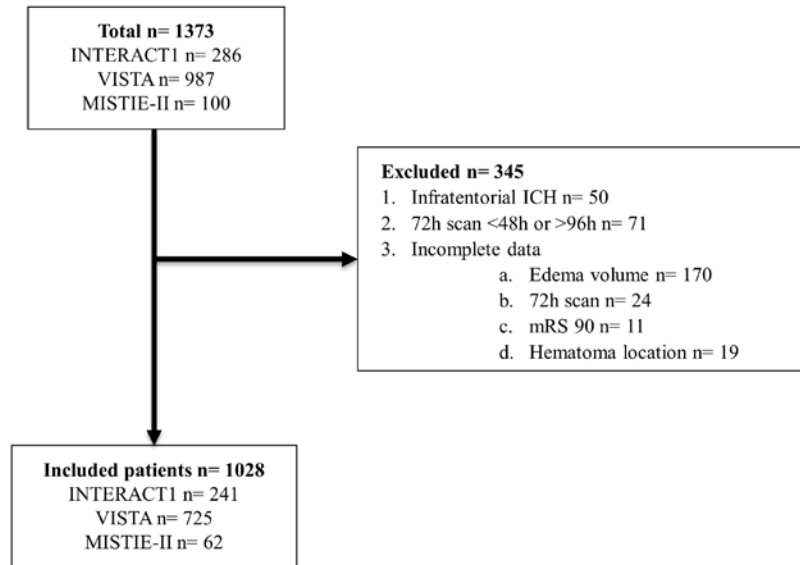
**Table 4:** Results of testing for associations with mRS at 90d – ordinal regression model. *CI= confidence interval, IVH= intraventricular haemorrhage*

<b>Predictor variable</b>	<b>Odds Ratio</b>	<b>Standard error</b>	<b>P value</b>	<b>Lower 95% CI</b>	<b>Higher 95% CI</b>
Male sex	0.78	0.09	0.035	0.61	0.98
Age	1.05	0.006	<0.001	1.04	1.06
Diabetes	1.65	0.27	0.002	1.20	2.29
Antiplatelet therapy	1.70	0.30	0.003	1.20	2.41
Anticoagulation	2.74	0.90	0.002	1.44	5.20
Statin	0.74	0.15	0.124	0.50	1.09
Lobar haemorrhage	0.59	0.11	0.003	0.41	0.84
Haematoma volume 72 hours	1.04	0.004	<0.01	1.04	1.06
Presence of IVH at 72 hours	2.68	0.34	<0.001	2.09	3.45
EED <sub>72-0</sub>	1.96	0.67	0.049	1.00	3.82

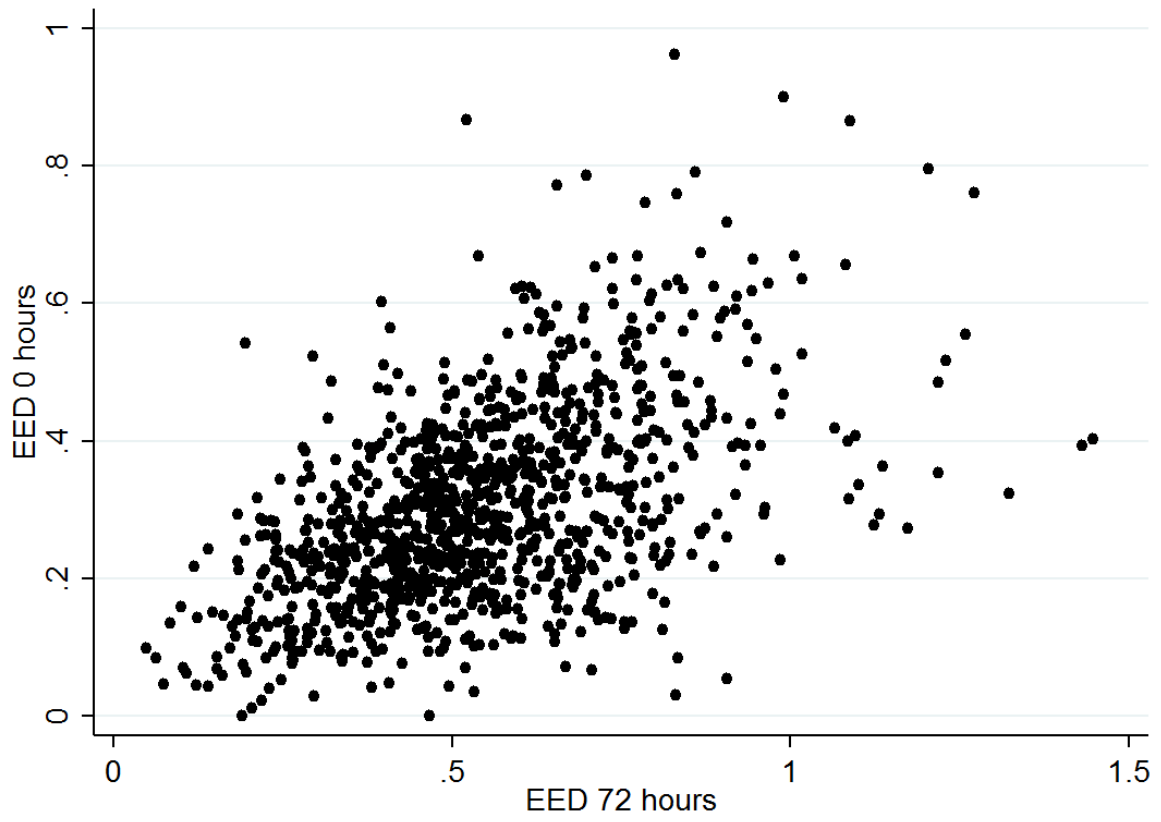


## Online Supplement

**Supplementary Figure I:** Flow diagram outlining patient exclusions.



**Supplementary Figure II:** scatterplot depicting the relationship between EED<sub>72</sub> and EED<sub>0</sub>. P= 0.53. *EED= oedema extension distance.*



**Supplementary Table I:** Results of testing for associations with mortality – Cox regression model. *EED*= oedema extension distance, *IVH*= intraventricular haemorrhage.

<b>Predictor variable</b>	<b>Hazard Ratio</b>	<b>Standard error</b>	<b>P value</b>	<b>Lower 95% CI</b>	<b>Higher 95% CI</b>
Age	1.04	0.01	<0.001	1.03	1.06
Male sex	1.72	0.36	0.009	1.14	2.60
Antiplatelet therapy	1.97	0.41	0.001	1.31	2.97
Presence of IVH at 72 hours	2.14	0.44	<0.001	1.43	3.20
EED <sub>72-0</sub>	2.21	1.02	0.085	0.90	5.47
Baseline haematoma volume	1.03	0.003	<0.001	1.02	1.03

**Supplementary Table II:** Sensitivity analysis of associations with mRS at 90d (ordinal regression model) in those without neurosurgical intervention. *EED*= oedema extension distance, *IVH*= intraventricular haemorrhage.

<b>Predictor variable</b>	<b>Odds Ratio</b>	<b>Standard error</b>	<b>P value</b>	<b>Lower 95% CI</b>	<b>Higher 95% CI</b>
Male sex	0.76	0.09	0.026	0.59	0.97
Age	1.05	0.006	<0.001	1.04	1.06
Diabetes	1.53	0.26	0.012	1.10	2.14
Antiplatelet therapy	1.61	0.30	0.011	1.11	2.32
Anticoagulation	2.30	0.82	0.019	1.15	4.63
Statin	0.68	0.14	0.065	0.45	1.02
Lobar haemorrhage	0.60	0.12	0.009	0.41	0.88
Haematoma volume 72 hours	1.05	0.004	<0.01	1.04	1.06
Presence of IVH at 72 hours	2.48	0.33	<0.001	1.91	3.22
EED <sub>72-0</sub>	1.95	0.69	0.060	0.97	3.92