

Perihematomal edema surrounding spontaneous intracerebral hemorrhage by CT

Ellipsoidal versus morphometric volumetry

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Abstract

Perihematomal edema (PHE) surrounding intracerebral hemorrhage (ICH) may contribute to disease-associated morbidity. Before quantifying PHE's effects on morbidity, a fast, accurate, and reproducible method for measuring PHE volume is needed. The aim of this study is to demonstrate the use of a semiautomated dual clustering segmentation algorithm to generate PHE volumetrics on noncontrast computed tomography (CT) of the head and compare this technique to physicians' manual calculations.

This is a single-center, retrospective imaging study that included head CTs performed from January 2008 to December 2014 on 154 patients with ICH. Subjects ≥ 18 years old who were admitted to the hospital with spontaneous ICH were included. Included subjects had head CTs performed upon admission and within 6 to 24 hours. Two neurologists, 2 neuroradiologists, and a computer program all calculated hemorrhage and PHE volumes. Inter-rater correlation was evaluated using 2 statistical methods: intraclass correlations (ICCs) and limits of agreement (LOA). Additionally, correlation between volumes was separately evaluated using Pearson correlation coefficient.

There was an excellent correlation between measurements performed by neurologists and neuroradiologists using ABC/2 for ICH (0.93) and PHE (0.78). There was a good correlation between measurements performed by neurologists using ABC/2 and the volume measurements generated by the algorithm for ICH (0.69) and PHE (0.70). There was a fair correlation between measurements performed by neuroradiologists using ABC/2 and volume measurements generated by the algorithm for ICH (0.47) and good correlation for PHE (0.73).

Although the ABC/2 method for measuring PHE is quick and practical, algorithms that do not assume ellipsoidal shape may be more accurate.

Abbreviations: 3D = three dimensions, CI = confidence interval, CT = computerized tomography, GM = gray matter, HCT = head computerized tomography, HRCT = high-resolution computerized tomography, HU = Hounsfield units, ICC = intraclass correlation, ICH = intracranial hemorrhage, IVH = intraventricular hemorrhage, LOA = limits of agreement, PHE = perihematomal edema, SAH = subarachnoid hemorrhage, SD = standard deviation, SDH = subdural hematoma, WM = white matter.

Keywords: intracerebral hemorrhage, peri-hematomal edema, semiautomated measurement

1. Introduction

Spontaneous, nontraumatic, intracerebral hemorrhage (ICH) comprises 6.5% to 19.6% of all strokes.^[1,2] The associated morbidity and mortality are high, with 30% to 40% mortality

within 30 days^[3–5] and only 20% of patients returning to their previous level of functioning. Unfortunately, the care of these patients is largely supportive. Apart from maintaining lower blood pressures and using hyperosmolar therapy, there are no specific treatments to target the ill effects of the hemorrhage.^[6]

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Perihematomal edema (PHE) surrounding the hemorrhage may account for some of the disability associated with ICH. Natural history suggests that PHE increases in the first few hours after hemorrhage, in both absolute and relative measurements.^[7] Other studies suggest that rapidly increasing rates of edema in lobar hemorrhages may worsen functional outcomes.^[8] In order to understand the effect that PHE may have on outcomes, an accurate and reliable means of measuring PHE is required.

The ABC/2 technique is a commonly used clinical tool for estimating the volume of intracerebral hemorrhage. This technique was first reported in 1982^[9] but did not gain popularity until its validation in 1996.^[10] It was developed from the equation for the volume of an ellipsoid, which is defined as $\frac{4}{3} \pi (\frac{A}{2}) (\frac{B}{2}) (\frac{C}{2})$; where A, B, and C are measurements of the length, width, and height of the edematous territory. To simplify the equation a bit, π is approximated as 3 which reduces the equation to ABC/2, thus the method's acronym. When measuring ICH, "A" represents the greatest hemorrhage diameter by CT, "B" represents the diameter perpendicular to "A," and "C" represents the approximate number of CT slices with hemorrhage multiplied by slice thickness.^[11] This is a validated formula and is widely used to estimate ICH volumes.^[10–12] However, limitations of this formula exist with irregular, nonellipsoid, and noncontiguous hemorrhage shapes and in cases of image acquisition with large slice thickness.^[12,13]

Despite many years of research relating to the practical and reliable measurement of ICH, far less attention has been paid to the measurement of PHE. Hence, while clinicians and neuroradiologists often note the presence of PHE, they do not typically quantify it or calculate volumes in daily clinical practice. However, prior research implies that there may be utility in applying ABC/2 as a proxy for other CT-based measurements, including for subdural hematoma (SDH).^[13] This raises the question of the utility of ABC/2 method for PHE volumetry, a closer approximation to an ellipsoid than SDH in most cases.

Because of the high morbidity associated with ICH and the paucity of research on the measurement of PHE, we undertook this retrospective study aiming to find a reliable and accurate methodology for measuring PHE and ICH. To this end, we developed a volumetry program based on the principles of dual-clustering and Hounsfield Units (HU) thresholding, which segments tissues according to their natural spatial distributions and is, therefore, more general, not assuming simplified geometries such as the ellipsoidal distributions. We compared the volumetry program to measurements completed by neurologists and neuroradiologists to evaluate the computer program's volumetric accuracy. We hypothesized that the computer volumetric program would be able to render statistically comparable measurements to those made by the neurologists and neuroradiologists.

2. Materials and methods

2.1. Study population

This is a retrospective single-institution imaging study of head CT (HCT) scans. Eligible patients were screened using the following criteria:

Inclusion criteria:

1. Age over 18
2. Admission to Boston Medical Center from January 2008 to December 2014 with a diagnosis of primary spontaneous ICH

3. Completion of noncontrast head CTs upon admission and within 6 to 24 hours following admission

Exclusion criteria:

1. Presence of multiple hemorrhages on initial or follow-up CT scan
2. Extensive postoperative changes seen on head CT
3. Evidence of hemorrhagic malignancy

The stability scan, that is the second HCT obtained in the first 24 hours after admission, was used for this analysis in order to allow PHE time to develop. A total of 276 scans were reviewed and 154 were included in the final statistical analysis. Thirty-six were excluded on initial evaluation due to multiple ICHs or ICH in combination with other bleeding types such as subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), and/or SDH. Other indications for exclusion included contrast administration, extensive postoperative changes, and hemorrhagic malignancy. Additionally, 86 scans were excluded on a secondary evaluation due to technical difficulties or incomplete data (Fig. 1). Specifically, technical difficulties included irregular slice thickness and discrepant scan dates or times. This study was approved by the Institutional Review Board of Boston University School of Medicine.

2.2. Volume estimates

ICH and PHE volume estimates were generated in 3 ways—neurologists performing ABC/2, neuroradiologists performing ABC/2, and computerized measurements via the dual-clustering segmentation algorithm. Specifically, ICH volumes and PHE volumes were calculated using the ABC/2 method by 2 neurologists (CET, JGS) and 2 neuroradiologists (AZM, MS). The neurologists each measured all 154 scans and their calculations were considered both individually and in average. The neuroradiologists divided the collection of head CTs included in the study, each measuring 77 of the 154 scans. Their contributions were considered in aggregate. For the purpose of this study, the aggregate of ICH and PHE volume estimates from the neuroradiologists was considered as the "clinical standard" and inter-rater correlation with estimates from the neurologists and computer-generated measurements were assessed.

2.3. Physician calculated volume measurements

Each rater completed 2 sets of measurements. In the first set, the rater selected the image where the hematoma area appeared the largest through visual inspection. After selecting an image, the rater measured the length and width of the area of the hemorrhage in centimeters. The rater then calculated the volume of the hemorrhage by estimating (length × width × height in cm)/2; that is ABC/2. The rater subsequently selected the image where PHE appeared the largest on visual inspection. The rater then measured the length and width of the combined hemorrhage and surrounding edema in centimeters and again used the ABC/2 formula, which produced the combined volume of the hemorrhage and the surrounding PHE. PHE volume was then determined by subtracting the hemorrhage volume from the combined volume.

2.4. Computer calculated volume measurements

Computerized ICH and PHE volume estimates were generated using a program written in SAS 9.4 (SAS Institute, Cary NC). The

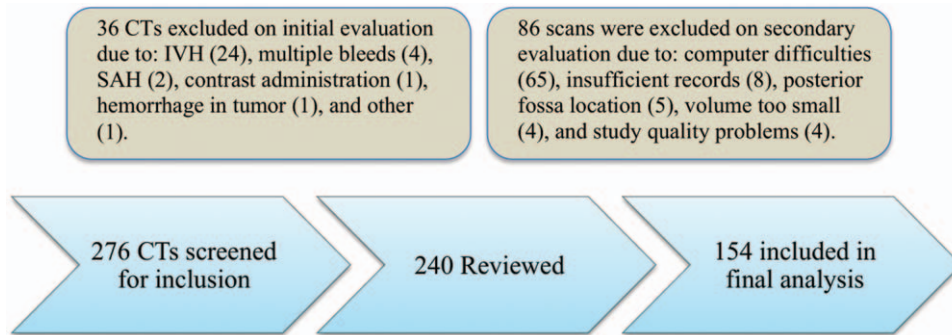


Figure 1. Indications for exclusion.

program combines the principles of dual-clustering^[14] for soft tissue identification—white matter (WM), gray matter (GM), and edema—and of targeted pixel intensity thresholding for the identification of the hemorrhage core as well as for the removal of bony structures.

The full image processing pipeline embodied in the Mathcad program consists of the following steps: load the full high-resolution computerized tomography (HRCT) dataset in binary format, extract brain tissue from skull [fully automated in 3 dimensions, (3D)], operator selects the brain quadrant of the hemorrhagic region, within this target volume, the program automatically segments the hemorrhage, and further identifies the PHE pixels by successive dilatation operations until reaching a preset limit coinciding with “normal brain” pixel intensities (Fig. 2). In this manner, the hemorrhage pixels are identified and the PHE pixels are categorized by successive dilation operations and the ICH and PHE volumes are generated by multiplying

the total number of pixels in each segment by the known voxel size.^[14]

2.5. Statistical analysis

The inter-rater correlation between neuroradiologist (clinical standard), neurologist, and computer-generated measurements was assessed by calculating intraclass correlations (ICCs) with a 95% confidence interval (95% CI). A 2-way random effects model (ICC, 2, 1, absolute agreement) was used to calculate ICCs and 95% confidence intervals (CI). Prior to data collection, the investigators predetermined the following thresholds to assess correlations: ICC < 0.40 was considered as poor; 0.40 to 0.59 as fair; 0.60 to 0.74 as good, and 0.75 to 1.00 as excellent.^[15] Also, we used the 95% limits of agreement (LOA) method as reported by Bland and Altman^[16] to further assess the inter-rater agreement. The mean difference (bias), the standard deviation of bias (SD), the

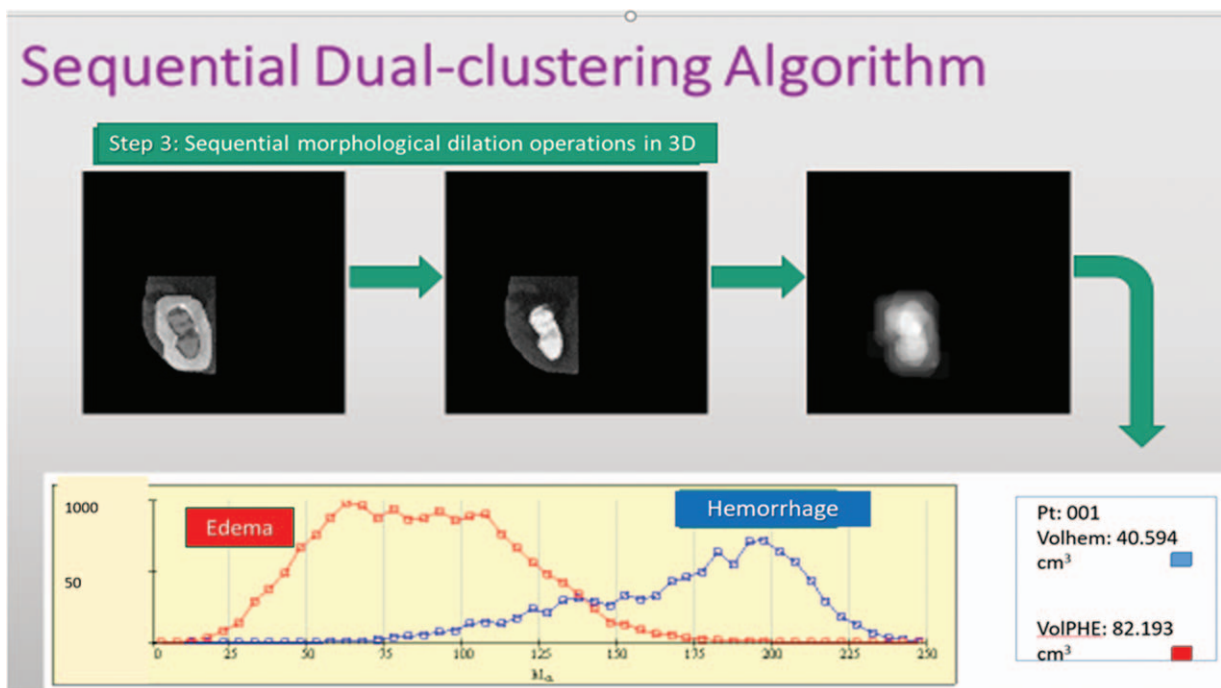


Figure 2. Semiautomated dual-clustering segmentation algorithm for determining ICH and PHE volumes. ICH = intracranial hemorrhage, PHE = perihematoma edema.

upper and lower LOA were calculated and presented. Each point on the scatter plot was determined using the formula $[(x+y)/2]$ for the x-coordinate and $(x - y)$ for the y-coordinate. Finally, the correlation between volumes was separately evaluated using the Pearson correlation coefficient with 95% CI.

All calculations were performed for both ICH and PHE volumes. Data were analyzed using IBM SPSS Statistics software, (version 24.0; IBM Corp) and MedCalc Statistical Software version 16.2.1 (MedCalc Software bvba, Ostend, Belgium).

3. Results

Mean ICH and PHE volumes with standard deviations as measured by different raters are presented in Table 1.

3.1. Interneurologists correlation

There was an excellent correlation between the 2 neurologists' measurements of ICH volume (ICC=0.93, 95% CI 0.90–0.95) (Table 2). The mean bias (SD) was 2.1 (10.2), with 95% LOA of –17.9 to 22.1. The Pearson correlation (95% CI) value was 0.93 (0.91–0.95). A weaker but excellent correlation was noted for PHE volume (ICC=0.78, 95% CI 0.71–0.84) (Table 3). The mean bias (SD) for PHE volume was 4.1 (17.6), with 95% LOA of –30.4 to 38.7. The Pearson correlation (95% CI) value was 0.83 (0.77–0.87).

Table 1

Mean ICH and perihematoma edema volumes by raters in 154 patients undergoing noncontrast head CT.

	ICH volume	Perihematoma edema	
		Mean (SD)	
Neuroradiologists	36.0 (41.8)	32.6 (30.8)	
Neurologists, average	23.9 (27.4)	23.5 (25.7)	
Neurologist (JGS)	25.0 (28.3)	25.7 (31.0)	
Neurologist (CET)	22.8 (27.4)	21.5 (22.7)	
Computer Software	13.9 (15.7)	35.5 (27.5)	

ICH = intracerebral hemorrhage, SD = standard deviation.

3.2. Neuroradiologist versus neurologist

For ICH volume, there was excellent correlation by ICC between the standard clinical measurement from neuroradiologists and average measurement from 2 neurologists (ICC=0.82, 95% CI 0.58–0.90) (Table 2). A similar correlation was also noted for PHE volume between the 2 rater groups (ICC=0.82, 95% CI 0.62–0.90) (Table 3). The mean bias (SD) for ICH volume was 12.1 (18.4), with 95% LOA of –23.9 to 48.1. For PHE volume, the mean bias (SD) was 9.1 (14.8) with 95% LOA of –19.8 to 38.0 (Fig. 3). Pearson correlation was 0.94 (95% CI 0.92–0.96) and 0.88 (95% CI 0.84–0.91) for ICH and PHE volumes, respectively.

Table 2

ICH volume agreement analysis (N = 154).

	ICC (95% CI)	Bland & Altman			r (95% CI)
		Δ	SD	95% LOA	
Neuroradiologists					
Computer Software	0.47 (0.12–0.68)	22.1	28.9	–34.4, 78.7	0.88 (0.84–0.91)
Neurologist (JGS)	0.82 (0.64–0.90)	11.0	19.1	–26.5, 48.5	0.92 (0.89–0.94)
Neurologist (CET)	0.80 (0.53–0.90)	13.1	19.0	–24.1, 50.3	0.93 (0.91–0.95)
Neurologist average	0.82 (0.58–0.90)	12.1	18.4	–23.9, 48.1	0.94 (0.92–0.96)
Computer Software					
Neurologist (JGS)	0.65 (0.35–0.80)	–11.1	16.9	–44.3, 22.1	0.86 (0.81–0.89)
Neurologist (CET)	0.69 (0.47–0.81)	–9.0	15.9	–40.1, 22.2	0.87 (0.82–0.90)
Neurologist average	0.69 (0.40–0.82)	–10.1	15.6	–40.6, 20.5	0.88 (0.83–0.91)
Neurologist (JS)					
Neurologist (CT)	0.93 (0.90–0.95)	2.1	10.2	–17.9, 22.1	0.93 (0.91–0.95)

Δ = mean difference (bias), CI = confidence interval, ICC = intraclass correlation, ICH = intracerebral hemorrhage, LOA = limits of agreement, N = number of CT scans, r = Pearson correlation coefficient, SD = standard deviation.

Table 3

Perihematoma edema agreement analysis (N = 154).

	ICC (95% CI)	Bland & Altman			r (95% CI)
		Δ	SD	95% LOA	
Neuroradiologists					
Computer Software	0.73 (0.64–0.79)	–2.9	21.4	–45.0, 39.1	0.74 (0.65–0.80)
Neurologist (JGS)	0.83 (0.74–0.89)	6.9	16.9	–26.2, 40.0	0.85 (0.80–0.89)
Neurologist (CET)	0.74 (0.47–0.85)	11.0	17.3	–22.8, 44.9	0.83 (0.77–0.88)
Neurologist average	0.82 (0.62–0.90)	9.1	14.8	–19.8, 38.0	0.88 (0.84–0.91)
Computer Software					
Neurologist (JGS)	0.72 (0.55–0.82)	9.8	20.5	–30.3, 50.0	0.76 (0.68–0.82)
Neurologist (CET)	0.60 (0.26–0.77)	14.0	19.7	–24.7, 52.6	0.71 (0.62–0.78)
Neurologist average	0.70 (0.40–0.83)	12.0	18.1	–23.4, 47.5	0.77 (0.70–0.83)
Neurologist (JGS)					
Neurologist (CET)	0.78 (0.71–0.84)	4.1	17.6	–30.4, 38.7	0.83 (0.77–0.87)

Δ = mean difference (bias), CI = confidence interval, ICC = intraclass correlation, LOA = limits of agreement, N = number of CT scans, r = Pearson correlation coefficient, SD = standard deviation.

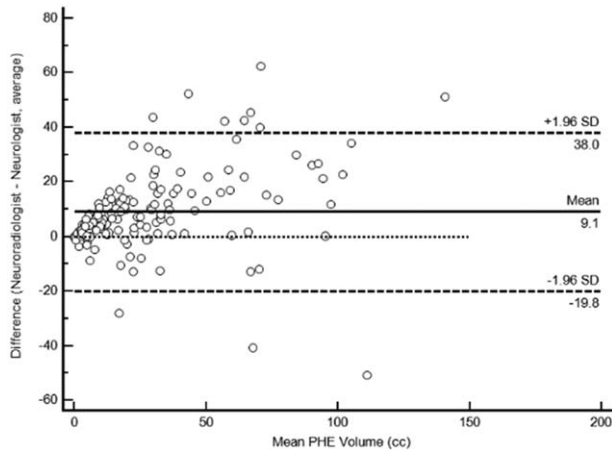


Figure 3. Bland-Altman plot of neuroradiologist vs neurologist PHE volumes.

3.3. Neuroradiologist versus computer program

There was a weaker but fair correlation between the ABC/2 measurements of neuroradiologists and the computer program for ICH volume (ICC=0.47, 95% CI 0.12–0.68). The bias between the 2 ratings was large (bias=22.1, SD=28.9) with wide 95% LOA of -34.4 to 78.7 (Fig. 4). The correlation improved when comparing these 2 ratings for PHE volume (ICC=0.73, 95% CI 0.64–0.79). The mean bias (SD) for PHE volume as was -2.9 (21.4) with 95% LOA of -45.0 to 39.1 (Fig. 4). Pearson correlation was 0.88 (95% CI 0.84–0.91) and 0.74 (95% CI 0.65–0.80) for ICH and PHE volumes, respectively.

3.4. Neurologists versus computer program

A good correlation was observed between average neurologist measurement and the computer program for both ICH volumes (ICC=0.69, 95% CI 0.40–0.82) and PHE volumes (ICC=0.70, 95% CI 0.40–0.83) (Tables 2 and 3). The mean bias (SD) for ICH volume as was -10.1 (15.6) with 95% LOA of -40.6 to 20.5, and for PHE volume, it was 12.0 (18.1) with a 95% LOA of -23.4 to 47.5. Pearson correlation was 0.88 (95% CI 0.83–0.91) and 0.77 (95% CI 0.70–0.83) for ICH and PHE volumes, respectively.

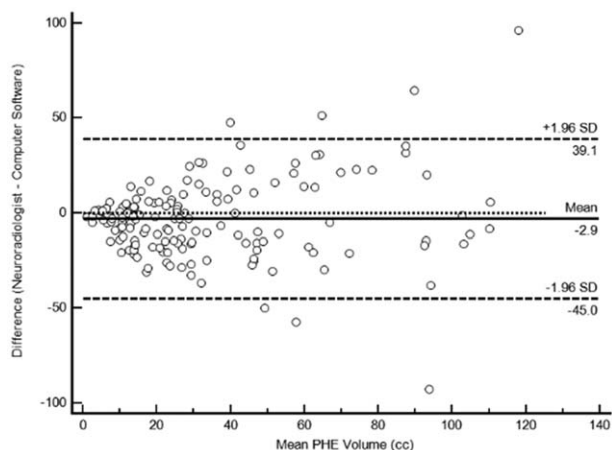


Figure 4. Bland-Altman plot of neuroradiologist vs computer PHE volumes.

The methodology and key results of this study are summarized in Figure 5.

4. Discussion

Study results show congruence between neurologists and neuroradiologists using the ABC/2 method. The stronger correlation between the 2 neurologists’ measurements when calculating ICH volume as compared with PHE volume is expected, given the well-known challenge of measuring PHE with indistinct borders.

The data demonstrated a strong agreement between neurologists and the computer program when measuring both ICH and PHE. The agreement between the neuroradiologists and the computer was fair for ICH measurements. The agreement between the neuroradiologists and computer improved and qualified as good for PHE measurements. We hypothesize that these discrepancies in correlation are related to the ABC/2 method. The ABC/2 method overestimates hemorrhage and edema volumes compared with the dual clustering segmentation method in some patients, particularly those with irregular, nonellipsoid shapes. We speculate that ABC/2 may consistently overestimate volumes because it assumes the same length and width are uniform throughout the hemorrhage. Yet, we know from clinical experience and visual inspection that most of the hemorrhage may be significantly smaller than its largest diameter. Even though we attempt to compensate for this (through dividing by 2), this estimate is coarse and does not incorporate the inevitable variation with each hemorrhage. Past studies also report problems with clinicians over-estimating hemorrhage volumes.^[17] In comparison, the dual-clustering method would often produce a more realistic 3D rendering of the edema and hemorrhage and could be more accurate with anatomically complex and irregular lesions.

These results provide evidence that neurologists may be consistent in their measurements and may perform similarly to neuroradiologists when estimating ICH and PHE volumes by ABC/2. These results suggest that further development and research on computer-based algorithms to measure PHE might be useful. If our program can be further refined, it would be suitable to compare its performance to radiologists in a prospective study. Notably, the computer is able to produce volumes in about 5 minutes. Given this production speed, future volumetric programs might be fast enough so they could be clinically useful as well. Our goal is to continue to optimize this program with the hope of ultimately making it fully-automated, faster, and more accurate than on-the-go clinical measurement tools, and accessible to practicing clinicians.

Limitations of this study include being conducted at a single medical center, limiting its generalizability to other centers. Also, we measured PHE on 24 hour postadmission HCTs. While in most cases the edema likely increased beyond that time frame, clinically stable patients do not routinely receive additional scans beyond the 24 hour posthemorrhage time point. Using only HCTs from beyond 24 hours posthemorrhage would have significantly decreased our number of eligible scans. A prospective multicenter study with specified time points for HCT acquisition would address these limitations in the future.

While our study is currently the largest in size to analyze PHE methodology, it would have been strengthened had we been able to include even more scans. In addition, the computer algorithm is limited due to its inability to distinguish adjacent intraventricular hemorrhage or other hemorrhage types (SAH, SDH, and

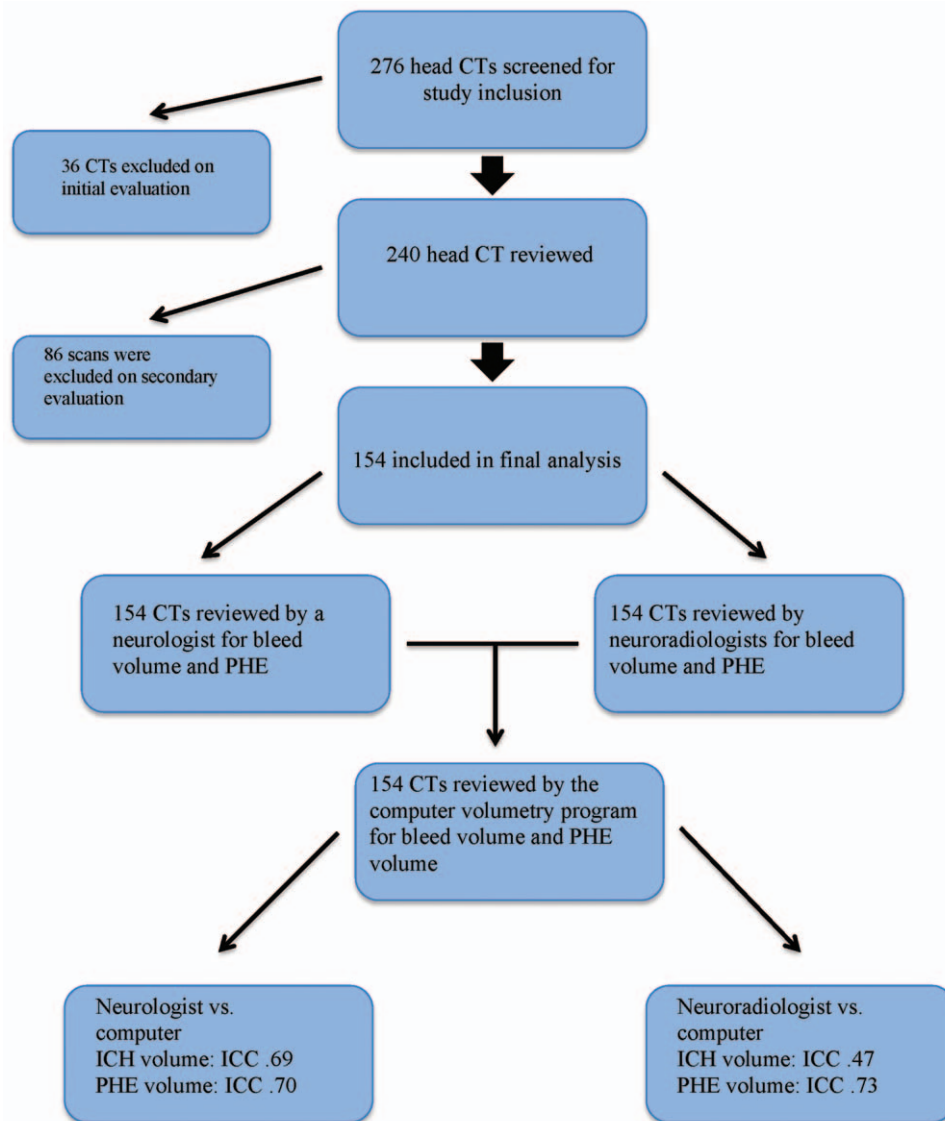


Figure 5. Summary of methodology and key results of this study.

IVH) from the ICH of interest, which decreased our number of analyzable scans.

Further refinement of the computer program and its semi-automated techniques could help to improve widespread applications. New techniques such as a multiplanar approach to calculate hemorrhage volume (e.g., using axial, coronal, and sagittal approaches) have the potential to further improve volumetric accuracy. Developing an accurate and reliable means of calculating PHE volumes will allow for further investigations into the role of PHE in morbidity and mortality associated with primary ICH. Current data suggest that PHE may be associated with worsened outcomes, hence, developing an accurate measurement tool would be an invaluable supplement to future research.^[18] Additionally, if hemorrhage and PHE can be accurately measured by computer algorithm, the algorithm may be utilized to calculate volumes of other types of hemorrhages.

Although the ellipsoidal method for PHE volumetry is quick and practical, volumetry algorithms that do not assume

ellipsoidal shape may be more accurate, particularly in cases with intricate ICH distributions. Further software developments, a prospective study, and research with precalibrated phantoms providing ground truth are needed to achieve clinical utility and generalizability.

Author contributions

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Writing – review & editing: Muhammad M. Qureshi, Anna M. Cervantes-Arslanian, Melissa Mercado, David Greer, Asim Z. Mian, Courtney Emi Takahashi.

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