SUPPLEMENTAL MATERIAL

Measurement of Peri-Hematomal Edema in Intracerebral Hemorrhage

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Itemized List of Figures and Tables:

Online Supplemental Methods

Figures I-VII outline the steps for ICH and PHE measurement using Analyze 11.0 (AnalyzeDirect, Overland Park, KS, USA).

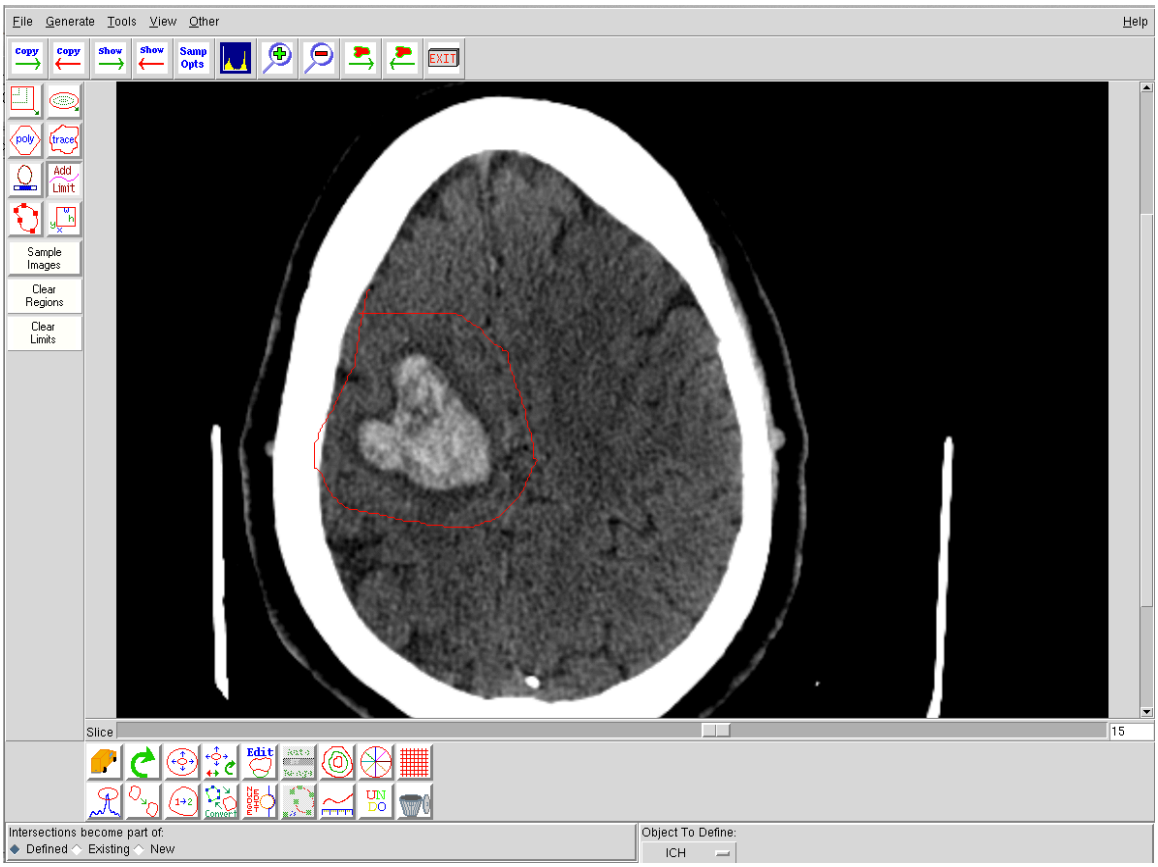

Figure I. In the Region of Interest module, click on the Add Limit icon and trace a limit line around the ICH. In this way the software's edge detection tool only calculates boundaries within the selected area.

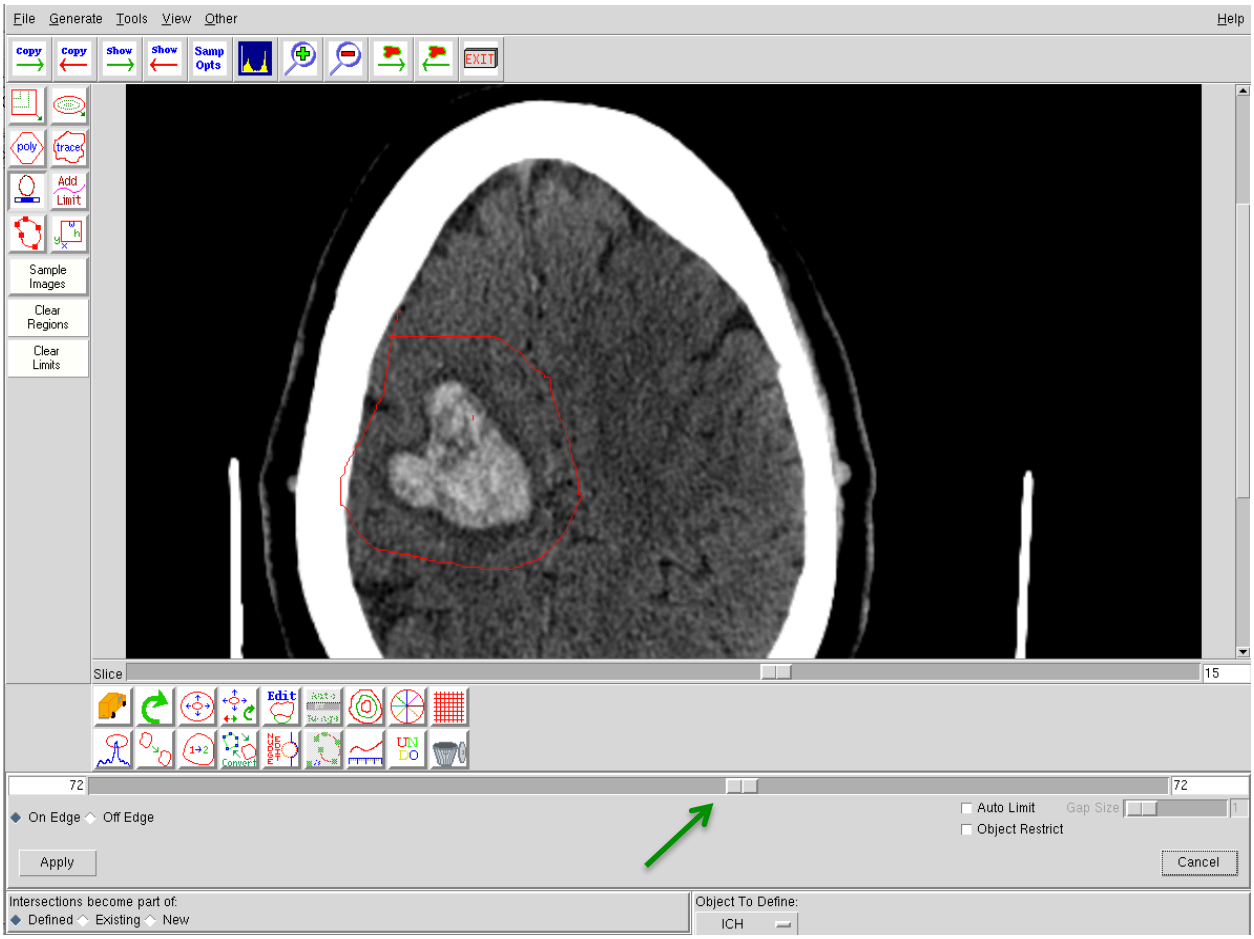

Figure II. Click on the AutoTrace tool icon (edge-detection tool) and then click on a hyperdense area of hemorrhage to set a 'seed point'. Once the 'seed point' is set, a slider bar appears (arrow). Grow the ICH boundary by dragging either side of the bar. Select the optimal boundary defining the hyperdense region of hemorrhage.

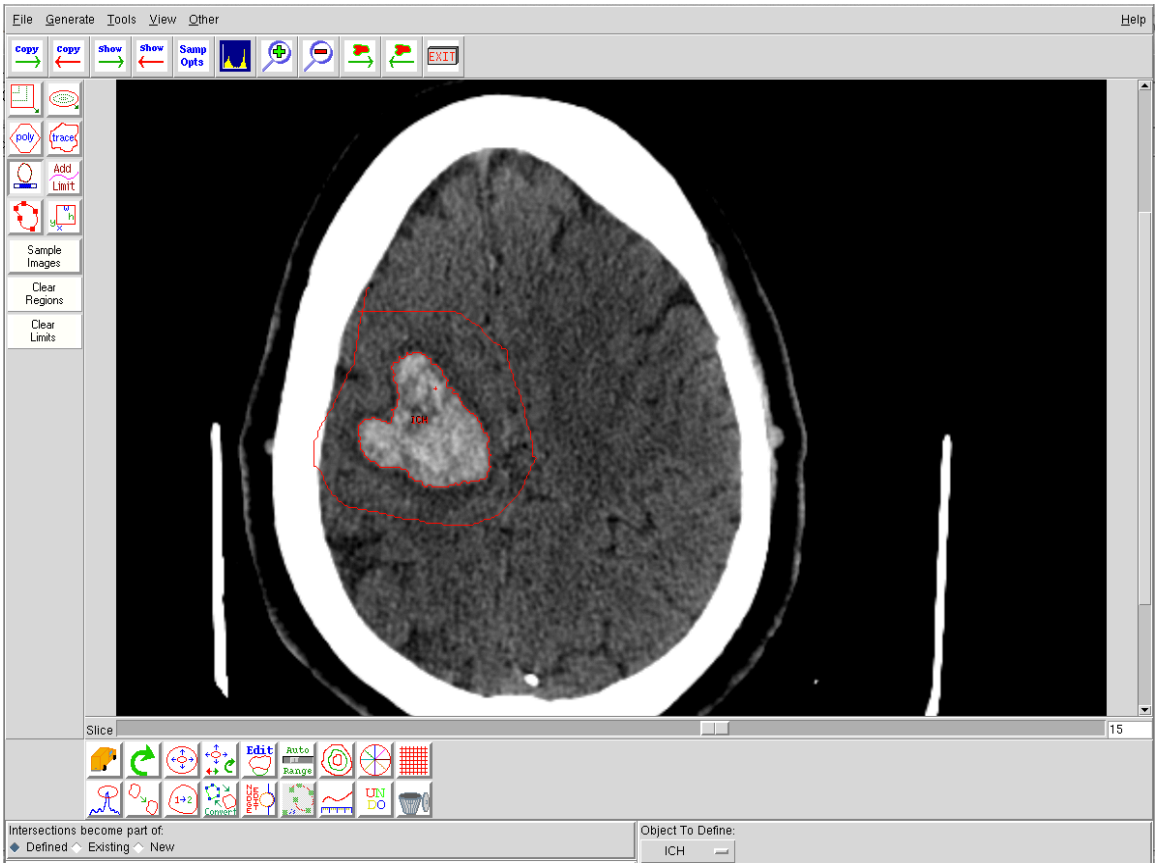

Figure III. Click Apply to set the ICH boundary. The step above can be repeated if needed to define multiple hemorrhages.

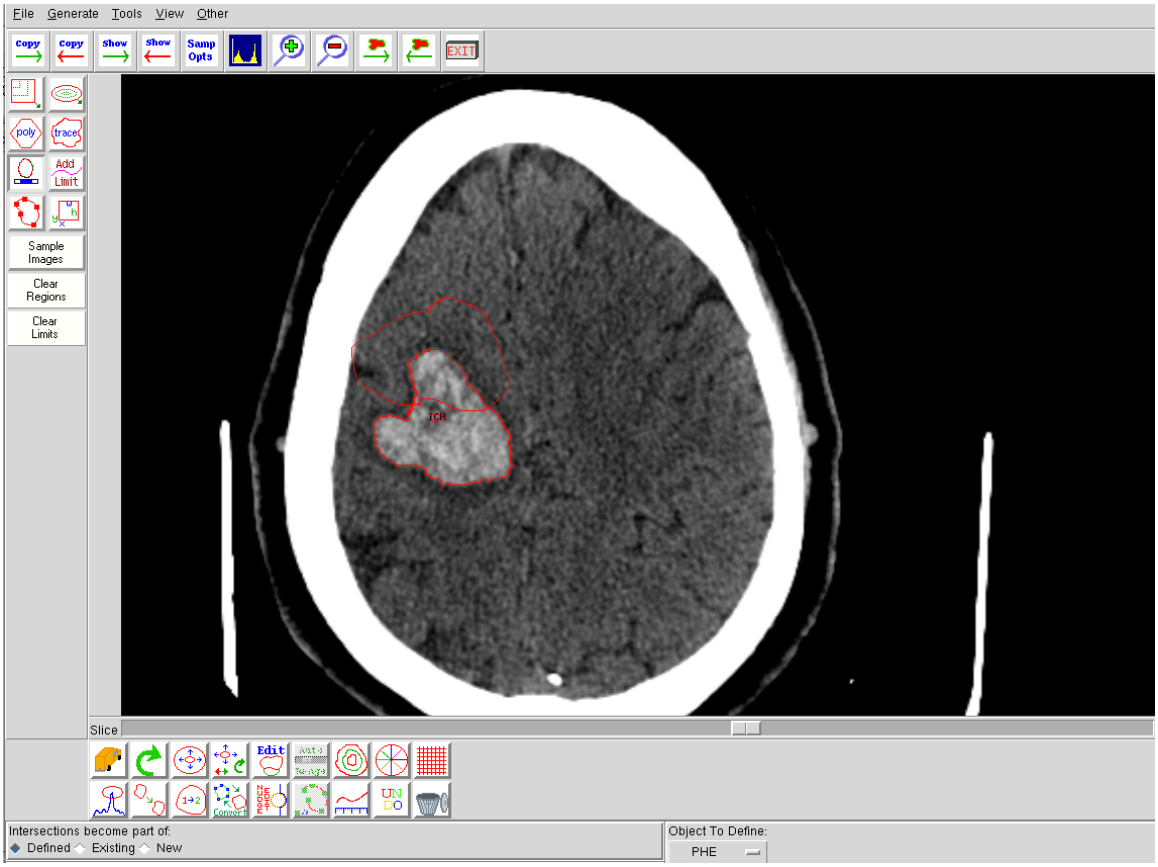

Figure IV. Click on the Add Limit icon and trace a limit line around a region that contains PHE. The rim of PHE is defined with the principle that it should be (a) more hypodense than the corresponding region in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage. As before, click on the Autotrace tool icon. Then click on a hypodense area of PHE to set a 'seed point'. Once the 'seed point' is set, a slider bar appears. Grow the PHE boundary by dragging either side of the bar. Select the optimal boundary defining the hypodense region of PHE.

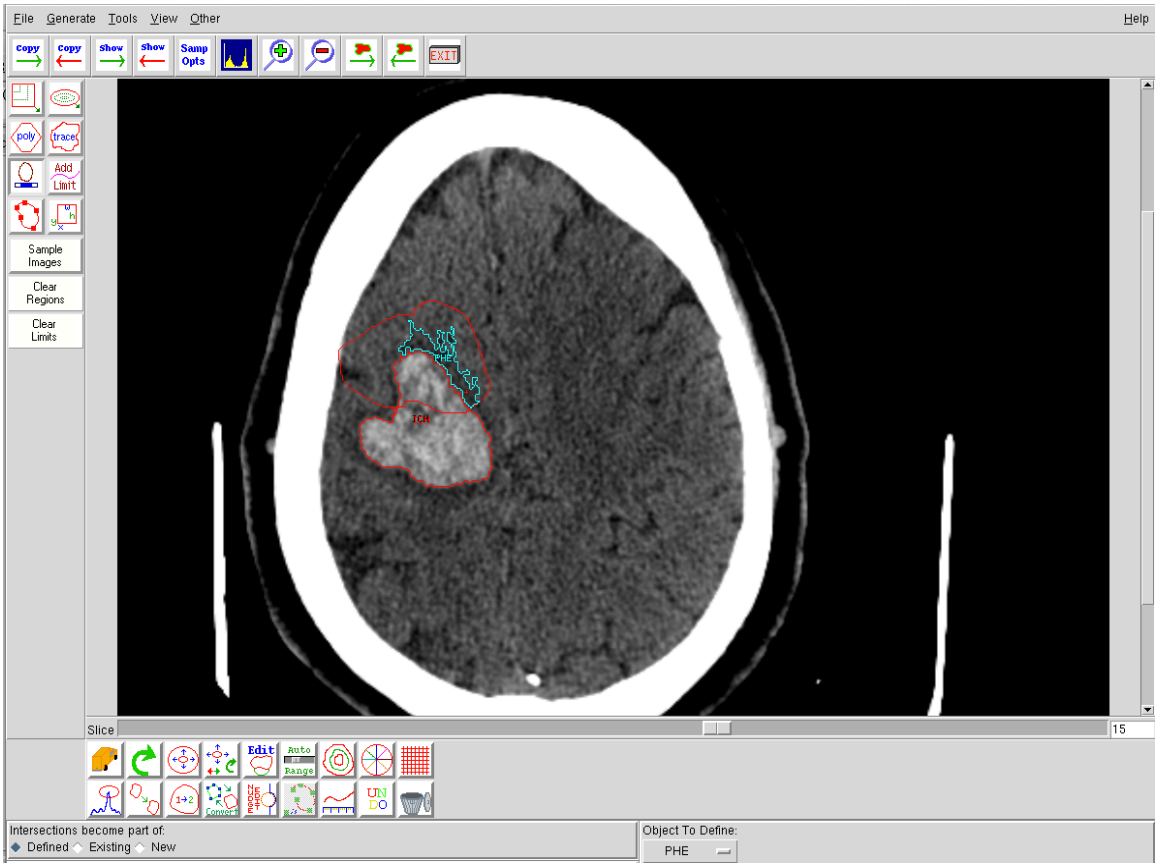

Figure V. Click Apply to set the PHE boundary.

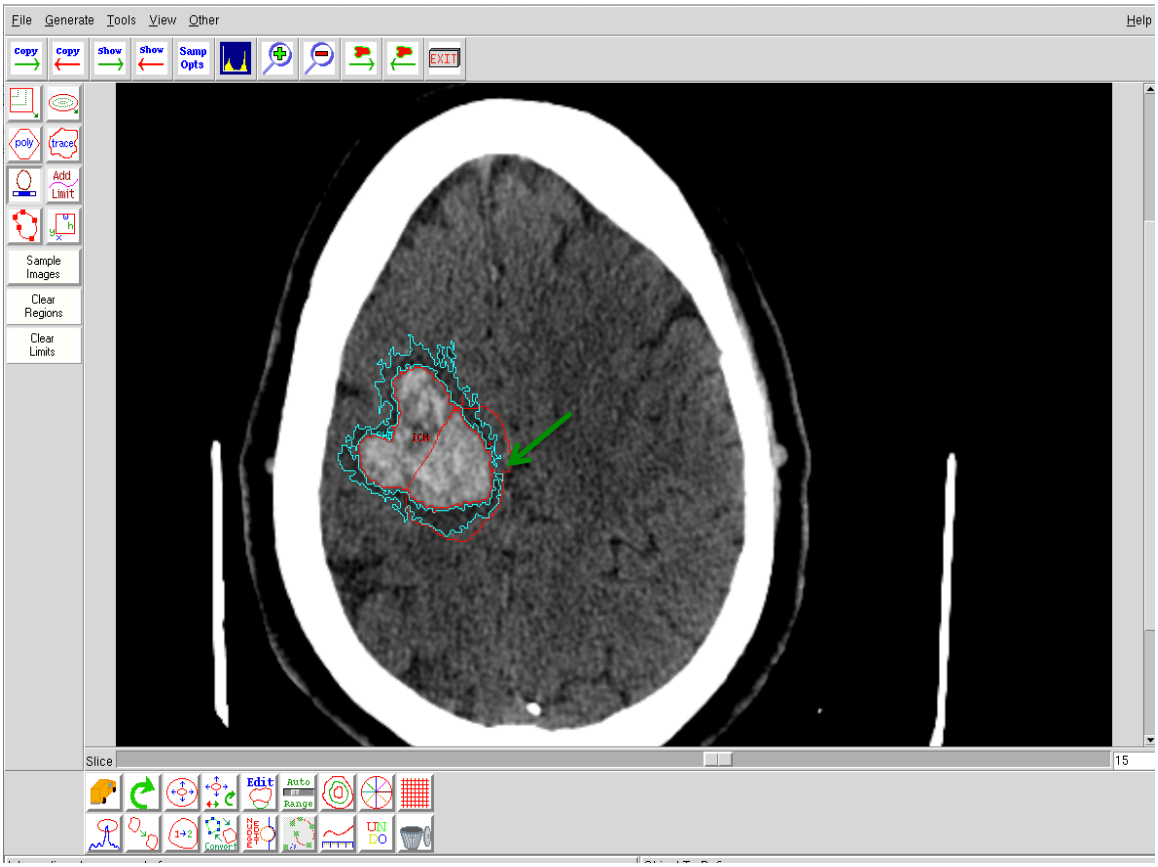

Figure VI. Example showing how the principle above was used to delineate PHE. Here a limit line is used to exclude a region that is more hypodense further out from the hemorrhage, rather than immediately surrounding the hemorrhage. In this case it corresponds to a sulci from the contralateral hemisphere.

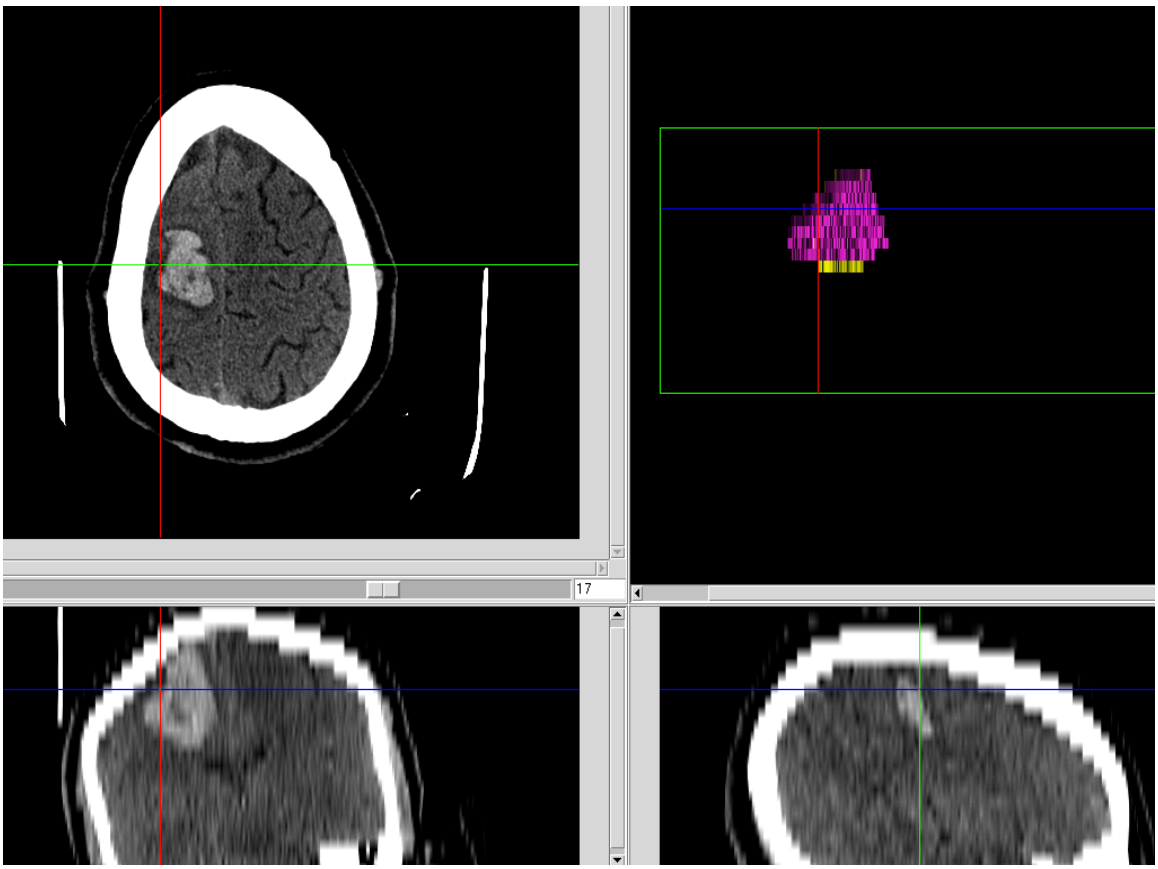

Figure VII. The Volume Edit module (shown above) provides a three-dimensional view of each lesion. It can be used to better visualize the extent and distribution of each lesion. It can be opened in parallel with the Region of Interest module to aid the operator in the selection of the optimal boundary for the lesion.

Online Supplemental Results

Table I. Selection of studies investigating PHE

Study	Software package for PHE quantification	Interrater/Intrarater ICCs (95% CI) for PHE quantification	Validation against MRI	Number of patients used for MRI validation	Method for PHE measurement
Gebel et al.[1]	In-house software	NA/NA	No	NA	Authors used a statistical algorithm. The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified
Sansing et al.[2]	MCID	NA/NA	No	NA	Authors used software with semiautomated edge detection. PHE was determined by selection of the hypodense area immediately surrounding the hemorrhage. The principles used to differentiate PHE from other entities that are also hypodense, or whether thresholds were used, are not specified
McCarron et al.[3]	Not specified	NA/0.96 (0.90-0.98)	No	NA	Authors used a modified version of the ABC/2 method. The principles used to differentiate PHE from other entities that are also hypodense, or whether thresholds were used, are not specified
Levine et al.[4]	Alice	0.98/NA	No	NA	Not specified
Mehdiratta et al.[5]	Not specified	0.90/0.95	No	NA	Authors used "automated threshold values". The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified
Arima et al.[6]	MIStar Version 3.2	0.91 (0.87-0.94)/NA	No	NA	Authors used computer-assisted multislice planimetric and voxel threshold techniques. The principles used to differentiate PHE from other entities that are also hypodense, or the thresholds used, are not specified
Volbers et al.[7]	Leonardo V	0.96 (0.93-0.99)/0.96 (0.93-0.99)	Yes	15	Authors used the 5-33 HU threshold. Authors differentiated PHE from other entities that are also hypodense by comparison to the contralateral hemisphere and a more restrictive definition of the region of interest
Appelboom et al.[8]	MIPAV	0.88/NA	No	NA	Not specified
McCourt et al.[9]	Analyze 11.0	0.99 (0.98-0.99)/NA	No	NA	Authors first manually traced PHE and then applied the 5-23 HU threshold. The principles used to differentiate PHE from other entities that are also hypodense are not specified
Present study	Analyze 11.0	0.98 (0.96-1.00)/0.99 (0.99-1.00)	Yes	18	Boundaries were outlined with an edge-detection tool and adjusted after inspection of the three orthogonal planes. PHE was delineated with the additional principle that it should be (a) more hypondense than the corresponding area in the contralateral hemisphere and (b) most hypodense immediately surrounding the hemorrhage.

HU, Hounsfield unit; ICC, intraclass correlation coefficient; NA, not applicable; PHE, peri-hematomal edema

Table II. Subject Characteristics	
	Total (n = 20)
Age, years, mean (SD)	64.6 (12.8)
Male, n, (%)	12 (60)
Race, n (%)	
White	20 (100)
GCS score, median (IQR)	14 (9-15)
Location of Hematoma, n (%)	
Lobar	8 (40%)
Deep	12 (60%)
Presence of IVH, n, (%)	8 (40%)
ICH volume, cc, median (IQR)	24.0 (10.5-39.6)
Onset to first scan, hours, median (IQR)	4.2 (2.9-8.9)

SD, standard deviation; n, number; cc, cubic centimeters; IQR, interquartile range

Table III. Summary of ICH measurements				
	Volume cc, median (IQR)	Wilcoxon rank-sum p-value	Interrater ICC (95% CI)	Intrarater ICC (95%, CI)
Baseline				
R1, R2	23.2 (10.9-35.6), 24.0 (11.5-38.7)	0.81	0.99 (0.99-1.00)	NA
R1 retest	24.2 (11.2-39.1)	0.91	NA	0.99 (0.99-1.00)
24-hours post-ICH				
R1, R2	23.3 (11.0-36.5), 24.1 (11.7-38.9)	0.85	0.99 (0.99-1.00)	NA
R1 retest	24.2 (11.7-39.8)	0.94	NA	0.99 (0.99-1.00)

R1, Rater 1; R2, Rater 2; cc, cubic centimeters; IQR, interquartile range; ICC, intraclass correlation coefficient; CI, confidence interval; NA, not applicable

Table IV. Summary of IVH measurements				
	Volume cc, median (IQR)	Wilcoxon rank-sum p-value	Interrater ICC (95% CI)	Intrarater ICC (95%, CI)
Baseline				
R1, R2	0 (0-5.1), 0 (0-5.6)	0.95	0.99 (0.99-1.00)	NA
R1 retest	0 (0-5.6)	0.98	NA	0.99 (0.99-1.00)
24-hours post-ICH				
R1, R2	0 (0-3.1), 0 (0-3.9)	0.81	0.99 (0.98-1.00)	NA
R1 retest	0 (0-3.8)	0.98	NA	0.99 (0.99-1.00)

R1 indicates Rater 1; R2, Rater 2; cc, cubic centimeters; IQR, interquartile range; ICC, intraclass correlation coefficient; CI, confidence interval; NA, not applicable

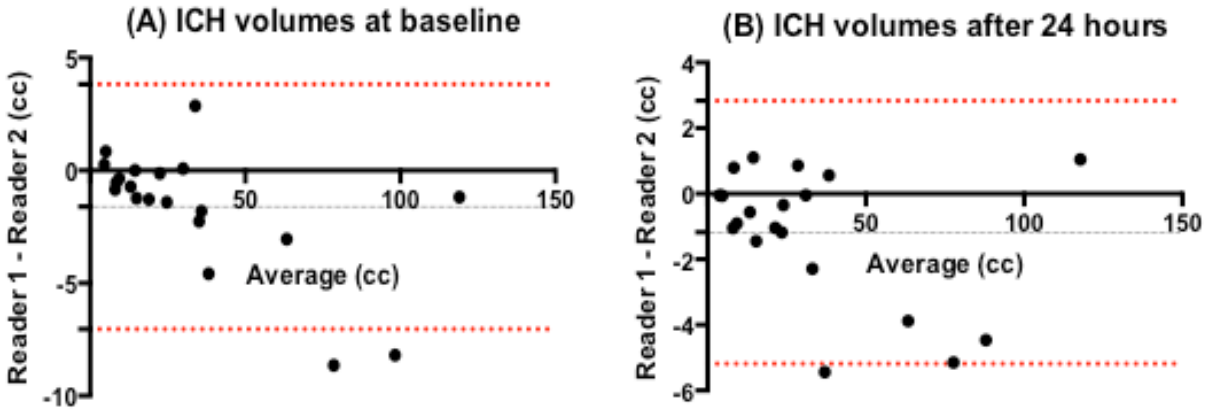

Figure VIII. Bland-Altman plots of inter-rater consistency of ICH measurements. Dashed black line represents the bias (mean of the difference between measurements). Dashed red lines represent the limits of agreement (mean ± 1.96 SD). At baseline and 24-hours post-ICH the bias was -1.6 cc (SD, 2.8) and -1.2 cc (SD, 2.0), respectively. The outliers corresponded to irregularly shaped hemorrhages.

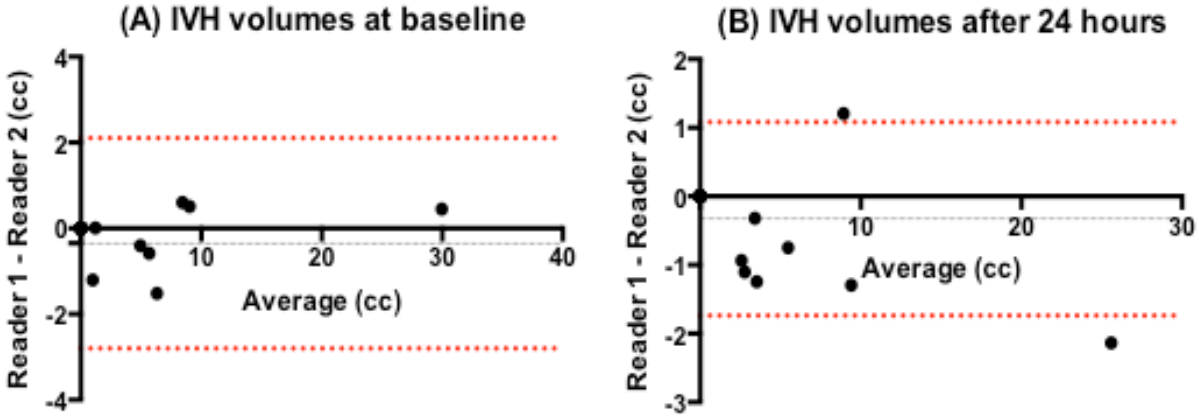

Figure IX. Bland-Altman plots of inter-rater consistency of IVH measurements. Dashed black line represents the bias (mean of the difference between measurements). Dashed red lines represent the limits of agreement (mean ± 1.96 SD). At baseline and 24-hours post-ICH the bias was -0.1 (SD, 0.5) and -0.3 (SD, 0.7), respectively. The outliers corresponded to hemorrhages with a faint boundary between ICH and IVH.

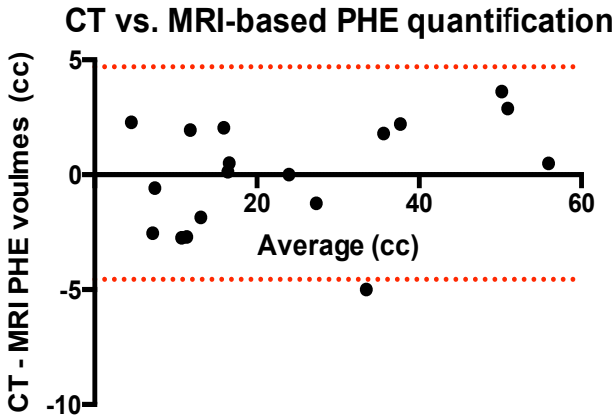

Figure X. Bland-Altman plots comparing CT and MRI-based PHE measurement. The dashed black line represents the bias (mean of the difference between measurements). The dashed red lines represent the limits of agreement (mean ± 1.96 SD). The bias was 0.07 cc (SD, 2.4).

Online Supplement References

1. Gebel JM, Jr., Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, et al. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke*. 2002;33:2631-2635
2. Sansing LH, Kaznatcheeva EA, Perkins CJ, Komaroff E, Gutman FB, Newman GC. Edema after intracerebral hemorrhage: Correlations with coagulation parameters and treatment. *J Neurosurg*. 2003;98:985-992
3. McCarron MO, McCarron P, Alberts MJ. Location characteristics of early perihaematomal oedema. *J Neurol Neurosurg Psychiatry*. 2006;77:378-380
4. Levine JM, Snider R, Finkelstein D, Gurol ME, Chanderraj R, Smith EE, et al. Early edema in warfarin-related intracerebral hemorrhage. *Neurocrit Care*. 2007;7:58-63
5. Mehdiratta M, Kumar S, Hackney D, Schlaug G, Selim M. Association between serum ferritin level and perihematoma edema volume in patients with spontaneous intracerebral hemorrhage. *Stroke*. 2008;39:1165-1170
6. Arima H, Wang JG, Huang Y, Heeley E, Skulina C, Parsons MW, et al. Significance of perihematomal edema in acute intracerebral hemorrhage the interact trial. *Neurology*. 2009;73:1963-1968
7. Volbers B, Staykov D, Wagner I, Dorfler A, Saake M, Schwab S, et al. Semi-automatic volumetric assessment of perihemorrhagic edema with computed tomography. *European Journal of Neurology*. 2011;18:1323-1328
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9. McCourt R, Gould B, Gioia L, Kate M, Coutts SB, Dowlatshahi D, et al. Cerebral perfusion and blood pressure do not affect perihematoma edema growth in acute intracerebral hemorrhage. *Stroke*. 2014;45:1292-1298