

MEASUREMENT AND PREDICTION OF EXPANSION OF HAEMATOMA AND PERIHAEMATOMAL OEDEMA IN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HAEMORRHAGE

Data from Tranexamic Acid for Spontaneous Intracerebral Haemorrhage-2 (TICH-2) Trial

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Abstract

Background:

Spontaneous intracerebral haemorrhage (ICH) is a form of stroke which often leads to severe disability and death. ICH-related poor outcomes are significantly due to haematoma expansion and perihaematomal oedema (PHO). The ability to identify patients who are most likely to experience haematoma expansion and PHO and benefit from treatments targeting expansion or oedema remains an unmet need. In this thesis data from the 'Tranexamic Acid in Intracerebral Haemorrhage -2' (TICH-2) was used to analyse the relationship of the baseline imaging characteristics to haematoma expansion and PHO expansion in patients with spontaneous ICH.

Methods:

Intra-and inter-observer reliability of haematoma and PHO volume measurement methods were first established using 20 samples randomly selected from 'Efficacy of Nitric Oxide in Stroke Trial' (ENOS). This confirmed that both techniques of haematoma volume segmentation, ABC/2 formula and semi-automated segmentation (SAS), and manual delineation of PHO volume were reliable methods for measuring both haematoma volumes and PHO volumes with high intra- and inter observer reliability. In the TICH-2 trial data, haematoma expansion was defined as an absolute increase in haematoma volume of more than 6 mL or relative increases of more than 33% in follow-up scan compared to the baseline haematoma volume. PHO expansion was defined as relative increase of more than 20% in PHO volume from baseline to follow-up. Follow-up scan was done at 24 hours after baseline scan. Participants were classified as favourable clinical outcome for mRs <3 and poor clinical outcome for mRs ≥3.

Results:

In 2254 participants with spontaneous ICH, haematoma volume measured with ABC/2 formula was significantly larger than haematoma volume quantified by SAS method. As the haematoma size increased, the difference between the ABC/2 and the SAS measurements was slightly increased. Haematoma volume measured by SAS method was significantly larger in regular shape of haematoma and lower in irregular shape of haematoma compared to ABC/2 formula. Both methods of haematoma volume quantification showed a significantly strong linear correlation.

Comparison of 1mm and 5mm slice thicknesses in haematoma and PHO volume quantification were analysed using 30 series of CT brain scans where two different slice thicknesses were available for each series. There was a small but significant difference in haematoma volume measured by SAS (0.44 mL), with larger volumes measured on the 5mm slice thicknesses, but no significant difference showed in haematoma volume segmentation by ABC/2 formula and PHO volume segmentation.

Data of 1035 participants in the placebo arm of the TICH-2 trial were analysed to compare the characteristics of participants with and without haematoma expansion. Baseline haematoma size was significantly larger in participants who experienced haematoma expansion. Out of 300 participants with haematoma expansion, the occurrence of haematoma expansion in irregular shape haematoma was significantly higher than in those with regular shape haematoma. The occurrence of haematoma expansion increased as the haematoma shape becomes more irregular. There was no significant difference of haematoma density between participants with and without haematoma expansion. Haematoma expansion was significantly more common in lobar haematoma.

548 participants were assessed for the relationship of adjudicated baseline imaging features of blend sign, black hole sign and island sign to haematoma expansion. Univariate analyses revealed that there was a statistically significant association between haematoma expansion and baseline imaging signs, with

haematoma expansion more common in participants with black hole sign and island sign.

In the multivariate imaging predictor model of haematoma expansion in 1035 participants, there were only 4 factors which independently predicted haematoma expansion; baseline NIHSS score ≥ 14, baseline haematoma volume, time-to-scan and brain atrophy. All these predictors were associated with increased odds ratio of haematoma expansion.

1012 participants were evaluated for the comparison of the characteristics between participants with PHO expansion and those without PHO expansion. Statistical analyses showed that there was a significant difference between some clinical variables; periventricular lucencies, baseline NIHSS score ≥ 14, time to scan, baseline PHO volume and haematoma expansion between participants with and without PHO expansion. There was no significant difference in baseline haematoma volume between groups.

The multivariate prediction model for PHO expansion revealed that periventricular lucencies, baseline NIHSS score ≥ 14, baseline haematoma volume, baseline PHO volume, haematoma expansion and time to scan all independently predicted PHO expansion. Baseline PHO volume and time to scan were inversely related to PHO expansion.

Analysis of 1012 participants for the probability of PHO volume as independent predictor for poor clinical outcomes in spontaneous ICH showed that there were 5 factors found to affect the clinical outcome significantly: age, periventricular lucencies, baseline NIHSS score ≥as, baseline haematoma volume and haematoma expansion. Baseline PHO volume and PHO expansion were not independent predictors for poor clinical outcome. However, PHO expansion and rate of PHO expansion were relevant to include in the model for predicting poor clinical outcome as these variables were previously reported in several studies as

showing significant association to poor clinical outcome in patients with spontaneous ICH.

Conclusion:

In summary, this study provides additional information on haematoma and PHO volume measurement and on multivariable models for predictors of haematoma and PHO expansion in patients with spontaneous ICH. The findings from this study could be useful to guide treatment for patients with spontaneous ICH and beneficial for future research and clinical trial that emphasized on haematoma expansion and PHO targeted therapy.

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Publications arising from this thesis

- Law ZK, **Ali A**, Krishnan K, Bischoff A, Appleton JP, Scutt P, Woodhouse L, Pszczolkowski S, Cala LA, Dineen RA, England TJ, Ozturk S, Roffe C, Bereczki D, Ciccone A, Christensen H, Ovesen C, Bath PM, Sprigg N; TICH-2 Investigators. "Noncontrast Computed Tomography Signs as Predictors of Hematoma Expansion, Clinical Outcome, and Response to Tranexamic Acid in Acute Intracerebral Hemorrhage." *Stroke*. 2020 Jan;51(1):121-128. doi: 10.1161/STROKEAHA.119.026128. Epub 2019 Nov 18. PMID: 31735141

- Pszczolkowski S, Manzano-Patrón JP, Law ZK, Krishnan K, **Ali A**, Bath PM, Sprigg N, Dineen RA. "Quantitative radiomics-based models for prediction of haematoma expansion and poor functional outcome in primary intracerebral haemorrhage." *Eur Radiol.* 2021 Oct;31(10):7945-7959. doi: 10.1007/s00330-021-07826-9. Epub 2021 Apr 16. PMID: 33860831

Abbreviations

ADC	Apparent diffusion coefficient
ANOVA	Analysis of variance
AOH	Acute obstructive hydrocephalus
ATACH	Antihypertensive Treatment of Acute Cerebral Haemorrhage
CD	Compact disc
CI	Confidence interval
csv	Comma separated values
CT	Computed tomography
CTA	Computed tomography angiography
CSF	Cerebrospinal fluid
DICOM	Digital Imaging Communications in Medicine
DRLSE	Distance Regularised Level Set Evolution
EDHD	Estimating epidural haematoma volume
ENOS	Efficacy of Nitric Oxide in Stroke
FAST	Factor Seven for Acute haemorrhagic Stroke Trial
FCM	Fuzzy C-means
FFP	Fresh frozen plasma
FLAIR	Fluid attenuated inversion recovery
GCS	Glasgow Coma Scale
GTN	Glyceryl trinitrate
GUSTO-1	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries
HU	Hounsfield Unit
ICC	Intraclass correlation coefficient
ICH	Intracerebral haemorrhage
ICH ADAPT	Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial
IML	Ideal midline
INCH	International Normalised ratio normalisation in Coumarin-related intracranial Haemorrhage
INR	International Normalised Ratio
INTERACT	Intensive blood pressure Reduction in Acute Cerebral haemorrhage Trial
IQR	Interquartile range
IVH	Intraventricular haemorrhage
MATLAB	Matrix Laboratory
MDCT	Multidetector-row computed tomography
MDRLSE	Modified Distance Regularised Level Set Evolution
mL	Millilitre
miRNA	Micro RNA
MIPAV	Medical Image Processing Analysis and Visualization
MLSA	Multi-level segmentation approach
MRI	Magnetic Resonance Imaging
mRs	modified Rankin scale
NIFTI	Neuroimaging Informatics Technology Initiative
NINDS r-tPA	National Institute of Neurological Disorders and Stroke recombinant tissue-type Plasminogen Activator
NIHSS	National Institute of Health Stroke Scale

NPV	Negative predictive value
OAT	Oral anti-coagulant
OD	Odds ratio
ODD	Oedema extension rate
PACS	Picture Archiving and Communication System
PCC	Prothrombin complex concentrate
PHO	Perihaematomal Oedema
PPV	Positive predictive value
PREDICT	Predicting intracerebral haemorrhage expansion with non-contrast Computed Tomography
RIGHT	Rapid Intervention with GTN in Hypertensive stroke Trial
ROC	Receiver-operating curve
ROI	Region of interest
Quantomo	Quantitative computed tomography
rFVIIa	Recombinant activated factor VII
SAS	Semi-automated segmentation
SD	Standard deviation
SPOT LIGHT	Spot sign of intracerebral haemorrhage to guide haemostatic therapy
SPECT	Single-photon emission computed tomography
SPSS	Statistical Package for Social Sciences
STOP-AUST	Spot sign and Tranexamic acid On Preventing ICH growth – Australia trial
STOP-IT	Spot sign for predicting and Treating ICH growth Study
TBV	Total brain volume
TICH-2	Tranexamic acid for Intracerebral Haemorrhage-2

Chapter 1 INTRODUCTION

1.1 Stroke

Stroke is a condition resulted from sudden impairment of blood flow to the brain or part of the brain. Stroke occurs approximately 152,000 times a year in the United Kingdom and becomes the fourth single largest cause of death in the UK and second in the world [1]. There are two main types of strokes: ischaemic (embolic or thrombotic) and haemorrhagic (intracerebral or subarachnoid). Ischaemic stroke is the most common type of stroke and occurs when there is an obstruction within a blood vessel supplying blood to the brain [2]. Lack of blood supply and oxygen to the affected region leads cells to die and leaves other cells damaged. Haemorrhagic stroke is a type of stroke that is generally considered more severe with a higher risk of mortality than ischaemic stroke [3] which occurs when a weakened blood vessel ruptures and causes blood to spill into brain parenchyma or on the surface of the brain. The effects of a stroke depend on how severe the condition is, and which area of the brain has been affected. Strokes may cause sudden focal neurological impairment such as motor weakness, loss of sensation, body imbalance, dysarthria, and language dysfunction such as aphasia. However, there has been a recent decline in stroke incidence and mortality because of recent research on stroke treatment and improvement in risk factor control [4]. Though, many of stroke survivors do not regain functional and vocational independence and are permanently disabled [5].

1.2 Types of Haemorrhagic Strokes

1.2.1 Spontaneous Intracerebral Haemorrhage (ICH)

Spontaneous intracerebral haemorrhage (ICH) is a second most common form of stroke [6]. It can be described as a condition of non-trauma bleeding into the brain parenchyma resulting from ruptured blood vessel [7],

representing about 15% of all strokes in West population and up to 40% in Asian population [8]**.** In spontaneous ICH, blood spills into brain parenchyma and compresses adjacent matter, damaging cells and tissue in the brain. This condition, if not given prompt attention, might lead to permanent damage and long-term disability or death. There is also a chance of haematoma expansion, which may be life threatening and lead to death. Expansion of haematoma is most likely due to continued bleeding from the primary source and to the mechanical disruption of surrounding vessels [9]. Major causes of spontaneous ICH are hypertension and cerebral amyloid angiopathy (common in elderly patients) which approximately occurs in 70 to 80% of cases [10][9]. The difference between spontaneous ICH and secondary ICH is the underlying cause. Secondary ICH occurs as a result from any other causes rather than mentioned above. It might be caused by brain trauma, ruptured aneurysm or vascular malformations, tumour, drugs, and other rarer causes.

The progression of ICH generally consists of three distinct stages; initial bleeding, haematoma enlargement (appears in up to 70% of patients) [11][12] and the development of perihaematomal oedema (PHO) around haematoma region [13][14] with increased intracranial pressure [9]. The latter two stages are considered common early complications of patients with ICH and act as a salient predictor of a poor clinical outcome and are a critical determinant of high morbidity and mortality rate. Nevertheless, there is some evidence that prompt treatment and intensive care could bring a favourable improvement upon patients with severe ICH [15]. Urgent treatment in initial phase of ICH is greatly important to prevent further complications and severe brain injury [13], thus increase the possibility of recovery and regain functional independence among patients with ICH.

1.2.2 Intraventricular Haemorrhage (IVH)

Intraventricular extension of haemorrhage (IVH) is a common condition after spontaneous ICH, in which bleeding resulting from ICH extending into the ventricular system of the brain. Extension of haemorrhage into the ventricles can be a devastating complication of spontaneous ICH [16] occurring in approximately 45% of cases [17] with expected mortality between 50% and 80% [18]. There are cases where no IVH presented on initial admission CT brain scan of patients with spontaneous ICH, but it subsequently develops during hospitalisation. This condition is called delayed IVH, occurring in 10% to 20% of cases and associated with ICH growth [19]. A previous study showed that delayed IVH occurs in every fifth spontaneous ICH patients and demonstrates a significant association to death and poor functional outcomes [20] with 30-day mortality rate five times higher than those without IVH extension [21]. Extension of haemorrhage into the ventricles contributes a detrimental effect to a normal flow of cerebrospinal fluid (CSF) and may lead to acute obstructive hydrocephalus (AOH), a life-threatening disorder, especially when third and fourth ventricles affected [6]. Typically, patient management for those presenting with IVH involves the external drainage of intraventricular haematoma, thus relieving the obstruction to CSF flow, reversing ventricular dilatation, and restoring normal intracerebral pressure.

1.3 Stroke Imaging

A number of clinical and imaging characteristics might predict the morbidity and mortality in patients with ICH. The goals of an imaging evaluation are to determine a diagnosis as early as possible and to obtain paramount information of the intracerebral vasculature to assist the selection of the appropriate therapy and patient's management. Imaging is essential to differentiate variants of intracranial haemorrhage, as the clinical features may be insufficient. A comprehensive approach to ICH therefore relies on imaging technique to disclose

pathophysiology, elucidate mechanism and thereby open further options to effective treatment.

1.3.1 Computed Tomography (CT)

CT is the preferred imaging technique in the initial assessment of most stroke patients [22] and becomes the first imaging modality of choice since it has the advantage of being available 24 hours a day in most modern acute stroke centres, and is reliable for excluding haemorrhage and other mimics of stroke in clinical setting [23]. Since it presentation, CT had diagnosed ICH more frequently with greater accuracy [24] and referred as standard method for the diagnosis of acute ICH rather than MRI [25]. Acute ICH on CT results in increased attenuation coefficient that makes CT very sensitive for ICH detection, and there is usually associated local mass effect. In initial phase of suspected spontaneous ICH, CT brain imaging has a crucial role as it has the ability to identify the presence of haemorrhage [26] and can identify potential complications such as intraventricular haemorrhage (IVH), brain oedema or hydrocephalus, thus providing information to physician necessary for deciding whether patients are suitable for emergency treatments.

1.3.2 Computed Tomography Angiography (CTA)

CTA is a minimally invasive radiologic examination using a computed tomography technique to visualize blood vessels. CTA requires a time optimized rapid injection of intravenous iodine-rich contrast material to enhance the arteries. Thin section helical CT images are obtained in the arterial phase [27]. In patients with spontaneous ICH, the presence of haematoma expansion is highly indicated by the appearance of contrast extravasation, so called spot signs, on CT brain scans [15][28]–[32]. Approximately 46% of patients with ICH have active extravasation of radiographic contrast into the haemorrhage following CTA [33] .

1.3.3 Magnetic Resonance Imaging (MRI)

A second choice of modality for screening the brain haemorrhage is Magnetic Resonance Imaging (MRI). MRI has advantages over CT scans since it can produce multi-planar images and allows anatomical appreciation of haematomas and the potential complications [25]. It is the best imaging modality of choice in detecting small and subtle lesions plus demonstrating microbleeds compared to CT scan. In term of scanning time, MRI usually takes about 30 to 40 minutes to complete the scan whereas CT only takes 5 to 10 minutes. Therefore, a patient with a severe ICH that needs prompt treatment might not be able to proceed with MRI. MRI has been proposed as an alternative to CT in the emergency stroke setting.

1.4 Randomised Clinical Trials on Spontaneous ICH

At present, there is no gold standard of care [34] and no specific available treatment for acute ICH that is considered effective to reduce the bleeding in brain parenchyma and improve the recovery stage, although surgery likely decreases mortality [33]. A large number of clinical trials have been conducted on patients with spontaneous ICH to study the efficacy of treatments and to provide the most reliable evidence to guide patient's management. The management of patients with spontaneous ICH commonly consist of blood pressure lowering, stroke intensive care, surgery and haemostatic therapy. The main goals of management in spontaneous ICH are to attenuate the primary and secondary brain injury caused by haematoma as well as prevention and treatment of complications.

1.4.1 Blood Pressure Reduction

As hypertension is the most important risk factor for spontaneous ICH, control of blood pressure is an important public health measure [12]. The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)

study has suggested that early intensive systolic blood pressure lowering could prevent haematoma expansion and PHO development at 24 hours after ICH [35]. Systolic blood pressure is the primary target as it has greater effect on haematoma expansion than diastolic blood pressure. They identified a strong relationship between increasing levels of blood pressure and poor ICH outcomes. The major outcome of most clinical trials was to assess the possibility of stroke patients to regain a functional independence and reduced the morbidity and mortality rate. The most common variables associated with outcomes include the Glasgow Coma Scale (GCS) score and haematoma volume at presentation [33]. In the pilot phase of the INTERACT study done in 2010, it showed that early intensive systolic blood pressure lowering to < 140 mmHg compared to < 180 mmHg gave beneficial effects to significantly reduce haematoma expansion (mean haematoma volume difference of 3.15 mL at 24 hours, $p = 0.004$) in patients treated within 6 hours after symptom ictus but no significant association to PHO [36][37]. Since haematoma expansion is considered a strong prognosticator to poor clinical outcome, these findings proposed that early intensive reduction in systolic blood pressure within the first 24 hours was likely to be greatly favourable in patients presenting spontaneous ICH. However, another study in 2010 explored the relationship between different variables of systolic blood pressure reduction and haematoma expansion, PHE and 3-months outcomes found no significant association between them [38]. Controlling blood pressure within the first 24 hours is particularly controversial since it leads to two competing justifications, either it may improve outcome, potentially by reducing the rate of haematoma expansion or it may exacerbate the cerebral injury adjacent to haematoma region because of a possibility of reduced blood flow to the brain. This uncertainty has led to a randomized clinical trial by K. Butcher et al [39] that examines two different blood pressure management strategies (blood pressure < 150 mmHg versus blood pressure < 180 mmHg)

called Intracerebral Haemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT).

The ICH ADAPT is a multi-centre randomised open-label, blinded end-point trial in 2010, designed to test the hypothesis that blood pressure reduction does not result in significant or harmful changes in cerebral blood flow in acute ICH [39]. This study also investigated the effect of systolic blood pressure and cerebral blood flow on PHO development since PHO in spontaneous ICH had been hypothesized to be ischaemic [39]. The primary outcome was cerebral blood flow in the PHO region, measured with CT perfusion, 2 hours after randomisation and secondary outcomes include the difference in blood pressure at 1- and 2-hours post-randomisation. Nevertheless, the result of the ICH ADAPT-3 in 2014, had confirmed that even though there was a significant difference in blood pressure between treatment groups (21.3 mmHg), early blood pressure treatment had no effect on PHO and cerebral blood flow and did not exacerbate oedema growth, [40]. However, this is a relatively small study with only 67 samples, and it remains possible that blood pressure treatment may be associated to PHO growth in some patients.

Another clinical trial in 2015, investigated the efficacy of nitric oxide for management of blood pressure in acute stroke (ENOS) which assessed the outcomes after acute stroke in patients given a study drug to lower their blood pressure [41]. In this multicentre, partial-factorial trial, they had found that transdermal GTN did not improve functional outcome in patients with high blood pressure, even though it had been confirmed that the use of this drug had lowered blood pressure and was safe to administer. However, in a prospective analysis of prespecified subgroup of patients randomized to GTN in the ENOS trial, it was reported to be associated with improved functional outcomes and fewer deaths when administered within 6 hours of stroke onset [42]. These positive findings replicate the results of another clinical trial in

2012; Rapid Intervention with GTN in Hypertensive Stroke Trial (RIGHT) [43]. In this small sample study (n = 41), the treatment of GTN was initiated in the ambulance, on average at 55 minutes after stroke onset. The results of both ENOS and RIGHT were compatible with earlier preclinical trials, whereby nitric oxide donors were effective at reducing the size of the lesion if administered early after stroke onset [44].

1.4.2 Haemostatic Agents

Another strategy in clinical trials to limit haematoma expansion involves the use of haemostatic agents. Haemostatic therapy of patients with spontaneous ICH has the potential to improve prognostic outcomes by arresting ongoing bleeding and minimizing increases in the volume of the haematoma. The use of a recombinant activated factor VII (rFVIIa) has extended beyond its original indication for haemophilia. An increasing number of studies reported the successful investigational use of rFVIIa to manage haemorrhage episodes in a diverse range of clinical settings such as severe traumatic injury, hepatic dysfunction, and rapid surgical interventions in patients with oral anticoagulants [45]. In a randomised, double-blinded, multicentre, multinational, parallel group, placebo-controlled clinical trial with 4 treatment arms (with 100 patients allocated to each arm) by S. A. Mayer et al [46] in 2005, they had found that the administration of rFVIIa within 4 hours after the onset of spontaneous ICH limited the growth of haematoma, reduced the mortality rate and improved the functional outcomes at 90 days. Haematoma volume increased more in the placebo group than in the rFVIIa groups (mean increase was 29% in placebo group, p = 0.01). There was an increased percentage of placebo-treated patients (69%) who died or were severely disabled (as defined by the modified Rankin scale (mRs) score 4 to 6) compared to the patients who were given rFVIIa treatment. Additionally, mortality at 90 days was greater (29%) in patients who received placebo as

compared with 18% in the rFVIIa groups (p = 0.02). Analysis of the same trial data by M. Diringer et al [47] in 2005 to determine whether rFVIIa had worsened oedema volume in acute ICH had found that the treatment did not result in exacerbation of oedema. Indeed, treatment with rFVIIa, in addition to significantly reducing haematoma expansion, also reduced oedema volume at 72 hours. However, patients with ICH have a high risk of thromboembolic events due to several factors such as age, hypertension, diabetes, atherosclerosis and immobility, and the use of rFVIIa could increases was associated with an increased risk of thromboembolic complications, including ischaemic stroke and myocardial infarction [48]. For this reason, the data from the troke FAST were reviewed by M. Diringer et al [49] in 2010 to define the frequency of and risk factors for thromboembolic events with rFVIIa. The findings of this analysis had confirmed that higher doses of rFVIIa in a high-risk population were associated with a small increased risk of what are usually minor cardiac events. They had concluded in their study that demonstration of the ability of rFVIIa to improve outcome in future studies should be driven by its effectiveness in slowing bleeding outweighing the risk of small increase in arterial thromboembolic events [49]. The important findings from FAST highlighted 2 important considerations. The first one is the need for improved selection and identification of ICH patients who are most likely to derive benefit from haemostatic therapy, and the second one is targeting haematoma expansion is time sensitive. Earlier study in 1997 had confirmed that haematoma expansion resulting in significant clinical deterioration occurs in 26% of patients within 1 hour of ICH onset, and in addition 12% of patients had substantial growth by 20 hours [50]. Because of this reason, several trials were reinvestigating the role of rFVIIa in ICH patients based on the presence of spot sign on CT angiography as an inclusion criteria. The Spot Sign for Predicting and Treating ICH Growth Study (STOP-IT) and The Spot Sign of Intracerebral Haemorrhage to Guide Haemostatic Therapy (SPOTLIGHT) trials

were recently re-examining the utility of rFVIIA as a potential treatment for ICH in spot sign positive patients only [51]. In this multicentre placebo-controlled randomized clinical trials, they found that rFVIIa did not significantly improve radiographic or clinical outcomes among patients with spot sign-positive.

It is well known that the ICH is a feared complication in those who are on treatment with vitamin K antagonist, in which the mortality may rise up to 67% [52][53]. In vitamin K antagonist-related ICH, intravenous vitamin K, prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP) are effective haemostatic agents. Current international treatment recommendations include FFP and PCC. It is known that these substances lower the international normalised ratio (INR). PCC normalises the INR more rapidly than FFP. It is assumed that normalisation of coagulopathy may lead to haemostasis and reduction of rebleeding. A randomised, prospective, multicentre trial known as International Normalised Ratio Normalisation in Patients with Coumarin-related Intracranial Haemorrhages (INCH) was designed by T. Steiner et al [54] in 2011 to compare biological safety, feasibility and preliminary efficacy of FFP and PCC in patients with ICH related to vitamin K antagonist with elevated INR. A complete result of the trial had confirmed that PCC might be superior to FFP with respect to normalising the INR, and faster INR normalisation seemed to be associated with the smaller haematoma expansion [55]. But this study only assigned 54 patients which is considered as small sample size. In another earlier study on PCC for emergency anticoagulation reversal by I. Pabinger et al [56] in 2008, 43 patients (26 requiring interventional procedures and 17 experiencing acute bleeding) were involved in the study and received vitamin K treatment at the standard dosage prior to PCC infusion. This study had found that PCC treatment served as an effective rapid haemorrhage control resource in the

emergency anticoagulant reversal setting. However, more widespread availability of PCC is warranted to ensure its benefits in appropriate patients.

Other than haemostatic agents mentioned above, the use of tranexamic acid for treatment of patients with spontaneous ICH in clinical trials is widely used. The first trial to evaluate the efficacy of tranexamic acid in ICH patients was introduced by A. Meretoja et al [57] in 2014. The patients were selected based on the spot sign presentation on CT angiography as an inclusion criteria and imaging biomarker of high likelihood of haematoma expansion in the Spot Sign and Tranexamic Acid on Preventing ICH Growth – AUStralia Trial (STOP-AUST). As demonstrated by the STOP-AUST, there was no significant difference in ICH growth between patients with a spot sign who received tranexamic acid and those who received placebo-treatment within 4.5 hours of stroke onset (p = 0.41). However, this study showed a trend towards reduced haematoma expansion in patients receiving tranexamic acid compared to those receiving placebo in the ultra-early window ($\leq$ 3 hours and $\leq$ 2 hours), which warranted further research. Recent published results of the Tranexamic Acid for Intracerebral Hamorrhage-2 (TICH-2) study reported the same findings. Fewer participants had haematoma expansion in the tranexamic acid group (25%) than in the placebo group (29%). The method and recent results of the TICH-2 study is explained in detail in the following paragraphs. The data from the TICH-2 trial was used in my study of measurement and prediction of haematoma and PHO expansion in patients with spontaneous ICH. Advances in clinical trials and new combination approaches of optimized medical and surgical therapies may result in significant improvements in the clinical outcomes of the spontaneous ICH patients in the near future.

1.5 Tranexamic Acid for Intracerebral Haemorrhage-2 (TICH 2) Study

The TICH-2 study was a phase 3 clinical trial done to assess whether tranexamic acid is safe to use, reduces haematoma expansion as well as death and dependency after hyperacute (within 8 hours after symptom onset) primary ICH and how do they recover. The secondary objective of this study was to assess the effect of tranexamic acid on secondary outcomes; clinical outcomes (disability, quality of life, mood, cognition), safety outcomes, cost, and radiological efficacy. The randomised controlled pilot trial of the study was describe early on previous publication on 2014 [58]. While the main analysis of phase 3 trial had been published on 2018 [59] and full report of the TICH-2 study was published on 2019 [60] . This study focused on a haemostatic approach to ICH where tranexamic acid was given to the patients to stop the bleeding in the first hours after ICH to promote a better recovery. The trial was approved by research ethics committee and had a regulatory authorization and performed according to the Declaration of Helsinki and Good Clinical Practice.

1.5.1 Patient Selection

A total of 2325 participants from 124 hospitals in 12 countries were enrolled between 2013 and 2017. The main inclusion criteria included adult patients aged ≥18 years, confirmed of having an acute spontaneous ICH on CT brain scan that occurs within 8 hours after the stroke ictus. Patients with secondary ICH due to consumption of anticoagulants, thrombolysis or known underlying structural abnormality such as venous malformation, aneurysm, tumour, or venous thrombosis are contraindicated to study. In addition to this, patients for whom tranexamic acid was thought to be contraindicated were also being excluded from this study as well as patients with severe pre-morbid disability (mRs >4 and GCS <5), or pre-stroke life expectancy not more than 3 months due to other disease such as advanced metastatic cancer and those who participated in another drug trial concurrently. Patients were recruited by

investigators from acute stroke services. Ethics approval was obtained in each site and country prior to the commencement of the study. The patients were given full-informed consent and consideration before randomization. For patients who lacked capacity, proxy consent was taken from a relative or representative. When consent was deferred or given by a proxy, the participants were informed about the trial as soon as possible and sought their consent for ongoing follow-up.

1.5.2 Trial Method

The TICH-2 trial was an international, prospective, randomised, placebo-controlled phase 3, blinded end point trial involved infusion of tranexamic acid in patients with acute spontaneous ICH. Patients were randomised centrally (1:1, 1161 participants were randomly assigned to received tranexamic acid and 1164 to receive placebo) using a secure internet site in real time. Participants were assigned to receive either an intravenous 1g tranexamic acid loading dose in 100 mL of 0.9% normal saline, followed by another 1g of intravenous tranexamic acid in 250 mL of 0.9% normal saline that was infused over 8 hours, or a matching placebo (0.9% saline) which was administered by identical regime. Randomisation involved stratification by country and minimisation on key prognostic factors; age, sex, time onset, systolic blood pressure, stroke severity [as measured using National Institute of Health Stroke Scale (NIHSS)], presence of IVH and known history of antiplatelet treatment before the stroke onset.

The patients underwent CT brain scans for both pre and post administration of tranexamic acid. Preliminary scan was done as part of routine care before enrolment to confirm the presence of haemorrhage. Post injection scan was done at 24 hours after the intervention to assess haematoma expansion and to evaluate the consequences of drug treatment. When multiple scans were done, the scan closest to 24 hours after randomisation was used.

Segmentation and quantification of haematoma volumes was done for both sequences of CT brain scan using semi-automated segmentation technique on Digital Imaging and Communications in Medicine (DICOM) images. The user-guided 3-dimensional active contour tool in the ITK SNAP software was used for haematoma volume segmentation by 3 independent assessors. All assessments were masked to treatment allocation. The haematoma volumes of baseline and 24 hours follow-up scan were compared to detect haematoma changes and to study the effect of tranexamic acid treatment on haematoma whether it is considered efficient to limit the haematoma growth or shows no significant difference. This study defined haematoma expansion as an increase in haematoma volume of greater than 6mL or relative growth of more than 33%. The primary outcome was functional status (death or dependency assessed with the ordinal shift on mRs) at day 90 which was administered by telephone or by postal questionnaire. Assessors were blinded to the clinical status of the patients whether they had received tranexamic acid or matching placebo to avoid bias in justification.

1.5.3 Pilot Study Phase Result

The TICH randomised controlled pilot trial showed that haematoma volume tended to increase in the control group compared to the treatment group, and there were no significant differences in functional outcomes between the groups. However, the number of samples in this pilot trial were too small (n = 24) to draw any conclusions on safety or efficacy of tranexamic acid and the result definitely cannot represent the population of the ICH patients. A review article published in 2017 had reported that tranexamic acid as a promising haemostatic agent in reducing bleeding rates in surgical and trauma patients, though there was insufficient evidence from completed trials to draw conclusion on the effect of tranexamic acid in spontaneous ICH [61].

1.5.4 Result of TICH-2

The result of the TICH-2 study showed no significant difference between the groups receiving tranexamic acid and those receiving placebo in the primary outcome of functional status at day 90 [59]. However, there were significant reductions in the prespecified secondary outcomes of early death, haematoma expansion and serious adverse events in tranexamic acid group. The small reduction in haematoma volume (1.37 mL smaller in tranexamic acid group compared to placebo group) might have been insufficient to confer a significant improvement of functional status in TICH-2 population. This study also found no evidence of an increase in venous thromboembolism in tranexamic acid group, as had been reported of increased risk of arterial occlusive events with rFVIIA [62]. In summary, the use of tranexamic acid in patients with spontaneous ICH did not affect functional status at day 90, even though there were reductions in haematoma expansion, early death, and serious adverse events. Thus, TICH-2 showed the safety of tranexamic acid but no significance for the primary clinical endpoint.

1.5.4.1 Strengths and Limitations

The TICH-2 study had several major strengths including its double-blinding, allocation concealment, low risk of bias, high adherence to treatment, very broad and generalised inclusion criteria, a therapeutic agent shown to slow traumatic bleeding with a good safety record, a large sample size for a stroke trial, and very few missing data on primary outcomes. A limitation of TICH-2 is its inclusion of participants in whom slowing of bleeding has minimal effect on patient outcome. Future research with larger sample should investigate which subgroups might be more likely to benefit from tranexamic acid, since tranexamic acid is widely available, inexpensive, easy to administer and seems to be safe. My study uses the data from the TICH-2 population to measure the

volume of haematoma and PHO using the widely used ABC/2 formula [63] and SAS technique with the use of ITK SNAP software. While the placebo-treated group from the TICH-2 population was used to create a predictor model for haematoma expansion, PHO expansion and poor functional outcome of patients with spontaneous ICH.

1.6 Segmentation of CT Brain Images in Patients with IVH and Spontaneous ICH

1.6.1 Haematoma Volume Measurement

Variations in haematoma volume measurement may affect treatment and prognostication [64][65]. Several methods have been studied in previous publications for volume measurement of haematomas. The most common techniques used to measure the size and volumes of haematomas are the ellipse volume, called the ABC/2 formula and the computer-aided volumetric analysis either semi-automated segmentation (SAS) or fully automated method. In most studies of haematoma volume estimation, SAS method is widely used rather than fully automated technique. There are various techniques of image processing applied in brain haematoma segmentation and volume calculation on CT brain images. These techniques encompassed various types of algorithm and used different steps of segmentation namely region growing technique, threshold-based segmentation, K-mean clustering, Fuzzy, GVF snake, watershed and step-section planimetry [66]–[68].

1.6.1.1 The ABC/2 Formula

Over the past two decades, the ABC method has gained widespread acceptance as the easiest bedside technique, reliable, and the most widely used method in assessment and estimation of haematoma volume in most cases [69]–[72]. It is derived from the mathematical formula for volume of an ellipsoid, with the underlying assumption that

the haematoma takes an ellipsoid-like shape [63]. Although this assumption may hold true in certain patients, the shapes of many haematomas are considerably deformed from ellipsoids. Therefore, validation of its use in clinical practice carries practical significance. This simple formula of volume measurement has been reported to have an inter-observer reliability of 0.99 [73]. Within this formula of calculation, 'A' refers to the largest diameter of haematoma in axial plane on any slice, while 'B' is the largest diameter of haematoma in 90° to 'A' in the same slice, and 'C' is the vertical diameter which is indicated by the number of slices showing the haematoma multiplied by slices thickness [74] as previously describe by J. P. Broderick et al [75]. The example of haematoma measurement using the ABC/2 formula is shown on Figure 1-1. While, in modified ABC/2 formula, only slices with at least 25% of the largest area of haematoma will include in calculation whereas the slices with less than this value were not included in 'C' [76]. There are different bedside methods of measuring ICH including ABC/2 formula and modified ABC/2. V. H. Lee et all [77] in their study showed that a modified ABC/2 and ABC/2 formula do not correlate and the differences between methods increases with larger ICH volumes.

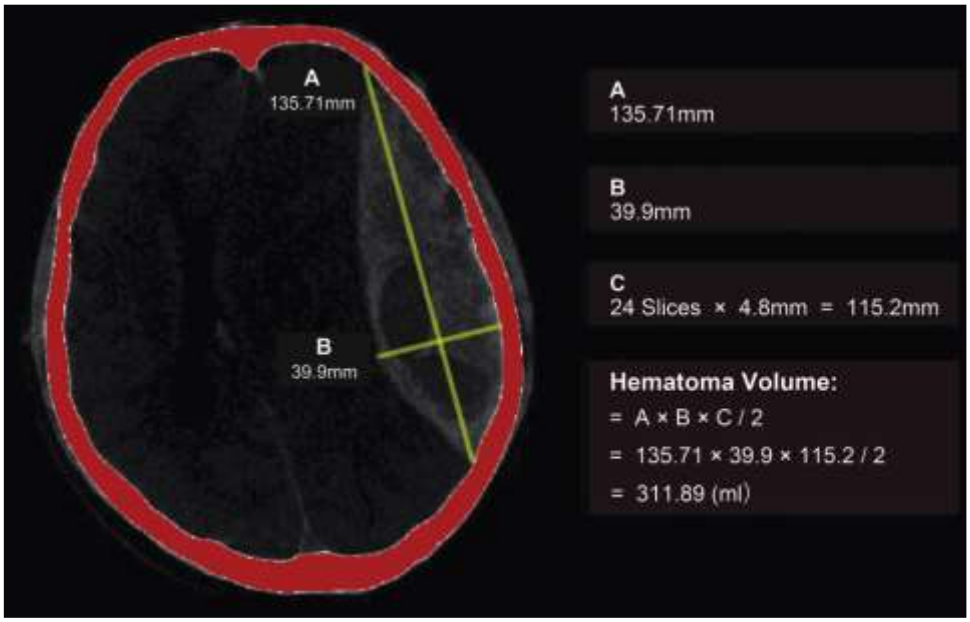


Figure 1-1 Application of the ABC/2 formula for intracranial haemorrhage volume. Image taken from T. Hu et al. (2015)

Nevertheless, it has been reported that the ABC/2 formula showed large errors when estimating the volume of haematomas of multi nodular or irregular in shape [78] especially in those patients who take an oral anti-coagulant therapy (OAT). ICH related to OAT had difference pathophysiological mechanism from that of primary ICH and tend to grow in various shapes and sizes of the haematoma [70]. As a result, the measurement accuracy seems to decrease with large, irregular and lobar clots [79]. Similarly, there was an overestimation of haematoma volume measured by ABC/2 formula and there was also significant association between the accuracy of measurement with the size and location [70]–[72]. For an irregular shape and separated haematomas, H. Huttner et al [29] suggested changing the dominator to 3 giving ABC/3 in order to obtain more precise volume estimation. In contrast, A. A. Divani et al [79] have reported in their study that both the ABC/2 and ABC/3 adjusted formulae resulted in underestimation of haematoma volumes, especially for irregular and discontinuous haematomas. Figure 1-2 shows the regular and irregular shapes of haematomas.

The ABC/2 method has been validated in multiple studies suggesting reasonable accuracy [80][81]. B. Zhao et al. [82] in their study had re-explored the formula of ABC/2 to find a method that can measure haematoma volumes on CT images accurately, reliably and quickly. They had investigated 7 formulas (π/6 ABC, ABC/2, ABC/3, 2/3 SH, ½ SH, π/6 SH and 2.5/6 ABC) and compared the measurement from each formula to 3D Slicer as the reference standard. π/6 ABC is the first formula developed for calculating haematoma volume introduced by A. Tada et al. [83]. Subsequently, other researchers continued and modify this to get ABC/2 [84], ABC/3 [70], 2/3 SH [85][86], ABC/2 with adjusted C values [63][79][87][88] and ABC/3 with adjusted C values [88]. In formula modified by K. J. Zhao [86], 'S' is referred to the largest axial haematoma slice area and 'H' represents the haematoma depth. 'S' and 'H' in turn multiplied by 2/3, which yielded haematoma volume in cubic centimetres.

ABC/2 is the most widely used method for estimating haematoma volume in clinical practice. However, this method generally overestimates the size of the haematoma volume and is better suited for calculating regular and small haematomas [78]. In contrast, ABC/3 generally underestimates haematoma volumes and is better suited for calculating irregular haematomas, especially lobulated haematomas [89]. The formula 2/3 SH requires further study. Additionally, the ABC/2 adjusted method and the ABC/3 adjusted method are less used because of their large underestimation of haematoma volumes [79][90]. The study done by B. Zhao et al [82] had discovered that the accuracy of the new formulas (1/2 SH, π/6 SH , and 2.5/6 ABC) was greater than that of the old formulas ((π/6 ABC, ABC/2, ABC/3, 2/3 SH). In addition, after layering the size, shape and location of haematoma, the accuracy

of the new formulas was almost higher than that of the old formulas. Their study had showed that the accuracy of ABC/2 was influenced by the shape and size of the haematomas, which consistent with this study and previous papers [70][91].

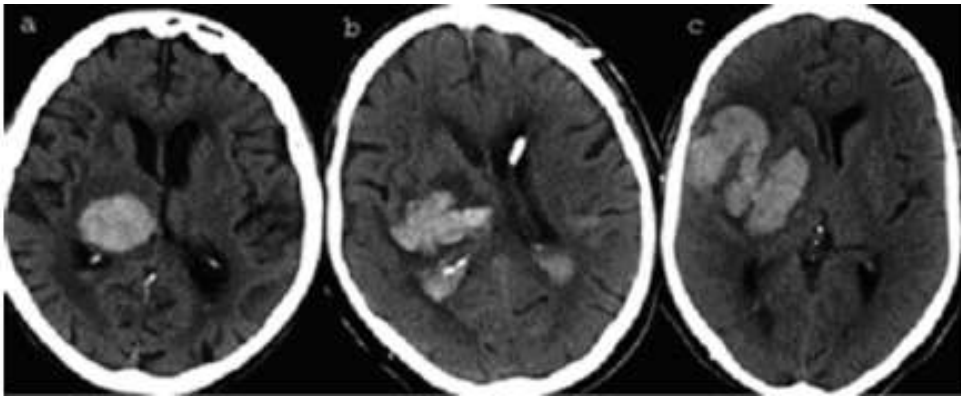
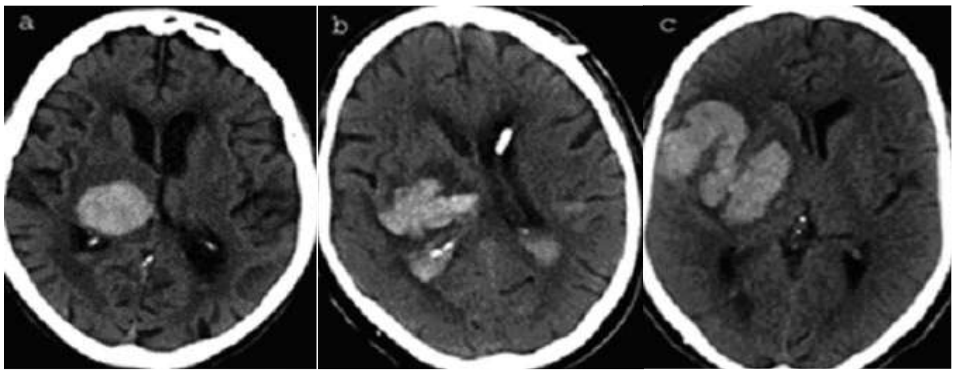


Figure 1-2 Regular (a), irregular (b), and separated (c) shapes of haematoma. Image taken from H. Huttner et al (2006)

1.6.1.2 Computer-Aided Haematoma Volume Analysis

Processing of the images and artificial intelligence are the components of the computer-aided volumetric analysis that is known as the gold standard for haematoma volume analysis. Investigators with the aim to provide the accurate volume estimation and rapid management of patients had improved this method of measurement. A new computer aided volumetric analysis for haematoma volume quantification becomes an alternative to conventional ABC/2 formula. Based on previous research done, there were several computer-aided software and techniques used in measuring the size and volume of haematoma enlargement such as MIPAV [71] "DICOM Work" [92] "Analyze" [93], "Quantomo" [94], and "ManSeg" while the most common techniques used in volume analysis are region growing, planimetric and 3D rendering [79][95][96][97]. Planimetric and 3D rendering approaches of haematoma segmentation with various shapes are shown on Figure 1-3 and Figure 1-4 respectively.



(a) (b) (c)

Figure 1-3 Example of planimetric approach in (a) regular, (b) irregular and (c) separated shapes of haematoma. Image taken from H. Huttner et al (2006)

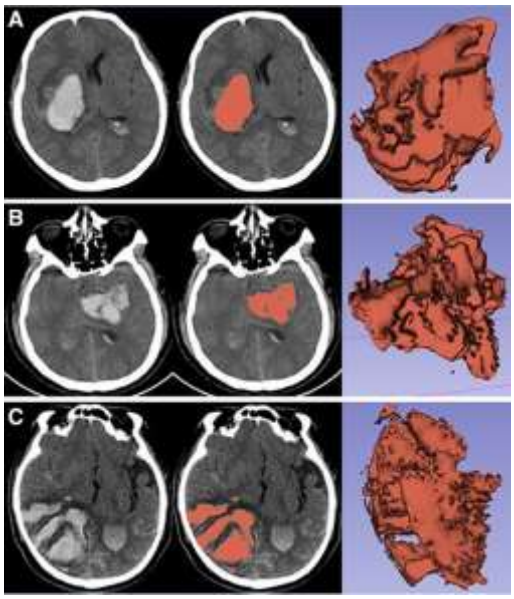


Figure 1-4 Example of 3D rendering in (a) regular, (b) irregular, and (c) separated shapes of haematoma. Image taken from X. Xu et al (2014)

One of the earliest approaches for haematoma segmentation is the one proposed by S. Loncaric et al. [98], where the input CT brain image was processed in two stages. The first stage used an unsupervised clustering algorithm, and the second stage was a rule-based system devoted to the interpretation of the clustering results. This method was based on

fuzzy clustering and expert system labelling, which enables automatic determination of the volume of the ICH region. However, the method did not always perform correct segmentation. This situation leads to the development of additional semi-automatic segmentation method which experts can use if he is not satisfied with the results of the automatic segmentation. Z. Majcenic and S. Loncaric [99] proposed a stochastic method based on simulated annealing algorithm for segmentation of CT images depicting spontaneous ICH. These experimental results have demonstrated good results and proved the usability of the method. The work by N. Perez et al. [100] proposed two semi-automated spontaneous ICH segmentation methods. The first method relied on the application of 3D mathematical morphology, histogram analysis, optimal thresholding, and prior geometric information techniques. While the second method was based on similarity, in which they combined live wire and graphical information retrieval techniques. These methods were applied successfully for segmentation and tracking of spontaneous ICH from CT brain images. Another semi-automated approach that combines a region growing technique to segment haematoma and a level-set method to delineate oedema in CT was presented by A. Bardera et al. [101]. The main novelty of this method was the strategy applied to define the propagation function required by the level set approach. The obtained results demonstrated that the proposed approach provides objective and reproducible segmentations that were similar to the results obtained manually. A study done by W. M. W. Zaki et al [102] introduced a Multi-level Local Segmentation Approach (MLSA) based on Fuzzy C-Means (FCM) clustering to segment intracranial structures of the CT brain images for haematoma detection. This approach had proved to be accurate and reliable that would provide a strong basis for the application in content-based medical image retrieval. A Modified

Distance Regularised Level Set Evolution (MDRLSE) algorithm for haematoma segmentation was proposed in the study by K. N. B. Prakash et al. [103]. This study included prep-processing (filtering and skull removal), segmentation (MDRLSE which is a 2-stage method with shrinking and expansion) with modified parameters for faster convergence and higher accuracy and post-processing (reduction in false positives and false negatives). This method had improved the accuracy and speed for segmentation and calculation of the haematoma volume compared to the original Distance Regularised Level Set Evolution (DRLSE) method. In the study by H. S. Bhadauria et al. [104], the authors presented a segmentation approach which combines the features of FCM clustering and a region-based active contour technique. The proposed method was suitable for medical images with intensity inhomogeneities because it used the intensity information in local regions to guide the contour towards the haematoma boundaries. The result of the proposed method correlates well within the expert's measurements and may be used for clinical purposes.

A. H. Ali et al [97] in their study had introduced a new SAS method for detection and segmentation of intracerebral haematoma using textural analysis on brain CT images. In this new approach, there were several steps involved in haematoma segmentation starting from the pre-processing stage to enhance the quality of CT brain images to qualify the brain images by various techniques and processes. At pre-processing stage, they used a region growing technique to group the pixels based on predefined criteria for growth, then they applied image masking to remove the cortex by using the logical operator and the last step was the application of filtering operation to remove the noise on CT images. Haematoma region was then being analysed using a thresholding technique, the simplest method that isolated the

haematoma area from the normal brain tissues. This method provides a good result for the detection and segmentation of haematoma with the help of statistical features.

In terms of the reliability comparison between the SAS and the ABC/2 formula, most of the previous research findings showed minimal variation in the intra and inter-observer variability of SAS method thus making the computer-aided analysis more precise in estimating of haematoma volumes compared to the ABC/2 formula [63][76][94] . In spite of this, as identified by T. T. Hu et al [72], the size of the actual haematoma volume is different from the volume estimated by the computer-aided technique although it was considered the most accurate method and served as the gold standard for method comparison. In addition, the segmentation process of haematoma volume for each slide is time consuming and volumetric measurement technique needs a post-processing of imaging data and requires expertise in using an imaging software package. These could be weaknesses that future studies should be concerned with.

1.6.2 PHO Volume Measurement

PHO volume quantification is the most challenging part in brain segmentation. This is due to unclear boundaries between oedema regions and normal brain parenchyma. Various methods and approaches in brain segmentation to quantify and detecting haematoma and PHO in patients with spontaneous ICH were reported in previous studies. Accurate segmentation of PHO and quantification of haematoma volume is important for diagnosis, monitoring and planning therapeutic intervention. Currently, there is no established method in PHO quantification so far that could be considered as gold standard in accurately depicting the oedematous tissue from normal brain parenchyma. Nonetheless, for PHO segmentation, there are two principal methods which

are manual segmentation approach, which is done with the help of medical experts, and another way is a computer-aided with the help of image processing algorithms. These two methods of PHO segmentation are performed based on the specific definition and appearance of PHO on radiographic images. The radiographic appearance of PHO is usually defined as the rim of perihaematomal hypodensity area [7][41][106][107] that always contiguous with the haematoma [101] within 1cm radius of normal brain [107] and represented as a lower Hounsfield Unit (HU) number (ranging from 5 to 33 HU) [40][108]. HU is a dimensionless unit universally used in CT scanning to express CT numbers in a standardised and convenient form. It is proportional to the degree of x-ray attenuation (grey scale) and allocated to each pixel to show the image that represents the density of the tissue [109]. The HU number in CT scan is affected by water content in local tissue. Different water content presents a different HU number. Hence, the appearance and disappearance of PHO could be manifested by the change of HU (or water content) in local brain tissue [110]

1.6.2.1 Manual PHO Segmentation

There is no gold standard in PHO segmentation currently, but the widely used technique in PHO volume estimation is manual tracing. It had been prove that despite a large number of literatures describe about the use of fully- and SAS method of brain segmentation, there are still have many studies that continue to use a manual delineation as the main technique of choice for brain segmentation [111]. This situation persists mainly because of the complicated user interfaces of fully- and SAS techniques which might require a high computational demand and expertise in mathematical formulation.

However, there are several studies that had compared the performance of manual segmentation to computer-aided quantification in terms of

their segmentation accuracy. A. Bardera et al [101] had reported a similar accuracy (0.85) between computer-aided oedema segmentation and manual tracing while M. Chen et al [107] and J. M Gebel et al [112] had reported a better accuracy of computer-aided analysis compared to manual delineation with 0.78 and 0.9744 respectively. A comparative result of the computer-aided segmentation and manual segmentation done by M. Chen is shown on Figure 1-5. Even though the manual segmentation of oedema has been reported of having comparative result to computer-aided quantification, the complexity and time-consuming nature of manual delineation might be the main factor that alleviates the performance of oedema segmentation.

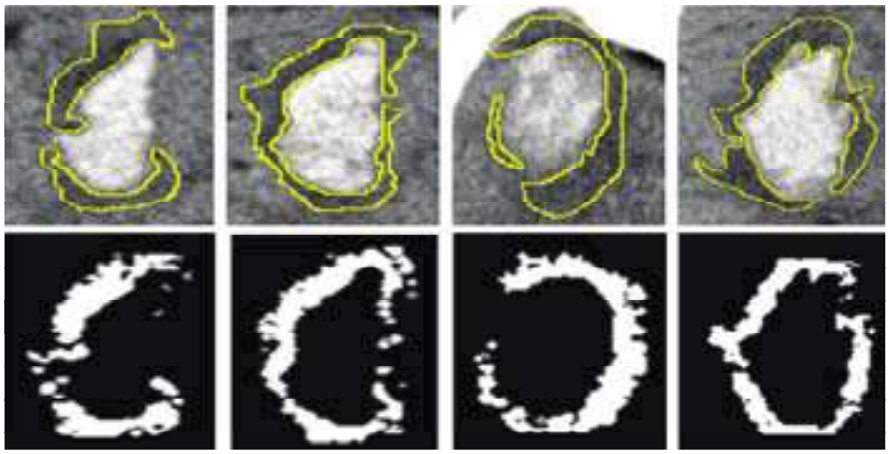


Figure 1-5 Manual tracing segmentation (gross yellow line) vs computer-aided segmentation (solid yellow area) shows a comparative result. Image taken from M. Chen et al (2013)

M. Joarder et al.[10] had introduced modified ellipsoid formula simply by ±6 ABC which practically amounts to ½ by ABC [63]. PHO volume (rim of hypodensity) was calculated by subtracting the haematoma volume from the combined haematoma and PHO.

1.6.2.2 Computer-Aided PHO Segmentation

Regarding the brain segmentation technique to extract the PHO in intracerebral haematoma related cases; MRI modality is considered as

having a superior sensitivity for detecting brain tissue abnormalities. Notwithstanding of the best performance of MRI in PHO delineation, CT becomes the gold standard for ICH imaging because of its excellent sensitivity for identifying acute ICH in the emergency department, plus its wide availability and rapid scanning capability compared to MRI [113]. This vital specification of CT becomes an integral part of brain imaging for patients with head injuries or brain anomalies who are subjected to prompt treatment and management. The most popular approaches of SAS brain segmentation are thresholding and region growing techniques. It has been used in several studies [101] regarding brain segmentation and has shown a significant improvement of oedema quantification in term of computational time and accuracy of measurement compared to manual delineation.

An automatic method was proposed to extract oedema around spontaneous ICH [114]. In this approach, the seeds for the region growing algorithm were obtained using the expectation-maximisation clustering method. This algorithm could provide a potential tool for neurosurgeons to quantify oedema and guide therapy of patients with spontaneous ICH. B. Volbers et al. [115] proposed to use a fixed threshold range between 5 and 33 HU in CT for oedema delineation. They further showed that the resulting segmentations in these CT images had a strong correlation with manual ones performed on their MRI counterparts. A. Bardera et al. [101] combines a region growing approach to segment the haematoma region and a level set segmentation technique to segment the oedema. This approach showed promising results, demonstrating its reliability and accuracy as well as the suitability of the level set approach for oedema segmentation. The K-mean clustering algorithm-based threshold was presented by J. M. Gebel et al [116]. This algorithm used to divide the region of interest

into foreground (haematoma) and background (PHO and brain parenchyma). PHO measurement was accomplished by "growing" thin layers (rings) sequentially outward from the edge of the haematoma. S. Urday et al. [108] measured the oedema volume using Analyze 11.0 software. Boundaries of PHO was outlined using the edge-detection tool and were adjusted after inspection of the volumes in each of the three orthogonal planes. Semi-automated threshold-based method (range of 5 – 33 HU) was also introduced by J. Yang et al. [117]. This threshold range was applied and adjusted to identify regions of PHO to estimate volumes from slice thickness separate to boundaries of haematoma.

A. B. I. Reig et al [118] had developed a SAS method of PHO quantification using a level set approach. This technique was introduced since the intensity thresholding technique is not possible due to the subtle difference of the intensity values between the damaged and healthy regions as well as the presentation of image noise. In this new technique, they applied the prior knowledge of PHO definition that the oedema is always contiguous with the haematoma and has a low intensity value compared to healthy tissues. However, they reported that there was no significant difference between SAS technique and manual oedema segmentation due to hard to define borders, which are very challenging to identify even for an expert operator. Nevertheless, the proposed approach had reduced the processing time for each study from 10 minutes by manual tracing to 4 minutes using level set strategy. The final stage of PHO delineation using level set strategy is shown on Figure 1-6.

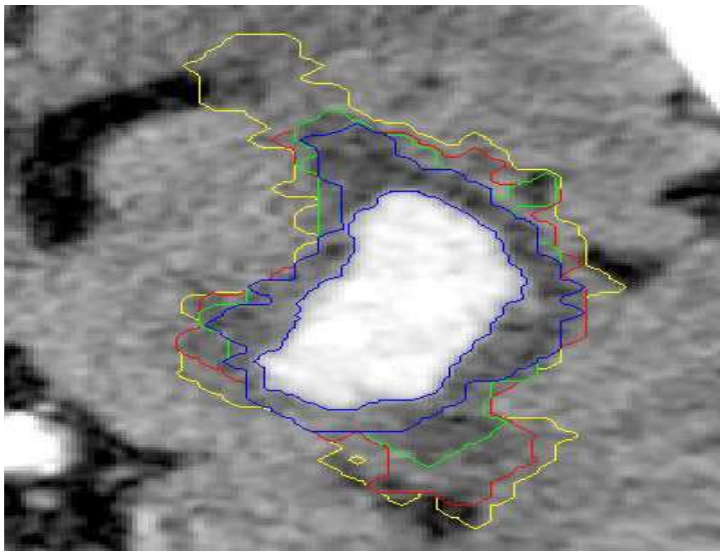


Figure 1-6 Level set approach of oedema segmentation. Image taken from A. Reig (2009)

1.6.2.3 Combination of Manual and Computer-Aided PHO Segmentation

Combination of manual and semi-automated approach was presented by R. McCourt et al [40], W. A. Mould et al. [119] and Y. Zhu et al. [120] in which PHO volume ROIs were first drawn manually on non-contrast CT by tracing the hyperdense perimeter representing haematoma (HU range 40 – 100HU). The hypodense region surrounding the haematoma, indicating PHO was obtained by applying threshold range of 5 to 23 HU [40] and 5 – 33 HU [119][120] to the manual ROIs, in each slice throughout the lesion. In a study done by S. H. Lee et al. [105], the authors manually drew region of interest by tracing the perimeter of appropriate hyperdense and hypodense area in each single slice throughout the lesion. Automated threshold values (33 and 5 HU), based on previous study [115] were then applied to differentiate haematoma from oedema and oedema from brain parenchyma, respectively. Another combination of manual tracing and semi-automated edge detection was

reported by L. H. Sansing et al. [121] in which, the hypodense area immediately surrounding haematoma region that representing PHO was selected manually by the viewer and the area was automatically outlined by the program. The area on each slice was then multiplied by the slice thickness to obtain PHO volume.

1.6.3 IVH Volume Measurement

Since extension of haemorrhage resulted from spontaneous ICH into ventricular system is considered very dangerous and life threatening, accurate detection and quantification of IVH volume is absolutely indispensable for precise patient management and treatment planning. Measurement of IVH in patients with spontaneous ICH has turn out to be as crucial as haematoma and PHO volume analysis. Detection and quantification of IVH volume might be challenging especially in those presenting with just a small amount of IVH volume. Realisation that this consequence might affect the final outcomes, E. M. Liotta et al [122] in their study had compared the sensitivity of MRI versus CT for accurate identification and quantification of IVH. The result reported that MRI was a more sensitive modality for IVH detection while CT imaging missed 3% of IVH diagnosis and yielded lower estimated of IVH than MRI. Nevertheless, there is no gold standard measures against which the IVH quantification by MRI and CT can be compared.

Typically, IVH volume is widely and accurately measured by manual methods rather than automatic segmentation [123]. Nonetheless, manual methods are time consuming, strenuous and might introduce variability when performed on large datasets. This situation promotes the introduction of computer-assisted planimetric volume measurement of IVH in 2012 by D. Dowlatshahi et al [124]. The reliability of SAS technique to estimate IVH volume had been evaluated, in which it was reported of having excellent intra- and inter-observer agreement. However, SAS approach is still considered operator-

dependent and need user interactions and this might introduce variability in results. Another study done in the same year, introduced a fully automatic, accurate and fast segmentation of IVH using brain CT images [123]. This study proposed the MDRLSE algorithm for IVH segmentation, and it confirmed of showing an improved accuracy and speed compared to the original DRLSE method.

1.7 Clinical Features of Patients with Spontaneous ICH

It is well known that spontaneous ICH is more fatal and disabling than ischaemic stroke or subarachnoid haemorrhage. Although there have been some advances in the treatment of ischaemic stroke and subarachnoid haemorrhage [125][126], there is no effective medical or surgical therapy for spontaneous ICH [127]. For this reason, there is a vital need in future research to publish prognostic models for mortality and functional outcomes of patients with spontaneous ICH. To create a prognostic model for spontaneous ICH, common clinical features of patients presenting with spontaneous ICH should be well understand and established.

1.7.1 National Institute of Health Stroke Scale (NIHSS)

The National Institute of Health Stroke Scale (NIHSS) score appears to be a recommended baseline routine score to assess the severity of stroke in patients with spontaneous ICH and becoming the standard assessment in all acute stroke patients [128]. NIHSS became the gold standard for stroke severity rating after the first successful trial in acute stroke therapy [129]; the National Institute of Neurological Disorders and Stroke recombinant tissue-type plasminogen activator for Acute Stroke Trial (NINDS r-tPA) [130]. The NIHSS is a serial measure of neurological deficit, composed of 42-point scale that quantifies neurological deficits in 11 categories: level of consciousness, best gaze, visual, facial palsy, motor arm, motor leg, limb ataxia, sensory, best language, speech and extinction and inattention. Each

category is evaluated with a score between 0 and 4 and some elements have a scale from 0 to 2. Score 0 typically indicates normal function in that specific ability, while higher score is indicative of some level impairment [130]. Low NIHSS score in patients with spontaneous ICH is associated with better outcomes (Table 1-1) [128].

Table 1-1 NIHSS Score

Score	Stroke Severity
0	No stroke symptoms
1 - 4	Minor stroke
5 - 15	Moderate stroke
16 - 20	Moderate to severe stroke
21 - 42	Severe stroke

1.7.2 modified Rankin scale (mRs)

The mRs is a clinician-reported global outcome 7-level rating scale (Table 1-2), used to measure the degree of disability or functional independence in patients who had a stroke [131]. It has been widely used for evaluating the recovery from stroke [132] and has been often used as a primary end point of patients with stroke in randomized clinical trials [131]. The mRs was analysed as a dichotomous variable, as this has been the standard in ICH clinical trials. A "favourable" functional outcome mostly defined as mRs grade 0 - 2 and "poor" functional outcome defined as mRs grade 3 – 6 at 90 days in majority of randomised clinical trials [54][105][133][134][135][136].

Table 1-2 modified Rankin scale score

Rankin Grade	Description

0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
3	Moderate disability: requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Death*

* Used commonly in clinical trials

1.7.3 Glasgow Coma Scale (GCS)

The GCS is a widely known, rapid, reliable, and reproducible tool to evaluate patients' consciousness. It was first introduced in 1974 as a method for evaluating the severity of brain dysfunction and has been used mainly in evaluating prognosis, comparing different groups of patients and monitoring the neurological status of patients after the occurrence of head trauma [137]. Nowadays, it is by far the most widely used score to assess the level of consciousness in patients with brain injury. The basic elements in GCS is the independent assessment of responses in 3 behavioural domains; eye opening (E), verbal response (V) and motor response (M) (Table 1-3) [138]. In patients who are fully conscious, alert, and oriented, the total GCS score is 15/15 (E4, V5 and M6) and the reduction in the score means there is a deterioration in the state of consciousness. The minimum score is 3/15 (E1 V1 and M1) which means no eye opening, no verbal response, and no motor

response to any type of stimuli. The GCS score of 3 - 5 is defined as having a deep coma [139]. Randomised clinical trials of patients with spontaneous ICH normally used GCS score of 6 or greater at the time of enrolment as an inclusion criteria for the patients to be included in clinical study [139][140]. The GCS has the advantage of being simpler to use, because it does not require analysis of brain imaging or measurement of haematoma volume to predict mortality and prognosis in patients with spontaneous ICH [141].

Table 1-3 Standard Glasgow Coma Scale

Eye Opening	Verbal Response	Motor Response
4 : spontaneous 3 : to speech 2 : to pain 1 : none	5 : oriented 4 : confused 3 : inappropriate words 2 : incomprehensible sounds 1 : none	6 : obeys commands 5 : localizes 4 : withdraws 3 : abnormal flexion 2 : extension 1 : none
Total GCS Score : 3 - 15		

1.8 Imaging Features of CT Brain Images in Patients with Spontaneous ICH

Haematoma expansion in patients with spontaneous ICH occurs in approximately one third of the cases and is commonly known as an independent predictor of poor clinical outcome[75][142]. To date, no medical or surgical therapy has been shown to improve outcome. Therefore, understanding the way ICH induces brain injury is critical to the development of effective treatments, and there is a critical need to establish imaging predictors of haematoma expansion that are rapidly and easily accessible. In addition, it has a great potential to be modified and improve outcome if the possibility of haematoma expansion is detected early enough. There

are several beneficial imaging features on initial non-contrast CT brain scan that can be used as a demarcation to initial development of haematoma expansion in spontaneous ICH such as baseline CT signs (blend sign, black hole sign and island sign), mass effect and midline shift.

1.8.1 Blend Sign

Haematoma blend sign has been recently referring to a CT appearance of a novel-imaging marker that predicts early haematoma expansion in spontaneous ICH. Blend sign is defined as blending of a relatively hypoattenuating area with adjacent hyperattenuating region within haematoma with a discrepancy of at least 18 HU between the 2 density regions. Based on previously published article [143], there is a well-defined margin between the hypoattenuating area and adjacent hyperattenuating region that is easily recognised by the naked eye. The hyperattenuating region of haematoma does not encapsulate the hypoattenuating area. To be defined as a blend sign, the haematoma has to meet all of the above-mentioned criteria. The example of blend sign on CT images is shown on Figure 1-7(a). Early identification of blend sign in spontaneous ICH is very valuable in prognostic stratification and may assist in a potential therapeutic target for prospective interventional studies. The first study regarding this concern was done by Q. Li et al [144] that investigated the prognostic value of CT blend sign in patients with spontaneous ICH. The finding had demonstrated that early haematoma expansion was much faster in patients with CT blend sign compared to those without the sign. CT blend sign was also reported as significantly associated with poor functional outcome at 3 months and can be deliberated as a novel imaging marker predicts haematoma expansion. Other than that, CT blend sign is also believed to have a strong relationship to secondary neurological deterioration after ICH. Recently published study [145] had confirmed this assumption in their finding

by showing a high correlation between CT non-contrast blend sign and CTA spot sign. This study also revealed that a novel CT blend sign was a reliable imaging predictor of secondary neurological deterioration after spontaneous ICH.

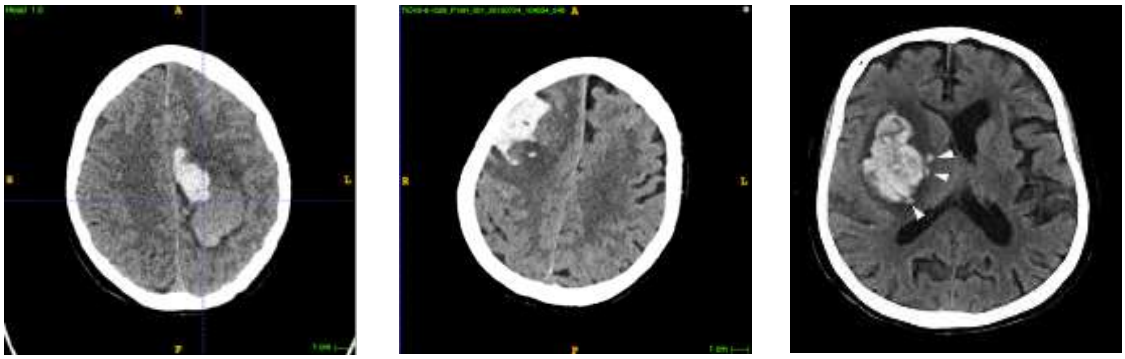
1.8.2 Black Hole Sign

Black hole sign is another imaging marker that assumed to be an indicator of initial haematoma expansion in spontaneous ICH. Black hole sign was firstly defined by Q. Li et al [146] as relatively hypoattenuating area with a well-defined border within the hyperattenuating haematoma region with a various shaped that could be round, oval or rod-like that was not connected with adjacent brain parenchyma. The black hole within the haematoma region should have at least 28 HU difference from hyperattenuating haematoma. The black hole sign on spontaneous ICH CT images is shown on Figure 1-7(b). The appearance of black hole sign within haematoma region on CT scan demarcates a different age of haemorrhage where an active and fresh bleeding within brain has a relatively high density (hyperattenuation) compared to older bleeding. This heterogeneity of haematoma has been described as showing a strong association with early haematoma expansion in several studies [69][147][148].

1.8.3 Island Sign

Several studies have reported that the chance of haematoma expansion in spontaneous ICH might be associated to the shape of the haematoma; in which the irregular shape of haematoma is at greater risk of expansion than the regular shape [149]. In previous studies, several researchers have categorized the shape of haematoma into two categories, round and irregular [142], wherein the most irregularly shape haematoma predicts haematoma expansion accurately. However, the shape of haematoma is extremely

variable and the definition of irregularly shape haematoma is very subjective and lack stringent morphological criteria. Therefore, using a well-characterized cohort including 252 ICH patients, island sign is firstly described by Q. Li et al [150] that can be evaluated on non-contrast CT brain images when there are three or more small haematomas, in which all separated from the main haematoma or at least four small haematomas, in which some of them might connected with the main haematoma. The separated small haematomas could be round or oval in shape while connected haematomas should be bubble-like or sprout-like but not lobulated. The island sign is a refinement of the shape of irregularity scale and represents extreme margin irregularities. Figure 1-7(c) illustrated the appearance of island sign on CT brain images (arrowheads).



(a) (b) (c)

Figure 1-7 Non enhanced CT images with (a) blend sign, (b) black hole sign and (c) island sign (arrowheads)

1.8.4 Mass Effect

Previous reports have suggested that haematomas exert clinically significant mass effect in a substantial number of patients [151]. Mass effect of haematoma and the associated PHO are commonly responsible for neurological deterioration and increasing intracranial pressure after

spontaneous ICH [152][153]. This clinical condition may eventually lead to complications including herniation, midline shift, hydrocephalus and increased neuronal death [152][153][154]. Mass effect after spontaneous ICH occurs in predictable stages. Effacement of the sulci adjacent to the lesion is followed by partial or complete effacement of the adjacent ventricles. Effacement of the sulci and ventricles may extend across the whole structures, and this is followed by displacement of midline structures, and then the effacement of the contralateral ventricles and sulci (Figure 1-8). In severe cases, CT brain may demonstrate herniation of structures through the incisura tentorii (the gap at the top of the tent normally occupied by the brain stem and basal cisterns), or coning (extrusion of the posterior fossa structures through the foramen magnum) [155]. These uncommon features are normally associated with extremely poor functional outcome. Previous methods of estimating mass effect have included assessment of ventricular and cisternal compression [156], measurement of transverse widening of the cerebral hemispheres, measurement of shift of midline structures and description of the presence of a "typical oedema pattern" surrounding the haematoma [153]. The mass effect after spontaneous ICH would continue for days until the haematoma was evacuated by surgical treatment [157]. Therefore, future research in developing predictor model for haematoma expansion becomes a vital need in patients with spontaneous ICH. It is of important necessity in clinical trials to recognize a candidate likely to benefit from surgical treatment in order to limit the mass effect and secondary brain injury, therefore, can improve the functional outcomes. Early identification of patients at high risk of death from mass effect would assist a decision in patient management.



Figure 1-8: A small ICH with PHO. The combination of the blood and oedema is causing mass effect: effacement of the adjacent sulci and partial effacement of the adjacent lateral ventricle [155].

1.8.5 Midline Shift

Midline shift of the brain refers to a displacement of brain tissue across the centre line of the brain. Brain shift is an important feature that can be measured using various imaging modalities to help diagnosing intracranial lesions, especially traumatic brain injury, stroke, brain tumour and abscess [158]. Both cerebrum and cerebellum are symmetric with lobes, ventricles and deep nuclei of similar size and shape in both hemispheres. Since symmetry plays a key role in radiologic evaluation of the brain, any shift of midline structures is presumed to represent a mass effect on the side from which the midline is displaced [158]. Measurement of midline shift is easily quantifiable compared to the assessment of mass effect, and its correlation with clinical deterioration has been well described. The most common approach for midline shift measurement is shown on Figure 1-9. The ideal

midline (IML) is determined as the connection line between the anterior-most point of anterior falx and the posterior-most point of posterior falx. Another parallel line passing through the septum pellucidum is plotted (dotted line), the midline shift can then be measured as the distance between these 2 lines ('C') [159]. Displacement of brain tissue across the IML of 0 to 3 mm was associated with alertness, 3 to 4 mm with drowsiness, 6 to 8.5 mm with stupor, and 8 to 13 mm with coma [160]. Most traumatic brain lesions including epidural, subdural, and ICH associated with a midline shift of 5 mm or more are surgically evacuated [161]. In patients with spontaneous ICH, several studies have shown that an increased midline shift was significantly associated to haematoma expansion and the formation of PHO, and this clinical condition might lead to secondary brain injury and poor clinical outcomes [135][153][162].

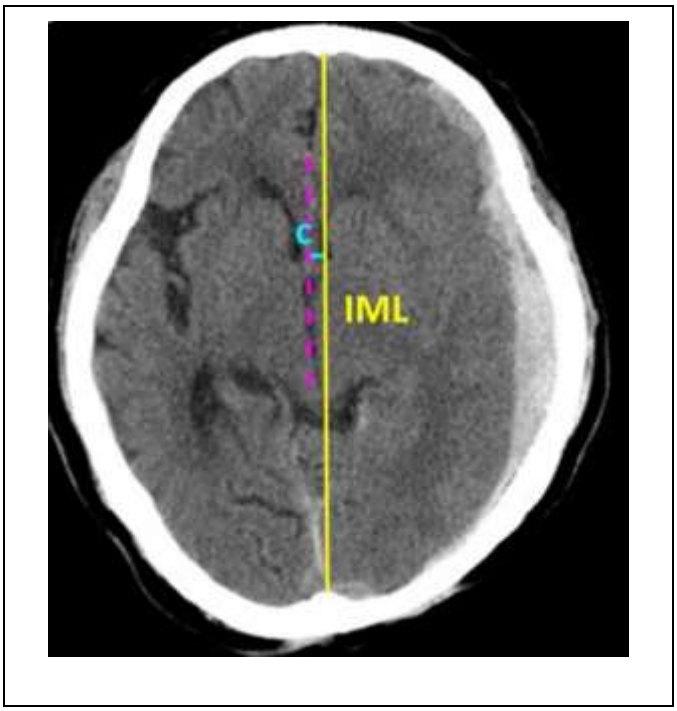


Figure 1-9: Measurement of midline shift. IML = ideal midline, C = midline shift

1.9 The Area of Uncertainty in Imaging Prediction of Haematoma Expansion and PHO

Spontaneous ICH remains the most devastating form of stroke with more than 40% 30-day mortality worldwide [163], notwithstanding of huge efforts in clinical trials to investigate and evaluate the principal independent predictor of haematoma expansion in order to develop future therapeutic strategies. Haematoma expansion, which occurs approximately in one third of patients with spontaneous ICH, is strongly predictive of early neurological deterioration and poor long-term clinical outcomes. However, it is potentially preventable if high-risk patients were identified in the early phase of ICH. Therefore, it is critical to find those haematoma predictors to stratify patients and manage intensive therapies timely and effectively for high-risk patients. Several retrospective studies have identified and investigated particular imaging predictors of haematoma expansion. The appearance of spot sign on CTA brain images has been reported as one of the well establish imaging predictor that might serve as a very efficient and straightforward method to indicate the growth of haematoma in numerous studies [15] [29]–[31][148][164]–[167]. Nonetheless, a spot sign imaging predictor only can be assessed with the use of CTA where iodinated contrast media being introduced into patients' body, while not all patients are eligible for contrast media. In addition, there are several hospitals in which CTA is not available. This unfavourable clinical condition leads to new discoveries and thoroughly studies on potential imaging predictor of haematoma expansion in spontaneous ICH especially on non-enhanced CT brain images.

Recent studies done by Q. Li et al had introduced several reliable imaging predictors to reflect haematoma expansion in spontaneous ICH including blend sign [143][144], black hole sign [168] and island sign [169]. Blend sign have been reported of having strong relationship with haematoma expansion and considered as novel and reliable imaging marker for early haematoma enlargement. Black

hole sign and island sign has also been acknowledged as simple, easy-to-use and reliable CT imaging marker that independently predict haematoma expansion and poor clinical outcome. P. Sporns et al [170] in their study comparing the spot sign, blend sign and black hole sign had confirmed that non-enhanced CT black hole sign and blend sign were correlated with the CTA spot sign and were reliable predictors for poor outcomes in patients with spontaneous ICH.

However, among all studies done previously to investigate a novel imaging marker for haematoma expansion on non-enhanced CT images, there is no single study done on relatively large sample size and described thoroughly which sign or combination of CT signs is the best predictor in predicting early haematoma expansion and how they are likely reflecting active bleeding in acute spontaneous ICH. Their independent contribution to outcome was also not been well explored. In relation with this circumstance, this study would explore and investigate further a sign and a combination of CT signs that reflect haematoma expansion in patients with spontaneous ICH on a relatively large sample size with various ethnicities and patient's background. This study would also examine and identified imaging markers and predictors for haematoma expansion and PHO expansion in patients presenting with spontaneous ICH. To date, there is no single study have been done to assess potential indicators and predictors for PHO enlargement although several studies have suggested PHO expansion is associated with poor prognosis in spontaneous ICH [8]. Accurate prediction of haematoma expansion and PHO expansion in spontaneous ICH patients is very crucial to ensure a reliable prognosis is given to patient as soon as possible and to set realistic rehabilitation goals and allocated resources in the most efficient way.

1.10 Summary

Stroke is considered the most devastating disease that occurs approximately 152000 times a year in the United Kingdom. There are 2 types of stroke: ischaemic stroke and haemorrhagic stroke (spontaneous ICH). There are cases in which

severe haemorrhagic stroke extent the bleeding into the ventricular system. This complication called intraventricular haemorrhage. A number of various imaging characteristic might predict the morbidity and severity of patients with spontaneous ICH including non-contrast CT brain scan, CTA and MRI. CT is the preferred imaging technique for initial evaluation of most stroke patients because of it ubiquitous present and fast screening. Patients with spontaneous ICH are highly indicated by the appearance of contrast extravasation on CTA. MRI is the best imaging modality of choice in detecting small and subtle lesions plus demonstrating microbleeds compared to CT scan. At present, there is no gold standard of care and no specific treatment for acute ICH that is effective to stop haemorrhage in brain parenchyma and improving the recovery stage. There are huge numbers of clinical trials conducted on patients presenting with spontaneous ICH to study the chances of efficient treatments and to provide the most reliable evidence to guide patients' management. The volume of haematoma on baseline scan has been reported to serve as an important study outcome in most clinical trials since it has a strong association to poor prognosis and might predict the risk of haematoma expansion and other potential complications. There are several methods and approaches available for haematoma volume segmentation and SAS technique is considered the gold standard for haematoma volume analysis. The ABC/2 formula is the simplest and easiest way to measure haematoma volume and widely used in clinical setting. Since this formula is highly operator-dependant, it might produce variability in volume measurement when used in large datasets. Other than baseline haematoma volume, there is a critical need to establish imaging predictors of haematoma expansion that are rapidly and easily accessible. Several studies done previously reported that blend sign, black hole sign and island sign could be used as demarcation to initial development of haematoma expansion in patients with spontaneous ICH. However, there is no study done thoroughly describe which signs combination that best predict haematoma expansion.

HYPOTHESES AND OBJECTIVES

Hypothesis

The aim of this study is to address the knowledge gaps highlighted in the previous section (section 1.9). Aforementioned area of uncertainty in imaging prediction of haematoma and PHO have been determined by testing the following hypotheses:

i. SAS technique with manual editing and manual delineation approach using ITK SNAP software are reliable methods for measuring haematoma and PHO volumes respectively in the ENOS trial sample.

ii. ABC/2 formula is a reliable method for haematoma volume analysis in the ENOS trial sample.

iii. Haematoma volume measured by ABC/2 formula provides a close approximation to haematoma volume derived by SAS technique especially in small (< 5cm in axial diameter) and regular shape haematoma and overestimates the haematoma volume particularly in large (> 5cm in axial diameter) and more irregular shape haematoma.

iv. Image reformatting from a thicker slice thickness of 5mm overestimates the haematoma and PHO volumes in the TICH-2 trial predominantly in small size of haematoma and PHO compared to image reformatting from a thinner slice thickness of 1mm.

v. There are significant difference of demographic characteristics, pre-existing pathology, clinical parameters, and time-to-scan between participants with haematoma expansion and without haematoma expansion in the placebo-treated TICH-2 population.

vi. A large volume, shorter time-to-scan, large size, lobar haematoma, irregular shape and heterogenous density of haematoma on baseline CT

brain images are associated with a high risk of haematoma expansion in the placebo-treated TICH-2 population.

vii. Haematoma expansion will be independently predicted by the presence of blend sign, black hole sign or island sign on baseline CT brain images of participants with spontaneous ICH in the placebo-treated TICH-2 clinical trial.

viii. A multivariate prediction for haematoma expansion in the placebo-treated TICH-2 population could be created based on baseline CT imaging characteristics.

ix. There are significant differences in clinical variables, baseline haematoma and PHO volume and the presence of haematoma expansion between participants with and without PHO expansion in the placebo-treated TICH-2 population.

x. A multivariate prediction model for PHO expansion could be developed based on the information of clinical variables, baseline haematoma and PHO volume and haematoma expansion.

xi. The volume of PHO and PHO expansion rate at 24 hours could be an independent predictor for poor clinical outcomes in patients with spontaneous ICH.

Objectives

To reflect to the hypotheses mentioned above in determination of the acquaintance gaps in imaging predictor of haematoma and PHO expansion, the main objective of this research is to study the relationship of the baseline adjudicated imaging characteristics to haematoma and PHO expansion in the TICH-2 population. The specific objectives are as follow:

i. To establish the inter- and intra-observer reliability of SAS approach using ITK-SNAP software with manual editing in haematoma volume analysis and manual delineation of PHO volumes using data from the ENOS trial sample.
ii. To determine the inter- and intra-observer reliability of ABC/2 formula in haematoma volume analysis using data from the ENOS trial sample.
iii. To test whether haematoma volume estimated from ABC/2 formula provides a close approximation of haematoma volume derived by SAS technique in the TICH-2 population, and to examine the effect of size and shape on the agreement between ABC/2 and SAS measurements.
iv. To examine the relationship of image reformatting from different volumetric acquisition slice thicknesses between 5mm and 1mm to haematoma and PHE volume measurements in a sample of the TICH-2 population for whom both slice thicknesses are available.
v. To compare the demographic characteristics, pre-existing pathology, clinical parameters, and time-to-scan between participants with haematoma expansion and without hematoma expansion in the placebo-treated TICH-2 population.
vi. To compare haematoma volume, haematoma size, location, shape and density on baseline CT brain images in the placebo-treated TICH-2 population between those with and without haematoma expansion.

vii. To evaluate the adjudicated baseline imaging features of blend sign, black hole sign and island sign as independent predictors of haematoma expansion in the placebo-treated TICH-2 population.

viii. To develop a multivariate prediction model for haematoma expansion in the placebo-treated TICH-2 population based on adjudicated CT baseline imaging characteristics.

ix. To compare the clinical variables, baseline haematoma and PHO volume and presentation of haematoma expansion for participants with and without PHO expansion.

x. To develop a multivariate prediction model for PHO expansion based on the information of clinical variables, baseline haematoma and PHO volume and the presentation of haematoma expansion.

xi. To assess the probability of PHO volume and PHO expansion rate at 24 hours as an independent predictor for poor clinical outcomes in patients with spontaneous ICH.

Chapter 2 SYSTEMATIC REVIEW

Comparison between SAS Haematoma Volume Analysis and the ABC/2 Formula in Patients with Spontaneous ICH from CT Brain Images

2.1 Introduction

Spontaneous ICH or haemorrhagic strokes occurs when an artery or arteriole bursts within the brain or on the surface of the brain leading to blood leaking out into the brain tissue at high pressure. The mechanical disruption caused by spontaneous ICH can be greater than those caused by ischaemic stroke since the haematoma itself can lead to secondary brain injury resulting in severe neurological deficits [151]. Furthermore, spontaneous ICH are generally more severe and are associated with a considerably higher risk of mortality within 3 months and beyond compared to ischaemic strokes.

The growth of haematoma in patients with spontaneous ICH is known to be a strong predictor for poor neurological outcomes and mortality. The volumes of haematoma as well as the change in the volume of haematomas are used in clinical trials to study the effect of intervention or therapy. The ability to measure the haematoma volumes quickly and easily at bedside is crucial in clinical setting to guide treatments, particularly surgical. On the other hand, in research setting and clinical trials, haematoma volume is used as an outcome measure; hence it is more important that the measurement is accurate to allow high quality research outcomes rather than being quick and simple.

The ABC/2 technique has been performed in clinical and research settings to estimate the volume of ICH since 1980s [171]. The ABC/2 technique is based on ellipsoid volume formula and therefore, haematoma volume calculated by the ABC/2 formula should be close to the true volume in round and ellipsoid shapes of haematomas but may be less accurate for haematomas which are irregular or spiculated [78]. However, despite wide usage, the ABC/2 is extremely operator

dependent, because observers have the freedom to choose the largest haematoma slice and maximal diameter. This situation leads to variability of haematoma volume measurements amongst raters. Hence, it is essential to investigate a more simple, accurate and reliable approach for calculating haematoma volume to meet the requirement for accurately treating patients with spontaneous ICH. The calculation of accurate haematoma volume at admission and its progression during hospitalisation is crucial for clinical prognosis.

A study done by K. Krishnan et al had compared several methods of haematoma volume measurement in spontaneous ICH on CT scanning and test the effect of haematoma shape and regularity on these measures. One of the major findings of this study was an excellent agreement within and between observers for haematoma volume measurement (ABC/2, modified ABC/2 and SAS) [76]. The effectiveness of ABC/2 method has been validated in regular haematomas but its accuracy in measuring the volume of complex irregular haematomas have been doubted. It has been suggested to adjust the dominator from 2 to 3 in standard ABC/2 for irregular shape haematomas to produce more accurate measures, but the study by K. Krishnan et al had reported that the haematoma volumes measured by modified ABC/2 were significantly lower than those measured by ABC/2 and SAS method. Combining these findings and published studies, it may be assumed that as the haematoma became more irregular, the surface area and volume changes more than the largest diameter. Hence, the area of the largest haematoma slice may be more representative of the total haematoma size than its diameter [76]. However, comparison to fully automated segmentation cannot be drawn as the attempt to perform a fully automated haematoma volume measurement was failed, as the software was unable to do segmentation in scans in which slice thicknesses varied. The high agreement of ABC/2 and SAS measurement approach reported in this study had motivate me to test my own reliability of proposed SAS technique in haematoma volume quantification and

compared the result to standard ABC/2 formula for haematomas with different shapes, sizes and locations.

2.2 Aims

This review aims to summarise the literature reporting the correspondence of the widely used ABC/2 formula to SAS volume analysis for haematoma volume estimation of patients with spontaneous ICH as reported in the literature. A secondary aim is to summarise observer reliability measures for ABC/2 and SAS measurements reported by these studies.

2.3 Search Method

A comprehensive literature search of the PubMed, Sciences Direct and Google Scholars databases was conducted by using the key words "spontaneous intracerebral haemorrhage" AND "quantitative" OR "quantification" OR "volumetric" OR "volumetry" OR "segmentation" OR "measurement" AND "Computed Tomography". The search was not limited to a time range. Studies were included if they reported the data on the technique of ICH volume estimation using SAS method and the ABC/2 formula. The inclusion criteria for studies were that they involved adult patients (more than 18 years of age) confirmed as having spontaneous ICH during CT brain imaging. Any other causes of haemorrhage rather than hypertension and amyloid angiopathy were excluded from this systematic review. Following the initial searches and after removal of duplicate studies, screening of potential studies was done by reading the title and abstract of each study. Any studies that did not fulfil the inclusion criteria were excluded from the review. After exclusions based on the title and abstract review, the remaining potential studies were read in full. All these studies were extracted into the data extraction form. For each study, the following information were extracted: author, year, number of participants, mean age, methods of haematoma volumes measurement, mean haematoma volume, deviation of the

ABC/2 and SAS, overestimation of the haematoma volume versus shape of haematoma by ABC/2 formula, haematoma shapes, haematoma locations, percentage of accuracy, intra and inter-observer reliability and reproducibility for each method. At this stage, any single study, which did not meet the inclusion criteria or did not give enough data information were excluded. The study to be included must have a clear explanation of the technique used to measure the haematoma volume and consist of at least two comparable methods of SAS and ABC/2 formula. The mean haematoma volumes obtained in each study for ABC/2 and SAS, and if available the results of the measurement reliability assessment, were extracted. The relationship between haematoma shape and overestimation or underestimation of the ABC/2 volume measurement technique was recorded, if described in the report. The modified Cochrane risk of bias tool was used to assess risk of bias. Bias was assessed as a judgement (high, low, unclear) for individual elements from five domains (sample selection, description of volume quantification methods, performance, reporting, and others).

2.4 Result of the Search

The Prisma flowchart of studies identified by the search is shown on Figure 2-1. From 275 non-duplicate citations screened, only 14 studies met the criteria, covering 2128 patients. Another 18 studies were excluded after full text screening and 2 of them excluded during data extraction. The characteristics of included and excluded studies are shown in sections below.

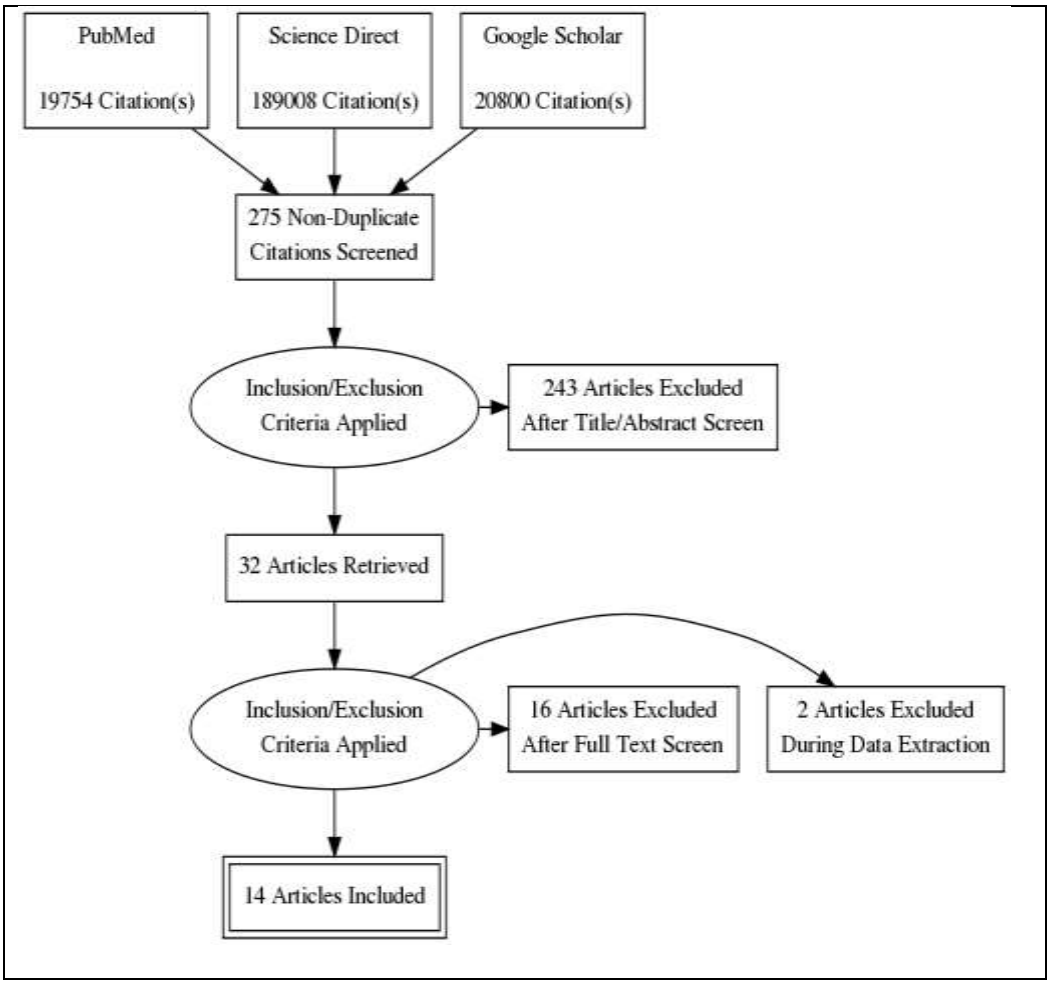


Figure 2-1 Prisma flowchart of search strategy for haematoma volume analysis

2.4.1 Characteristics of Included Studies

There are 14 studies that met the inclusion criteria included in this review. The details of the studies are as follows:-

Table 2-1 Comparison of the ABC Estimation Technique to Computer-Assisted Volumetric Analysis of Intraparenchyma and Subdural Haematomas Complicating the GUSTO-1 Trial

Authors	J.M. Gebel et al [112]
Publication Year	1998
Number of Participants	244
Mean Age	Not given
Study Design	Retrospective study

Objective	To compare the estimation method of haematoma volume to a computer-assisted volumetric analysis in a large series of intracranial haemorrhage.
Outcomes	Correlation between ABC/2 technique and the computer-assisted volumetric technique.
Software used / Measurement Formula	- ABC/2 - SAS (propriety software, Centre for Computer-Assisted Neurosurgery, Cleveland Clinical Foundation, run on Sun Microsystems Spark station)
Included / Excluded	Included

Table 2-2 Haematoma Shape, Haematoma Size, Glasgow Coma Scale Score and ICH Score: Which Predicts the 30-Day Mortality Better for Intracerebral Haematoma

Authors	C. W. Wang et al [172]
Publication Year	2014
Number of Participants	106
Mean Age	62.8 years
Study Design	Retrospective study
Objective	- To investigate the performance of haematoma shape, haematoma size, GCS score and ICH score in predicting the 30-day mortality for ICH patients. - To examine the influence of the estimation error of haematoma size on the prediction of 30-day mortality.
Outcomes	- Haematoma shape - Haematoma size - ICH score - GCS score
Software used / Measurement Formula	- ABC/2 - SAS (MATLAB)
Included / Excluded	Included

Table 2-3 Reliability of Haematoma Volume Measurement at Local Sites in a Multicentre Acute Intracerebral Haemorrhage Clinical Trial

Authors	H. Hussein et al [71]

Publication Year	2013
Number of Participants	56
Mean Age	62 years
Study Design	Retrospective study (analysed data from ATACH trial).
Objective	- To examine the accuracy of haematoma volume measurement using ABC/2 method by multiple investigators. - To assess the impact of utilizing the ABC/2 method in eligibility determination.
Outcomes	- On-site haematoma volume. - Haematoma volume measured at Core Imaging Laboratory. - Central haematoma volume.
Software used / Measurement Formula	- ABC/2 - SAS (MIPAV)
Included / Excluded	Included

Table 2-4 Comparison of ABC/2 Estimation Technique to Computer-Assisted Planimetric Analysis in Warfarin-Related Intracerebral Parenchyma Haemorrhage

Authors	H. B. Huttner et al [70]
Publication Year	2006
Number of Participants	83
Mean Age	Not given
Study Design	Prospective study
Objective	To validate the ABC/2 technique based on analyses of the haematoma shapes in OAT-related ICH.
Outcomes	- Haematoma location - Haematoma shapes - Haematoma volume
Software used / Measurement Formula	- ABC/2 - ABC/3 - SAS (Osiris)
Included / Excluded	Included

Table 2-5 Quantomo : Validation of a Computer-Assisted Methodology for the Volumetric Analysis of Intracerebral Haemorrhage

Authors	J. C. Kosior et al [94]
Publication Year	2011
Number of Participants	30
Mean Age	Not given
Study Design	Prospective study
Objective	To establish the reliability of haematoma volume measurements obtained using a computer-assisted method called Quantomo (for quantitative tomography) and the ABC/2 method.
Outcomes	- ICH volume - Interrater variability - Intrarater variability
Software used / Measurement Formula	- SAS (Quantomo) - ABC/2
Included / Excluded	Included

Table 2-6 Performance Characteristics of Methods for Quantifying Spontaneous Intracerebral Haemorrhage: Data from the Efficacy of Nitric Oxide in Stroke (ENOS) Trial

Authors	K. Krishnan et al [76]
Publication Year	2015
Number of Participants	548
Mean Age	Not given
Study Design	Prospective study (data from ENOS trial)
Objective	To study the performance of haemorrhage descriptors in large clinical trials.
Outcomes	- IVH volume - haematoma volume - haematoma shape - haematoma density
Software used / Measurement Formula	- ABC/2 - Modified ABC/2 - SAS (OsiriX) - Fully automated segmentation (AVC, using 3D rendering of 2D slices)
Included / Excluded	Included

Table 2-7 Haematoma Volumes of Spontaneous Intracerebral Haemorrhage: The Ellipse (ABC/2) Method Yielded Smaller than those Measured using the Planimetric Method

Authors	A. K. Maeda et al [95]
Publication Year	2013
Number of Participants	20
Mean Age	Not given
Study Design	Retrospective study
Objective	To compare two different methods for measuring intracerebral haemorrhage (ICH) volume; the ellipse volume (ABC/2) and software-aided planimetric.
Outcomes	- ICH volume - Intra observer variability rate - Inter observer variability rate
Software used / Measurement Formula	- ABC/2 (DICOM) - SAS (Brain Lab)
Included / Excluded	Included

Table 2-8 Comparison of the Tada Formula with Software Slicer: Precise and Low-Cost Method for Volume Assessment of Intracerebral Haematoma

Authors	X. Xu et al [78]
Publication Year	2014
Number of Participants	294
Mean Age	Not given
Study Design	Retrospective study
Objective	To compare the accuracy of the ABC/2 formula with open-source software Slicer.
Outcomes	- Hematoma volume - Hematoma size - Hematoma shape (regular, irregular, multilobar)
Software used / Measurement Formula	- ABC/2 - SAS (3D Slicer)
Included / Excluded	Included

Table 2-9 The ABCs of Measuring Intracerebral Haemorrhage Volumes

Authors	R. U. Kothari et al [63]
Publication Year	1996
Number of Participants	118
Mean Age	Not given
Study Design	Prospective study
Objective	To compare a bedside method of measuring CT ICH volume with measurements made by computer-assisted planimetric image analysis.
Outcomes	ICH volume
Software used / Measurement Formula	- ABC/2 - SAS (planimetric)
Included / Excluded	Included

Table 2-10 A New Practical Intracerebral Haematoma Volume Calculation Method and Comparison to Simple ABC/2

Authors	F. Cuce et al [173]
Publication Year	2020
Number of Participants	78
Mean Age	Not given
Study Design	Prospective study
Objective	To find more practical and effectuve formula than the simple ABC/2 (sABC/2) to calculate the haematoma volume in patients with subdural and parenchyma haemorrhage.
Outcomes	Haematoma volume
Software used / Measurement Formula	- Simple ABC/2 - SAS (planimetrics)
Included / Excluded	Inlcuded

Table 2-11 Perihematomal Oedema Surrounding Spontaneous Intracerebral Haemorrhage by CT: Ellipsoidal versus Morphometric Volumetry

Authors	J. G. Shulman et al [174]
Publication Year	2020
Number of Participants	154
Mean Age	Not given

Study Design	Retrospective study
Objective	To demonstrate the use of an SAS to generate ICH volumetrics on non-contrast CT of the head and compare this technique to physician's manual calculations.
Outcomes	- ICH volume - PHE volume
Software used / Measurement Formula	- ABC/2 formula - SAS
Included / Excluded	Included

Table 2-12 1/2SH: A Simple, Accurate and Reliable Method of Calculating the Haematoma Volume of Spontaneous Intracerebral Haemorrhage

Authors	B. Zhao et al [82]
Publication Year	2020
Number of Participants	257
Mean Age	Not given
Study Design	Retrospective study
Objective	To find a method that can calculate haematoma volumes accurately, reliably, and quickly.
Outcomes	Haematoma volume
Software used / Measurement Formula	- SAS (3D Slicer) - ABC/2 - Modified ABC/2
Included / Excluded	Included

Table 2-13 Comparison of Intracerebral Haemorrhage Volume Calculation Methods and Their Impact on Scoring Tools

Authors	M. Khan et al [87]
Publication Year	2017
Number of Participants	135
Mean Age	71.06 years
Study Design	Retrospective study
Objective	To compare the original ABC/2 method and simplified ABC/2 (sABC/2) with the planimetric method.

Outcomes	Haematoma volume
Software used / Measurement Formula	- ABC/2 - Simplified ABC/2 - SAS (planimetrics)
Included / Excluded	Included

Table 2-14 Computer-Assisted Volumetric Analysis Compared with ABC/2 Method for Assessing Warfarin-related Intracranial Haemorrhage Volumes

Authors	W. D. Freeman et al [80]
Publication Year	2008
Number of Participants	8
Mean Age	Not given
Study Design	Retrospective study
Objective	To compare 2 methods of measuring ICH volume in patients with warfarin-related ICH (ABC/2 vs SAS).
Outcomes	Haematoma volume
Software used / Measurement Formula	- ABC/2 - SAS (Analyze 6.0)
Included / Excluded	Included

2.4.2 Characteristics of Excluded Studies

There are 18 studies excluded from this review because they have not met the inclusion criteria. The details of the studies are as follows:-

Table 2-15 Volume of Intracerebral Haemorrhage: A Powerful and Easy-to-Use Predictor of 30-Day Mortality

Authors	J. P. Broderick et al [75]
Publication Year	1993
Number of Participants	188
Mean Age	Not given
Study Design	Retrospective study
Objective	To determine the 30-day mortality and, morbidity of ICH in a large metropolitan population.

	To determine the most important predictors of 30-day outcome
Outcomes	- Haemorrhage volumes - GCS
Software used / Measurement Formula	- Ellipsoid - (4/3 π abc) a, b and c represent the respective radius in 3 dimensions
Included / Excluded	Excluded (no comparison to computer-assisted)

Table 2-16 The ABCs of Accurate Volumetric Measurement of Cerebral Haematoma

Authors	A. A. Divani et al [79]
Publication Year	2011
Number of Participants	Used plastic and cadaveric phantoms
Mean Age	Not given
Study Design	In-vitro
Objective	To determine the accuracy of different CT protocols and haematoma volume measurement techniques - planimetry - ABC/2 - 3 D rendering
Outcomes	Haematoma volume of regular and irregular shape
Software used / Measurement Formula	- MIPAV – planimetry - Analyze – image segmentation and volume rendering - ABC/2 (when the values of π is approximated to 3) - ABC/2 with adjusted C values
Included / Excluded	Excluded (study on phantom)

Table 2-17 CTA Spot Sign Predicts Haematoma Expansion in Patients with Delayed Presentation after Intracerebral Haemorrhage

Authors	H. B. Brouwers et al [167]
Publication Year	2012
Number of Participants	391

Mean Age	71.9 years
Study Design	Retrospective analysis from ongoing cohort study
Objective	To investigate the prevalence of haematoma expansion and assessed the accuracy of the CTA spot sign for identifying of haematoma expansion
Outcomes	- Mortality and functional outcome – mRs - ICH volume - IVH volume
Software used / Measurement Formula	- Alice (PAREXEL International Corporation) - Analyze 9.0 (Mayo Clinic)
Included / Excluded	Excluded (no comparison to ABC/2 formula)

Table 2-18 Assessment of the ABC/2 Method of Epidural Haematoma Volume Measurement as Compared to Computer-Assisted Planimetric Analysis

Authors	T.-T. Hu et al [72]
Publication Year	2015
Number of Participants	35
Median Age	32.6 years
Study Design	Prospective cohort study
Objective	To determine the accuracy and reliability of the widely used volume measurement method ABC/2 in estimating epidural haematoma volume (EDHV) by comparing it to the computer-assisted planimetric method
Outcomes	- Haematoma volume - Haematoma shape
Software used / Measurement Formula	- ABC/2 - Planimetric - ITK SNAP 3.0.0 (2 D and 3D visualization)
Included / Excluded	Excluded (epidural haematoma)

Table 2-19 ABC/2 Estimating Intracerebral Haemorrhage Volume and Total Brain Volume and Predicting Outcome in Children

Authors	J. T. Kleinman et al [74]
Publication Year	2010
Number of Participants	23

Median Age	6 years
Study Design	Retrospective hospital-based cohort study
Objective	- To develop a bedside method of total brain volume (TBV) estimation using typical hospital imaging software - To validate the ABC/2 method for children in order to determine ICH volume and aid prognosis
Outcomes	- ICH volume - Interrater reliability
Software used / Measurement Formula	ABC/2 – volume estimation XYZ/2 – TBV estimation
Included / Excluded	Excluded (no comparison to computer-assisted method, children)

Table 2-20 Perinephric Haematoma : Computer-Assisted Quantification of Volume on MDCT: A Feasibility Study

Authors	P. Rezai et al [175]
Publication Year	2011
Number of Participants	63
Median Age	49 years
Study Design	Retrospective study
Objective	To evaluate feasibility and reproducibility of quantification of perinephric haematoma volume on multidetector-row CT (MDCT)
Outcomes	Perinephric haematoma volume
Software used / Measurement Formula	CT oncology, Siemens Medical Solution
Included / Excluded	Excluded (perinephric haematoma)

Table 2-21 Comparison of Haematoma Shape and Volume Estimates in Warfarin versus Non-Warfarin Intracerebral Haemorrhage

Authors	K. N. Sheth et al [81]
Publication Year	2010
Number of Participants	50
Age Range	67 – 83 years

Study Design	Case control analysis of prospective cohort
Objective	To examine hematoma shape and methods of volume assessment in patients with OAT-ICH
Outcomes	- Haematoma shape (regular and irregular) - Haematoma volume
Software used / Measurement Formula	- ABC/2 - ABC/3
Included / Excluded	Excluded (no comparison to computer-assisted method)

Table 2-22 The Value of XYZ Technique Compared with Computer-Assisted Volumetric Analysis to Estimate the Volume of Chronic Subdural Haematoma

Authors	H. K. Sucu et al [92]
Publication Year	2005
Number of Participants	22
Mean Age	Not given
Study Design	Retrospective
Objective	To determine the value of XYZ/2 method to estimate the volume of chronic subdural haematoma when compared with computer-assisted volumetric analysis.
Outcomes	Chronic subdural haematoma volume
Software used / Measurement Formula	5 different XYZ/2 formulas (1) XY1 Z1 /2 (2) XY2 Z2 /2 (3) XY2 Z3 /2 (4) XY3 Z4 /2 (5) XY1 Z4 /2 - DICOM work
Included / Excluded	Excluded (subdural hematoma)

Table 2-23 Early Intracerebral Haematoma Expansion after Aneurysmal Rupture

Authors	C. J. J. van Asch et al [176]
Publication Year	2010
Number of Participants	49

Mean Age	54.6 years
Study Design	Prospective study
Objective	To study how often haematoma expansion in patients with ICH from a ruptured aneurysm is caused by re-rupture of the aneurysm.
Outcomes	- Haematoma expansion - Haematoma volume
Software used / Measurement Formula	ABC/2
Included / Excluded	Excluded (no comparison to computer-assisted method)

Table 2-24 Radiologic Estimation of Haematoma Volume in Intracerebral Haemorrhage Trial by CT Scan

Authors	R. D. Zimmerman et al [93]
Publication Year	2006
Number of Participants	399
Age Range	>18 years
Study Design	Prospective study
Objective	- To examine the use of CT to quantify haematoma volume in patients with intracerebral haemorrhage - To evaluate the expansion/ extension of haematomas by using established software packages
Outcomes	- ICH, IVH and oedema volumes - Intraclass variability
Software used / Measurement Formula	Analyze
Included / Excluded	Excluded (no comparison with ABC/2 formula)

Table 2-25 Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT): A Randomised Pilot Trial

Authors	C. S. Anderson et al [36]
Publication Year	2008
Number of Participants	404

Age Range	> 18 years
Study Design	Randomised pilot trial
Objective	To assess the safety and efficiency of the treatment, as a run-in phase to a larger trial.
Outcomes	Primary - Proportional change in haematoma volume Secondary – other measurements of hematoma volume
Software used / Measurement Formula	- ABC/2 - Computer assisted multislice planimetric and voxel threshold (MIStar version 3.2)
Included / Excluded	Excluded (no comparison between ABC/2 and planimetric measurements)

Table 2-26 Effect of Celecoxib on Haematoma and Oedema Volumes in Primary Intracerebral Haemorrhage: A Multicentre Randomised Controlled Trial

Authors	S. H. Lee et al [105]
Publication Year	2013
Number of Participants	44
Mean Age	63.5 years
Study Design	Multicentre, randomized, controlled and open with blinded end-point trial
Objective	To investigate the effect of celecoxib, a selective inhibitor of cyclo-oxygenase 2 in patients with ICH
Outcomes	Primary – number of patients with a change in the volume of PHE as assessed by CT Secondary – expansion rates in PHE and ICH volumes
Software used / Measurement Formula	SAS (Image J)
Included / Excluded	Excluded (no comparison with ABC/2 formula)

Table 2-27 Computer-Assisted Volumetric Assessment of Perihaemorrhagic Oedema with Computed Tomography

Authors	B. Volbers et al [115]
Publication Year	2011
Number of Participants	49

Age Range	46-89 years
Study Design	Prospective study
Objective	To establish and validate an observer independent method for quantification of PHO on CT by comparing with simultaneously performed MRI
Outcomes	Volume for PHO and ICH
Software used / Measurement Formula	MRI volumetry Manual CT volumetry Computer-assisted CT volumetry
Included / Excluded	Excluded (no comparison with ABC/2 formula)

Table 2-28 Planimetric Haematoma Measurement in Patients with Intraventricular Haemorrhage: Is Total Volume a Preferred Target for Reliable Analysis?

Authors	D. Dowlatshashi et al [124]
Publication Year	2013
Number of Participants	20
Age Range	Not given
Study Design	Retrospective study
Objective	To evaluate the reliability of computer-assisted planimetric volume measurements of IVH
Outcomes	- IVH volume - Inter-rater reliability - Inta-rater reliability
Software used / Measurement Formula	SAS (Quantomo)
Included / Excluded	Excluded (IVH))

Table 2-29 Automated Assessment of Haematoma Volume of Rodents Subjected to Experimental Intracerebral Haemorrhagic Stroke by Bayes Segmentation Approach

Authors	Z. Zhang et al [177]
Publication Year	2020
Number of Participants	In-vitro
Age Range	-
Study Design	Experimental study

Objective	To develop an automated method that can accurately and efficiently obtain unbiased cerebral haematoma volume.
Outcomes	Haematoma volumes
Software used / Measurement Formula	Automated segmentation (MATLAB)
Included / Excluded	Excluded (animal model)

Table 2-30 Comparison of Common Methods for Precision Volume Measurement of Haematoma

Authors	M. Chen et al [178]
Publication Year	2020
Number of Participants	198
Mean Age	Not given
Study Design	Retrospective study
Objective	To conduct analysis and comparison of some methods commonly used to measure the volume of haematoma, for example, slice method, voxelization method, and 3D slicer software method (projection method).
Outcomes	Haematoma volume
Software used / Measurement Formula	- Slice method - Voxelization method - 3D Slicer method
Included / Excluded	Excluded (no comparison to ABC/2 formula)

Table 2-31 Intracerebral Haemorrhage Volume Estimation: Is Modification of the ABC/2 Formula Necessary According to the Haematoma Shape?

Authors	D.D. Oge et al [179]
Publication Year	2021
Number of Participants	133
Age Range	66 years
Study Design	Retrospective study
Objective	To modify the ABC/2 formula to ABC/3 for irregular-shaped ICH volume estimation.

Outcomes	ICH volume
Software used / Measurement Formula	- ABC/2 - ABC/3
Included / Excluded	Excluded (no comparison to SAS)

Table 2-32 Three-Dimensional Reconstruction of Intracranial Haemorrhage and its Mass Effect

Authors	H. M. Strik et al [180]
Publication Year	2005
Number of Participants	12
Mean Age	68 years
Study Design	Retrospective study
Objective	To investigate whether 3D, voxel-based volumetry of the haemorrhage and its mass effect is feasible with routine CT scans.
Outcomes	Volumes of haematoma, ventricles, midline shift, intracranial volume, and ventricular compression.
Software used / Measurement Formula	3D-voxel-based volumetry
Included / Excluded	Excluded (no comparison to ABC/2 formula)

Table 2-33 Fully Automated Segmentation Algorithm for Haematoma Volumetric Analysis in Spontaneous Intracerebral Haemorrhage

Authors	N. Ironside et al [181]
Publication Year	2019
Number of Participants	3000
Mean Age	Not given
Study Design	Prospective study
Objective	- To derive and validate a fully automated segmentation algorithm for ICH volumetric analysis using deep learning methods.
Outcomes	Haematoma volume
Software used / Measurement Formula	- Fully automated segmentation - SAS - Manual segmentation

Included / Excluded	Excluded (no comparison to ABC/2 formula)

2.5 Result of Data Extraction

There are 14 papers looking at the estimation discrepancies and reliability assessment of SAS and the ABC/2 techniques in haematoma volume analysis included in this review. The techniques of haematoma volume analysis used in each study are shown in Table 2-34. There are 11 studies that calculated a measurement with the use of both SAS and the ABC/2 formula, 1 study used all 4 methods of volumes measurement (SAS, ABC/2, modified ABC/2 and fully automated) and 2 studies performed the volume measurement using 3 quantification techniques (SAS, ABC/2 formula and modified ABC/2 technique).

The ABC/2 formula overestimated the haematoma volume in 9 studies compared to SAS with average of 8.8 mL (Table 2-35), typically in irregular (34.6%) and spiculated (34.5%) shapes of haematoma as demonstrated in Table 2-36. All patients in selected studies have different locations of intracerebral haematoma. The most common locations of haematoma are deep haemorrhage (62%), followed by lobar (19.5%), cerebellum (9.5%) and brain stem (9%). However, not all included studies reported the locations of haematoma.

Table 2-34 Methods of haematoma volume measurement of selected studies

Authors	Year	Sample (n)	Methods of Haematoma Volume Estimation
A. K. Maeda et al [95]	2013	20	SAS + ABC/2 Formula
C. W. Wang et al [172]	2014	106	SAS + ABC/2 Formula
H. Hussein et al [71]	2013	56	SAS + ABC/2 Formula
H. B. Huttner et al [70]	2006	83	SAS + ABC/2 Formula

J. M. Gebel et al [112]	1998	244	SAS + ABC/2 Formula
J. C. Kosior et al [94]	2011	30	SAS + ABC/2 Formula
K. Krishan et al [76]	2015	548	SAS + ABC/2 + Modified ABC/2+Fully Automated
R. U. Kothari et al [63]	1996	118	SAS + ABC/2 Formula
X. Xu et al [78]	2014	294	SAS + ABC/2 Formula
F. Cuce et al [173]	2020	78	SAS + ABC/2 + Modified ABC/2
J. G. Shulman et al [174]	2020	154	SAS + ABC/2 Formula
B. Zhao et al [82]	2020	257	SAS + ABC/2 Formula
M. Khan et al [87]	2017	135	SAS + ABC/2 + Modified ABC/2
W. D. Freeman et al [80]	2008	5	SAS + ABC/2 Formula

Table 2-35 Mean haematoma volume and deviation of the ABC/2method vs. SAS technique

Authors	Mean Haematoma Volume (mL)				Deviation of ABC/2 vs SAS (mL)	ABC/2 vs SAS haematoma volume measurement	Correlation Coefficient
	Semi-Auto	ABC/2	Fully Auto	Modified ABC/2			
A. K. Maeda et al [95]	15.04	12.8	-	-	(-) 2.24 (p< 0.001)	underestimate	0.984 (p <0.001)
C. W. Wang et al [172]	27.8	38.7	-	-	(+) 10.9 (p <0.001)	overestimate	0.965 (p <0.001)
H. Hussein et al [71]	13.9	14.75	-	-	(+) 0.85 (p <0.001)	overestimate	0.63 -
H. B. Huttner	36.6	40.83	-	-	(+) 4.23	overestimate	-

Authors	Mean Haematoma Volume (mL)				Deviation of ABC/2 vs SAS (mL)	ABC/2 vs SAS haematoma volume measurement	Correlation Coefficient
	Semi-Auto	ABC/2	Fully Auto	Modified ABC/2			
et al [70]					-		
J. M. Gebel et al [112]	63.3	68.7	-	-	(+) 5.4 -	overestimate	0.929 -
J. C. Kosior et al [94]	33.1	48.0	-	-	(+) 14.9 -	overestimate	-
K. Krishan et al [76]	12.4	11.9	-	9.3	(-) 0.5 (p <0.001)	underestimate	-
R. U. Kothari et al [63]	31.7	34.4	-	-	(+) 2.7 -	overestimate	0.96 -
X. Xu et al [78]	50.38	58.41	-	-	(+) 8.03 (p < 0.01)	overestimate	-
F. Cuce et al [173]	58.95	50.16	-	60.09	(-) 8.51 -	underestimate	-
J. G. Shulman et al[174]	13.9	36.0	-	-	(+) 22.1 -	overestimate	-
B. Zhao et al [82]	32.37	42.49	-	-	(+) 10.12 (p< 0.001)	overestimate	-

Authors	Mean Haematoma Volume (mL)				Deviation of ABC/2 vs SAS (mL)	ABC/2 vs SAS haematoma volume measurement	Correlation Coefficient
	Semi-Auto	ABC/2	Fully Auto	Modified ABC/2			
M. Khan et al [87]			-	-	(-) 7.29	underestimate	-
W. D. Freeman et al [80]	71.2	69.8	-	-	(-) 1.4	underestimate	-

Table 2-36 Overestimation of haematoma volume vs. shape of haematoma for ABC/2 formula

Authors	Overestimation of ABC/2		
	Regular	Irregular	Spiculated
A. K. Maeda et al [95]	6.68%	14.85%	32.11%
C. W. Wang et al [172]	-	-	-
H. Hussein et al [71]	-	-	-
H. B. Huttner et al [70]	6.69%	14.85%	32.11%
J. M. Gebel et al [112]	-	-	-
J. C. Kosior et al [94]	21.36%	90.35%	-
K. Krishan et al [76]	-	-	-
R. U. Kothari et al [63]	-	-	-
X. Xu et al [78]	9.76%	18.37%	39.12%
F. Cuce et al [173]	-	-	-
J. G. Shulman et al [174]	-	-	-
B. Zhao et al [82]	-	-	-
M. Khan et al [87]	-	-	-
W. D. Freeman et al [80]	-	-	-
Average	11.1%	34.6%	34.5%

Table 2-37 Inter- and intra-observer reliability of SAS and ABC/2 technique

Authors	Inter-observer Reliability	Intra-observer Reliability	Type of Agreement Test

	Semi-auto	ABC/2	Semi-Auto	ABC/2	
J. C. Kosior [94]	0.99	0.98	0.99	0.90	ANOVA
K. Krishnan [76]	0.985	0.965	0.93	0.88	ICC
R. U. Kothari [63]	0.99	0.99	0.99	0.99	ICC

Three studies reported a high accuracy of the ABC/2 formula as compared with the SAS technique as gold standard [63][70][78] while 1 study showed a vice versa [172]. Intra-observer reliability of SAS and the ABC/2 method that reported by J. C. Kosior et al [94] was 0.99 and 0.90 respectively, by K. Krishnan et al [76] was 0.93 and 0.88 respectively, while R. U. Kothari et al [63] reported intra-observer reliability of 0.99 for both estimation techniques. The inter-observer reliability of both SAS and the ABC/2 method was 0.99 and 0.98 (J. C. Kosior et al), 0.985 and 0.965 (K. Krishnan et al) and 0.99 for both (R. U. Kothari et al) respectively as demonstrated on Table 2-37.

2.6 Interpretation

Fourteen relevant studies have been identified that fulfil the search criteria (details of the studies were described on 2.4.2). Studies used different methods of haematoma segmentations and reported different valuable findings regarding the performance of each method. All studies gave a clear definition of patients selected, the variables measured and the relevant study outcomes.

In general, the ABC/2 formula tends to overestimate the haematoma volume in 9 studies [63][70][71][78][82][94][112][172][174] compared to the computer-aided segmentation method and modified ABC/2 method. Haematoma volumes computed by modified ABC/2 method were significantly smaller than the volumes

computed using the ABC/2 formula and computer-aided approach [76]. In the modified ABC/2 method, the area of haematoma seen on a slice has to be at least 25% of the largest haematoma. If the area of haematoma is more than 75%, the slice counts as 1 and if the measured value of the area is between 25% and 75%, the slice counts as 0.5 [76]. While in the ABC/2 estimation formula, all slices showing haematoma are taken into account in haematoma volume quantification. However, the largest diameter is measured only in the axial plane, which might not be the largest diameter of haematoma. This circumstance becomes one of the disadvantages of the ABC/2 formula in accurately assessing the haematoma volume. The variance of volume measured became larger when there was an increased haematoma size and when haematoma was more irregular and spiculated in shape. This findings were significantly showed in four studies [70][78][94][95]. One study only categorized the haematoma shape into regular and irregular [94], but this also showed that irregularity led to a huge overestimation of haematoma volume derived by ABC/2 formula.

A relationship between the shapes of haematoma and the haematoma volumes measured is considered an important consideration in research regarding intracerebral haemorrhage since this data will guide the decision of selecting the best and reliable technique of haematoma volume estimation. In addition, the shapes of haematoma are varied from regular to irregular and spiculated. It can be said that most of selected studies in this systematic review did not report this vital information.

The study done by K. Krishnan et al [76] is considered the first study in comparing 4 different methods of estimating haematoma volumes and intraventricular haemorrhage. However, from total of 548 patients, only 5% of them (23 patients) had scans that were amenable to being measured by a fully automated technique because of varying CT slice thickness which the software was unable to work with. The attempt to compare 4 different methods of haematoma volume

measurements is a good effort to clearly demonstrate the performance of each single technique in accurately and precisely measuring the haematoma volume.

H. Hussein et al [71] in their study has determined the accuracy of ABC/2 method as an on-site test in comparison with the gold standard central haematoma volume assessment and semi-automatic volume measurement. This study analysed the data from an acute multicentre clinical trial (ATACH)[182]. To determine the eligibility, on-site haematoma volume was measured by the site investigator using the ABC/2 method on the initial CT brain scan. For central ABC/2 assessment, haematoma volume was remeasured independently using haematoma volume calculator. Central ABC/2 was performed to differentiate the error of ABC/2 formula and the inaccuracy of on-site ABC/2 as well as to identify haematoma characteristics that may contribute to inaccuracy of on-site ABC/2. On-site haematoma volumes were measured by multi observers with varying level of experience, while the central haematoma volumes were measured by a single experienced observer. In general, both on-site ABC/2 and central ABC/2 method overestimated haematoma volume, which is in agreement with previous studies. This study stated that the location (lobar vs. deep) of haematoma affected the accuracy of haematoma volume measurement but they did not report in detail the relationship between haematoma volume and haematoma location with a proof of statistical analysis. The discrepancy of haematoma volume measurement in different shapes of haematoma was also not reported in this study.

Only three of the studies identified in the literature search reported inter and intra-observer reliability of SAS method and the ABC/2 formula [63][76][94]. These studies reported the reliability of the quantification method using intraclass correlation coefficient (ICC) assessment and a two-way random-effects analysis of variance (ANOVA). The ICC is a descriptive statistic that can be used when quantitative comparisons are made on units that are organized into groups. It describes how strongly units in the same group resemble each other. The ICC

interpretation using a number, usually found to have a value between 0 and 1 [183]. Based on 95% confidence interval of the ICC estimate, values less than 0.5 were indicative for poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability, and values greater than 0.90 indicate excellent reliability [184]. 95% limit of agreement was used, and a value of $p < 0.05$ was considered statistically significant. For SAS, inter-observer reliability ranged from 0.985 to 0.99 and for intra-observer reliability ranged from 0.93 to 0.99. Whereas for ABC/2 formula, the inter-observer reliability ranged from 0.965 to 0.99 and intra-observer reliability ranged from 0.88 to 0.99. There was an excellent correlation between both techniques with a high inter- and intra-observer reliability, in which it can be said that both techniques were equally reliable in measuring the haematoma volume. However, the rest of the selected studies did not report the reliability of each technique used in haematoma volume analysis. This is a limitation of these research studies and may be relevant to the variability in research outcomes of the studies.

Since the measurement of haematoma from CT brain images is an independent prognostic factor and may have relevance for treatments selection, the use of SAS technique could be useful for physicians or researchers involved in the treatment or investigation of intracerebral brain haemorrhage and still considered as a gold standard in haematoma volume analysis. Nevertheless, this systematic review involved only small number of studies, hence the data provided were not strong enough to answer the main research question. There were also some limitations in this systematic review where only the published articles were included in the review and the authors were not contacted to obtain the original data. This might contribute to publication and reporting bias. Furthermore, a literature search only identified English language studies with a potential language bias.

2.7 Summary

This systematic review of published data is conducted to address the research question: In patients with spontaneous ICH, does a widely used ABC/2 formula provides a close approximation and reliability of haematoma volume measurement to SAS method? Fourteen eligible studies reported valid comparison of haematoma volume quantification between semi-automated segmentation and the ABC/2 formula. The studies varied from 5 [80] to 548 [76] samples and majority of studies only reported summary estimates of association or mean agreement. Compared to measurements by SAS, haematoma volumes measured with the ABC/2 formula tended to increase as the haematoma size increases and the haematoma shape becomes irregular and spiculated. The deviation under certain conditions of ABC/2 measurements from measurements by SAS (which in theory provide closer estimation of the ground truth haematoma volume) combined with the slightly greater inter- and intra-observer reliability of SAS, favour the use of SAS if this is feasible in the setting where measurements are being made. This systematic review has some limitations in the potential for publication, language, and reporting biases. Even the total number of participants across all studies (n = 2128) suggesting sufficient homogeneity to undertake a meta-analysis, but there are not enough statistical data available. There were only 3 studies reporting on reliability, in which 1 study used ANOVA and the rest 2 studies used ICC without detailed explanation on the types of ICC used, make it not possible to run meta-analysis.

Chapter 3 SYSTEMATIC REVIEW

Perihaematomal Oedema Volume Segmentation in Patients with Spontaneous ICH

3.1 Introduction

Spontaneous ICH is considered the most severe form of stroke with a high mortality and morbidity rate. The progression of ICH generally consists of three distinct stages; initial bleeding, haematoma expansion and the development of perihaematomal oedema (PHO) around the haematoma [13]. PHO is often seen in patients with ICH and causes mass effect on adjacent brain structures, elevation in intracranial pressure, hydrocephalus or brain herniation often leading to clinical deterioration [185]. PHO growth is associated with decline in neurological examination during hospitalisation [186] and is related to death or dependency at 90 days [116][187]. Therefore, the quantification of PHO is important for research and therapies that may affect the PHO volume. However, PHO delineation on CT brain images is a challenging task since the exact differentiation between PHO and normal brain parenchyma may be difficult because of unclear boundaries and overlap of CT density values of oedematous and normal brain tissue [115][187]. This is particularly problematic if there is pre-existing brain pathology resulting in low parenchyma densities such as white matter chronic small vessels diseases.

PHO has been reported as having an association with ICH prognosis. Therefore, a reliable method for PHO segmentation and volume measurement has become a beneficial tool in research setting. However, despite many years of research relating to the practical and reliable measurement of ICH, far less attention has been paid to the measurement of PHO. Hence, while clinicians and neuroradiologist often note the presence of PHO, they do not typically quantify it or calculate volumes in daily clinical practice. There are numerous methods available to measure the volume of PHO on CT images ranging from linear manual

segmentation, ABC/2 formula, SAS method and fully automated measurement. These different types of measurement methods offer various levels of performances, accurateness, reliability, and reproducibility rate as well as calculation time. Presently, there is no gold standard in PHO segmentation and the most widely used method in PHO volume estimation is manual tracing. Manual segmentation method consumes a lot of time and greatly depends on operator. Thus, the SAS segmentation is commonly preferred to manual method because of its faster speed and is not generally operator dependent as various approaches based on different parameters have been proposed [188]. However, the selection of the parameters, which is in the hand of the operator (unless a strict pre-defined protocol is followed), can introduce a degree of operator dependence.

3.2 Aims

The main objective of this review is to identify the different methods used for PHO segmentation on CT scan images in people with spontaneous ICH, and to summarise and compare the observer reliability characteristics of these methods.

3.3 Search Method

A systematic review of the literature was conducted using secondary data analysis of published studies and therefore, ethical approval and data protection permissions were not required. All available studies including retrospective, prospective, cohort studies or clinical trials if eligible were included in this systematic review. There were several criteria for inclusion; adult patients $\geq$ 18 years of age who had diagnosed with spontaneous ICH with CT imaging modality and underwent PHO segmentation and volume assessment using any available method on CT brain images. The exclusion criteria were ICH resulted from other causes rather than hypertension and amyloid angiopathy. The exclusion criteria were also including the study of patients with evidence of subdural haemorrhage, patients with ICH after head trauma and ICH related to tumours. The studies run

on cadaveric phantoms or animals were also excluded. Potential studies were search via electronic database; PubMed, Sciences Direct and Google Scholars using different combination of appropriate keywords as "perihaematomal oedema" AND "quantitative" OR "quantification" OR "volumetric" OR "volumetry" OR "segmentation" OR "measurement" AND "Computed Tomography". Further relevant papers were identified by screening the reference list, related articles, and citation list of each of the paper acknowledge in the initial searches. For duplicated papers, only main papers or the most informative study was chosen to include in the review. Initial screening of the potential studies to be included was done by reading their abstracts and the final chosen studies were read in full. Types of outcomes measured in potential studies were related to the methodology for measuring PHO on CT images in term of their definitions for identifying boundaries of PHO, optimal threshold of images for PHO segmentation and the technique used in oedema volume measurement. Performance characteristics of each segmentation method were also analysed, and this element consist of the reliability of each technique compared to manual segmentation as gold standard, and the reproducibility of PHO assessment. Figure 3-1 shows a prism flowchart of relevant studies searched. There are 25 articles included in this review that consist of 1899 patients with spontaneous ICH.

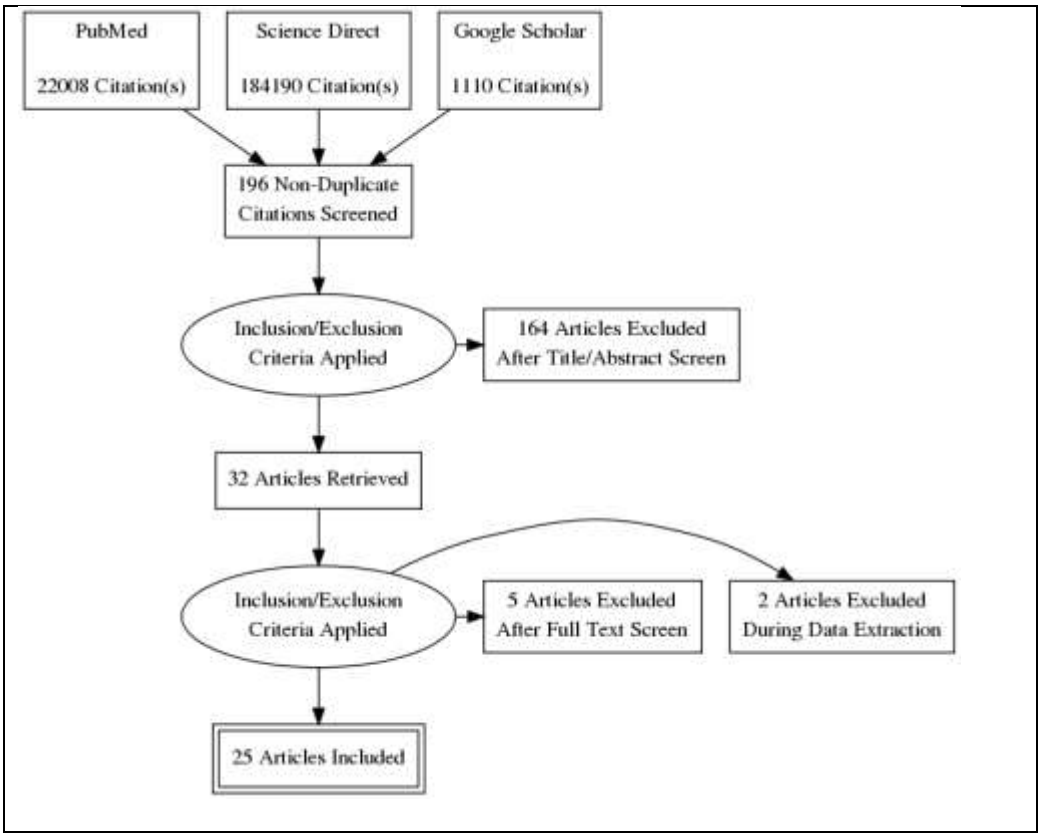


Figure 3-1 Prisma flowchart of relevant studies searched for PHO volume segmentation

3.4 Result of the Search

3.4.1 Characteristics of Included Studies

There are 25 studies that met the inclusion criteria included in this review. The details of the studies are presented on the tables below (Table 3-1 - Table 3-25).

Table 3-1 Semi-automated Method for Brain Haematoma and Oedema Quantification using CT

Authors	A. Bardera et al [101]
Publication Year	2009
Number of Participants	18
Mean Age	Not given
Study Design	Experimental study

Objective	To propose SAS approach for brain haematoma and oedema quantification on CT image
Outcomes	Haematoma and oedema volume
Method of Segmentation	SAS + ABC/2 method
Included / Excluded	Included

Table 3-2 Association of Serum Glucose Concentrations during Acute Hospitalisation with Haematoma Expansion, Perihematomal Oedema, and Three-Month Outcome Among Patients with Intracerebral Haemorrhage

Authors	A. I. Qureshi et al [189]
Publication Year	2011
Number of Participants	60
Mean Age	62 years
Study Design	Post-hoc analysis
Objective	To explore the relationship between various parameters of serum glucose concentrations measured during acute hospitalisation and haematoma expansion, PHO and 3-month outcome among subjects with ICH.
Outcomes	- Serum glucose concentration - Haematoma and PHO volume
Method of Segmentation	ABC/2 method
Included / Excluded	Included

Table 3-3 Semi-automatic Volumetric Assessment of Perihaemorhagic Oedema with Computed Tomography

Authors	B. Volbers et al [115]
Publication Year	2011
Number of Participants	49
Mean Age	70 years
Study Design	Prospective study
Objective	To establish and validate an observer independent method for quantification of PHO on CT by comparing with simultaneously performed MRI.
Outcomes	PHO volume
Method of Segmentation	SAS + ABC/2 method

Included / Excluded	Included

Table 3-4 Effects of Early Intensive Blood Pressure-Lowering Treatment on the Growth of Haematoma and Perihematomal Oedema in Acute Intracerebral Haemorrhage

Authors	C. S. Anderson et al [35]
Publication Year	2010
Number of Participants	270
Mean Age	62.5 years
Study Design	Prospective study
Objective	To determine the effects of treatment on haematoma and PHO over 72 hours.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-5 Perfusion CT Hyperacute Cerebral Haemorrhage within 3 Hours after Symptom Onset: Is There an Early Perihaemorrhagic Penumbra?

Authors	C. Herweh et al [190]
Publication Year	2010
Number of Participants	17
Median Age	71
Study Design	Prospective study
Objective	To clarify whether there exists an early reduction of cerebral perfusion in the perihaemorrhagic area in patients presenting with hyperacute ICH < 3 hours after symptom onset.
Outcomes	ICH size and PHO volume
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-6 CT Perfusion Mapping of Hemodynamic Disturbances Associated to Acute Spontaneous Intracerebral Haemorrhage

Authors	E. Fainardi et al [191]
Publication Year	2008
Number of Participants	89

Mean Age	68.1 years
Study Design	Prospective study
Objective	To quantify perfusion changes associated to acute spontaneous ICH by means of CT perfusion imaging.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	ABC/2 method
Included / Excluded	Included

Table 3-7 Significance of Perihematomal Oedema in Acute Intracerebral Haemorrhage

Authors	H. Arima et al [187]
Publication Year	2009
Number of Participants	270
Mean Age	63 years
Study Design	Prospective study
Objective	To determine the predictors and prognostic significance of PHO over 72 hours after ICH.
Outcomes	Haematoma and PHO volume
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-8 Natural History of Perihaematomal Oedema in Patients with Hyperacute Spontaneous Intracerebral Hameorrhage

Authors	J. M. Gebel et al [192]
Publication Year	2002
Number of Participants	142
Mean Age	Not given
Study Design	Secondary analysis of prospective study
Objective	- To summarize oedema volumes in both absolute and relative terms - To explore the presence of associations between oedema volume and relevant clinical and radiological variables.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-9 A Study on-effect of Haematoma and Perihematomal Oedema Volume on GCS at the Time of Admission in Patients with Spontaneous Lobar and Basal Ganglia Haemorrhage

Authors	J. MA et al [8]
Publication Year	2014
Number of Participants	48
Mean Age	58 years
Study Design	Cross sectional study
Objective	To know the effect of haematoma and PHO volume on GCS at the time of admission in patients with spontaneous lobar and basal ganglia haemorrhage.
Outcomes	Haematoma and PHO volume
Method of Segmentation	Modified ABC/2 method
Included / Excluded	Included

Table 3-10 Human Brain Haemorrhage: Quantification of Perihematomal Oedema by Use of Diffusion-Weighted Imaging

Authors	J. R. Carhuapoma et al [193]
Publication Year	2008
Number of Participants	9
Median Age	63.4 years
Study Design	Pilot study
Objective	To test the hypothesis that there is a dose-effect relationship between blood clot volume and tissue water content as an indirect measure of severity of blood-brain-barrier breakdown and vasogenic brain oedema formation.
Outcomes	Haematoma volume and PHO volume
Method of Segmentation	Manual segmentation
Included / Excluded	Included

Table 3-11 No Exacerbation of Perihematomal Oedema with Intraclot Urokinase in Patients with Spontaneous Intracerebral Haemorrhage

Authors	L. Lian et al [194]
Publication Year	2014

Number of Participants	110
Mean Age	54.1 years
Study Design	Retrospective study
Objective	To investigate the effects of minimally invasive surgery and urokinase on PHO.
Outcomes	Haematoma volume, PHO volume, midline shift
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-12 Location Characteristics of Early Perihaematomal Oedema

Authors	M. McCaron et al [106]
Publication Year	2006
Number of Participants	44
Mean Age	61.5 years
Study Design	Prospective study
Objective	To compare an early PHO volume as a ratio of haematoma volume in different brain locations in patients admitted to hospital with a diagnosis of spontaneous ICH.
Outcomes	ICH volume and PHO volume
Method of Segmentation	Modified ABC/2 method
Included / Excluded	Included

Table 3-13 Segmentation of Cerebral Oedema Around Spontaneous Intracerebral Haemorrhage

Authors	M. Chen et al [107]
Publication Year	2013
Number of Participants	36
Mean Age	Not given
Study Design	Experimental study
Objective	To propose and validate an automatic algorithm to segment cerebral oedema of patient with spontaneous ICH.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	Fully automated + Manual segmentation

Included / Excluded	Included

Table 3-14 Hypothermia Reduces Perihaemorrhagic Oedema after Intracerebral Haemorrhage

Authors	R. Kollmar et al [195]
Publication Year	2010
Number of Participants	50
Mean Age	63.5 years
Study Design	Prospective pilot study
Objective	To investigate the effect of mild hypothermia over a period of 10 days in patients who require intensive care treatment because of large supratentorial spontaneous ICH.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS + ABC/2 method
Included / Excluded	Included

Table 3-15 Cerebral Perfusion and Blood Pressure do not Affect Perihaematomal Oedema Growth in Acute Intracerebral Haemorrhage

Authors	R. McCourt et al [40]
Publication Year	2014
Number of Participants	67
Mean Age	70 years
Study Design	Prospective study
Objective	To test the hypothesis that oedema growth is associated with reduced cerebral blood flow and lower systolic blood pressure.
Outcomes	Haematoma and PHO volume
Method of Segmentation	SAS +ABC/2 method
Included / Excluded	Included

Table 3-16 Radiologic Estimation of Haematoma Volume in Intracerebral Haemorrhage Trial by CT Scan

Authors	R. Zimmerman et al [93]
Publication Year	2006

Number of Participants	399
Mean Age	Not given
Study Design	Multicentre randomised clinical trial
Objective	To provide accurate measurements of the change in haematoma volume, IVH volume, and oedema volume To evaluate the use of CT scans as a predictor of patient outcomes To demonstrate that haematoma volume can serve as a surrogate marker for ICH clinical progression.
Outcomes	Haematoma, IVH and oedema volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-17 Effects of Celecoxib on Haematoma and Oedema Volumes in Primary Intracerebral Haemorrhage: A Multicentre Randomised Controlled Trial

Authors	S. H. Lee et al [105]
Publication Year	2013
Number of Participants	44
Mean Age	63.6 years
Study Design	Multicentre, randomised, controlled clinical trial
Objective	To investigate the effect of celecoxib in patients with ICH.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-18 Measurement of Perihaematomal Oedema in Intracerebral Haemorrhage

Authors	S. Urday et al [196]
Publication Year	2015
Number of Participants	20
Mean Age	Not given
Study Design	Retrospective study
Objective	To develop a systematic approach for CT-based measurement of PHO

Outcomes	ICH, IVH and PHO volume
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-19 Minimally Invasive Surgery Plus Recombinant Tissue-type Plasminogen Activator for Intracerebral Haemorrhage Evacuation Decreases Perihaematomal Oedema

Authors	W. A. Mould et al [119]
Publication Year	2013
Number of Participants	118
Mean Age	60.8 years
Study Design	Multicentre, randomised, prospective trial
Objective	To test the hypothesis that haematoma removal in patients treated with MIS and rt-PA would lead to concomitant reduction of oedema volume at the end of treatment as compared to ICH patients treated with medical management.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-20 Association of Altered Serum MicroRNAs with Perihaematomal Oedema after Acute Intracerebral Haemorrhage

Authors	Y. Zhu et al [120]
Publication Year	2015
Number of Participants	33
Median Age	57.37 years
Study Design	Prospective study
Objective	To test the hypothesis that altered miRNA levels are associated with PHO in ICH patients.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	Manual segmentation
Included / Excluded	Included

Table 3-21 Deep Learning for Automated Measurement of Haemorrhage and Perihaematomal Oedema in Supratentorial Intracerebral Haemorrhage

Authors	R. Dhar et al [197]
Publication Year	2020
Number of Participants	124
Mean Age	Not given
Study Design	Prospective study
Objective	To develop a deep learning-based imaging algorithm capable of accurately measuring haematoma and PHO volumes.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	Automated segmentation
Included / Excluded	Included

Table 3-22 Perihaematomal Oedema Surrounding Spontaneous Intracerebral Haemorrhage by CT: Ellipsoidal versus Morphometric Volumetry

Authors	J. G. Shulman et al [174]
Publication Year	2020
Number of Participants	154
Mean Age	Not given
Study Design	Retrospective study
Objective	To demonstrate the use of an SAS algorithm to generate PHO volumetrics on non-contrast CT of the head and compare this technique to physician's manual calculation.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	SAS + ABC/2
Included / Excluded	Included

Table 3-23 Association of Baseline Haematoma and Oedema Volumes with 1-Year Outcome and Long-Term Survival after Spontaneous Intracerebral Haemorrhage: A Community-Based Inception Cohort Study

Authors	J. J. Loan et al [198]
Publication Year	2021
Number of Participants	342
Median Age	78

Study Design	Prospective community-based inception cohort study
Objective	To investigate the existence, strength, and independence of associations between intracerebral haemorrhage and PHO volumes on diagnostic brain CT and one-year functional outcome and long-term survival.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Included

Table 3-24 Antihyperthermic Treatment Decreases Perihaematomal Hypodensity

Authors	P. Hervella et al [199]
Publication Year	2020
Number of Participants	795
Mean Age	74 years
Study Design	Retrospective study
Objective	To investigate the effect of perihaematomal hypodensity and outcome of a decrease in body temperature in the first 24 hours in patients with ICH.
Outcomes	PHO volume and clinical outcomes
Method of Segmentation	Fully automated segmentation + ABC/2
Included / Excluded	Included

Table 3-25 Software Output from Semi-Automated Planimetry can Underestimate Intracerebral Haemorrhage and Perihaematomal Oedema Volumes by up to 41%

Authors	Y. Y. Wu et al [200]
Publication Year	2016
Number of Participants	100
Median Age	69 years
Study Design	Retrospective study
Objective	To assess reliability of semi-automated CT planimetry using Analyze and Osirix software
Outcomes	ICH and PHO volumes

Method of Segmentation	SAS
Included / Excluded	Included

3.4.2 Characteristics of Excluded Studies

There are 7 studies excluded from this review because they have not met the inclusion criteria. The details of excluded studies are presented on the tables below (Table 3-26 - Table 3-32).

Table 3-26 Impact of Hypothermia Initiation and Duration on Perihaemorrhagic Oedema Evolution after Intracerebral Haemorrhage

Authors	B. Volbers et al [201]
Publication Year	2016
Number of Participants	53
Mean Age	63.8 years
Study Design	Retrospective, single centre, case control study
Objective	To examine the impact of therapeutic hypothermia timing and duration on PHO evolution.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHO, optimal threshold and reliability assessment)

Table 3-27 Impact of Perihaemorrhagic Oedema on Short-Term Outcome after Intracerebral Haemorrhage

Authors	B. Volbers et al [202]
Publication Year	2016
Number of Participants	220
Mean Age	69.5 years
Study Design	Monocentric retrospective cohort study
Objective	To evaluate PHO over a longer period of time and investigated its impact on short-term clinical outcome.
Outcomes	ICH and PHO volumes

Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHP, optimal threshold and reliability assessment)

Table 3-28 Perihaemetomal Oedema in Primary Intracerebral Haemorrhage is Plasma Derived

Authors	K. S. Butcher et al [203]
Publication Year	2004
Number of Participants	21
Mean Age	64.2 years
Study Design	Prospective study
Objective	To test the hypothesis that any observed perihaematomal hypoperfusion resulting in ischaemia would be associated with decreases in the apparent diffusion coefficient (ADC)
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHO, optimal threshold and reliability assessment)

Table 3-29 Natural Course of Perihaemorrhagic Oedema after Intracerebral Haemorrhage

Authors	D. Staykov et al [204]
Publication Year	2011
Number of Participants	219
Mean Age	69.9 years
Study Design	Retrospective study
Objective	To investigate the chronological PHO course and its relation to in-hospital mortality in a large retrospective ICH cohort.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHO, optimal threshold and reliability assessment)

Table 3-30 Effects of Continuous Hypertonic Saline Infusion on Perihaemorrhagic Oedema Evolution

Authors	I. Wagner et al [205]
Publication Year	2011
Number of Participants	64
Mean Age	66 years
Study Design	Retrospective study
Objective	To study the effect of early continuous hypertonic saline infusion on development of perihaematomal oedema after severe spontaneous supratentorial ICH.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHO, optimal threshold and reliability assessment)

Table 3-31 Perihaematomal Oedema as Predictor of Outcome in Spontaneous Intracerebral Haemorrhage

Authors	M. Gupta et al [206]
Publication Year	2014
Number of Participants	44
Mean Age	54.95 years
Study Design	Prospective case-controlled study
Objective	To evaluate the prognostic influence of absolute and relative oedema (ratio of absolute oedema to haematoma volume) in the patients of spontaneous ICH.
Outcomes	Haematoma and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No definition of PHO, optimal threshold and reliability assessment)

Table 3-32 Rate of Perihaematomal Oedema Expansion Predicts Outcome after Intracerebral Haemorrhage

Authors	S. Urday et al [108]
Publication Year	2016

Number of Participants	139
Mean Age	Not given
Study Design	Retrospective cohort study
Objective	To determine whether PHO expansion rate predicts outcome after ICH.
Outcomes	ICH and PHO volumes
Method of Segmentation	SAS
Included / Excluded	Excluded (No optimal threshold and reliability assessment)

3.5 Result of Data Extraction

There are 25 studies included in this review with total of 3815 patients. Eleven studies had used a single SAS technique in PHO segmentation, 5 studies used a combination of SAS and ABC/2 method, 2 studies applied the ABC/2 and modified ABC/2 alone, 2 studies run only a manual segmentation, 2 studies run a combination of fully automated technique and manual quantification and 1 study used a combination of fully automated segmentation and ABC/2 formula. Table 3-33 provides the methods of PHO volume measurement of selected studies.

Table 3-33 Methods of PHE volume segmentation for selected studies

Authors	Year	Sample n	Methods of Segmentation
A. Bardera et al [101]	2009	18	SAS + ABC/2
A. I. Qureshi et al [189]	2011	60	ABC/2 Method
B. Volbers et al [115]	2011	49	SAS + ABC/2
C. S. Anderson et al [35]	2010	270	SAS
C. Herweh et al [190]	2010	17	SAS
E. Fainardi et al [191]	2008	89	ABC/2 Method
H. Arima et al [152]	2009	270	SAS
J. M. Gebel et al [192]	2002	142	SAS

Authors	Year	Sample n	Methods of Segmentation
J. MA et al [8]	2014	48	Modified ABC/2 Method
J. R. Carhuapoma et al [193]	2008	15	Manual Segmentation
L. Lian et al [194]	2014	110	SAS
M. McCarron et al [106]	2006	44	Modified ABC/2 Method
M. Chen et al [107]	2013	36	Fully Automated + Manual Segmentation
R. Kollmar et al [195]	2010	50	SAS + ABC/2
R. McCourt et al [40]	2014	67	SAS + ABC/2
R. Zimmerman et al [93]	2006	399	SAS
S. H. Lee et al [105]	2013	44	SAS
S. Urday et al [196]	2015	20	SAS
W. A. Mould et al [119]	2013	118	SAS
Y. Zhu et al [120]	2015	33	Manual Segmentation
R. Dhar et al [197]	2020	124	Fully Automated + Manual Segmentation
J. G. Shulman et al [174]	2020	154	SAS + ABC/2
J. J. Loan et al [198]	2021	78	SAS
P. Hervella et al [199]	2020	795	Fully Automated + ABC/2
T. Y. Wu et al [200]	2016	100	SAS

From the total of 25 studies, 18 studies gave a clear definition of PHO on CT brain images. Seven studies did not report a clear radiological definition of PHO. Study by M. Chen et al had defined PHO as a low grayscale region around haematoma within 1cm radius of normal brain tissue and the mirror area on the other side of the brain [107], and the rest had given almost the similar definitions. In general,

for studies that reported a radiological definition of PHO on CT brain images, the definition was broadly consistent in all studies.

The definition of PHO on CT brain images and optimal thresholding recommended for oedema segmentation of selected studies is presented in Table 3-34. The key features that emerge across the published definitions is that PHO was defined as a hypodense area around the haematoma region and represented with a lower HU in the threshold range between 5 – 33 HU. The use of an optimal threshold of 5 – 33 HU was reported in 7 studies. However, studies by M. Chen et al [107] and R. McCourt et al had reported of an optimal threshold of 12 – 50 HU and 5 – 23 HU respectively.

Table 3-34 PHO definition and optimal threshold range

Authors	PHO Definition	Optimal Threshold
A. Bardera et al [101]	Oedema is always contiguous with the haematoma and has low-density values with respect to the rest of the voxels.	NOT GIVEN
A. I. Qureshi et al [189]	Rim of hypodensity area surround the haematoma.	NOT GIVEN
B. Volbers et al [115]	Perifocal of hypodensity area surrounding the haemorrhage.	5 – 33 HU
C. Herweh et al [190]	Area and degree of low attenuation.	NOT GIVEN
E. Fainardi et al [191]	Area of low density	NOT GIVEN
J. M. Gebel et al [192]	Growing thin layers of sequentially outward from the edge of the haematoma.	NOT GIVEN
J. MA et al [8]	Rim of hypodensity area surround haematoma.	NOT GIVEN
J. R. Carhuapoma et al [193]	Hypodensity surrounding haematoma region.	NOT GIVEN
L. Lian et al [194]	Hypodensity surrounding haematoma.	NOT GIVEN

Authors	PHO Definition	Optimal Threshold
M. McCarron et al [106]	Rim of hypodensity area surround haematoma.	NOT GIVEN
M. Chen et al [107]	Low grayscale regions around spontaneous ICH within 1cm radius of normal brain tissue and the mirror area on the other side.	12 – 50 HU
R. Kollmar et al [195]	Perihaemorrhagic hypodense area.	5 – 33 HU
R. McCourt et al [40]	Area of diminished density occurring around haematoma region and represented as a lower HU number.	5 – 23 HU
S. H. Lee et al [105]	Hypodense area around haemorrhage region.	5 – 33 HU
S. Urday et al [196]	More hyperdense than the corresponding region in the contralateral hemisphere and most hypodense immediately surrounding the haematoma.	NOT GIVEN
W. A. Mould et al [119]	NOT GIVEN	5 – 33 HU
Y. Zhu et al [120]	Hypodense area surrounding haematoma.	5 – 33 HU
J. J. Loan et al [198]	Perihaematomal hypoattenuation	5 – 33 HU
P. Hervella et al [199]	Perihaematomal hypodensity	NOT GIVEN
T. Y. Wu et al [200]	NOT GIVEN	5 – 33 HU

There were only few studies reported on reliability of each method. Reliability refers to the reproducibility of values of a test, assay or other measurement in repeated trials on the same individuals [207]. Better reliability implies better precision of single measurements and better tracking of changes in measurements in research or practical settings. One study reported inter-operator reliability by

defining the inter-operator variance with manual tracing (I_M) and semi-automated (I_A) segmentation algorithm as:

$$I_M = 1 - \frac{A_{M1} \cap A_{M2}}{A_{M1} \cup A_{M2}}$$

and

$$I_A = 1 - \frac{A_{A1} \cap A_{A2}}{A_{A1} \cup A_{A2}},$$

where A_{M1} and A_{M2} are the manually segmented regions obtained by operator 1 and operator 2, respectively, on the same image and in the same way, A_{A1} and A_{A2} are the regions obtained with the semi-automated method for both operators on the same image [101]. A value of 0 shows perfect reliability, while a value of 1 shows no reliability. The inter-observer reliability for semi-automated and manual tracing was 0.42 and 0.36 respectively. This study revealed that the inter-observer consistency with the manual segmentation method is much better than the semi-automated approach. However, there is no significant difference reported in the measurements of oedema volume between both methods. The rest studies have reported the inter-observer reliability using ICC and Kappa test. ICC is used when comparing agreement between measurements made on a continuous scale, whereas kappa is used for looking agreement of categorical variables. The average inter-observer reliability of SAS and manual segmentation using ICC evaluation was 0.886 (95% CI, 0.70 – 0.98) and 0.92 (95% CI, 0.89 – 0.95) respectively. Whereas average intra-observer reliability in PHO segmentation using ICC evaluation was 0.892 (95% CI, 0.7266 – 0.99) for SAS technique as reported in 8 studies [35][93][115][174][196][198][200], 0.9 [95% CI, 0.8-0.95] for manual segmentation [115] and 0.959 (95% CI, 0.897 – 0.984) for ABC/2 method [106]. One study analysed the intra- and inter-observer reliability of SAS segmentation methods for the grading of PHO volumes using Kappa test, k = 0.86 and k = 0.83 respectively[194] and 1 study only reported inter-observer reliability of k = 0.84 [105]. For kappa analysis of agreement, based on 95% confidence interval, value less than 0 were indicative for poor agreement, values between 0.01 and 0.20

indicate slight agreement, values between 0.21 and 0.40 indicate fair agreement, values between 0.41 and 0.60 indicate moderate agreement, value between 0.61 and 0.80 indicate substantial agreement and values between 0.81 and 1.00 indicate an almost perfect agreement [208]. The overviews of inter and intra-observer reliability for each PHO segmentation technique is shown on Table 3-35.

Table 3-35 Intra and inter-observer reliability of PHO segmentation methods

Authors	Intra-observer Reliability				Inter-observer Reliability				Agreement Test
	Semi-Auto	Manual	ABC/2	Fully-Auto	Semi-Auto	Manual	Fully-Auto	ABC/2	
A. Bardera et al [101]					0.42	0.36			Algorithm
B. Volbers et al [115]	0.96 [0.93 – 0.99]	0.9 [0.8 – 0.95]	-		0.96 [0.93 – 0.99]	0.89 [0.75 – 0.95]			ICC
C. S. Anderson et al [35]	0.91 [0.87 – 0.94]	-	-		-	-			ICC
H. Arima et al [187]	-0.91 [0.87 – 0.94]	-	-			-			ICC
L. Lian et al [194]	0.86	-	-		0.83	-			Kappa test
M. McCarron et al [106]	-	-	0.959 [0.897 – 0.984]		-	-			ICC

Authors	Intra-observer Reliability				Inter-observer Reliability				Agreement Test
	Semi-Auto	Manual	ABC/2	Fully-Auto	Semi-Auto	Manual	Fully-Auto	ABC/2	
R. McCourt et al [40]	-	-	-		0.92 [0.86 – 0.95]	0.95 [0.91 – 0.97]			ICC
R. Zimmerman et al [93]	0.7266	-	-		0.7363	-			ICC
S. Lee et al [105]	-	-	-		0.84	-			Kappa test
S. Urday et al [196]	0.99 [0.99 – 1.00]	-	-		0.98 [0.96 – 1.00]	-			ICC
R. Dhar et al [197]				0.83			0.92		
J. G. Shulman et al [174]	0.73				0.70			0.82	
J. J. Loan et al [198]	0.93				0.98				ICC (mixed and random effect model)
T. Y. Wu et al [200]	0.983				0.952				ICC (2-way random effects

Authors	Intra-observer Reliability				Inter-observer Reliability				Agreement Test
	Semi-Auto	Manual	ABC/2	Fully-Auto	Semi-Auto	Manual	Fully-Auto	ABC/2	
									model)

3.6 Interpretation

This systematic review identified 25 studies fulfilling the inclusion criteria and 7 studies were not fulfilling those standards. The study designs were mostly involved retrospective studies, prospective cohort studies and randomized clinical trials. Although several studies had defined PHO very clearly and gave the exact range of optimal thresholding for PHO segmentation, only few studies reported on reliability of each method of PHO quantification, leaving the research question not fully answered.

In general, the definition of PHO on CT brain images has been described as rim of hypodense area around haematoma region in most studies [8][40][101][105][106][115][120][189][190][191][193][194][195][196][198][199]. Some studies used strictly defined radiological criteria of PHO that it is always contiguous to the haematoma and appear as low intensity values as compared to the rest of the brain parenchyma voxel [101] and has been described as low grayscale area within 1cm radius from haematoma [107]. Seven studies did not report any definition of PHO [35][93][119][152][174][197][200]. The knowledge regarding the radiological definition of PHO becomes a vital element in PHO segmentation on CT brain images to accurately delineate PHO region from normal brain parenchyma. Because of that, any studies related to PHO segmentation on CT brain images should give a clear definition of PHO that be used as a radiological guide in PHO quantification.

Generally, the available data demonstrate a consistent approach in PHO volume segmentation based on radiological definition of PHO on CT image reported in included studies. A good intra- and inter-observer reliability was demonstrated in SAS, manual segmentation, and ABC/2 formula with mostly more than 0.800 absolute agreement. Additionally, some studies applied the ABC/2 [189][191] and modified ABC/2 formula [8][106] in quantifying the PHO volume, a technique commonly used for haematoma volume estimation. However, only 2 studies reported the intra- and inter-observer reliability of ABC/2 formula of 0.95 [106] and 0.82 [174] respectively.

The suggested threshold range of 5 – 33 HU is considered a useful tool for PHO segmentation and had been used in several studies regarding PHO quantification. This threshold range was first being suggested by B. Volbers et al [115] in their study on 49 samples to establish an observer independent method of PHO quantification on CT by comparing with simultaneously performed MRI. This suggestion had been made based on several reasons. First, they used the fluid attenuated inversion recovery (FLAIR) sequences of MRI as a reference to define the threshold range until the best approximation was found. Second, the threshold values were being tested at various time-points and the result showed an identical finding. Third, this method approach had a strong correlation with MRI and with this recommended threshold range, PHO volumes on CT brain images were certainly being segmented with high inter- and intra-reliability than manually PHO tracing. Otherwise, M. Chen et al [209] had reported a different finding regarding the optimal threshold for PHO segmentation. They had compared their proposed threshold of 12 – 50 HU to the fixed and widely used 5 – 33 HU on 36 samples and concluded that region growing with fixed threshold performed less well than the proposed algorithm in PHO segmentation. M. Chen et al in their studies had reported that the image characteristic of cerebral oedema may vary with time and seriousness of spontaneous ICH. PHO can be divided into 3 levels according to water content clinically; mild PHO when CT value is 4 – 8 HU lower than normal

tissue, moderate PHO when CT value is 8 – 16 HU lower than the normal tissue, and severe PHO when CT value is more than 16 HU lower than the normal tissue. The optimal threshold of 12 – 50 HU was proposed by M. Chen to include even a mild to moderate PHO into consideration for automatic segmentation. However, an automatic segmentation method proposed cannot performed well when haematoma breaks into ventricles to have an area contact between oedema and CSF. This is because, the boundary between oedema and CSF is hard to define even for medical experts. This proposed method of automatic segmentation was reported as not performed well for large haematoma or at subacute stage, where the contrast may be high or low.

J. M Gebel et al [192] had reported there was more objective and accurate quantification of oedema volume when using SAS method with respect to the conventional planimetric oedema volume segmentation with an overall Spearman correlation coefficient of 0.9744. Another 2 studies had reported different finding regarding the accuracy of SAS technique in PHO segmentation. One study reported that SAS method of PHO segmentation showed a similar accuracy as compared with manual PHO tracing of 0.65 with higher reproducibility [115] and another 1 study reported a better accuracy of SAS quantification of 0.76 [107]. The rest studies did not report any data on accuracy of segmentation methods. In PHO volume segmentation technique, a good accuracy indicated the proper technique in PHO quantification while a poor accuracy reflected the complexity and difficulty to segment the brain oedema.

The intra- and inter-observer reliability of SAS oedema segmentation was reported of having a high correlation across studies ranged from 0.7266 to 0.99 and 0.70 to 0.98 respectively. Only 2 studies [40][115] reported the intra- and inter-observer reliability of manual PHO segmentation. Study by B. Volbers et al reported the excellence intra- and good inter-observer reliability of manual PHO segmentation of 0.9 [0.8 – 0.95] and 0.89 [0.75 – 0.95] respectively. However,

study by R. McCourt et al only reported an excellence inter-observer reliability of of 0.95 [0.91 – 0.97] for manual PHO segmentation but did not state the inter-observer reliability for the same technique [40]. In addition, B. Volbers et al [115] reported that there was no significant difference between SAS technique and manual PHO segmentation.

Both methods of quantification were considered reliable techniques for PHO segmentation with a high intra-observer and inter-observer reliability. However, manual tracing of PHO might be subjected to inter-observers' differences and may cause some potential errors since it was reported that the most difficult and challenging part in PHO segmentation was to define PHO boundaries on CT images even with the help of medical experts. This review might be subjected to some limitations since it only included a small number of studies in which only few papers reported on reliability assessment. There was also a limited data on accuracy and reproducibility of each segmentation technique and the authors of selected studies were not contacted to clarify the reported data more precisely.

3.7 Summary

This systematic review is conducted to address the research question: In patients with spontaneous ICH, is there any reliable method in PHO segmentation and volume estimation on CT brain images. Potential eligible studies were searched on 3 different databases: PubMed, Sciences Direct and Google Scholar with a combination of 3 different keywords. There are 25 studies included that involved 3815 number of patients. Among 25 studies, there are only 18 studies that give a clear definition of PHO on CT brain images, in which it has been defined as a hypodense area around haematoma region within 1cm radius with a lower HU number compared to adjacent normal parenchyma. The optimal range for PHO segmentation was 5 – 33 HU as being reported in several studies. In general, SAS and manual PHO segmentation give a high intra and inter-observer reliability and both methods have been considered a reliable technique for PHO volume

quantification. The present systematic review has some limitations. Even the total number of participants across all studies suggesting sufficient homogeneity to undertake a meta-analysis, but there are not enough statistical data available. There were 14 studies reporting on reliability using difference types of reliability assessment. However, without detailed explanation on the types of ICC used, make it not possible to run meta-analysis. Authors were not contacted to obtain the original data for each of the eligible studies, which might have minimised any reporting bias. The other limitation of this review is the number of small eligible studies involved and limited data on accuracy and reproducibility. In conclusion, further appropriate powered studies using the best available technique in PHO quantification, consistent thresholding range and standardized PHO definition are required before translating study results into clinical practice.

Chapter 4 VOLUMETRIC METHOD AND IMAGE SEGMENTATION: DESCRIPTION AND RELIABILITY ANALYSIS

4.1 Introduction

In medical image analysis for computer aided diagnosis, segmentation is often performed as a preliminary step. Segmentation of the brain is important prior to quantitative analysis of tumours, oedema, haematoma, or other abnormalities. However, due to complex structure of the brain, it becomes a difficult and challenging task. Non-contrast CT scan is most widely used as the basis for segmentation of haematoma and PHO because of its widely availability and is the predominant imaging modality for spontaneous ICH care clinical trials [210]. This chapter will present the method and reliability assessment for haematoma and PHO volume quantification. Measurement of haematoma volume is performed using two different methods described in Chapter 1; the ABC/2 formula and the SAS method using region growing technique with manual editing while PHO volume is measured using manual delineation.

Both methods of haematoma volume measurement (SAS and ABC/2) have potential advantages and disadvantages. Computer-assisted volume analysis techniques such as SAS are considered the gold standard and most exact method of volume quantification with high degree of inter- and intra-observer agreement [101] and has better precision compared to ABC/2 formula [94]. However, in routine clinical practice, this volume estimation technique is not yet available. In contrast, the ABC/2 formula is a simple and fast bedside volume estimation method that is widely used in clinical settings [63] and correlates well with the computer-assisted volume analysis with a satisfactory reliability [72]. The systematic review presented in Chapter 2 has reported a strong agreement and correlation between both techniques of quantification. Nevertheless, a high

operator-dependency of ABC/2 formula may generate human errors which may be a particular problem if a study involves several operators. The use of SAS segmentation technique in a large sample is considered more practical than manual segmentation for measurement of haematoma volume of various sizes and shapes and might be used as an alternative to ABC/2 formula. This is because ABC/2 volume estimation is based upon the volume of an ellipsoid [77] and has been reported to overestimate haematoma volume especially in large and irregular shaped ICH [211]. While the systematic review presented in Chapter 2 shows high reliability in measurement of ABC/2 and SAS in the published literature, the high operator dependency means that it is still important to establish the intra- and inter-observer reliability for these methods for the specific observers who will make the measurements on the TICH-2 data. This will provide re-assurance that the individuals performing the measurements on the TICH-2 data are performing to a high standard and at a level similar to that found in the systematic review.

It is well established that haematoma and PHO volume act as independent predictors of clinical outcomes and one of the scoring parameters used to predict morbidity and mortality [87][174][196] . Since haematoma and PHO volume changes are important outcomes in the TICH-2 study [59], it is therefore important to demonstrate high intra- and inter-observer reliability for the volumetric measurements in this dataset. It is also important to demonstrate that the haematoma volume measurement obtained by SAS with manual editing correspond closely to volume estimation by ABC/2 formula. Several studies have reported the high intra- and inter-observer reliability of these techniques (as presented in Chapter 2) and a number of studies have directly compared the volumes obtained by these 2 measures. Notwithstanding, for PHO volume estimation, only 2 studies reported high reliability of manual segmentation. PHO quantification on CT image is quite challenging, and there is variability and a lack of consensus in how to define PHO boundaries for volume measurement. Because

of that, this study utilizes manual delineation of PHO volume estimation since this technique offers a simple segmentation method without using a complicated mathematical algorithm.

In the TICH-2 clinical trial, all CT brain scans were performed as per local protocol. There were no restrictions on CT scanner manufacturer, CT scanner setting and slice thickness of 124 participating centres. Nevertheless, only axial scans were accepted in this study. Because of that, CT data from TICH-2 participants consists of variable slice thicknesses. Since accurate delineation of haematoma and PHO volume is required to ensure treatment efficacy and for stratification in clinical trials of patients with ICH, it is therefore important to evaluate the impacts of CT slice thickness on haematoma and PHO volume estimation.

4.1.1 Hypotheses

The hypotheses constructed for this chapter are based on reliability assessment of proposed SAS technique with manual editing for haematoma volume analysis and manual delineation of PHO volume quantification in patients with spontaneous ICH. The main hypotheses are as follows:

i. SAS technique with manual editing and manual delineation approach using ITK-SNAP software are reliable methods for measuring haematoma and PHO volumes respectively in the ENOS trial sample.

ii. ABC/2 formula is a reliable method for haematoma volume analysis in the ENOS trial sample.

iii. Haematoma volume measured by ABC/2 formula provides a close approximation to haematoma volume derived by SAS technique especially in small (< 5cm in axial diameter) and regular shape haematoma and overestimates the haematoma volume particularly in large (> 5cm in axial diameter) and more irregular shape haematoma.

iv. Image reformatting from a thicker slice thickness of 5mm overestimates the haematoma and PHO volumes in the TICH-2 trial predominantly in small size of haematoma and PHO compared to image reformatting from a thinner slice thickness of 1mm.

4.1.2 Objectives

The aims of this chapter are to establish the performance characteristics of methods for haematoma and PHO volumes determination for the TICH-2 trial. The specific components of this are as follows:

i. To establish the inter- and intra-observer reliability of SAS approach using ITK-SNAP software with manual editing in haematoma volume analysis and manual delineation of PHO volumes using sample from the ENOS trial population.
ii. To determine the inter- and intra-observer reliability of ABC/2 formula in haematoma volume analysis using sample from the ENOS trial population.
iii. To test whether haematoma volume estimated from ABC/2 formula provides a close approximation of haematoma volume derived by SAS technique in the TICH-2 population, and to examine the effect of size and shape on the agreement between ABC/2 and SAS measurements.
iv. To examine the relationship of image reformatting from different volumetric acquisition slice thicknesses between 5mm and 1mm to haematoma and PHO volume measurement in a sample of the TICH-2 population for whom both slice thicknesses are available.

4.2 Methods

4.2.1 Assessment of Observer Reliability

To address the issue of observer reliability, 20 samples of consecutive patients with haemorrhagic stroke were selected from international multicentre ENOS

trial [41], a study of blood pressure management in patients with acute ischaemic stroke or ICH, and high blood pressure [59], without knowing the participant's characteristics. This initial testing of reliability of the proposed method is useful before it can be used in the large TICH-2 dataset. In addition, the previous study by K. Krishnan evaluating the performance characteristics of methods for quantifying spontaneous ICH was done using the same sample from ENOS trial [76]. To assess intra- and inter-observer reliability, haematoma and PHO volume quantifications were performed by 2 independent observers (ZKL and AA) in 2 independent sessions, blinded to patient identity, clinical data and treatment allocation to avoid bias. The original CT image format of DICOM was saved into Neuroimaging Informatics Technology Initiative (NIFTI) after volume quantification.

4.2.2 Comparison of Haematoma Volume Measurement Technique between SAS Method and ABC/2 Formula

For a comparison of SAS technique with manual editing against ABC/2, the haematoma volumes were measured for the whole TICH-2 population of 2325 participants by 3 independent observers blinded to clinical data (ZKL, neurologist; AA, radiographer; KK, stroke physician)[59]. TICH-2 trial tested the efficacy and safety of intravenous tranexamic acid in people with acute spontaneous ICH presenting within 8 hours of symptom onset. Only participants with baseline scans available were included in this study (n = 2254). Soft copy files of scans in DICOM format were uploaded into a web-based data submission platform. Alternatively, encrypted DICOM files were copied onto compact discs (CD) and mailed to the coordinating centre and were then uploaded by the image coordinators. Seventy-one participants were excluded for analysis due to technical reasons as follow: - participants

with unprocessable baseline DICOM scan, participants with only CTA available on baseline scan and CT scan DICOM to NIFTI conversion failure.

4.2.3 Comparison of Haematoma and PHO Volume in Difference Slice Thickness

To examine the impact of slice thickness on haematoma and PHO volume quantification, CT brain scans for which both 1mm and 5mm slice thicknesses available were identified in the TICH-2 dataset. Only 30 out of 2254 series of scans were amenable to analyse as the rest scans provided only 1 slice thickness. Haematoma and PHO volumes were measured by 2 independent observers (ZKL and AA) in 2 independent sessions, blinded to each other's measurements. The flow chart showing numbers included in the analysis is presented on Figure 4-1.

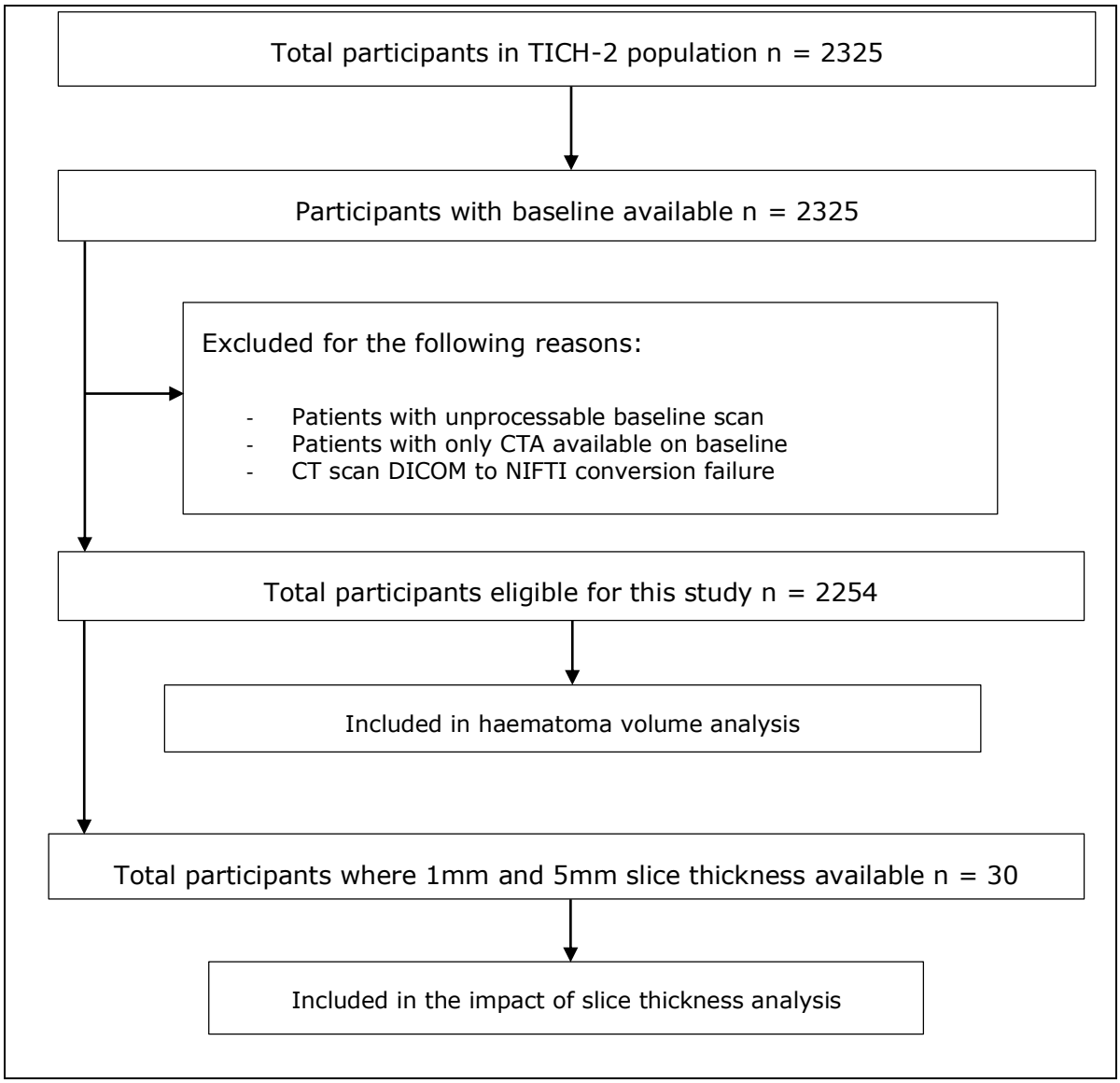


Figure 4-1 Study inclusion flowchart

4.2.4 ITK-SNAP Software for CT Image Segmentation and Volume Measurement

A number of software packages are available for volumetric analysis of medical imaging data such as CT scans. Packages used previously for segmentation of ICH and PHO include Osiris [70], MIPAV [71], ITK-SNAP [72], Analyze [79][167], Quantomo [94], OsiriX [76] and 3D slicer [78] [111][178][212]. For this analysis I required a segmentation software that allowed simple and fast 3D volume segmentation without the need of an

expertise in mathematical algorithm and image analysis. The software chosen for the volumetric segmentation is ITK-SNAP (described in more detail below), which was selected because of its combination of SAS using active contour methods as well as manual delineation and image navigation. ITK-SNAP allows a manual segmentation in 3 orthogonal planes at once and support for many different 3D image formats, including NIFTI and DICOM. Other than that, ITK-SNAP also has support for concurrent, linked viewing and segmentation of multiple images with an extensive tutorial and video documentation. Compared to other, larger open-source image analysis tools, ITK-SNAP design focuses specifically on image segmentation, and extraneous unrelated features are kept to a minimum. The design also emphasizes interaction and ease of use, in which it provides an integrated toolbox for manual post-processing of segmentation results.

The ITK-SNAP is a software application providing active contour segmentation for clinical imaging researchers (http://www.itksnap.org/pmwiki/pmwiki.php) [111]. Compared to other SAS software such as a 3D slicer, ITK-SNAP is a segmentation-only software and has interesting tools for the task. There are few tools available that make it easier for the user to learn. The SAS method proposed by ITK-SNAP is very complete and allows to obtain good results once the tool is understood and mastered by the user. Moreover, the keyboard and mouse shortcuts (zoom, navigation between slices) are similar to those used in medical imaging field, allowing certain fluidity in the use. However, a small number of tools penalizes the user when faced with a segmentation difficulty, since it has no other tools that can be used to establish a workaround. 3D Slicer is a global and general software in the field of image processing and has several modules available, including one specifically dedicated to segmentation. It also provides the user with a variety of tools for SAS such as level tracing, growth from seed, thresholding, scissors, and

island, which the user can combine to obtain the desired result. Whereas the ITK-SNAP software only has the snake tool for this type of measurement. It is largely due to the presence of all those segmentation tools that 3D Slicer takes a little longer to learn than ITK-SNAP. Regarding the support of medical images (especially in DICOM format), the results of the segmentations and the available formats for data export, both software are appropriate and compatible in an automatic segmentation project using deep learning methods.

In this study, a planimetry measurement was done using ITK-SNAP (Version 3.4.0-beta) and was visualized on a 26-inches Apple iMac. The ROI was obtained on native space of DICOM images, and the final segmented image was saved into NIFTI format.

4.2.5 SAS Haematoma Volume Measurement

Active contour SAS using a region growing technique was recommended in this study since it is considered a fast and simple method for volume segmentation compared to the other quantification strategy. It is also classified as a pixel-based image segmentation method since it involves the selection of initial seed points that develops into a group of connected pixels with similar properties. This technique consists of a few simple steps implemented in the region growing tool; tissue contrast pre-processing, tissue volume optimization, thresholding, region growing, manual correction and editing and saving the final segmentation output.

4.2.5.1 Tissue Contrast Pre-Processing

The initial step was to run pre-processing of images being segmented. Linear contrast adjustments were made to those CT images which were originally saved in bone window or other tissue contrast settings. A

minimum and maximum HU value of contrast was set to 0 and 80 respectively. This 80 HU range of contrast is the best value for brain soft tissue and haematoma visualization. The original image and the image after contrast adjustment are shown on Figure 4-2(a) and (b) respectively.

4.2.5.2 Tissue Volume Optimization

The tissue volume for inclusion in the region growing area was then manually optimised as a cuboid box surrounding the haematoma. This was done to eliminate unnecessary soft tissue inclusion within the area for interrogating. The edge of the box around the haematoma area was adjusted to include only the region of interest into the active contour segmentation as illustrated on Figure 4-2(c).

4.2.5.3 Thresholding

The next step of image segmentation was to set the upper and lower threshold values for optimal selecting haematoma pixels. Three threshold modes (combination of upper and lower threshold, upper threshold, and lower threshold) can be used to inhibit growth of the region-of-interest (ROI) into areas above or below the set values. To some extent, the limitations applied were dependent on location of the haematoma in the brain. For example, haematoma located very closed to the skull required a combination of upper and lower thresholding with the value of upper threshold set to 100 HU to prevent growth of the ROI into bone (which also appears dense on CT) and the value of lower threshold set to 45 HU.

4.2.5.4 Region Growing

The following step was the region growing process. This technique detects a region by identifying the neighbouring pixels in the image that have similar grey level as the starting point (seed). The initial step of region growing involved the process of setting an initial spherical seed point centrally within the haematoma. The seed can be entered by clicking the mouse on the image. The seed defines the starting point for growth of the ROI; smooth, round, or ovoid haematomas may require only a single seed (Figure 4-2d), but large or complex-shaped haematomas may be optimally segmented by planting several seed points in different components of the haematoma. The region growing algorithm was then run, which used image characteristics to group adjacent pixels together (in all three dimensions) into 3D region by comparing the value of the pixels with their neighbours using similarity measures. If the pixels met the criteria, they were added to the formed group of pixels. The process continued until all the matched pixels added to the region and the boundary of the haematoma area was appropriately defined as demonstrated on Figure 4-2(e).

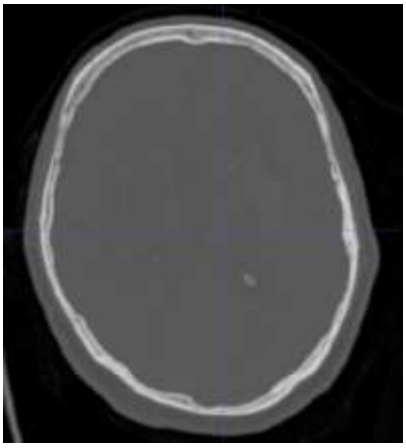
4.2.5.5 Manual Correction and Editing

After the ROI of haematoma had been defined automatically by the region growing process, it has then been checked by visual inspection whether the ROI grown by the algorithm accurately delineated the haematoma region. If there was an error of the process, for example not all pixels within haematoma region were grown into the ROI, manual correction and editing was done to manually add those pixels into the ROI. This was done by selecting the active label (using quick label picker

on ITK-SNAP toolbox) and drawing over the pixels that need to add into the ROI (Figure 4-2f).

4.2.5.6 Final Image Output

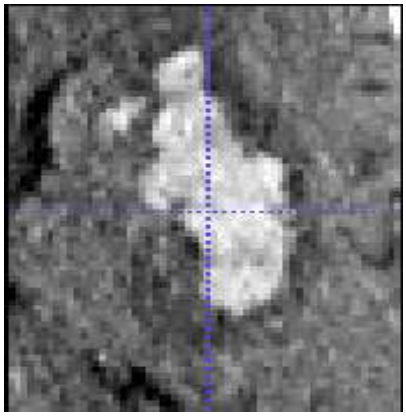
The final output of image segmentation is shown on Figure 4-2f, which consists of the segmented image with highlighted haematoma region. The segmented image that had been drawn was saved in the same folder of the original image as NIFTI format. The volumetric results were shown on Volumes and Statistics features of ITK-SNAP in mm^3 and then been saved in the same folder of the original image as comma separated values (csv) file. The folder was then exported into the TICH-2 server.



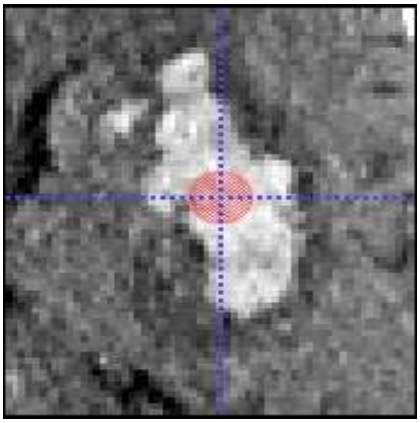
(a) Original image



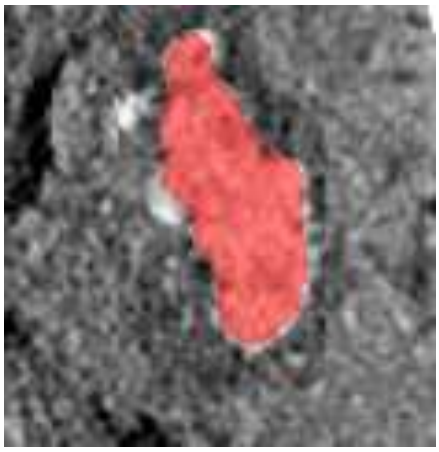
(b) After contrast adjustment



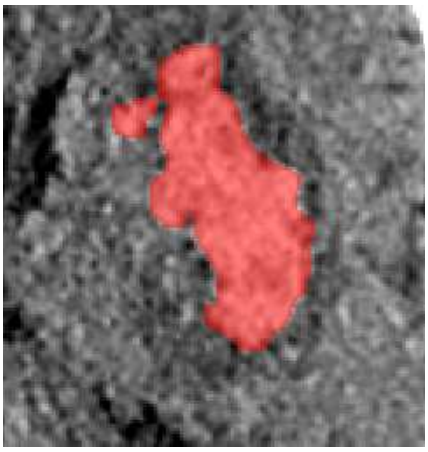
(c) Tissue volume optimization



(d) Placement of seed point



(e) Region growing process



(f) Final image after manual editing

Figure 4-2 The whole process of haematoma volume segmentation by ITK-SNAP semi-automatic region growing technique

4.2.6 Haematoma Volume Measurement with the ABC/2 Formula

The ABC/2 method of haematoma volume measurement is constructed based on the assumption and simplification of the ellipsoid volume equation. The first step in the ABC/2 formula was soft tissue contrast adjustment.

The next step in the ABC/2 formula was identifying CT slice with the largest haematoma. Linear measurements were then made on the slice such that, A refers to the longest diameter or maximum length (in cm) of the haematoma

in axial section, B represents the longest diameter of haematoma perpendicular to A on the same CT slice, and C is the slice thickness (in cm) multiplied by the number of slices showing haematoma. All measurements for A and B were made on the DICOM CT data viewed in ITK-SNAP using the image calliper annotation tool. A, B and C were then multiplied, and the product was divided by 2, which yielded the estimated volume of haematoma in cubic centimetres (cm^3). Figure 4-3 demonstrates the diameter of A and B in axial plain using the ABC/2 formula based upon prior published description.

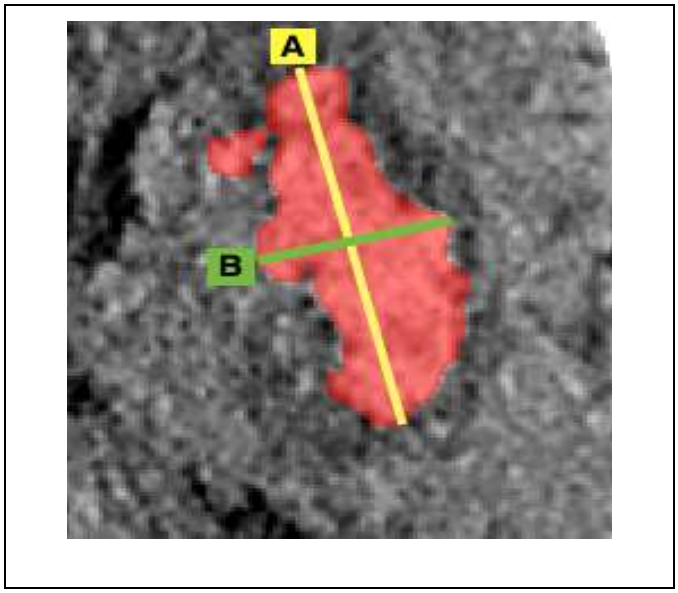


Figure 4-3 Diameter of A and B in ABC/2 haematoma volume measurement

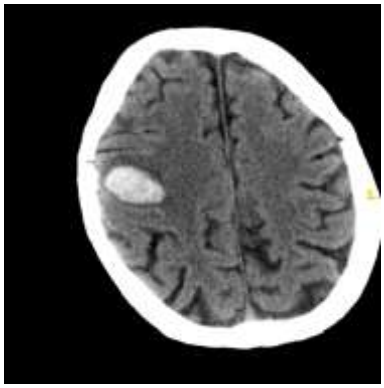
4.2.7 Haematoma Size and Shape Classification

Haematoma sizes were divided into four groups; < 3cm, 3 – 5cm, 5 – 8cm and > 8cm based on the largest area of haematoma showing on axial slice. Whereas the irregularity of shape of haematoma were assessed by visual inspection and rated using the scale of Barras et al [69], reflecting the spectrum of appearance of haematoma shape to provide and agreed visual representation of the terms "regular/irregular". The shape scales ranges from 1 (most regular shape) to 5 (most irregular shape) as shown on Table 4-1.

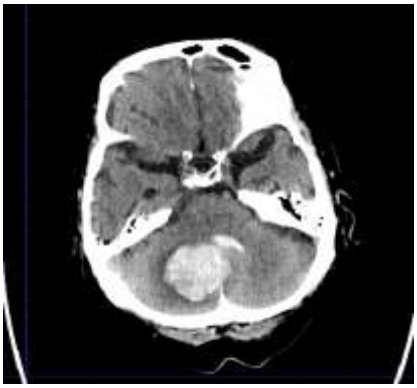
Each progressive category is defined by an extra lesion edge irregularity on the shape scale. Shape was defined as regular when rating was 1 or 2 on the visuals scale and categorized as irregular when the total rating was 3, 4 or 5 (Figure 4-4). Shape scores were analysed using the largest axial slice showing haematoma. Both of these categorizations were made by the adjudicator panel of experienced neuroradiologists who reviewed the images and blinded to baseline clinical characteristics, treatment allocation and outcome.

Table 4-1 Barras score for haematoma shapes

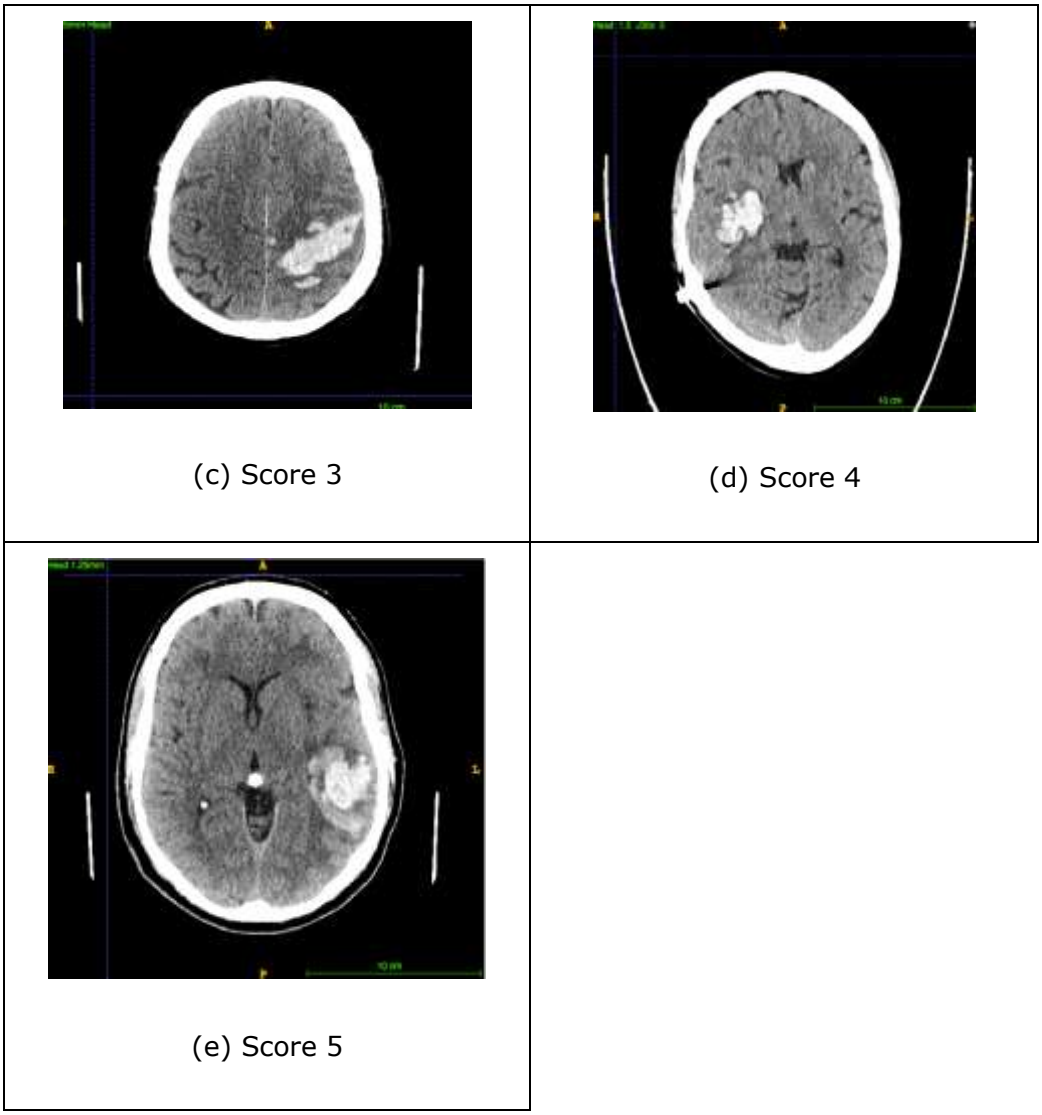
Barras Score	**Haematoma Shapes**
1	Most regular shape
2	Regular shape
3	Slightly irregular shape
4	Irregular shape
5	Most irregular shape



(a) Score 1



(b) Score 2



(c) Score 3

(d) Score 4

(e) Score 5

Figure 4-4 Categorization of haematoma shape regarding Barras score in TICH-2 population

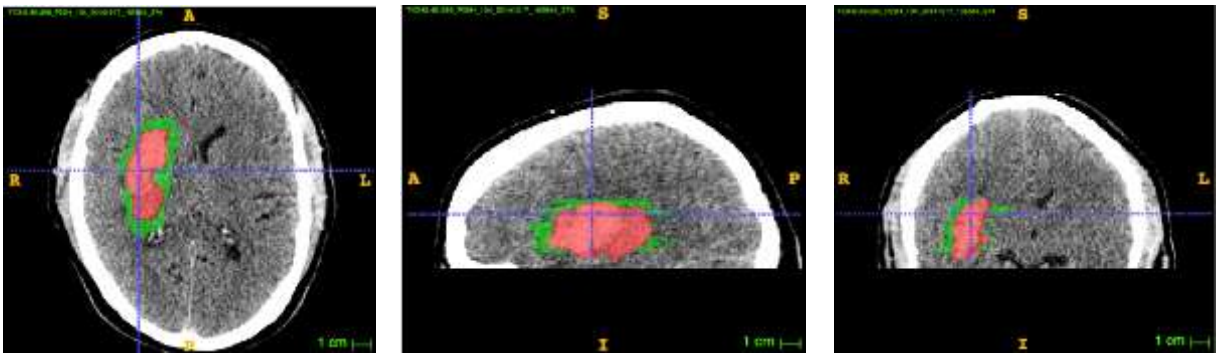
4.2.8 PHO Volume Measurement

The approach to segmenting PHO fundamentally differs from that for haematoma segmentation because the SAS region-growing approach fails for PHO. This is due to unclear boundaries and subtle variance in CT density between oedematous tissue and normal brain parenchyma in which the system fails to recognize and accurately differentiate. This study employs a manual delineation technique for PHO volume quantification since to date,

manual PHO tracing is the most widely used method in clinical setting and several studies have confirmed the intra- and inter-observer reliability of this approach (Chapter 3).

4.2.8.1 Manual Tracing Technique

Manual PHO delineation was done based on predefined criteria reported by Sebastian et al [196], of which it should be more hypodense than the corresponding region in the contralateral hemisphere and most hypodense immediately surrounding the haemorrhage. The rationale for the latter is that after ICH, transendothelial water flux from the intravascular to the interstitial compartments, both before and after rank blood-brain-barriers disruption, occurs initially immediately adjacent to the haematoma area [213]. Therefore, if a less hypodense area adjacent to the haematoma is followed by a more hypodense area further outward, the latter could represent entity like an old infarct. The area of identified PHO was usually between 1cm radius from the haematoma region [209] and this segmentation runs in the 3 dimensional planes; axial, sagittal and coronal. This step was repeated for every single CT slice containing PHO and the segmented images and volumetric result were saved in the same manner as haematoma segmentation mentioned in 4.2.5.6. The segmented PHO region in 3 dimensions is illustrated on Figure 4-5.



(a) (b) (c)

Figure 4-5 PHO (area in green) volume segmentation in (a) axial, (b) sagittal, and (c) coronal plane

4.2.9 Statistical Methods

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 24.0. After confirmation of normal distribution of the data by using the Shapiro-Wilk test, normally distributed data are expressed as mean ± SD and were compared using paired sample T-test, while non-normally distributed data are reported as median and interquartile range (IQR) and were compared by Wilcoxon Sign-Rank test. Measurements by all independent observers were averaged to yield mean values for analysis of inter-operator agreement. Measurement of inter-observer and intra-observer reliability was assessed using the intraclass correlation coefficient (ICC) with 95% CI. Intra-observer variability was evaluated by comparing initial measurements of haematoma and PHO volumes of non-enhanced CT brain images of spontaneous ICH with repeated measurements by the same investigator in 2 weeks' time interval, blinded to the result of the first measurement. Inter-observer variability was evaluated by comparing the result of these measurements by two independent investigators in 2 independent sessions. A p-value of < 0.05 was considered statistically

significant. Interpretation of the ICC results used the same categorisation as described in Chapter 2.

4.3 Results

4.3.1 Observer Reliability of SAS Technique in Haematoma Volume Quantification and Manual Delineation in PHO Volume Measurement.

Twenty non-enhanced CT brain scans presenting spontaneous ICH from ENOS clinical trial were used for reliability assessment. The ENOS participants came from a similar population of people presenting with acute ICH recruited to a clinical trial but were not specifically matched for baseline characteristics. ENOS trial was a partial-factorial randomised controlled trial aimed to assess the safety and efficacy of GTN given within 48 hours to patients with acute ischaemic or haemorrhagic stroke and high blood pressure. Between July 20, 2001, and October 14, 2013, 4011 patients were enrolled and randomly assigned to 7 days of transdermal GTN (5 mg per day), started within 48 hours of stroke onset, or to no GTN (control group). Functional outcome at day 90 did not differ between groups – the adjusted common odds ratio (OD) for worse outcome with GTN was 1.01 (95% CI, 0.91 – 1.13; $p = 0.83$).

Reliability assessment for both volume quantifications was done by 2 independent observers in 2 independent sessions. The result of normality test as demonstrates on Table 4-2 shows that the data was non-normally distributed in terms of the skewness and kurtosis, for both haematoma and PHO volumes measured by both observers. The same result was also shown by the Shapiro-Wilk test with $p < 0.05$.

Table 4-2 Normality test on haematoma and PHO volumes measured by both observers

Normality Test	Haematoma Volume		PHO Volume	
	Observer 1	Observer 2	Observer 1	Observer 2
Shapiro-Wilk	< 0.05	< 0.05	< 0.05	< 0.05
Skewness z-value	2.553	2.432	3.824	3.592
Kurtosis z-value	0.372	0.247	3.089	2.761

The median haematoma volume measured by Observer 1 was 5.58 mL (IQR, 3.02 – 42.92; range 0.68 mL – 85.9 mL) and by observer 2 was 8.08 mL (IQR, 4.20 – 40.71; range 1.7 mL – 87.73 mL). Wilcoxon Signed Rank Test shows no significant difference of haematoma volume measured by Observer 1 and Observer 2 (p = 0.218). The median for PHO volume measured by Observer 1 was 4.5 mL (IQR, 2.99 – 22.56; range 1.24 mL – 136.89 mL) and by Observer 2 was 9.81 mL (IQR, 6.98 – 46.22; range 4.43 mL – 134.84 mL). There was significant difference of PHO volume quantification between both observers (p = 0.002) (Table 4-3). The volumes distribution for haematoma and PHO measured by both observers is illustrated on Figure 4-6.

The ICC assessment showed excellent agreement for haematoma volume quantification (p < 0.001). The intra-observer reliability for both observers was 0.999 and the inter-observer agreement was 0.984. For PHO volume quantification, there was excellent intra-observer correlation (0.997) demonstrated by Observer 1 (p < 0.001) and good intra-observer agreement (0.834) showed by Observer 2 (p < 0.001). There was also excellent inter-observer agreement of 0.987 (p < 0.001) achieved for PHO volume quantification (Table 4-4).

Table 4-3 Wilcoxon Signed Rank Test for haematoma and PHO volume quantification

Statistics	Haematoma Volume, mL (n = 20)		PHO Volume, mL (n = 20)	
	Observer 1	Observer 2	Observer 1	Observer 2
Median, [IQR]	5.58 [3.02 – 42.92]	8.08 [4.20 – 40.71]	4.50 [2.99 – 22.56]	9.81 [6.98 – 46.22]
Variance	711.21	687.42	1481.69	1338.89
Range (min, max)	0.68,85.9	1.7,83.73	1.24,136.89	4.43,134.84
p value	0.218		0.002	

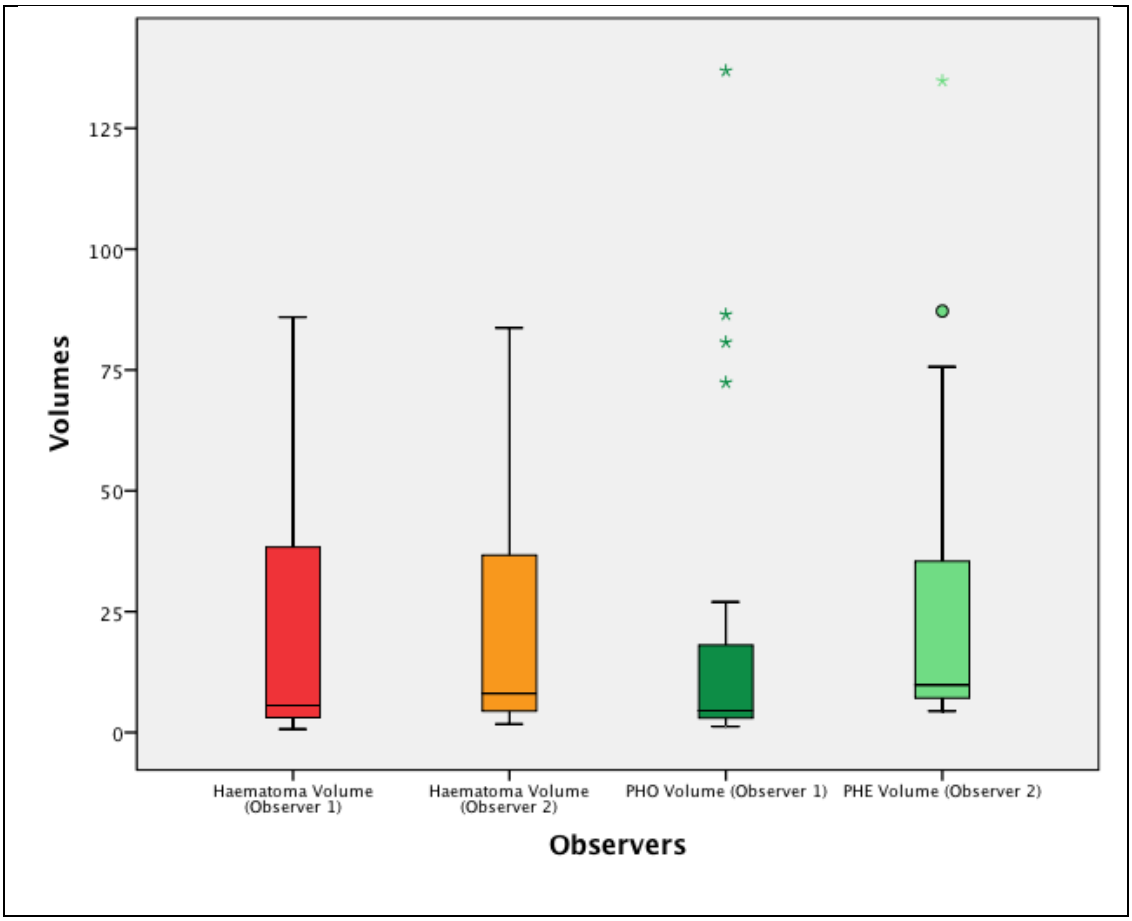


Figure 4-6 Distribution of haematoma and PHO volumes measured by both observers. Boxes represent the interquartile range, and the whiskers indicate the 5th-95th centiles. The round circle indicates a value above the 95th centile and the asterisks indicate values above the 99th centile.

Table 4-4 Reliability assessment of haematoma and PHO volumes quantification

Validation Type	Intra-observer Observer 1	Intra-observer Observer 2	Inter-observer
Haematoma Volume Quantification			
ICC	0.999	0.999	0.984
P Value	< 0.001	< 0.001	< 0.001
PHO Volume Quantification			
ICC	0.997	0.834	0.987
P Value	< 0.001	< 0.001	< 0.001

4.3.2 Observer Reliability of ABC/2 for Haematoma Volume Measurement

Twenty of non-enhanced CT brain images of spontaneous ICH from the ENOS clinical trial were assessed by 2 independent observers. The Shapiro-Wilk normality test showed that the data of hematoma volume measured with ABC/2 formula by both observers was non-normally distributed ($p < 0.05$) with z-values of Skewness and Kurtosis was 2.667 and 0.425 respectively for Observer 1 and 2.672 and 0.283 respectively for Observer 2 as shown on Table 4-5.

Table 4-5 Normality test for haematoma volumes measured by ABC/2 by both observers

Normality Test	Observer 1	Observer 2
Shapiro-Wilk	< 0.05	< 0.05
Skewness z-value	2.667	2.672

Kurtosis z-value	0.425	0.283

The median volume of haematoma measured by Observer 1 was 7.25 mL (IQR, 3.455 – 39.36) ranged 0.7 mL – 94.31 mL and 6.825 mL (IQR, 3.563 – 35.6), ranged 1.25 mL – 93.91 mL by Observer 2. There was no significant difference of haematoma volume segmentation by the ABC/2 formula between both observers (p = 0.911). Figure 4-7 illustrates the distribution of the volume's quantification by both observers.

Table 4-6 Wilcoxon Signed Rank Test of haematoma volume measured by ABC/2 formula

Statistic	Haematoma Volume (mL) n = 20	
	Observer 1	Observer 2
Median [IQR]	7.25 [3.455 – 39.36]	6.825 [3.563 – 35.6]
Variance	962.33	1050.27
Range	0.7 – 94.31	1.25 – 93.91
p value	0.911	

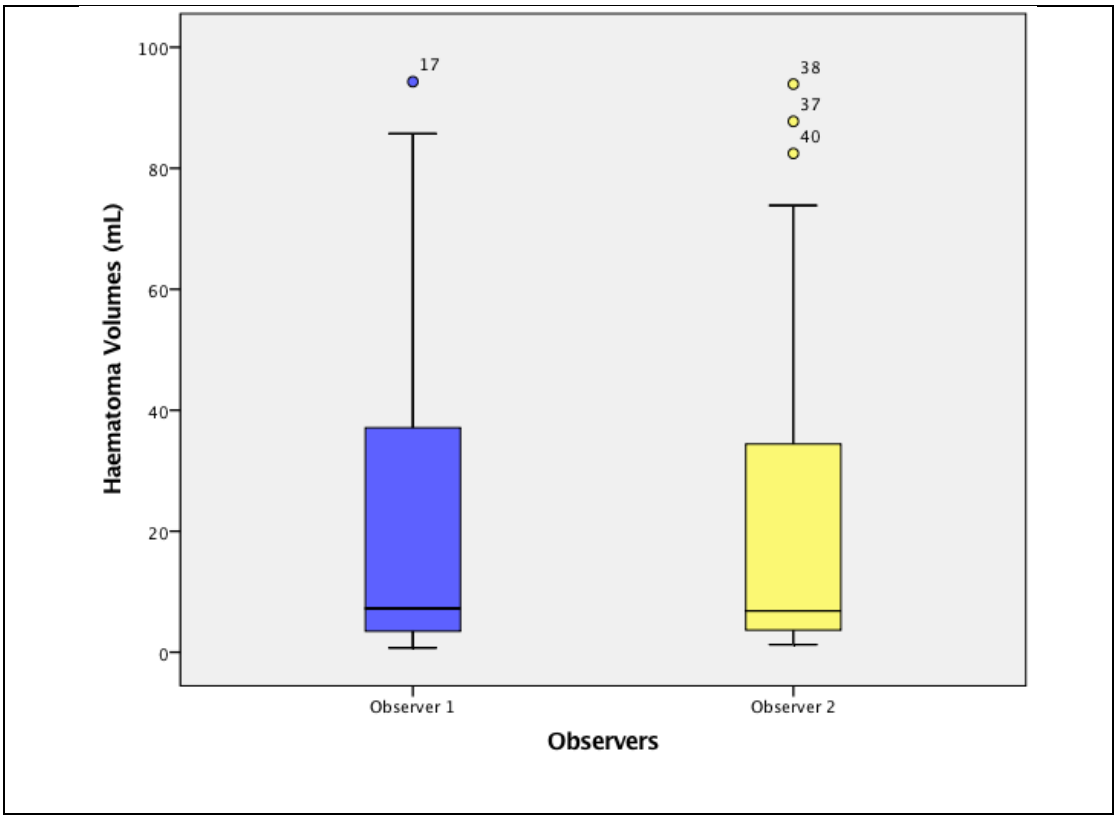


Figure 4-7 Distribution of haematoma volumes measured by ABC/2 formula by both observers

There was excellent intra- and inter-observer reliability of haematoma volume quantification using the ABC/2 formula by both observers as shown on Table 4-7. The intra-observer agreement of Observer 1 was 0.999 ($p < 0.001$) and 0.996 ($p < 0.001$) of Observer 2, while the inter-observer agreement was 0.988 ($p < 0.001$).

Table 4-7 Reliability assessment of haematoma volume quantification using ABC/2 formula

Validation Type	Intra-observer Observer 1	Intra-observer Observer 2	Inter-observer
ICC	0.999	0.996	0.988
P Value	< 0.001	< 0.001	< 0.001

4.3.3 Comparison of Haematoma Volume Measurement by SAS and ABC/2 in the TICH-2 Population

There were 2254 participants presenting with spontaneous ICH in the TICH-2 population, of which 1261 (56%) were males and 993 (44%) were females (median age 71, IQR 60 – 80 years) involved in this study. The Shapiro-Wilk test showed that the data of haematoma volumes measured by SAS and ABC/2 techniques were non-normally distributed ($p < 0.05$) with Skewness and Kurtosis z-values of 36.4 and 38.5 for SAS, and 39.1 and 46.5 for ABC/2 formula respectively as demonstrated on Table 4-8.

Table 4-8 Normality test on haematoma volumes measured by both methods of quantification

Normality Test	SAS	ABC/2
Shapiro-Wilk	< 0.05	< 0.05
Skewness z-value	36.4	39.1
Kurtosis z-value	38.5	46.5

The median haematoma volume quantified by SAS method was 13.36 mL (IQR 5.51 – 32.32), ranged 0.10 mL – 206.8 mL, and the median volume quantified by ABC/2 method was 14.58 mL (IQR 5.55 – 36.91), range 0.07 mL – 236.6 mL. The haematoma volumes measured by SAS shows a significant difference to the ABC/2 formula ($p < 0.001$). The whole result of haematoma volume quantification from both methods is shown on Table 4-9 and the volume distribution is illustrated on Figure 4-8. There was a significant difference of haematoma volume measured between both techniques, when divided into different size and shape as shown on Table 4-10. Across the haematoma visual size categories, haematoma volumes calculated by the ABC/2 method were

significantly larger than haematoma volumes quantified by the SAS technique ($p < 0.001$). As the haematoma size category increased, the difference between the ABC/2 and the SAS measurements were slightly increased.

The most common shape of haematoma was irregular (72.8%), followed by regular haematoma (27.2%). Haematoma volumes measured by the SAS method were significantly larger in regular shape haematoma compared to those measured by the ABC/2 ($p < 0.001$) while in irregular shape of haematoma, the volumes measured by the ABC/2 method were significantly larger than the volumes measured by the SAS ($p < 0.001$). When compared by shape, the difference of haematoma volumes between the SAS and the ABC/2 methods were slightly increased as the shape of haematoma changed from regular (Score 1 and 2) to irregular (Score 3 to 5) (Figure 4-11).

The relationship of haematoma volume quantification between SAS and ABC/2 is demonstrated in Table 4-10 and illustrated oi Figure 4-9 as scatterplot with linear correlation, and in Figure 4-10 as scatterplot with non-linear (quadratic) fitted curve. A strong linear correlation of r = 0.938 ($p < 0.01$) was shown between haematoma volume measured by SAS and ABC/2, especially in small size haematoma. The non-linear (quadratic) curve fitted the data marginally better than the liner fit line (r = 0.942 compared to 0.938 respectively). Based on the plotted graph, the differences between volumes measured by SAS and ABC/2 increased with larger haematoma volume, with volume estimates by ABC/2 being larger than volume measurements by SAS for the larger haematoma sizes.

Table 4-9 Haematoma volumes by SAS and ABC/2 quantifications

	Hematoma Volume SAS (mL) n = 2254	Hematoma Volume ABC/2 (mL) n = 2254
Range (Min- Max)	0.10 - 206.8	0.07 – 236.6
Median	13.36	14.58
IQR [lower, upper]	5.51 – 32.32	5.55 – 36.91
Variance	740.46	978.91

Table 4-10 Comparison of haematoma volume quantification between SAS and ABC/2 based on haematoma size and shape

Group	Haematoma Volume, mL		Deviation (%)	P value
	SAS	ABC/2		
Haematoma size				
< 3cm (n = 1260)	6.34 [3.08 – 11.33]	6.51 [2.98 – 12.15]	2.68	< 0.001
3 – 5cm (n = 520)	22.6 [15.5 – 34.6]	25.0 [16.22 – 39.5]	10.6	< 0.001
5 – 8cm (n = 401)	53.8 [34.4 – 75.2]	57.3 [38.3 – 80.8]	6.5	< 0.001
> 8cm (n = 73)	84.9 [64.4 – 101.6]	96.5 [69.6 – 125.3]	13.67	< 0.001
Haematoma shapes				
Regular (n = 612)				
Score 1 (n = 190)	1.76 [0.88 – 4.55]	1.62 [0.74 – 4.77]	-7.95	< 0.001
Score 2 (n = 422)	5.52 [2.77 – 11.4]	5.42 [2.68 – 11.29]	-1.81	< 0.001
Irregular (n = 1642)				
Score 3 (n = 522)	9.66 [5.4 – 17.72]	10.1 [5.57 – 20.56]	4.55	0.019
Score 4 (n = 399)	16.7 [7.76 – 31.23]	17.6 [8.81 – 32.2]	6.31	< 0.001
Score 5 (n = 721)	36.9 [19.2 – 65.7]	42.6 [21.5 – 69.8]	15.45	< 0.001

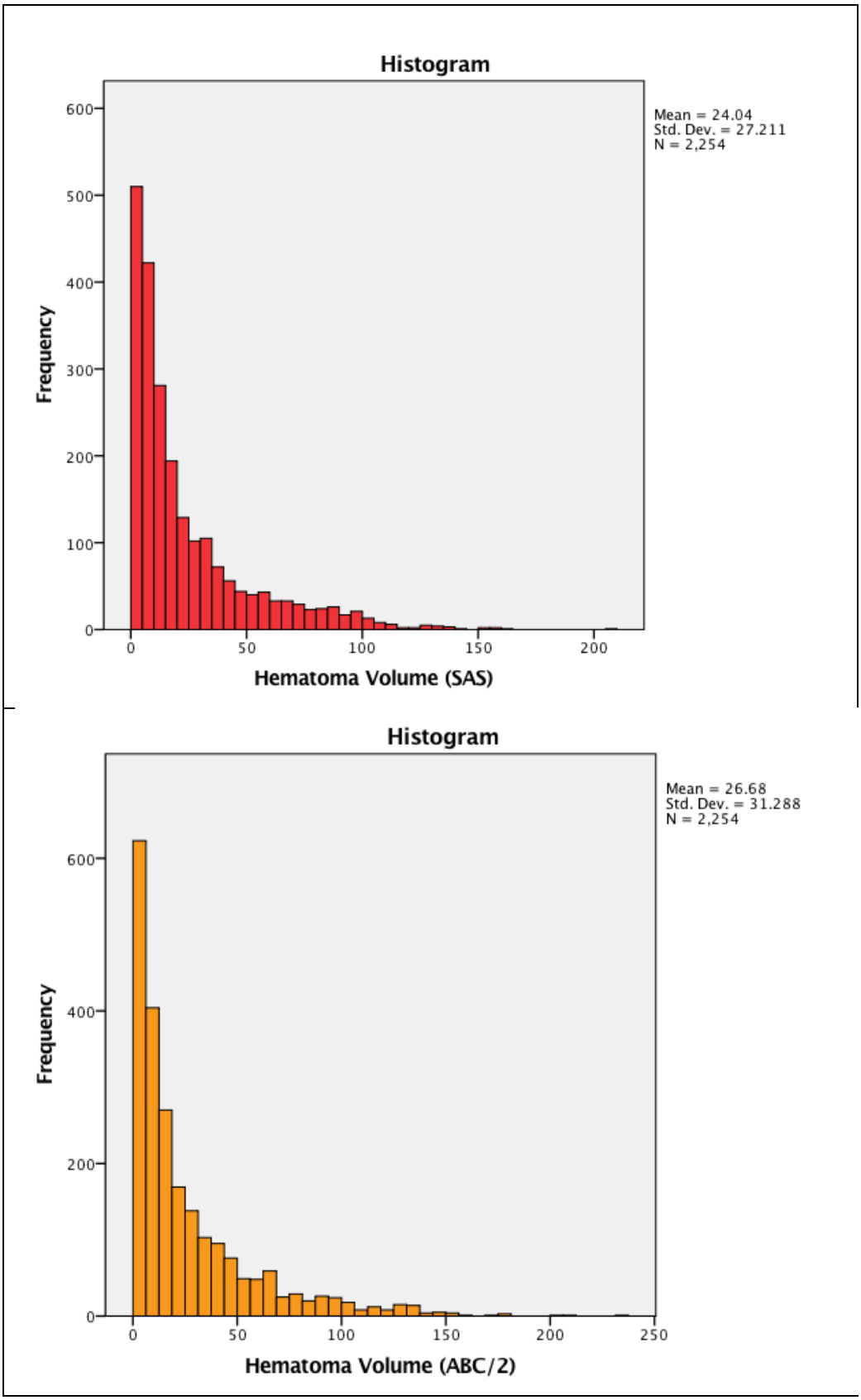


Figure 4-8 Distribution of haematoma volumes measured by both methods of quantification

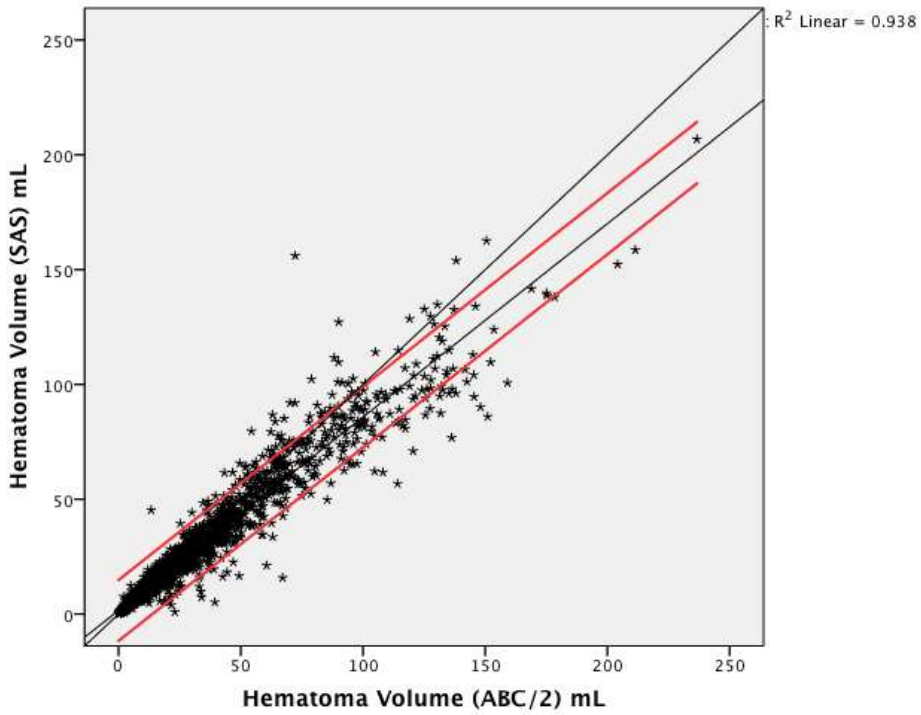


Figure 4-9 Linear correlation of haematoma volume measured by SAS and ABC/2 methods

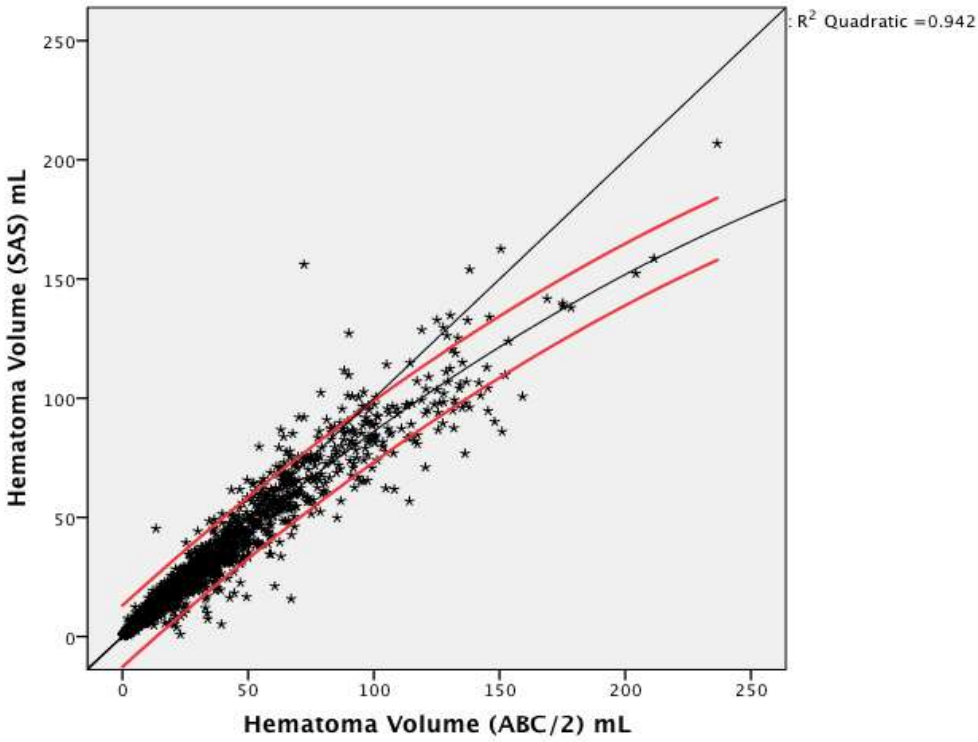


Figure 4-10 Non-linear correlation of haematoma volume measured by SAS and ABC/2 methods

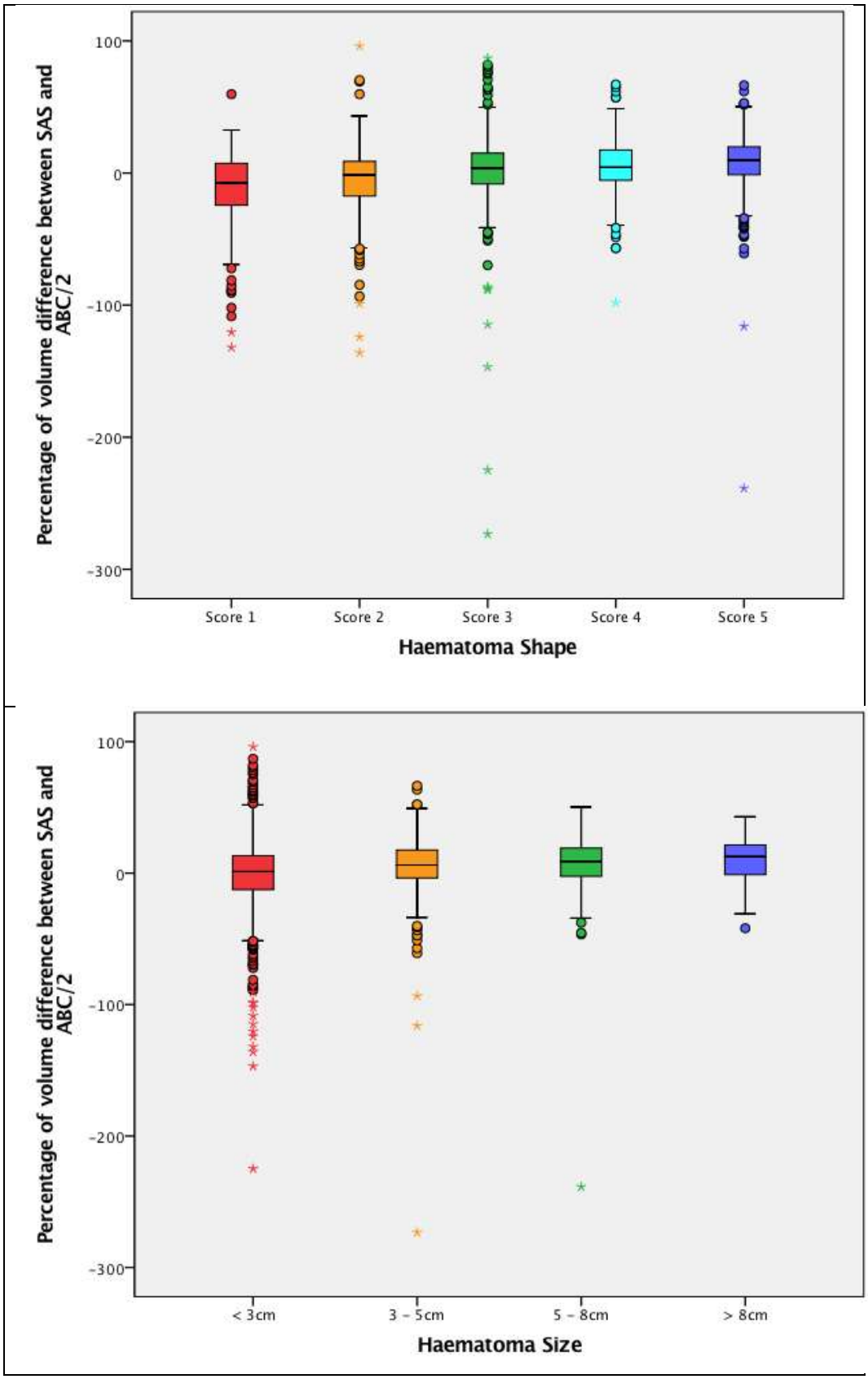


Figure 4-11 Percentage of difference of haematoma volume between SAS and ABC/2 based on haematoma shape and size

4.3.4 Comparison of Haematoma and PHO Measurements from CT Images of Different Slice Thickness

The effect of slice thickness on haematoma and PHO volumes quantification was examined using a series of 30 CT brain scans from the TICH-2 population where 2 different slice thicknesses of 1mm and 5mm are available for each series. The quantifications of both volumes were measured using the same techniques as mentioned previously (SAS technique with manual editing and ABC/2 formula for haematoma volume estimation and manual delineation for PHO volume quantification).

The median volume of hematoma using SAS for 1mm slice thickness was 12.41 mL (IQR 5.83 – 22.01) and for 5mm slice thickness was 12.85 mL (IQR 4.94 – 26.59). Hematoma measured using ABC/2 formula median volume was 15.19 mL (IQR 5.57 – 25.33) for 1mm slice thickness and 15.64 mL (IQR 5.26 – 28.05) for 5mm slice thickness. While median volume for PHO in 1mm slice thickness was 9.98 mL (IQR 4.89 – 19.96) compared with 12.18 mL (IQR 5.96 – 19.49) in 5mm slice thickness. There was a small but significant difference in haematoma volume measured using SAS (0.44 mL) between 1mm and 5mm slice thicknesses (wilcoxson signed rank test, $p = 0.008$), with larger volumes measured on the 5mm slice thickness, but no significant difference in haematoma volume measured with ABC/2 formula (wilcoxson signed rank test, $p = 0.178$). There was also no significant difference in PHO volumes between 1mm and 5mm slice thicknesses (wilcoxson signed rank test, $p = 0.633$). The whole results for haematoma and PHO volumes segmentations are demonstrated on Table 4-11. Table 4-12 shows a difference in haematoma and PHO volume segmentations between 1mm and 5mm slice thickness when categorized by haematoma and PHO size. There were no significant differences of both haematoma and PHO volumes

segmentation in both slice thicknesses. However, there was not enough amenable data to compare the segmentation between 1mm and 5mm slice thickness in haematoma size > 5cm and PHO volume > 30mL.

A scatterplot on Figure 4-13 to Figure 4-15 illustrates the relationship of hematoma and PHO volumes between both slice thicknesses. Haematoma volume measured by SAS and ABC/2 formula demonstrated an excellent relationship between 1mm and 5mm slice thickness of $R^2 = 0.981$ and $R^2 = 0.935$, respectively. The quantification of PHO volume also showed a strong relationship between both slice thicknesses of $R^2 = 0.918$.

Table 4-11 Wilcoxon Signed Rank Test for haematoma and PHO volumes estimation for 1mm and 5mm slice thicknesses

Statistic	Hematoma Volume SAS (1mm s.t)	Hematoma Volume SAS (5mm s.t)	Hematoma Volume ABC/2 (1mm s.t)	Hematoma Volume ABC/2 (5mm s.t)	PHO Volume (1mm s.t)	PHO Volume (5mm s.t)
Median [IQR]	12.41 [5.83 – 22.01]	12.85 [4.94 – 26.59]	15.19 [5.57 – 25.33]	15.64 [5.26 – 28.05]	9.98 [4.89 – 19.96]	12.18 [5.96 – 19.49]
Variance	384.2	480.9	695	771.7	750.2	625.4
Minimum	1.627	1.499	1.319	1.5	0	0
Maximum	93.25	93.19	120.5	119.4	139.2	121.7
p value	*0.008*		*0.178*		*0.633*	

Table 4-12 Comparison of haematoma and PHO volume quantification between 1mm and 5 mm slice thicknesses

Haematoma Size	SAS (1mm s.t)	SAS (5mm s.t)	p value	ABC/2 (1mm s.t)	ABC/2 (5mm s.t)	*p* value
< 3 cm	4.73 (2.02 – 12.39)	4.34 (3.04 – 12.60)	0.345	5.99 (2.25 – 13.32)	5.14 (2.70 – 15.08)	0.753

3 – 5 cm	15.62 (10.20 – 24.46)	15.96 (10.34 – 27.43)	0.560	18.02 (14.08 – 26.86)	16.80 (13.59 – 31.22)	0.221
> 5 cm	-					
PHO Size	Manual (1mm s.t)	Manual (5mm s.t)				
< 30mL	9.84 (4.62 – 17.43)	11.96 (4.86 – 19.08)	0.568			
> 30mL	-					

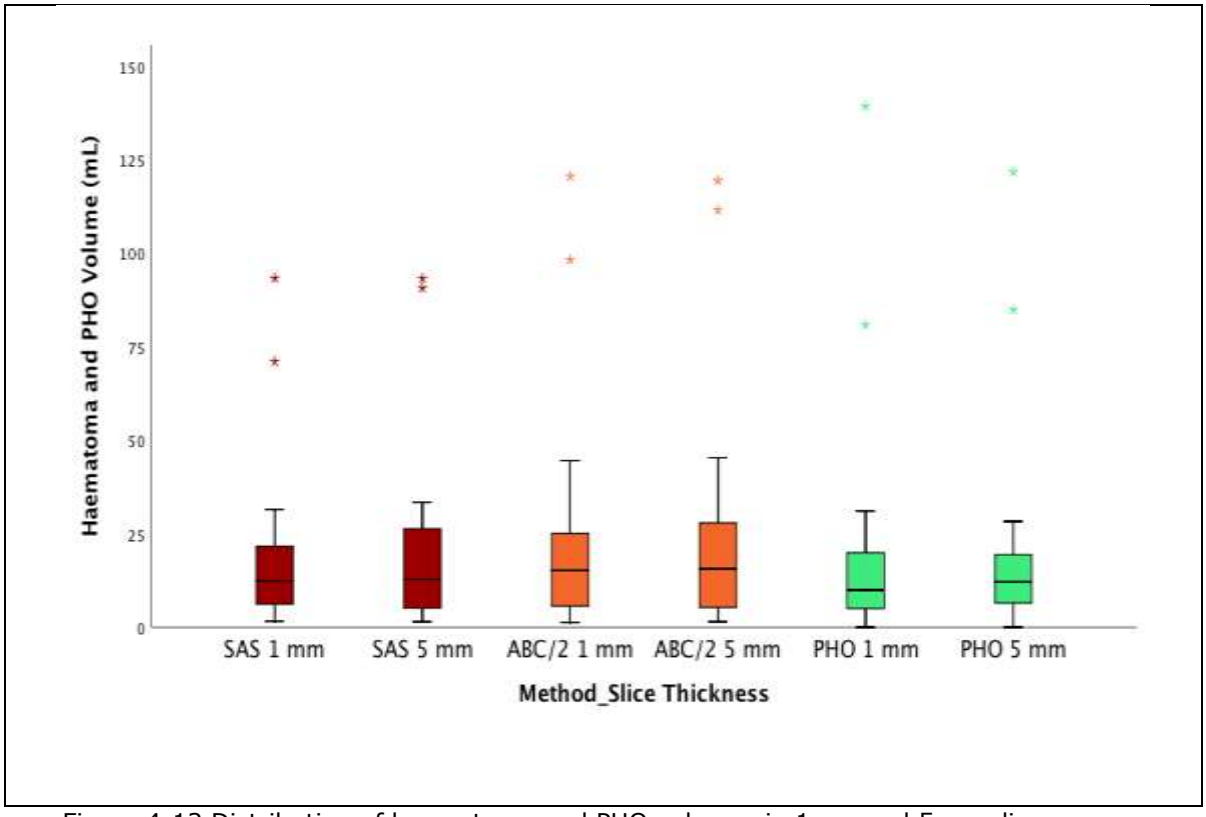


Figure 4-12 Distribution of haematoma and PHO volumes in 1mm and 5mm slice thicknesses

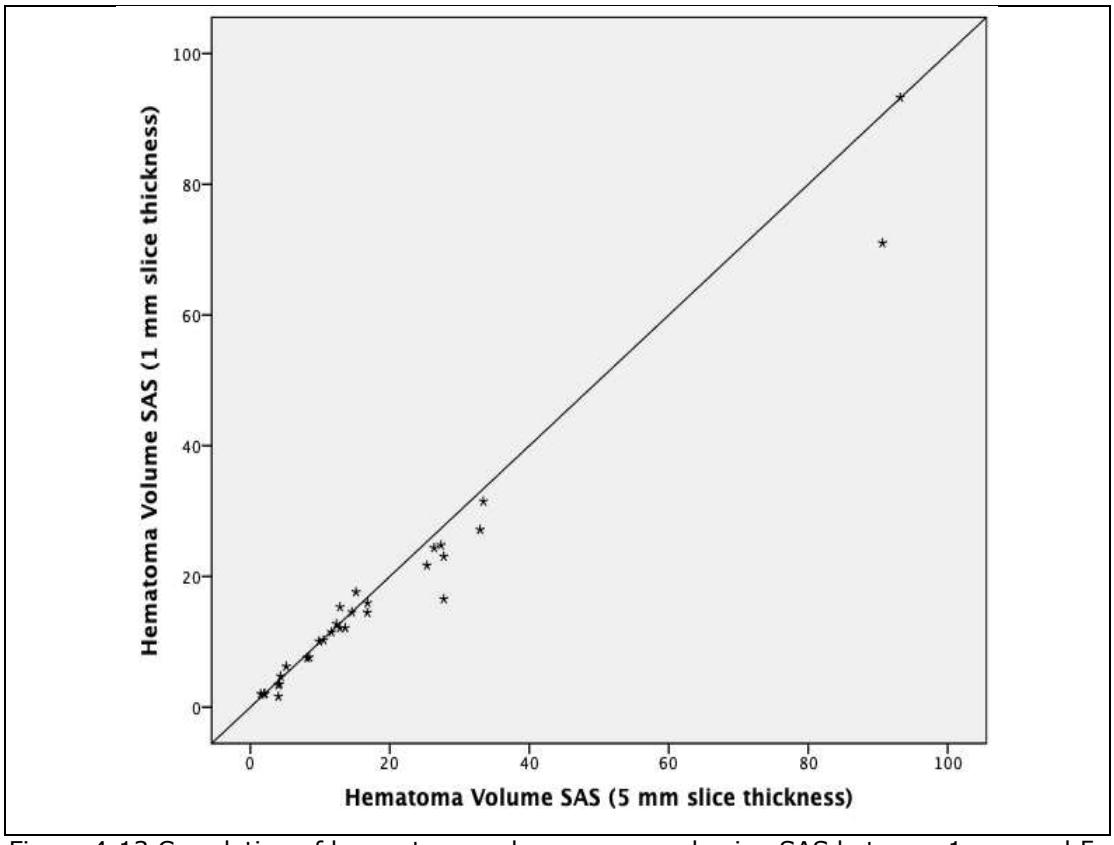


Figure 4-13 Correlation of haematoma volume measured using SAS between 1 mm and 5 mm slice thicknesses [x=y]

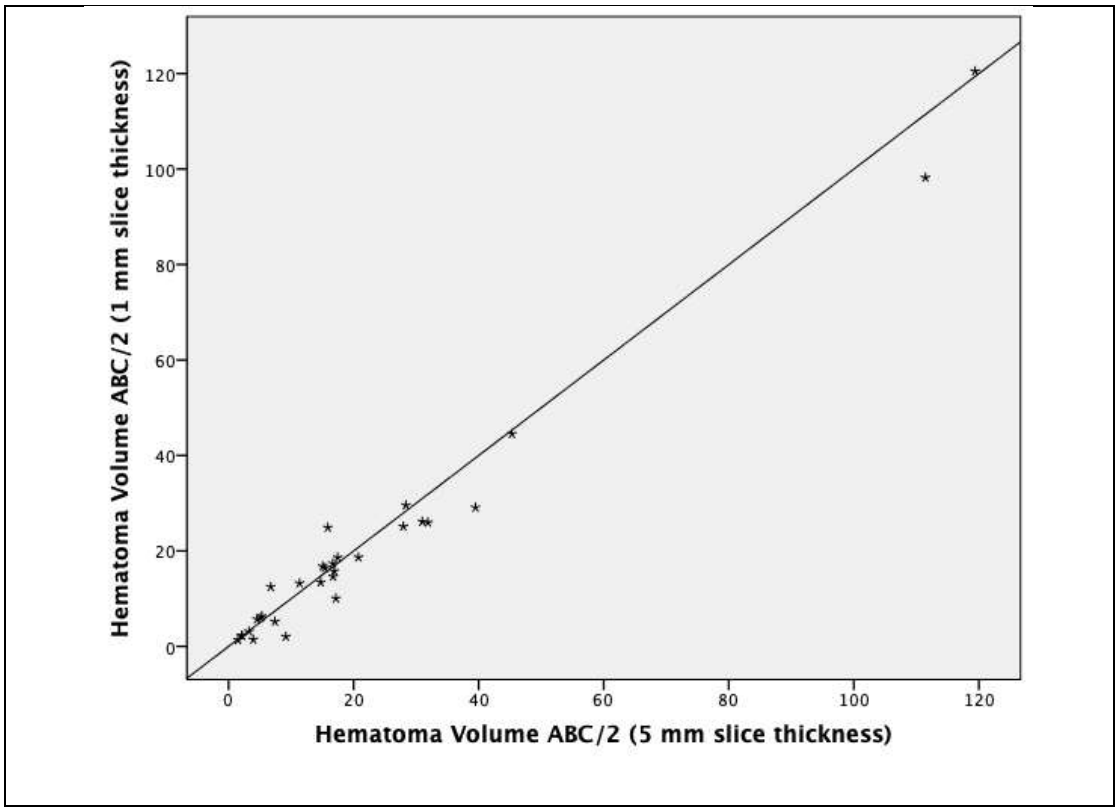


Figure 4-14 Correlation of haematoma volume measured using ABC/2 formula between 1 mm and 5 mm slice thicknesses [x=y]

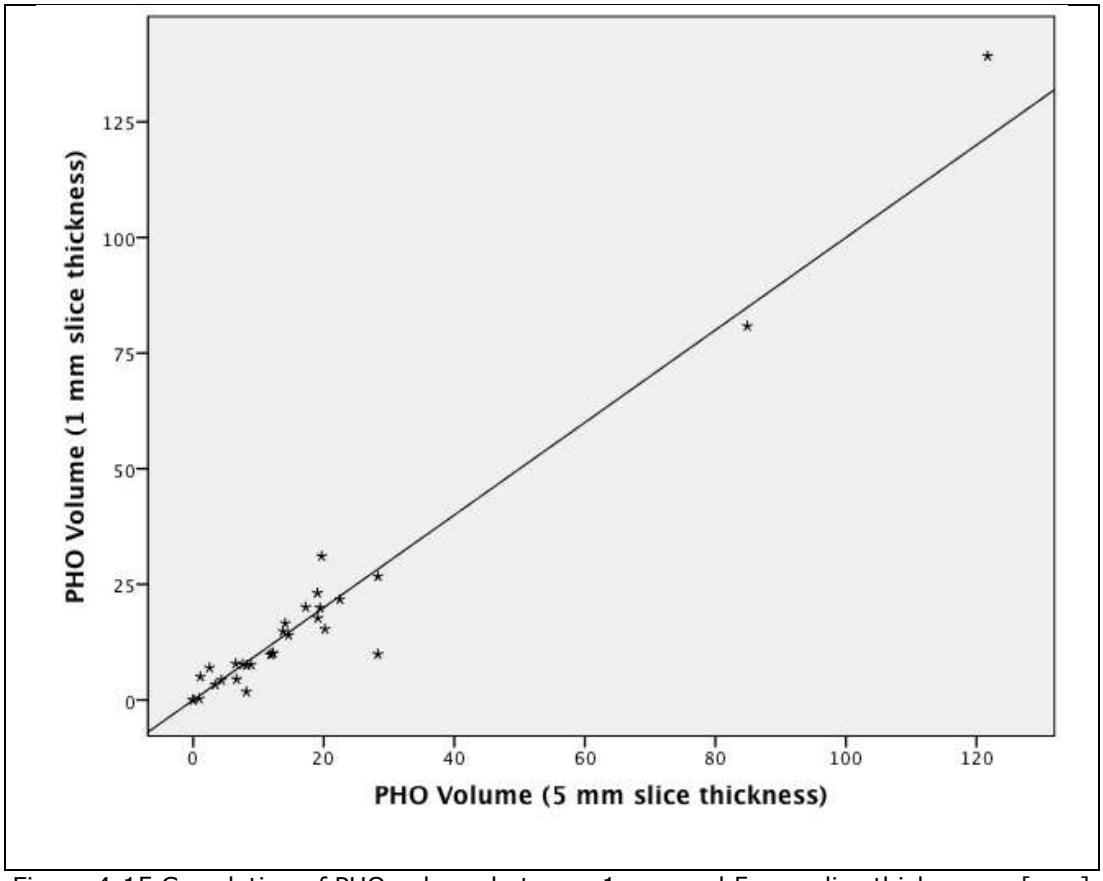


Figure 4-15 Correlation of PHO volume between 1 mm and 5 mm slice thicknesses [x=y]

4.4 Discussion

This chapter reports the methods and reliability of haematoma and PHO volume quantification, and presents a comparison of both measurement reliability, and absolute volumes for measurements made using SAS and ABC/2. The chapter also reports a comparison of haematoma and PHO volume measurements when slice thickness varies. The major findings are: (1) The agreement within and between observers was excellent for measurement of haematoma and PHO volume using SAS and manual allocation respectively; (2) The ABC/2 formula was also showing an excellent intra- and inter-observer reliability in measuring haematoma volume; (3) Haematoma volumes measured by ABC/2 were significantly larger from those quantified by SAS; the discrepancy increased as haematoma size became larger and irregular; (4) The haematoma volume measured by SAS technique was marginally larger in 5mm compared to 1mm slice thickness, although this difference was found to be statistically significant. In contrast no significant difference in haematoma volumes measured by ABC/2 and PHO volume by manual tracing was found as slice thickness varied.

Reliable quantification of both haematoma and PHO volume is important for clinical trials to measure the effects of potential interventions in patients with spontaneous ICH. Systematic reviews were performed in Chapter 2 and Chapter 3 to compare the reliability established in this study with previously published works on ICH and PHO volume measures. All included studies in Chapter 2 that reported on reliability have shown an excellent intra- and inter-observer reliability of SAS method (ICC above 0.9) in measuring haematoma volume. In this study, haematoma volume quantification by SAS approach has been confirms to have a high intra- (Observer 1 = 0.999, Observer 2 = 0.999) and inter-observer reliability (0.984) and is comparable to previously reported result by K. Krishnan et al [76] (intra-observer reliability = 0.93, inter-observer reliability = 0.985), J. C. Kosior et al [94] (intra-

observer reliability = 0.99, inter-observer reliability = 0.99) and Kothari et al [63] (intra-observer reliability = 0.99, inter-observer reliability = 0.99). J. C. Kosior et al [94] was developed a haematoma volume estimation tool called Quantomo with the aid of the region growing segmentation, a similar approach used in this study with an excellent inter- and intra-observer reliability. Nonetheless, the SAS quantification introduced by K. Krishnan and his colleagues is quite varied. They measured haematoma volume using the upper and lower attenuation values (40 – 80 HU) of haemorrhage by sampling from the haemorrhage and normal brain. After manual editing, the area of each slice was measured and multiplied by scan thickness to obtain SAS volume. This approach of SAS volume estimation method also showed an excellent inter- and intra-observer reliability. The intraclass reliability in this study was only tested on a series of 20 brain images, (of similar size as done by R. U. Kothari et al [63]) compared to 47 segmentations done by K. Krishnan et al [76] and 30 scans by Kosior et al [94]. Good results of inter- and intra-observer reliability of this approach make it appropriate to use as volume quantification technique in larger data of TICH-2 population.

This study used a manual delineation of PHO on CT brain images using ITK-SNAP software and shows good inter- (0.987) and intra-observer reliability (Observer 1 = 0.997 and Observer 2 = 0.834,) when tested on 20 brain images. Compared to previous studies done on PHO volume analysis, most studies reported the intraclass reliability of SAS methods [35][40][93][105][106][115] [187][194][196] and only 2 studies reported reliability of manual PHO tracing [40][115]. The reliability analysis of PHO volume quantification result from this study is consistent with previous study done by R. McCourt et al [40] (intra-observer reliability = 0.95) and B. Volbers et al [115] (intra-observer reliability = 0.96, inter-observer reliability = 0.89). The study done by these 2 authors additionally had compared the technique of PHO volume quantification between manual tracing and SAS method and the result showed that manual PHO

quantification had comparable intraclass correlation coefficient with those measured by SAS approach. Because of the variable and often subtle reductions in tissue density of oedema on CT scan, PHO segmentation on CT images is quite challenging and it is difficult to discriminate between the oedematous tissues and normal brain parenchyma with the naked eye. Because of that, the superior imaging modality and gold standard for PHO volume quantification is still MRI because of high contrast of PHO on FLAIR or T-2 weighted sequences [115]. CT becomes an imaging modality of choice because of its widely accessible, fast screening time and can be performed in almost all patients including critically ill patients. Compared to previously published study, semi-automatic CT-based segmentation of PHO using a threshold range of 5 – 33 HU is said to represent a useful tool for PHO quantification since the threshold was defined using FLAIR MRI sequences as a reference and the approach revealed a strong correlation with MRI and show a high intra and inter reliability compared to manually tracing PHO on CT.

SAS segmentation of haematoma volume has been shown to provide reliable measurement and correlated well with the widely used ABC/2 formula throughout the haematoma segmentation process (r_s = 0.982, ABC/2 vs. region growing ITK-SNAP). However, haematoma volumes measured by ABC/2 were significantly larger from those quantified by SAS and the discrepancy increased as haematoma size became larger and irregular. Based on these results, clinicians need to be aware that the ABC/2 method provides an approximation of haematoma volume, but ABC/2 measurements may vary from the true volume measurements and this effect may be more marked under certain conditions such as large or irregular haematomas. Where treatment decisions are based on volume measurements, especially if the haematoma volume is close to a threshold for starting or discounting a particular treatment, then the more robust SAS method may be more appropriate. This result is comparable to the previous findings by R. U.

Kothari et al (r = 0.96, ABC/2 vs. computed planimetric) [63], H. Hussein et al. (r = 0.93, central ABC/2 (measured by single experienced rater) vs MIPAV)[71] and J. M. Gebel et al (r = 0.929, ABC/2 vs. computer-assisted volumetric technique)[112]. However, a strong agreement between central ABC/2 and MIPAV was significantly reduced (r = 0.63, on-site ABC/2 vs MIPAV) when the ABC/2 method was used by multiple trial investigators with variable familiarity with the ABC/2 method [71] . The reliability of on-site ABC/2 was slightly reduced compared to the results reported in this research and in previous aforementioned studies[78][90]. In general, this study had proven that ABC/2 volume estimation gives a very close approximation to SAS in most cases. The method did, however, generally overestimate haematoma volume, especially when haematoma had a nonellipsoid shape (the percentage difference between the 2 methods was larger in the most irregular shape group). These results are not surprising, given that the underlying assumption of the ABC/2 method is that the haematoma has an ellipsoid-like shape. Nevertheless, SAS still offers the theoretical advantage that it should more closely reflects the true haematoma volume because the complexity of the shape is taken into account in the contouring of the haematoma outline. In the current and previous studies, SAS technique was considered the gold standard against which the ABC/2 method was compared [63][70] [80][82][92][112][214]. However, it is important to remember that SAS method is subject to certain measurement biases too. As only CT slices are clinically accessible, and a limited number of CT slices cannot possibly contain all information about the haematoma, there must be differences between the volume estimated using SAS technique and the actual haematoma volume. Despite such potential bias, however, the SAS method is still the most accurate method available for estimating haematoma volume in vivo, and it is considered sufficient to serve as the gold standard for method comparison. Although both techniques of volume quantification show excellent intra- and inter-observer reliability, ABC/2 has the advantage that it is

fairly quick whereas SAS comes at the cost that it is time consuming and at times technically challenging and requires segmentation software. As an example, for haematoma that was adjacent to the bone, it was difficult to set segmentation parameters to identify a haematoma and the threshold may miss an area of haematoma [76]. Additionally, the threshold method will not account for PHO, which increases the mass effect; thus, the space occupying effect of the haematoma may be much larger than its measured hyperattenuated area. As segmentation is semiautomatic, it is feasible to adjust manually for errors if they are apparent. All images require visual checking and manual correction; failure to do so would result in erroneous measurements. The problem is compounded by more irregular spontaneous ICH.

A small but statistically significant difference between haematoma volumes measured by SAS technique on 1mm and 5mm slice thicknesses has been shown by SAS segmentation technique. However, haematoma and PHO volume measure by the ABC/2 formula and manual tracing respectively show no significant difference, thus fails to reject a null hypothesis. Unfortunately, the sample is too small (n = 30) to support the assumption. This finding contradicted with a previously published study of which they reported that volume increased 1 – 2% for 1mm, 1.25mm, 2mm, and 2.5mm, and decreased with the 5mm slice thickness [215]. A routine brain non-contrast CT protocol usually employs a slice thickness of 4 to 5mm [216], which is too thick to show the presence of thrombi in small intracranial arteries. There are several clinical settings where slice thickness reconstructions of less than 5mm may be needed such as in patients with ICH, when the volume of haematoma need to be measured accurately. Slice thickness in CT scan plays an important role in CT image quality since it is related to image noise and diagnostic content [217]. However, clinical imaging standard slice thickness have often restricted the resolution that can be reconstructed, thus limiting the level of details. This loss of feature distinction can result in potential

misidentification as well as the loss of lesion visualisation. Therefore, thinner slice thickness is required to accurately measure the actual volume of haematoma and PHO especially in small size haematomas. Although it is well known that thinner slices increase image noise, however, the visibility of small lesion is improved by providing more diagnostic content. Thus, the volume estimation is more accurate in thinner slice thickness. The thickness of slice also gives a great impact on image volume. In measuring haematoma and PHO volume in 1mm and 5mm slice thicknesses, it is assumed that greater slice thickness overestimated the volume especially in small size. However, since this study involves a very small sample with limited haematoma sizes, it is not strong enough to support the statement of the effect of slice thicknesses on haematoma and PHO volume estimation. In addition, CT brain scans acquired in the TICH-2 trial were performed as per local protocol in 124 participating centres. There was no standard protocol, CT scanner setting or slice thickness restricted for CT brain scan (but only the axial scans were analysed in this study). These variations of CT parameters might affect the result of haematoma and PHO volume measurements especially in small size haematoma and PHO. In sequential CT scan, the patient is moved through the CT with short pauses to capture images at each position. While the data acquisition in helical technique is continuous, which results in an improvement in post processing and image segmentation compared to sequential CT scanning. The data obtained from helical CT is often excellent for 3D imaging because of the lack of motion mis-registration and the increased of image resolution. Because of this, it can be said that helical CT scan is superior for haematoma and PHO volume segmentation compared to sequential scanning method. As far as I know, there are no studies assessing the variability of CT slice thickness and scanning protocols and their impact on hematoma and PHO volume quantifications. However, the impact of CT scan protocols and slice thickness cannot be withdrawn in this study since there was not enough samples being analysed and there was no information gained for

the type of CT scan and protocol that have been used. This practical limitation leads to underpowered analysis. A larger sample size of scan acquisition with different slice thickness of 5mm and 1mm is needed to make the result more powerful.

The strength of TICH-2 population is the use of a large sample size and good availability of CT scans, making this study among the largest volume analysis in spontaneous ICH. Since this study applied the volume quantification method on the large sample of the international randomized clinical trial data (TICH-2) from acute stroke units at 124 hospital sites in 12 countries around the world, it can simply demonstrate the validity and applicability of the proposed volume estimation technique to a rather diverse variable quality of CT scan images and CT population from various centres around the world. This study also used multiple assessors to measure haematoma volume. The assessors were from a range of background (neurologist, radiographer, and stroke physician). To minimise measurement error, observers were trained to use ITK SNAP software for measuring brain CT scan parameters and in recognition of haematoma and PHO. A wide range of haematoma volumes from a very small to a very large haematoma reflects of real-world patients with spontaneous ICH, thus represent the population of patients presenting of spontaneous ICH. The validation of volume estimation methods with excellent intraclass reliability for both haematoma and PHO quantifications contributes important implications on the next chapters in this study. Valid and reliable estimation method has valuable clinical utility especially for appropriately defined and measured haematoma expansion and PHO expansion in large sample size. The TICH-2 trial analysis published previously used the SAS measurement. My analysis showed that there was a difference in measurement between SAS (median haematoma volume = 13.36 mL) and ABC/2 (median haematoma volume = 14.58 mL). This measurement-related difference in medians (1.22 mL is less than the average group difference found in the trial

suggesting that the result may not have been altered. However, it is important to note that I have looked at the agreement between ABC/2 and SAS for measurement of haematoma volume, not for detection of change in haematoma volume, which is a slightly different question. To address the latter would re-analysis of the TICH-2 trial data using ABC/2 in place of SAS which is outside of the scope of this thesis.

Nevertheless, there are three major limitations to this study. First, the data come from a randomised placebo-controlled trial in hyperacute primary ICH. Trial exclusion criteria can limit the type of patients (and therefore variation of haematoma) so that the data set studied here did not include patients with ICH secondary to anticoagulation, thrombolysis, trauma or a known underlying structural abnormality, patients for whom TA was thought to be contraindicated, prestroke dependence (modified Rankin scale (mRs) score > 4), life expectancy less than 3 months and Glasgow Coma Scale (GCS) score less than 5. As a result, patients with very large haematoma were under re-presented. Secondly, since there were no restrictions on manufacturers scanner and protocol settings, there were some technical errors regarding image registration and segmentation that need to be solve by an expert. The segmentation process of haematoma and PHO in a very thin slice thickness was very time consuming because the manual editing of haematoma and manual delineation of PHO was done for every single slice that consist of haematoma and PHO, and this might involve of hundreds slices per scan. In addition, a wide range of haematoma and PHO features make the segmentation more complex and challenging, thus increase the segmentation time. The segmentation was done on post processed data in DICOM format while the final segmentation output was saved in NIFTI format. Participants with unprocessable baseline DICOM scan and final segmentation DICOM to NIFTI conversion failure were excluded from this analysis, meaning the sample size of participants eligible for this study reduced. Finally, there were a limited number of participants with

both 1mm and 5mm slice thickness variation scan available. Therefore, the result of the analysis was underpowered and was not strong enough to represent a population.

Chapter 5 HAEMATOMA VOLUME EXPANSION IN THE TICH-2 POPULATION

5.1 Introduction

This chapter evaluates the relationship between the size, location, shape and density of the haematoma on non-enhanced CT brain images and haematoma expansion in the placebo-treated TICH-2 population. In addition, this chapter will also explore the adjudicated baseline CT characteristics of blend sign, black hole sign and island sign and their relationship to haematoma expansion. Finally, a novel regression model of multivariate predictors including imaging features is created to predict haematoma expansion in patients with spontaneous ICH.

Haematoma expansion is the most common complication in patients with spontaneous ICH. Initial haematoma expansion which occurs in approximately 30% of patients with ICH [218] is the strongest predictor of mortality [167] and leads to worse clinical outcomes [219]. For each 10% increase in haematoma expansion, there is a 5% increased hazard of death and 16% greater likelihood of worsening by one point on the mRs score [220]. Given the association of poor clinical outcome with haematoma expansion, therapeutic intervention aimed at preventing such expansion could represent an acute treatment paradigm for patients with spontaneous ICH. However, haemostatic treatments such as rFVIIa shows reductions in haematoma expansion [46], but fails to show improved clinical outcomes in many patients [62]. This apparent discrepancy might be due to inclusion criteria patients that were at low risk of haematoma expansion and hence unlikely to benefit from haemostatic therapy.

Haematoma expansion is a potentially modifiable predictor of outcomes in ICH patients [221] particularly if high-risk patients are identified in the initial phase of ICH [163]. Several clinical trials have focussed on restricting haematoma expansion following acute spontaneous ICH, but selecting those patients at highest

risk of haematoma expansion is challenging [219]. Therefore, it is of key importance to establish reliable imaging predictors of haematoma expansion that are rapidly and easily accessible in order to accomplish therapeutic strategies to help reduce the morbidity and mortality associated with haematoma expansion.

Several prognostic models for ICH have been developed incorporating both clinical and radiological variables. Larger baseline haematoma volume, shorter onset-to-CT scan time and prior antiplatelet were identified as independent predictors and predict subsequent haematoma expansion [69][222][223]. The predicted probability of haematoma expansion increased with large haematoma volume while the probability of haematoma expansion was the highest in patients with onset-to-CT scan time of < 3 hours [223]. Other than that, non -contrast CT markers of heterogenous density and irregular shape have also been identified as predictors of haematoma expansion in ICH. The appearance of spot sign on CT angiographic images was first proposed in 2007 [224] and has been reported to be a principal prognosticator of spontaneous ICH growth [165][225][226]. CTA spot sign is being prospectively validated in multiple centres worldwide [227]. However, a study done by D. Dowlatshashi et al showed that not all positive spot signs represent on-going bleeding [228]. Recently, different imaging characteristics for prediction of haematoma expansion have been introduced by Q. Li et al including CT blend sign [143], black hole sign [146] and island sign [150] which are obtainable on non-enhanced CT images. Compared to CTA spot sign, identifiable imaging markers based on non-enhanced CT is crucial for triaging patients for future therapeutics interventions since CTA examination is not readily available or routinely acquired in many institutions.

Nevertheless, these imaging features have not been comprehensively studied and it is unclear which sign or combinations of CT signs and features is the best predictor of early haematoma expansion and how they are likely to indicate active bleeding in acute spontaneous ICH. To address these radiological uncertainties,

this study aimed to investigate the value of various baseline CT adjudication features and signs for predicting naturally-evolving haematoma expansion on placebo data set from the TICH-2 trial.

5.1.1 Hypotheses

The aim of this thesis is to address the knowledge gap and uncertainty in imaging predictors of haematoma expansion as highlighted in section 1.9. All these particular radiology uncertainties will be investigated by testing the following hypotheses:

i. There are significant differences in demographic characteristics, pre-existing pathology, clinical parameters, and time-to-scan between participants with haematoma expansion and without haematoma expansion in the placebo-treated TICH-2 population.

ii. A large volume, shorter time-to-scan, large haematoma size, deep haematoma, irregular shape, and heterogeneous density of haematoma on baseline CT brain images are associated with a high risk of haematoma expansion in the placebo-treated TICH-2 population.

iii. Haematoma expansion will be independently predicted by the presence of blend sign, black hole sign or island sign on baseline CT brain images of participants with spontaneous ICH in the placebo-treated TICH-2 clinical trial.

iv. A multivariate prediction model for haematoma expansion in the placebo-treated TICH-2 population could be created based on baseline CT imaging characteristics.

5.1.2 Objectives

To answer the hypotheses regarding the potential of baseline imaging predictors of haematoma expansion in spontaneous ICH, the following objectives are constructed in this study:

i. To compare the demographic characteristics, pre-existing pathology, clinical parameters, and time-to-scan between participants with haematoma expansion and without haematoma expansion in the placebo treated TICH-2 population.

ii. To compare haematoma volume, haematoma size, location, shape, and density on baseline CT brain images in the placebo-treated TICH-2 population between those with and without haematoma expansion.

iii. To evaluate the adjudicated baseline imaging features of blend sign, black hole sign and island sign as independent predictors of haematoma expansion in the placebo-treated TICH-2 population.

iv. To develop a multivariate prediction model for haematoma expansion in the placebo-treated TICH-2 population based on adjudicated CT baseline imaging characteristics.

5.2 Methods

5.2.1 Participants

The data set of this study consisted of the participants with spontaneous ICH from the TICH-2 clinical trial. CT brain scans were obtained within 8 hours of symptom onset. Briefly, TICH-2 was an international double-blinded, randomised placebo-controlled, parallel group, phase 3 trial of tranexamic acid for improving outcomes in spontaneous ICH. This trial involved 2325 participants from acute stroke units at 124 hospital sites in 12 countries. One thousand, one hundred and sixty-one participants received tranexamic acid

and 1164 participants received placebo. From this total number, only participants from placebo group were eligible to be included for analysis in this study. This was so to ensure that the analysis looked only at the 'natural history' of haematoma expansion, rather than the modulating effect of tranexamic acid.

From the total number of 1164 participants from placebo group, only 1035 were eligible for analyses, while 129 participants were excluded for analysis for the following reasons: - participants with unprocessable baseline or follow-up scan, participants with only CTA available on baseline or follow-up, participants who had undergone surgical evacuation of haematoma before follow-up scans and failure of DICOM to NIFTI conversion format. The flow chart showing number of participants included in the analysis is presented on Figure 5-1. All adjudications and haematoma measurements were made blind to baseline and follow-up clinical information and other imaging assignment. I was partly involved in scan analysis, specifically in image segmentation for haematoma and PHE volume quantification and also in evaluation of CT baseline signs (blend sign, black hole sign and island sign) together with another 2 operators (ZKL and KK). The rest components of the scan analysis were performed by the TICH-2 independent experts adjudicators.

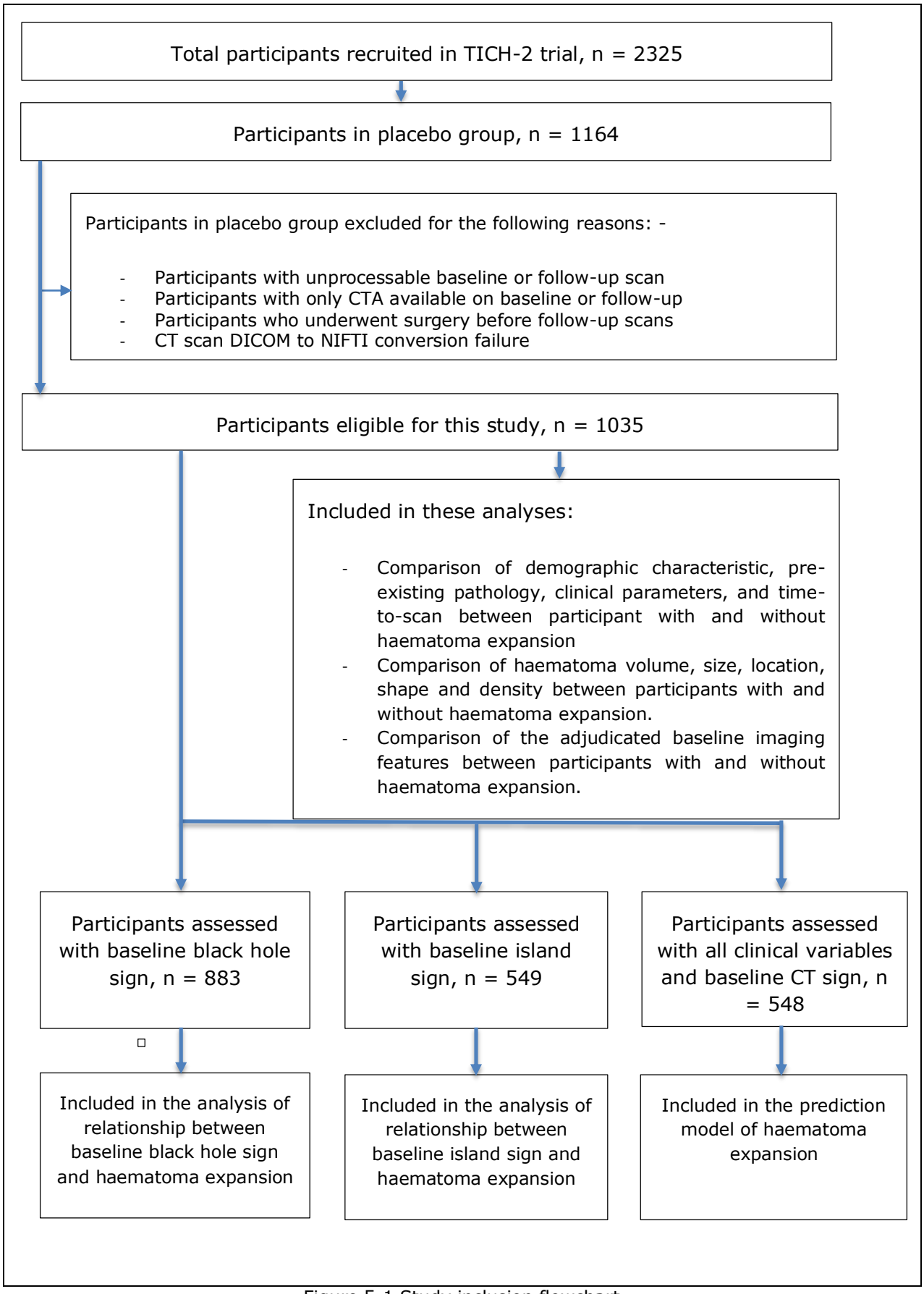


Figure 5-1 Study inclusion flowchart

5.2.2 Demographic and Clinical Data Acquisition

Demographic characteristics (age and sex) and clinical parameters (NIHSS score, GCS score, mRs score, previous antiplatelet therapy, and the presence of IVH) were recorded for each participant at randomisation.

5.2.3 Acquisition of Non-contrast CT Brain Images

A non-contrast CT scan was required for the diagnosis of spontaneous ICH prior to recruitment and randomisation in TICH-2 study. Onset to baseline CT imaging time (time-to-scan) for each participant was recorded. It was the time between the symptom of stroke onset and the baseline CT imaging (measured in hours). Baseline scans were obtained within 8 hours of symptom onset and before randomisation, while follow-up scans were performed at 24 $\pm$ 12 hours after baseline scans [229]. When multiple scans were available, the scan closest to 24 hours after randomisation was used as the follow-up scan to determine haematoma expansion. Time-to-baseline CT is important for two main reasons. Firstly, it is an indicator of how quickly the patient deteriorates after the onset. Patients who become sick very quickly are more likely to undergo emergency imaging than those who remain relatively well. Secondly, it allows an assessment of how quickly the haematoma expanded over the pre-CT period. For example, it is reasonable to assume that a large haematoma on a scan performed 3 hours after onset has expanded quicker than a small haematoma on a scan performed 3 hours after onset.

5.2.4 Measurements of Baseline and Follow-up Haematoma Volume

Haematoma volume for baseline and 24-hours follow-up were measured using semi-automated region growing technique with the use of user-guided three-dimensional active contour tool in the ITK SNAP software version 3.6.0 as being reported on Chapter 4 (4.3.1) demonstrating inter- and intra-observer

intraclass correlation coefficient of 0.984 and 0.999 respectively. Measurement of haematoma volumes was performed by 3 independent observers blinded to clinical data (AA, ZKL and KK). The volumetric methodology of haematoma was described in detailed in Chapter 4 (4.2.5). IVH volumes if presented were calculated independently using the same method as haematoma.

5.2.5 Definition of Haematoma Expansion

Haematoma expansion was defined as an absolute increases in haematoma volume of more than 6 mL (follow-up haematoma volume – baseline haematoma volume) or relative increases of more than 33% (absolute growth/baseline haematoma volume) on the follow-up scan compared to the baseline haematoma volume, similar to several previous studies [166][230][231].

5.2.6 Determination of Adjudicator's Variables on Baseline CT Images

5.2.6.1 Determination of Size and Shape of Haematoma

Determination of haematoma volume, size, and shape were thoroughly described in 4.2.5 and 4.2.7 respectively. As a clinically-useful approximation for haematoma size, haematomas were divided into four groups based on the maximum axial diameter; < 3cm, 3 – 5cm, 5 – 8cm and > 8cm based on the largest area of haematoma showing on axial slice. Whereas the irregularity of shape of haematoma were assessed by visual inspection and rated using the scale of Barras et al [69].

5.2.6.2 Determination of Haematoma Density

Heterogeneity of haematoma density were assessed by visual inspection and rated using the Barras scale [69], reflecting the spectrum of haematoma Hounsfield unit density to provide an agreed visual

representation of the terms "homogenous/heterogeneous". The density scales range from 1 (most homogenous density) to 5 (most heterogeneous density) as shown on Table 5-1. Each progressive category is defined by a degree of density variation on the density scale. Density was defined as homogenous when rating was 1 or 2 on the visual scale and heterogenous when the total rating was 3, 4 or 5. Density scores were analysed using the largest axial slice showing haematoma.

Table 5-1 Barras score for haematoma density

Barras Score	**Haematoma Density**
1	Most homogenous density
2	Homogenous density
3	Slightly heterogenous density
4	Heterogenous density
5	Most heterogenous density

5.2.6.3 Determination of Haematoma Location

Haematoma locations were identified by central independent expert adjudicators who were blinded to treatment assignment using web-based adjudication system. The locations were recognised as lobar, deep (caudate nucleus, thalamus and putamen) and infratentorial or any combinations of aforementioned locations if haematoma occurs in more than one location.

5.2.6.4 Assessment of Pre-existing Pathology (Brain Atrophy, Periventricular Lucencies and Old Vascular Lesion)

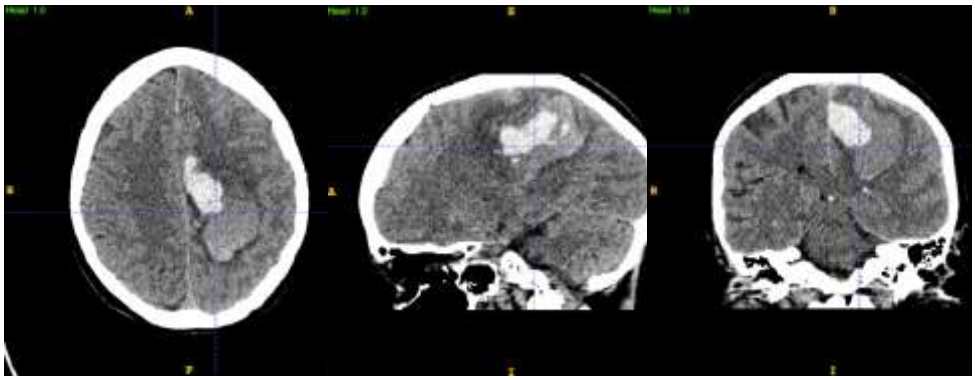
The expert TICH-2 CT adjudicators rated atrophy, periventricular lucencies and old vascular lesions as follows. Atrophy was assessed separately in cortical and central regions, defined as 0 = absent, 1 = moderate, or 2 = severe, based on comparison with a standard template used previously for the IST-3 trial [232]. The scores were dichotomised into atrophy absent (score <1) or present (score ≥1). Periventricular lucencies were assessed separately in anterior and posterior brain regions according to the widely used van Swieten scale [232] defined as 0 = no lucency, 1 = lucency restricted to region adjoining ventricles, or 2 = lucency covering entire region from lateral ventricle to cortex, providing a maximum score of 4. The scores were dichotomised into periventricular lucencies absent (score <1) or present (score ≥1). Old vascular lesions/infarcts were classified by location (e.g., cortical, striatocapsular, border zone, lacunar). For the analysis, the recording of an old vascular lesion/infarct at any of these sites was considered as positive for old vascular lesions/infarcts.

5.2.7 Recognition of Imaging Signs on Baseline CT Brain Images

5.2.7.1 Blend Sign

Blend sign on CT brain images was identified based on former study done by Q. Li et al [143] as a well-defined areas of different intensity. These two regions should have a difference in density of at least 18 HU that can obviously be seen by the naked eye. CT blend sign was also recognised as blending relatively hypointense area with adjacent hyperintense region within haematoma and the relatively hypoattenuating area was not encapsulated by the hyperattenuating

region. The haematoma has to meet all those criteria to be defined as blend sign. The recognition of blend sign on CT brain images of patients with spontaneous ICH is shown on Figure 5-2.



(a) (b) I

Figure 5-2 Investigation of CT blend sign on (a) axial, (b) sagittal and (c) coronal plane on CT brain images in TICH-2 study

5.2.7.2 Black Hole Sign

CT black hole sign was identified based on previously described criteria by Q. Li et al [146] as having a relatively hypoattenuated area encapsulated within the hyperattenuating haematoma region. The various shapes of the black hole sign could be round, oval or rod-like shape. The hypoattenuating area was contained within the haematoma region but was not connected with the adjacent brain parenchyma. The relatively hypoattenuated area should have a clearly identifiable border and show a minimum 28 HU difference between two density regions within the haematoma. Figure 5-3 shows the black hole sign on axial CT brain image in patient with spontaneous ICH.

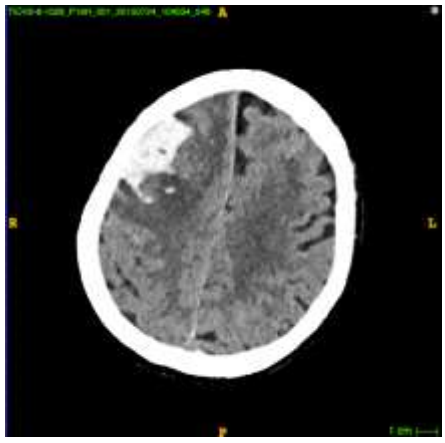


Figure 5-3 Recognition of black hole sign on axial plane of CT brain image in TICH-2 study

5.2.7.3 Island Sign

CT island sign was identified and defined based on recently published work by Q. Li et al in a cohort of 252 patients [150] as three or more small scattered haematomas which are all separate from the main haematoma region. Alternatively, the presence of four or more small haematomas, some or all of which may connect with the main haematoma is considered a positive island sign as well. The scattered small haematomas could be round or oval in shape while the small-connected haematomas should be bubble-like or sprout-like but not lobulated. Figure 5-4 depicts the island sign on axial CT brain image of patients with spontaneous ICH.

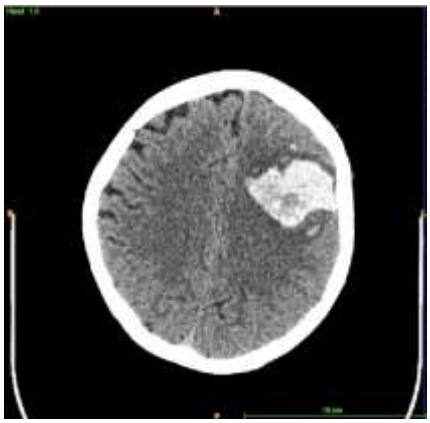


Figure 5-4 Recognition of island sign on axial plane of CT brain image in TICH-2 study

5.2.8 Statistical Methods

All statistical analyses were performed by using a commercially available software package (SPSS, Version 26). Standard tests for normality were applied. Given that many of the outcomes were not consistent with a normal distribution, non-parametric methods were used for comparisons citing median values IQRs. Categorical data are presented as percentages and continuous variables are presented as mean ± SDs or median (IQRs) when appropriate. The baseline characteristics of participants with and without haematoma expansion were compared using Mann-Whitney U test or Chi Square test as appropriate. The sensitivity, specificity, positive and negative predictive value of each CT baseline sign were analysed individually.

Binary logistic regression analysis was used to model the relationship between various clinical and radiological parameters and early haematoma expansion. The multivariate model of the likelihood of haematoma expansion was attempted in a sample of 548 participants in TICH-2 clinical trial. The dependent variable in the model was haematoma expansion, where "haematoma expansion" group was the target category and "no haematoma expansion" was the reference category. The predictors in the model consist of (1) demographic characteristics: age, gender (reference = females), (2) pre-existing pathologies: brain atrophy (reference = no), periventricular lucencies (reference = no), old vascular lesion (reference = no), (3) clinical variables: NIHSS (reference = <14), GCS (reference = >9), mRs (reference = <3), prior antiplatelet (reference = no), IVH presence (reference = no), (4) measured volumes: baseline haematoma volume, (5) adjudicators variables: baseline haematoma size (reference: < 5cm), baseline haematoma shapes (reference = regular), baseline haematoma density (reference = homogenous), location of haematoma (reference = lobar haematoma), site of haematoma (reference = outside basal ganglia), (6) baseline CT sign: blend

sign (reference = no), black hole sign (reference = no) and island sign (reference = no) and (7) time-to-scan.

In univariable binary logistic regression, each variable was tested separately as a predictor of haematoma expansion: demographic variables (age and sex), pre-existing pathology (brain tissue volume reduction, periventricular lucencies and old vascular lesion), clinical variables (baseline NIHSS score, baseline GCS score, baseline mRs score, previous antiplatelet therapy and IVH presence) measured volume (baseline haematoma volume), adjudicators' variables (baseline haematoma size, baseline haematoma shape, baseline haematoma density, haematoma location and haematoma site), baseline CT sign (blend sign, black hole sign and island sign) and time-to-scan. All variables were considered as forced variables using enter method regression. The variables that were retained in the multivariate logistic regression model were variables that showed a significant association to haematoma expansion in the univariate logistic regression, plus the variables that were clinically relevant and reported as predictors to haematoma expansion in previous clinical studies. The multivariate logistic regression analysis was build using forward stepwise method. A $p < 0.05$ was considered statistically significant.

5.3 Result

5.3.1 Comparison of Demographic Characteristics, Pre-Existing Pathology, Clinical Parameters and Time-to-Scan between Participants with Haematoma Expansion and without Haematoma Expansion

The data of demographic characteristics and clinical parameters of participants were shown on Table 5-7. From a total number of 1035 participants, there were 583 (56%) males and 452 (44%) females from the placebo group of the TICH-2 clinical trial were included in the analysis. The

median age was 70 years (IQR, –8 - 79), ranged from 20 to 101 years. Haematoma expansion was observed in 300 participants (29%). Of the 300 numbers of participants with haematoma expansion, 176 (58.7%) were males and 124 (41.3%) were females. The median age of participants with haematoma expansion was 71 years (IQR, 60 – 80), age ranged from 28 – 97 years, while the median age of 735 participants (71%) with no haematoma expansion was of 70 years (IQR, 58 – 79), age ranged from 20 – 101 years. There were no significant difference of gender (p = 0.333) and median age (p = 0.549) between participants with haematoma expansion and no haematoma expansion.

There were 944 (91.2%) participants recorded of having brain atrophy in which 665 (70.4%) of them have no haematoma expansion and 279 (29.6%) with haematoma expansion. Four hundred and seventy-two participants (45.6%) had a history of periventricular lucencies with 351 (74.4%) of them had no haematoma expansion and 121 (25.6%) with haematoma expansion. While 631 (60.9%) participants had been diagnosed with previous old vascular lesion, 446 (70.7%) had no haematoma expansion and 185 (29.3%) with haematoma expansion. Based on these findings, there was a significant difference of periventricular lucencies between participants with haematoma expansion and those without haematoma expansion (p = 0.030) and no significant difference of brain atrophy (p = 0.193) and old vascular disease (p = 0.768).

Median NIHSS score of participants with haematoma expansion was significantly higher (15 [8 – 20]) compared to those with no haematoma expansion (11 [6 - 17], p < 0.001). Whereas from the total number of 300 participants with haematoma expansion, 167 (55.7%) of them have NIHSS score ≥14.

There was no significant difference of GCS score between these 2 groups (p = 0.302). Participants with no haematoma expansion had median GCS score (15 [13 – 15]) one level higher compared to participants presenting with haematoma expansion (14 [12 – 15]). Twenty-three participants (2.2%) from the whole population had GCS score < 9. Only 8 (34.8%) of them had haematoma expansion and the rest had no haematoma expansion (65.2%).

Median score of mRs also showed no significant difference between participants with haematoma expansion and those without haematoma expansion with p = 0.160.

Previous antiplatelet therapy showed a significant difference (p = 0.008) between participants with haematoma expansion and those without haematoma expansion. Eighty-eight (29.3%) out of 300 participants with haematoma expansion had a history of previous antiplatelet therapy compared to 159 (21.6%) out of 735 participants without haematoma expansion.

Onset-to-CT scan time and the presentation of IVH also showed a significant difference (time-to-scan, p = 0.012 and IVH, p = 0.033) between both groups of participants.

5.3.2 Comparison of Baseline Volume, Size, Shape, Density and Location of Haematoma between Participants with Haematoma Expansion and without Haematoma Expansion

The median baseline haematoma volume in participants with and without haematoma expansion was 19.55mL (IQR, 6.61 – 39.52) and 9.74 mL (IQR, 4.57 – 24.89) respectively. Participants with haematoma expansion significantly had a larger baseline haematoma volume (ranged 0.29 mL – 138.8 mL) compared to those with no haematoma expansion (ranged 0.10 mL – 154 mL) (p < 0.001).

All participants were classified into four groups of haematoma's axial diameter measurement based on the largest haematoma showed on axial CT section: < 3cm (614, 59.3%), 3 – 5cm (243, 23.5%), 5 – 8cm (154, 14.9%) and > 8cm (24, 2.3%). From a total number of 300 participants with a significant haematoma expansion, 219 participants (73%) had a haematoma size below 5cm and only 81 participants (27%) had a haematoma size greater than 5cm. However, when compared within each group of haematoma size (Table 5-2), the incidence of haematoma expansion was the highest (46.8%) in participants with large (5 – 8cm) haematoma, followed by 37.5% in those with a very large haematoma (> 8 cm), 33.3% in those with a medium-sized haematoma (3 – 5cm) and only 22.5% in those with a small haematoma size (< 3cm). Haematoma size was significantly larger in participants presenting haematoma expansion (p < 0.001). Whereas, from a total number of the whole placebo-treated TICH-2 population (n = 1035), 178 participants had haematoma size greater than 5cm. Out of 178 participants, 81 participants (45.5%) had a significant growth of haematoma. A distribution of haematoma expansion in each group of haematoma size is shown on Figure 5-5 and a proportion of haematoma expansion by haematoma size is shown on Figure 5-8. The highest proportion of haematoma expansions was in 5 – 8cm size of haematoma.

Table 5-3 illustrates the relationship between the incidence of haematoma expansion and haematoma shape. Haematoma expansions mostly occurred in those with Score 5 (35.2%) followed by Score 4 (34.7%), Score 1 (25.8%), Score 3 (24.6%) and the least occurrence was in Score 2 (20%). Out of 300 participants with haematoma expansion, the occurrence of haematoma expansion in irregularly shaped haematomas (Barras score 3 to 5) was significantly higher (31.8%) than in regularly shaped haematomas (Barras score 1 and 2, 21.8%) with p < 0.001 [Table 5-3 and Table 5-7]. The proportion of haematoma expansion by haematoma shape is shown on

Figure 5-9. There was an increment in percentage of haematoma expansion occurrence as haematoma shape score increases. The occurrence of haematoma expansion increases as the haematoma shape becomes more irregular.

The association of haematoma expansion and haematoma density is shown on Table 5-4. Density category distribution shows a predominance of Score 1 (792, 76.5%) followed by Score 2 (142, 13.7%), Score 3 (65, 6.3%), Score 4 (23, 2.2%) and Score 5 (13, 1.3%). The highest percentage of haematoma expansion occurs in those with haematoma density Score 4 (52.2%), followed by haematoma density Score 3 (30.8%), Score 2 (30.2%), Score 1 (28%) and the lowest incidence of haematoma expansion in Score 5 (23.1%). The proportion of haematoma expansion by each score of haematoma density is illustrated on Figure 5-11. It is shown that haematoma expansion was not significantly related to haematoma density with $p = 0.147$ [Table 5-7].

When divided by haematoma location, there were only 2 incidences of haematoma expansion out of 3 cases occurring in both deep and infratentorial locations making them invalid to represent the incidence of haematoma expansion in those locations (Table 5-7). However, out of 300 with haematoma expansion, more than half cases were deep haemorrhage (163, 54.3%) 109 as lobar haemorrhage (36.3%), 16 cases of infratentorial haemorrhage (5.3%), 10 cases of lobar and deep haemorrhage (3.3%) and only 2 cases of haematoma expansion in both deep and infratentorial (0.7%) (Table 5-7). There was a significant difference of haematoma location between participants presenting with haematoma expansion and those without haematoma expansion ($p = 0.006$). The proportion of haematoma expansion by haematoma location is shown on Figure 5-13.

The incidence of haematoma expansion in different site is shown on Table 5-6. There was no significant difference of haematoma site between participants

with haematoma expansion and without haematoma expansion (p = 0.162). The proportion of haematoma expansion in each site of haematoma is shown on Figure 5-14. It is illustrated that midbrain haematoma showed the highest proportion of haematoma expansion compared to the other haematoma site. However, out of 300 participants with haematoma expansion in this study, there were 187 (62.3%) cases of haematoma in basal ganglia which is the highest occurrence, followed by parietal by 38 cases (12.7%), frontal haematoma in 30 cases (10%), temporal haematoma in 23 cases (7.7%), pontine haematoma in 11 cases (3.7%), occipital haematoma in 5 cases (1.7%), cerebellar haematoma in 4 cases (1.3%) and only 2 cases in midbrain (0.4%).

Table 5-2 Relationship between the incidence of hematoma expansion and haematoma size

Haematoma Size	Haematoma Expansion		Total no of cases	Incidence of Haematoma Expansion
	Yes	No		
< 3 cm	138	476	614	22.5%
3 – 5 cm	81	162	243	33.3%
5 – 8 cm	72	82	154	46.8%
> 8 cm	9	15	24	37.5%

Table 5-3 Relationship between the incidence of haematoma expansion and haematoma shape

Haematoma Shape	Haematoma Expansion		Total no of cases	Incidence of Haematoma Expansion
	Yes	No		
Score 1	25	72	97	25.8%
Score 2	40	160	200	20.0%
Score 3	55	169	224	24.6%
Score 4	74	139	213	34.7%
Score 5	106	195	301	35.2%

Table 5-4 Relationship between the incidence of haematoma expansion and haematoma density

Haematoma Density	Haematoma Expansion		Total no of cases	Incidence of Haematoma Expansion
	Yes	No		
Score 1	222	570	792	28.0%
Score 2	43	99	142	30.2%
Score 3	20	45	65	30.8%
Score 4	12	11	23	52.2%
Score 5	3	10	13	23.1%

Table 5-5 Relationship between the incidence of haematoma expansion and haematoma location

Haematoma Location	Haematoma Expansion		Total no of cases	Incidence of Haematoma Expansion
	Yes	No		
Lobar	109	194	303	35.9%
Deep	163	476	639	25.5%
Infratentorial	16	50	66	24.2%
Lobar and Deep	10	13	23	43.4%
Deep and Infratentorial	2	1	3	66.7%
Lobar and Infratentorial	0	1	1	0%

Table 5-6 Relationship between the incidence of haematoma expansion and haematoma site

Haematoma Site	Haematoma Expansion		Total no of cases	Incidence Haematoma Expansion
	Yes	No		
Basal Ganglia / Thalamus	187	489	676	27.7%
Frontal	30	47	77	38.9%
Parietal	38	86	124	30.6%
Occipital	5	17	22	22.7%
Temporal	23	49	72	31.9%
Midbrain	2	1	3	66.7%
Pontine	11	12	33	33.3%
Cerebellar	4	24	28	14.3%

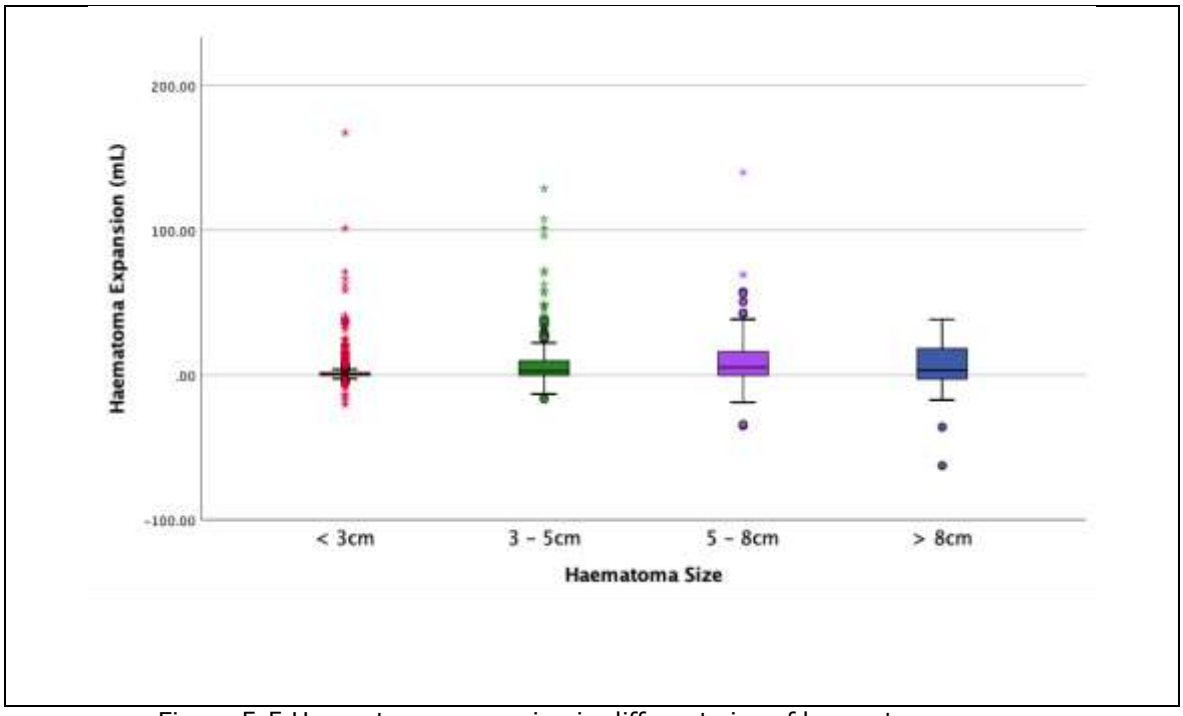


Figure 5-5 Haematoma expansion in different size of haematoma

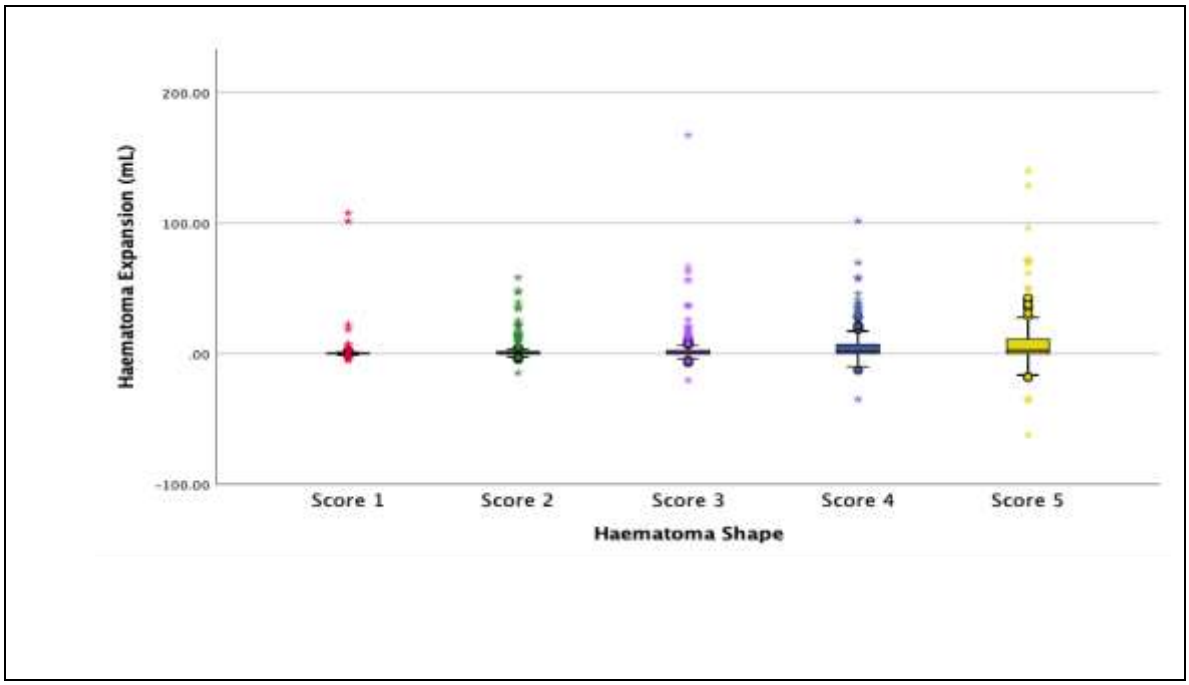


Figure 5-6 Haematoma expansion in different shape of haematoma

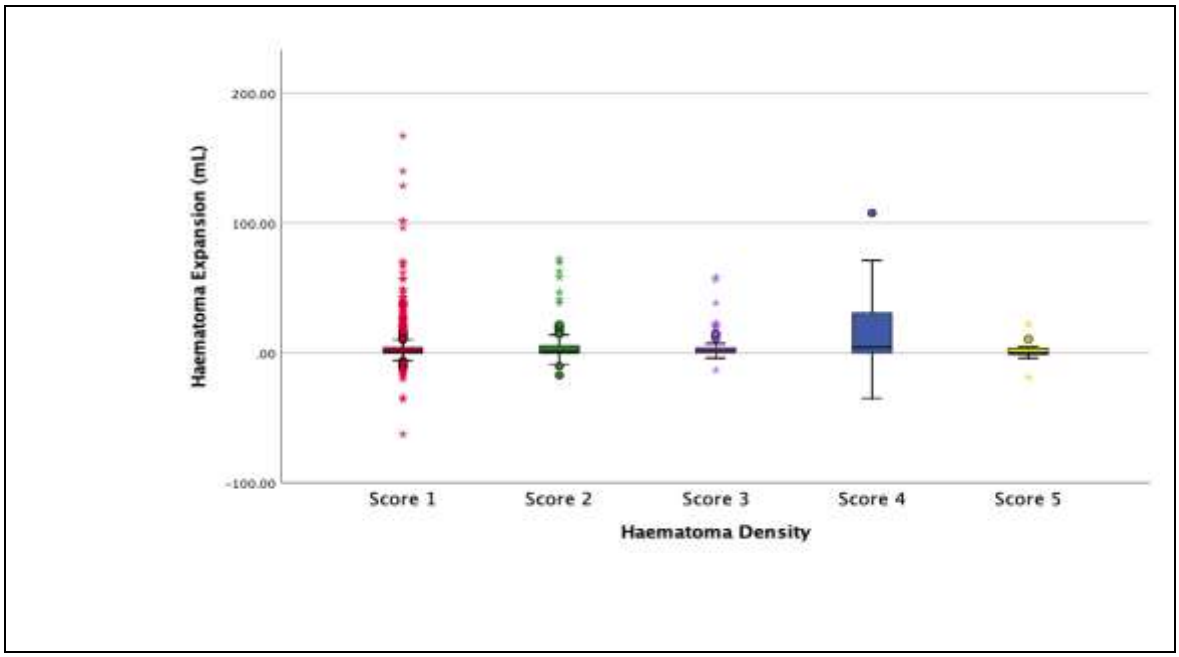


Figure 5-7 Haematoma expansion in different haematoma density

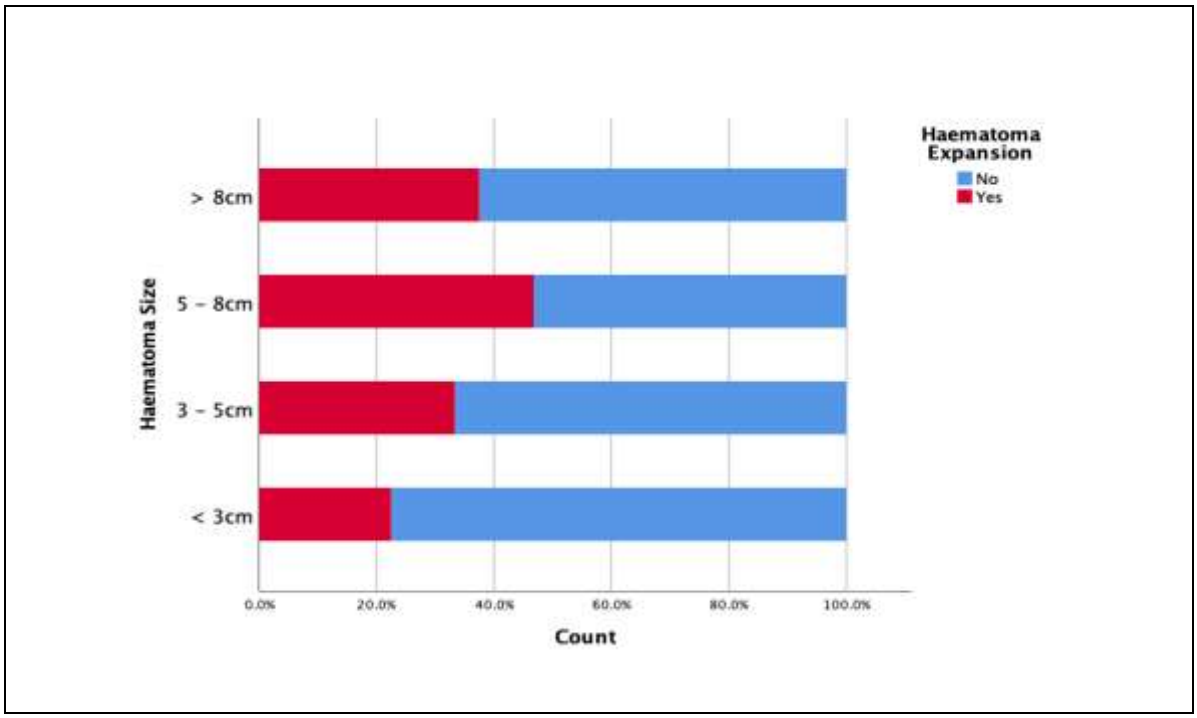


Figure 5-8 Proportion of haematoma expansion by haematoma size

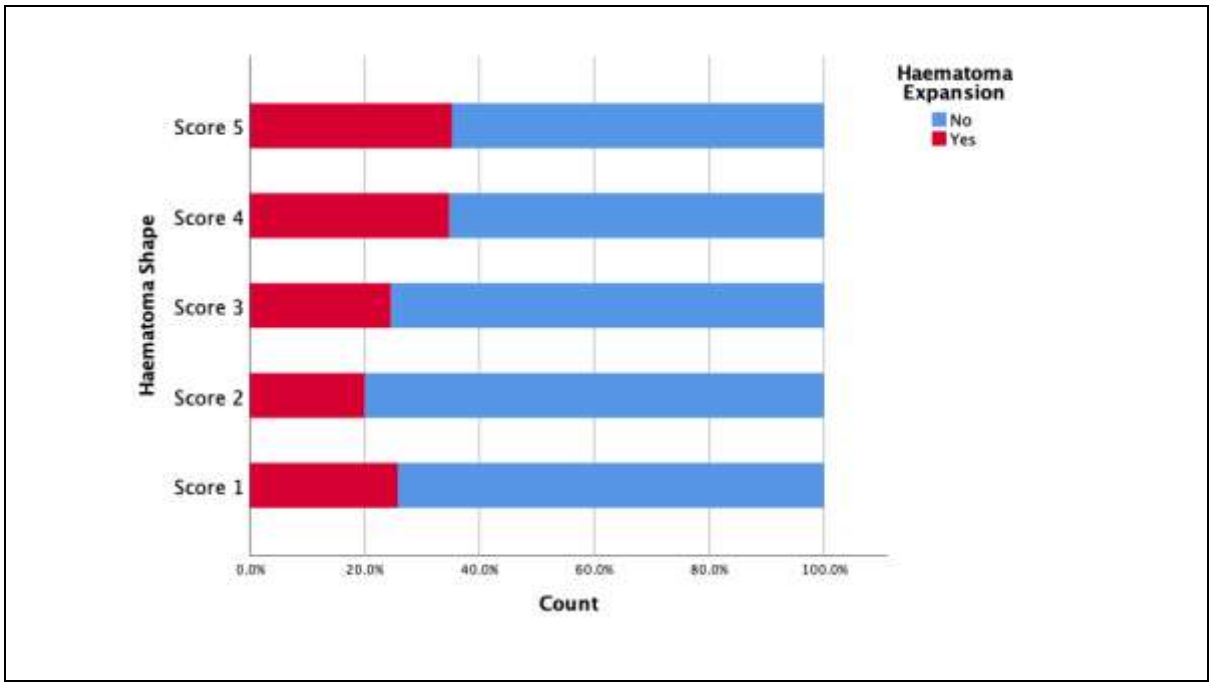


Figure 5-9 Proportion of haematoma expansion by haematoma shape

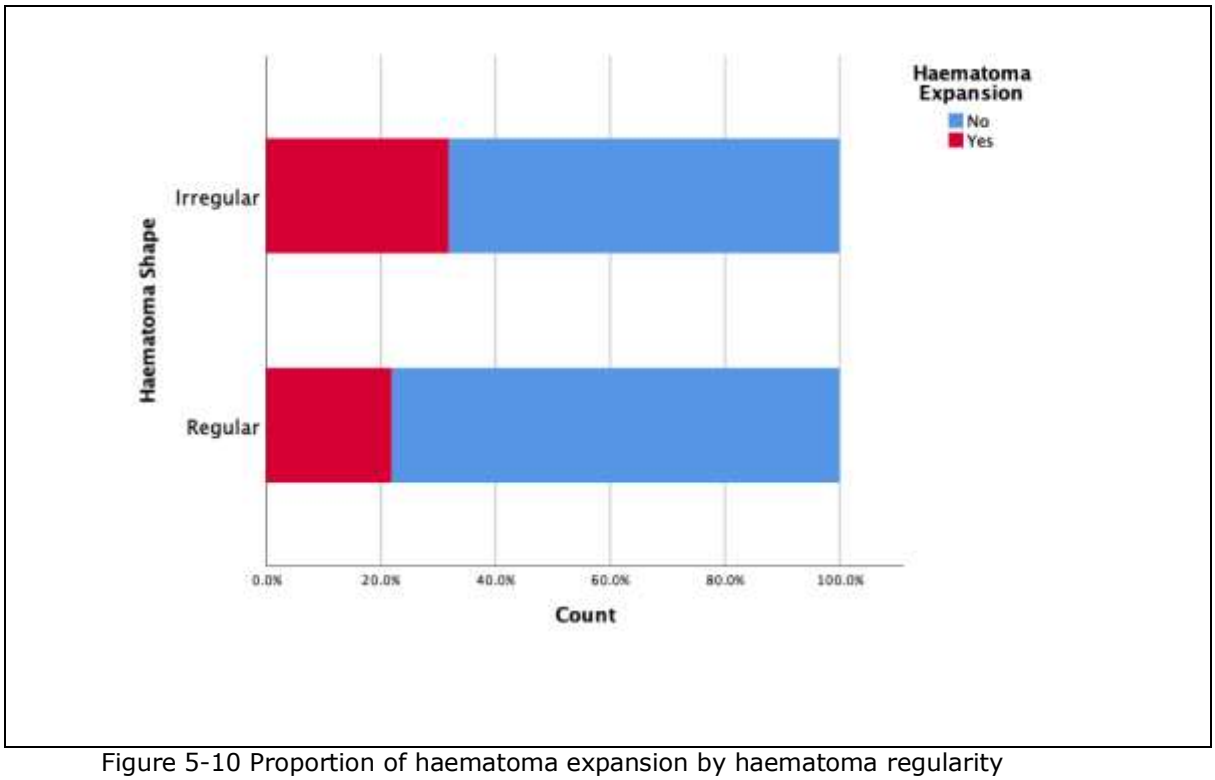


Figure 5-10 Proportion of haematoma expansion by haematoma regularity

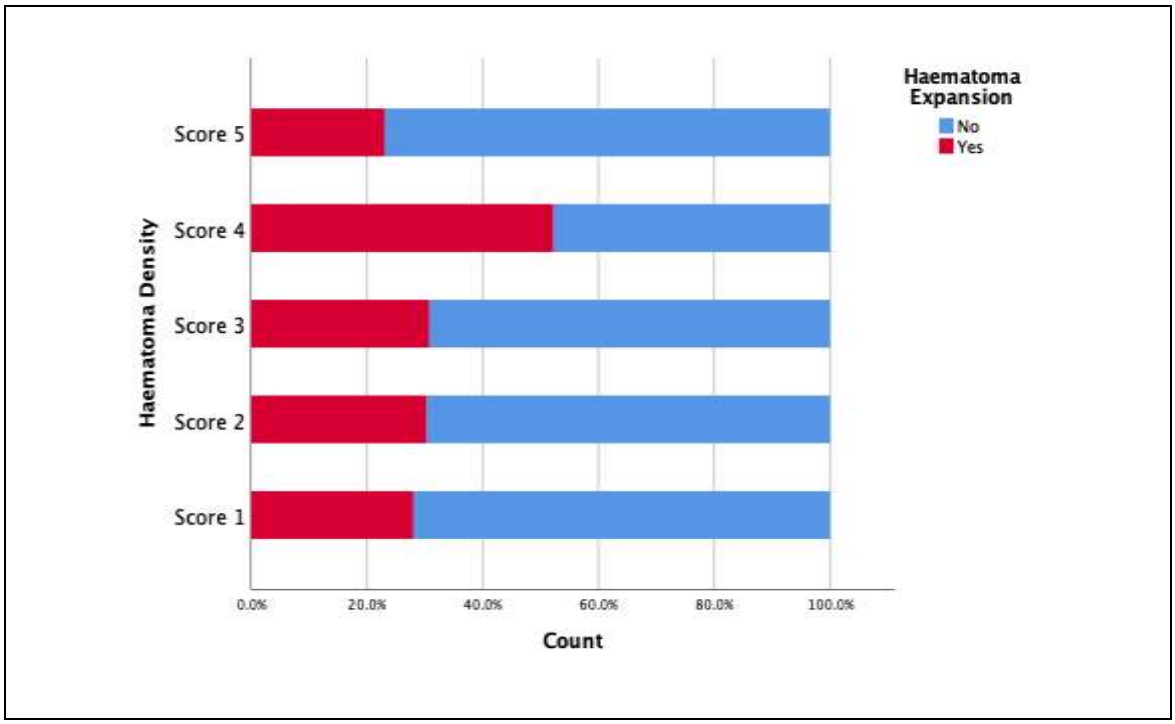


Figure 5-11 Proportion of haematoma expansion by haematoma density

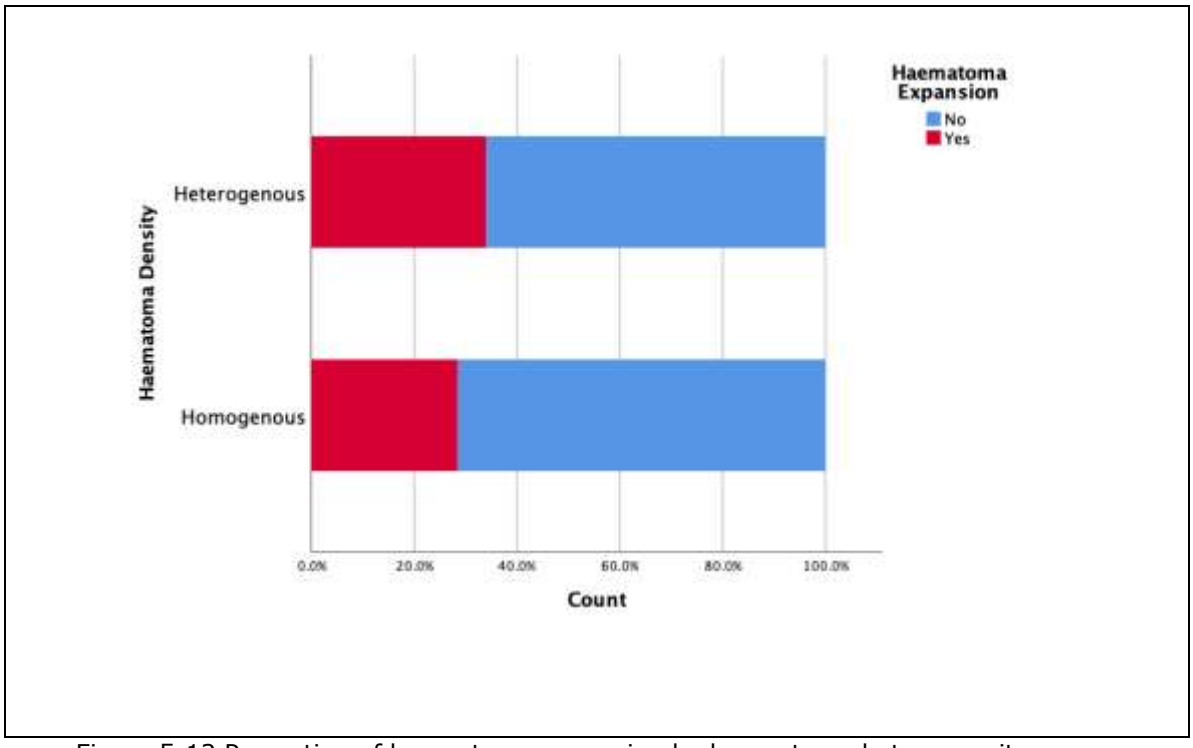


Figure 5-12 Proportion of haematoma expansion by haematoma heterogeneity

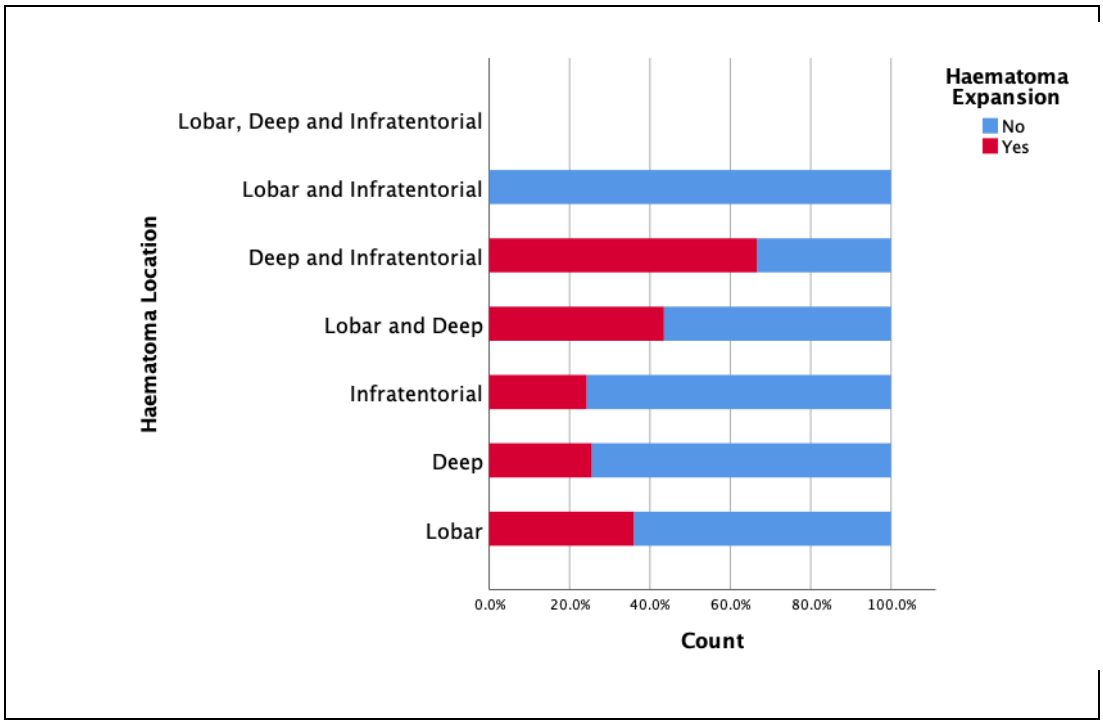


Figure 5-13 Proportion of haematoma expansion by haematoma location

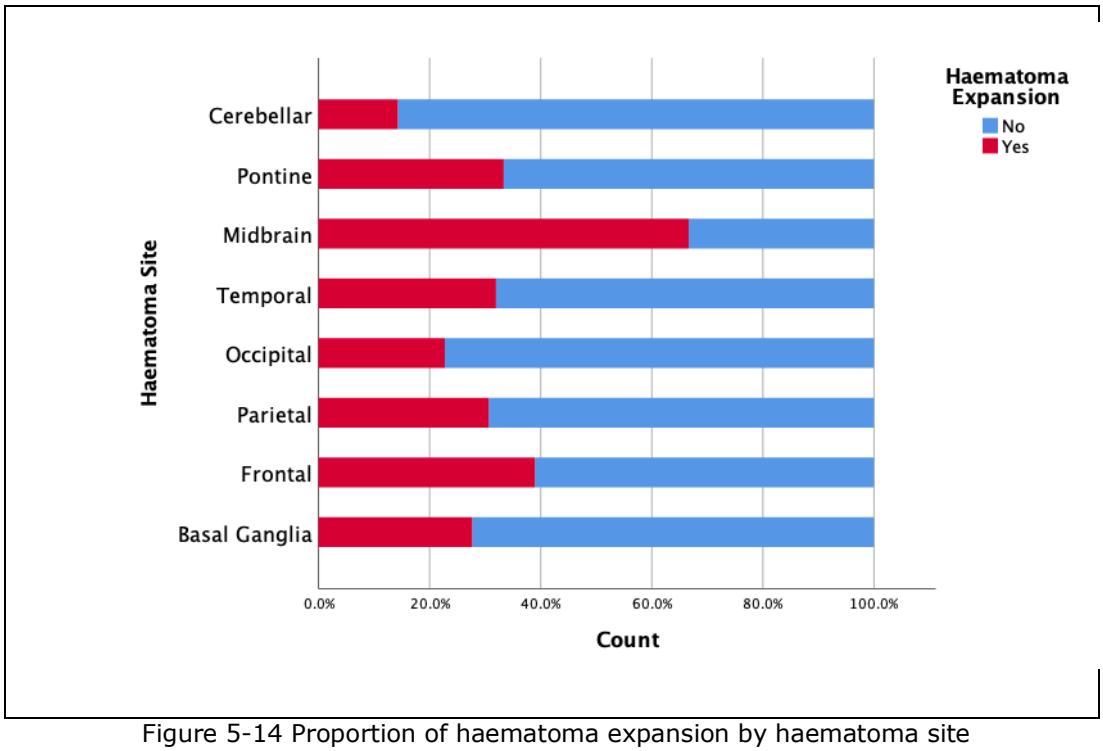


Figure 5-14 Proportion of haematoma expansion by haematoma site

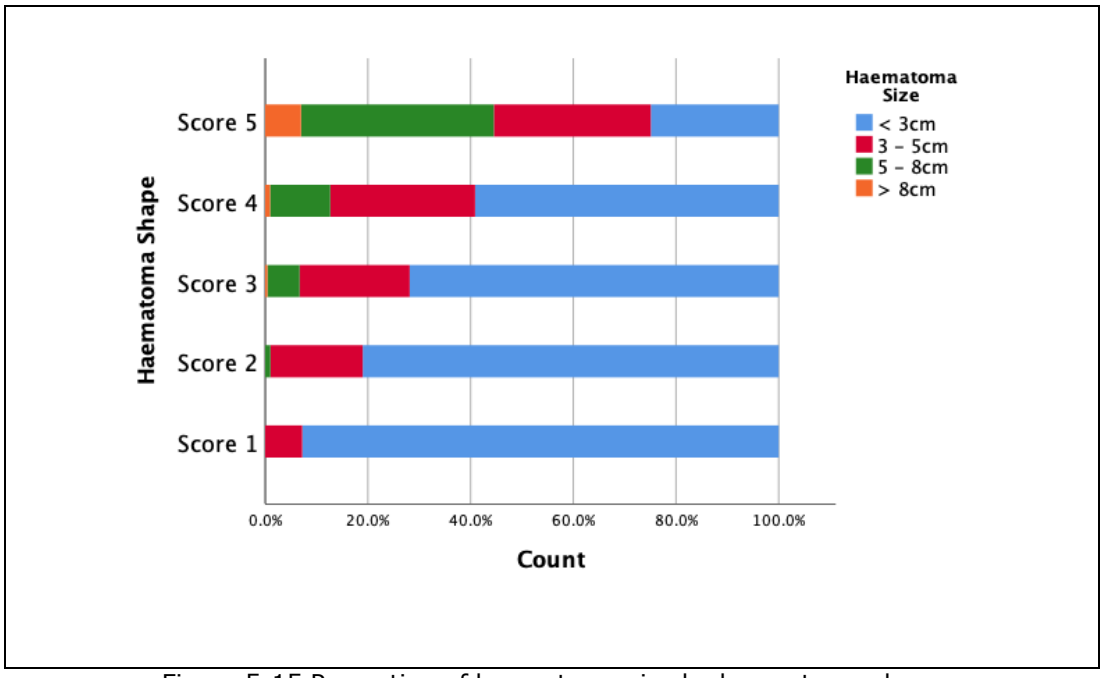


Figure 5-15 Proportion of haematoma size by haematoma shape

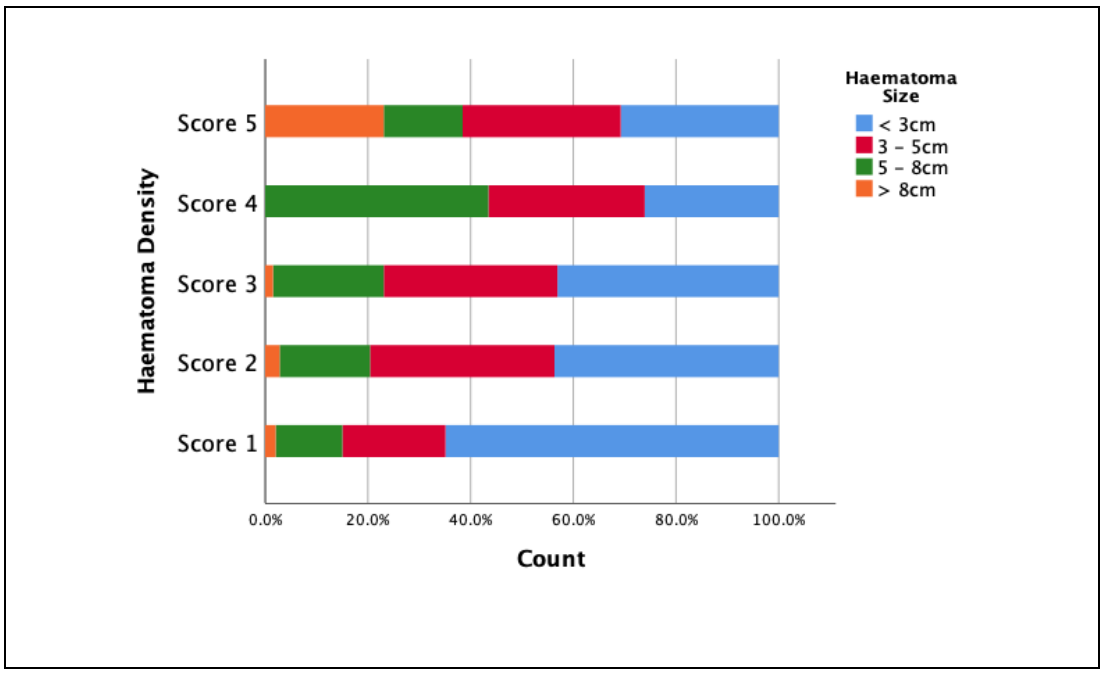


Figure 5-16 Proportion of haematoma size by haematoma density

Table 5-7 Comparison of demographic and clinical data of patients with haematoma expansion and without haematoma expansion

Variables	Whole Population (n = 1035)	Haematoma Expansion (n = 300, 29%)	No Haematoma Expansion (n = 735, 71%)	*P* value
Age, median [IQR]	70 [58 – 79]	71 [–0 – 80]	70 [58 – 79]	0.549
Sex, male, n (%)	583 (56.3)	176 (58.7)	407(55.4)	0.333
Pre-existing Pathology				
Brain atrophy, n (%)	944 (91.2)	279 (93)	665 (90.5)	0.193
Periventricular lucencies, n (%)	472 (45.6)	121 (40.3)	351 (47.8)	0.030
Old vascular lesion, n (%)	631 (61)	185 (61.7)	446 (60.7	0.768
NIHSS (/42)				
median [IQR]	11 [6 – 18]	15 [8 – 20]	11 [6 – 17]	< 0.001
NIHSS ≥14, n (%)	431 (41.6)	167 (55.7)	264 (35.9)	
GCS (/15)				
median [IQR]	15 [13 – 15]	14 [12 – 15]	15 [13 – 15]	0.302
GCS <9, n (%)	23 (2.2)	8 (2.7)	15 (2)	
mRs (/6)				
median [IQR]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0.160
mRs ≥3, n (%)	87 (8.4)	28 (9.3)	59 (8)	
Antiplatelet use, n (%)	247 (23.9)	88 (29.3)	159 (21.6)	0.008
Time-to-scan, hours				0.012
Median [IQR]	3.66 [2.55 – 5.03]	3.53 [2.44 – 4.72]	3.71 [2.61 – 5.2]	
MEASURED VOLUME				
Haematoma volumes				

Baseline,				
Range (m–n - max)	0.104 – 154	0.29 – 138.8	0.10 – 154	< 0.001
Median [IQR]	11.91 [5.06 – 28.25]	19.55 [6.61 – 39.52]	9.74 [4.57 – 24.89]	
ADJUDICATORS				
Haematoma Size				
< 3cm, n (%)	614 (59.3)	138 (46)	476 (64.8)	
3 – 5 cm, n (%)	243 (23.5)	81 (27)	162 (22)	< 0.001
5 – 8cm, n (%)	154 (14.9)	72 (24	82 (11.2)	
> 8cm, n (%)	24 (2.3)	9 (3.0)	15 (2)	
Haematoma shapes (Barras score)				
Score 1, n (%)	97 (9.4)	25 (8.3)	72 (9.8)	
Score 2, n (%)	200 (19.3)	40 (13.3)	160 (21.8)	
Score 3, n (%)	224 (21.6)	55 (18.3)	169 (23)	
Score 4, n (%)	213 (20.6)	74 (24.7)	139 (18.9)	0.001
Score 5, n (%)	301 (29.1)	106 (35.3)	195 (26.5)	
Regular, n (%)	297 (28.7)	65 (21.7)	232 (31.6)	
Irregular, n (%)	738 (71.3)	235 (78.3)	503 (68.4)	
Haematoma Density (Barras Score)				
Score 1, n (%)	792 (76.5)	222 (74)	570 (77.6)	
Score 2, n (%)	142 (13.7)	43 (14.3)	99 (13.5)	
Score 3, n (%)	65 (6.3)	20 (6.7)	45 (6.1)	
Score 4, n (%)	23 (2.2)	12 (4)	11 (1.5)	0.147
Score 5, n (%)	13 (1.3)	3 (1)	10 (1.4)	

Homogenous, n (%)	935 (90.3)	266 (88.7)	669 (91)	
Heterogeneous, n (%)	100 (9.7)	34 (11.3)	66 (9)	
Location of haemorrhage				
Lobar, n (%)	303 (29.3)	109 (36.3)	194 (26.4)	
Deep, n (%)	639 (61.7)	163 (54.3)	476 (64.8)	0.006
Infratentorial, n (%)	66 (6.4)	16 (5.3)	50 (6.8)	
Lobar and Deep, n (%)	23 (2.2)	10 (3.3)	13 (1.8)	
Deep and Infratentorial, n (%)	3 (0.3)	2 (0.7)	1 (0.1)	
Lobar and Infratentorial, n (%)	1 (0.1)	-	1 (0.1)	
Haematoma Site				
Basal Ganglia / Thalamus, n (%)	676 (65.3)	187 (62.3)	489 (66.5)	
Frontal, n (%)	77 (7.4)	30 (10)	47 (6.4)	
Parietal, n (%)	124(12)	38 (12.7)	86 (11.7)	
Occipital, n (%)	22 (2.1)	5 (1.7)	17 (2.3)	0.162
Temporal, (%)	72 (7.0)	23 (7.7)	49 (6.7)	
Midbrain, n (%)	3 (0.3)	2 (0.7)	1 (0.1)	
Pontine, n (%)	33 (3.2)	11 (3.7)	22 (3)	
Cerebellar, n (%)	28 (2.7)	4 (1.3)	24 (3.3)	
Presence of IVH, n (%)	315 (30.4)	77 (25.7)	238 (32.4)	0.033
Blend sign +ve, n (%)	155 (15.0)	70 (23.3)	85 (11.6)	< 0.001

Variables	Whole Population (n = 883)	Haematoma Expansion (n = 250, 28.3%)	No Haematoma Expansion (n = 633, 71.6%)	P Value
Black hole sign +ve, n (%)	142 (16.1)	57 (22.5)	85 (13.4)	0.001
Variables	Whole Population (n = 549)	Haematoma Expansion (n = 154, 28.1%)	No Haematoma Expansion (n = 395,71.9%)	P Value
Island sign +ve, n (%)	55 (10)	22 (14.3)	33 (8.4)	0.038

Data are mean (standard deviation), median [interquartile range] or number (%). GCS = Glasgow Coma Scale; IVH = intraventricular haemorrhage; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale. Statistics are Chi-square and Mann-Whitney U test.

5.3.3 Comparison of the Adjudicated Baseline Imaging Features of Blend Sign, Black Hole Sign, and Island Sign between Participants with Haematoma Expansion and without Haematoma Expansion

Out of 1035 participants, 155 (15%) were identified of showing blend sign on baseline CT scan and 70 (45.1%) of them had haematoma expansion. Eight hundreds and eighty-three participants were assessed for black hole sign on baseline CT, 142 (16.1%) were identified with the presence of black hole sign and 57 (40.1%) of them were confirmed of having haematoma expansion. While 55 (10%) participants out of 549 were diagnosed of having island sign on baseline CT, and 22 (40%) were showing haematoma expansion. Relationship between the incidence of haematoma expansion and baseline CT sign is shown on Table 5-8 to Table 5-10 and illustrated on Figure 5-17 to Figure 5-19. Analyses revealed that there was statistically significant difference of baseline CT signs between participants with haematoma expansion and without haematoma expansion (blend sign, $p < 0.001$; black hole sign, $p = 0.001$ and island sign, $p = 0.038$) (Table 5-7). In participants presenting with CT baseline signs, the baseline haematoma volume was significantly higher (Table 5-13). The proportions of the haematoma expansion by CT baseline signs are shown on Figure 5-17 to Figure 5-19. The figures show that the proportions of participants with haematoma expansion were higher in those with CT baseline signs. Participants with haematoma expansion were more likely to have haematoma with blend sign, black hole sign and island sign.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of baseline CT sign for predicting haematoma expansion were 23.3%, 88.4%, 45.1% and 73.9% for blend sign, 22.8%,

86.6%, 40.1% and 73.9% for black hole sign and 14.2%, 91.6%, 40% and 73.3% for island sign respectively. Baseline CT signs had low sensitivity (14.2% - 23.3%) and high specificity (86.6% - 91.6%) for haematoma expansion with island sign having the highest specificity (91.6%) but lowest sensitivity (14.2%) as shown on Table 5-12.

Table 5-8 Relationship between the incidence of haematoma expansion and baseline CT sign

Baseline CT Sign	Haematoma Expansion		Total no of cases	Incidence of Haematoma Expansion
	Yes	No		
Blend Sign	70	85	155	45.1%
Black Hole Sign	57	85	142	40.1%
Island Sign	22	33	55	40.0%

Table 5-9 Baseline CT Blend Sign Diagnostic Accuracy

	Haematoma Expansion +ve	Haematoma Expansion -ve	Total
Blend Sign +ve	70	85	155
Blend Sign -ve	230	650	880
Total	300	735	1035

+ve = positive (present of disease); -ve = negative (absent of disease)

Table 5-10 Baseline CT Black Hole Sign Diagnostic Accuracy

	Haematoma Expansion +ve	Haematoma Expansion -ve	Total
Black Hole Sign +ve	57	85	142
Black Hole Sign -ve	193	548	741
Total	250	633	883

+ve = positive (present of disease); -ve = negative (absent of disease)

Table 5-11 Baseline CT Island Sign Diagnostic Accuracy

	Haematoma Expansion +ve	Haematoma Expansion -ve	Total
Island Sign +ve	22	33	55
Island Sign -ve	132	362	494
Total	154	395	549

+ve = positive (present of disease); -ve = negative (absent of disease)

Table 5-12 Sensitivity, specificity, and predictive values of baseline CT signs

Baseline CT Signs	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %
Blend Sign	23.3	88.4	45.1	73.9
Black Hole Sign	22.8	86.6	40.1	73.9
Island Sign	14.2	91.6	40.0	73.3

Table 5-13 Comparison of baseline haematoma volume in participants with and without baseline CT signs

Baseline CT Signs	Baseline Haematoma Volume	P value
Blend Sign +ve	34.30 (15.94 – 57.56)	< 0.001
Blend Sign -ve	9.59 (4.42 – 22.72)	
Black Hole Sign +ve	30.95 (15.73 – 54.04)	< 0.001
Black Hole Sign -ve	9.74 (4.24 – 23.37)	
Island Sign +ve	54.02 (31.58 – 76.45)	< 0.001
Island Sign -ve	10.55 (4.77 – 24.58)	

+ve = positive (present of disease); -ve = negative (absent of disease)

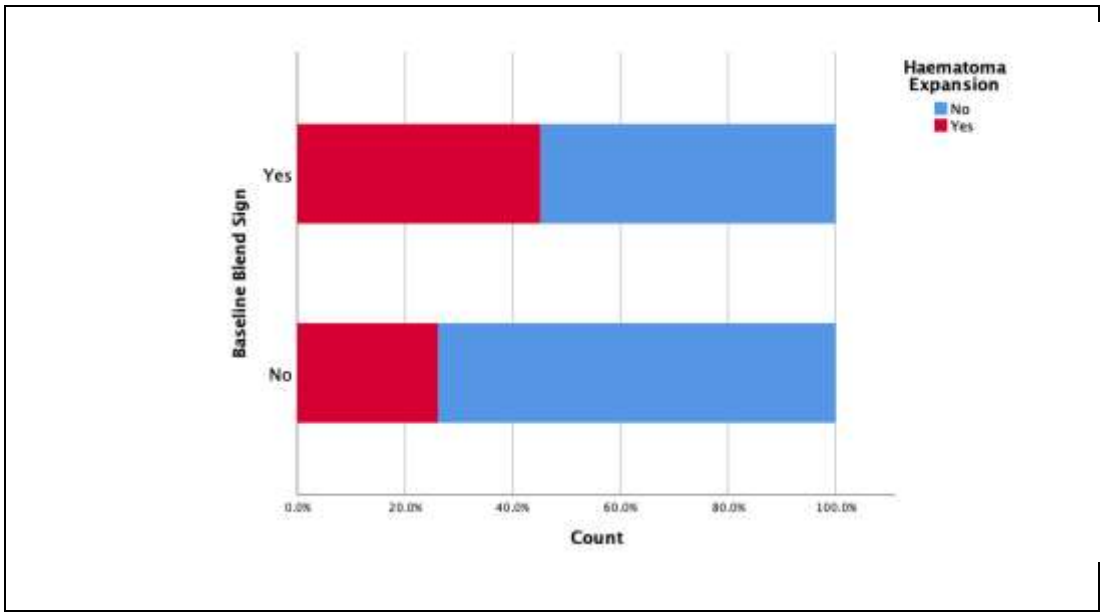


Figure 5-17 Proportion of haematoma expansion by blend sign on baseline

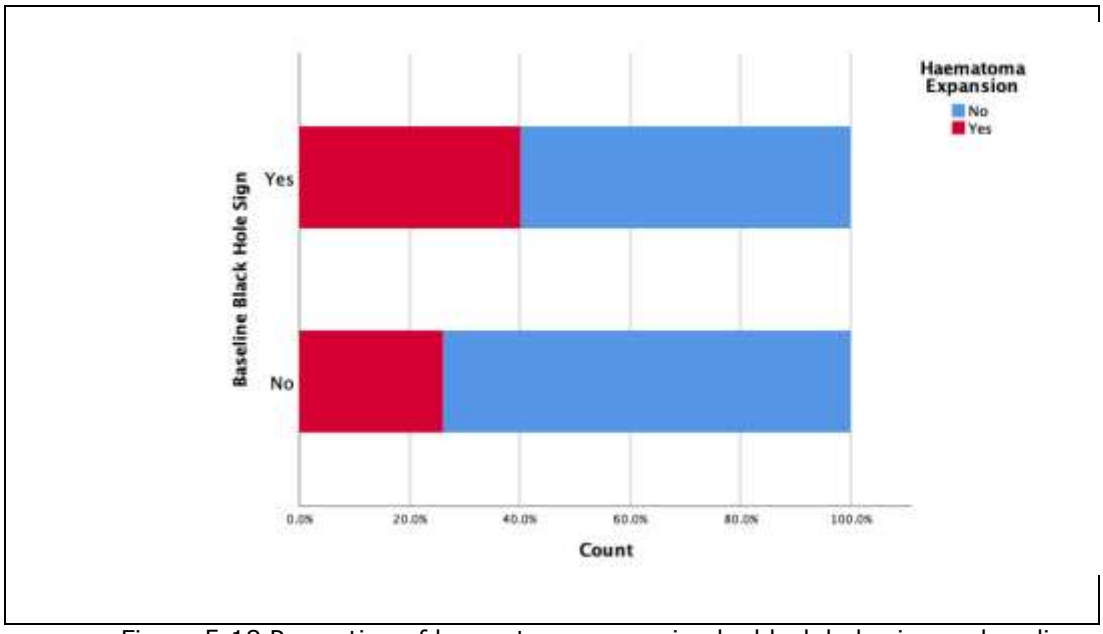


Figure 5-18 Proportion of haematoma expansion by black hole sign on baseline

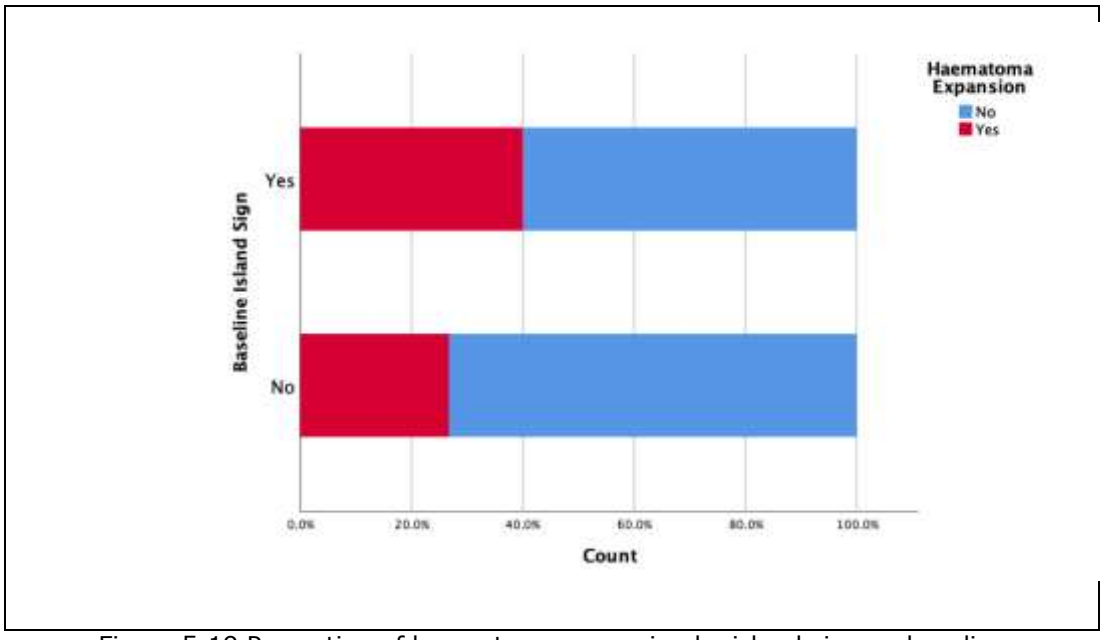


Figure 5-19 Proportion of haematoma expansion by island sign on baseline

5.3.4 Multivariate Imaging Predictor Model for Haematoma Expansion in the Placebo-Treated TICH-2 Population Based on Adjudicated Baseline Imaging Characteristics

Univariate logistic regression analysis showed haematoma expansion was significantly associated with the presentation of brain atrophy (OR, 2.372; p = 0.040), baseline NIHSS score ≥ 14 (OR, 2.441; $p < 0.001$), shorter time-to-scan (OR, 0.866, p = 0.013), larger baseline haematoma volume (OR, 1.017; $p < 0.001$), larger baseline haematoma size (OR, 3.162; $p < 0.001$) and the presence of CT black hole sign (OR, 2.099; p = 0.002) and CT island sign (OR, 1.823, p = 0.041) (Table 5-14). All these variables increased the odds ratio of haematoma expansion. Multivariate logistic regression models were then constructed to explore the significance of the combination of these variables plus the known predictor variables from previous clinical studies in predicting haematoma expansion.

Multivariate regression model revealed that there were only 4 factors showed significant statistical association to haematoma expansion: baseline NIHSS ≥

14 (OR, 1.811; p = 0.007), baseline haematoma volume (OR, 1.012; p = 0.011), time-to-scan (OR, 0.887, p = 0.047) and brain atrophy (OR, 2.621; p = 0.027) (Table 5-15).

Based on this multivariable predictor model of haematoma expansion, participants with NIHSS score ≥ 14 had an odds ratio of having haematoma expansion by 1.811 (81%). In other words, the odds of having haematoma expansion in participants with NIHSS score ≥ 14 has 1.8 times greater likelihood compared to those who had NIHSS score < 14. Larger baseline haematoma volume strongly predicts haematoma expansion. For every 1mL of haematoma volume, the odds of haematoma expansion increase by 1.012 (1.2%). The odds of haematoma expansion increased by 2.621 in participants with brain atrophy. The time-to-scan (OR, 0.887) was negatively related to haematoma expansion since the odd ratio showed the value of less than 1. This means that the odd ratio of haematoma expansion was increased in a shorter stroke onset to scan time (Table 5-15).

CT baseline signs (blend sign, black hole sign and island sign) were not significantly associated to haematoma expansion in multivariate analysis, neither a predictor of haematoma expansion.

Table 5-14 Univariate logistic regression of predictor for haematoma expansion

Variables	Haematoma Expansion		
	Odd Ratios	95% Confidence Interval	*P* Value
Demographic			
Age	1.006	0.992 – 1.020	0.381
Sex	1.218	0.834 – 1.780	0.307
Pre-existing pathology			
Brain atrophy	2.372	1.039 – 5.418	0.040
Periventricular lucencies	0.797	0.548 – 1.160	0.236

Variables	Haematoma Expansion		
	Odd Ratios	95% Confidence Interval	*P* Value
Old vascular lesion	1.049	0.716 – 1.536	0.806
Clinical Variables			
NIHSS, ≥ 14	2.441	1.669 – 3.572	< 0.001
GCS, < 9	0.457	0.100 – 2.086	0.312
mRs, ≥ 3	0.562	0.255 – 1.241	0.154
Prior Antiplatelet Therapy	1.481	0.974 – 2.251	0.066
IVH Presence	1.370	0.900 – 2.087	0.142
Scan Time			
Time-to-scan, hours	0.866	0.773 – 0.970	0.013
Measured Volume			
Baseline haematoma volume	1.017	1.009 – 1.024	< 0.001
Adjudicators			
Baseline haematoma size, > 5 cm	3.162	2.024 – 4.939	< 0.001
Baseline haematoma shapes, irregular	0.664	0.432 – 1.021	0.062
Baseline haematoma density, heterogenous	1.218	0.691 – 2.147	0.495
Haematoma location, deep	0.753	0.513 – 1.104	0.146
Site of haematoma, basal ganglia	0.976	0.660 – 1.443	0.904
Baseline Sign			
Blend sign on baseline	1.549	0.964 – 2.466	0.071
Black hole sign on baseline	2.099	1.303 – 3.381	0.002
Island sign on baseline	1.823	1.026 – 3.241	0.041

GCS = Glasgow Coma Scale; IVH = intraventricular haemorrhage; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale

Table 5-15 Multivariate logistic regression of predictors for haematoma expansion

Variables	Haematoma Expansion		
	Odd Ratios*	95% Confidence Interval	*P* Value
NIHSS, ≥ 14	1.811	1.180 – 2.779	0.007
Baseline haematoma volume	1.012	1.003 – 1.021	0.011
Time-to-scan, hours	0.887	0.787 – 0.988	0.047
Brain atrophy	2.621	1.115 – 6.163	0.027

NIHSS = National Institute of Health Stroke Scale. *The odds ratio is adjusted for brain atrophy, NIHSS, baseline haematoma size, haematoma shape, haematoma density, previous antiplatelet therapy, old vascular lesion, GCS < 9, baseline blend sign, baseline black hole sign and baseline island sign.

5.4 Discussion

Haematoma expansion is a potentially modifiable predictor of poor outcome following and acute spontaneous ICH. The ability to identify patients with spontaneous ICH who are likeliest to experience haematoma expansion and therefore likeliest to benefit from expansion-targeted treatments remain an unmet need. The objectives of this study are to compare the characteristics of participants between those with and without haematoma expansion and to assess their associated risk. Hence, this chapter reports the characteristics of participants with and without haematoma expansion and also the association of baseline and adjudicated CT imaging features to early haematoma expansion in the placebo group of the TICH-2 population. Based on these imaging features, a multivariate imaging predictor model for haematoma expansion had been developed.

In order to deliver the objectives, this study defined haematoma expansion as the increase of the haematoma volume by > 6 mL or > 33% between baseline and follow-up CT scan, similar to the definition of haematoma expansion in the TICH-2 clinical trial and in several clinical studies [30][225][233][234]. As reported in Chapter 4, the inter-observer measurement variation was 3 – 5 mL. This is an

important point and was the motivation for looking in detail at the measurement variation. Measurements always have some degree of error, and this is true for haematoma volume measurements, which could result in misclassification of haematoma expansion. It is important to quantify this error so that researchers are aware, but until more accurate and reliable measurement tools are available, some misclassifications are unavoidable.

Using spontaneous ICH patient data from the placebo-treated TICH-2 clinical trial, this study confirmed that there were no significant differences of demographic criteria (age and gender), pre-existing pathology (except for periventricular lucencies), baseline GCS and mRs score, and haematoma site between participants presented with haematoma expansion and without haematoma expansion. This study also showed no significant difference of haematoma density between the groups, which is contradicted to C. D. Barras et al [69]. In univariate analyses, when compared to those without haematoma expansion, participants with haematoma expansion were more likely to have pre-existing periventricular lucencies, presented with IVH, baseline NIHSS score $\geq$ 14, taking previous antiplatelet therapy, shorter onset to baseline CT imaging time, larger baseline haematoma volume, irregular haematoma shape, small haematoma size (< 5cm in axial diameter) and haematoma located in deep brain structures. Compared to participants without haematoma expansion, those with haematoma expansion were more likely to have a presentation of baseline CT signs (blend sign, black hole sign and island sign). These findings are consistent with the published literature suggesting an association between clinical measures (baseline NIHSS and prior antiplatelet use) [235], baseline haematoma volume [69][222], haematoma shape [69] haematoma location and baseline CT sign to haematoma expansion [143][170][212][236].

Previous reports proposed several imaging predictors for identifying the haematomas that will expand [143][165][166][237]. The CTA spot sign has been

well established as an imaging predictor of haematoma expansion in patients with spontaneous ICH [30][164][165][167][225]. More recently, several CTA-based imaging markers, such as spot-and-tail sign and the leakage sign, have been shown to be independent predictors of haematoma expansion [238][239]. All the above-mentioned imaging predictors, however, have the disadvantage of requiring emergency CTA with contrast administration, which is not readily available in many institutions. Hence, there is growing need for non-contrast CT imaging predictors of haematoma expansion that are readily available and easy to use in clinical practice.

This study had proposed the blend sign, black hole sign and island sign as non-contrast imaging markers for predicting haematoma expansion. All these baseline CT signs demonstrated a high specificity (blend sign 88.4%, black hole sign 86.6%, island sign 91.6%) in detecting haematoma expansion. Nevertheless, the sensitivity of these imaging markers as predictors of haematoma expansion was quite low (blend sign 23.3%, black hole sign 22.8%, island sign 14.2%). These findings were comparable with the previous clinical study reports. Blend sign was first reported by Q. Li et al. [143] and considered to represent bleeding with different ages. In their study, the specificity and sensitivity of blend sign for predicting haematoma expansion were 96% and 39%, respectively. Study by J. Zheng et al. [240] suggested the specificity and sensitivity of blend sign for predicting haematoma were 89% and 43% , respectively. Y. W. Huang et al. [212] in their study had reported almost the same result, in which the specificity and the sensitivity of blend sign for predicting haematoma expansion were 83% and 34%, respectively. However, in G. Boulouis et al.'s [230] study, even though the specificity of blend sign for predicting haematoma expansion was 87%, the sensitivity was only 15%. A. Morotti et al.[241] analysed the association between blend sign and haematoma expansion in Anti-hypertensive Treatment of Acute Cerebral Haemorrhage II study (ATACH-2), in which the specificity and sensitivity of blend sign for predicting haematoma expansion were 93% and 13%,

respectively. Meta-analysis of 5 studies (2248 participants) on performance of blend sign in predicting haematoma expansion by Z. Yu et al [242] had reported that the pooled specificity and sensitivity of blend sign for predicting haematoma expansion to be 92% (88% - 95%) and 28% (16% - 46%), respectively. These results also suggested that blend sign had high specificity for predicting haematoma expansion, but the sensitivity was low.

For the sensitivity and the specificity of the black hole sign in detecting haematoma expansion, there were several studies reporting almost the same findings. The high specificity and low sensitivity of black hole sign in detecting haematoma expansion was also reported by X. Xiong et al [243] as showing 95.3% specificity and only 33.8% sensitivity. Whereas, the most recent publication by M. R. Shakya et al [244] had reported a quite low specificity (79.3%) and higher rate of sensitivity (47.5%) compared to my study and previous published articles. However, the sensitivity of black hole sign still considered as low. In prior studies, it has been demonstrated that there is an association of haematoma heterogeneity and haematoma expansion [230]. The black hole sign as a novel sign to determine heterogeneity for the evaluation of haematoma expansion was first proposed by Q. Li et al [146] in 2016. It had high specificity (94.1%) and low sensitivity (31.9%), which is similar to my study (specificity = 86.6%, sensitivity = 22.8%). Pathologically, the hypoattenuated region in baseline CT signs indicates the presence of fresh blood, and the hyperattenuated region indicates the blood serum that has been isolated out of the haematoma after clot formation. Thus, positive black hole sign suggests the ejection of blood over a period of time [146]. A second meta-analysis of 5 studies (1495 participants) reported a pooled specificity and sensitivity of 91% (87% – 94%) and 30% (20% - 41%) respectively for black hole sign [245]. My study similarly found CT blend sign and black hole signs to be highly specific but not very sensitive for prediction of haematoma expansion. The low sensitivity may be due to the small sample size of haematoma expansion with positive baseline CT signs.

The island sign was of particular interest as it was found to be very specific, albeit less sensitive, than the other CT baseline signs. The island sign was first reported as a predictor of haematoma expansion and poor functional outcome in a single centre study by Q. Li et al [150]. Similarly, I found the island sign to have high specificity but low sensitivity in detecting haematoma expansion. However, after accounting for haematoma volume and time-to-scan, the island sign did not independently predict haematoma expansion. This might be due to the prevalence of island sign in this study was relatively low (16.1%).

On the other hand, even though the baseline CT signs were very specific in detecting haematoma expansion, this study did not find the blend sign to be an independent predictor of haematoma expansion in both univariate and multivariate analysis. While the black hole sign and the island sign only showed significant association in univariate analysis, they did not significantly predicts haematoma expansion in multivariate analysis when baseline haematoma volume and time-to-scan had been controlled. The same finding of non-significant association of black hole sign in multivariate analysis was also reported by M. R. Shakya et al [244]. This finding was contradicted to previous clinical trials that showed the significance of blend sign, black hole sign and island sign as independent predictor for haematoma expansion in both univariate and multivariate analysis [146][150][246]. In term of the effect size of these CT baseline sign, the odd ratios for all 3 baseline CT signs in univariable analysis were too small (blend sign = 1.594, black hole sign = 2.099, island sign = 1.823) compared to previous primary studies (blend sign = 13.75, black hole sign 7.55, island sign = 44.20) by Q. Li et al [143][146][150]. This might be due to the different threshold of haematoma expansion used in our studies (> 6 mL OR > 33% in my study compared to > 12.5mL OR 33% in Q. Li eta al). The prevalence of blend sign and black hole sign in this study was comparable to other studies [143][146][246]. However, the prevalence of island sign was lower compared to the previous primary study [150]. My result of analysis was also contradicted to

study done by Z. K. Law et al [246]. Their study showed significant association of blend sign and black hole sign to haematoma expansion. We used the same data of TICH-2 population. Z. K. Law et al used both groups of TICH-2 population, while my study only involved the placebo-treated group. The contradicted result might be due to different sample size used in our analysis in which the sample size in Z. K. Law et al study consists of almost double size of mine.

According to the Predicting Haematoma Expansion and Outcome in Intracerebral Haemorrhage Using Contrast Bolus CT (PREDICT) study, the sensitivity and specificity of the CTA spot sign for predicting haematoma expansion were 51% and 85% respectively [166]. Although the reported sensitivity of CT blend sign, black hole sign and island sign is lower than CTA spot sign, all these baseline CT signs are highly specific for predicting haematoma expansion and this finding support the previous primary studies by Q. Li et al [143][146][150] and Z. K. Law et al [246]. On the other hand, even though the CTA spot sign had higher sensitivity, any non-contrast CT signs may still be regarded as a fair predictor of haematoma expansion when CTA is not available [244].

Multivariate analysis of predictors for haematoma expansion showed that haematoma expansion was more likely occurred in participants with NIHSS score $\geq$ 14, OR 1.811 (1.180 – 2.779), larger baseline haematoma volume, OR 1.012 (1.003 – 1.021), shorter interval of ICH stroke onset to baseline CT scan, OR 0.887 (0.787 – 0.988), and having a history of pre-existing brain atrophy, OR 2.621 (1.115 – 6.163). Previous clinical studies had proved that baseline haematoma volume has a significantly positive association to haematoma expansion [75][247][248]. Many studies demonstrated that a large volume (> 20 mL) was more likely to associated with haematoma expansion, whereas a small volume (< 20 mL) meant lower risk of developing haematoma expansion [249]. This might be due to the assumption that early haematoma expansion may be associated with greater baseline haematoma volume and larger haematomas are

more likely to experience haematoma expansion as stated in the study by Y. W. Huang et. al as "worse haematomas get worse" [212]. In my analysis, increase in 1 mL baseline haematoma volume will increase the odds ratio of haematoma expansion by 1.012. Therefore, greater baseline haematoma volume predicts haematoma expansion (p = 0.011).

Some clinical studies reported that the incidence of haematoma expansion decreased as the interval time from ICH stroke onset to baseline CT scan time increased [219]. It meant that the interval time from ICH stroke onset to baseline CT scan time is a strong predictor of an ultra-early haematoma expansion. One prospective cohort study proved that shorter interval time from stroke onset to baseline CT scan (≤ 6 hours) meant the greater possibility of haematoma expansion than a later presentation (> 6 hours) [219]. This is because, the ICH is a dynamic illness, patients with haematoma expansion may be still in the acute period of ICH and the bleeding is still ongoing [212]. According to their findings, my analysis confirmed that time to baseline CT scan was one of significant predictors for haematoma expansion (p = 0.047).

This study found that brain atrophy showed a significant association to haematoma expansion in both univariate and multivariate analysis (p = 0.04 and p = 0.027 respectively). Reduction in brain tissue volume is mainly refers to the brain atrophy. It is well known that human brain atrophies with age, and generally, this atrophy reflects a decrease in grey- and white matter tissue [250]. Total brain tissue volume is important measure for assessing whole-brain atrophy in patient with spontaneous ICH. As age progressed, brain parenchyma width decreased and cortical atrophy increased [251]. Spontaneous ICH found to be correlated with increased brain atrophy [251]. These findings indicate that pre-existing brain volume reduction is a factor influencing the development of ICH and might be a confounding predictor to haematoma expansion. Greater atrophy possibly allows haematomas to expand more because there is less of a direct compressive effect

of the surrounding brain tissue on the haematoma. Further study on this possible impact might assist in better understanding of the relationship between brain atrophy and haematoma expansion.

This study overlapped with the study done by Z. K. Law et al [246] which also used data from the TICH-2 trial. However, there is an important difference between the analysis of Law et al and the analysis that I present here. In the present work I only include data from the placebo group, allowing me to assess the relationship between baseline imaging signs and haematoma expansion without any confounding effects on haematoma expansion due to the haemostatic agent tranexamic acid. In contrast, the study by Z. K. Law et al included both tranexamic acid and placebo groups, but then controlled for group allocation in the statistical analysis. Another study done by Z. K. Law et al [252] with the same data population went on to look specifically for interactions between treatment allocation and haematoma expansion in the presence of different radiological signs. There were some contradicting findings between these 2 studies in analysing the independent predictors of haematoma expansion. My analysis did not find any significant association between baseline CT signs and haematoma expansion in multivariate analysis, while Z. K. Law et. al found that blend sign and black hole sign shown significant association to haematoma expansion and can act as independent predictors of haematoma expansion in spontaneous ICH. Both studies however agreed that the island sign was not a significant independent predictor of haematoma expansion. The approach taken by Z. K. Law et al with inclusion of both treatment groups has the advantage that the sample size is considerably larger (n=2077 compared to n= 548 in the present analysis of predictor model for haematoma expansion) but required statistical controlling to account for effects of tranexamic acid on haematoma expansion in relation to the radiological signs. Although my analysis has a smaller sample size, which reduces the statistical power, it can be considered to be a study of the

'natural history' of haematoma expansion (with the context of a clinical trial) in relation to the radiological signs.

In term of the sample size, this study has a large sample size compared to the previous similar studies; A. K. Maeda et al [95] 20 participants, J. C. Koisor et al [94] 30 participants, H. Hussein et al [71] 56 participants, H. B. Huttner et al [70] 83 participants, R. U. Kothari et al [63] 118 participants, J. M. Gebel et al [112] 244 participants, X. Xu et al [78] 294 participants and K. Krishnan et al [76] 548 participants (with the exception of Z. K. Law et al, as explained above). A large sample dataset which comes from more than 100 hospitals in 12 countries making the findings of this study more powerful and accurately represent the population compared to some of the single centre studies. However, a large sample size has a great tendency of having a large number of natural outliers in haematoma volume measurement.

Chapter 6 PHO VOLUMES AND EXPANSION IN THE TICH-2 POPULATION

6.1 Introduction

Spontaneous ICH is a form of cerebrovascular accident with a very high rate of morbidity and mortality. The inflammation and coagulation response after ICH could accelerate the formation of brain oedema around hematoma, resulting in a more severe and durable injury. It has long been known that the haematoma size and expansion have a negative impact on the outcome of spontaneous ICH. The previous chapter has reported the association of baseline CT adjudication features to haematoma expansion. These findings supported previous clinical studies on haematoma expansion and also discovered new contradicted findings on haematoma expansion predictors. Nevertheless, in the case of PHO, prediction of PHO expansion and the rate of growth has not been studied to the same extent as haematoma expansion. The findings derived from existing studies on PHO are disparate and unclear. While it is generally accepted that haematoma-induced brain injury is irreversible, the secondary injury resulted from PHO may be reversible. Thus, identification of people at risk of PHO expansion may be helpful for the selection of people for therapeutic target and aggressive oedema reduction strategies.

Numerous preclinical and clinical studies have demonstrated that PHO after spontaneous ICH is associated with a poor prognosis, resulting in approximately 2.8 million people die of ICH each year worldwide [253] and only 25% of ICH survivors are able to live independently 6 months after ICH onset [254]. The functional neurological outcome of ICH is associated with mechanical destruction of nerve fibres and ICH-induced secondary brain injury [255]. An increase in absolute PHO volume of 10 mL increases mortality by three times [256]. In

addition, the rate of increase in PHO volume is an independent predictor of mortality and poor functional outcomes [257].

In patients with spontaneous ICH, large haematoma volume causes midline shift and fatal herniation syndrome [160]. Midline shift of the brain is an important feature in diagnosing intracranial lesions, especially traumatic brain injury (might be due to PHO formation) and can be measured directly on CT images. Furthermore, while the relationship between the presence of PHO and intracranial mass effect may seem intuitive, this relationship may not be straightforward because of confounding effect of haematoma volume (and potentially other factors such as the presence of intraventricular haemorrhage and hydrocephalus, brain parenchyma volumes and brain compliance). The demonstration of an independent relationship between PHO volume and markers of intracranial mass effect (principally midline shift) would be valuable because it would suggest that therapies aimed at reducing PHO will have a beneficial effect on intracranial mass effect. Not only would this finding be supportive of trials of therapies targeting PHO, but it would also indicate that measurements of midline shift or other 'simple' markers of mass effect could provide a useful outcome measure that are easier to access than the more complicated (and subjective) measurement of PHO volume.

6.2 Hypotheses

The hypotheses of this study are constructed based on the probable relationship of adjudicated baseline imaging characteristics to predict the growth of PHO in patients with spontaneous ICH in the TICH-2 population. The components of the hypotheses are as follow:

i. There are significant differences in clinical variables, baseline haematoma and PHO volume and the presence of haematoma expansion between

participants with and without PHO expansion in the placebo-treated TICH-2 population.

ii. A multivariate prediction model for PHO expansion could be developed based on the information of clinical variables, baseline haematoma and PHO volume and presentation of haematoma expansion.

iii. The volume of PHO and PHO expansion rate at 24 hours could be an independent predictor for poor clinical outcomes in patients with spontaneous ICH.

6.3 Objectives

The main objective of this chapter is to study the differentiation of the adjudicated baseline imaging characteristics between participants with and without PHO expansion in the placebo-treated TICH-2 populations. The specific objectives are as follow:

i. To compare the clinical variables, baseline haematoma and PHO volume and presentation of haematoma expansion for participants with and without PHO expansion.

ii. To develop a multivariate prediction model for PHO expansion based on the information of clinical variables, baseline haematoma and PHO volume and presentation of haematoma expansion.

iii. To assess the probability of PHO volume and PHO expansion rate at 24 hours as an independent predictor for poor clinical outcomes in patients with spontaneous ICH.

6.4 Methods

6.4.1 Participants

This chapter used data from the TICH-2 clinical trial. The TICH-2 cohort used in this study consisted of participants in the placebo-controlled arm presenting with non-contrast CT proven ICH within 8 hours of symptom onset and with

baseline clinical and radiological data. All participants had follow-up non-contrast CT scan at 24 hours and 90-day mRs scores. Participants with missing data, showing no evidence of PHO formation, unprocessable scan of baseline or follow-up, only CTA available on baseline or follow-up scan, underwent surgical evacuation of haematoma before follow-up scan, and failure of CT scan DICOM to NIFTI conversion format were excluded from this study. Figure 6-1 presents the flow chart showing number of participants included in the analysis.

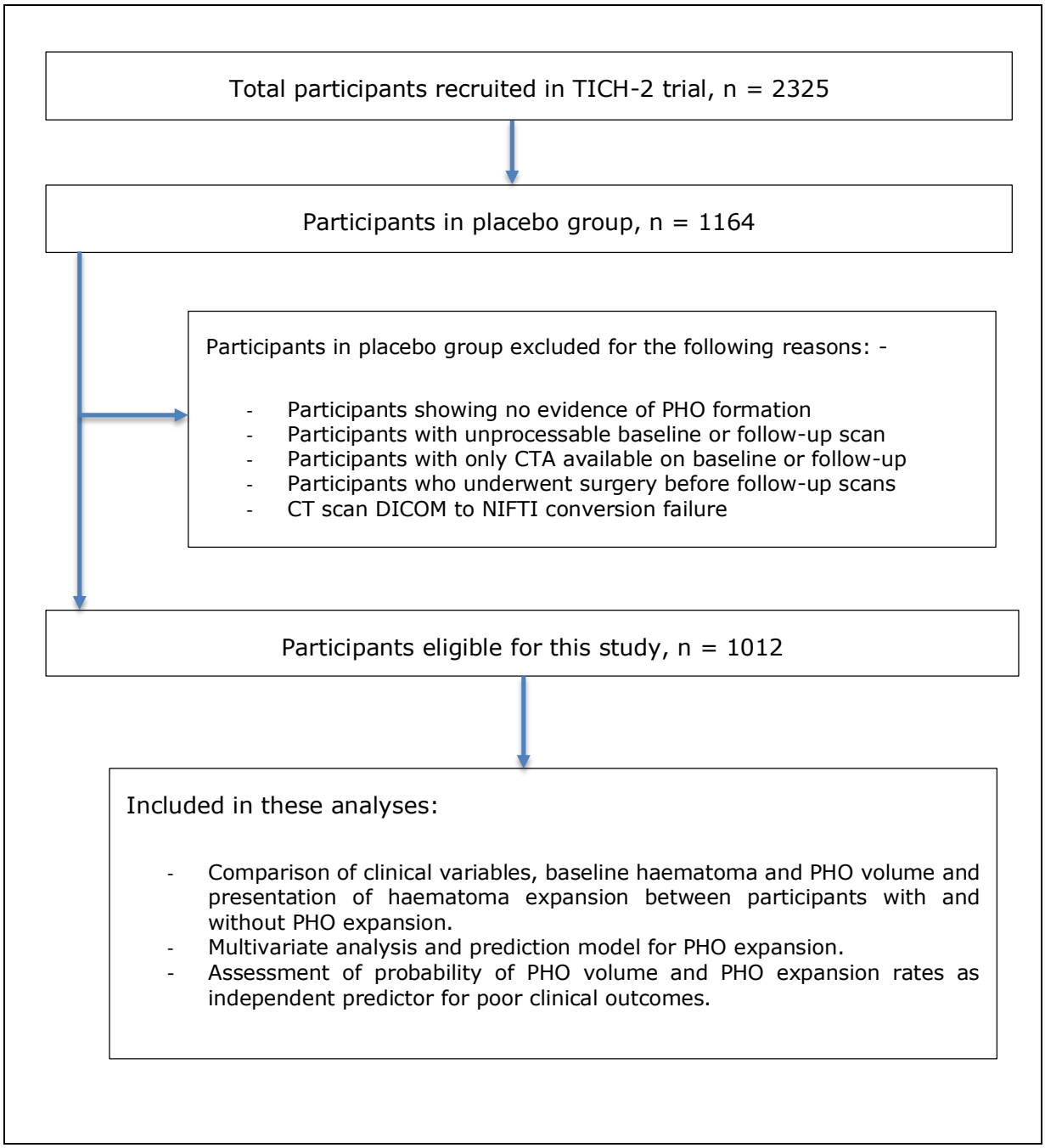


Figure 6-1 Study inclusion flowchart

6.4.2 Clinical Data Acquisition

From each centre, investigators assessed prestroke dependence with the mRs and stroke severity using the NIHSS and GCS score. Participants reviewed at day 2, day 7 and the day of hospital discharge or death (whichever came first) to gather the information on clinical assessment. Follow-up of patients' condition was done via telephone call at day 90. However, this study only used the score at baseline and 90 days for analysis.

6.4.3 Measurement of Mass Effect

Mass effect was rated to a 7-point visual rating scale by the TICH-2 CT adjudicators as: 0 = no swelling, 1 = effacement of the sulci overlying the stroke, 2 = minor effacement of adjacent lateral ventricle, 3 = complete effacement of lateral ventricle, 4 = effacement of the lateral and third ventricle, 5 = shift of the midline away from the side of the ventricle and 6 = effacement of the basal cisterns.

6.4.4 Measurement of Midline Shift

Measurement of midline shift was done by 2 independents observers (AA and ZKL). Because the skull was not always symmetrical and the participants may not be perfectly aligned during CT examination, midline shift was calculated by first drawing the imaginary midline joining the anterior and posterior visible points on the falx, and then measuring the farthest point on septum pellucidum as perpendicular to the imaginary midline (Figure 6-2). This method has been shown to have high inter-observer agreement (ICC = 0.833) in patients with spontaneous ICH [258]. Moreover, determining the imaginary midline is easier than determining of intracranial space when the skull is deformed or removed by surgery or trauma [158].



Figure 6-2 Measurement of midline shift on CT image of spontaneous ICH

6.4.5 Measurement of PHO Volume

Thorough explanations on PHO volume measurement were described in Chapter 4 (4.2.8). The PHO segmentation used a manual PHO delineation based on predefined criteria described by S. Urday et al [196]. Measurements of PHO volumes were performed by 3 independent raters (AA, ZKL and KK) blinded to clinical data and each other's measurements.

6.4.6 Definition of Haematoma Expansion

Definition of haematoma expansion and the method of haematoma volume measurement were thoroughly described on Chapter 4 (4.2.5). Haematoma expansion was defined as increase in haematoma volume on follow-up scan of > 6 mL or > 33% from baseline haematoma. Haematoma volumes were measured by three independent observers using SAS segmentation tools of ITK-SNAP software, blinded to clinical data and each other's measurements.

6.4.7 Definition of PHO Expansion

In the absence of a standardized definition of PHO expansion, this study used a previously validated measure of PHO by S. H. Lee et. al, defined as relative increase of more than 20% in PHO volume from baseline to 24 hours [105].

6.4.8 Measurement of PHO Expansion Rate

PHO expansion rate was calculated as the difference between the baseline and the follow-up PHO volumes, divided by the time interval between the 2 scans using the formula (PHO volume at 24 hours – PHO volume at baseline)/(24 hours).

6.4.9 Outcome Assessment

The evaluation of participants' clinical outcome was based on functional status at 90 days after the spontaneous ICH onset, as assessed with the mRs, which was administered by telephone or postal questionnaire and masked to treatment allocation. The mRs is the most prevalent functional outcome measure in contemporary stroke research. Clinical trials use of the mRs is global and often used by research nurses and professions allied to medicine. The mRs scale is a 7-level ordered outcome ranked as 0 (no symptoms at all), 1 (no significant disability, despite symptoms), 2 (slight disability but able to look after own affairs), 3 (moderate disability but able to walk without assistance), 4 (moderately severe disability; unable to walk or attend to own bodily needs), 5 (severe disability; bedridden and requiring constant nursing care) or 6 (death). It is the most commonly used primary outcome in context of acute stroke trials and is recommended in international guidelines. Participants were classified as favourable outcome for mRs <3 and poor outcome for mRs ≥3 as being used in previous related studies [108][116] [206].

6.4.10 Statistical Methods

Statistical analyses were performed using SPSS Version 26. Standard test for normality were applied. Given that many of the outcomes were not consistent with a normal distribution, non-parametric methods were used for comparisons citing median values with IQRs. Categorical data presented as number percentages and continuous variables presented as mean ± SDs or median (IQRs) when appropriate. The continuous groups were compared by Mann-Whitney U test while categorical groups were compared by Chi-square (X^2) test.

Binary logistic regression was used to assess the association between PHO (dependent variable) and baseline haematoma volume, presentation of haematoma expansion and clinical variables. The target category was "PHO expansion" and "no PHO expansion" was the reference category. The predictors in the model consist of (1) demographic characteristics: age and gender (reference = females), (2) pre-existing pathology; brain atrophy (reference = no), periventricular lucencies (reference = no) and old vascular lesion (reference = no), (3) clinical variable; baseline NIHSS (reference = < 14), GCS (reference < 9), mRs at day 90 (reference = <3), prior antiplatelet therapy (reference = no), IVH presence (reference = no), midline shift, mass effect and time to scan, (4) measured volume; baseline haematoma volume, baseline PHO volume and presentation of haematoma expansion (reference = no). All these variables were first analysed for their univariate association with the PHO expansion. Variables found to have a statistically significant association with PHO expansion in univariate analysis and variables that were clinically relevant and reported as predictors to PHO expansion in previous clinical studies were then entered into multivariate logistic regression models to determine whether such association would remain significant when the other variables were controlled.

To study the probability of PHO volume as independent predictor of poor clinical outcome, the same method of logistic regression model was used. Baseline PHO volume and other relevant clinical and radiological variables were first analysed for their univariate association with the poor clinical outcome. Categorical reference used were the same as previous analyses of PHO expansion plus additional variable of PHO expansion rates at 24 hours after ICH. Variables found to have a statistically significant association with poor clinical outcome in univariate analysis and known predictors reported in previous clinical trials were then entered into multivariate logistic regressions models to determine whether such associations would remain significant when other variables were controlled. A standard level of significance ($p < 0.05$) was used, and the data were reported as odds ratios and 95% CIs.

6.5 Results

6.5.1 Comparison of Clinical Variables, Baseline Haematoma Volume, Baseline PHO Volume, and Presentation of Haematoma Expansion between Participants with PHO Expansion and without PHO Expansion

The demographics and baseline characteristics of the participants are shown in Table 6-1. This study consists of 1012 participants from placebo-treated TICH-2 study. The median age was 70 years [58 – 79] ranged from 20 to 101 years with predominantly males (56.2% versus 43.8% females). The participants were assessed for pre-existing pathologies. Brain atrophy occurred in 922 (91.1%) participants, followed by old vascular lesion in 617 (61%) and periventricular lucencies in 460 (45.5%). The median score of NIHSS and GCS were 11.5 [6 – 18] and 15 [13 – 15] respectively. Seventy three percent of participants have Score 0 (no symptoms at all) for mRs, followed by Score 1 (no significant disability, despite syndrome) of 11.7%, Score 2 (slight disability but able to look after own affairs) of 6.6%, Score 3

(moderate disability but able to walk without assistance) of 6.4% and Score 4 (moderately severe disability; unable to walk or attend to own bodily needs) of 2.1%. In this study, there were no participants recorded of getting Score 5 (severe disability; bedridden and requiring constant nursing care) in mRs at baseline.

PHO expansion was observed in 675 (66.7%) participants with median age of 70 years [57 – 79] ranged from 28 to 97 years. There were no significant differences in the median age, gender, pre-existing pathologies of brain atrophy and old vascular lesion, GCS score and mRs score ($p > 0.05$) between participants with PHO expansion and those without PHO expansion. There were also no significant differences in median systolic ($p = 0.800$) and diastolic ($p = 0.165$) blood pressure between these 2 groups of participants. The median systolic and diastolic blood pressure for participants with PHO expansion was 175 [155 – 195] and 94 [81 – 195] respectively and the median of systolic and diastolic blood pressure for participants without PHO expansion was 175 [157 – 193.5] and 95 [83 – 107] correspondingly.

As depicted on Table 6-1, the median haematoma volume showed no significant difference between participants with PHO expansion (12.67, 5.74 – 29.21) and no PHO expansion (10.69, 4.24 – 27.48) with $p = 0.058$, even there was a slightly larger baseline haematoma volume in those with PHO expansion. However, the median PHO volume in those with no PHO expansion (8.26, 3.96 – 17.89) was significantly higher than those with PHO expansion (6.48, 3.41 – 13.81) with $p = 0.003$. Participants presented with haematoma expansion having a significantly higher chance of having PHO expansion ($p < 0.001$) compared to those without haematoma expansion. Furthermore, time interval between the ICH stroke onset to CT baseline scan also showing a significant different between these 2 groups of participants ($p < 0.001$). Median time-to-scan of participants with PHO expansion (3.56, 2.51 – 4.69)

was significantly shorter than those without PHO expansion (3.88, 2.80 – 5.65). Finally, neither midline shift (p = 0.378) nor mass effect (p = 0.585) was significantly associated with PHO expansion.

Table 6-1 Baseline demographic and clinical data of patients with PHO expansion and without PHO expansion

Variables	Whole Population (n = 1012)	PHO Expansion (n = 675, 66.7%)	No PHO Expansion (n = 337, 33.3%)	*P* value
Median age [IQR]	70 [58 – 79]	70 [57 – 79]	71 [60 – 80]	0.335
Sex				
Males, n (%)	569 (56.2)	375 (55.6)	194 (57.6)	0.543
Females, n (%)	443 (43.8)	300 (44.4)	143 (42.4)	
Pre-existing Pathology				
Brain atrophy, n (%)	922 (91.1)	608 (90.1)	314 (93.2)	0.102
Periventricular lucencies, n (%)	460 (45.5)	284 (42.1)	176 (52.2)	0.002
Old vascular lesion, n (%)	617 (61)	400 (59.3)	217 (64.4)	0.115
Clinical Variables				
NIHSS (/42), median [IQR]	11.5 [6 – 18]	13 [7 – 18]	10 [5 – 17]	0.017
NIHSS ≥14, n (%)	424 (41.9)	304 (45)	120 (35.6)	
GCS (/15), median [IQR]	15 [13 – 15]	15 [13 – 15]	15 [13 – 15]	0.751
GCS < 9, n (%)	22 (2.2)	15 (2.2)	7 (2.1)	
mRs (/6), n (%)				
Score 0	741 (73.2)	502 (74.4)	239 (70.9)	0.927
Score 1	118 (11.7)	78 (11.6)	40 (11.9)	
Score 2	67 (6.6)	41 (6.1)	26 (7.7)	
Score 3	65 (6.4)	40 (5.9)	25 (7.4)	
Score 4	21 (2.1)	14 (2.1)	7 (2.1)	
Score 5	-	-	-	
Antiplatelet use, n (%)	242 (23.9)	162 (24)	80 (23.7)	0.927

Variables	Whole Population (n = 1012)	PHO Expansion (n = 675, 66.7%)	No PHO Expansion (n = 337, 33.3%)	*P* value
IVH, n (%)	295 (29.2)	189 (28)	106 (31.5)	0.254
Systolic BP, mean (SD)	176.13 (29.13)	176.01 (29.73)	176.39 (27.94)	
Range (min – max)	96 – 280	96 – 280	109 – 261	0.800
Median [IQR]	175 [155 – 194]	175 [155 – 195]	175 [157 – 193.5]	
Diastolic BP, mean (SD)	95.27 (19.97)	94.49 (19.98)	96.84 (19.89)	
Range (min – max)	34 -196	34 – 190	57 – 196	0.165
Median [IQR]	94 [81 – 107]	94 [81 – 106]	95 [83 – 107]	
Time-to-Scan (hours), median [IQR]	3.66 [2.55 – 4.99]	3.56 [2.51 – 4.69]	3.88 [2.80 – 5.65]	< 0.001
Measured Volume				
Haematoma volumes				
Baseline, mean (SD)	21.44 (23.88)	21.48 (22.80)	21.37 (25.93)	0.058
Range (min – max)	0.248 – 154	0.248 – 138.8	0.38 – 154	
Median [IQR]	12.12 [5.15 – 28.72]	12.67 [5.74 – 29.21]	10.69 [4.24 – 27.48]	
PHO volumes				
Baseline, mean (SD)	12.04(14.34)	10.51 (11.20)	15.10 (18.79)	
Range (min – max)	0 – 152	0.1 – 89.78	0 – 152.1	0.003
Median [IQR]	7.15 [3.5 – 15.40]	6.48 [3.41 – 13.81]	8.26 [3.96 – 17.89]	
Haematoma Expansion, n (%)	297 (29.3)	255 (37.8)	42 (12.5)	< 0.001
Midline shift ≥ 5 mm, n (%)	279 (27.57)	192 (28.4)	87 (25.8)	0.378
Midline shift ≥ 5 mm, median [IQR]	48.5 [36.3 – 69.0]	48.9 [35.5 – 68.3]	47.7 [38.0 – 72.1]	
Mass effect, n (%)				
Score 0	186 (18.4)	124 (18.4)	62 (18.4)	

Variables	Whole Population (n = 1012)	PHO Expansion (n = 675, 66.7%)	No PHO Expansion (n = 337, 33.3%)	*P* value
Score 1	179 (17.7)	118 (17.5)	61 (18.1)	
Score 2	540 (53.4)	358 (53.0)	182 (54.0)	0.585
Score 3	43 (4.2)	34 (5.0)	9 (2.7)	
Score 4	18 (1.8)	13 (1.9)	5 (1.5)	
Score 5	36 (3.6)	23 (3.4)	13 (3.9)	
Score 6	10 (1.0)	5 (0.7)	5 (1.5)	

Data are mean (standard deviation), median [interquartile range] or number (%). BP = blood pressure; GCS = Glasgow Coma Scale; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale; PHO = perihematomal oedema. Statistics are Chi-square and Mann Whitney U test.

6.5.2 Multivariate Prediction Model for PHO Expansion based on Baseline Haematoma Volume, Presentation of Haematoma Expansion and Clinical Variables

Univariate logistic regression was performed to analyse the predictors of PHO expansion in participants with spontaneous ICH (Table 6-2). In this analysis, the baseline NIHSS ≥ 14 (OR, 1.482; p = 0.004), periventricular lucencies (OR, 0.664; p = 0.002), time to scan (OR, 0.854; p < 0.001), baseline PHO volume (OR, 0.934; p < 0.001) and haematoma expansion (OR, 4.174; p < 0.001) showed significant association to PHO expansion. Demographic and another baseline clinical variable showed no significant association to PHO expansion with p > 0.05.

In multivariate analysis, this model had shown that 5 factors showed significant association with PHO expansion (Table 6-3): periventricular lucencies (OR, 0.686; p = 0.009), baseline haematoma volume (OR, 1.023; p < 0.001), baseline PHO volume (OR, 0.937; p < 0.001), haematoma expansion (OR, 4.245; p < 0.001) and time to scan (OR, 0.882; p = 0.003).

Based on this multivariable predictor of PHO expansion, the presence of haematoma expansion increased the odd ratio of PHO expansion by 4.245 and increase in 1mL in baseline haematoma volume will increase the odd ratio of PHO expansion by 1.023. Nevertheless, periventricular lucencies, baseline PHO volume and time to scan were showing inverse relationships to PHO expansion by 0.686, 0.937 and 0.882 respectively. Thus, the presence of periventricular lucencies, higher baseline PHO volume and increase time to scan were associated with a decreased probability of PHO expansion.

Table 6-2 Univariate logistic regression of predictor for PHO expansion in spontaneous ICH

Variables	PHO Expansion > 20%		
	Odd Ratios	95% Confidence Interval	*P* Value
Demographic			
Age	0.995	0.986 – 1.005	0.314
Sex	0.921	0.708 – 1.200	0.543
Pre-existing pathology			
Brain atrophy	0.665	0.406 – 1.088	0.104
Periventricular lucencies	0.664	0.511 – 0.864	0.002
Old vascular lesion	0.804	0.614 – 1.054	0.115
Clinical Variables			
NIHSS, ≥ 14	1.482	1.132 – 1.940	0.004
GCS, < 9	1.071	0.433 – 2.653	0.881
mRs, > 3	1.147	0.863 – 1.525	0.346
Prior Antiplatelet	1.014	0.746 – 1.376	0.927
IVH Presence	0.847	0.637 – 1.127	0.255
Scan Time			
Time-to-scan, (hours)	0.854	0.790 – 0.923	< 0.001
Radiological Variables			
Mass effect	0.997	0.893 – 1.114	0.960
Midline shift ≥ 5 mm	0.959	0.864 – 1.065	0.437
Measured Volume			
Baseline haematoma volume	1.000	0.995 – 1.006	0.946
Baseline PHO volume	0.934	0.915 – 0.953	< 0.001
Haematoma Expansion	4.174	2.688 – 6.480	< 0.001

GCS = Glasgow Coma Scale; IVH = intraventricular haemorrhage; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale; PHO = perihematomal oedema.

Table 6-3 Multivariate logistic regression of predictors for PHO expansion in spontaneous ICH

Variables	PHO Expansion		
	Odd Ratios*	95% Confidence Interval	*P* Value
Periventricular lucencies	0.686	0.517 – 0.910	0.009
NIHSS ≥ 14	1.342	0.966– 1.864	0.080
Baseline haematoma volume, mL	1.023	1.010 – 1.036	< 0.001
Baseline PHO volume, mL	0.937	0.918 – 0.957	< 0.001
Haematoma expansion	4.245	2.891 – 6.234	< 0.001
Time to scan, hours	0.882	0.812 – 0.959	0.003

NIHSS = National Institute of Health Stroke Scale; PHO = perihematomal oedema. *The odds ratio is adjusted for baseline haematoma volume, baseline PHO volume, periventricular lucencies, haematoma expansion, time-to-scan, NIHSS ≥ 14, mass effect and midline shift.

6.5.3 Probability of PHO Volume as Independent Predictor for Poor Clinical Outcomes in Spontaneous ICH

Table 6-4 illustrates the demographic and baseline clinical variables between favourable (mRs < 3) and poor clinical outcome (mRs ≥ 3) in participants with spontaneous ICH. Notably, of all the demographic characteristics and major clinical variables, only time from ICH symptom onset to baseline CT scan (p = 0.903) and the presence of PHO expansion (p = 0.346) did not show a significant difference between the 2 groups of clinical outcomes. The baseline haematoma (median 17.32, IQR 7 – 37.88) and PHO volume (median 8.91, IQR 4.4 – 18.6) were significantly higher in the group with poor clinical outcome with mRs ≥ 3 (p < 0.001) compared to the group with favourable outcome with mRs < 3 at day 90. Systolic and diastolic blood pressure seem to have a significant difference between those with favourable and poor clinical outcome. The median systolic (180, IQR 162 – 199.75) and diastolic blood pressure (100, IQR (89 – 111) were significantly higher in favourable

outcome group. The participants with haematoma expansion ($p < 0.001$), midline shift ($p < 0.001$) and mass effect ($p < 0.001$) tend to have a poor clinical outcome compared to those without.

In univariate analyses, there were 14 factors showed a significant association to poor clinical outcomes (Table 6-5); age (OR, 1.051; $p < 0.001$), sex (OR, 0.653; $p = 0.003$), brain atrophy (OR, 1.881; $p = 0.005$), periventricular lucencies (OR, 2.200; $p < 0.001$), old vascular lesion (OR, 1.442; $p = 0.009$) NIHSS ≥ 14 (OR, 9.21; $p < 0.001$), prior antiplatelet (OR, 1.860; $p < 0.001$), presentation of IVH (OR, 3.195; $p < 0.001$), midline shift (OR, 4.939; $p < 0.001$), mass effect (OR, 2.003; $p < 0.001$), baseline haematoma volume (OR, 1.059; $p < 0.001$), baseline PHO volume (OR, 1.086; $p < 0.001$), the presence of haematoma expansion (OR, 2.370; $p < 0.001$) and PHO expansion rates (OR, 1.087; $p < 0.001$).

Analyzing all predictors together, the multivariate logistic regression revealed 8 factors that found to affect the clinical outcomes significantly (Table 6-6). The increase in 1 year of age will increase the odd ratio of poor clinical outcomes by 1.057 ($p < 0.001$). Participants with baseline NIHSS ≥ 14 will increase the odd ratio of poor clinical outcomes by 6.759 ($p < 0.001$). The baseline haematoma volume was also having a significant association with poor clinical outcomes in which, the odd ratio of poor clinical outcomes increased by 1.034 ($p < 0.001$) in each increase of 1mL haematoma volume. Participants with periventricular lucencies, IVH and haematoma expansion will increase the odd ratio of poor clinical outcomes by 1.633 ($p = 0.009$), 1.808 ($p = 0.009$) and 1.753 ($p = 0.008$) respectively. The presence of mass effect will increase the odd ratio of poor clinical outcome by 1.344, while participants with PHO expansion rate more than 1mL/hour will increase the odd ratio of poor clinical outcome by 1.053.

Table 6-4 Comparison of demographic and baseline clinical variables between favourable and poor clinical outcome

Variables	Whole Population (n = 1012)	mRs <3 (n = 296, 29.2%)	mRs ≥3 (n = 716, 70.8%)	*P* value
Median age [IQR]	70 [58 – 79]	62 [53 – 71]	73 [62 – 81]	< 0.001
Sex				
Males, n (%)	569 (56.2)	188 (63.5)	381 (53.2)	0.003
Females, n (%)	443 (43.8)	108 (36.5)	335 (46.8)	
Pre-existing Pathology				
Brain atrophy, n (%)	922 (91.1)	258 (87.2)	664 (92.7)	0.005
Periventricular lucencies, n (%)	460 (45.5)	95 (32.1)	365 (51.0)	< 0.001
Old vascular lesion, n (%)	617 (61)	162 (54.7)	455 (63.5)	0.009
Clinical Variables				
NIHSS (/42), Median [IQR]	11.5 [6 – 18]	6 [3 – 10]	14.5 [10 – 20]	< 0.001
NIHSS ≥14, n (%)	424 (41.9)			
GCS (/15), Median [IQR]	15 [13 – 15]	15 [15 – 15]	14 [12 – 15]	< 0.001
GCS < 9, n (%)	22 (2.2)	0 (0)	22 (3.1)	
Antiplatelet use, n (%)	242 (23.9)	49 (16.6)	193 (27)	< 0.001
IVH, n (%)	295 (29.2)	43 (14.5)	252 (35.2)	< 0.001
Systolic BP, Mean (SD)	176.13 (29.13)	181.77 (28.52)	173.8 (29.08)	
Range (min – max)	96 – 280	120 – 180	96 – 267	< 0.001
Median [IQR]	175 [155 – 194]	180 [162 – 199.75]	173 [154 – 191.75]	
Diastolic BP, mean (SD)	95.27 (19.97)	101.42 (20.39)	92.73 (92.00)	
Range (min – max)	34 -196	20 – 190	34 – 196	< 0.001

Variables	Whole Population (n = 1012)	mRs <3 (n = 296, 29.2%)	mRs ≥3 (n = 716, 70.8%)	*P* value
Median [IQR]	94 [81 – 107]	100 [89 – 111]	92 [92 – 105]	
Time-to-Scan (hours), median [IQR]	3.66 [2.55 – 4.99]	3.66 [2.58 – 5.18]	3.66 [2.55 – 4.95]	0.903
Measured Volume				
Haematoma volumes				
Baseline, Mean (SD)	21.44 (23.88)	9.91 (11.87)	26.21 (25.89)	
Range (min – max)	0.248 – 154	0.248 – 86.75	0.37 – 154	< 0.001
Median [IQR]	12.12 [5.15 – 28.72]	6.29 [2.79 – 12.09]	17.32 [7.00 – 37.88]	
PHO volumes				
Baseline, Mean (SD)	12.04(14.34)	6.53 (6.65)	14.31 (15.97)	
Range (min – max)	0 – 152	0 – 37.65	0.1 – 152.1	< 0.001
Median [IQR]	7.15 [3.5 – 15.40]	4.86 [2.39 – 8.24]	8.91 [4.4 – 18.60]	
Haematoma Expansion, n (%)	297 (29.3)	53 (17.9)	244 (34.1)	< 0.001
PHO Expansion	675 (66.7)	191 (64.5)	484 (67.6)	0.346
PHO Expansion Rate, mL/hour	0.848 [0.074 – 2.672]	0.496 [0.032 – 1.371]	1.127 [0.110 – 3.6141]	< 0.001
Midline shift ≥ 5 mm, n (%)	279 (27.6)	29 (9.8)	250 (34.9)	< 0.001
Midline shift ≥ 5 mm, median (IQR)	48.5 (36.3 – 69.0)	41 (33.7 – 62.3)	48.9 (37.3 – 70.8)	
Mass effect, n (%)				
Score 0	186 (18.4)	93 (31.4)	93 (13.0)	
Score 1	179 (17.7)	79 (26.7)	100 (14.0)	
Score 2	540 (53.4)	116 (39.2)	424 (59.2)	< 0.001
Score 3	43 (4.2)	6 (2.0)	37 (5.2)	
Score 4	18 (1.8)	1 (0.3)	17 (2.4)	

Variables	Whole Population (n = 1012)	mRs <3 (n = 296, 29.2%)	mRs ≥3 (n = 716, 70.8%)	*P* value
Score 5	36 (3.6)	1 (0.3)	35 (4.9)	
Score 6	10 (1.0)	-	10 (1.4)	
Median [IQR]	2 [1 – 2]	1 [0 – 2]	2 [1 – 2]	

Data are mean (standard deviation), median [interquartile range], or number (%). BP = blood pressure; GCS = Glasgow Coma Scale; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale; PHO = perihematomal oedema. Statistics are Chi-square and Mann Whitney U tes

Table 6-5 Univariate logistic regression of predictors for poor clinical outcomes in spontaneous ICH

Variables	Poor Clinical Outcome (mRs ≥ 3)		
	Odd Ratios	95% Confidence Interval	*P* Value
Demographic			
Age	1.051	1.040 – 1.062	< 0.001
Sex	0.653	0.495 – 0.863	0.003
Pre-existing pathology			
Brain atrophy	1.881	1.208 – 2.927	0.005
Periventricular lucencies	2.200	1.655 – 2.925	< 0.001
Old vascular lesion	1.442	1.095 – 1.898	0.009
Clinical Variables			
NIHSS ≥ 14	9.219	6.264 – 13.566	< 0.001
GCS < 9	0.855	0.725 – 1.007	0.998
Prior Antiplatelet	1.860	1.313 – 2.635	< 0.001
IVH Presence	3.195	2.234 – 4.570	< 0.001
Radiological Variables			
Midline shift ≥ 5 mm	4.939	3.269 – 7.464	< 0.001
Mass effect	2.003	1.724 – 2.328	< 0.001
Scan Time			
Time-to-scan, (hours)	0.992	0.915 – 1.076	0.845
Measured Volume			
Baseline haematoma volume	1.059	1.046 – 1.072	< 0.001
Baseline PHO volume	1.086	1.063 – 1.109	< 0.001
Haematoma Expansion	2.370	1.606 – 83.313	< 0.001
PHO expansion	1.147	0.863 – 1.525	0.346
PHO expansion rates, mL/hour	1.087	1.044 – 1.131	< 0.001

GCS = Glasgow Coma Scale; IVH = intraventricular haemorrhage; mRs = modified Rankin scale; NIHSS = National Institute of Health Stroke Scale; PHO = perihematomal oedema.

Table 6-6 Multivariate logistic regression of predictor for poor clinical outcome

Variables	Poor Clinical Outcome (mRs ≥3)		
	Odd Ratios*	95% Confidence Interval	*P* Value
Age	1.057	1.042 – 1.072	< 0.001
Periventricular lucencies	1.633	1.128 – 2.363	0.009
NIHSS ≥ 14	6.759	4.303 – 10.618	< 0.001
IVH Presence	1.808	1.161 – 2.815	0.009
Mass effect	1.344	1.114 – 1.622	0.002
Baseline haematoma volume	1.034	1.018 – 1.050	< 0.001
Haematoma expansion	1.753	1.160 – 2.648	0.008
PHO expansion rates, mL/hour	1.053	1.041 – 1.081	< 0.001

NIHSS = National Institute of Health Stroke Scale; IVH = intraventricular haemorrhage; mRs = modified Rankin scale; PHO = perihaematomal oedema. *The odds ratio is adjusted for all variables.

6.6 Discussion

Little is known about the relationship between PHO in spontaneous ICH and clinical outcomes [116]. This chapter reported the association between baseline clinical variables and PHO expansion and the probability of PHO volume and PHO expansion rates in prediction of the poor clinical outcome in patient presence with spontaneous ICH. These analyses included a large number of participants (n= 1012) from the placebo-treated TICH-2 clinical trial with CT-confirmed ICH who were assessed within 8 hours after the symptom onset and prospectively followed up. A standardized measure of PHO volume segmentation (as being described in

Chapter 4) with good intra- and inter-observer reliability (above 0.8 of ICC) was used to measure baseline and follow-up PHO volumes.

There were confirmed findings from previous observational and clinical trial studies [187][192][259] which indicate that initial PHO develops within a few hours after the onset of ICH. In the analyses of factors contributing to PHO expansion, the role of age, gender, brain atrophy, periventricular lucencies, old vascular lesion, NIHSS score ≥ 14, GCS < 9, mRs > 3, prior antiplatelet use, presentation of IVH, midline shift more than 5 mm, mass effect, baseline haematoma and PHO volume, haematoma expansion, and the time between acquisition of scan and the symptom onset were examined. Multivariable analyses in this study confirmed that periventricular lucencies, baseline haematoma volume, baseline PHO volume, haematoma expansion and time-to-scan were significantly associated with the PHO expansion in patients with spontaneous ICH after adjustment of some variables. The significant association of haematoma expansion and PHO expansion was confirmed by several studies from ICH models that used histopathology, CT analysis, single-photon emission computed tomography (SPECT) and both conventional CT and CTA techniques [260], in which they have suggested that secondary multifocal bleeding into perihematomal region is more likely to occur in individuals who experience early haematoma expansion.

It is surprising that this study found inverse association between periventricular lucencies (OR, 0.686; $p = 0.009$) and baseline PHO volume (OR, 0.937; $p < 0.001$) and PHO expansion in multivariate analyses. The periventricular hypodense nonenhancing lesion demonstrated on CT scans have been attributed to chronic small vessel disease [261] and predating intracerebral haematoma. Clinical studies have indicated a connection between this radiological finding of periventricular lucencies and neurological changes [262]. It is well established that PHO is the radiological manifestation of secondary injury of brain parenchyma after spontaneous ICH [263]. As periventricular white matter broadly represents

chronic damage to brain tissue, it was expected an increase in oedema on the basis that tissue integrity would be reduced and so the microscopic barriers to growth of oedema would be reduced in those with more severe white matter hypodensities. However, the inverse relationship of aforementioned variables to PHO expansion in this study can be described as related to the origin of PHO and the phase of PHO growth. PHO presumably originated from leakage from capillaries in the brain tissue around the haematoma. But if the patient has compromised microcirculation, it may be that the formation of PHO is impeded. Classically, studies of PHO using CT scan describe 2 major phases of growth [259]; the first phase begins 24hours and peaks within 2 to 5 days of the spontaneous ICH [121][192][264]. PHO during the second phase has been associated with significant neurologic deterioration [265] compared to the first phase of PHO growth. Since this study only measured the PHO expansion at the first 24 hours, a significant association of neurologic deterioration and baseline PHO volume to PHO expansion cannot be fully drawn. Furthermore, there are various factors contributing to PHO formation and growth. The dynamics of PHO evolution, PHO extent, PHO duration and PHO pattern as well as the factors predictive of this have been less well studied. In addition, complications such as fever and systemic infections may also dictate how PHO evolves [265]. Thus, further studies are needed regarding markers of PHO expansion.

Mechanistically, haematoma with relatively greater amounts of PHO volume would be expected to contribute additional mass effect and may lead to further neurological deterioration by exerting both biological injury and brain-tissue shifts that compress vital structures [160], thereby worsening clinical outcome. Although PHO expansion has been consistently associated with poorer clinical outcomes [10][116][117][206], there are conflicting results showing no effect [266][267], positive effect [268] and negative effect [116] on the relationship between PHO volume at baseline and clinical outcomes. My analysis suggests that some studies may not have found an association between PHO and clinical

outcome because the parameters of PHO expansion, mass effects and midline shift were not thoroughly explored. In study done by H. Arima et al [152] on 270 patients showed that absolute PHO expansion at 72 hours post-ICH did not independently predict poor outcome (defined as death or dependency at 90 days) which was indicated by mRs scores ≥ 3. However, the investigators subsequently showed that PHO expansion does independently predict poor outcome in larger sample of 1138 patients [117]. In my analysis on 1012 participants, significantly larger ($p < 0.001$) baseline PHO volume was found in those with poor clinical outcome, but the multivariate logistic regression failed to confirm that baseline PHO volume was a significant predictor of poor outcome. PHO expansion was not showing significant association in both univariate ($p = 0.346$) and multivariate analysis ($p = 0.729$), thus did not significantly predict poor clinical outcome in participants with spontaneous ICH. My study had verified the findings of the previous studies [260][269] regarding the role of haematoma expansion in predicting poor clinical outcome in both univariate and multivariate analyses. Early haematoma expansion is consistently associated with poor clinical outcomes and higher mortality rates versus no expansion. My study also revealed that the mass effect (OR, 1.344; $p = 0.002$) and faster PHO rate at 24 hours post spontaneous ICH (OR, 1.053; $p < 0.001$) are strongly associated with worse clinical outcome. The association of both variables to poor clinical outcome persisted even after adjustment for all clinical and radiological variables. This study investigated the rate of PHO expansion because there are other examples in clinical neurology in which the rate at which a mass expands influences patient's clinical outcome [28][108]. The contribution of PHO to participant's outcome may depend on the rate of expansion, with PHO that expands more rapidly producing more stress on the brain system than PHO that accumulates gradually. However, there was a limitation in defining PHO expansion rate since it was calculated as having expansion rate at 24 hours, whereas the actual follow up scans were slightly varied.

This study has discovered in univariate analyses that the age, gender, pre-existing pathology of brain atrophy, periventricular lucencies and old vascular lesion, NIHSS score ≥ 14, prior antiplatelet use, presentation of IVH, midline shift, mass effect, baseline haematoma volume, baseline PHO volume, haematoma expansion and PHO expansion rates were significantly correlated with poor clinical outcome ($p < 0.05$). These findings had support M. Castellanos et al [270] in their study evaluating the predictors of outcome in spontaneous ICH. They found that male gender, pre-existing arterial hypertension, intraventricular contamination, mass effect and greater haematoma volume predicted a poor prognosis that might lead to a poor clinical outcome. The GCS score and time to scan in my univariate analysis however showed no significant association to poor clinical outcome. Determination of potential predictors of good clinical outcomes in spontaneous ICH could be useful for selecting patients who might benefit from surgical procedures.

However, there are some limitations in this study. The first one includes the standard definition of PHO expansion. This study defines PHO expansion as an increase in PHO volume of more than 20% from baseline to 24hours. This definition of PHO expansion was firstly introduced by S. H. Lee et. al[105]. In their study, decreases of more than 20% from initial PHO volumes were coded as 'decreased' PHO volume; increases of more than 20% were coded as 'increased' PHO volume, and changes between -20% and 20% were coded as 'unchanged'. However, considering some possible errors in the measurement of PHO volume, they did not clarify the justification of using the cut-off value of 20% for PHO expansion in their study. Recent study by X.-N. Lv et. al [271] defined PHO expansion as an absolute increase in PHO volume of > 6 mL from baseline to 24hours. A receiver-operating characteristics (ROC) curve was generated to determine the cutoff value of PHO expansion. There are no consistent or uniform parameters of PHO expansion in use. Various parameters and definitions for PHO have been used in various studies. These include absolute PHO, relative PHO, rate of PHO growth (volume/time or % change/ time), oedema extension distance

(ODD), rate of change in ODD (volume/time or % change/ time). Each of these parameters has its advantages and limitations. In the absence of standardized definition of PHO expansion, the exact correlation between potential predictors and PHO expansion cannot be drawn and the probability of PHO expansion to predict poor clinical outcomes was underestimated. Additionally, I did not test any other percentage of PHO expansion. The choice of 20% is arbitrary but was chosen for this analysis based on the prior study using this threshold. Further work could more rigorously assess the choice of threshold, which ideally needs to be above the measurement error.

The second limitation was a definition of PHO on CT brain imaging. This study has defined the PHO on CT images as a rim of hypodensity area surrounding the haematoma. The definition was based on several previous studies on PHO segmentation [10][105][106][115][120][194][195]. Nevertheless, PHO manifest as hypodensity can be challenging to distinguish from normal brain parenchyma and other entities that are also hypodense such as infarction [196], small vessel ischemic disease, cerebrospinal fluid spaces and hydrocephalus [265]. Other processes may also coexist to produce hypodensity on CT images, such as extruded serum from haematoma coagulation and contraction [272]. Additionally, manual delineation of the PHO region on CT is also imprecise when microangiopathy is present [115] and may also lead to some potential errors in the exact delineation of PHO boundary. PHO is much easier to delineate on MRI compared to CT scan. However, MRI is not routinely performed during the hyperacute phase of ICH and is more expensive and time consuming.

The third limitation was an evaluation of PHO expansion. PHO expansion was measured only in the first 24hours after the ICH onset. PHO is recognised to increase in volume beyond this time point, reaching a peak in growth after at least several days, and sometimes a few weeks, in some patients [192]. Variability in timing of PHO expansion makes it difficult to fully ascertain the relationship

between PHO and long-term functional outcomes after spontaneous ICH. Thus, the findings of this study may have underestimated the association of baseline PHO volume and PHO expansion, and the effect of late PHO expansion on clinical outcomes. To accurately determine the impact of PHO on outcomes, future studies should be prospective, have pre-specified methods, parameters and endpoints, as well as have adequate sample size calculations and statistical power.

Chapter 7 DISCUSSION AND CONCLUSIONS

7.1 Summary of Key Findings

Spontaneous ICH is the second most common subtype of stroke and a critical disease that usually leads to severe disability [3] and is more fatal and disabling than other stroke subtypes [273]. Neurological deterioration is a devastating complication after spontaneous ICH, but little is known about its time course and predictors. Haematoma expansion is a principal cause of early neurological deterioration [274], while PHO is considered to be a radiological marker of secondary injury to brain parenchyma [275]. There is also evidence that PHO might contribute to poor clinical outcome in patients with spontaneous ICH. Because of prognostic significance, haematoma volume is frequently used as one of the criteria for enrolment or stratification in clinical trials involving spontaneous ICH [182] and PHO is used as a translational target or radiological marker to examine the efficacy of interventions aiming to mitigate secondary injury in spontaneous ICH [275]. Thus, accurate predictions of those at risk of haematoma expansion and PHO expansion is extremely important.

The main purpose of this thesis was to measure the haematoma and PHO volume, and to develop a predictor model for haematoma expansion, PHO expansion and clinical outcome of patients with spontaneous ICH. This thesis started with introduction to spontaneous ICH, its diagnostic imaging, clinical trials involved, segmentation of CT brain images, clinical features, and imaging features of spontaneous ICH (Chapter 1). The next two chapters (Chapter 2 and Chapter 3) reported a systematic review regarding the method of haematoma and PHO volume segmentation available in clinical and research settings. Chapter 4 described in detailed the volumetric method and image segmentation of haematoma and PHO on CT brain images. Chapter 5 described the predictors of haematoma expansion and Chapter 6 reported the predictors of PHO expansion

and poor clinical outcome in patients with spontaneous ICH. This study analysed data from placebo-treated TICH-2 population. The findings from these analyses have been discussed in detail in the individual chapters. The following paragraph summarises the key findings in each chapter.

7.1.1 Chapter 1 : Introduction

The first chapter described the overview of spontaneous ICH and its related issues. At present, there is no gold standard and effective therapy for spontaneous ICH. Previous and current management strategy involved blood pressure reduction [35][36][38][39][40][41] and the used of haemostatic agents [45][46][47][49][51][54]. There was also a description of the method of the TICH-2 and its findings in Chapter 1 in which, the data was used in my analysis for haematoma and PHO segmentation and also to develop predictors in a model for haematoma expansion, PHO expansion and clinical outcome in patients with spontaneous ICH. TICH-2 clinical trial studied the role of tranexamic acid to reduce haematoma expansion and to improve outcome in adults with stroke due to spontaneous ICH. However, the main trial findings showed no significant difference between the patients who received tranexamic acid and those who received placebo in the primary outcome of functional status at 90 days [59]. There is vital need in future research to publish prognostic models for mortality and functional outcomes, and this needs a good understanding of the relationship between common clinical assessment scores and radiological features in patients with spontaneous ICH. Haematoma expansion and PHO formation are the most common complications after ICH. The available methods of haematoma expansion and PHO volume segmentations were described thoroughly in Chapter 1. The ABC/2 formula is the most widely used method to measure haematoma in clinical settings, derived from the mathematical formula for volume of an ellipsoid by J. P. Broderick et al [75] but this method generally overestimates

haematoma volumes especially in large and irregular shape [79]. Computer-aided SAS is known as the gold standard for haematoma volume segmentation with high reliability and accuracy, making them more precise in estimating haematoma volume compared to ABC/2 formula [63][76][94]. Currently, there is no gold standard for PHO quantification, but the most widely used method is manual tracing [111]. With this background knowledge in mind, the next 2 chapters (Chapter 2 and Chapter 3) systematically explored the available segmentation methods for both haematoma and PHO volumes.

7.1.2 Chapter 2 : Systematic Review : Comparison between SAS Haematoma Volume Analysis and ABC/2 Formula in Patients with Spontaneous ICH from CT Brain Images

Chapter 2 dealt with the systematic review of the methods of haematoma volume segmentation to address the research question: In patients with spontaneous ICH, does a widely used ABC/2 formula provides a close approximation and reliability of haematoma volume measurement to SAS? This was necessary because previous studies have reported overestimation of haematoma volume measured by ABC/2 especially in large and irregular shape haematomas. Hence, a systematic review was performed for all published studies comparing 2 widely used methods of haematoma volume segmentation in clinical and research settings (SAS versus ABC/2) in term of their volume estimation and their observer reliability. There were 14 studies included 2128 patients were identified. The reliability of the SAS technique and ABC/2 formula for haematoma volume measurements were comparable, and both techniques were reported as having an excellent intra- and inter-observer reliability. Haematoma volume measured by ABC/2 formula tended to increase as the haematoma size increases and haematoma shape becomes irregular and spiculated, thus favour the use of SAS in haematoma

segmentation in research setting. However, there were not enough statistical data available in systematic review, make it not possible to run meta-analysis.

7.1.3 Chapter 3 : Systematic Review : Perihaemetomal Oedema Volume Segmentation in Patients with Spontaneous ICH

Chapter 3 described the systematic review of PHO volume segmentation. Previous studies had reported the challenges of manual PHO segmentation due to slight differences of tissue density between oedematous and normal parenchyma. A systematic review was performed for all published articles reporting the radiological definition of PHO, the optimal threshold and reliability assessment. The main objectives of this chapter were to identify the different methods used for PHO segmentation on CT brain images and to summarise the observer reliability of these available methods. There were 25 studies that included 3815 patients using various PHO segmentation methods (SAS, ABC/2, modified ABC/2 and fully automated segmentation). Most studies defined PHO as a rim of hypodensity surrounding haematoma with optimal threshold of 5 – 33 HU. In general, SAS and manual delineation of PHO segmentation gave a high intra- and inter-observer reliability and both methods can be considered reliable techniques for PHO volume quantification. However, there were only a few studies reporting reliability assessment and the type of reliability test was not clearly described in majority of the studies making it not possible for meta-analysis. As far as I know, this is the first systematic review reporting reliability of PHO segmentation methods, therefore, a novel contribution in future research of image segmentation. The performance and reliability of each segmentation method is very crucial in identification of patients at risk of developing PHO expansion or who may benefit from treatments and interventions.

7.1.4 Chapter 4 : Volumetric Method and Image Segmentation: Description and Reliability Analysis

Chapter 4 presents haematoma and PHO volume segmentation in CT brain images using a combination of thresholding and region growing technique with manual editing for haematoma volume measurement while manual delineation was used for PHO volume quantification. It was hypothesized that SAS technique with manual editing and manual delineation approach using ITK SNAP software would be reliable methods for measuring haematoma and PHO volumes. This hypothesis was tested using an ENOS trial sample. This hypothesis was supported by the findings of this study that confirmed the reliability of both methods in measuring haematoma and PHO volumes. There was a significant difference in median PHO volume between Observer 1 and Observer 2, but the interobserver reliability of PHO volume quantification showed an excellent agreement (ICC = 0.987).

The SAS technique was comparable to widely used ABC/2 formula in measuring haematoma volume. Both techniques of haematoma volume quantifications showed excellent intra- and inter-observer reliability (ICC above 0.900). Thus, the hypothesis that haematoma volume measured by ABC/2 formula provides a close approximation to haematoma volume derived by SAS technique has been supported. This result of excellent reliability enables the application of these segmentation approaches in a larger sample (TICH-2 population).

There was a strong linear correlation of haematoma volume segmentation between SAS method and ABC/2 formula especially in smaller volume haematoma, but the shape of correlation became slightly deviated when haematoma volume increased. The percentage deviation of haematoma volume segmentation between SAS and ABC/2 formula was regularly increased when the size of haematoma increased. The same increment of

deviation was also shown when the haematoma shape became more irregular. These findings support the hypothesis of overestimation of haematoma volume measurement using ABC/2 formula in large and irregular shape haematomas.

The effect of different slice thicknesses between 1mm and 5mm used in CT protocol was evaluated in both segmentations of haematoma and PHO volumes. It was assumed that a thicker slice thickness of 5mm overestimates the haematoma and PHO volumes in the TICH-2 trial predominantly in small size of haematoma and PHO compared to thinner slice thickness of 1mm. Nevertheless, there was no significant difference of haematoma volume measured by ABC/2 formula and PHO volume measured by manual delineation between 5mm and 1mm slice thicknesses. In haematoma volume measured by SAS method however, there was a small significant difference between the volume measured in 5mm slice thickness and 1mm slice thickness, in which, haematoma volume measured in 5mm slice thickness was significantly higher (0.44 mL) compared to 1mm slice thickness. This finding however, still not strong enough to support the hypothesis, since it cannot be proved that a significant difference occurred in small size haematoma because of the extremely small number of samples available for analysis. In addition, there was no restriction of CT slice thickness and protocol used in TICH-2 study, and these variations need to be explored further to draw conclusions of the relationship between CT slice thickness and various CT scan settings to measure volume of haematoma and PHO.

This chapter reports the main findings of the relationship between the SAS and ABC/2 methods in haematoma volume measurement in a very large dataset compared to the previous similar studies. These novel findings provide powerful statistical data for future contribution as a training set in an artificial intelligence study.

7.1.5 Chapter 5 : Haematoma Volume Expansion in the TICH-2 Population

The association of baseline characteristics and clinical variables to haematoma expansion has been discussed in Chapter 5. Haematoma expansion defined as an absolute increased in haematoma volume of more than 6 mL or relative increase of more than 33% on the 24 hours follow-up scan compared to the initial baseline haematoma volume. The assumption of a large haematoma volume and size, shorter time-to-scan, deep haematoma, irregular shape, and heterogeneous density of haematoma on baseline CT brain images are associated with a high risk of haematoma expansion in the placebo-treated TICH-2 population was not fully supported. Compared to patients without haematoma expansion, patients with haematoma expansion significantly had pre-existing pathology of periventricular lucencies, greater baseline NIHSS score, had a previous antiplatelet therapy, large baseline haematoma volume, large haematoma size, irregular shape of haematoma, deep haematoma, shorter time-to-scan and presentation of IVH. However, the heterogeneity of density of haematoma between participants with haematoma expansion and those without haematoma expansion was not significantly different. In term of CT baseline signs (blend sign, black hole sign and island sign), there were significant difference of the presentation of all these signs between participants with haematoma expansion and no haematoma expansion. Participants presenting with baseline CT signs tend to experience haematoma expansion with significantly larger baseline haematoma volume compared to those without the signs. Baseline CT signs had low sensitivity and high specificity for detection of haematoma expansion with island sign having the highest specificity but lowest sensitivity.

There were 7 factors predicting haematoma expansion in univariate analyses. Patients with haematoma expansion were significantly had pre-existing

pathology of brain atrophy, baseline NIHSS score ≥ 14, shorter time-to-scan, greater baseline haematoma volume, baseline haematoma size greater than 5cm, and the presentation of CT black hole and island signs on baseline scans. However, the multivariate imaging model of haematoma expansion predictors revealed that the baseline NIHSS score ≥ 14, baseline haematoma volume, time-to-scan and brain atrophy were independent predictors of haematoma expansion in participants presenting with spontaneous ICH. These variables retained a significant association to haematoma expansion after adjustment of some relevant variables. Time-to-scan showed an inverse relationship to haematoma expansion, which means that shorter time interval between baseline CT scan and stroke onset will increase the odd ratio of haematoma expansion. The hypothesis that the presentation of blend sign, black hole sign and island sign on baseline CT brain images predict haematoma expansion in spontaneous ICH was not fully supported since black hole sign and island sign only showed a significant association in univariate analysis while CT blend sign showed no significant association in both univariate and multivariate analysis. It can be concluded that a multivariate prediction model for haematoma expansion can be created based on baseline CT imaging characteristics, but the hypothesis was not fully supported since only 4 variables predict haematoma expansion on multivariate analysis after adjustment of some variables.

7.1.6 Chapter 6 : PHO Volumes and Expansion in the TICH-2 Population

Chapter 6 discussed the characteristics of participants with and without PHO expansion. This study defined PHO expansion as relative increase of more than 20% in PHO volume at 24 hours follow-up scan compared to baseline CT scan. This definition was based on previous PHO analysis by S. H. Lee et al [105]. The findings revealed that there were significant differences of

periventricular lucencies, baseline NIHSS score, time to scan, baseline PHO volumes and the presentation of haematoma expansion between participants with PHO expansion and without PHO expansion. Smaller baseline PHO volume and the presentation of haematoma expansion were significantly associated to PHO expansion in patients with spontaneous ICH. There was no significant difference in baseline haematoma volume between participants with and without PHO expansion.

A multivariate prediction model for PHO expansion could be created based on the information of clinical variables, baseline haematoma and PHO volume. The presence of periventricular lucencies, baseline haematoma and PHO volume, haematoma expansion and time to scan were found to be predictors of PHO expansion in spontaneous ICH. Thus, the hypothesis that addresses this assumption had been supported. Periventricular lucencies, baseline PHO volume and time to scan however, showed indirect relationships to PHO expansion. Meanwhile, independent predictors for poor clinical outcomes were revealed by multivariate analysis in which, increase in age, presentation of periventricular lucencies, baseline NIHSS score $\geq$ 14, larger baseline haematoma volume, presentation of haematoma expansion, presentation of IVH, and PHO expansion rates at 24 hours were found to be predictors for poor clinical outcomes in spontaneous ICH.

7.2 Discussion of Relevance / Implications

This thesis confirms that the SAS technique and ABC/2 formula are reliable for calculation of haematoma volume. ABC/2 is rapid to perform and is readily suited to use in clinical practice as it requires relatively little training and the linear measurement tools are widely available on hospital's Picture Archiving and Communication Systems (PACS). Hence ABC/2 can be performed in the emergency department or on the hospital ward without specialist training and software. Conceptually, the ABC/2 formula approximates all haematoma volumes

as ellipsoid with axes defined as the maximal extent in 3 perpendicular dimensions, which can lead to an overestimation of volume and increased variability for large and irregular haematoma [94]. However, in clinical setting, the haematomas tend to be in various shapes and sizes. Though yet to be quantified, the error of the ABC/2 formula measurement is likely to increase as the shape from which it is derived becomes more irregular and increased in size. Haematoma volume derived by SAS method in this study make it possible to obtain more reliable volume measurements in both research and clinical settings without the need for such approximations. However, SAS is more time consuming as segmentation errors require manual correction. In addition, the software is generally not integrated into clinical PACS systems and use of the software requires a longer period of training than for ABC/2 measurement.

It is also important to bear in mind that in the past few years there has been a rapid growth in interest of machine learning and other artificial intelligence approaches for segmentation and measurement of haematoma and PHO volumes. These approaches have the potential to be very fast, however, they require a training dataset based on manual or SAS quantification. Hence, the findings reported in this study that confirm the reliability of SAS method for haematoma volume measurement and manual delineation for PHO quantification is important for providing robust datasets that artificial intelligence and machine learning approaches can be trained on. The advantage of using these approaches include the limitation of subjective biases that occur when operator-dependant segmentation used. However, the algorithm could be biased if there are errors in the datasets. Unusual haematomas that are well represented in the training datasets may not be well segmented by the algorithm. At present, these segmentation tools are a long way from being integrated in clinical PACS systems. Consequently, it may be good for research but not yet useful clinically.

Recent studies suggest that ICH is a dynamic event, and early identification of patients at risk for further haematoma expansion is important in terms of therapeutic intervention [139][276]. To date, the most reliable predictor of haematoma expansion is a visible area of contrast extravasation within a primary ICH on a CTA of the brain. However, early CTA examination is limited to some medical centres and requires iodinated contrast media that may increase allergy reactions as well as contraindications especially for patients presenting with impaired renal function. Therefore, scrutinising non contrast CT for possible imaging markers predicting haematoma expansion might address some of these issues. Non-contrast CT scan is considered as a standard diagnostic technique for patients with ICH, which should be performed as early as possible. Unlike CTA, non-contrast CT is affordable, universally available in all clinical settings and becomes a primary modality for diagnosing patients with ICH. With the non-contrast CT baseline signs as promising radiological predictor of haematoma expansion, it may be possible to select patients for emerging ICH therapies.

Critical care management of the complications of spontaneous ICH is extremely important. Most ICH trials have aimed to restrict haematoma expansion or to reduce haematoma volume because haematoma size has been consistent predictor of poor clinical outcome [75] while PHO is thought to be an epiphenomenon of haematoma size and lead to neurological deterioration, herniation and death [275]. While our understanding of this severe neurological disease has been developed in the previous years, there was no specific treatment that has been shown to improve clinical outcome, although this is currently a major target for research. This study was done to investigate easily identifiable predictors of a poor clinical outcome in spontaneous ICH, thus suitable for selecting patients who might benefit from surgical procedures while avoiding the harmful effects of surgery in those with potential for spontaneous recovery. This is considered a crucial finding in clinical research related to spontaneous ICH since some studies have reported a lack of efficacy of surgical evacuation

[277][278][279][280] when compared with initial conservative treatment. This is mainly due to a large layer of brain tissue that must be crossed during surgical evacuation, which may cause iatrogenic damage of healthy brain parenchyma [281].

7.3 Future Directions

Spontaneous ICH is the most devastating type of stroke for which effective treatment remains elusive. Haematoma expansion and secondary brain injury due to the formation of PHO are the most common complications after ICH and associated to a poor clinical outcome and prognosis. Therefore, patients at high risk of developing haematoma and PHO expansion commonly become an obvious treatment target for clinical trials and interventions. In view of its prognostic value, calculation of haematoma volume and PHO should perhaps be recommended as a routine clinical practice. Accuracy of haematoma and PHO volume segmentation is also crucial for analysis of haematoma and PHO expansion. A combination of techniques when used rather than using a single technique might give better segmentation results. In future works, the use of machine learning, unsupervised clustering techniques and other artificial intelligence approaches could be more widespread for haematoma and PHO volume calculation. As noted above, the development, training and validation of such algorithms will rely on the 'traditional' methods of volumetric measurement, such as SAS, explored in Chapter 4. My analysis consists of a large sample size of 2254 participants for haematoma segmentation and 1012 participants for PHO quantification. A large sample size which comes from more than 100 centres with a various shape, sizes, and locations of haematomas, accurately represent the population, and contributes a strong statistical dataset. It is hoped that a training and validation of proposed artificial intelligence works on a large dataset might improve the accuracy, reliability and efficiency of haematoma and PHO volume quantification.

Advancement in brain image segmentation technology could enhance the assessment of potential therapeutic targets. Many research groups are now testing artificial intelligence approaches to perform haematoma segmentation. As an example, deep learning-based algorithm capable of accurately measuring haematoma and PHO volumes was developed by R. Dhar et al [197]. This algorithm exhibited consistently high accuracy when applied to scans from several external sites, a critical but often under-appreciated validation step for machine learning algorithms. T. Wang et al [282] in their study had evaluated the performance and accuracy of a deep-learning automated-based segmentation algorithm in segmenting spontaneous ICH, and this proposed method accurately quantified volumes of spontaneous ICH with high fidelity and greater efficiency compared to manual segmentation. A review conducted by Y. Y. M. Aung et al [283] revealed that artificial intelligence can ultimately prove beneficial in healthcare, but requires meticulous governance similar to the governance of physician conduct. If these approaches prove to be successful, then the need for manual or SAS approaches may be reduced. However, there may still be a role for ABC/2 as it is such a rapid estimate of ICH volume that can be performed at the bedside.

The identification of baseline CT predictors of haematoma expansion and PHO expansion is important goal with the potential to aid in selection of patients for future haemostatic therapy, particularly when other data may be limited or unavailable. This study developed a predictor model to identify those who are likely to experience haematoma expansion, PHO expansion and poor clinical outcome. Firstly, for better selection of patients at risk, a study of well-established clinical variables and radiological findings are important. By combining different variables, including participants' demographic parameters, clinical variables and radiological features, my study developed a prediction model to predict haematoma expansion, PHO expansion and poor clinical outcome in patients with spontaneous ICH using placebo-treated TICH-2 population. Assessing a simple

marker on non-contrast CT seems to be a straightforward way of stratifying patients at higher risk for haematoma and PHO expansion. Non-contrast CT scan is simple and easy to operate. As a common and necessary examination step for patients with acute ICH, the sign of haematoma expansion has gained a hot spot in recent studies. Research about non-contrast image features in the prediction of haematoma expansion has already achieved positive results. The blend sign, CT hypodensities, black hole sign and island sign in non-contrast CT images have been reported in succession related with haematoma expansion [143][150][230][246]. Findings from Chapter 5 were in keeping with previous studies that showed that baseline CT signs (blend sign, black hole sign and island sign) were highly specific to detect haematoma expansion [143][212][230][241][242][243]. Specificity is the ability of the test to correctly identify people without the disease. There was a significant association of black hole sign and island sign to haematoma expansion in univariate analyses, but blend sign was not. However, there was no significant association of all these signs in multivariate analyses after adjustment of some variables. This findings was contradicted with the study by Z. K. Law et al [246] that used both arms of TICH-2 population. Z. K. Law et al found that blend sign and black hole sign were predictive of haematoma expansion, but island sign was not. This might be due to larger sample size (n = 2077) compared to my study that included only the sample that have been assessed for all CT signs (n = 548) among placebo-treated TICH-2 population. To empower a statistical analysis of a relationship between CT signs and haematoma expansion, it is suggested to use both arms of treatment groups as been taken by Z. K. Law et al. But this approach required statistical controlling to account for effect of treatment on haematoma expansion. However, despite the high specificity of CT signs in detecting haematoma expansion, the disadvantages of these imaging markers are that they are all highly subjective. The results of their interpretation are influenced by the doctors who interpret the image, such that the results in clinical practice show a huge variation. Moreover, there may be

more complex connections between them, which are difficult to identify and summarize with naked eye. Additionally, there is a need to identify the image features before the prediction analysis. This situation leads to the development of an artificial intelligence such as deep-learning model, as one introduced by L. Teng et al [284], in which the processed images can be automatically imported into the model without pre-set variables. The model can automatically learn and extract image features, greatly avoiding the loss of potential image feature information, so as to improve the specificity and sensitivity of prediction. Identifying patients who can benefit from expansion-targeting treatment has important implications for future studies. Several predictive scoring systems for haematoma expansion have been developed in the past taking into account factors such as baseline haematoma volume, onset to CT scan time, history of antiplatelet use, presentation of ICH, GCS, NIHSS, blend sign and hypodensities [233][241][249][285]. Notwithstanding, further prospective studies are still needed to confirm the validity of this model and to establish a more reliable logistic regression model for clinical use and for future research in artificial intelligence.

There is growing interest in developing interventions to target the cascade of events that ensues following spontaneous ICH and secondary brain injury precipitated by blood and its degradation products. PHO is believed to represent an easy radiological marker of secondary brain injury and is being increasingly employed as an endpoint to assess the efficacy of these interventions. PHO has been considered as an important target for treatment of spontaneous ICH. Although many previous studies have suggested PHO may be associated with clinical outcome in spontaneous ICH, the PHO measured are various and the results are conflicting [116][187][206]. The failure of previous interventions and clinical trials aiming to reduce haematoma expansion in order to improve outcomes [59][62] plus the understanding of the underlying mechanism of secondary brain injury in spontaneous ICH, there is ongoing interest in developing and testing new therapies and trials targeting secondary injury.

Hence, further studies are therefore required to elucidate the prognostic significance of PHO in spontaneous ICH. New approaches aimed at PHO expansion rate as a surrogate measure to assess the efficacy of these therapies and trials are hoped can improve prognosis of patients presenting with spontaneous ICH. Findings from Chapter 6 showed the impact of PHO on clinical outcome. My analysis found that acutely (up to 24 hours after ictus), rapid PHO expansion predicts poor clinical outcome. The findings that a faster PHO expansion rate between baseline and 24 hours is detrimental from a translational perspective, because it provides a relatively wide window for therapeutic intervention. Most ICH clinical trials have focused on reducing haematoma expansion (SPOTLIGHT and STOP-IT [51], INCH [55], TICH-2 [60], ATACH [286]), since it is strongly associated with poor clinical outcome [59]. However, most haematoma expansion occurs within 24 hours after the ictus, limiting the therapeutic window [151]. Hence, targeting PHO expansion rate at 24 hours could be valuable adjunct therapeutic approach to improve clinical outcome in patients with spontaneous ICH. My study had confirmed the findings of a previous investigation that showed that PHO expansion rate at 24 hours was independently associated with worse clinical outcome in an ordinal shift analysis of the mRs [108]. The large sample size from placebo-treated TICH-2 population (n = 1012) in my study supports the research findings of the association of PHO expansion rate at 24 hours with poor clinical outcome. This can be said as my novel contribution in the research regarding the impact of PHO on ICH prognosis and might impact a clinical practice. Findings from my study are particularly relevant now that a better understanding of the pathophysiology of PHO and its potential effects has led to the emergence of potential molecular targets and therapies to improve clinical outcome in patients with spontaneous ICH. For example, a recent clinical trial on the effects of different types of oral anticoagulant associated ICH (AOC-ICH) on PHO by J. Nawabi et al [135], showed that an increase of early PHO volume did not increase the likelihood of poor outcome in AOC-ICH, but was independently associated with poor

outcome in non OAC-ICH. In another early-phased study by Y. Fu et al [140], reported that an anti-inflammatory agent (fingolimoid) given at 72 hours after the ICH onset, reduced the progression of PHO and was associated with an increased likelihood of functional independence at 90 days compared to control group.

Careful appraisal of the strengths and limitations of using PHO as a therapeutic target and surrogate measure of efficacy is essential to improve the study design and the interpretation of the results to successfully develop innovative and effective therapies for spontaneous ICH in the future.

7.4 Limitations

This study has some limitations. Since the sample population of this study is derived from the TICH-2 clinical trial, there might be a bias in sample selection to represent all spontaneous ICH populations, based on the specific inclusion and exclusion criteria for that trial. My analysis of haematoma and PHO expansion considers only those participants included in the placebo arm of the trial, to avoid the confounding effect of tranexamic acid treatment on haematoma or PHO expansion. This reduced the sample size to approximately half of the TICH-2 dataset but means that there can be no bias introduced based on treatment allocation. An alternative approach could have been to include all data (increasing the statistical power) and controlling for the effect of treatment allocation in the statistical analysis, and this was the approach taking by Z. K. Law et al [231].

The relationship between the rate of PHO expansion and clinical outcome has been the subject of recent investigations. This study measured the PHO expansion rate at 24 hours. In the TICH-2 study, the follow-up scans performed at 24 ± 12 hours after baseline scans, and the scan closest to 24 hours after randomisation was used if there were multiple scans available. However, due to the time constrains and limited access to the whole data of the TICH-2 population, it was presumed

that they were performed at exactly 24 hours (to my knowledge, most of the follow-up scans in the TICH-2 study were performed closest to 24 hours). This limitation inhibits the accuracy of PHO rate expansion measurement and its potential impact on neurological outcomes. More rapid PHO expansion may produce more damage than gradual progression. To get a more accurate PHO expansion rate and their relationship to clinical outcome, it is important to look at the actual timing of the follow-up CT scans. This can be the most appropriate approach for future research.

Other limitation of this study is time course and natural history of PHO expansion. This study had defined PHO expansion as an increase in PHO volume in 24 hours follow-up scan of more than 20% compared to baseline PHO volume. In my analysis, the 20% criterion was applied as previously mentioned in the PHO analysis by S. H. Lee et al [105]. However, observational and retrospective studies indicate that although PHO progression is fastest during the first few days after ICH onset, PHO continues to grow at a slower rate afterwards reaching its peak between 2 or 3 weeks after ictus. Because of this, the analysis of PHO expansion predictors and the analysis of the relationship between PHO expansion and clinical outcome in this study is considered underpowered and not strong enough to support the specific hypothesis, since limiting the assessment of PHO expansion to 24 hours post-ictus is likely to miss the PHO peak. Thus, a repeat follow-up scan at day 14 onwards and the analysis of various percentage and absolute increase in PHO volume might better assess the relationship of PHO expansion with the clinical outcome. Nevertheless, another limitation is that boundaries of PHO become less clear over time, particularly with subacute to chronic degradation of the haematoma, in which it can therefore be challenging to define PHO on CT images in the later stages of spontaneous ICH. Given the aforementioned limitations of CT imaging modality, it might be helpful for future studies using MRI for the detection of PHO. However, although MRI is more sensitive, the logistics

and cost of performing MRI in acutely ill patients may limit its use in the clinical setting.

Despite of some limitations, this study has a large sample size and good availability of CT scans, which give a remarkable strength and making this study the largest imaging analysis in spontaneous ICH. There is a wide range of haematoma volumes from very small to very large haematoma reflective of real-world patients with spontaneous ICH thus represent the population of patients with spontaneous ICH.

7.5 Conclusions

This study has demonstrated that both SAS technique and ABC/2 formula were reliable methods for haematoma volume segmentation on CT brain images, but ABC/2 formula overestimated large size and irregular shape haematoma. Baseline NIHSS score $\geq$ 14, baseline haematoma volume, time-to-scan and brain atrophy predict haematoma expansion in spontaneous ICH. Time-to-scan was indirectly related to haematoma expansion in the placebo-treated TICH-2 population. Multivariable prediction model of PHO expansion revealed that periventricular lucencies, baseline haematoma volume, presentation of haematoma expansion and time-to-scan predict PHO expansion in spontaneous ICH. However, periventricular lucencies, and time-to-scan were indirectly related to PHE expansion. The predictors for poor clinical outcome in patients presenting spontaneous ICH were increased age, pre-existing pathology of periventricular lucencies, baseline NIHSS score $\geq$ 14, mass effect, baseline haematoma volume, haematoma expansion, IVH and PHO expansion rate. The baseline PHO volume otherwise did not predict a poor clinical outcome.

In conclusion, stratification of spontaneous ICH based on clinical, laboratory and imaging findings could enable appropriate treatment and assessment of patients at risk of haematoma expansion in order to prevent clinical deterioration and adverse sequelae.

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Appendix 1: Summary of Included Studies in Systematic Review of Haematoma Volume Segmentation

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
J.M. Gebel et al [112]	1998	244	Not given	Retrospective study	To compare the estimation method of haematoma volume to a computer-assisted volumetric analysis in a large series of intracranial haemorrhage.	Correlation between ABC/2 technique and the computer-assisted volumetric technique.	- ABC/2 SAS (propriety software, Centre for Computer-Assisted Neurosurgery, Cleveland Clinical Foundation, run on Sun Microsystems Spark station)
C. W. Wang et al [172]	2014	106	62.8	Retrospective Study	- To investigate the performance of haematoma shape, haematoma size, GCS score and ICH score in predicting the 30-day mortality for ICH patients. - To examine the influence of the estimation error of haematoma size on	- Haematoma shape - Haematoma size - ICH score - GCS score	- ABC/2 - SAS (MATLAB)

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
					the prediction of 30-day mortality.		
H. Hussein et al [71]	2013	56	62	Retrospective Study (analysed data from ATACH trial)	- To examine the accuracy of haematoma volume measurement using ABC/2 method by multiple investigators. - To assess the impact of utilizing the ABC/2 method in eligibility determination.	- On-site haematoma volume. - Haematoma volume measured at Core Imaging Laboratory. - Central haematoma volume.	- ABC/2 SAS (MIPAV)
H. B. Huttner et al [70]	2006	83	Not given	Prospective Study	To validate the ABC/2 technique based on analyses of the haematoma shapes in OAT-related ICH.	- Haematoma location - Haematoma shapes - Haematoma volume	- ABC/2 - ABC/3 - SAS (Osiris)
J. C. Kosior	2011	30	Not given	Prospective Study	To establish the reliability of haematoma volume	- ICH volume - Interrater variability - Intrarater variability	- SAS (Quantomo) - ABC/2

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
et al [94]					measurements obtained using a computer-assisted method called Quantomo (for quantitative tomography) and the ABC/2 method.		
K. Krishnan et al [76]	2015	548	Not given	Prospective Study (data from ENOS trial)	To study the performance of haemorrhage descriptors in large clinical trials.	- IVH volume - haematoma volume - haematoma shape - haematoma density	- ABC/2 - Modified ABC/2 - SAS (OsiriX) - Fully automated segmentation (AVC, using 3D rendering of 2D slices)
A. K. Maeda et al [95]	2013	20	Not given	Retrospective Study	To compare two different methods for measuring intracerebral haemorrhage (ICH) volume; the ellipse volume (ABC/2) and	- ICH volume - Intra observer variability rate - Inter observer variability rate	- ABC/2 (DICOM) - SAS (Brain Lab)

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
					software-aided planimetric.		
X. Xu et al [78]	2014	294	Not given	Retrospective Study	To compare the accuracy of the ABC/2 formula with open-source software Slicer.	- Hematoma volume - Hematoma size - Hematoma shape (regular, irregular, multilobar)	- ABC/2 - SAS (3D Slicer)
R. U. Kothari et al [63]	1996	118	Not given	Prospective Study	To compare a bedside method of measuring CT ICH volume with measurements made by computer-assisted planimetric image analysis.	ICH volume	- ABC/2 - SAS (planimetric)
F. Cuce et al [173]	2020	78	Not given	Prospective Study	To find more practical and effectuve formula than the simple ABC/2 (sABC/2) to calculate the haematoma volume in patients with subdural and parenchyma haemorrhage.	Haematoma volume	- Simple ABC/2 - SAS (planimetric)

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
J. G. Shulman et al [174]	2020	154	Nor given	Retrospective Study	To demonstrate the use of an SAS to generate ICH volumetrics on non-contrast CT of the head and compare this technique to physician's manual calculations.	- ICH volume - PHE volume	- ABC/2 formula - SAS
B. Zhao et al [82]	2020	257	Not given	Retrospective Study	To find a method that can calculate haematoma volumes accurately, reliably, and quickly.	Haematoma volume	- SAS (3D Slicer) - ABC/2 - Modified ABC/2
M. Khan et al [87]	2017	135	71.06	Retrospective Study	To compare the original ABC/2 method and simplified ABC/2 (sABC/2) with the planimetric method.	Haematoma volume	- ABC/2 - Simplified ABC/2 - SAS (planimetric)
W. D. Freeman	2008	8	Not given	Retrospective Study	To compare 2 methods of measuring ICH volume in patients	Haematoma volume	- ABC/2 - SAS (Analyze 6.0)

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
et al [80]					with warfarin-related ICH (ABC/2 vs SAS).		

Appendix 2 Summary of Included Studies in Systematic Review of PHO Segmentation

Authors	Publication Year	No. of Samples	Mean Age (Years)	Study Design	Objectives	Outcome	Measurement Method
A. Bardera et al Bardera et al [101]	2009	18	Not given	Experimental Study	To propose SAS approach for brain haematoma and oedema quantification on CT image	Haematoma and oedema volume	SAS + ABC/2 method
A. I. Qureshi et al [189]	2011	60	62	Post-hoc analysis	To explore the relationship between various parameters of serum glucose concentrations measured during acute hospitalisation and haematoma expansion, PHO and 3-month outcome among subjects with ICH.	- Serum glucose concentration - Haematoma and PHO volume	ABC/2 method
B. Volbers et al [115]	2011	49	70	Prospective Study	To establish and validate an observer independent method for quantification of	PHO volume	SAS + ABC/2 method

					PHO on CT by comparing with simultaneously performed MRI.		
C. S. Anderson et al [35]	2010	270	62.5	Prospective Study	To determine the effects of treatment on haematoma and PHO over 72 hours.	Haematoma and PHO volume	SAS
C. Herweh et al [190]	2010	17	71	Prospective Study	To clarify whether there exists an early reduction of cerebral perfusion in the perihaemorrhagic area in patients presenting with hyperacute ICH < 3 hours after symptom onset.	ICH size and PHO volume	SAS
E. Fainardi et al [191]	2008	89	68.1	Prospective Study	To quantify perfusion changes associated to acute spontaneous ICH by means of CT perfusion imaging.	Haematoma and PHO volumes	ABC/2 method
J. M. Gebel et al [192]	2002	142	Not given	Secondary analysis	- To summarize oedema volumes in both absolute and relative terms	Haematoma and PHO volume	SAS

				prospective study	- To explore the presence of associations between oedema volume and relevant clinical and radiological variables.		
J. MA et al [8]	2014	48	58	Cross sectional study	To know the effect of haematoma and PHO volume on GCS at the time of admission in patients with spontaneous lobar and basal ganglia haemorrhage.	Haematoma and PHO volume	Modified ABC/2 method
J. R. Carhuapoma et al [193]	2008	9	63.4	Pilot Study	To test the hypotheses that there is a dose-effect relationship between blood clot volume and tissue water content as an indirect measure of severity of blood-brain-barrier breakdown and	Haematoma volume and PHO	Manual segmentation

					vasogenic brain oedema formation.		
L. Lian et al [194]	2014	110	54.1	Retrospective Study	To investigate the effects of minimally invasive surgery and urokinase on PHO.	Haematoma volume, PHO volume, midline shift	SAS
M. McCaron et al [106]	2006	44	61.5	Prospective Study	To compare an early PHO volume as a ratio of haematoma volume in different brain locations in patients admitted to hospital with a diagnosis of spontaneous ICH.	ICH volume and PHO volume	Modified ABC/2 method
M. Chen et al [107]	2013	36	Not given	Experimental Study	To propose and validate an automatic algorithm to segment cerebral oedema of patient with spontaneous ICH.	Haematoma and PHO volumes	Fully automated and manual segmentation
R. Kollmar et al [195]	2010	50	63.5	Prospective pilot study	To investigate the effect of mild hypothermia over a period of 10 days in patients who require	ICH and PHO volume	ASA & ABC/2 moethod

					intensive care treatment because of large supratentorial spontaneous ICH.		
R. McCourt et al [40]	2014	67	70	Prospective Study	To test the hypothesis that oedema growth is associated with reduced cerebral blood flow and lower systolic blood pressure.	Haematoma& PHO	SAS + ABC/2 method
R. Zimmerman et al [93]	2006	399	Not given	Multicentre randomised clinical trial	To provide accurate measurements of the change in haematoma volume, IVH volume, and oedema volume To evaluate the use of CT scans as a predictor of patient outcomes To demonstrate that haematoma volume can serve as a surrogate marker for ICH clinical progression.	Haematoma, IVH and oedema volume	SAS

S. H. Lee et al [105]	2013	44	63.6	Multicentre, randomised, controlled clinical trial	To investigate the effect of celecoxib in patients with ICH.	ICH and PHO volume	SAS
S. Urday et al [196]	2015	20	Not given	Retrospective Study	To develop a systematic approach for CT-based measurement of PHO	ICH, IVH and PHO volume	SAS
W. A. Mould et al [119]	2013	118	60.8	Multicentre, randomised, prospective trial	To test the hypothesis that haematoma removal in patients treated with MIS and rt-PA would lead to concomitant reduction of oedema volume at the end of treatment as compared to ICH patients treated with medical management.	Haematoma and PHO volumes	SAS
Y. Zhu et al [120]	2015	33	57.37	Prospective Study	To test the hypothesis that altered miRNA levels are associated with PHO in ICH patients.	Haematoma and PHO volume	Manual segmentation

R. Dhar et al [197]	2020	124	Not given	Prospective Study	To develop a deep learning-based imaging algorithm capable of accurately measuring haematoma and PHO volumes.	Haematoma and PHO volume	Automated segmentation
J. G. Shulman et al [174]	2020	154	Not given	Retrospective Study	To demonstrate the use of an SAS algorithm to generate PHO volumetrics on non-contrast CT of the head and compare this technique to physician's manual calculation.	Haematoma and PHO volume	SAS and ABC/2 method
J. J. Loan et al [198]	2021	342	78	Prospective community-based inception cohort study	To investigate the existence, strength, and independence of associations between intracerebral haemorrhage and PHO volumes on diagnostic brain CT and one-year functional outcome and long-term survival.	ICH and PHO volumes	SAS

P. Hervella et al [199]	2020	795	74	Retrospective Study	To investigate the effect of perihaematomal hypodensity and outcome of a decrease in body temperature in the first 24 hours in patients with ICH.	PHO volume and clinical outcomes	Fully automated segmentation + ABC/2
Y. Y. Wu et al [200]	2016	100	69	Retrospective Study	To assess reliability of semi-automated CT planimetry using Analyze and Osirix software	ICH and PHO volumes	SAS