Faculty of Medicine
School of Epidemiology, Public Health, and Preventive Medicine

Improving our Ability to Define and Predict Hematoma Expansion in Intracerebral Hemorrhage: *A Detailed Analysis of Prospective Intracerebral Hemorrhage Cohorts*

Vignan Yogendrakumar MD, MSc Candidate

Thesis Advisory Committee:
Dar Dowlatshahi MD, PhD, FRCPC (Thesis Supervisor)
Tim Ramsay PhD (Thesis Co-Supervisor)
Dean Fergusson MHA, PhD

Thesis Submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for a Masters of Science in Epidemiology and Biostatistics

PREFACE

This thesis is formally categorized as a *Secondary Analysis* project. It follows an article-based format consisting of eight major chapters and five component articles. The primary author, Dr. Vignan Yogendrakumar, was responsible for the conceptualization, design, and manuscript drafting of all chapters and component articles. Statistical analysis was performed by Dr. Yogendrakumar with the oversight and guidance of Drs. Ramsay, Fergusson, and Dowlatshahi. Dr. Yogendrakumar had full access to all data used in this thesis and gained permission from the publication committee of each respective dataset. The datasets in question acquired ethics approval from each enrolling site. Hence, local approval from the University of Ottawa Research Ethics board was not required. Dr. Yogendrakumar takes responsibility for the integrity of the data and the accuracy of the analysis. The exact role of all other co-authors are listed within each respective component article.

THESIS ABSTRACT

Spontaneous intracerebral hemorrhage, the non-traumatic rupture of cerebral blood vessels, is the most devastating form of stroke. The disease is dynamic, unpredictable, and patients can worsen acutely within the first 24 hours secondary to ***hematoma expansion***: re-bleeding of a baseline hemorrhage. Hematoma expansion is a major predictor of mortality and poor long-term outcome. This *secondary analysis* thesis proposes to advance the current understanding of this phenomenon through three separate research endeavors: 1) a scoping review of hematoma expansion prediction scores, 2) an independent validation of a non-contrast prediction score, and 3) an assessment and revision of the dichotomous definition of hematoma expansion used in clinical trials. These three projects will offer different contributions that will advance the science of intracerebral hemorrhage, a field where treatment options, outcome measures, and basic definitions, are all under active debate.

ACKNOWLEDGEMENTS

This work would not have been possible without the guidance and mentorship provided by my thesis advisory committee: Drs. Dar Dowlatshahi, Tim Ramsay, and Dean Fergusson.

I would like to particularly acknowledge the unwavering support of Dr. Dowlatshahi and the Ottawa Stroke Program, who have supported my career since the start of my residency at the University of Ottawa.

Lastly, I would like to thank my family and friends for their ongoing love and support.

GLOSSARY

AUC: Area under the curve

CT: Computed Tomography

CTA: Computed Tomography Angiography

GCS: Glasgow coma scale

HE: Hematoma Expansion

HEP: Hematoma Expansion Prediction

ICH: Intracerebral Hemorrhage

IV: Intravenous

IVH: Intraventricular Hemorrhage

NIHSS: National Institute of Health Stroke Scale

MRI: Magnetic Resonance Imaging

ROC: Receiver Operating Characteristic

SAH: Subarachnoid Hemorrhage

TABLE OF CONTENTS

CHAPTER ONE: THESIS OVERVIEW

1.1 PRIMARY RESEARCH OBJECTIVES:

Spontaneous intracerebral hemorrhage, the non-traumatic rupture of cerebral blood vessels, is the most devastating form of stroke. The disease is dynamic, unpredictable, and patients can worsen acutely within the first 24 hours secondary to ***hematoma expansion***: ongoing bleeding of a baseline hemorrhage. Hematoma expansion is a major predictor of mortality and poor long-term outcome.

This secondary analysis thesis proposes to advance the current understanding of this phenomenon through three separate research projects, presented in the five principal chapters of this thesis:

1. A systematic scoping review of the literature assessing the diagnostic capabilities of clinical tools developed to predict hematoma expansion (Chapters 3 and 4).
2. Independent validation of a non-contrast hematoma expansion prediction score (Chapter 5).
3. An assessment of whether the definition of hematoma expansion can be optimized with the incorporation of total blood volume (Chapter 6 and 7).

These three projects offer different contributions that advance the science of intracerebral hemorrhage, a field where treatment options, outcome measures, and basic definitions, are all under active debate.

1.2 OVERVIEW OF CHAPTERS:

Chapter 2 – Background

This chapter outlines our current understanding of intracerebral hemorrhage and hematoma expansion. A particular focus has been placed on reviewing hematoma expansion definitions, pathophysiology, and clinical/radiological predictors. We discuss the challenges in predicting hematoma expansion in the clinical environment and review the current clinical and radiological predictors studied in the literature. We also provide the historical context as to how hematoma expansion definitions have developed and changed over the past 30 years. Finally, we discuss the gaps in our knowledge that we hope to address in our thesis. Although not formally a component article, we incorporate portions of the manuscript "Expansion of Intracerebral Hemorrhage", recently published as a textbook chapter in the first edition of *Complications of Acute Stroke: A Concise Guide to Prevention, Recognition, and Management* (Appendix VI).

Publication: Yogendrakumar V, Goldstein JN, Dowlatshahi D. "Expansion of Intracerebral Hemorrhage." *Complications of Acute Stroke: A Concise Guide to Prevention, Recognition, and Management*. Ed: R Behrouz, L Birnbaum. New York: Springer Publishing Company, 2019.

Chapters 3 and 4 – Scoping Review of Hematoma Expansion Prediction Scores

In these two chapters, we summarize and describe the existing prediction scores for hematoma expansion. We performed a scoping review of the literature assessing the development, predictive capabilities, and extent of use of hematoma expansion scores currently developed for clinical practice and treatment trials. These two chapters incorporate both the protocol manuscript "Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review", published in *BMJ Open* (Chapter 3) and the review manuscript "Evaluating Hematoma Expansion Scores in Acute

Intracerebral Hemorrhage: A Systematic Scoping Review", presently under review at *Stroke* (Chapter 4).

Publication: Yogendrakumar V, Moores M, Sikora L, Ramsay T, Fergusson D, Dowlatshahi D. Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review. *BMJ Open.* 2019;9:e024744.

Publication: Yogendrakumar V, Moores M, Sikora L, Shamy M, Ramsay T, Fergusson D, Dowlatshahi D. Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review. *Stroke.* Under Review (May 2019).

Chapter 5 – Independent Validation of a Non-Contrast Hematoma Expansion Prediction Score

This chapter describes our attempt to independently validate the Hematoma Expansion Prediction (HEP) score, a nomogram-derived prediction scale, using data from a prospectively collected intracerebral hemorrhage cohort. The HEP score was developed as a prediction method that could be used to predict the risk of significant hematoma expansion without the need for contrast administration. We compared the predictive capabilities of the HEP score to a commonly used contrast marker: the Spot Sign. This chapter incorporates the manuscript "Independent Validation of the Hematoma Expansion Prediction Score: A Non-contrast Score Equivalent in Accuracy to the Spot Sign.", published in *Neurocritical Care*.

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Selim M, Dowlatshahi D. Independent Validation of the Hematoma Expansion Prediction Score: A Non-contrast Score Equivalent in Accuracy to the Spot Sign.. *Neurocritical Care.* Published ahead of print: May 2019. doi.org/10.1007/s12028-019-00740-5.

Chapters 6 and 7 – Redefining Hematoma Expansion Using Total Blood Volume

In these two chapters we aimed to determine whether the use of total blood volume (intraparenchymal and intraventricular hemorrhage) when defining hematoma expansion improves our predictive potential of long-term outcome. This project was completed in two phases. In the first phase, we sought to understand the effect that ventricular hemorrhage expansion has on long-term outcome. This is presented in the manuscript "New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage", accepted for publication at *Neurology* (Chapter 6). In the second phase, we re-defined hematoma expansion using both intraparenchymal and intraventricular hemorrhage and compared the refined definition to conventional definitions in use today. This comparative analysis is presented in the manuscript "Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth", presently under review at *Neurology* (Chapter 7).

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Warren AD, Anderson CD, Gurol ME, Greenberg SM, Viswanathan A, Rosand J, Goldstein JN, Dowlatshahi D. New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage. *Neurology*. Accepted, in press: April 2019.

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Goldstein JN, Dowlatshahi D. Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth. *Neurology*. Under Review May 2019.

Chapter 8 – Summary and Discussion

This chapter provides a summary of the thesis and key findings. We also outline steps and directions for future research.

2.1 INTRACEREBRAL HEMORRHAGE:

Spontaneous intracerebral hemorrhage, caused by the nontraumatic rupture of cerebral blood vessels, is the most devastating stroke subtype and is a major cause of morbidity and mortality across the world.[1] It is the second most common form of stroke and accounts for approximately 10-30% of first ever stroke presentations.[2] In addition to a 1-month mortality ranging from 30-55%, approximately 75% of survivors continue to suffer severe disability long term.[2,3]

The annual incidence of hemorrhage is reported to be 10-30 per 100,000.[1] While individual countries have reported varying changes in hemorrhage rates, a large meta-analysis of 8,000+ patients assessed from 1980 to 2008 reported an overall incidence worldwide of 24.6 per 100,000 person years (95% CI: 19.7-30.7).[4,5] Intracerebral hemorrhage is increasingly seen with age and may relate to the increased use of anticoagulation in the elderly and the higher prevalence of amyloid angiopathy and hypertension.[1]

Intracerebral hemorrhage presently stands as an emerging public health issue. Due to limited treatment options and our aging population, hospital admissions for intracerebral hemorrhage increased by 18% from 1990-2000[1] and are projected to increase further. Care of patients with intracerebral hemorrhage is further complicated by the dynamic nature of the disease. Patients are often subject to rapid changes in their clinical status within the first few hours to days of symptom onset.[6] These changes are often associated with complications such as fever, seizure, intraventricular extension, hematoma expansion, and can lead to clinical deterioration.[7,8]

Hematoma expansion after arrival stands as one of the most critical and frequent contributors to poor outcome. It occurs early in presentation and is the therapeutic target of many clinical trials. An improved understanding of this process can ultimately lead to treatments that are successful at preventing it. The following chapter will focus specifically on our current understandings of hematoma expansion: how it occurs, what best predicts it, and how we define it.

2.2 PATHOPHYSIOLOGY:

The exact mechanisms that underlie hematoma formation and expansion are complex and not fully clear. Hematoma formation and expansion is a heterogenous process with multiple events occurring in parallel. Through pathological studies and translational models, we believe that the pathophysiologic events of an intracerebral hemorrhage occur in four major phases: vessel rupture, baseline hematoma formation, hematoma expansion, and edema formation (the latter will not be a primary focus of this thesis).[9]

The mechanisms leading to vessel rupture vary widely based on pathology. Intracerebral hemorrhage is broadly divided into primary and secondary forms. Primary intracerebral hemorrhages result from changes in cerebral vasculature brought on by hypertension and cerebral amyloid angiopathy. In hypertension, smooth muscle cells can proliferate and undergo necrosis concurrently, resulting in collagen deposition and vessel stiffening. In addition, end vessels exposed to chronically high pressures can also develop Charcot-Bouchart aneurysms. This results in brittle and stiff vessels which can rupture spontaneously when exposed to high enough pressure.[10] In contrast, β-amyloid deposition in small and mid-sized cortical blood vessels is the hallmark feature of cerebral amyloid angiopathy. β-amyloid deposition results in micro-aneurysm formations, fibrinoid necrosis, smooth muscle cell replacement, and

perivascular leakage.[11] Secondary intracerebral hemorrhages are caused by a variety of pathologies including brain tumors, aneurysms, and vascular malformations.[10]

Initial hematoma development is rapid. The forming hematoma faces little counter pressure from the surrounding tissue initially. This is believed to result in the sudden onset of symptoms seen in the majority of clinical cases. As bleeding continues in the hyperacute phase (within the first hour), counter pressure from the tissue increases. Cessation of baseline hematoma formation is believed to occur when the counter pressure from the adjacent brain tissue overcomes the force of the blood leaving the vessel.[10]

Hematoma expansion was originally hypothesized to be caused by a single vessel that bursts, causing the original hemorrhage event, which then continues to bleed, resulting in expansion.[3] However, no direct pathological evidence has been found to support this notion, and expansion can occur many hours after an initial bleed event – this makes the concept of a single vessel bursting and then continuing to actively bleed less likely.[3,12] Our most current understanding of expansion originates from the pathological studies of hemorrhage by C.M. Fisher.[13] Most notable in his observations was the presence of multiple sites of arterial bleeding located at the periphery of the primary hematoma. These additional sites appeared to be smaller arterioles adjacent to the primary hematoma that were mechanically disrupted, resulting in sources of secondary bleeding. Fisher described these sources of additional bleeding to occur in an "avalanche fashion".[13] Studies have since provided increasing support to Fisher's Avalanche Theory of hematoma expansion. Hematomas have been observed to change the axial direction of growth over time and are commonly noted to exhibit irregular shapes as they grow and expand.[10,14] Computational

models designed to test the avalanche theory have been able to reliably re-create models that carried characteristics similar to clinically observed hemorrhage events.[15]

Irrespective of the underlying pathophysiology, the goal of hemorrhage treatment has largely been to mitigate expansion, thereby preventing further deterioration and improving outcomes. The priority is to investigate these pathophysiological changes in the context of attempting to identify biomarkers (clinical, biochemical, or radiological) predictive of hematoma expansion. It is the hope that with acute identification of expansion risk factors we can try to mitigate this risk and prevent hematoma enlargement.

2.3 RADIOLOGICAL PREDICTORS:

Given that the diagnosis of intracerebral hemorrhage is confirmed with imaging, the bulk of identified expansion predictors are radiological. Imaging biomarkers are divided broadly into two categories based on the presence or absence of contrast use. Non-contrast imaging markers involve assessing the characteristics of the hematoma and include baseline volume, margin irregularity, and heterogeneity. Contrast biomarkers are associated with the presence of contrast extravasation during computed tomography angiography (CTA).

2.3.1 Non-Contrast Predictors:

Volume:

Baseline hematoma volume is a consistent predictor of hematoma expansion.[3,16–19] Independent of the time to computed tomography (CT) and other confounders, large volume hemorrhages are at increased risk of expansion. There is no established threshold of baseline volume that is

predictive of hematoma expansion; however, hemorrhage volumes greater than 10 mL may act as a threshold point.[16] Small volume hemorrhages are often stable and less prone to expansion. Hemorrhages with baseline volumes <10 mL have a low likelihood of subsequent growth and are associated with good long-term outcomes.[20]

Shape and Margin Irregularity:

The shape of a hematoma is influenced by the nature of adjacent tissue and potential for secondary vessel rupture. As such, hemorrhage shapes are not always spheroid or ellipsoid. Irregular margins are commonly observed and are associated with hematoma expansion. Fuji et al.[21] first categorized hematoma shape into three broad forms: spherical with smooth margins, irregular shaped with irregular margins, and separated with fluid levels. Hemorrhages with irregular margins were associated with expansion in his study of 419 patients.[22] Later work by Barras et al. graded the degree of margin irregularity with 1-5 scale,[16] and Blacquiere et al. used this scale to associate margin irregularity with hematoma expansion (Sensitivity: 69% [95% CI: 59-78], Specificity 46% [95% CI: 40-53] for highest grades of margin irregularity [4 or 5]).[23] As noted before, irregular margins may reflect ongoing secondary vessel rupture and therefore, represent an "intermediate stage of maturity" as the bleed continues to its final volume.[24]

Heterogeneity: The Swirl, Black Hole, Blend, Island, and Satellite Signs:

As a hemorrhage forms and evolves it becomes increasingly hyperdense relative to the surrounding tissue. Heterogeneity, a mixture of hypo and hyperattenuation within a hematoma, is often observed and has been studied extensively. First noted during the 1980's in extra-axial hematomas, the "swirl sign" is defined as an area of low attenuation within an extra-axial bleed

(i.e. an epidural hematoma).[25] This area of low attenuation, often isoattenuating relative to brain tissue, is thought to represent extravasating blood, and correlate with areas of active bleeding seen during surgical evacuations.[25] Work by Selariu et al. attempted to adapt the swirl sign to intracerebral hemorrhage patients,[26] hematoma expansion, however, was not explicitly assessed. A smaller study conducted prior by Kim et al. in 2008, did not find an association between swirl sign and expansion.[27]

In 2016, Li et al. introduced the "black hole" sign.[28] Extending on previous hematoma heterogeneity work, the black hole sign is described as a region of relative hypoattenuation that is encapsulated within the hematoma and does not connect with adjacent brain tissue. In an attempt to create a degree of objectivity to hematoma heterogeneity, the authors stipulated that a Hounsfield difference of >28 units be observed between the region of hypoattenuation and the rest of the hematoma. In a single center, prospective study (n=206), the black hole sign was observed in 30 patients. Similar to the swirl sign, the black hole sign was associated with larger baseline volumes and was independently associated with expansion (>12.5 mL or > 33%) when adjusted for baseline volume and time to CT .[28] The same authors have also looked at hypoattenuation surrounding a hematoma and adjacent to brain tissue. This concept, termed the "blend sign" is seen in approximately 17% of hemorrhage patients and in a retrospective analysis of 172 patients was independently associated with hematoma expansion, adjusting for baseline volume and time to CT.[29] In the past year, two signs based on the presence of smaller hemorrhages adjacent to the primary hematoma have been developed: Island sign, smaller bleeds scattered adjacently to the primary hematoma,[30] and Satellite Sign, defined as a single smaller hemorrhage (diameter <10mm) located 1-20 mm from the primary hematoma.[31]

Although each sign shows individual promise, the baseline prevalence of each is highly variable and the replication of findings have not been consistent.[24,32,33] This creates the argument that perhaps, rather than specific signs, simply, the presence or absence of heterogeneity in any form is sufficient to predict expansion.[24] Work by Boulouis et al. assessed this concept in a large cohort of 1029 patients.[17] Heterogeneity, simply defined as observing hypoattenuation and/or fluid levels within a hematoma, was observed in 28.3% of a developmental cohort (n=784) and 40.4% of a replication cohort (n=245). More than 50% of patients with hypoattenuation were associated with hematoma expansion and independent of baseline volume, time to CT, warfarin use, and spot sign (aOR 3.42 [95% CI: 2.21-5.31]).

2.3.2 Contrast Predictors:

Contrast manifests in intracerebral hemorrhage as an area of hyper-density seen within a hematoma during CTA.[34] It is hypothesized that the presence of these hyper-densities are representative of contrast extravasation from blood vessels and may represent ongoing bleeding.[35]

Contrast extravasating from blood vessels during an acute hemorrhage was first observed in formal angiography studies throughout the 1970s and early 1990s.[36] Becker et al. and Murai et al. were the first to investigate the use of iodinated contrast in hemorrhage and found an association between contrast hyperdensity presence and mortality.[37,38] With CTA gaining prominence in clinical practice, Goldstein et al. and Kim et al. noted an association between contrast presence and hematoma expansion.[27,36] Subsequent studies have had similar findings, albeit, each of these studies used differing descriptions and definitions of contrast presence.[34]

The term “spot sign” was first introduced by Wada et al. in 2007 and is formally defined as “1 or more 1-to 2-mm foci of enhancement within the hematoma on CTA source images”.[39] Subsequent studies have adopted Wada’s definition and spot sign was formally tested in the PREDICT observational cohort study.[40] Looking at patients presenting <6 hours from multiple centers, patients were provided baseline CT, CTA, follow-up imaging at 24 hours and clinical follow-up at 90 days. Adjusting for relevant covariates, spot sign was found to be independently predictive of hematoma expansion (defined in this case as >6mL or >33%). PREDICT reported a sensitivity and specificity of 51% (39–63) and 85% (78–90), respectively. An association between spot sign and mortality was also observed.[40] Spot sign has since become the dominant representation of contrast extravasation.

2.4 CLINICAL PREDICTORS:

The time to CT is one of the most consistently associated clinical predictors of expansion.[41–43] Anticoagulant use, in particular warfarin, is clinical factor also strongly associated with hematoma expansion.[44,45]

Studies looking at additional clinical markers have yielded inconsistent findings. Baseline Glasgow coma scale (GCS), National Institute of Heath Stroke Scale (NIHSS) scores, C-reactive protein, D-dimer, and increased serum creatinine have all been linked with expansion, albeit, replication of these findings are limited and conflicting.[2,41,46] Associations between reduced platelet activity and expansion have been observed in a single center prospective study[47], however links between the use of antiplatelet drugs and expansion are conflicting.[48,49]

The relationships between blood pressure and hemorrhage are intuitive and have been studied extensively. Patients with an acute hemorrhage often exhibit an increased blood pressure on presentation to the emergency room. There is concern that increased blood pressure may increase the risk of hematoma expansion, as studies where patients have had serial blood pressure measurements found associations between maximal systolic pressure and expansion.[50] Furthermore, findings from the SAMURAI-ICH[51] study show that patients with elevated blood pressure, even after anti-hypertensive treatment, have an increased risk of poor long-term outcome. However, associations between blood pressure and expansion are present in some studies but absent in others. This is likely due the confounding elements of treatment and the inherent difficulty of recording blood pressure in observational studies when the assessment of blood pressure is not the sole goal. Ultimately, while observational studies have shown links between blood pressure and expansion, subsequent intervention studies have not shown causation.[52,53]

2.5 DEFINING HEMATOMA EXPANSION:

Formally, hematoma expansion is simply defined as an enlargement in hematoma volume when comparing a baseline scan to subsequent imaging. Yet, the amount of expansion required to be deemed significant has been a subject of continued debate. Moreover, the frequency and occurrence of hematoma expansion varies depending on the definition used.[3]

Hematoma expansion has been an area of active investigation over the last 30 years as brain imaging has become more accessible. Early expansion definitions first used in the late 1980's were varied, largely arbitrary, and without statistical basis. Using the ABC/2 approximation

method, common definitions included absolute volume enlargements of >2mL or >20mL and relative volume increases of 50% or more.[54,55] The first attempt to derive a statistically based definition of hematoma expansion was conducted by Kazui et al. in the mid 1990s. Using a consensus of five readers as a gold standard, changes in hematoma volume over a mean time course of 35 (±31.1) hours were assessed via a receiver operating characteristic (ROC) curve. A mathematically optimal cut-point was calculated to be at 12.5 mL and 40%.[54] The absolute definition of ≥12.5 mL representing significant hematoma expansion has since been used in a number of studies and continues to be actively used today. In contrast, the definition of 40% was not widely adopted. A relative definition of >33% was introduced by Brott et al.[56] The rationale proposed to use 33% was two-fold. First, a change in hematoma volume of at least 33% relative to the baseline correlates with a 10% change in the diameter of a hematoma. Brott et al. argued that this would be easy to detect by a physician during an acute assessment.[56] Second, it was deemed that a change of 33% or greater would represent true growth and not variability secondary to imaging technique. Since its introduction in 1997, this definition has been adopted widely and used for a number of subsequent studies.[57] Another definition, ≥6 mL, loosely based on expansion definitions used in neurotrauma and neurosurgical circles to evaluate traumatic intraparenchymal hemorrhages, has also been used by several subsequent studies.[57,58]

These definitions were all formally re-evaluated by Dowlatshahi et al. in 2011. Changes in hematoma volume over the course of 24 hours (in patients presenting under 6 hours of symptom onset) were compared to poor clinical outcome of a 90-day mRS score of 4 or higher. All definitions (≥3 mL, ≥6 mL, ≥12.5 mL, ≥ 26%, ≥ 33%) were independently predictive of poor outcome.[57] Of note, specificity increased with higher threshold definitions, but at cost of

decreased sensitivity. Additional analysis also showed that absolute definitions were slightly more predictive of poor outcome than relative definitions, especially when severe disability or death (mRS 5-6, 6) were assessed. Similar findings (using definitions: ≤5 mL, 5.1-12.5 mL, >12.5 mL, ≤33%, 34-50%, >50%) were reported in a concurrent study by Delcourt et al.[59]

Regardless of the definition used, the definition must be greater than the minimal detectable difference of the measuring technique used. Brott et al. had used a sufficiently large threshold in order to ensure enlargement was detectable by the human eye.[56] This may be valid when dealing with moderately sized hematomas, but may not be sensitive in very small hematomas, such as those under 5 mL. Indeed, the minimal detectable difference of commonly used planimetric volume assessment programs exceeds 33% in hematomas less than 15 mL in volume.[60] Conversely, the minimal detectable differences become very large, and larger than the absolute thresholds of 6 mL, as hematoma volume increases, or when anatomical boundaries are altered/compressed.[61]

2.6 KNOWLEDGE GAPS

Hematoma expansion is a dynamic process, and a potential target for therapeutic intervention. However, our understanding of its pathophysiology is limited and there remains fundamental questions in terms of how we predict and define it.

Prediction:

Numerous clinical and radiological variables are associated with expansion. Recognizing the limitations of solely using individual biomarkers, investigators have turned to combining

radiological and clinical variables in the form clinical prediction rules. Such prediction rules and risk scores have the potential to assist with recruitment for clinical trials and could eventually help guide clinical management at the bedside. Over the course of 10 years, a number of clinical expansion scores have been developed. However, the adoption of these scores appear to be largely minimal. The underlying cause for this is not clear. In addition, there has been no comparative analysis or evaluation of these scores and their development. No systematic or scoping review has been conducted to date. We investigate these elements further in Chapters 3, 4, and 5.

Definition:

As one of the primary outcomes of interest in hemostatic trials, optimally defining hematoma expansion is a fundamental step to ensuring that we are adequately evaluating potential therapies. Through the extensive investigations highlighted above, numerous definitions are in present use today: ≥3 mL, ≥6 mL, ≥12.5 mL, ≥ 26%, ≥ 33%. Of note, these current measures are designed to only assess changes in intraparenchymal bleeding, defined as blood that is located within brain tissue. Blood that is found within the ventricles of brain (intraventricular bleeding) is not incorporated in these measures. The presence of intraventricular hemorrhage is an independent predictor of poor outcome, but no current definition of hematoma expansion includes it in risk stratification. Furthermore, baseline measurements of total blood volume, the sum intraparenchymal and intraventricular blood volumes, have been shown to be a stronger predictor of poor outcome compared to intraparenchymal volume. There is potential that expansion definitions incorporating the details of total blood volume and intraventricular hemorrhage presence may better predict long-term outcome and we explore this in Chapters 6 and 7.

3.1 PREFACE:

In this chapter we outline our methodological protocol for a scoping review of hematoma expansion scores. Ottawa Health Science Network Research Ethics Board approval for this study was not required. Drs. Yogendrakumar, Fergusson, and Dowlatshahi drafted the manuscript protocol and contributed to the development of the selection criteria, article screening strategy, and data extraction criteria. Dr. Yogendrakumar and Ms. Sikora developed the search strategy. Dr. Moores and Ramsay reviewed the protocol manuscript for intellectual content. All authors read, provided feedback and approved the final protocol. This chapter presents the protocol manuscript "Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review", published in *BMJ Open.* A publisher's PDF of this manuscript is available in Appendix I.

Publication: Yogendrakumar V, Moores M, Sikora L, Ramsay T, Fergusson D, Dowlatshahi D. **Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review**. *BMJ Open.* 2019;9:e024744.

Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review

Vignan Yogendrakumar[1], Margaret Moores[1], Lindsey Sikora[2] Tim Ramsay[3], Dean Fergusson[3], Dar Dowlatshahi[1]

[1]Ottawa Stroke Program, The Ottawa Hospital: Division of Neurology. University of Ottawa.
[2]Health Sciences Library, University of Ottawa
[3]Ottawa Hospital Research Institute, Ottawa Methods Center. University of Ottawa School of Epidemiology, Public Health and Preventative Medicine.

3.2 ABSTRACT

Introduction: Patients presenting with acute intracerebral hemorrhage are at a high risk of exhibiting hematoma expansion, a phenomenon that can significantly worsen long-term functioning. Numerous clinical and radiological factors are associated with expansion. In a bid to better select patients at increased risk of expanding, these factors have been collated together into clinical scores. Several clinical scores have been developed, but comparisons of diagnostic potential between these scores are limited and the frequency of use in clinical trial enrollment is unknown.

Objective: To perform a scoping review of hematoma expansion scores and explore numerous factors such as methodology of development, and diagnostic capabilities.

Methods and Analysis: MEDLINE, PUBMED, EMBASE, CENTRAL, and ClinicalTrials.org will be searched with assistance from an experienced information specialist. Eligible studies will involve adults presenting with spontaneous intracerebral hemorrhage who received baseline assessments, follow-up imaging, and risk stratification through a hematoma expansion score. Reviewers will independently extract data from the included studies and will collect data on patient demographics and medical history, details on score development, diagnostic capabilities, and usage proportions. Analysis of extracted data will focus on comparing the predictive capability of each score and similarities/differences in score development. The exact analysis technique will be dictated on the type of data extracted.

Ethics and dissemination: Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through conference presentations, and peer-reviewed publications.

Registration: This protocol is registered and hosted at the University of Ottawa Research Repository (URL: http://hdl.handle.net/10393/38034).

3.3 STRENGTHS AND LIMITATIONS OF THIS STUDY:

- This review will perform a detailed assessment of prediction scores in their current form which has not been conducted previously.
- The use of a scoping review methodology allows flexibility in assessment and may assist in the preparation of a formal diagnostic test accuracy systematic review
- Quality of evidence will not be evaluated in this scoping review.
- Limitations in this study include heterogeneity in the primary outcome measure (several definitions of hematoma expansion exist in the literature, not all studies may use the same definition) and changes in the overall management of intracerebral hemorrhage that may limit the extent of hematoma expansion observed.
- This study may highlight unexpected strengths, weaknesses, and areas requiring increased focus for future prediction tool development.

3.4 INTRODUCTION:

Intracerebral Hemorrhage and Hematoma Expansion:

Spontaneous intracerebral hemorrhage, the non-traumatic rupture of cerebral blood vessels, is the most devastating stroke subtype and is a major cause of morbidity and mortality across the world.[1] One-month mortality can be high as 55% and a large proportion of survivors often suffer severe long-term disability.[2] The high morbidity and mortality associated with intracerebral hemorrhage is secondary to the dynamic nature of the disease. The size of an intracerebral hemorrhage is rarely a static fixture: it can change after initial presentation, often enlarging in size. This enlargement of hematoma volume, formally termed as hematoma expansion, is a major cause of poor long-term outcome.[3] It occurs early in presentation, and has become the therapeutic target of choice in recent clinical trials.[4–6]

Unfortunately, therapies that are designed to mitigate hematoma expansion date have been largely unsuccessful at improving patient outcomes.[6–8] An inability to precisely select the patients most at risk of expansion, and therefore most likely to benefit from therapy, has been considered a potential reason for this lack of success. As such, investigation into the predictors of hematoma expansion has been a major research focus for intracerebral hemorrhage experts worldwide. It is the hope that by accurately selecting patients who are at the highest risk of expansion, future trials will be better able to evaluate the effectiveness of their respective treatments.

Predicting Hematoma Expansion:

Given that the diagnosis of intracerebral hemorrhage is confirmed with imaging, the majority of expansion predictors are radiological. A multitude of imaging variables have been identified as potential predictors.[9,10] Certain clinical variables, such as concomitant antithrombotic use and time of presentation, also play a significant role in influencing expansion.[11] These factors are used together in combination to develop predictive models designed to optimize patient selection accuracy. These models are subsequently simplified into clinical scores for ease of use in day-to-day practice. In the past five years alone, several prediction scores were created.[12–14] Whilst the diagnostic capabilities of each score have been assessed by the creating teams on an individual basis, there is no clear consensus of which tool has the best predictive capability. No in-depth or comparative analysis of the scores have been performed and no systematic or scoping review has been conducted to date. It is also unclear whether these tools have been utilized in recent or ongoing clinical trials.

Objective:

Perform a scoping review of the literature assessing the predictive capabilities and extent of use of hematoma expansion scores developed for use in clinical treatment trials. Using the PCC (Population, Concept, Context) elements our clinical objectives are as follows:

1. Describe the characteristics of each score and how each score was developed.
2. Outside of the original derivation studies, have scores been externally validated, used in recent randomized controlled trials, or been proposed for use in upcoming studies?

3. Collate and compare the diagnostic capabilities between scores (discrimination, calibration, sensitivity, specificity, positive predictive, negative predictive values)

3.5 METHODS:

Study Registration:

This study will be conducted based on the guidelines of the Johana Briggs Institute (JBI) Methodology for Scoping Reviews.[15] The findings of this study will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of scoping reviews (PRISMA-SCR). This protocol will be reported, using PRISMA-P and JBI guidelines[15,16], and is registered and hosted at the University of Ottawa Research Repository (URL: http://hdl.handle.net/10393/38034).

Inclusion/Exclusion Criteria:

Eligibility criteria was established using the PCC (Population, Concept, Context) framework. Studies will be selected according to the following criteria:

Participants:

Included studies will involve adult patients (≥ 18 years of age) presenting with spontaneous intracerebral hemorrhage (hemorrhagic stroke), confirmed with either CT or MRI. Eighteen is the threshold age for adulthood used in the majority of hemorrhage trials. Pediatric intracerebral hemorrhage is more often secondary to intravascular lesions and malignancy and hence will not be included in this review. Patients presenting solely with a hemorrhage of another type

(subarachnoid, subdural, epidural) with not be included in this review. Hemorrhages with a known secondary etiology (tumor, vascular malformation, trauma) will also be excluded.

Concept:

The major concepts we hope to explore in this scoping review is hematoma expansion and the predictive models, hematoma expansion scores, that have been developed to try and accurately predict this phenomenon in patients presenting with acute intracerebral hemorrhage. An expansion score is defined as a collection of variables, clinical, radiological, or both, that have been identified and weighted in a way such that patients presenting with higher cumulative scores are at a higher risk of exhibiting an expansion of their baseline hematoma. We aim to look at the original studies which derived a respective score, subsequent studies that validated and compared different scores to each other, and clinical trials or observational cohorts which used these scores as a clinical tool. Because our primary objective is to learn about both the diagnostic capability and prevalence of use of these scores, we will be evaluating original research contributions, systematic reviews, meta-analysis, and guideline documents where appropriate. Studies focused solely on a single clinical or radiological predictor (e.g. blend sign) will be excluded from our analysis. There is clear evidence to show that no single variable adequately predicts hematoma expansion.[9,17]

Hematoma expansion acts as the outcome of interest in this scoping review. Expansion is evaluated by assessing the change in hematoma volume at initial presentation to follow-up imaging usually performed at the 24-48 hour mark. Expansion can be reported as the net change in volume or as a dichotomous outcome via a predetermined definition of hematoma expansion

(e.g. hematoma enlargement > 6 mL). There are several definitions of hematoma expansion in current use today and we will utilize whichever definitions have been decided upon by the study authors. However, only studies that provide a dichotomous definition of hematoma expansion would be utilized in any subsequent summary analysis.

Context:

There is no restriction on healthcare locations, albeit we expect most studies will involve patients who were treated in an emergency room, intensive care unit, or neurological/neurosurgical ward. We also have no restrictions on country of study, ethnicity, gender, or socio-economic status.

Information Sources and Search Strategy:

For the purposes of our scoping review, we will include data from primary research studies (with no limitation to study design), previously published systematic reviews, meta-analysis, and guidelines that pertain to the topics of hematoma expansion and predictive scores. We will only include studies that are presented in the English language due to constraints in translational resources. A search strategy was developed (see Table 1) using keywords and MeSH terms relating to intracerebral hemorrhage and hematoma expansion. This search strategy will be used on the following four databases: MEDLINE (via Ovid), Embase (via Ovid), PubMed, Cochrane CENTRAL (via Ovid), from date of inception to June 2018. Supplemental searches will include scanning the reference list of included studies and reviews identified through the primary search. Released abstracts from the last 10 years in the International Stroke Conference, European Stroke Organization Conference, or American Academy of Neurology Annual Meeting that have

not been published in full manuscript form will also be screened to ensure completeness. Study authors will be contacted for further information as required.

Study Records:

Data Management:

Database search results will be downloaded and imported to EndNote Reference Manager Software (Clarivate Analytics, Philadelphia, PA, USA) and then transferred to Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). After removal of duplicate results, citation titles and abstracts will be screened.

Selection Process:

At least two reviewers will independently screen articles in a two-level process. Level one will involve a title and abstract screening for potentially eligible studies. Studies that score a "Yes" or "Unsure" in this phase will be brought forward for full-text (level two) evaluation. Full-text screening will use a pre-created article screening form. In the event of a disagreement between the two authors in either stage, a third party neurologist will adjudicate. The process of study selection will be described using a PRISMA flow diagram.

Data Extraction Process and Summarization of Results:

Reviewers will independently extract data from the included studies using an a priori designed data extraction form. We will collect basic publication data (e.g. year and journal of publication, authorship list, funding), study population information (demographic and medical history measures), details on score development (variables involved, development or validation

methodology), definition of hematoma expansion used, and markers of diagnostic accuracy (c-statistic, calibration, sensitivity/specificity/positive and negative predictive values). The basic make-up of each score will be compared side-to-side in a tabular format. The underlying methodology used to develop each score will be described descriptively. Study authors will be contacted for further information on score development if deemed necessary.

The analysis of diagnostic summary markers will ultimately be dependent on the data we are able to extract from each study. If possible, we aim to compare the accuracy of each score through multiple pairwise comparisons. Because each score is reported on a continuous scale, multiple positivity thresholds may exist. In this case we would aim to make comparisons based on summary ROC curves. Due to the potential concern of data paucity, we plan to utilize test accuracy data from all eligible studies that have evaluated one or more of these scores and will include data from both derivation and validation cohorts. If possible data from validation cohorts will be examined separately in a sensitivity analysis. To account for changes in clinical practice and ICH management, studies published in differing time periods or studies with significant differences in baseline populations may be assessed separately in sensitivity analysis. If the data extracted makes meta-analysis not possible, we will compare the diagnostic summary markers descriptively. As data synthesis is not the primary aim of a scoping review, a formal assessment of methodological quality of the included studies will not performed.

3.6 PATIENT AND PUBLIC INVOLVEMENT:

Because the collected data within this scoping review originates from previously published studies, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

3.7 ETHICS AND DISSEMINATION:

This study does not require primary data collection and no local research ethics board approvals was acquired. The findings of this review and analysis may aid scientists in future clinical trial development and guide future research endeavors, including the development of a formal diagnostic test accuracy systematic review. We will therefore disseminate the findings of our work through conference presentations, the popular press, and a peer-reviewed publication.

3.8 CONCLUSION:

Early hematoma expansion presents a compelling therapeutic target for spontaneous intracerebral hemorrhage. Optimal patient selection is critical to identify those at highest risk of expansion for enrollment into future intracerebral hemorrhage trials. Expansion scores have been proposed as a method to improve patient selection. Our study will inform future clinical trials by systematically assessing the literature to identify and analyze the diagnostic abilities and potential limitations of existing hematoma expansion scores.

This protocol is for an original systematic scoping review, not an update to a previous review.

Author's Contributions:

VY is the guarantor. VY, MM, TR, DF, and DD drafted the manuscript protocol. VY, DF, and DD contributed to the development of the selection criteria, article screening strategy, and data extraction criteria. VY and LS developed the search strategy. All authors read, provided feedback and approved the final protocol.

Competing Interests:

There are no competing interests for any author.

Financial Support/Sponsor Disclosures:

This study did not receive any specific funding or sponsor supports. Dr. Dowlatshahi is supported by a Heart and Stroke Foundation New Investigator Award and a University of Ottawa Department of Medicine Clinician-Scientist Chair.

Acknowledgements:

None

3.9 MANUSCRIPT REFERENCES:

1 Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet (London, England)* 2009;**373**:1632–44. doi:10.1016/S0140-6736(09)60371-8

2 Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol* 2012;**11**:101–18. doi:10.1016/S1474-4422(11)70264-2

3 Dowlatshahi D, Demchuk AM, Flaherty ML, *et al.* Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology* 2011;**76**:1238–44. doi:10.1212/WNL.0b013e3182143317

4 Mayer SA, Brun NC, Begtrup K, *et al.* Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;**352**:777–85. doi:10.1056/NEJMoa042991

5 Anderson CS, Huang Y, Wang JG, *et al.* Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008;**7**:391–9. doi:10.1016/S1474-4422(08)70069-3

6 Mayer SA, Brun NC, Begtrup K, *et al.* Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;**358**:2127–37. doi:10.1056/NEJMoa0707534

7 Qureshi AI, Palesch YY, Barsan WG, *et al.* Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med* 2016;**375**:1033–43. doi:10.1056/NEJMoa1603460

8 Sprigg N, Flaherty K, Appleton JP, *et al.* Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled,

phase 3 superiority trial. *Lancet (London, England)* 2018;**391**:2107–15. doi:10.1016/S0140-6736(18)31033-X

9 Boulouis G, Morotti A, Charidimou A, *et al.* Noncontrast Computed Tomography Markers of Intracerebral Hemorrhage Expansion. *Stroke* 2017;**48**:1120–5. doi:10.1161/STROKEAHA.116.015062

10 Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, *et al.* Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol* 2012;**11**:307–14. doi:10.1016/S1474-4422(12)70038-8

11 Broderick JP, Diringer MN, Hill MD, *et al.* Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* 2007;**38**:1072–5. doi:10.1161/01.STR.0000258078.35316.30

12 Yao X, Xu Y, Siwila-Sackman E, *et al.* The HEP Score: A Nomogram-Derived Hematoma Expansion Prediction Scale. *Neurocrit Care* 2015;**23**:179–87. doi:10.1007/s12028-015-0147-4

13 Huynh TJ, Aviv RI, Dowlatshahi D, *et al.* Validation of the 9-Point and 24-Point Hematoma Expansion Prediction Scores and Derivation of the PREDICT A/B Scores. *Stroke* 2015;**46**:3105–10. doi:10.1161/STROKEAHA.115.009893

14 Wang X, Arima H, Al-Shahi Salman R, *et al.* Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. *Stroke* 2015;**46**:376–81. doi:10.1161/STROKEAHA.114.006910

15 Institute TJB. *Methdology for Scoping Reviews: Joanna Briggs Institute Reviewers' Manual: 2015 edition / Supplement*. Adelaide: : The Joanna Briggs Institute 2015.

16 Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;**4**:1. doi:10.1186/2046-4053-4-1

17 Dowlatshahi D, Brouwers HB, Demchuk AM, *et al.* Predicting Intracerebral Hemorrhage Growth With the Spot Sign: The Effect of Onset-to-Scan Time. *Stroke* 2016;**47**:695–700. doi:10.1161/STROKEAHA.115.012012

3.10 TABLES

Table 1: Search Terms

1. cerebral hemorrhage/ or basal ganglia hemorrhage/ or putaminal hemorrhage/ or cerebral intraventricular hemorrhage/
2. intracranial hemorrhages/ or intracranial hemorrhage, hypertensive/
3. (intracerebral adj2 h?emorrhage*).tw.
4. (h?emorrhagic adj2 stroke*).tw.
5. (cerebral adj3 h?emorrhage*).tw.
6. (putam* adj2 h?emorrhage).tw.
7. (intracerebral adj2 h?ematoma).tw.
8. (basal gangl* adj2 h?emorrhage).tw.
9. (intraventricular adj2 h?emorrhage).tw.
10. (intraventricular adj2 h?ematoma).tw.
11. (basal gangl* adj2 h?ematoma).tw.
12. ICH*.tw.
13. (intracerebral adj3 bleed*).tw.
14. exp hematoma/
15. (h?ematoma* adj2 expansion*).tw.
16. (h?ematoma* adj3 enlarg*).tw.
17. recurrent bleeding.tw.
18. (H?ematoma* adj2 growth).tw.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
20. 14 or 15 or 16 or 17 or 18
21. 19 and 20

4.1 PREFACE:

In this chapter we performed a systematic scoping review of hematoma expansion scores. Ottawa Health Science Network Research Ethics Board approval of this study was not required. Drs. Yogendrakumar, Fergusson, and Dowlatshahi drafted the manuscript and contributed to the development of the selection criteria, article screening strategy, and data extraction criteria. Article screening and data extraction was performed by Drs. Yogendrakumar and Moores. Drs. Ramsay and Shamy revised the manuscript for intellectual content. Dr. Yogendrakumar and Ms. Sikora developed the search strategy. All authors read, provided feedback and approved the final protocol. This chapter incorporates the manuscript: "Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review", currently under review at *Stroke.* A confirmation of submission is available in Appendix II.

Publication: Yogendrakumar V, Moores M, Sikora L, Shamy M, Ramsay T, Fergusson D, Dowlatshahi D. **Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage**: A Systematic Scoping Review. *Stroke.* Under Review (May 2019).

Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review

Vignan Yogendrakumar MD[1], Margaret Moores MD[1], Lindsey Sikora MLIS[2], Michel Shamy MD[1], Tim Ramsay PhD[3], Dean Fergusson PhD[3], Dar Dowlatshahi MD PhD[1]

[1]Department of Medicine (Division of Neurology). University of Ottawa. Ottawa, Ontario, Canada
[2]Health Sciences Library, University of Ottawa. Ottawa, Ontario, Canada
[3]Ottawa Hospital Research Institute. School of Epidemiology, Public Health and Preventative Medicine. University of Ottawa. Ottawa, Ontario, Canada

Corresponding Author:
Dr. Vignan Yogendrakumar

Cover Title: Hematoma Expansion Scores: A Scoping Review
Tables: 4; Figures: 1
Supplemental Tables: 4
Keywords: hematoma, intracerebral hemorrhage, expansion, prognosis, imaging
Subject Terms: Intracranial Hemorrhage
Word Count: 5,352
Abstract Word Count: 293

Figure Legend:
Figure 1: PRISMA Flow Diagram

Table Legend:

Table 1: Characteristics of Included Studies

Table 2: Summary of Hematoma Expansion Prediction Scores

Table 3: Framework for Hematoma Expansion Score Development and Validation

Table 4: Diagnostic Performance of Hematoma Expansion Scores

Online-Only Supplement (Included at end of Chapter):

Table 1: Baseline Patient Characteristics of Development Cohort

Table 2: Baseline Patient Characteristics of Validation Studies

Table 3: Risk of Hematoma Expansion, Stratified by Individual Score Points

4.2 ABSTRACT

Introduction: Multiple hematoma expansion scores, incorporating diverse clinical and radiological parameters, have been proposed for use in clinical and trial environments. It is unclear how these scores perform relative to each other, and which may be more commonly used in clinical research.

Objective: Perform a systematic scoping review to identify all existing hematoma expansion scores and describe their development, validation and relative performance.

Methods: Two reviewers searched MEDLINE, PUBMED, EMBASE, CENTRAL, from date of inception to June 2018. We focused on studies that either derived or validated a prediction score for hematoma expansion in adults presenting with spontaneous ICH. We collected information on patient demographics, medical history, details on score development, diagnostic performance, and usage proportions. We performed a descriptive analysis of the extracted data, focusing on comparing the predictive capability of each score and similarities/differences in score development.

Results: Of the 14,434 records retrieved, 15 studies met inclusion criteria and 10 prediction scores were identified. Individual components observed frequently between scores include "time from symptom onset to computed tomography scan" (6/9), "anticoagulant use" (7/9), and "baseline ICH volume" (4/9). Four studies (Spot Sign Score, 9-Point, PREDICT A/B, Acute ICH Growth Score) used data that required IV contrast use. Validation analysis using independent samples was performed in 9 studies on five scores. All derivation studies reported high performance with c-statistics ranging from 0.72-0.93. In validation, the range was broader with studies reporting c-statistics from 0.62 to 0.77. For every score, the risk of hematoma expansion increased with each point increase, though patients with high scores were rare.

Conclusions: At present, 10 different hematoma expansion scores have been developed. Only five have been externally validated. The validation studies found real world performance to be substantially below than that suggested in the derivation studies.

4.3 INTRODUCTION:

Up to a third of patients who present with acute intracerebral hemorrhage (ICH) are at risk of poor long-term outcomes due to a rapidly expanding hematoma.[1,2] Hematoma expansion (HE) is therefore a therapeutic target in ongoing acute ICH clinical trials.[3,4]

Unfortunately, trials aimed at mitigating HE have had limited success.[5–7] Because not all patients with ICH will exhibit hematoma growth, the effect of treatments targeting HE are potentially diluted. As such, a strategy to select patients at highest risk for HE has led to treatment trials requiring certain radiological markers for enrolment. However, the sensitivity of individual radiological markers varies from study to study and generally exhibit a lower than expected frequency. These factors have led to challenges in meeting enrolment targets.[8]

Efforts to better identify patients for treatment trials have resulted in the development of several prediction scores for HE, incorporating clinical and radiological parameters. However, it is not immediately apparent how these scores have been developed, whether they have been validated, or how they might compare to each other.

Objectives:

The goal of our study is to perform a systematic scoping review to identify all HE scores, describe their development and validation, and compare and contrast their respective diagnostic accuracies.

4.4 METHODS:

Protocol and Registration:

The protocol for this study was first hosted on the University of Ottawa research depository (First available: August 2018; http://hdl.handle.net/10393/38034) and was subsequently published on January 21, 2019.[9] This study was conducted using guideline recommendations developed by the Joanna Briggs Institute[10] and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension statement incorporating the use of scoping reviews.[11]

Eligibility Criteria:

All included articles were required to meet the following criteria:

1. A study population of adult patients (≥ 18 years of age) presenting with spontaneous ICH, confirmed with either computed tomography (CT) or magnetic resonance imaging (MRI).
2. A new HE prediction score was derived, or an existing score was externally validated. An expansion score was defined as a collection of variables (clinical, radiological, or both) that have been identified and weighted such that patients presenting with higher cumulative scores are at a higher risk of exhibiting HE.
3. HE as the primary outcome of interest. Expansion could be reported as the net change in volume or as a dichotomous outcome via a predetermined definition of hematoma expansion (e.g. hematoma enlargement > 6 mL). As several definitions of HE are used in the literature, we did not restrict our search to a specific definition.

As a scoping review, our aim was to look at original studies that derived a score, subsequent studies that validated or compared different scores to each other, and clinical trials or observational cohorts that used these scores as a patient selection tool. As such, we chose to evaluate original research contributions, systematic reviews, meta-analyses, and guideline documents where appropriate. Abstracts from the last 10 years that have not been published in full manuscript form were also screened to ensure completeness.

Studies that were excluded from our review included those involving pediatric patients and patients with ICH secondary to a specific lesion (tumor, vascular malformation, trauma) or with another kind of intracranial hemorrhage (subarachnoid, subdural, epidural). In addition, studies that focused solely on a single clinical or radiological element were excluded from our analysis. Finally, we had no restrictions on country of study, ethnicity, sex, socio-economic status of study populations, or healthcare location of research.

Information Sources and Search:

Four databases were searched: MEDLINE (via Ovid), Embase (via Ovid), PubMed, Cochrane CENTRAL (via Ovid), from date of inception to June 2018. Supplementary searches included scanning the reference list of included studies and reviews identified through the primary search. Please see Chapter 3 for a detailed search strategy using keywords and Medical Subject Headings (MeSH) terms relating to intracerebral haemorrhage and hematoma expansion.

Selection of Sources of Evidence:

A two-stage screening process was performed by two independent reviewers (VY and MM). In stage one, abstracts and titles were screened for potentially relevant articles. In stage two, full-text screening was performed. Reasons for exclusion were required for all studies assessed in the second stage. Screening and full-text review was conducted using Covidence Systematic Review software (Covidence, Melbourne, Victoria, Australia). Disputes were resolved by a third party (DD).

Data Charting Process:

Data charting was conducted independently by each reviewer. All extracted data was verified and confirmed by primary author VY.

Data Items:

We collected basic publication data (e.g. year and journal of publication, authorship list, funding), study population information (demographic and medical history measures), details on score development (variables involved, development or validation methodology), definition of hematoma expansion used, and markers of diagnostic accuracy (c-statistic, calibration, sensitivity/specificity/positive and negative predictive values).

Critical Appraisal of Individual Sources of Evidence

As per current guidelines, a formal assessment of methodological quality was not performed.[9,10]

Synthesis of Results:

Diagnostic summary scores were described qualitatively. Using the prediction rule development hierarchy framework proposed by McGinn and colleagues,[12] we graded each score on their derivation and validation processes. This included collecting detailed information on the derivation techniques used to develop each score and assessing the methods, populations, and outcomes used for score validation. Score performance was compared by c-statistics reported for each study in addition to assessing the incidence of hematoma expansion at each score point.

4.5 RESULTS:

Study Selection and Characteristics:

Among the 14,434 records retrieved, title and abstract screening narrowed our search to 57 articles, 15 of which met inclusion criteria. Reasons for exclusion (Figure 1) included: a lack of described outcome,[13,14] assessment of different outcome, such as mortality,[15] and a lack of full description of a developed score.[16]All included studies were original research contributions using observational cohort or clinical trial data. Aside from a single narrative review looking at select scores,[17] we did not identify alternate studies such as clinical trials, guidelines or systematic reviews/meta-analysis that assessed or discussed HE prediction scores.

Of the 15 included studies, 13 were full length manuscripts and 2 were abstracts. Eight of the 13 manuscripts described the development of scores, while the remaining 5 were solely validation studies of pre-existing scores. Both abstracts described the development of new scores. One of the scores first described in abstract form during our search and included in our study was later published as a full-length manuscript, and so we included the manuscript rather than the abstract. As a result, 14 full length manuscripts[18,19,28–31,20–27] and 1 abstract[32] were subsequently assessed (Table 1). Thirteen of the 15 evaluated studies were performed retrospectively, and nine studies took place at a single center. The median sample size of the derivation and validation cohorts were 323 (Range: 118-964) and 228 (Range: 122-954), respectively. The BRAIN and BAT studies used notably larger patient populations. Almost every study used dichotomous hematoma expansion thresholds: >6mL, >33%, or a combination of both as their primary outcome measure.

Score Details and Development

In total, ten scores were assessed in this review: the Spot Sign Score, 9-Point, BRAIN, PREDICT A/B, HEP, Acute ICH Growth Score, HEAVN, BAT, Basal Ganglia Score, and NAG score. Each score and their point allocations are described in detail in Table 2. The spot sign score was based purely on radiological features; all others used a combination of clinical and radiological data. Four studies (Spot Sign Score, 9-Point, PREDICT A/B, Acute ICH Growth Score) require IV contrast use. Common individual components observed between scores included the "time from onset to computerized tomography (CT)" (6/9), "anticoagulant use" (7/9), and "baseline ICH volume" (4/9). Clinical severity and hematoma characteristics (heterogeneity/blend sign/hypodensities etc.) was utilized in 3 of the 9 scores.

Baseline patient characteristics for each development study are detailed in Supplemental Table 1. The incidence of hematoma expansion (as defined by each study) ranged from 9.8 to 32%. Score development techniques were similar between studies. Almost every study performed exploratory univariate analysis to determine associations between candidate variables and the primary outcome. Using a threshold of either $p<0.10$ or $p<0.05$, candidate variables were then entered into multivariable logistic regression models to adjust for confounding, first order interactions, and co-linearity. Nuances in regression techniques varied between studies and included stepwise modeling and/or bootstrapping. The resultant prediction scores were then created based on the parameter estimates (β coefficients) from the final regression model using techniques previously described by Sullivan[33] and Moons.[34] Three of the nine radiological/clinical scores preselected variables of interest (HEP, HEAVN, BAT).[27–29] The development of the spot sign score varied slightly in the fact that univariate analysis was not

performed. Instead candidate variables, characteristics of spot sign were selected a priori and entered into a logistic model. Details of the Acute ICH Growth Score development are not presently available.

Validation:

Validation analysis using independent samples was performed in 9 studies on five scores: Spot Sign Score, 9-Point, BRAIN, HEAVN, BAT. Baseline patient characteristics for each validation study are detailed on Supplemental Table 2. The spot sign score underwent validation in four separate studies. The BRAIN score, derived using data from the INTERACT2 study[35] was independently validated within the same study using INTERACT1 data[2] and has been subsequently assessed in two additional studies with independently collected data. The 9-Point score was validated by study authors using a separate hospital cohort within the original development study and has since been assessed in separate analysis by Huynh et al. with data from the PREDICT (P*redicting* hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT) observational study.[26] Both the HEAVN and BAT score have not undergone validation in separate studies but underwent validation using separate hemorrhage cohorts by the original development authors. The HEP score was internally validated by resampling from the original derivation dataset.

As per the clinical prediction rule development hierarchy framework,[12] all scores are supported by level 3 to 4 evidence, indicating derivation and validation in similar clinical settings, but with limited validation in broader clinical populations and a lack of assessment on impact to clinical outcomes (Table 3). Impact analysis, defined as an assessment of whether a clinical prediction

rule changes bedside decision making or improves patient outcomes, has not been performed for any of the scores.[12]

Score Performance:

Each study evaluated overall score performance using a combination of the following methods:

- Sensitivity/specificity of individual score points or pre-determined threshold
- Incidence of hematoma expansion as per each score point or pre-determined threshold
- C-Statistics

The majority of studies evaluated score performance with c-statistics and assessment of incidence of hematoma expansion per score point. Due to a relative paucity of studies for each score (1-3 studies per score) and heterogeneity in outcome selected (definition of HE used) we did not conduct a meta-analysis but rather diagnostic summary markers were compared descriptively.

C-statistics of overall score performance are stratified by derivation/validation cohorts in Table 4. All derivation studies reported high performance with c-statistics ranging from 0.72-0.93. In the validation analysis, the range was broader with studies reporting c-statistics from 0.62 to 0.77. The spot sign score reported an c-statistic of 0.93 in its original derivation analysis.[18] A prospective validation analysis reported an c-statistic of 0.91, however a second validation analysis using multicenter data reported a lower c-statistic of 0.63.[21] Both the 9-Point and BRAIN scores reported similar c-statistics in derivation and validation analysis. For every score

evaluated, the risk of hematoma expansion increased with each point increase (Supplemental Table 3), however, patients with high scores made up a minority of patients in each study.

4.6 DISCUSSION:

This systematic scoping review yielded 15 eligible articles pertaining to hematoma expansion prediction scores for patients presenting with an acute intracerebral hemorrhage. The goal of 10/15 articles were to derive a score, while the remaining five focused solely on independently validating pre-existing scores.

The spot sign score was developed in the early years of spot sign's introduction to the literature. Initial performance in single center cohorts was strong, however subsequent assessments with multicenter and prospective cohorts reported reduced c-statistic performance[21] and non-significant associations with hematoma expansion in multivariable modeling.[22] The inclusion of clinical information with the spot sign via the 9-Point score resulted in more consistent predictive performance in external validation (C-Statistic Range: 0.72-0.77).

Notably absent from more recent scores is the utilization of the spot sign. Instead, there has been an increased focus on non-contrast markers such as hypoattenuation, fluid levels, or margin irregularity. This shift away from the spot sign may be due to concerns around its modest and mixed sensitivity in the literature,[22,36] and the recognition that access to IV contrast remains limited in many parts of the world. The complexity of these scores vary widely. Scores such as BAT, and NAG only require data collection of 3 variables, while in contrast, the BRAIN and Basal Ganglia scores require users to collect data on up to 7 variables. The extent of external validation also varies widely: the BRAIN score, performed consistently in validation cohorts (0.62-0.72), yet many of the scores published in the last two years are lacking validation by independent third parties.

While all studies expressed moderate/strong predictive capability, the adoption of these scores outside their original derivation/validation analysis is extremely limited. With the exception of the SCORE-IT sub-study,[22] the application of scores in trial environments or prospective cohorts was not found.

Our assessment identifies several limitations in performance and accessibility that may explain this restricted use and highlights potential areas of improvement for future score development. The majority of scores were developed using logistic regression models and parameter estimates. While this technique is well established, it cannot exclude associations between predictors and outcomes unique to the dataset, in particular when smaller samples are used for derivation. In our review, the majority of the identified articles retroactively analyzed observational data from a single center with small to moderately sized cohorts. Moreover, candidate variables differed significantly between studies, and some predictors solely unique to their respective score were not assessed or used in other scores. Predictor selection idiosyncrasies may be avoided through the use of larger cohorts,[12] and future scores may benefit from pre-selecting variables that have been consistently observed in our review (time to CT, anticoagulant use, and baseline ICH volume) and in a large individual patient data meta-analysis recently performed by Salman and colleagues.[37]

In regard to accessibility, certain scores require imaging expertise beyond what would be expected from frontline staff and, depending on the institution, access to neuroradiology may not be guaranteed. These issues render certain scores difficult to use and create barriers to

accessibility. Fortunately, technological advances such as health record software with embedded clinical decision support mechanisms[38] and automated imaging[39,40] may increase accessibility without disrupting workflow, and help integrate complex expansion scores into the clinical workspace. In addition, our study highlights that even simpler scores (requiring <5 variables of interest) can possess similar predictive potential to their more elaborate counterparts. This allows users to select a score of their preference based on need (bedside use, clinical trial enrolment) or resources (rural, urban, developing regions).

Conclusion:

Our review was able to highlight ten hematoma expansion scores that presently exist in the literature. Only five have been externally validated, and we identified limitations in predictive capabilities when compared to the derivation studies. Although scores have the potential to support clinicians at the bedside and optimize patient selection for future trials, our work highlights the importance of externally validating prediction rules prior to their use in clinical practice or as a selection tool in clinical trials.

ACKNOWLEDGEMENTS:

Drs. Yogendrakumar, Fergusson, and Dowlatshahi designed and conceptualized study and drafted the manuscript for intellectual content. Drs. Yogendrakumar and Moores performed article screening and data extraction. Ms. Sikora developed our search strategy and reviewed the manuscript for intellectual content. Drs. Ramsay, and Shamy assisted with study conceptualization and reviewed the manuscript for intellectual and methodological content.

SOURCES OF FUNDING:

This study had no funding supports. Dr. Yogendrakumar is supported by the Canadian Institute of Health Banting and Best Graduate Scholarship and the Queen Elizabeth II Graduate Scholarship in Science and Technology. Dr. Dowlatshahi is supported by a Heart & Stroke Foundation of Canada Clinician-Scientist Award.

DISCLOSURES:

The study authors have no relevant disclosures

4.7 MANUSCRIPT REFERENCES:

1. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. 2011;76(14):1238-1244. doi:10.1212/WNL.0b013e3182143317
2. Delcourt C, Huang Y, Arima H, et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology*. 2012;79(4):314-319. doi:10.1212/WNL.0b013e318260cbba
3. Liu L, Wang Y, Meng X, et al. Tranexamic acid for acute intracerebral hemorrhage growth predicted by spot sign trial: Rationale and design. *Int J Stroke*. 2017;12(3):326-331. doi:10.1177/1747493017694394
4. Meretoja A, Churilov L, Campbell BC V, et al. The spot sign and tranexamic acid on preventing ICH growth--AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. *Int J Stroke*. 2014;9(4):519-524. doi:10.1111/ijs.12132
5. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet (London, England)*. 2018;391(10135):2107-2115. doi:10.1016/S0140-6736(18)31033-X
6. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358(20):2127-2137. doi:10.1056/NEJMoa0707534
7. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med*. 2016;375(11):1033-1043.

doi:10.1056/NEJMoa1603460

8. Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants. Unmet Needs and Challenges in Clinical Research of Intracerebral Hemorrhage. *Stroke*. 2018;49(5):1299-1307. doi:10.1161/STROKEAHA.117.019541
9. Yogendrakumar V, Moores M, Sikora L, Ramsay T, Fergusson DA, Dowlatshahi D. Evaluating the predictive capabilities of haematoma expansion scores in patients with acute intracerebral haemorrhage: protocol for a scoping review. *BMJ Open*. 2019;9(1):e024744. doi:10.1136/bmjopen-2018-024744
10. Institute TJB. *Methdology for Scoping Reviews: Joanna Briggs Institute Reviewers' Manual: 2015 Edition / Supplement*. Adelaide: The Joanna Briggs Institute; 2015.
11. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850
12. McGinn T, Wyer P, McCullagh L, et al. Clinical Prediction Rules. In: Guyatt GH, Rennie D, Meade MO, Cook DJ, eds. *Users' Guides to the Medical Literature. A Manual For Evidence-Based Clinical Practice*. Third Edit. McGraw-Hill Education; 2008:407-418.
13. Co KA, Navarro J. Assessing clinical outcome using brain score as a predictor of hematoma growth in acute spontaneous intracerebral hemorrhage (ICH) patients in a tertiary hospital in Manila. *J Neurol Sci*. 2017;381:405-406. doi:10.1016/j.jns.2017.08.3358
14. Mu Z, Xue R, Li B, Wang T, Sun M, Gu H. The value of nine points method in the prediction of primary cerebral hemorrhage patients with hematoma enlargement and adverse clinical outcomes. *J Am Geriatr Soc*. 2015;63:S323-S410. doi:10.1111/jgs.13704

15. Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke*. 2010;41(1):54-60. doi:10.1161/STROKEAHA.109.565382

16. Di Napoli M, Meligeni F, Gentileschi E, et al. A prediction score for hematoma expansion following acute vitamin K antagonist associated intracerebral hemorrhage (VKA-ICH). *Thromb Res*. 2014;134(Suppl 2).

17. Chen S, Zhao B, Wang W, Shi L, Reis C, Zhang J. Predictors of hematoma expansion predictors after intracerebral hemorrhage. *Oncotarget*. 2017;8(51):89348-89363. doi:10.18632/oncotarget.19366

18. Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. *Stroke*. 2009;40(9):2994-3000.

19. Romero JM, Heit JJ, Delgado Almandoz JE, et al. Spot sign score predicts rapid bleeding in spontaneous intracerebral hemorrhage. *Emerg Radiol*. 2012;19(3):195-202. doi:10.1007/s10140-012-1020-9

20. Romero JM, Brouwers HB, Lu J, et al. Prospective validation of the computed tomographic angiography spot sign score for intracerebral hemorrhage. *Stroke*. 2013;44(11):3097-3102. doi:10.1161/STROKEAHA.113.002752

21. Huynh TJ, Demchuk AM, Dowlatshahi D, et al. Spot sign number is the most important spot sign characteristic for predicting hematoma expansion using first-pass computed tomography angiography: analysis from the PREDICT study. *Stroke*. 2013;44(4):972-977.

doi:10.1161/STROKEAHA.111.000410

22. Morotti A, Brouwers HB, Romero JM, et al. Intensive Blood Pressure Reduction and Spot Sign in Intracerebral Hemorrhage: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Neurol*. 2017;74(8):950-960. doi:10.1001/jamaneurol.2017.1014
23. Brouwers HB, Chang Y, Falcone G, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. *JAMA Neurol*. 2014;71(2):158-164. doi:10.1001/jamaneurol.2013.5433
24. Wang X, Arima H, Al-Shahi Salman R, et al. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. *Stroke*. 2015;46(2):376-381. doi:10.1161/STROKEAHA.114.006910
25. VanDerWerf J, Kurowski D, Siegler J, Ganguly T, Cucchiara B. Combination of Intra-Hematomal Hypodensity on CT and BRAIN Scoring Improves Prediction of Hemorrhage Expansion in ICH. *Neurocrit Care*. February 2018. doi:10.1007/s12028-018-0507-y
26. Huynh TJ, Aviv RI, Dowlatshahi D, et al. Validation of the 9-Point and 24-Point Hematoma Expansion Prediction Scores and Derivation of the PREDICT A/B Scores. *Stroke*. 2015;46(11):3105-3110. doi:10.1161/STROKEAHA.115.009893
27. Yao X, Xu Y, Siwila-Sackman E, Wu B, Selim M. The HEP Score: A Nomogram-Derived Hematoma Expansion Prediction Scale. *Neurocrit Care*. 2015;23(2):179-187. doi:10.1007/s12028-015-0147-4
28. Miyahara M, Noda R, Yamaguchi S, et al. New Prediction Score for Hematoma Expansion and Neurological Deterioration after Spontaneous Intracerebral Hemorrhage: A Hospital-Based Retrospective Cohort Study. *J Stroke Cerebrovasc Dis*. 2018;27(9):2543-2550. doi:10.1016/j.jstrokecerebrovasdis.2018.05.018

29. Morotti A, Dowlatshahi D, Boulouis G, et al. Predicting Intracerebral Hemorrhage Expansion With Noncontrast Computed Tomography: The BAT Score. *Stroke*. 2018;49(5):1163-1169. doi:10.1161/STROKEAHA.117.020138

30. Huang Y, Zhang Q, Yang M. A reliable grading system for prediction of hematoma expansion in intracerebral hemorrhage in the basal ganglia. *Biosci Trends*. 2018;12(2):193-200. doi:10.5582/bst.2018.01061

31. Sakuta K, Sato T, Komatsu T, et al. The NAG scale: Noble Predictive Scale for Hematoma Expansion in Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis*. 2018;27(10):2606-2612. doi:10.1016/j.jstrokecerebrovasdis.2018.05.020

32. Al-Ajlan F, Demchuk AM, Aviv RI, et al. The Acute ICH Growth Score: Simple and Accurate Predictor of Hematoma Expansion in Patients with Acute Intracerebral Hemorrhage. *Stroke*. 2017;48(AWP372).

33. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med*. 2004;23(10):1631-1660. doi:10.1002/sim.1742

34. Moons KGM, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients? *J Clin Epidemiol*. 2002;55(10):1054-1055. http://www.ncbi.nlm.nih.gov/pubmed/12464384.

35. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355-2365. doi:10.1056/NEJMoa1214609

36. Du F-Z, Jiang R, Gu M, He C, Guan J. The Accuracy of Spot Sign in Predicting Hematoma Expansion after Intracerebral Hemorrhage: A Systematic Review and Meta-

Analysis. Keep R, ed. *PLoS One*. 2014;9(12):e115777. doi:10.1371/journal.pone.0115777

37. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. 2018;17(10):885-894. doi:10.1016/S1474-4422(18)30253-9

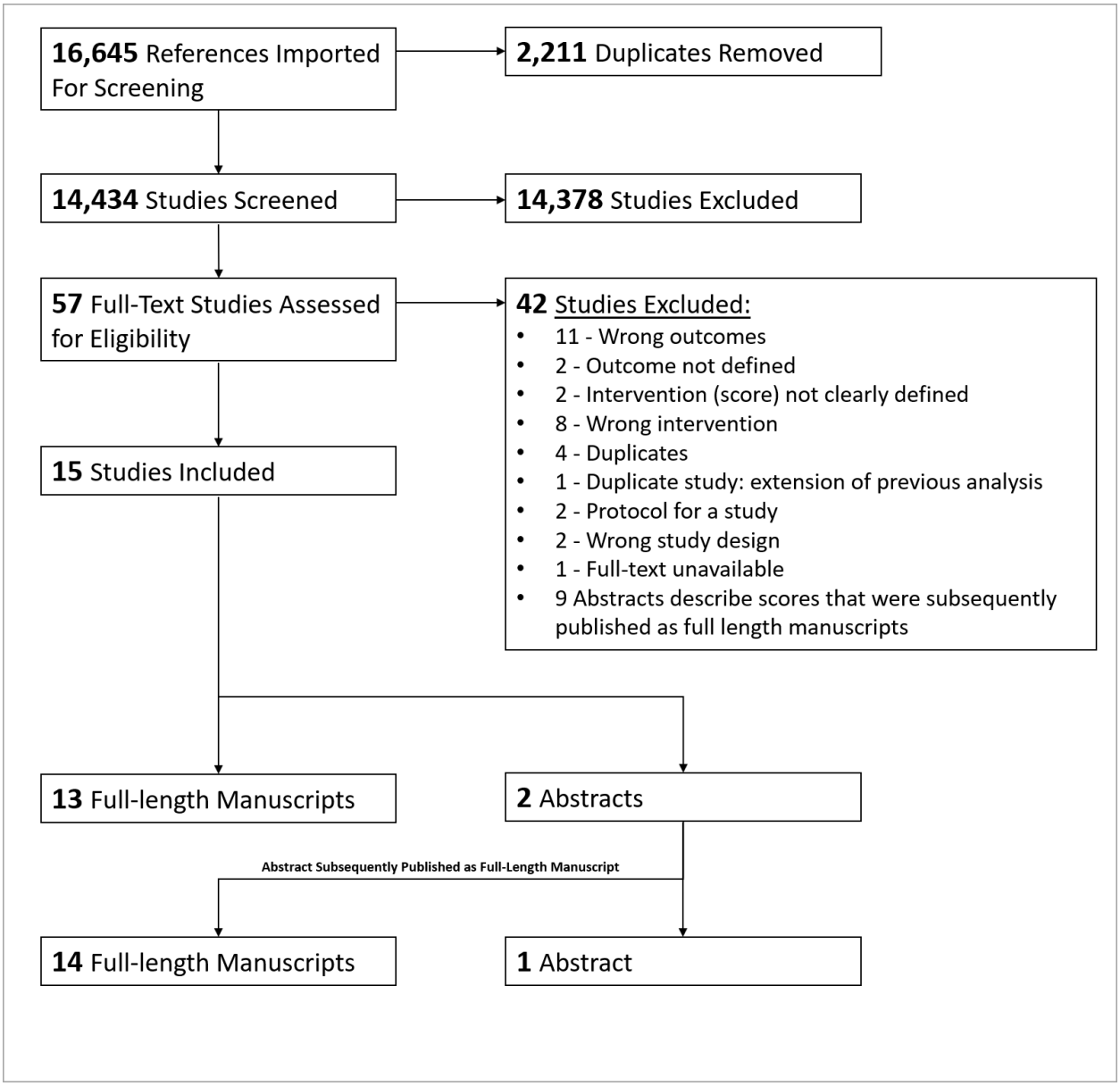
38. Bookman K, West D, Ginde A, et al. Embedded Clinical Decision Support in Electronic Health Record Decreases Use of High-cost Imaging in the Emergency Department: EmbED study. *Acad Emerg Med*. 2017;24(7):839-845. doi:10.1111/acem.13195

39. Krishnan K, Mukhtar SF, Lingard J, et al. Performance characteristics of methods for quantifying spontaneous intracerebral haemorrhage: data from the Efficacy of Nitric Oxide in Stroke (ENOS) trial. *J Neurol Neurosurg Psychiatry*. 2015;86(11):1258-1266. doi:10.1136/jnnp-2014-309845

40. Scherer M, Cordes J, Younsi A, et al. Development and Validation of an Automatic Segmentation Algorithm for Quantification of Intracerebral Hemorrhage. *Stroke*. 2016;47(11):2776-2782. doi:10.1161/STROKEAHA.116.013779

4.8 FIGURES

Figure 1: PRISMA Flow Diagram



4.9 TABLES

Table 1: Characteristics of Included Studies

Author, year	Score	Study Design	Number of Centers	Derivation	Derivation Sample Size	Independent Validation*	Validation Sample Size	Primary Outcome
Full-Length Manuscripts								
Delgado Almandoz (2009)[18]	Spot Sign Score	Retrospective	Single	Yes	367	No	-	>6 mL or > 30%
Romero (2012)[19]	Spot Sign Score	Retrospective	Single	No	-	Yes	367	ICH expansion rate (mL/hr)
Romero (2013)[20]	Spot Sign Score	Prospective	Single	No	-	Yes	131	>6 mL or > 33%
Huynh (2013)[21]	Spot Sign Score	Retrospective	Multicenter	No	-	Yes	228	>6 mL or > 33%
Morotti (2017)[22]	Spot Sign Score	Prospective	Multicenter	No	-	Yes	133	>33%
Brouwers (2014)[23]	9-Point	Retrospective	Single	Yes	817	Yes	195	>6 mL or > 33%
Wang (2015)[24]	BRAIN	Retrospective	Multicenter	Yes	964	Yes	346	>6 mL
VanDerWerf (2018)[25]	BRAIN	Retrospective	Single	No	-	Yes	122	>6 mL
Huynh (2015)[26]	9-Point BRAIN PREDICT A/B	Retrospective	Multicenter	Yes (PREDICT A/B)	301	Yes (9-Point and BRAIN)	301	>6 mL or > 33%
Yao (2015)[27]	HEP	Retrospective	Single	Yes	237	No	-	>6 mL or > 33%
Miyahara (2018)[28]	HEAVN	Retrospective	Single	Yes	457	Yes	165	> 33% or 5 mm of the maximum

								diameter from baseline CT
Morotti (2018)[29]	BAT	Retrospective	Multicenter	Yes	344	Yes	954/241	>6 mL or > 33%
Huang (2018)[30]	Basal Ganglia Score	Retrospective	Single	Yes	266	No	-	>6 mL or > 33%
Sakuta (2018)[31]	NAG Score	Retrospective	Single	Yes	118	No	-	>6 mL or > 33%
Abstracts								
Al-Ajlan (2017)[32]	Acute ICH Growth Score	Retrospective	Multicenter	Yes	301	No	-	>6 mL or > 33%

*Defined as validation in an independent sample of patients. Split sampling was not considered as independent validation

Table 2: Summary of Hematoma Expansion Prediction Scores

Score	**Components**
Spot Sign Score Total Score: 4	Number of spot signs: 1 to 2 – **1**; ≥3 – **2** Maximum axial dimension: 1-4mm – **0**; ≥5mm – **1** Maximum attenuation: 120-179 HU – **0**; ≥180 – **1**
9-Point Total Score: 9	Warfarin use: Present – **2**; Absent – **0** Time to initial CT: <6 hours – **2**; >6 hours – **0**; Baseline hemorrhage volume, mL: <30 - **0**; 30-60 - **1**; >60 - **2** CT Angiography spot sign: Present - **3**; Absent - **0**; Unavailable – **1**
24-Point (BRAIN) Total Score: 24	Baseline ICH volume: <10mL – **0**; 10-20mL – **5**; >20 – **7** Recurrent ICH: Present – **4**; Absent – **0** Anticoagulation Use: Present – **6**; Absent – **0** IVH: Present – **2**; Absent – **0** Hours to baseline CT from symptom onset: for each hour **5 to 0**
PREDICT A/B Total Score: 23 (A), 28 (B)	Hours to baseline CT from symptom onset: for each hour **5 to 0** Warfarin Use: Present – **6**; Absent – **0** CTA Spot Sign Number: ≥ 2 spots – **8**; 1 spot – **4**; none – **0** GCS: 14-15 – **0**; ≤13 – **4** [A-Score] NIHSS: 0-4 – **0**; 5-14 – **4**; ≥15 – **7** [B-Score]
HEP Total Score: 18	Time from onset to scan: < 3 hours: Present – **3**; Absent – **0** Dementia: Present – **4**; Absent – **0** Current Smoking: Present – **3**; Absent – **0** Antiplatelet Use: Present – **3**; Absent – **0** GCS Score: (3-5; **3**/6-8; **2**/ 9-11; **1**/ 12-15; **0**) SAH on CT: Present – **2**; Absent – **0**
HEAVN Total Score: 8	Heterogeneity: Present – **2**; Absent – **0** Peripheral Edema: Present – **1**; Absent – **0** Anticoagulant Use: Present – **2**; Absent – **0** Volume>30 mL: Present – **1**; Absent – **0** Niveau Formation: Present – **2**; Absent – **0**
BAT Total Score: 5	Blend Sign Present: Present – **1**; Absent – **0** Any Hypodensity: Present – **2**; Absent – **0** Time onset to CT < 2.5 hours: Present – **2**; Absent – **0**
Basal Ganglia Score Total Score: 7	Hours from onset to CT (h) <6: Present – **1**; Absent – **0** Baseline ICH volume (mL) ≥30: Present – **1**; Absent – **0** Island sign present : Present – **1**; Absent – **0** Blend sign present: Present – **1**; Absent – **0** Swirl sign present: Present – **1**; Absent – **0** Anticoagulant use or an INR > 1.5: Present – **1**; Absent – **0** IVH extension present: Present – **1**; Absent – **0**
NAG Score Total Score: 3	Anticoagulant Use: Present – **1**; Absent – **0** NIHSS ≥ 10: Present – **1**; Absent – **0** Serum Glucose ≥133 mg/dL: Present – **1**; Absent – **0**
Acute ICH Growth Score	Ultra-early hematoma grow > 5 mL/hour: Present – **1**; Absent – **0** Irregular morphology: Present – **1**; Absent – **0**

Total Score: 7	Density Heterogeneity: Present – **1**; Absent – **0** Presence of Fluid-blood Levels: Present – **1**; Absent – **0** Spot Sign: Present – **1**; Absent – **0** Anticoagulant Use: Present – **2**; Absent – **0**

Table 3: Framework for Hematoma Expansion Score Development and Validation

Score	Derivation	Narrow Validation*	Broad Validation†	Impact Analysis	Level of Evidence
Spot Sign Score	X	X	-	-	3
9-Point	X	X	-	-	3
24-Point (BRAIN)	X	X	-	-	3
PREDICT A/B	X	-	-	-	4
HEP	X	-	-	-	4
HEAVN	X	X	-	-	3
BAT	X	X	-	-	3
Basal Ganglia Score	X	-	-	-	4
NAG Score	X	-	-	-	4
Acute ICH Growth Score‡	-	-	-	-	n/a

*Defined as the application of a score in a similar setting and population as the derivation cohort

†Defined as the application of the score in a multiple settings with varying outcomes assessed

‡Denotes scores developed and published in abstract format only

Table 4: Diagnostic Performance of Hematoma Expansion Scores

		Derivation Cohorts	Validation Cohorts
Score	**Outcome**	**Performance C-Index (95% CI)**	**Performance C-Index (95% CI)**
Spot Sign Score	>6 mL or > 30%	0.93 (0.89-0.95)[18]	-
	>6 mL or > 33%	-	0.93 (0.89-0.95)[20] 0.68 (0.61-0.74)[21]
9-Point	>6 mL or > 33%	0.72 (95% CI NR)[23]	0.77 (95% CI NR)[23] 0.71 (0.65-0.77)[26]
	>6 mL	-	0.76 (0.70-0.82)[26]
BRAIN	>6 mL	0.73 (95% CI NR)[24]	0.73 (95% CI NR)[24] 0.62 (95% CI NR)[25] 0.76 (0.69-0.81)[26]
	>6 mL or > 33%	-	0.67 (0.61-0.74)[26]
	≥12.5 mL	-	0.76 (0.69-0.83)[26]
PREDICT A/B	>6 mL or > 33%	PREDICT A – 0.78 (0.73-0.84)[26] PREDICT B – 0.77 (0.72-0.83)[26]	-
	>6 mL	PREDICT A – 0.82 (0.77-0.88) PREDICT B – 0.80 (0.75-0.86)	
	≥12.5 mL	PREDICT A – 0.86 (0.80-0.91) PREDICT B – 0.84 (0.78-0.89)	
HEP	>6 mL or > 33%	0.74 (0.67-0.81)[27]	-
HEAVN	> 33% or 5 mm of the maximum diameter from baseline CT	0.81(95% CI NR)[28]	0.80 (95% CI NR)[28]

BAT	>6 mL or > 33%	0.77 (0.70-0.83)	Validation Cohort 1: 0.65 (0.61-0.68) Validation Cohort 2: 0.70 (0.64-0.77)
Basal Ganglia Score	>6 mL or > 33%	NR	-
NAG	>6 mL or > 33%	0.81 (0.72-0.90)	-
Acute ICH Growth Score	>6 mL or > 30%	0.76 (95% CI NR)	-

Abbreviations: NR = not reported

4.11 SUPPLEMENTAL TABLES

Supplementary Table 1: Baseline Patient Characteristics of Development Cohort

	Spot Sign Score[18] (n=367)	9-Point[23] (n=817)	BRAIN[24]		PREDICT A/B[26] (n=301)	HEP[27] (n=237)	HEAVN[28]		BAT[29] (n=344)	Basal Ganglia Score[30]		NAG Score[31]
Hematoma Expansion (HE)	56 (15%)	156 (19%)	HE (n=181)	No HE (n=783)	97 (32%)	74 (31%)	HE (n=45)	No HE (n=412)	62 (18%)	HE (n=99)	No HE (n=167)	30 (25%)
Age	Reported as categorical variable	72 (13)	67 (56-76)*	67 (55-77)*	70 (57-80)*	73 (59-82)*	63 (15)	66 (18)	70 (13.7)	59.6 (10.4)	58.4 (11.5)	63 (54-73)*
Male (n, %)	214 (58%)	456 (55%)	123 (68%)	483 (62%)	179 (59%)	140 (59%)	29 (64%)	238 (57%)	188 (55%)	56 (56%)	117 (70%)	78 (66%)
Hypertension (n,%)	237 (65%)	645 (79%)	129 (71%)	558 (71%)	62 (21%)	174 (77%)	NR	NR	281 (82%)	NR	NR	92 (78%)
Time to CT hours (mean, SD)	Reported as categorical variable	5.0 (2.6-8.3)*	1.7 (1.2-2.4)*	1.8 (1.3-2.7)*	2.3 (1.5-3.6)*	21.4 (10.6-42.7)*	NR	NR	3.1 (1.6-4.8)*	5 (4-8)*	6 (5-8)*	2.1 (1.5-5.9)*
Anticoagulant Use (n,%)	NR	173 (21%)	21 (12%)	30 (4%)	29 (10%)	55 (23%)	5 (11%)	16 (4%)	NR	27 (27%)	17 (10%)	8 (7%)
Antiplatelet Use (n,%)	116 (32%)	345 (43%)	33 (18%)	129 (17%)	29 (10%)	94 (39%)	8 (18%)	57 (14%)	NR	NR	NR	11 (9%)
SBP (mmHg)	NR	179 (154-200)*	180 (17.4)	179 (16.8)	NR	175 (152-197)*	170 (138-207)*	177 (157-202)	182 (36)	NR	NR	180 (166-203)*
DBP (mmHg)	NR	NR	99 (15.7)	98 (15.5)	NR	90 (80-104)*	NR	NR	97 (26)	NR	NR	105 (90-117)*
Baseline ICH Volume (mL)	Reported as categorical variable	16 (7-37)*	17.9 (11.3-29.4)*	9.3 (4.8-16.6)*	12.5 (6.3-26.0)*	Reported as categorical variable	Reported as categorical variable	Reported as categorical variable	15.0 (7.4-29.0)*	16.3 (8.4-29.3)*	14.8 (6.9-22.6)*	9.7 (4.2-19.2)*

Mean (SD) unless otherwise specified. *median (IQR) // Abbreviations: CT=computed tomography, SBP=systolic blood pressure, DBP=diastolic blood pressure, ICH=intracerebral hemorrhage

Supplementary Table 2: Baseline Patient Characteristics of Validation Studies

	Spot Sign Score				9-Point	BRAIN				HEAVN		BAT[29]	
	Romero 2012[19] (n=367)	Romero 2013[20] (n=131)	Huynh 2013[21] (n=228)	Morotti 2017[22] (n=133)	Brouwers 2014[23] (n=195)	Wang 2015[24] (n=346)		VanDerWerf 2018[25] (n=122)	PREDICT A/B[26] (n=301)	Miyahara 2018[28] (n=165)		Validation 1 (n=954)	Validation 2 (n=241)
Hematoma Expansion (HE)	0.8 (5.1) mL/h	25 (19%)	73 (23%)	24 (19.5%)	31 (16%)	HE (n=43)	No HE (n=303)	52 (43%)	97 (32%)	HE (n=22)	No HE (n=143)	236 (25%)	71 (30%)
Age	66 (15)	72 (15)	69 (14)	62 (13)	71 (15)	60 (47-69)*	64 (53-73)*	63 (13)	70 (57-80)*	76 (13)	68 (15)	62 (13)	66 (15)
Male (n, %)	213 (58%)	79 (61%)	130 (57%)	83 (62%)	107 (55%)	28 (65%)	194 (64%)	65 (53%)	179 (59%)	15 (68%)	87 (61%)	590 (62%)	145 (60%)
Hypertension (n,%)	250 (68%)	92 (70%)	NR	77/96 (80%)	NR	34 (79%)	221 (73%)	109 (89%)	62 (21%)	NR	NR	754 (79%)	171 (71%)
Time to CT hours (mean, SD)	2.4 (3.3)	13.7 (8.7)	2.3 (1.5-3.8)*	1.8 (0.9)	5.8 (3.5-8.5)*	1.4 (1.0-1.8)*	1.8 (1.1-2.6)*	2 (1-3.3)*	2.3 (1.5-3.6)*	NR	NR	1.4 (1.0-2.2)*	2.3 (1.5-3.3)*
Anticoagulant Use (n,%)	59 (16%)	24 (18%)	NR	NR	40 (21%)	2 (5%)	1 (0%)	16 (13%)	29 (10%)	5 (13%)	15 (4%)	NR	NR
Antiplatelet Use (n,%)	117 (32%)	46 (35%)	NR	NR	NR	5 (12%)	22 (7%)	44 (36%)	29 (10%)	3 (14%)	22 (15%)	NR	NR
SBP (mmHg)	NR	NR	NR	204 (25)	NR	187 (17)	180 (18)	192 (36)	NR	170 (138-207)*	177 (157-202)	201 (27)	175 (32)
DBP (mmHg)	NR	NR	NR	NR	NR	107 (14)	102 (14)	NR	NR	NR	NR	111 (21)	95 (19)
Baseline ICH Volume (mL)	31.3 (33.7)	26.1 (28)	12.4 (5.8-24.5)*	10.5 (0.7-65.5)	15 (6-44)*	17.9 (9.1-30.0)*	8.7 (4.5-14.7)*	12.8 (5.8-23.4)*	12.5 (6.3-26.0)*	Categorical variable	Categorical variable	10.2 (5.1-18.2)*	11.9 (6.2-24.1)*

Mean (SD) unless otherwise specified

*median (IQR)

Abbreviations: CT=computed tomography, SBP=systolic blood pressure, DBP=diastolic blood pressure, ICH=intracerebral hemorrhage

Supplemental Table 3: Risk of Hematoma Expansion, Stratified by Individual Score Points

Score	Outcome	Derivation Cohorts	Validation Cohorts	
Spot Sign Score	>6 mL or > 30%[18]	0: 6/296 (2.0) 1: 6/ 18 (33.0) 2: 9/18 (50.0) 3: 17/18 (94.0) 4:17/17 (100.0)	-	
	Rate of ICH Expansion[19]	-	0: ~0 mL/hr 1: 0.50 mL/hr 2: 1.00 mL/hr 3: 3.50 mL/hr 4: 16 mL/hr	
	>6 mL or > 33%	-	Romero et al.[20] 0: 8.5% 1: 42% 2: 54% 3: 50% 4: 100%	Huynh et al.[21] 0: 36/167 (21.6%) 1: 14/25 (56.0%) 2: 14/22 (63.6%) 3: 7/10 (70.0%) 4: 2/4 (50.0%)
	>33%	-	Relative Risk[22] 0: 1.02 (0.31-3.38), p=0.96 (n=80) 1: 1.11 (0.18-6.94), p=0.91 (n=27) ≥2: 0.75 (0.18-3.19), p=0.70 (n=26)	
9-Point	>6 mL or > 33%	Brouwers et al.[23] 0: 4/70 (5.7) 1: 12/108 (11.1) 2: 15/196 (7.7) 3: 35/16 (17.9) 4: 32/108 (29.6) 5: 29/82 (35.4) 6: 15/28 (53.6) 7: 10/22 (45.5) 8: 0/2 (0.0) 9: 4/5 (80.0)	Brouwers et al.[23] 0: 1/17 (5.9) 1: 2/38 (5.3) 2: 1/44 (2.3) 3: 9/40 (22.5) 4: 2/24 (8.3) 5: 10/16 (62.5) 6: 0/6 (0.0) 7: 5/9 (55.6) 8: 1/1 (100.0) 9: N/A	Huynh et al.[26] 2: 30/168 (17.9%) 3: 7/24 (29.2%) 4: 11/22 (50.0%) 5: 25/45 (55.6%) 6: 13/26 (50.0%) 7: 9/13 (69.2%) 8: 2/3 (66.7%)

BRAIN	>6 mL	Wang et al.[24] 0: 3.4% 1: 4.2% 2: 5.1% 3: 6.3% 4: 7.7% 5: 9.4% 6: 11.3% 7: 13.7% 8: 16.4% 9: 19.5% 10: 23.1% 11: 27.2%	12: 31.6% 13: 36.4% 14: 41.5% 15: 46.7% 16: 52.1% 17: 57.4% 18: 62.5% 19: 67.4% 20: 71.9% 21: 76.0% 22: 79.7% 23: 83.0% 24: 85.8%	Huynh et al.[26] 0-4: 4/82 (4.9) 4-8: 12/68 (17.6) 9-12: 40/118 (33.9) 13-16: 16/25 (64.0) 17-24: 3/8 (37.5)	VanDerWeerf et al.[25] 0-5: 11 6-9: 23 10-11: 43 12-24: 57
	>6 mL or > 33%	-		VanDerWeerf et al.[25] 0-5: 32 6-9: 35 10-11: 52 12-24: 57	
PREDICT A/B[26]	>6 mL or > 33%	0-2: 4/56 (7.1) 3-5: 18/99 (18.2) 6-8: 25/68 (36.8) 9-11: 13/23 (56.5) 12-14: 23/35 (65.7) 15-23: 14/20 (70.0)	0-5: 3/54 (5.6) 6-10: 25/114 (21.9) 11-15: 37/85 (43.5) 16-20: 21/33 (63.6) 21-28: 11/15 (73.3)	-	
HEP[27]	>6 mL or > 33%	0: (8.9) 1: (21.0) 2: 42.0 3: 66.3 4: 84.3 5: 93.6 6: 97.5 7: 99.1 8: 99.7 9: 99.9 ≥10 (100.0)		-	
HEAVN[28]	> 33% or 5 mm of the maximum diameter from baseline CT	0-2: 15/374 (4.0) 3-4: 25/77 (32.4) 5-6: 5/6 (83.3)		0-2: 12/137 (8.7) 3-4: 5-6: 3/5 (60.0)	
BAT[29]	>6 mL or > 33%	0-1: 14/193 (7.3)		0-1: 15/145 (10.3)	0-1: 3/46 (6.5)

		2: 17/90 (18.9) 3: 10/22 (45.5) 4: 18/35 (51.4) 5: 3/4 (75.0)	2: 114/541 (21.1) 3: 14/44 (31.8) 4: 74/192 (38.5) 5: 19/32 (59.4)_	2: 18/83 (21.7) 3: 8/17 (47.1) 4: 26/65 (40.0) 5: 16/30 (53.3)
Basal Ganglia Score[30]	>6 mL or > 33%	0: 1/29 (3.5) 1: 13/71 (18.3) 2: 27/83 (32.5) 3: 30/49 (61.2) 4: 19/24 (79.2) 5: 6/7 (85.7) ≥6: 3/3 (100)	-	
NAG[31]	>6 mL or > 33%	0: 4% 1: 25% 2: 60% 3: 100%	-	
Acute ICH Growth Score[32]	>6 mL or > 30%	0: 0/0 (0.0) 1: 4/44 (9.1) 2: 10/78 (12.8) 3: 20/87 (23.0) 4: 40/68 (58.8) 5: 9/16 (56.2) 6: 4/7 (57.1) 7: 2/3 (66.7)	-	

CHAPTER 5: INDEPENDENT VALIDATION OF A NON-CONTRAST HEMATOMA EXPANSION PREDICTION SCORE

5.1 PREFACE:

In this chapter, we independently validated the Hematoma Expansion Prediction (HEP) score, a nomogram-derived prediction scale, using data from a prospectively collected intracerebral hemorrhage cohort, and performed a comparative analysis comparing the predictive capability of the HEP score to a commonly used contrast marker, the Spot Sign. Local research ethics board approval was obtained at the enrolling sites of this dataset and therefore Ottawa Health Science Network Research Ethics Board approval for this study was not required.

Drs. Yogendrakumar, Ramsay, Selim, and Dowlatshahi were responsible for study concept, design and statistical analysis. Drs. Yogendrakumar and Dowlatshahi were responsible for drafting the manuscript. All other authors participated in acquisition of data and in critical revisions of the manuscript for intellectual content. This chapter presents the manuscript "Independent Validation of the Hematoma Expansion Prediction (HEP) Score: A Non-Contrast Score Equivalent in Accuracy to the Spot Sign". This manuscript was accepted for publication in *Neurocritical Care* in May 2019. A publisher's PDF of this manuscript is available in Appendix III.

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Selim M, Dowlatshahi D. **Independent Validation of the Hematoma Expansion Prediction (HEP) Score: A Non-Contrast Score Equivalent in Accuracy to the Spot Sign**. *Neurocritical Care.* Published ahead of print: May 2019. doi.org/10.1007/s12028-019-00740-5

Independent Validation of the Hematoma Expansion Prediction (HEP) Score: A Non-Contrast Score Equivalent in Accuracy to the Spot Sign

Authors: Vignan Yogendrakumar MD[1], Tim Ramsay PhD[2,3], Dean A Fergusson PhD[2,3], Andrew M Demchuk MD[4], Richard I Aviv MBChB[5], David Rodriguez-Luna MD[6], Carlos A Molina MD PhD[6], Yolanda Silva Blas MD PhD[7], Imanuel Dzialowski MD[8], Adam Kobayashi MD PhD[9], Jean-Martin Boulanger MD[10], Cheemun Lum MD*, Gord Gubitz MD[11], Padma Srivastava MD[12], Jayanta Roy MD[13], Carlos S. Kase MD[14], Rohit Bhatia MD[12], Michael D Hill MD MSc[4], Magdy Selim MD PhD[15], and Dar Dowlatshahi MD PhD[1,3], On behalf of the PREDICT/Sunnybrook CTA Study Group

*Deceased

[1]Ottawa Stroke Program. Department of Medicine (Neurology), University of Ottawa, Ottawa, Canada

[2]Ottawa Methods Center, University of Ottawa, Ottawa, Canada

[3]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada

[4]Calgary Stroke Program, Department of Clinical Neurosciences, Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

[5]Division of Neuroradiology and Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

[6]Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[7]Department of Neurology, Dr. Josep Trueta University Hospital, Institut d'Investigació Biomèdica Girona (IDIBGi) Foundation, Girona, Spain

[8]Department of Neurology, Elblandklinikum Meissen Academic Teaching Hospital of the Technische University, Dresden, Germany

[9]2nd Department of Neurology, Institute of Psychiatry and Neurology, and Department of Experimental and Clinical Pharmacology, Warsaw, Poland

[10]Department of Medicine, Charles LeMoyne Hospital, University of Sherbrooke, Longueuil, Canada

[11]Department of Neurology, Dalhousie University, Halifax, Canada

[12]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

[13]Apollo Gleneagles Hospitals, Kolkata

[14]Department of Neurology, Boston Medical Center, Boston, USA

[15]Department of Neurology, Beth Israel Deaconess Medical Centre, Boston, USA

Figures Legend:

Figure 1: Receiver Operating Characteristic Curve

Tables Legend:

Table 1: Hematoma Expansion Prediction Score Summary

Table 2: Baseline Patient Characteristics

Table 3: Multiple Logistic Regression (HEP as a Continuous Variable)

Table 4: Diagnostic Capabilities of Spot Sign and HEP Score

Table 5: Direct Comparisons of Hematoma Expansion (HEP) Score and Spot Sign

Supplement (Included At End of Chapter):

Supplementary Table 1: Univariate Predictors of Hematoma Expansion

Supplementary Table 2: Diagnostic Performance of HEP Score

DETAILS:

This manuscript complies with the instructions provided by *Neurocritical Care.* All authors meet the requirements for authorship. Their roles and contributions to this manuscript are listed below:

Name	Location	Contribution
Vignan Yogendrakumar, MD	University of Ottawa	Protocol/Project development; Data Analysis; Manuscript writing/editing
Tim Ramsay PhD	University of Ottawa	Data Analysis; Manuscript writing/editing
Andrew M Demchuk MD	University of Calgary	Data collection or management
Richard I Aviv MBChB	University of Toronto	Data collection or management
David Rodriguez-Luna MD	Hospital Universitari Vall d'Hebron	Data collection or management
Carlos A Molina MD PhD	Hospital Universitari Vall d'Hebron	Data collection or management
Yolanda Silva Blas MD	Dr. Josep Trueta University Hospital	Data collection or management
Imanuel Dzialowski MD	Technische University	Data collection or management
Adam Kobayashi MD PhD	2nd Department of Neurology, Warsaw Poland	Data collection or management
Jean-Martin Boulanger MD	University of Sherbrooke	Data collection or management
Cheemun Lum MD	University of Ottawa	Data collection or management
Gord Gubitz MD	Dalhousie University	Data collection or management
Padma Srivastava MD	All India Institute of Medical Sciences	Data collection or management
Jayanta Roy MD	Apollo Gleaneagles Hospital	Data collection or management
Carlos S. Kase MD	Boston Medical Center	Data collection or management
Rohit Bhatia MD	All India Institute of Medical Sciences	Data collection or management
Michael D. Hill MD	University of Calgary	Data collection or management; Manuscript writing/editing
Dean Fergusson PhD	University of Ottawa	Manuscript writing/editing
Magdy Selim MD PhD	Harvard University	Protocol/Project development; Manuscript writing/editing
Dar Dowlatshahi MD PhD	University of Ottawa	Protocol/Project development; Data Analysis; Manuscript writing/editing

The final manuscript has been approved by all authors. This manuscript has not been published elsewhere and is not under consideration by another journal.

Study Sponsorship or Funding:

There was no support for this work.

Ethics: Local research ethics board approval was obtained at all enrolling sites and written informed consent was obtained from all participants.

Trial registration number: n/a

Conflict of Interest Disclosures:

Dr. Yogendrakumar has nothing to disclose.

Dr. Ramsay has nothing to disclose.

Dr. Fergusson has nothing to disclose.

Dr. Demchuk reports grants from NovoNordisk Canada, during the conduct of the study; .

Dr. Aviv has nothing to disclose.

Dr. Rodriguez-Luna has nothing to disclose.

Dr. Molina has nothing to disclose.

Dr. Silva has nothing to disclose.

Dr. Dzialowski has nothing to disclose.

Dr. Kobayashi has nothing to disclose.

Dr. Boulanger reports other from Pfizer, other from Novartis, outside the submitted work.

Dr. Lum has deceased.

Dr. Gubitz has nothing to disclose.

Dr. Srivastava has nothing to disclose.

Dr. Kase has nothing to disclose.

Dr. Roy has nothing to disclose.

Dr. Hill reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, grants from Covidien (Medtronic), grants from Boehringer-Ingleheim, grants from Stryker Inc., grants from Medtronic LLC, grants from NoNO Inc., outside the submitted work; In addition, Dr. Hill has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, National Institutes of Neurological Disorders and Stroke.

Dr. Bhatia has nothing to disclose.

Dr. Selim reports grants from NIH/NINDS, during the conduct of the study.

Dr. Dowlatshahi has nothing to disclose.

5.2 ABSTRACT

Background and Purpose: The CTA spot sign is widely used to assess the risk of hematoma expansion following acute intracerebral hemorrhage (ICH). However, not all patients can receive intravenous contrast nor are all hospital systems equipped with this technology. We aimed to independently validate the Hematoma Expansion Prediction (HEP) Score, an 18-point non-contrast prediction scale, in an external cohort and compare its diagnostic capability to the CTA spot sign.

Methods: We performed a retrospective analysis of the PREDICT-ICH Cohort Study. Primary outcome was significant hematoma expansion (≥6mL or ≥33%). We generated a receiver operating characteristic (ROC) curve comparing the HEP score to significant expansion. We calculated sensitivity, specificity, positive and negative predictive values (PPV/NPV) for each score point. We determined independent predictors of significant hematoma expansion via logistic regression.

Results: 292 patients were included in primary analysis. Hematoma growth of ≥6mL or ≥33% occurred in 94 patients (32%). The HEP score was associated with significant expansion (adjusted odds ratio [aOR]: 1.14, 95% Confidence Interval [CI]: 1.01-1.30). ROC curves comparing HEP score to significant expansion had an area under the curve of 0.64 (95% CI: 0.57-0.71). Youden's method showed an optimum score of 4. HEP Scores ≥ 4 (n=100, Sensitivity 49%, Specificity 73%, PPV 46%, NPV 75%, aOR 1.99, 95% CI: 1.09-3.64) accurately predicted significant expansion. PPV increased with higher HEP scores, but at the cost of lower sensitivity. The diagnostic characteristics of the spot sign (n=82, Sensitivity 49%, Specificity 81%, PPV 55%, NPV 76%, aOR 2.95, 95% CI: 1.61-5.42) were similar to HEP scores ≥ 4.

Conclusion: The HEP score is predictive of significant expansion (≥6mL or ≥33%) and is comparable to the spot sign in diagnostic accuracy. Non-contrast prediction tools may have a potential role in the recruitment of patients in future ICH trials.

5.3 INTRODUCTION:

Hematoma expansion is a major contributor to the morbidity and mortality associated with intracerebral hemorrhage (ICH).[1] Current therapeutic approaches have had limited success in preventing hematoma expansion and improving outcomes. As only a proportion of patients experience hematoma expansion, optimizing patient selection to identify those at highest risk of expansion can increase the success of future trials.[2]

Several baseline variables are associated with hematoma expansion, and have been incorporated into prediction scores for bedside use.[3–6] Prediction scores allow selection of high risk patients for enrollment in treatment trials, and can also help clinicians identify patients at highest risk of deterioration. However, many scores require the use of intravenous (IV) contrast.[5] While the use of CT has increased worldwide, access to IV contrast remains limited in certain jurisdictions. Most scores also require an accurate measurement of baseline ICH volume, which is a limiting factor for primary stroke centers who may not have 24-hour access to neuro-radiological expertise.[5–7] As a result, the wide-spread implementation of these scores for trial recruitment or bedside practice is not always possible, and potentially limited to comprehensive care centers with advanced stroke expertise. An easy to use non-contrast prediction tool could be used to improve trial recruitment and may significantly improve triaging and resource allocation for primary stroke centers and acute stroke-ready community hospital systems.

The Hematoma Expansion Prediction (HEP) Score is an 18-point nomogram-derived non-contrast scale based on patient characteristics that can be easily acquired at the bedside.[8] We aimed to independently validate this tool, and to evaluate its predictive potential against the spot

sign, a CT-angiogram marker of hematoma expansion currently used in ongoing intracerebral hemorrhage treatment trials.[9]

5.4 SUBJECTS and METHODS:

Patients were participants in the Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study.[10] Local research ethics board approval was obtained at all enrolling sites and written informed consent was obtained from all participants. The dataset is available for access to all PREDICT investigators and qualified researchers trained in human subject confidentiality protocols collaborating with PREDICT investigators.

Patients:

Patients were participants consecutively enrolled from June 2006 to July 2012 into PREDICT, a prospective multicenter observational study of patients presenting with spontaneous ICH under 6 hours. Patients had baseline CT and CT-angiogram (CTA), follow-up imaging at 24 hours post-event, and serial clinical assessments. Exclusion criteria was ICH >100mL, known renal impairment precluding CTA, baseline modified Rankin scale >3, or terminal illness. For this study, patients who lacked follow-up imaging or information related to HEP scoring were excluded. Also excluded were patients who received recombinant Factor VIIa or had craniotomy for hematoma evacuation or ventricular drainage prior to repeat imaging, as these interventions directly affect final hemorrhage volume at follow-up assessment.

Primary Exposure and Primary Outcome:

The primary exposure was the HEP score at initial presentation. The HEP score is an 18-point nomogram is dependent on six variables: 1) time to CT, 2) dementia history, 3) smoking status, 4) antiplatelet use, 5) Glasgow coma scale, and 6) presence of subarachnoid hemorrhage.[8] The

points allocated to each variable are highlighted in TABLE 1. Five of the six variables were originally collected by PREDICT-ICH investigators during primary data collection at the time of first presentation (time from symptom onset to CT, dementia status, smoking status, antiplatelet use, baseline GCS). Dementia status was not distinguished by sub-type. Authors VY and DD assessed subarachnoid hemorrhage by reviewing baseline imaging data of all enrolled patients. Subarachnoid hemorrhage was defined as the presence of subarachnoid blood either adjacent or distinct to the primary hematoma. HEP scores were then calculated for each patient. The primary outcome of this study was significant hematoma expansion, defined as an absolute ICH growth of ≥ 6 mL or a relative growth of ≥ 33% on follow-up imaging.[11] Because varying definitions of hematoma growth may be used, the performance of the HEP score was also tested with another commonly used definition of hematoma expansion (≥ 12.5 mL or ≥ 33%) in a sensitivity analysis.

Statistical Analysis:

A receiver operating characteristic (ROC) curve was generated by comparing HEP scores of each patient to the primary outcome. An area under the curve (AUC) with 95% confidence intervals (95% CI) was computed using stratified bootstrap replicates. We calculated the sensitivity, specificity, positive and negative predictive values for each score point. In addition, the method of Youden was used to derive a mathematically optimal threshold score. Because the optimal cut-point derived from Youden's method is not an integer, several score thresholds were selected for further analysis. Multivariable logistic regression was used to adjust for potential confounding. Candidate covariates were derived with exploratory univariate analysis. Fisher's exact test, ANOVA, or Mann-Whitney U tests were used as appropriate ($p < 0.10$). Continuous

variables that did not conform to the linearity assumption were re-categorized into dichotomous or ordinal variables.[12] Potential interactions were assessed using Wald or likelihood ratio testing. Baseline ICH volume, anticoagulant use, and spot sign are known major predictors of hematoma expansion[13] and were therefore forced into multivariable models *a priori*. Dichotomous threshold scores and the overall score (as a continuous variable) were both evaluated. Competing model accuracies expressed as AUCs were compared using deLong's method.[14] To further investigate the generalizability of the HEP score, the occurrence of each individual variable that makes up patient's individual HEP scores were calculated and the associations between each individual variable and hematoma expansion was also explored.

In post hoc analysis, spot sign was compared to the HEP score further by assessing the differences in predictive capability of patients who were spot sign positive but did not have sufficiently high HEP scores, to patients who were HEP ≥ 3 or HEP ≥ 4 and spot sign negative. We looked for a potential biological interaction (synergism) when combining spot sign with high threshold HEP scores through testing of relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S) measures. In addition, both HEP score (as an ordinal variable) and spot sign were entered into linear regression models to better determine whether either variable is associated with hematoma growth that may be below pre-determined thresholds. Statistical analysis was performed using SPSS v24.0 (IBM, Armonk, NY) and SAS v9.4 (SAS Institute Inc, Cary, NC).

5.5 RESULTS:

The PREDICT study prospectively enrolled 390 patients presenting with spontaneous ICH. Of these, 98 were excluded from our study: 17 patients were excluded due to delayed presentation or having an alternative diagnosis other than spontaneous ICH (e.g. tumour). Twenty-four patients did not receive baseline or follow-up imaging. Thirty-one patients were treated with recombinant FVIIa treatment or surgical intervention prior to follow-up imaging, and 26 patients lacked data on Glasgow coma scale or subarachnoid hemorrhage status. Our primary analysis population included 292 patients. The occurrence of each variable associated with the HEP score is outlined in TABLE 1. Presentation within 3 hours of symptom onset was observed in 65% of the primary analysis cohort. The presence of the other variables only ranged from 3 to 19%. Baseline patient characteristics are outlined in TABLE 2. Those excluded were similar to the primary analysis cohort on measured baseline factors. However, patients excluded from this study had larger baseline ICH and intraventricular (IVH) volumes.

Thirty-two percent (94/292) of the PREDICT cohort exhibited significant hematoma expansion. Exploratory analysis revealed associations between the primary outcome and anticoagulant use, history of previous stroke, baseline national institute of health stroke scale (NIHSS), partial thromboplastin time (PTT), serum creatinine, HEP score, baseline ICH volume, and spot sign status ($p<0.1$, Supplement Table 1). PTT, baseline ICH volume, and baseline NIHSS did not meet linearity assumptions. As such, PTT was re-categorized as a dichotomous variable, >35 seconds. Baseline ICH volume was re-categorized as: <10, 10-30, >30 mL, reflecting past ICH analysis by Dowlatshahi et al.[15,16] and large meta-analysis findings by Al-Shahi and colleagues.[13] Baseline NIHSS was re-categorized as ≤5, 6-13, ≥14.[17] Adjusting for the relevant co-variates,

including spot sign, each 1-point increase in the HEP score was associated with a 14% increased odds of significant hematoma expansion (TABLE 3). Similar results were observed in a sensitivity analysis using ≥ 12.5 mL or ≥ 33% as the definition of significant expansion (83 expansion events, aOR: 1.13 per 1-point increase, 95% CI: 0.99-1.29). A ROC curve comparing HEP score to significant expansion possessed an AUC of 0.64 (FIGURE 1). The discriminative capability of the HEP score was similar to the spot sign (AUC=0.65, p=0.68).

The calculated sensitivities, specificities, positive and negative predictive values of each HEP score point is summarized in Supplement Table 2. Positive predictive values increased with increasing scores, and sensitivity decreased correspondingly. As per the method of Youden, the mathematically optimal HEP threshold score was at 3.5. This clinically corresponds to HEP scores of 3 or 4. Two hundred and nineteen (75%) patients had HEP scores ≥ 3. One hundred patients (34%) had HEP scores ≥ 4. After adjusting for the relevant co-variates, threshold scores of ≥ 3 and ≥ 4 were associated with significant hematoma expansion (HEP ≥ 3: adjusted Odds Ratio [aOR]: 2.13, 95% Confidence Intervals [CI]: 1.04-4.37 // HEP ≥ 4: aOR: 2.13, 95% CI: 1.19-380). The diagnostic performance of spot sign was marginally better than that of the threshold scores (TABLE 4). The model c-statistics of both HEP ≥ 3 and HEP ≥ 4 were similar to the spot sign (0.73 vs. 0.76, p=0.16; 0.74 vs. 0.76, p=0.44). There was no clear difference in predictive performance when patients who were solely spot sign positive were directly compared to spot sign negative patients with HEP scores ≥ 4 in regression modeling (TABLE 5). Combining spot sign with the HEP score did not appear to have a synergistic effect on predicting significant hematoma expansion. In a univariate linear model, HEP score was significantly associated with any hematoma expansion (Parameter estimate: 0.88; p=0.03). After adjusting for

the relevant co-variates, HEP score was not significantly associated with any hematoma expansion. In contrast, spot sign presence was associated with any hematoma expansion, even after adjusting for the relevant covariates (Parameter estimate: 9.86; $p<0.05$).

5.6 DISCUSSION:

We aimed to independently validate the HEP score and compare its predictive potential to the commonly used CTA spot sign. Our study used a real-world, pragmatic, observational ICH population with study subjects originating from 6 different countries (Canada, USA, Germany, Poland, Spain, and India) and data collected prospectively at the time of presentation. Our findings show that the HEP score independently predicts significant hematoma expansion and has similar test characteristics to the spot sign.

Our base findings reflect that of Yao and colleagues' original study on the HEP score. Baseline patient characteristics between the development cohort and the primary analysis population were largely similar. There was a higher proportion of warfarin use and a higher median ICH volume reported in the development cohort,[8] which is likely due to the exclusion of patients with hemorrhage volumes >100 mL in the PREDICT study. Thirty-two percent of patients exhibited significant expansion, which is in keeping with prior reports and with the original development cohort.[8,18–20] We found that HEP scores > 3 were at highest risk of expansion and our calculated c-statistics were similar to that of the development cohort.[8] The consistency in these findings support the generalizability of the HEP score.

By using the PREDICT study, we were able to compare the performance of HEP to that of the CTA spot sign. TABLE 4 highlights our key findings and highlights that HEP scores ≥ 4 exhibited similar sensitivities/specificities to that of the spot sign. Spot sign had an improved specificity, but the discriminative capacity, indicated by the model c-statistics, were virtually identical. In addition, our post-hoc analysis did not show a superiority in predictive performance

between spot sign and HEP score in direct comparison. These findings are in keeping with previous studies[4,7] and lend support to the notion that non-contrast predictive models have the capability of predicting hematoma expansion with an accuracy that can match the spot sign. Moreover, the proportion of patients observed with HEP scores ≥ 4 was greater than those observed with spot sign (34.2% vs 28.3% respectively). Given spot sign ICH trials have experienced recruitment challenges (STOP-IT, NCT00810888/SPOTLIGHT, NCT01359202), non-contrast tools such as HEP may be a compelling alternative.

Al-Shahi and colleagues recently identified baseline hemorrhage volume, time to CT, antiplatelet and anticoagulant use, and spot sign, as predictors of hematoma expansion in a large individual patient data meta-analysis.[13] The HEP score complements these findings by utilizing two of the four major variables (antiplatelet use and early time to CT). As baseline hematoma volume assessment and IV contrast use may be challenging in primary stroke centers, the HEP score may act as a suitable substitute tool to use in these particular scenarios. Our findings show that the HEP score was predictive of significant expansion, independent of anti-coagulant use. Anti-coagulant use is well associated with hematoma expansion and rapid reversal has already been shown to improve outcomes.[21]

The components of the HEP score can be automatically calculated using information available in modern electronic medical records (EMR). This allows for its use as an EMR-based clinical decision rule or an automated clinical support application, analogous to VIZ.ai and MaxQ AI. Such applications can facilitate acute care decision making in the neurocritical care setting.

Our study has several limitations. Unlike the development cohort used by Yao and colleagues, the PREDICT cohort reported significantly lower rates of dementia and antiplatelet use.[8] The former may be explained by the fact that the majority of ICH in the PREDICT cohort were non-lobar (70%), and therefore less likely to be associated with conditions such as amyloid angiopathy or dementia.[22,23] The incidence of subarachnoid hemorrhage was comparable, but the number of patients with a time to CT < 3 hours was significantly higher in the PREDICT population. Further work in a larger dataset is warranted to ensure generalizability. In addition, data around the early withdrawal of care was not available in this cohort. This introduces the potential for bias as these patients can be excluded from analysis due to lack of follow-up imaging. We also could not rule out a selection bias when excluding patients who underwent surgery or received hemostatic agents. Indeed, the primary difference between those included vs. excluded from primary analysis was the higher ICH and IVH volumes observed in those, which is an independent predictor of hematoma expansion.[13,15,24,25] Finally, while our study validates the use of HEP score to predict pre-specified hematoma expansion definitions, it does not imply that its components are directly related to the mechanistic aspects or pathophysiology of hematoma expansion. We see evidence of this in our post-hoc linear regression analysis, where after adjusting for confounding, the HEP score is not associated with a range of hematoma growth. The HEP score, and the majority of other scores developed, was primarily designed to assess a threshold of hematoma expansion and these findings provide useful information regarding the limitations of this type of predictive modeling.

CONCLUSION:

In an independent, real-world cohort we confirmed that the HEP score is predictive of significant hematoma expansion. The HEP score is comparable to the spot sign in diagnostic accuracy and frequency when a threshold of significant expansion is used and may have a role in recruitment for future ICH treatment trials. However, the HEP score is limited in predictive capabilities when assessing lesser amounts of hematoma expansion.

Acknowledgements:

None

5.7 MANUSCRIPT REFERENCES:

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet (London, England) 2009;373(9675):1632–44.

2. Gonzales NR. Ongoing clinical trials in intracerebral hemorrhage. Stroke 2013;44(6 Suppl 1):S70-3.

3. VanDerWerf J, Kurowski D, Siegler J, Ganguly T, Cucchiara B. Combination of Intra-Hematomal Hypodensity on CT and BRAIN Scoring Improves Prediction of Hemorrhage Expansion in ICH. Neurocrit Care [Internet] 2018;Available from: http://www.ncbi.nlm.nih.gov/pubmed/29411303

4. Morotti A, Dowlatshahi D, Boulouis G, et al. Predicting Intracerebral Hemorrhage Expansion With Noncontrast Computed Tomography: The BAT Score. Stroke [Internet] 2018;49(5):1163–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29669875

5. Huynh TJ, Aviv RI, Dowlatshahi D, et al. Validation of the 9-Point and 24-Point Hematoma Expansion Prediction Scores and Derivation of the PREDICT A/B Scores. Stroke 2015;46(11):3105–10.

6. Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. Stroke 2010;41(1):54–60.

7. Wang X, Arima H, Al-Shahi Salman R, et al. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. Stroke 2015;46(2):376–81.

8. Yao X, Xu Y, Siwila-Sackman E, Wu B, Selim M. The HEP Score: A Nomogram-Derived Hematoma Expansion Prediction Scale. Neurocrit Care 2015;23(2):179–87.

9. Meretoja A, Churilov L, Campbell BC V, et al. The spot sign and tranexamic acid on preventing ICH growth--AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. Int J Stroke 2014;9(4):519–24.

10. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurol 2012;11(4):307–14.

11. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology [Internet] 2011;76(14):1238–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21346218

12. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28(5):964–74.

13. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol 2018;17(10):885–94.

14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837–45.

15. Dowlatshahi D, Smith EE, Flaherty ML, et al. Small intracerebral haemorrhages are

associated with less haematoma expansion and better outcomes. Int J Stroke 2011;6(3):201–6.

16. Dowlatshahi D, Yogendrakumar V, Aviv RIRI, et al. Small intracerebral hemorrhages have a low spot sign prevalence and are less likely to expand. Int J Stroke 2016;11(2):191–7.

17. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke 2003;34(1):134–7.

18. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. Lancet Neurol 2012;11(1):101–18.

19. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 1996;27(10):1783–7.

20. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 1997;28(1):1–5.

21. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA 2015;313(8):824–36.

22. Cordonnier C, Leys D, Dumont F, et al. What are the causes of pre-existing dementia in patients with intracerebral haemorrhages? Brain 2010;133(11):3281–9.

23. Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid

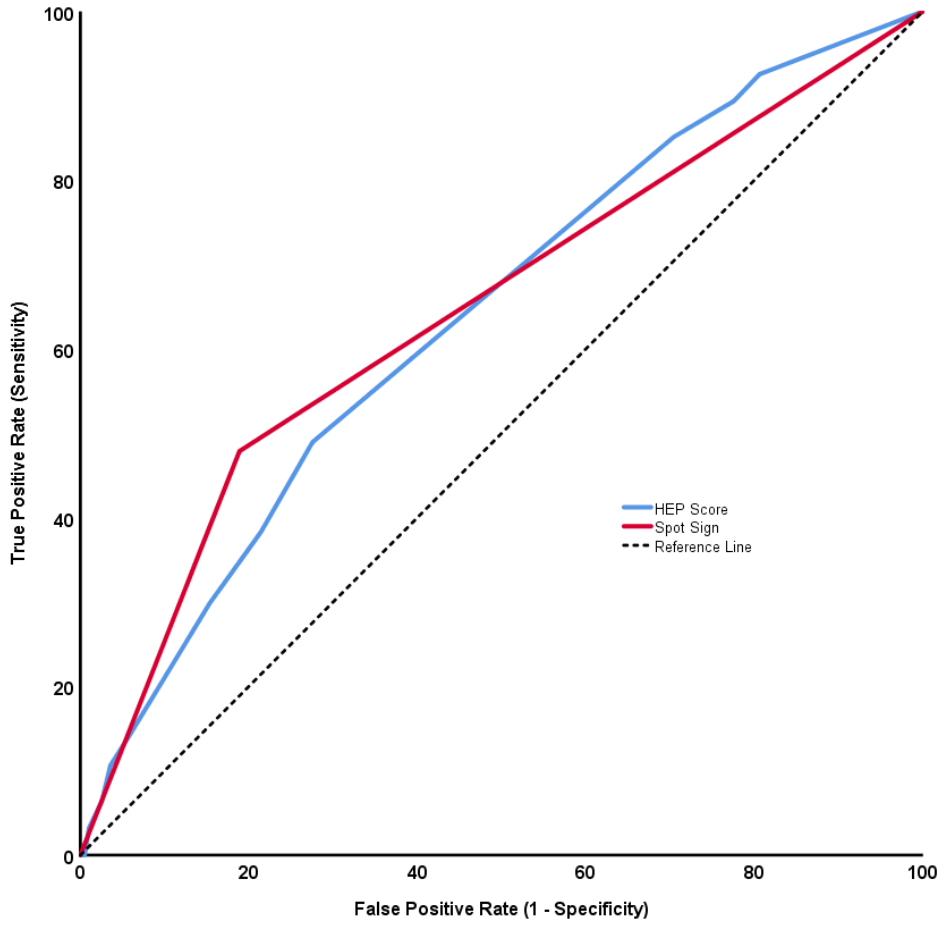
angiopathy: model development and diagnostic test accuracy study. Lancet Neurol 2018;17(3):232–40.

24. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast Computed Tomography Markers of Intracerebral Hemorrhage Expansion. Stroke 2017;48(4):1120–5.

25. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993;24(7):987–93.

5.8 FIGURES

Figure 1: Receiver Operating Characteristic Curve Comparing Hematoma Expansion Prediction (HEP) Score and Spot Sign to Significant Hematoma Expansion (≥6 mL or ≥33%). HEP Score, Area under the curve (AUC): 0.64 (95% Confidence Interval: 0.57-0.71). Youden's Index: 3.5. Spot Sign, AUC: 0.65 (95% Confidence Interval: 0.58-0.72).



5.9 TABLES

Table 1: Summary of the Hematoma Expansion Prediction Score

Risk Factor	**Categories**	**Point**	**Occurrence in PREDICT Cohort (n=292)**
Time to baseline CT < 3 hours	No	0	34.9%
	Yes	3	65.1%
Diagnosis of Dementia	No	0	94.5%
	Yes	4	5.5%
Current Smoker	No	0	88.4%
	Yes	3	11.6%
Antiplatelet Drug Use	No	0	90.1%
	Yes	3	9.9%
GCS Score at Presentation	3-5	3	0.3%
	6-8	2	3.1%
	9-11	1	14.7%
	12-15	0	81.8%
SAH at baseline	No	0	81.2%
	Yes	2	18.8%

Abbreviations: CT: Computed Tomography, GCS: Glasgow coma scale, SAH: subarachnoid hemorrhage

Table 2: Baseline Patient Characteristics of the Primary Analysis Cohort

Characteristics	**Included (N = 292)**	**Excluded (N = 98)**	**P**
Age, years (median; IQR)	71 (57-80)	68 (56-78)*	0.47
Male Sex (n, %)	174 (60%)	55/97 (57%)	0.61
Medical History (n, %)			
Hypertension	218 (75%)	59/97 (61%)	0.01
Coronary Artery Disease	30 (10%)	7/52 (14%)	0.49
Congestive Heart Failure	5 (2%)	0/52 (0%)	0.34
Atrial Fibrillation	29 (10%)	6/52 (12%)	0.83
Hypercholesterolaemia	62 (21%)	15/52 (29%)	0.22
Diabetes Mellitus	54 (19%)	7/52 (14%)	0.38
Anticoagulant Usage	26 (9%)	11/97 (11%)	0.48
Previous Stroke	26 (9%)	8/52 (15%)	0.15
Prior Hemorrhage	11 (4%)	3/52 (6%)	0.50
Baseline Clinical Information (median; IQR)			
Systolic Blood Pressure, mmHg	173 (150-196)	172 (147-200)‡	0.89
Diastolic Blood Pressure, mmHg	93 (80-109)	82 (81-110)‡	0.43
Glucose, mmol/L	7 (6-9.1)*	7 (6-8.6)§	0.99
National Institute of Health Stroke Scale	14 (7-18)†	14 (7-20)†	0.33
premorbid modified Rankin Score	0 (0-0)‡	0(0-0)#	0.18
International normalized ratio	1.0 (1.0-1.1)§	1.0 (0.9-1.2)§	0.92
Partial Thromboplastin Time, seconds	29 (27-32)| |	30 (28-34)* *	0.02
Platelets, $x10^9$ cells per L	221 (180-272)‡	241 (203-299)[h]	0.06
Creatinine, μmol/L	77 (65-92)‡	80 (65-93)[i]	0.39
Hematoma Expansion Scale Characteristics			
Time to CT, minutes (median; IQR)	142 (90-223)	130 (80-257)*	0.91
Dementia (n, %)	16 (6%)	0/52 (0%)	0.08
Current Smoker (n, %)	34 (12%)	8/52 (15%)	0.45
Antiplatelet Usage (n, %)	29 (10%)	10/97 (10%)	0.91
Glasgow Coma Scale (median, IQR)	15 (13-15)	14 (10-15)[j]	0.02
Subarachnoid Hemorrhage (n, %)	55 (19%)	25/93 (27%)	0.09
HEP Score (median; IQR)	3 (2-5)	4 (3-6)[k]	0.03
Imaging (median; IQR)			
ICH Volume, mL	12.1 (6.1-25.9)	18.7 (9.9-44.6)[l]	<0.01
IVH Volume, mL	0.0 (0-1.9)	1.0 (0.0-8.4)[l]	<0.01
Spot Sign Positive	82/290 (28%)	34/96 (35%)	0.19

Equal variances not assumed for students t-tests

[*]Missing 1 value, †Missing 2 values, ‡Missing 3 values, §Missing 4 values, | |Missing 7 values, #Missing 49 values * *Missing 11 values [h]Missing 5 values [i]Missing 50 values, [j]Missing 51 values, [k]Missing 55 values, [l]Missing 8 values

Abbreviations: IQR: Interquartile Range. HEP: Hematoma Expansion Prediction Score. ICH: Intracerebral Hemorrhage. IVH: Intraventricular Hemorrhage.

Table 3: Multivariable-Adjusted Relationship Between HEP Score (as a Continuous Variable) and Significant Hematoma Expansion

Variable	**Adjusted OR**	**95% CI**
HEP Score	1.14	1.01-1.30
Spot Sign	2.71	1.47-5.00
Anticoagulant Use	5.01	1.96-12.78
Creatinine	1.01	1.00-1.02
National Institute of Health Stroke Scale		
≤ 5 (Ref)	-	-
6-13	1.44	0.55-3.79
≥14	2.93	1.11-7.08
Baseline Intracerebral Hemorrhage Volume		
<10 mL (Ref)	-	-
10-30 mL	1.13	0.54-2.35)
> 30 mL	1.07	0.44-2.57

C-Statistic: 0.77, Hosmer and Lemeshow Goodness-of-Fit: p=0.76

Table 4: Diagnostic Capabilities Of Spot Sign and HEP Score

	Frequency	**Sensitivity (%)**	**Specificity (%)**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**	**Adjusted OR (95% CI)***	**Model C-Statistic**
Spot Sign	82 (28.3%)†	47.9	81.1	54.9	76.4	2.95 (1.61-5.42)	0.76
HEP ≥ 3	219 (75.0%)	85.1	29.8	36.5	80.8	2.14 (1.04-4.41)	0.73
HEP ≥ 4	100 (34.2%)	48.9	72.7	46.0	75.0	1.99 (1.09-3.64)	0.74

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10-30 mL, > 30 mL), and baseline National Institute of Health Stroke Scale (≤5, 6-13, ≥14).

†Missing 2 values

Table 5: Direct Comparisons of Hematoma Expansion (HEP) Score and Spot Sign

	Adjusted OR (95% CI)*		**Adjusted OR (95% CI)***
Spot Sign - & HEP < 3	Ref	**Spot Sign - & HEP < 4**	Ref
Spot Sign + & HEP < 3	13.38 (2.33-77.01)	**Spot Sign + & HEP < 4**	3.79 (1.68-8.59)
Spot Sign - & HEP ≥ 3	3.06 (1.22-7.73)	**Spot Sign - & HEP ≥ 4**	2.56 (1.19-5.51)
Spot Sign + & HEP ≥ 3	7.08 (2.62-19.16)	**Spot Sign + & HEP ≥ 4**	5.86 (2.45-14.08)
Additive Measures (95% CI)			
RERI	-8.37 (-30.42 – 13.69)	**RERI**	0.51 (-4.43 – 5.36)
AP	-1.18 (-4.21 – 1.85)	**AP**	0.09 (-0.70 – 0.87)
S Index	0.42 (0.09 – 1.89)	**S Index**	1.12 (0.40 – 3.16)

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10-30 mL, > 30 mL) and baseline National Institute of Health Stroke Scale (≤5, 6-13, ≥14)

5.10 SUPPLEMENT TABLES:

Table 1: Univariate Analysis of Significant Hematoma Expansion

Variable	**Sig. HE (n=94)**	**No Sig. HE (n=198)**	**P-Value**
Age, years (median; IQR)	72 (61-82)	70 (56-80)	0.347
Male Sex (n, %)	56 (60%)	118 (60%)	0.997
Medical History (n, %)			
Hypertension	71 (76%)	147 (74%)	0.813
Coronary Artery Disease	10 (11%)	20 (10%)	0.888
Congestive Heart Failure	2 (2%)	3 (2%)	0.706
Hypercholesterolaemia	14 (15%)	48 (16%)	0.068
Diabetes Mellitus	18 (19%)	36 (18%)	0.842
Anticoagulant Usage	17 (18%)	9 (5%)	<0.001
Previous Stroke	14 (15%)	12 (6%)	0.013
Prior Hemorrhage	4 (4%)	7 (3%)	0.763
Baseline Clinical Information (median; IQR)			
Systolic Blood Pressure, mmHg	170 (144-190)	177 (155-198)	0.067
Diastolic Blood Pressure, mmHg	93 (75-106)	93 (82-110)	0.277
Glucose, mmol/L	6.9 (5.8-8.9)	7.1 (6.0-9.1)	0.572
NIH Stroke Scale	17 (12-19)	11 (6-17)	<0.001
premorbid modified Rankin Score	0 (0-0)	0 (0-0)	0.614
International normalized ratio	1.03 (1-1.3)	1.04 (1-1.1)	0.208
Partial Thromboplastin Time, seconds	30 (28-33)	29 (27-31)	0.026
Platelets, $x10^9$ cells per L	210 (165-267)	224 (185-276)	0.250
Creatinine, μmol/L	80 (67-94)	75 (63-90)	0.063
Hematoma Expansion Scale Characteristics			
Time to CT, minutes (median; IQR)	119 (81-196)	150 (100-230)	0.004
Dementia (n, %)	7 (7%)	9 (5%)	0.309
Current Smoker (n, %)	14 (15%)	20 (10%)	0.233
Antiplatelet Usage (n, %)	14 (15%)	15 (8%)	0.051
Glasgow Coma Scale (median, IQR)	14 (11-15)	15 (13-15)	0.001
Subarachnoid Hemorrhage (n, %)	23 (25%)	32 (16%)	0.090
HEP Score (median; IQR)	3 (3-6)	3 (2-4)	<0.001
Imaging			
ICH Volume, mL (median; IQR)	18.50 (8.97 – 32.92)	10.19 (4.79-22.63)	<0.001
IVH Volume, mL (median; IQR)	0 (0-3.7)	0 (0-1.28)	0.358
Spot Sign Positive (n, %)	45 (48%)	37/196 (19%)	<0.001

Supplement Table 2: Diagnostic Performance of the HEP Score

Score Threshold	**Sensitivity (%)**	**Specificity (%)**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**
≥ 1	92.6	19.7	29.8	84.8
≥ 2	89.4	22.7	35.4	81.8
≥ 3	85.1	29.8	36.5	80.8
≥ 4	48.9	72.7	46.0	75.0
≥ 5	38.3	78.8	46.2	72.9
≥ 6	29.8	84.8	48.3	71.8
≥ 7	13.8	94.4	54.2	69.8
≥ 8	10.6	96.5	58.8	69.5
≥ 9	6.4	97.5	54.5	68.7
≥ 10	3.2	99.0	60.0	68.3

6.1 PREFACE:

In this chapter, we sought to better understand the relationship between new or expanding ventricular blood and long-term recovery. We derived and validated this relationship using two separate intracerebral hemorrhage patient cohorts. Local Research Ethics Board approval was obtained at the enrolling sites of both data set and Ottawa Health Science Network Research Ethics Board approval for this study was not required.

Drs. Yogendrakumar, Ramsay, Goldstein, and Dowlatshahi were responsible for study concept, design and statistical analysis. Drs. Yogendrakumar and Dowlatshahi were responsible for drafting the manuscript. All other authors participated in acquisition of data and in critical revisions of the manuscript for intellectual content. This chapter presents the manuscript "New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage". This manuscript was accepted for publication in *Neurology* in April 2019. A confirmation of acceptance is available in Appendix IV.

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Warren AD, Anderson CD, Gurol ME, Greenberg SM, Viswanathan A, Rosand J, Goldstein JN, Dowlatshahi D. **New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage**. *Neurology*. Accepted, in press: April 2019.

New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage

Authors: Vignan Yogendrakumar MD[1], Tim Ramsay PhD[2,3], Dean Fergusson PhD[2,3], Andrew M Demchuk MD[4], Richard I Aviv MBChB[5], David Rodriguez-Luna MD[6], Carlos A Molina MD PhD[6], Yolanda Silva MD[7], Imanuel Dzialowski MD[8], Adam Kobayashi MD PhD[9], Jean-Martin Boulanger MD[10], Cheemun Lum MD*, Gord Gubitz MD[11], Padma Srivastava MD[12], Jayanta Roy MD[13], Carlos S. Kase MD[14], Rohit Bhatia MD[12], Michael D Hill MD MSc[4], Andrew D Warren BSc[15], Christopher D Anderson MD MMSc[15], Mahmut E Gurol MD[15], Steve M Greenberg MD PhD[15], Anand Viswanathan MD PhD[15], Jonathan Rosand MD MSc[15,16], Joshua N. Goldstein MD PhD[17], and Dar Dowlatshahi MD PhD[1,3], and the PREDICT/Sunnybrook CTA Study Group

*Deceased

[1]Ottawa Stroke Program. Department of Medicine (Neurology), University of Ottawa, Ottawa, Canada

[2]Ottawa Methods Center, University of Ottawa, Ottawa, Canada

[3]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada

[4]Calgary Stroke Program, Department of Clinical Neurosciences, Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

[5]Division of Neuroradiology and Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

[6]Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[7]Department of Neurology, Dr. Josep Trueta University Hospital, Institut d'Investigació Biomèdica Girona (IDIBGi) Foundation, Girona, Spain

[8]Department of Neurology, Elblandklinikum Meissen Academic Teaching Hospital of the Technische University, Dresden, Germany

[9]Interventional Stroke and Cerebrovascular Treatment Center and 2nd Department of Neurology, Institute of Psychiatry and Neurology, and Department of Experimental and Clinical Pharmacology, Warsaw, Poland

[10]Department of Medicine, Charles LeMoyne Hospital, University of Sherbrooke, Longueuil, Canada
[11]Department of Neurology, Dalhousie University, Halifax, Canada
[12]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India
[13]Apollo Gleneagles Hospitals, Kolkata
[14]Department of Neurology, Boston Medical Center, Boston, USA
[15]Department of Neurology, Massachusetts General Hospital, Boston, USA
[16]Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, USA
[17]Department of Emergency Medicine, Massachusetts General Hospital, Boston, USA

Figures Legend:

Figure 1: Flowchart for PREDICT Cohort (Derivation Cohort)

Figure 2: Flowchart for MGH Cohort (Validation Cohort)

Figure 3: IVH Expansion Outcome Probability Distribution

Tables Legend:

Table 1: Baseline Patient Characteristics (Derivation and Validation Cohorts)

Table 2: Univariate Predictors of Poor Outcome

Table 3: Sensitivity and Specificity IVH Expansion Thresholds (Derivation and Validation Cohorts)

Table 4: Multivariable Logistic Regression Models (Derivation Cohort)

6.2 ABSTRACT:

Objective: To describe the relationship between intraventricular hemorrhage (IVH) expansion and long-term outcome and use this relationship to select and validate clinically relevant thresholds of IVH expansion in two separate intracerebral hemorrhage (ICH) populations.

Methods: We used fractional polynomial analysis to test linear and non-linear models of 24-hour IVH volume change and clinical outcome with data from the PREDICT-ICH study. The primary outcome was poor clinical outcome (mRS 4-6) at 90 days. We derived dichotomous thresholds from the selected model and calculated diagnostic accuracy measures. We validated all thresholds in an independent single center ICH cohort (Massachusetts General Hospital).

Results: Of the 256 patients from PREDICT, 127 (49.6%) had a mRS of 4-6. 24-hour IVH volume change and poor outcome fit a non-linear relationship, where minimal increases in IVH were associated with a high probability of mRS 4-6. IVH expansion ≥ 1 mL (n=53, Sensitivity 33%, Specificity 92%, aOR 2.68 [95% CI: 1.11-6.46]) and development of any new IVH (n= 74, Sensitivity 43%, Specificity 85%, aOR 2.53 [95% CI: 1.22-5.26]) strongly predicted poor outcome at 90 days. The dichotomous thresholds reproduced well in a validation cohort of 169 patients.

Conclusion: IVH expansion, as small as 1 mL, or any new IVH is strongly predictive of poor outcome. These findings may assist clinicians with bedside prognostication and could be incorporated into definitions of hematoma expansion to inform future ICH treatment trials.

6.3 INTRODUCTION:

Intraventricular hemorrhage (IVH) is a well-established predictor of poor clinical outcome.[1,2] The concurrent presence of IVH is associated with a mortality rate as high as 50-75%.[1,3] The mechanisms of IVH related brain injury vary and may involve the exertion of mass effect on brain structures, development of obstructive hydrocephalus, and global dysfunction secondary to the contamination of cerebrospinal fluid with blood.[1,4,5]

IVH is a dynamic process: several studies have observed interval increases in IVH volume, as well as the "delayed" development of IVH on subsequent imaging.[4,6,7] However, questions remain as to what degree of IVH expansion impacts clinical outcome. The presence of new IVH on successive imaging appears associated with poor outcome, yet attempts to validate this finding have led to conflicting results.[6,7] Steiner and colleagues showed a strong relationship between IVH expansion > 2mL and poor outcome at 90 days, but the choice of 2 mL as a threshold was not empirically driven.[4] As it stands, the exact relationship between IVH expansion and patient outcome remains unclear.

Our primary objective was to assess and describe the relationship between IVH expansion and long-term outcome using two independent ICH cohorts. Using this relationship, we sought to derive and validate clinically relevant thresholds of IVH expansion that could be applied to bedside evaluations of acute patients or be incorporated into future definitions of hematoma expansion for future ICH treatment trials.

6.4 SUBJECTS and METHODS:

Study Design:

We performed our study in two stages using data from two prospectively collected ICH observational cohorts. In the first stage we used fractional polynomial modelling to describe a relationship between IVH expansion and long-term outcome. We then used the resultant probability distribution to select clinically relevant thresholds that could be practically applied by clinicians at the bedside. We subsequently validated our findings in the second stage of our study.

Subjects:

Derivation Cohort: Subjects were participants enrolled in the Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study.[8] Briefly, PREDICT was a prospective multicenter observational study (12 centers in 6 countries) of patients presenting with spontaneous ICH under 6 hours enrolled from June 2006 to July 2012. Enrolled patients had baseline CT and CT-angiogram (CTA), follow-up imaging at 24 hours post-event, and serial clinical assessments including 90-day modified Rankin scale (mRS). Exclusion criteria was ICH >100mL, known renal impairment precluding CTA, baseline modified Rankin scale (mRS) >3, or terminal illness. For our study, we further excluded patients who lacked follow-up imaging or 90-day mRS. We also excluded patients who received recombinant Factor VIIa, craniotomy for hematoma evacuation or ventricular drainage prior to 24-hour repeat imaging, as these interventions directly affect hemorrhage volume at follow-up assessment.

Validation Cohort: Patients presenting with ICH at Massachusetts General Hospital (MGH, Boston, USA) were screened and recruited consecutively, enrolled from January 2000 to December 2017, as part of an ongoing prospective cohort study.[9] Eligible patients required both baseline and follow-up imaging. Patients with suspected secondary cause (tumor, underlying vascular malformation, trauma) to their ICH were excluded. For our study, we further excluded patients who underwent major interventions (craniotomy, ventricular drainage, recombinant Factor VIIa), presented over 6 hours from symptom onset, had missing imaging, or missing mRS data.

Primary Exposure and Outcome:

The primary exposure was IVH expansion (including development of new IVH) at 24 hours, calculated as the difference in IVH volume between the 24-hour CT follow-up to and the baseline CT. Repeat imaging was standardized in the PREDICT study (derivation cohort) and all study participants received follow-up imaging at 24 hours. Repeat imaging in the validation cohort was at the discretion of the treating physician. As such, we used data, whenever possible, from the 24-hour scan to calculate interval IVH and ICH change. If 24-hour imaging was not available, we would use imaging collected at 48 hours, 72 hours, or < 24 hours (in that order of preference). We assessed hematoma volumes in a blinded fashion at a central laboratory using computerized-planimetry software (Derivation cohort: Quantomo Software, Cybertrial Inc., Calgary, Canada)[8,10,11] or volumetric analysis (Validation cohort: Analyze Software, Mayo Clinic, Rochester, USA)[9] validated for ICH measurements. The primary outcome was poor clinical outcome at 90 days, defined as a modified Rankin Scale (mRS) of 4-6.[12,13] Because the definition of poor clinical outcome in ICH trials is still an area of debate, our secondary outcome

was the reclassification of poor clinical outcome as mRS 2-6, 3-6, 5-6, or 6 (death).[12] If the proportional odds assumption could be met, a mRS shift analysis would also be performed. In both the derivation and validation cohorts, acquisition of primary and secondary outcomes were blinded; the evaluators were not aware of previous volumetric assessments when undertaking evaluation of the 90-day mRS.

Statistical Analysis:

Developing the Relationship between IVH Expansion and Clinical Outcome:

We hypothesized that the relationship between IVH expansion and clinical outcome may not be simply linear. As such, in the derivation cohort, we parameterized the relationship between net IVH change and poor clinical outcome using fractional polynomial modeling as implemented in the R software package 'mfp' (R Project, Vienna, Austria).[14,15] Fractional polynomial (logistic) regression selects a curved function by choosing the best approximated fit from a set of transformations of the independent variable. It also formally tests whether or not this curved fit is statistically superior to a simple linear fit using likelihood ratio testing. For this analysis we assumed that intraventricular hemorrhage contraction (a net IVH change < 0 mL) would not have an impact on our primary outcome, as previously observed by Klar et al.[16] Any net IVH change < 0 mL was converted to zero.

Selecting and Validating Clinically Relevant Thresholds of IVH Expansion:

We plotted the curved relationship between IVH expansion and probability of poor outcome and used this plot to identify clinically useful thresholds for IVH expansion. IVH expansion > 2 mL, as initially proposed by Steiner et al.[4] was also evaluated. We calculated the sensitivity and

specificity for these dichotomous thresholds and used multivariable logistic regression with stepwise selection to adjust for potential confounding of important risk factors. Nonsignificant variables ($p > 0.05$) were eliminated in a backward stepwise fashion. Since baseline hemorrhage volume, 24-hour ICH change, and intraventricular expansion may be all part of the same biological pathway, we cannot fully exclude collinearity and/or interactions between these variables. As such, baseline hemorrhage and 24-hour ICH change were forced into two separate logistic regression models *a priori*. A third model including both variables was also generated. The remaining candidate covariates were derived with exploratory univariate analysis. Fisher's exact test, ANOVA, or Mann-Whitney U tests were used as appropriate ($p < 0.10$). Continuous variables that did not conform to the linearity assumption were re-categorized into dichotomous or ordinal variables. Sensitivities and specificities of the dichotomous definitions were calculated in the validation cohort. We performed all statistical analysis other than fitting the fractional polynomial model using SPSS v25.0 (IBM, Armonk, NY) and SAS v9.4 (SAS Institute Inc, Cary, NC).

Standard Protocol Approvals, Registrations, and Patient Consents:

Local research ethics board approval was obtained at all PREDICT enrolling sites. A local institutional review board approved recruitment at Massachusetts General Hospital. Written consent was provided by patients or their respective surrogates in both cohort populations.

Data Availability Statement:

The PREDICT-ICH dataset is available for access to all PREDICT-ICH investigators and qualified researchers trained in human subject confidentiality protocols and collaborating with

PREDICT-ICH investigators. Access to data collected at Massachusetts General Hospital is available upon formal request for those who are actively collaborating with MGH investigators.

6.5 RESULTS:

Cohort Characteristics:

The PREDICT study prospectively enrolled 390 patients presenting with spontaneous ICH and meeting inclusion criteria (Figure 1). Of these, 134 were excluded from our study: 32 patients were treated with recombinant Factor VIIa or surgical intervention (12 cases of emergent extra-ventricular drainage) prior to follow-up imaging, 78 patients did not receive baseline or follow-up mRS scoring, and 24 patients were excluded due to missing imaging, delayed presentation, or having an alternative diagnosis other than spontaneous ICH (e.g. tumour). Those excluded were similar to the primary analysis cohort on measured baseline factors. However, patients excluded from this study had larger baseline intraventricular (IVH) volumes, larger net ICH volume change, and a greater proportion of spot sign presence.

Our primary analysis population included 256 patients. Almost 50% of patients (127/256) exhibited a poor clinical outcome (mRS 4-6) at 3 months. Eighty-four patients (33%) had IVH at initial presentation. Baseline IVH was associated with concurrent thalamic ICH (48% vs. 15%, $p<0.001$). At 24 hours, 116 patients (45%) had IVH; 33 (28%) of these were new cases of IVH development (i.e. not initially present at baseline). New IVH development was associated with concurrent lobar hemorrhage (55% vs. 25%, $p=0.001$). IVH clot retraction (IVH change < 0 mL) was observed in 40 patients (15.6%), with one patient exhibiting full resolution of IVH at follow-up.

The Massachusetts General Hospital ICH cohort enrolled 2,409 patients over the course of 17 years. 90-day mRS was only available in 781 patients. Of these 781 patients, 169 were included

in the primary analysis: 123 patients were excluded secondary to surgical intervention prior to follow-up imaging (91 cases underwent extra-ventricular drain placement), 460 patients presented outside of 6 hours, and follow-up imaging was not available for 29 patients (Figure 2). One-hundred and sixteen patients received follow-up imaging at 24 hours (69%). Of the remaining patients, 16 (9.5%) had imaging at 48 hours, 3 (1.8%) had imaging at 72 hours, and 16 (20%) had imaging collected before the 24-hour mark. Fifty-five subjects (32%) exhibited a poor clinical outcome at 3 months. Forty-one patients (24%) had IVH at initial presentation. IVH clot retraction (IVH change < 0 mL) was observed in 24 patients (14.2%), with four patients exhibiting full resolution of IVH at follow-up. On follow-up imaging, 49 patients (29%) had IVH; 12 (24%) of these were new cases of IVH development. Baseline characteristics are outlined alongside the PREDICT cohort in Table 1. No significant differences are noted between the validation and derivation cohort.

Relationship between IVH Expansion and Outcome:

To best approximate a potential non-linear relationship we utilized multiple fractional polynomial modeling. The fractional polynomial model fit the following relationship between 24-hour IVH volume change and the primary outcome:

$$log\left(\frac{p}{1-p}\right) = 1.57 - 0.63 \times (IVH\ Change + 0.1)^{-0.5}$$

This model (with p equal to the probability of a poor outcome) was determined to fit the data best and was significantly better than a simple logistic model (p=0.009). Minimal increases in IVH of 1 mL or greater were associated with a high probability of poor outcome (Figure 3). With

no intraventricular expansion, the probability of a poor outcome was 40% (33%-47%). With an interval increase of 1 mL this probability increased to 73% (62%-81%).

Selection and Validation of Clinical Thresholds:

Based on these observations, we selected IVH expansion ≥ 1 mL and any new IVH expansion as clinically relevant thresholds to examine further. The calculated sensitivities and specificities for each derived threshold and IVH expansion > 2 mL are summarized in Table 3. IVH expansion was associated with modest sensitivities (IVH ≥ 1 mL: 23.1 - 45.8% // Any IVH expansion: 30.7 – 55.9%) but consistently high specificity (IVH ≥ 1 mL: 86.8 – 91.5% // Any IVH expansion: 77.2 - 85.3%).

We entered selected thresholds into backwards conditional regression models. Initial univariable analysis revealed statistically significant associations between the primary outcome and age, anticoagulant pre-treatment, prior stroke, serum glucose, international normalized ratio (INR), baseline National Institute of Heath Stroke Scale (NIHSS), spot sign status, and lobar hemorrhage location ($p<0.1$ for each comparison, Table 2). Baseline NIHSS, 24-hour ICH change, and INR did not meet linearity assumptions. As such, baseline NIHSS was re-categorized as ≤5, 6-13, ≥14.[17] INR was re-categorized as a dichotomous variable, >2, and 24-hour ICH change was categorized as a dichotomous variable representing significant hematoma expansion (≥ 6 mL or ≥ 33% growth).[12] When adjusted for the relevant covariates, IVH expansion ≥ 1 mL was significantly associated with poor clinical outcome in all three models (Table 4). Any IVH expansion and IVH expansion > 2 mL was associated with poor clinical outcome in both models 1 and 2 (significant hematoma expansion and baseline hemorrhage

models, respectively) but this association was not statistically significant in the combined model. Both IVH expansion ≥ 1 mL and any new IVH expansion were significantly associated with 90-day mRS 5-6, and death (mRS 6). We performed a mRS shift analysis, but the proportional odds assumption was violated and therefore the results were not valid.

The derived dichotomous definitions reproduced well in the validation population (Table 3). As in the derivation cohort, the threshold scores exhibited high specificity, for both primary and secondary outcomes (IVH expansion ≥ 1 mL: 91.1 – 100.0% // Any IVH Development: 86.3 – 96.2%). Sensitivities seen in the validation cohort continued to be modest in magnitude.

6.6 DISCUSSION:

In this study, we identified a novel non-linear association between IVH expansion and long-term clinical outcome. Our analysis suggests that the probability of poor outcome is significantly high even with small interval increases in IVH volume. Our two selected dichotomous thresholds, IVH expansion ≥ 1 mL and any IVH expansion, were strongly associated with poor clinical outcome in both derivation and validation cohorts.

Our findings are in line with the work conducted by previous investigators who have looked at IVH dynamics. Maas and colleagues showed that the development of new IVH ("delayed" IVH) is associated with a shift in the 90 day mRS.[6] Witsch et al.[7] presented similar findings, although these associations were not statically significant. Our study provides further evidence to support Maas and colleagues' original hypothesis and expands on it by also showing that the expansion of baseline IVH is also associated poor outcome. Most worrisome is that *any* IVH expansion is associated with poor outcome and the predictive power of this finding is comparable to IVH expansion > 2 mL, a marker previously shown to be associated with poor outcome and mortality.[4] It is unclear why minimal ventricular expansion can be associated with such poor outcomes. Animal models suggest iron accumulation associated with ventricular hemorrhage can increase the risk of fibrosis and chronic hydrocephalus, hippocampal tissue loss, and ependymal cilia damage.[18,19] Further investigation is required.

Our study is strengthened by the use of the PREDICT cohort, a pragmatic, observational multi-center study involving 12 different centers in 6 countries, and the independent validation of our findings in the MGH cohort, a single center observational cohort reflective of real-world

practice. The prevalence of IVH and new IVH development at 24 hours in both cohorts are similar to previously reported studies.[3,6,7] The degree of clot retraction seen in the first 24 hours is also in keeping with previous work conducted by the CLEAR-IVH investigators.[20] Of note, our findings remained consistent across the two cohorts, even with variations in the timing of serial imaging. Imaging was standardized to the 24-hour mark within PREDICT, but there was significant variation in the MGH cohort. While this may increase the risk of potential confounding, variability in follow-up imaging is more reflective of bedside practice. We were able to successfully reproduce our findings in a validation cohort that is more reflective of the clinical environment; this supports the generalizability of our findings to day-to-day practice.

The application of our findings extends beyond clinical practice. While several definitions for significant hematoma expansion are currently in use, none incorporates IVH expansion.[12] Furthermore, with the exception of INTERACT1,[21] FAST,[22] and the ongoing STOP-AUST study,[23] IVH expansion has not been typically reported in the primary results of ICH treatment trials.[24–26] Our study highlights the importance of IVH expansion on overall outcome, and we argue for its inclusion into revised definitions of hematoma expansion, and emerging ICH trials.

Our study has several important limitations. In both cohorts, we excluded patients who received an intervention or rFVIIa, as well as those who had missing 90-day mRS data. The excluded population exhibited large baseline ICH and IVH volumes. This is of particular importance as IVH can cause hydrocephalus requiring extra-ventricular drainage.[5,27] Because intervention patients were excluded, our cohorts may be biased towards mild-moderate severity IVH. Fortunately, in the PREDICT cohort, only 12 patients received drain placement, thereby

reducing the risk of selection bias. However, 91 patients of the MGH cohort underwent drainage placement. The difference in drainage placement number is not fully clear but may relate to differences in regular practice standards at Massachusetts General Hospital versus the PREDICT recruiting sites. The combination of increased intervention frequency and lower baseline ICH and IVH volumes observed in the 169 patients included in primary analysis may suggest that the validation cohort consists of an increased proportion of mild to moderate IVH. This may further explain the reduced amount of IVH expansion observed within the validation cohort and the resultant lower sensitivities observed. Finally, while our study shows IVH expansion is strongly associated with poor outcome, it does not necessarily follow that reduction of IVH expansion will improve outcome. CLEAR III demonstrated that reducing IVH volume did not lead to a reduction in disability, although there was a reduction in mortality.[28] The effect of mitigating IVH expansion or preventing delayed IVH formation needs to be assessed in a clinical trial.

Conclusions:

Any new IVH, or IVH expansion as little as 1 mL is associated with poor functional outcome following acute ICH. These findings can be helpful for bedside prognostication, and to inform clinical trials for ICH therapy; we suggest incorporating IVH expansion into current hematoma expansion definitions.

6.7 MANUSCRIPT REFERENCES:

1. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. Lancet Neurol. 2012;11:101–118.

2. Tuhrim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an important determinant of outcome in supratentorial intracerebral hemorrhage. Crit Care Med. 1999;27:617–621.

3. Hanley DF. Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. Stroke. 2009;40:1533–1538.

4. Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. Neurosurgery 2006;59:767-773.

5. Bu Y, Chen M, Gao T, Wang X, Li X, Gao F. Mechanisms of hydrocephalus after intraventricular haemorrhage in adults. Stroke Vasc Neurol. 2016;1:23–27.

6. Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. Neurology. 2013;80:1295–1299.

7. Witsch J, Bruce E, Meyers E, et al. Intraventricular hemorrhage expansion in patients with spontaneous intracerebral hemorrhage. Neurology. 2015;84:989–994.

8. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot

sign (PREDICT): a prospective observational study. Lancet Neurol. 2012;11:307–314.

9. Morotti A, Boulouis G, Charidimou A, et al. Integration of Computed Tomographic Angiography Spot Sign and Noncontrast Computed Tomographic Hypodensities to Predict Hematoma Expansion. Stroke. 2018;49:2067–2073.

10. Kosior JC, Idris S, Dowlatshahi D, et al. Quantomo: validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. Int J Stroke. 2011;6:302–305.

11. Dowlatshahi D, Kosior JC, Idris S, et al. Planimetric Hematoma Measurement in Patients With Intraventricular Hemorrhage: Is Total Volume a Preferred Target for Reliable Analysis? Stroke. 2012;43:1961–1963.

12. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology. 2011;76:1238–1244.

13. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2005;352:777–785.

14. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol. 1999;28:964–974.

15. original by Gareth Ambler and modified by Axel Benner. mfp: Multivariable Fractional Polynomials. R Packag version 152. Epub 2015. Accessed at: https://cran.r-project.org/package=mfp.

16. Klahr AC, Kate M, Kosior J, et al. Early hematoma retraction in intracerebral hemorrhage

is uncommon and does not predict outcome. PLoS One. 2018;13:e0205436.

17. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke. 2003;34:134–137.

18. Chen Z, Gao C, Hua Y, Keep RF, Muraszko K, Xi G. Role of iron in brain injury after intraventricular hemorrhage. Stroke. 2011;42:465–470.

19. Chen Q, Tang J, Tan L, et al. Intracerebral Hematoma Contributes to Hydrocephalus After Intraventricular Hemorrhage via Aggravating Iron Accumulation. Stroke. 2015;46:2902–2908.

20. Webb AJS, Ullman NL, Mann S, Muschelli J, Awad IA, Hanley DF. Resolution of intraventricular hemorrhage varies by ventricular region and dose of intraventricular thrombolytic: the Clot Lysis: Evaluating Accelerated Resolution of IVH (CLEAR IVH) program. Stroke. 2012;43:1666–1668.

21. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008;7:391–399.

22. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358:2127–2137.

23. Meretoja A, Churilov L, Campbell BC V, et al. The spot sign and tranexamic acid on preventing ICH growth--AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. Int J Stroke. 2014;9:519–524.

24. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018;391:2107–2115.

25. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. N Engl J Med. 2016;375:1033–1043.

26. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355–2365.

27. Jaffe J, Melnychuk E, Muschelli J, et al. Ventricular catheter location and the clearance of intraventricular hemorrhage. Neurosurgery. 2012;70:1258-1263

28. Hanley DF, Lane K, McBee N, et al. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. Lancet. 2017;389:603–611.

Acknowledgements:

None.

Study Sponsorship or Funding:

Dr. Dowlatshahi was funded by a University of Ottawa Department of Medicine Clinician-Scientist Research Chair award and a Heart & Stroke Foundation of Canada Clinician-Scientist Award. Dr. Yogendrakumar is supported by the Queen Elizabeth II Graduate Scholarship for Science and Technology and the Canadian Health Institute of Research Banting and Best Graduate Scholarship. Dr. Anderson is supported by the US NIH (R01NS103924, K23NS086873), and the American Heart Association (18SFRN34110082).

Disclosures:

The study authors have no relevant disclosures

Author Contributions

Vignan Yogendrakumar	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Tim Ramsay	Author	Interpreted the data; assisted in data analysis; revised the manuscript for intellectual content
Dean Fergusson	Author	Interpreted the data; revised the manuscript for intellectual content
Andrew M Demchuk	Author	Major role in data acquisition
Richard I Aviv	Author	Major role in data acquisition
David Rodriguez-Luna	Author	Major role in data acquisition
Carlos A Molina	Author	Major role in data acquisition
Yolanda Silva Blas	Author	Major role in data acquisition
Imanuel Dzialowski	Author	Major role in data acquisition
Adam Kobayashi	Author	Major role in data acquisition
Jean-Martin Boulanger	Author	Major role in data acquisition
Cheemun Lum	Author	Major role in data acquisition
Gord Gubitz	Author	Major role in data acquisition
Vasantha Padma	Author	Major role in data acquisition
Jayanta Roy	Author	Major role in data acquisition
Carlos S. Kase	Author	Major role in data acquisition
Rohit Bhatia	Author	Major role in data acquisition
Michael D. Hill	Author	Major role in the acquisition of data; revised the manuscript for intellectual content
Andrew D Warren	Author	Dataset Organization, revised the manuscript for intellectual content
Christopher D Anderson	Author	Major role in the acquisition of data; revised the manuscript for intellectual content
Mahmut E Gurol	Author	Major role in data acquisition
Steve M Greenberg	Author	Major role in data acquisition
Anand Viswanathan	Author	Major role in data acquisition
Jonathan Rosand	Author	Major role in data acquisition
Joshua N Goldstein	Author	Major role in the acquisition of data; Assisted with study design; revised the manuscript for intellectual content
Dar Dowlatshahi	Author	Major role in the acquisition of data; design and conceptualized study; revised the manuscript for intellectual content

6.8 FIGURES

Figure 1: Flowchart of Patient Selection for Derivation Analysis (PREDICT Cohort)

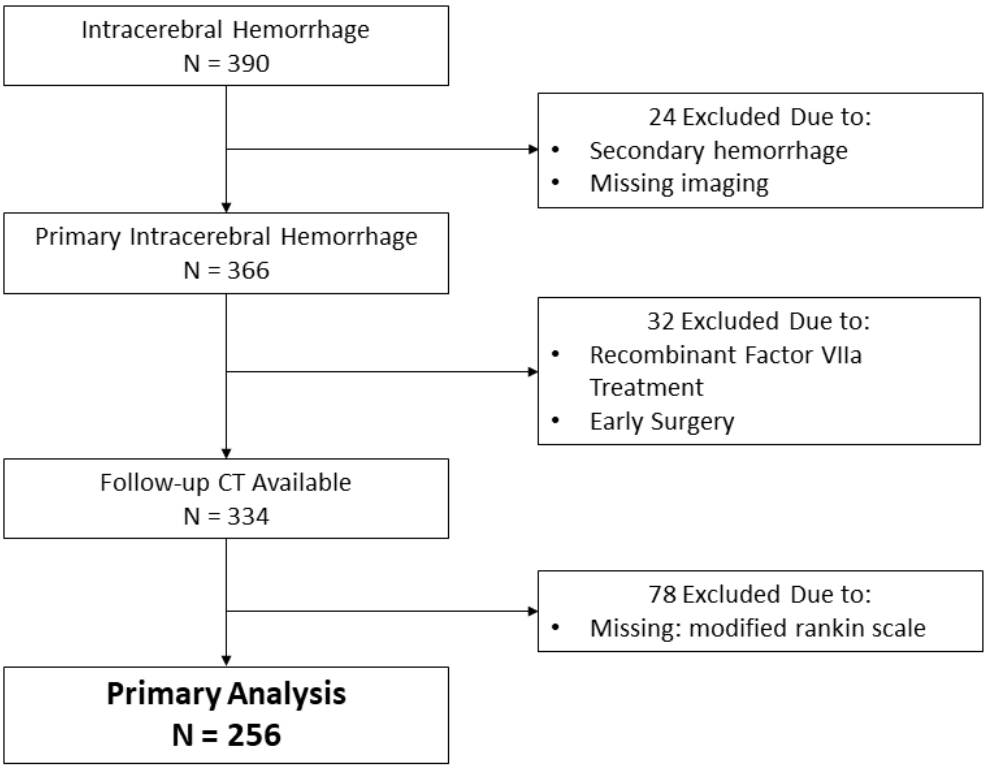


Figure 2: Flowchart of Patient Selection for Validation Analysis (Massachusetts General Hospital Cohort)

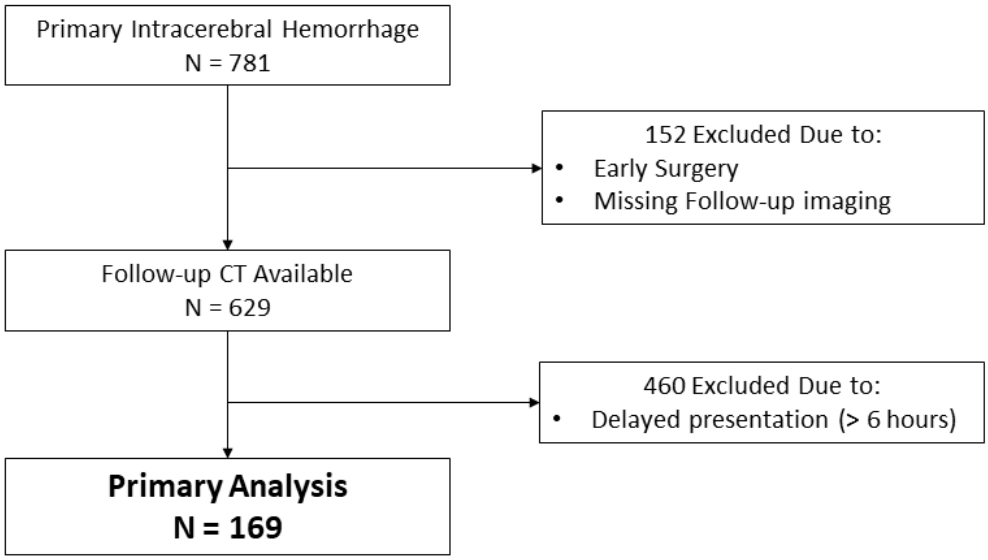
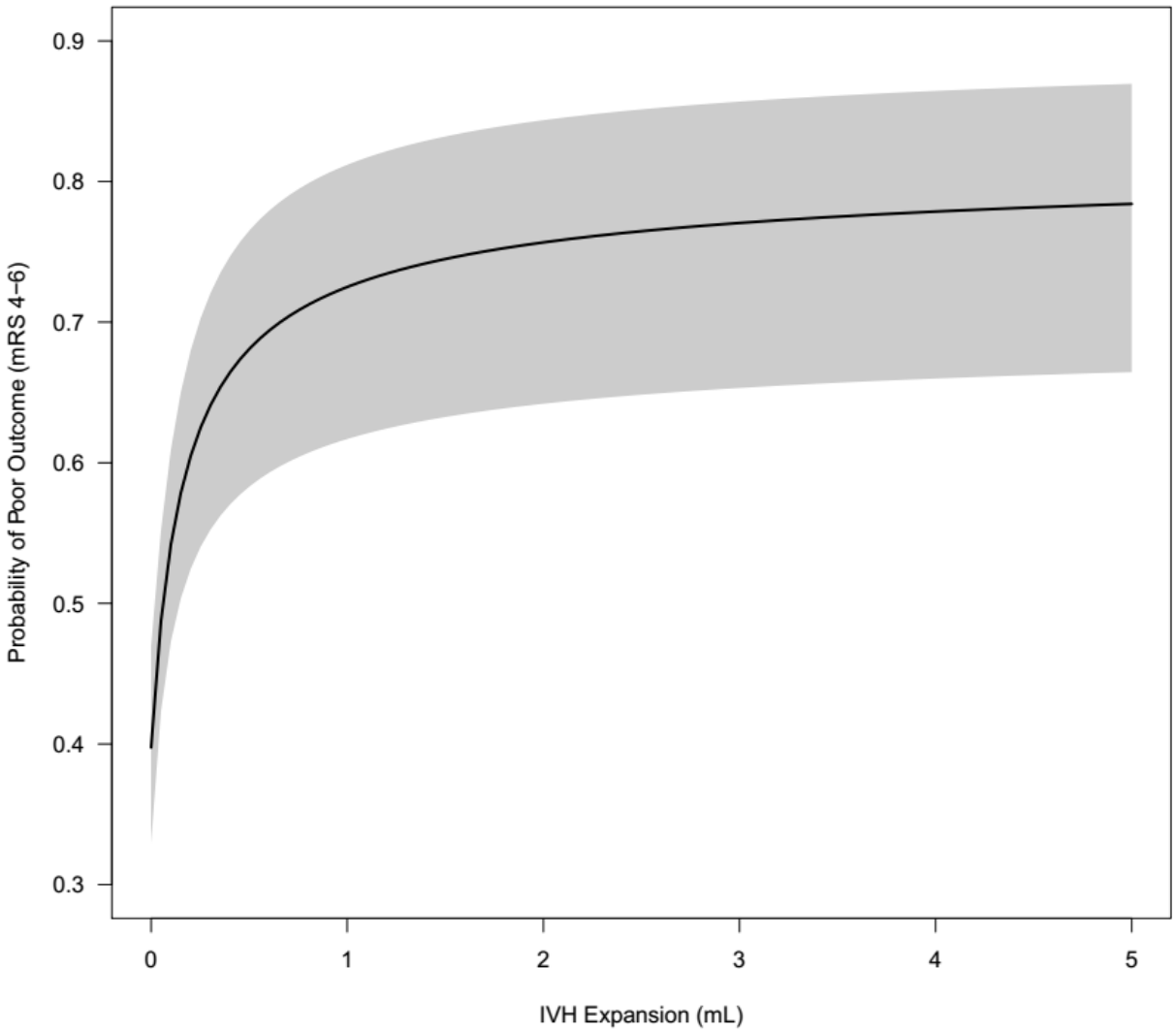


Figure 3: Intraventricular Hemorrhage (IVH) Expansion Probability Distribution (PREDICT; Derivation Cohort, n=256). Solid line indicates predicted probability and the shaded areas indicate 95% confidence intervals.



6.9 TABLES:

Table 1: Baseline Population Characteristics of the PREDICT (Derivation) and Massachusetts General Hospital (MGH; Validation) Intracerebral Hemorrhage Cohorts:

Baseline Characteristics	**PREDICT (N = 256)**	**MGH (N = 169)**
Age, years (median; IQR)	70 (57-79)	71 (62-80)
Male Sex (n, %)	155 (60.5%)	95 (55.9%)
Medical History (n, %)		
Hypertension	190 (74.2%)	133 (78.7%)
Coronary Artery Disease	24 (9.4%)	29 (17.2%)
Congestive Heart Failure	4 (1.6%)	-
Hypercholesterolaemia	58 (22.7%)	76 (45.0%)
Diabetes Mellitus	48 (18.8%)	34/169 (20.1%)
Antiplatelet Usage	23 (9.0%)	-
Anticoagulant Usage	20 (7.8%)	26 (15.4%)
Previous Stroke	23 (9.0%)	22/167 (13.0%)
Prior Hemorrhage	7 (2.7%)	5/168 (3.0%)
Baseline Clinical Information (median; IQR)		
Systolic Blood Pressure, mmHg	173 (151-195)	180 (154-202)[a]
Diastolic Blood Pressure, mmHg	93 (80-105)	93 (78-108)[a]
Glucose, mmol/L	7.1 (6.1-9.1)[b]	6.8 (5.8-8.4)
NIH Stroke Scale	14 (6-18)[b]	-
International normalized ratio	1.0 (1.0-1.1)[a]	1.0 (1.0-1.2)[c]
Partial Thromboplastin Time, seconds	29 (26-31)[d]	26 (24-29)[e]
Platelets, $x10^9$ cells per L	215 (175-266)[a]	-
Time to CT, min	137 (89-221)	120 (90-240)
Imaging		
Baseline ICH Volume, mL (median; IQR)	12.94 (6.02-26.14)	8.00 (3.00-20.81)
Baseline IVH Volume, mL (mean; SD)	3.04 (7.30)	1.11 (3.05)
Lobar Hemorrhage (n,%)	74/255 (29.0%)	45 (26.6%)
Spot Sign Positive (n,%)	67 (26.5%)	26/113 (23.0%)

[a]Missing 3 values, [b]Missing 2 values, [c]Missing 6 values, [d]Missing 7 values, [e]Missing 22 values,

Abbreviations: ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; IQR: interquartile range; SD: standard deviation

Table 2: Univariate Predictors of Poor Outcome (PREDICT; Derivation Population, n=256)

Baseline Characteristics	**mRS 4-6 (N = 127)**	**mRS 0-3 (N =129)**	**P**
Age, years (median; IQR)	75 (17)	62 (20)	<0.001
Male Sex (n, %)	72 (56.7%)	83 (64.3%)	0.211
Medical History (n, %)			
Hypertension	97 (76.4%)	93 (72.1%)	0.433
Coronary Artery Disease	13 (10.2%)	11 (8.5%)	0.639
Congestive Heart Failure	2 (1.6%)	2 (1.6%)	0.987
Hypercholesterolaemia	26 (20.5%)	32 (24.8%)	0.408
Diabetes Mellitus	25 (19.7%)	23 (17.8%)	0.704
Antiplatelet Usage	12 (9.4%)	11 (8.5%)	0.797
Anticoagulant Usage	14 (11.0%)	6 (4.7%)	0.057
Previous Stroke	16 (12.6%)	7 (5.4%)	0.045
Prior Hemorrhage	5 (3.9%)	2 (1.6%)	0.242
Baseline Clinical Information (median; IQR)			
Systolic Blood Pressure, mmHg	174 (43)	170 (43)	0.650
Diastolic Blood Pressure, mmHg	93 (24)	92 (27)	0.220
Glucose, mmol/L	7.3 (3.3)	6.8 (2.9)	0.074
National Institute of Health Stroke Scale	17 (6)	7 (10)	<0.001
premorbid modified Rankin Score	0 (0)	0 (0)	0.137
International normalized ratio > 2, (n, %)	14/125 (11.2%)	5/128 (3.9%)	0.028
Partial Thromboplastin Time, seconds	28 (6)	29 (4)	0.456
Platelets, $x10^9$ cells per L	212 (107)	224 (85)	0.591
Time to CT, min	131 (119)	143 (149)	0.286
Imaging (mean; Standard deviation)			
Baseline ICH Volume, mL	26.7 (19.9)	11.24 (11.4)	<0.001
ICH Change, mL	12.8 (22.4)	2.7 (6.8)	<0.001
Baseline IVH Volume, mL	4.6 (9.4)	1.6 (4.0)	<0.001
IVH Change, mL	3.8 (11.8)	0.4 (2.9)	<0.001
Lobar Hemorrhage (n,%)	47/126 (37.3%)	27 (20.9%)	0.004
Spot Sign Positive (n,%)	44/126 (34.9%)	23/127 (18.1%)	0.002

Abbreviations: ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; IQR:

interquartile range

Table 3: Sensitivity and Specificity of Intraventricular Hemorrhage (IVH) Expansion Thresholds for Prediction of Primary (Bolded) and Secondary Outcomes

	Derivation Cohort (n=256)		**Validation Cohort (n=169)**	
Outcome Range (mRS)	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**
IVH Expansion ≥ 1 mL	n = 53 (21%)		n = 16 (9%)	
2-6	23.1	87.7	13.8	100.0
3-6	26.2	89.8	14.1	96.1
4-6	**33.1**	**91.5**	**16.4**	**93.9**
5-6	40.3	87.7	33.3	93.4
6	45.8	86.8	50.0	91.0
Any IVH Expansion	n = 74 (29%)		n = 24 (14%)	
2-6	30.7	77.2	19.0	96.2
3-6	35.1	83.0	18.5	90.9
4-6	**43.3**	**85.3**	**23.6**	**90.4**
5-6	49.4	79.9	33.3	88.1
6	55.9	79.2	50.0	86.2
IVH Expansion > 2 mL	n = 43 (17%)		n = 7 (4%)	
2-6	18.6	89.5	6.0	100.0
3-6	20.8	90.9	5.4	97.4
4-6	**26.8**	**93.0**	**7.3**	**97.4**
5-6	35.1	91.1	11.1	96.7
6	40.7	90.4	0.0	95.8

Table 4: Multivariable Logistic Regression Models of Intraventricular Hemorrhage Expansion Thresholds for Prediction of Primary (Bolded) and Secondary Outcomes (PREDICT; Derivation Cohort n=256)

Outcome Range (mRS)	Model 1[a] aOR (95% CI)	Model 2[b] aOR (95% CI)	Model 3[c] aOR (95% CI)
IVH Expansion ≥ 1 mL			
2-6	1.33 (0.52-3.41)	0.94 (0.35-2.55)	0.94 (0.35-2.55)
3-6	2.19 (0.97-4.96)	1.39 (0.56-3.45)	1.09 (0.42-2.83)
4-6	**3.30 (1.38-7.87)**	**3.27 (1.40-7.66)**	**2.68 (1.11-6.46)**
5-6	3.41 (1.58-7.36)	3.27 (1.50-7.14)	2.63 (1.16-5.95)
6	3.22 (1.40-7.41)	3.73 (1.65-8.43)	2.85 (1.22-6.69)
Any IVH Expansion			
2-6	0.76 (0.34-1.70)	0.61 (0.26-1.42)	0.61 (0.26-1.42)
3-6	1.14 (0.52-2.52)	1.16 (0.53-2.53)	0.90 (0.39-2.08)
4-6	**2.53 (1.22-5.26)**	**2.53 (1.22-5.26)**	**2.10 (0.98-4.50)**
5-6	2.36 (1.17-4.73)	2.09 (1.02-4.28)	1.78 (0.85-3.72)
6	2.66 (1.25-5.66)	2.91 (1.37-6.16)	2.35 (1.08-5.10)
IVH Expansion > 2 mL			
2-6	1.12 (0.37-3.36)	0.83 (0.28-2.45)	0.80 (0.24-2.59)
3-6	1.11 (0.40-3.09)	1.10 (0.41-2.93)	0.71 (0.24-2.12)
4-6	**3.14 (1.18-8.34)**	**2.98 (1.17-7.62)**	**2.20 (0.80-6.02)**
5-6	3.78 (1.57-9.10)	4.06 (1.74-9.47)	3.10 (1.25-7.71)
6	4.06 (1.62-10.19)	4.71 (1.96-11.33)	3.31 (1.30-8.46)

[a]Adjusted for Significant Expansion (≥6 mL or 33%), Age, Serum glucose, Baseline NIHSS Score (0-5, 6-13, 14+)

[b]Adjusted for Baseline ICH Volume, Age, Baseline NIHSS Score (0-5, 6-13, 14+)

[c]Adjusted for Significant Expansion (≥6 mL or 33%), Baseline ICH Volume, Age, Baseline NIHSS Score (0-5, 6-13, 14+)

Abbreviations: ICH = Intracerebral Hemorrhage; IVH = Intraventricular Hemorrhage; NIHSS = NIH Stroke Scale; mRS = modified rankin scale; PPV = positive predictive value; NPV = negative predictive value; aOR = adjusted odds ratio

CHAPTER 7: REDEFINING HEMATOMA EXPANSION – Creation and Comparative Analysis of a Refined Definition Of Hematoma Expansion

7.1 PREFACE:

In this chapter we developed a new definition of hematoma expansion using the variable "total blood volume", the sum intraparenchymal and intraventricular hemorrhage, and performed a comparative analysis of our refined definition to conventional definitions presently use in clinical trials. We derived the new definition using data from a prospectively collected intracerebral hemorrhage cohort. Local Research Ethics Board approval was obtained at the enrolling sites of this dataset. Ottawa Health Science Network Research Ethics Board approval of this study was not required.

Drs. Yogendrakumar, Ramsay, Goldstein, and Dowlatshahi were responsible for study concept, design and statistical analysis. Drs. Yogendrakumar and Dowlatshahi were responsible for drafting the manuscript. All other authors participated in acquisition of data and in critical revisions of the manuscript for intellectual content. This chapter incorporates the manuscript "Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth". This manuscript was submitted for publication in *Neurology* in May 2019. A confirmation of submission is available in Appendix V.

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Goldstein JN, Dowlatshahi D. **Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth**. *Neurology*. Under Review (May 2019).

Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth

Authors: Vignan Yogendrakumar MD[1], Tim Ramsay PhD[2,3], Dean Fergusson PhD[2,3], Andrew M Demchuk MD[4], Richard I Aviv MBChB[5], David Rodriguez-Luna MD[6], Carlos A Molina MD PhD[6], Yolanda Silva MD[7], Imanuel Dzialowski MD[8], Adam Kobayashi MD PhD[9], Jean-Martin Boulanger MD[10], Gord Gubitz MD[11], Padma Srivastava MD[12], Jayanta Roy MD[13], Carlos S. Kase MD[14], Rohit Bhatia MD[12], Michael D Hill MD MSc[4], Joshua N. Goldstein MD PhD[15], and Dar Dowlatshahi MD PhD[1,3], and the PREDICT/Sunnybrook CTA Study Group

[1]Ottawa Stroke Program. Department of Medicine (Neurology), University of Ottawa, Ottawa, Canada
[2]Ottawa Methods Center, University of Ottawa, Ottawa, Canada
[3]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada
[4]Calgary Stroke Program, Department of Clinical Neurosciences, Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada
[5]Division of Neuroradiology and Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[6]Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[7]Department of Neurology, Dr. Josep Trueta University Hospital, Institut d'Investigació Biomèdica Girona (IDIBGi) Foundation, Girona, Spain
[8]Department of Neurology, Elblandklinikum Meissen Academic Teaching Hospital of the Technische University, Dresden, Germany
[9]Interventional Stroke and Cerebrovascular Treatment Center and 2nd Department of Neurology, Institute of Psychiatry and Neurology, and Department of Experimental and Clinical Pharmacology, Warsaw, Poland
[10]Department of Medicine, Charles LeMoyne Hospital, University of Sherbrooke, Longueuil, Canada
[11]Department of Neurology, Dalhousie University, Halifax, Canada
[12]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India
[13]Apollo Gleneagles Hospitals, Kolkata

[14]Department of Neurology, Boston Medical Center, Boston, USA
[15]Department of Emergency Medicine, Massachusetts General Hospital, Boston, USA

Statistical Analysis was performed by: Dr. Vignan Yogendrakumar and Dr. Tim Ramsay (University of Ottawa)

Corresponding Author:
Dr. Vignan Yogendrakumar MD

Total Word Count: 2,242
Abstract Word Count: 203
Search Terms: [7] Intracerebral hemorrhage; [54] Cohort studies; [119] CT; expansion; intraventricular hemorrhage

Number of Figures: 1
Number of Tables: 5

Figures Legend:
Figure 1: Flowchart for PREDICT Cohort
Tables Legend:
Table 1: Baseline Patient Characteristics
Table 2: Revised Definition: Detailed Cohort Characteristics
Table 3: Sensitivity and Specificity of Revised and Conventional Definitions
Table 4: Univariate Predictors of Poor Outcome
Table 5: Multivariable Logistic Regression Models of Revised and Conventional Definitions

Study Sponsorship or Funding:

This study received no direct funding support. The original PREDICT study received funding support from the Canadian Stroke Consortium and NovoNordisk Canada.

Disclosure Statement:

V. YOGENDRAKUMAR is supported by the Queen Elizabeth II Graduate Scholarship for Science and Technology and the Canadian Health Institute of Research Banting and Best Graduate Scholarship.

T. RAMSAY reports no disclosures relevant to the manuscript.

D. FERGUSSON reports no disclosures relevant to the manuscript.

A. DEMCHUK reports no disclosures relevant to the manuscript.

R. AVIV reports no disclosures relevant to the manuscript.

D. RODRIGUEZ-LUNA reports no disclosures relevant to the manuscript.

C. MOLINA reports no disclosures relevant to the manuscript.

Y. SILVA reports no disclosures relevant to the manuscript.

I. DZIALOWSKI reports no disclosures relevant to the manuscript.

A. KOBAYASHI reports no disclosures relevant to the manuscript.

J. BOULANGER reports no disclosures relevant to the manuscript.

C. LUM is deceased; disclosures are not included for this author.

G. GUBITZ reports no disclosures relevant to the manuscript.

P. SRIVASTAVA reports no disclosures relevant to the manuscript.

J. ROY reports no disclosures relevant to the manuscript.

C. KASE reports no disclosures relevant to the manuscript.

R. BHATIA reports no disclosures relevant to the manuscript.

M. HILL reports no disclosures relevant to the manuscript.

J. GOLDSTEIN has received consulting fees from CSL Behring, Octapharma, Portola, and Phillips healthcare and research funding from Pfizer and Octapharma.

D. DOWLATSHAHI was funded by a University of Ottawa Brain & Mind Institute Research Award and a Heart & Stroke Foundation of Canada Clinician Scientist Award.

7.2 ABSTRACT:

OBJECTIVE: To determine whether including intraventricular hemorrhage expansion to current definitions of hematoma expansion improves the ability to predict 90-day outcome.

METHODS: Using data from the PREDICT-ICH study, we compared a standard definition of hematoma expansion (≥6mL or ≥33%) to a revised definition that includes new intraventricular hemorrhage development or expansion (≥6mL or ≥33% or Any IVH). The primary outcome was poor clinical outcome (mRS 4-6) at 90 days. Diagnostic accuracy measures were calculated for each definition and c-statistics for each definition were compared using non-parametric methods.

RESULTS: Of the 256 patients eligible for primary analysis, 127 (49.6%) had a mRS of 4-6. Sensitivity and specificity for the standard definition (n=80) was 45.7% (95% CI: 36.8 – 54.7) and 82.9% (95% CI: 75.3-88.9), respectively. The revised definition of hematoma expansion (n=113) possessed a sensitivity of 63.8% (95% CI: 54.8-72.1) and specificity of 75.2% (95% CI: 66.8-82.4). Overall accuracy was significantly improved with the revised definition (p=0.013). Adjusting for relevant co-variates, a revised definition of hematoma growth was associated with a 2.58-fold increased odds (95% CI: 1.33-4.99) of poor outcome at 90 days.

CONCLUSIONS: Including intraventricular hemorrhage expansion in the definition of hematoma expansion improves sensitivity without significant decreases to specificity in predicting 90-day outcome.

7.3 INTRODUCTION:

Hematoma expansion is a key potential therapeutic targets for acute intracerebral hemorrhage (ICH) treatment. While several clinical trials have shown successful reductions in hematoma expansion, improvements in long-term outcome remain elusive.[1–3] Each of these trials and other non-randomized trials have defined hematoma expansion differently,[4–7] and none have included intraventricular hemorrhage in their definition.

The extension of hemorrhage into the ventricular space is a predictor of poor outcome.[8,9] It is however, often assessed as a static factor (presence versus absence). A growing body of work shows that interval IVH growth is a significant predictor of poor outcome, independent of changes to intraparenchymal hemorrhage volume.[10–12] Previously, Steiner et al.[13] showed that an IVH expansion threshold of 2 mL or greater was associated with poor outcome. In a recent analysis, Yogendrakumar and colleagues[14] showed that any new IVH expansion is a robust predictor of death and disability.

We hypothesized that incorporating IVH expansion in our definitions of hematoma expansion will improve our ability to better predict long-term outcome. We tested this hypothesis by performing a comparative analysis of conventional hematoma expansion definitions against a refined definition of hematoma expansion which includes IVH expansion.

7.4 SUBJECTS and METHODS:

Subjects:

Subjects were participants enrolled in the Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT (PREDICT) study.[15] Briefly, PREDICT was a prospective multicenter observational study of patients presenting with spontaneous hemorrhage under 6 hours enrolled from June 2006 to July 2012. Enrolled patients had baseline CT and CT-angiogram (CTA), follow-up imaging at 24 hours post-event, and serial clinical assessments including 90-day modified Rankin scale (mRS). Exclusion criteria was baseline hemorrhage volume >100mL, renal impairment precluding CTA, baseline modified Rankin scale (mRS) >3, and treatment with recombinant Factor VIIa, craniotomy for hematoma evacuation, or ventricular drainage prior to 24-hour repeat imaging. We further excluded patients who lacked follow-up imaging or 90-day mRS.

Primary Exposure and Outcome:

Our primary exposure was a revised definition of significant hematoma expansion. These new definitions were created by incorporating IVH expansion thresholds to pre-established absolute and relative thresholds. We chose "≥ 6 mL" and "≥6 mL or ≥33%" as our conventional definitions to modify due to their high frequency of use.[1,7,16,17] We used two IVH expansion thresholds in our comparative analysis, "IVH expansion ≥1 mL" and "any IVH expansion", as both have been shown to robustly predict poor outcome.[14] "Any IVH expansion" is defined as an interval increase in IVH hemorrhage volume or de novo IVH development at follow-up imaging. Repeat imaging was standardized in the PREDICT study at 24 hours. We assessed hematoma volumes in a blinded fashion at a central laboratory using computerized-planimetry software

(Quantomo Software, Cybertrial Inc., Calgary, Canada)[15,18,19] The revised definitions we assessed are as follows:

- ≥6 mL or ≥33% or IVH expansion ≥1 mL
- ≥6 mL or ≥33% or any IVH expansion
- ≥ 6 mL or IVH expansion ≥1 mL
- ≥ 6 mL or any IVH expansion

The primary outcome was poor clinical outcome at 90 days, defined as a modified Rankin Scale (mRS) of 4-6. Our secondary outcome was the reclassification of poor clinical outcome as mRS 2-6, 3-6, 5-6, or 6 (death).[20]

Statistical Analysis:

We calculated the sensitivity and specificity for all definitions. The overall diagnostic accuracy of each definition was expressed as a C-statistic and comparative analysis was performed using a non-parametric approach first proposed by deLong.[21] We built multivariable logistic regression models to test the relationships between the various definitions of hematoma expansion and the primary and secondary outcomes while adjusting for potential confounders. Backwards conditional stepwise selection was used to build a minimal model. Candidate covariates were derived with exploratory univariate analysis. Fisher's exact test, ANOVA, or Mann-Whitney U tests were used as appropriate. Continuous variables that did not conform to the linearity assumption were re-categorized into dichotomous or ordinal variables. We performed all

statistical analysis using SPSS v25.0 (IBM, Armonk, NY) and SAS v9.4 (SAS Institute Inc, Cary, NC).

Standard Protocol Approvals, Registrations, and Patient Consents:

Local research ethics board approval was obtained at all PREDICT-ICH enrolling sites. All patients provided written consent as per ethics board requirements at each site.

Data Availability Statement:

The PREDICT-ICH dataset is available for access to all PREDICT-ICH investigators and qualified researchers trained in human subject confidentiality protocols collaborating with PREDICT-ICH investigators.

7.5 RESULTS:

Cohort Characteristics:

The prospective PREDICT study enrolled 390 patients. Our primary analysis population included 256 patients who met the inclusion criteria (Figure 1). One hundred and thirty-four patients were excluded from our study: 32 patients were treated with recombinant Factor VIIa or surgical intervention (12 cases of emergent extra-ventricular drainage) prior to follow-up imaging and thus would confound interpretation of findings, 78 patients did not receive baseline or follow-up mRS scoring, and 24 patients were excluded due to missing imaging, delayed presentation, or having an alternative diagnosis other than ICH. Baseline patient characteristics are summarized in Table 1. Patients excluded from this study had larger baseline IVH volumes, larger net ICH volume change, and a greater proportion of spot sign presence.

At initial presentation, 84 patients (33%) had IVH. Baseline IVH was associated with concurrent thalamic ICH (62% [41/66] vs. 23% [43/190], $p<0.001$). Cases of de novo IVH development (i.e. not initially present at baseline) occurred in 33 (13%) patients and was associated with concurrent lobar hemorrhage. One patient exhibited full resolution of IVH at follow-up. At 24-hours, 116 patients (45%) had IVH. Twenty-four hour IVH was associated with thalamic ICH (68% [44/65] vs. 38% [72/191], $p<0.001$). Fifty-three patients (20.7%) had an interval IVH expansion of 1 mL or greater. IVH expansion of any form was observed in 74 patients (28.9%). Hematoma expansion, defined as "≥6 mL" or "≥6 mL or ≥33%" was observed in 66 (26%) and 80 (31%) patients, respectively. The number of patients classified with hematoma expansion increased with the use of revised definitions (Table 2).

Detailed cohort characteristics for each revised definition are outlined on Table 2 with stratification by hemorrhage expansion sub-type: standalone ICH expansion, standalone IVH expansion (ICH non-expanders) and individuals who had interval hematoma growth in both compartments. Approximately a third of patients had dual compartment hematoma expansion; this was consistently associated with spot sign presence. Between 20-29%, depending on the definition in use, exhibited IVH expansion without concurrent ICH growth. Standalone IVH expansion was consistently associated with thalamic ICH location. No significant differences in baseline ICH and IVH volume were observed between expansion sub-types.

Definition Performance:

Approximately 50% of patients (127/256) exhibited a poor clinical outcome (mRS 4-6) at 3 months. The calculated sensitivities and specificities for each definition are summarized in Table 3. For mRS 4-6, the revised definitions possessed higher sensitivities and lower specificities than the conventional definitions. This pattern was seen with both primary and secondary outcome measures. The overall diagnostic performance of revised definitions, "≥6mL or IVH expansion ≥ 1 mL", "≥6mL or any IVH expansion", "≥6 mL or ≥33% or any IVH expansion" was significantly better than either conventional definition tested.

All definitions were investigated with backwards conditional regression models. Exploratory analysis revealed associations between the primary outcome and age, previous stroke, history of anti-coagulant use, serum glucose, international normalized ratio (INR), baseline ICH volume, lobar location, spot sign presence, and baseline National Institute of Health Stroke Scale (NIHSS) scores ($p<0.10$ for each comparison, Table 4). Both baseline NIHSS, and INR did not

meet linearity assumptions. As such, baseline NIHSS was re-categorized as ≤5, 6-13, ≥14.[22] INR was re-categorized as a dichotomous variable, >2. Multivariable-adjusted regression analysis confirmed that all definitions independently predicted the primary outcome (Table 5). All definitions independently predicted secondary outcome ranges: mRS 5-6 and mRS 6 (death). None of the tested definitions showed strong associations with wider mRS ranges (2-6 and 3-6).

7.6 DISCUSSION:

In this study we aimed to determine whether the inclusion of IVH growth in current definitions of hematoma expansion could improve the predictive capability of long-term outcome. We found that revised definitions, which included IVH expansion thresholds of 1 mL or any IVH growth, possessed superior diagnostic accuracy compared to their contemporary counterparts. As one of the cornerstone outcome measures of both past and present ICH trials, the definition of significant hematoma expansion has undergone multiple iterative changes over the past 30 years.[20,23,24] This process is necessary, as how we define hematoma expansion is critical to ensuring that we do not under- or overestimate the treatment effects of potential therapies. The results of our analysis contribute to this iterative process and introduces IVH expansion as an important factor to account for when assessing hematoma expansion.

The performance of the two selected conventional definitions are in line with previous studies.[20,25] Both definitions were highly specific and independently associated with the primary outcome. However, both possessed modest sensitivities to detect poor clinical outcome. As a result, only a third of patients were classified as exhibiting hematoma expansion. Given that the majority of potential therapies are designed specifically to limit or prevent hematoma expansion, having only a minority of patients exhibit the event in question may result in an under-estimation of the treatment effect of a candidate therapy.

In contrast, the revised definitions exhibited significantly higher sensitivities and subsequently, more patients were classified with hematoma expansion. Using an IVH expansion threshold of 1

mL or greater resulted in 8% more patients (20/256 and 21/256) being classified with hematoma expansion. The use of a more liberal threshold of any IVH expansion resulted in a 13% increase (33/256 and 37/256). Naturally with an increase in sensitivity, a reduction is specificity is expected. This was observed with the revised definitions, however the reduction in magnitude only ranged from 75% to 83% compared to a range of 83% to 88%. As a result, the overall diagnostic accuracy was superior with each of the revised definitions.

A closer look at the hematoma expansion subgroups indicates to us that IVH growth occurs in a number of cases. Alongside the patients that had standalone IVH expansion (approximately a quarter of cases), a third of patients exhibited both intraparenchymal and intraventricular hemorrhage growth. Within each conventional definition, this sub-group accounts for 41% (33/80; ≥ 6mL or ≥ 33%) and 48% (32/66; ≥ 6mL) of expanders. Only a marginal majority of patients within the conventional definition possessed standalone ICH expansion. Standalone IVH expansion was associated with thalamic ICH location, a finding that is consistent with previous studies on IVH localalization.[26] A statistically significant relationship between the other locations and hemorrhage expansion sub-groups were not observed, however standalone ICH expansion and concurrent expansion appear to favor lobar and basal ganglia locations, respectively. Further investigations are warranted.

In comparison to each other, both revised thresholds performed similarly in regard to sensitivity, specificity, and overall diagnostic accuracy. The use of an ≥ 6mL combined with any IVH expansion appears to perform the best, however differences between each definition are difficult

to discriminate. One of the reasons a threshold of any IVH expansion was selected in our original study[14] was because it could be more easily applied by practicing clinicians at the bedside. Whilst the use of imaging technology has allowed us to make IVH measurements with relatively high precision,[27] changes in IVH volume are difficult to assess in real time. Using either threshold may be appropriate in clinical trial scenarios where post-processing can be easily conducted by blinded investigators, whereas the use of any IVH expansion has more universal appeal overall.

To account for variability in hematoma measurement techniques, we have previously argued that planimetric ICH volume assessment should be expressed as total volume (ICH + IVH).[19] It therefore follows that a revised definition incorporating IVH growth should be expressed as a threshold for total expansion, rather than our current proposal for a combination of expansion thresholds within the respective compartments. But we have since demonstrated that the relationship between IVH expansion and clinical outcome is non-linear and mathematically complex: minimal amounts of IVH growth are associated with significant increases in poor outcome.[14] Therefore, the use of total volume as a hematoma expansion definition requires a mathematical model that differentially weights volume changes in each compartment. This need to measure individual compartments negates the aforementioned advantage of using total volume planimetric assessment, and also introduces a more complex formula to determine hematoma expansion.

This study has several limitations. For the purposes of maintaining analytic rigor we excluded patients with missing imaging and outcome data. We also excluded patients who had undergone hematoma evacuation or ventricular drainage placement prior to 24-hour repeat imaging, as these interventions directly affect hemorrhage volume. These actions may bias our sample towards a primary analysis population less severely affected by their hemorrhage. Withdrawal of care information was also not collected and therefore it is not clear whether the presence of intraparenchymal or intraventricular expansion influenced this particular decision.[20] In addition, each definition was not significantly associated with broader mRS ranges (2-6, 3-6). While most studies utilize 4-6 or higher, a small number have also utilized mRS 3-6[28] and this may limit the applicability of these definitions. Finally, while our study was performed in a well characterized prospective cohort, this was a retrospective analysis and further validation in independent datasets is required to ensure generalizability. If independent and prospective validation confirms the results of our study, application of these revised definitions in future hemostatic trials could be considered.

Conclusions:

Definitions of hematoma expansion are improved when they incorporate intraventricular expansion. These revised definitions possess superior diagnostic accuracy compared to their conventional counterparts and may inform future hemostatic ICH trials.

Author Contributions

Vignan Yogendrakumar, MD	University of Ottawa	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Tim Ramsay, PhD	University of Ottawa	Author	Interpreted the data; assisted in data analysis; revised the manuscript for intellectual content
Dean Fergusson, PhD	University of Ottawa	Author	Interpreted the data; revised the manuscript for intellectual content
Andrew M Demchuk, MD	University of Calgary	Author	Major role in the acquisition of data; revised the manuscript for intellectual content
Richard I Aviv, MBChB	University of Toronto	Author	Major role in data acquisition
David Rodriguez-Luna, MD	Hospital Universitari Vall d'Hebron	Author	Major role in data acquisition
Carlos A Molina, MD PhD	Hospital Universitari Vall d'Hebron	Author	Major role in data acquisition
Yolanda Silva Blas, MD	Dr. Josep Trueta University Hospital	Author	Major role in data acquisition
Imanuel Dzialowski, MD	Technische University	Author	Major role in data acquisition
Adam Kobayashi, MD PhD	2nd Department of Neurology, Warsaw Poland	Author	Major role in data acquisition
Jean-Martin Boulanger, MD	University of Sherbrooke	Author	Major role in data acquisition
Cheemun Lum, MD	University of Ottawa	Author	Major role in data acquisition
Gord Gubitz, MD	Dalhousie University	Author	Major role in data acquisition
Vasantha Padma, MD	All India Institute of Medical Sciences	Author	Major role in data acquisition
Jayanta Roy, MD	Apollo Gleaneagles Hospital	Author	Major role in data acquisition
Carlos S. Kase, MD	Boston Medical Center	Author	Major role in data acquisition
Rohit Bhatia, MD	All India Institute of Medical Sciences	Author	Major role in data acquisition
Michael D. Hill, MD	University of Calgary	Author	Major role in the acquisition of data; revised the manuscript for intellectual content
Joshua N Goldstein, MD PhD	Harvard University	Author	Major role in the acquisition of data; Assisted with study design; revised the manuscript for intellectual content
Dar Dowlatshahi, MD PhD	University of Ottawa	Author	Major role in the acquisition of data; design and conceptualized study; revised the manuscript for intellectual content

7.7 MANUSCRIPT REFERENCES:

1. Sprigg N, Flaherty K, Appleton JP, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet (London, England)*. 2018;391(10135):2107-2115.

2. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med*. 2016;375(11):1033-1043.

3. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358(20):2127-2137.

4. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke*. 2004;35(6):1364-1367.

5. Wang X, Arima H, Al-Shahi Salman R, et al. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. *Stroke*. 2015;46(2):376-381.

6. Broderick JP, Diringer MN, Hill MD, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke*. 2007;38(3):1072-1075.

7. Meretoja A, Churilov L, Campbell BC V, et al. The spot sign and tranexamic acid on preventing ICH growth--AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. *Int J Stroke*. 2014;9(4):519-524.

8. Tuhrim S, Horowitz DR, Sacher M, Godbold JH. Volume of ventricular blood is an

important determinant of outcome in supratentorial intracerebral hemorrhage. *Crit Care Med*. 1999;27(3):617-621.

9. Hanley DF. Intraventricular hemorrhage: severity factor and treatment target in spontaneous intracerebral hemorrhage. *Stroke*. 2009;40(4):1533-1538.

10. Maas MB, Nemeth AJ, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Delayed intraventricular hemorrhage is common and worsens outcomes in intracerebral hemorrhage. *Neurology*. 2013;80(14):1295-1299.

11. Witsch J, Bruce E, Meyers E, et al. Intraventricular hemorrhage expansion in patients with spontaneous intracerebral hemorrhage. *Neurology*. 2015;84(10):989-994.

12. Dowlatshahi D, Deshpande A, Aviv RI, et al. Do Intracerebral Hemorrhage Nonexpanders Actually Expand Into the Ventricular Space? *Stroke*. 2018;49(1):201-203.

13. Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. *Neurosurgery*. 2006;59(4):767-773.

14. Yogendrakumar V, Ramsay T, Fergusson D, et al. New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage. *Neurology*. 2019;Accepted:In press.

15. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol*. 2012;11(4):307-314.

16. Qureshi AI, Palesch YY, Barsan WG, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med*. 2016;375(11):1033-1043.

17. Liu L, Wang Y, Meng X, et al. Tranexamic acid for acute intracerebral hemorrhage growth predicted by spot sign trial: Rationale and design. *Int J Stroke*. 2017;12(3):326-331.

18. Kosior JC, Idris S, Dowlatshahi D, et al. Quantomo: validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. *Int J Stroke*. 2011;6(4):302-305.

19. Dowlatshahi D, Kosior JC, Idris S, et al. Planimetric Hematoma Measurement in Patients With Intraventricular Hemorrhage: Is Total Volume a Preferred Target for Reliable Analysis? *Stroke*. 2012;43(7):1961-1963.

20. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. 2011;76(14):1238-1244.

21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.

22. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. *Stroke*. 2003;34(1):134-137.

23. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28(1):1-5.

24. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. 1996;27(10):1783-1787.

25. Brouwers HB, Chang Y, Falcone GJ, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. *JAMA Neurol*. 2014;71(2):158-164.

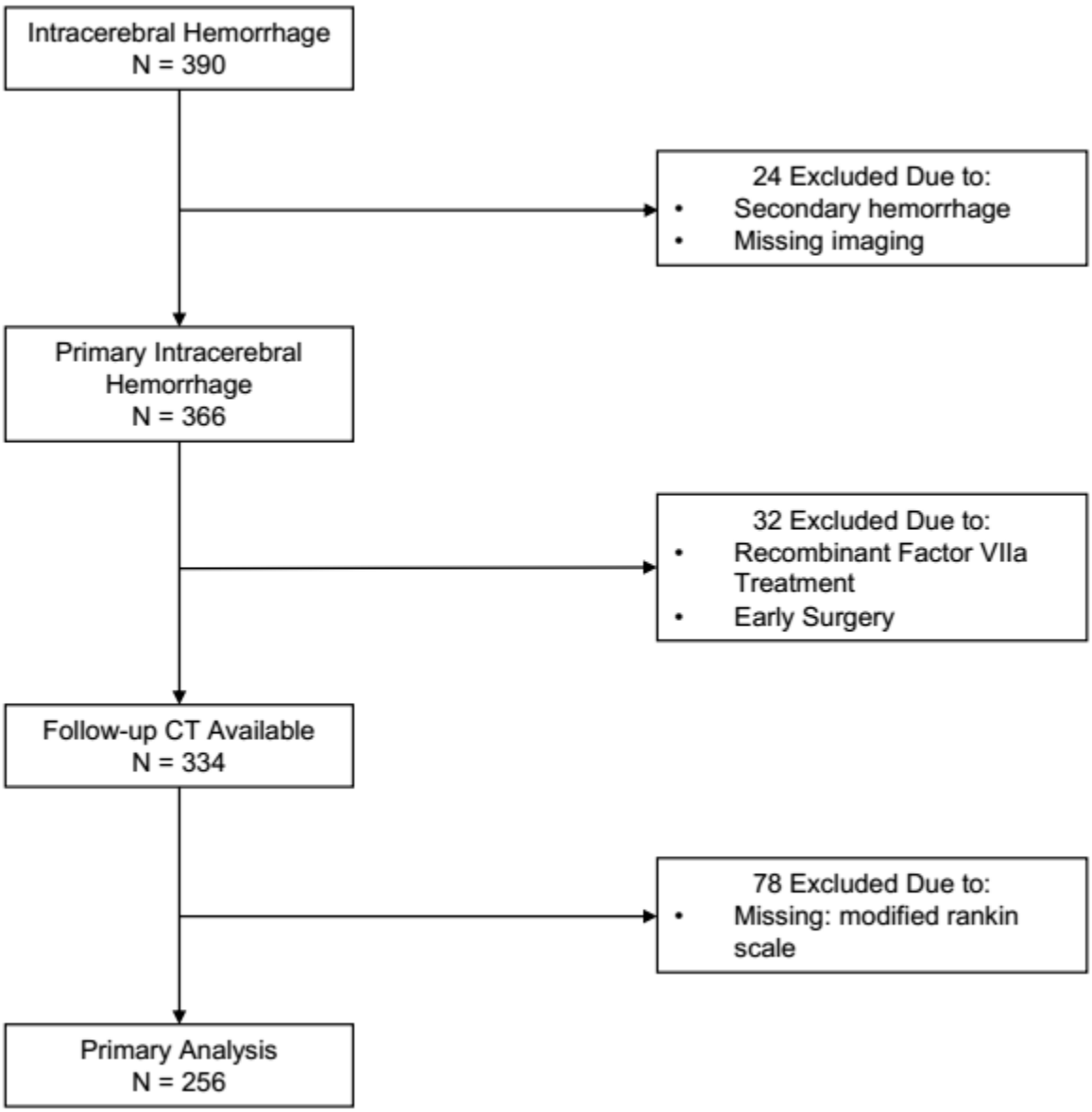
26. Hallevi H, Albright KC, Aronowski J, et al. Intraventricular hemorrhage: Anatomic relationships and clinical implications. *Neurology*. 2008;70(11):848-852.

27. Dowlatshahi D, Kosior JC, Idris S, et al. Planimetric hematoma measurement in patients with intraventricular hemorrhage: is total volume a preferred target for reliable analysis? *Stroke*. 2012;43(7):1961-1963.

28. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355-2365.

7.8 FIGURES:

Figure 1: Patient Selection Flowchart:



7.9 TABLES:

Table 1: Baseline Patient Characteristics:

Characteristics	Included (N = 256)	Excluded (N=134)	P-value
Age, years (median; IQR)	70 (57-79)	69 (57-81)[a]	0.649
Male Sex (n, %)	155 (60.5%)	74 (55.6%)	0.351
Medical History (n, %)			
Hypertension	190 (74.2%)	87 (65.4%)	0.069
Coronary Artery Disease	24 (9.4%)	13/88 (14.8%)	0.159
Congestive Heart Failure	4 (1.6%)	1/88 (1.1%)	0.773
Hypercholesterolaemia	58 (22.7%)	19/88 (21.6%)	0.836
Diabetes Mellitus	48 (18.8%)	13/88 (14.8%)	0.399
Antiplatelet Usage	23 (9.0%)	16 (12.0%)	0.343
Anticoagulant Usage	20 (7.8%)	17 (12.8%)	0.113
Previous Stroke	23 (9.0%)	11/88 (12.5%)	0.340
Prior Hemorrhage	7 (2.7%)	7/88 (8.0%)	0.033
Baseline Clinical Information (median; IQR)			
Systolic Blood Pressure, mmHg	173 (151-195)	173 (147-200)[b]	0.914
Diastolic Blood Pressure, mmHg	93 (80-105)	96 (80-110)[b]	0.128
Glucose, mmol/L	7.1 (6.1-9.1)[c]	7.0 (5.9-8.6)[b]	0.279
NIH Stroke Scale	14 (6-18)[c]	14 (8-19)[c]	0.236
International normalized ratio	1.0 (1.0-1.1)[b]	1.0 (0.9-1.1)[d]	0.689
Partial Thromboplastin Time, seconds	29 (26-31)[e]	30 (28-34)[f]	0.006
Platelets, $x10^9$ cells per L	215 (175-266)[b]	242 (207-296)[d]	0.001
Time to CT, min	137 (89-221)	143 (88-246)[a]	0.285
Imaging			
Baseline ICH Volume, mL (median; IQR)	12.94 (6.02-26.14)	15.95 (8.45-35.83)[g]	0.035
Baseline IVH Volume, mL (mean; SD)	3.04 (7.30)	6.19 (11.15)[g]	<0.001
Lobar Hemorrhage (n,%)	74/255 (29.0%)	44/126 (34.9%)	0.241
Spot Sign Positive (n,%)	67 (26.5%)	49 (36.8%)	0.035

[a]Missing 1 value, [b]Missing 3 values, [c]Missing 2 values, [d]Missing 5 values, [e]Missing 7 values, [f]Missing 11 values, [g]Missing 8 values

Abbreviations: ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; IQR: interquartile range; SD: standard deviation

Table 2: Cohort Characteristics of each Revised Definition: Stratified by Hemorrhage Expansion Type

	≥ 6mL or ≥ 33% or IVH Expansion ≥ 1mL (100/256)			**≥ 6mL or ≥ 33% or Any IVH Expansion (113/256)**		
	Concurrent Expansion (n=33)	ICH Expansion Alone (n=47)	IVH Expansion Alone (n=20)	Concurrent Expansion (n=41)	ICH Expansion Alone (n=39)	IVH Expansion Alone (n=33)
Baseline Location (n, %)						
Lobar Location	11 (33.3%)	21 (44.7%)	8 (40.0%)	12 (29.3%)	20 (51.2%)	14 (42.4%)
Thalamic Location	8 (24.2%)	7 (14.9%)	9 (45.0%)*	10 (24.4%)	5 (12.8%)	13 (39.4%)*
Basal Ganglia Location	18 (54.5%)*	21 (44.7%)	4 (20.0%)	22 (53.7%)	17 (43.6%)	9 (27.3%)
Spot Sign (n, %)	22 (66.7%)*	13 (27.7%)	5 (25.0%)	25 (61.0%)*	10 (25.6%)	10 (31.3%)
Baseline ICH Volume (mL, mean, SD)	26.54 (16.05)	23.11 (19.56)	29.99 (24.74)	24.59 (16.11)	24.44 (20.31)	28.58 (22.49)
Baseline IVH Volume (mL, mean, SD)	5.63 (9.56)	2.23 (6.92)	5.61 (6.01)	4.90 (8.78)	2.30 (7.48)	4.07 (5.23)
	≥ 6mL or IVH Expansion ≥ 1mL (87/256)			**≥ 6mL or Any IVH Expansion (103/256)**		
	Concurrent Expansion (n=32)	ICH Expansion Alone (n=34)	IVH Expansion Alone (n=21)	Concurrent Expansion (n=37)	ICH Expansion Alone (n=29)	IVH Expansion Alone (n=37)
Baseline Location (n, %)						
Lobar Location	11 (34.4%)	19 (55.9%)	8 (38.1%)	12 (32.4%)	18 (62.1%)*	14 (37.8%)
Thalamic Location	7 (21.9%)	2 (5.9%)	10 (47.6%)*	8 (21.6%)	1 (3.4%)	15 (40.5%)*
Basal Ganglia Location	17 (53.1%)	16 (47.1%)	5 (23.8%)	20 (54.1%)	13 (44.8%)	11 (29.7%)
Spot Sign (n, %)	22 (68.8%)*	12 (35.3%)	5 (25.0%)	25 (67.6%)*	9 (31.0%)	10 (27.0%)
Baseline ICH Volume (mL, mean, SD)	26.94 (16.14)	29.40 (19.47)	29.22 (24.37)	26.49 (15.76)	30.39 (20.26)	26.26 (22.31)
Baseline IVH Volume (mL, mean, SD)	5.31 (9.53)	2.29 (7.84)	6.10 (6.27)	4.79 (9.01)	2.44 (8.41)	4.27 (5.40)

* $p<0.05$; χ^2 or Fisher's test

Abbreviations: ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; SD: standard deviation

Table 3: Direct Comparisons of the Sensitivity and Specificity of the Revised and Conventional Definitions of Hematoma Expansion

	Conventional Definition		**IVH Expansion ≥ 1mL**		**Any IVH Expansion**	
mRS Range	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
≥ 6mL or ≥ 33%						
2-6	34.7 (28.1 – 41.7)	80.7 (68.1 – 89.9)	43.2 (36.2 – 50.4)	75.4 (62.2 – 85.9)	48.2 (41.1 – 55.4)	70.2 (56.6 – 81.6)
3-6	39.9 (32.4 – 47.7)	85.2 (76.1 – 91.9)	49.4 (41.6 – 57.2)	80.7 (70.8 – 88.3)	55.4 (47.5 – 63.0)	77.3 (67.1 – 85.5)
4-6	**45.7 (36.8 – 54.7)**	**82.9 (75.3 – 88.9)**	**56.7 (47.6 – 65.5)**	**78.3 (70.2 – 85.1)**	**63.8 (54.8 – 72.1)**	**75.2 (66.8 – 82.4)**
5-6	51.9 (40.3 – 63.5)	77.7 (70.8 – 83.5)	61.0 (49.3 – 71.9)	70.4 (63.1 – 76.9)	67.5 (55.9 – 77.8)	65.9 (58.5 – 72.8)
6	59.3 (45.8 – 71.9)	77.2 (70.7 – 82.8)	69.5 (53.1 – 80.8)	70.1 (63.1 – 76.4)	76.3 (63.4 – 86.4)	65.5 (58.4 – 72.1)
C-Statistic*	0.64		0.67 (p=0.057) †		0.69 (p=0.013) †	
≥ 6mL						
2-6	29.6 (23.4 – 36.5)	87.7 (76.3 – 94.9)	38.7 (31.9 – 45.8)	82.5 (70.1 – 91.3)	44.7 (37.7 – 51.9)	75.4 (62.2 – 85.9)
3-6	33.9 (26.8 – 41.6)	89.8 (81.5 – 95.2)	44.0 (36.4 – 51.9)	85.2 (76.1 – 91.9)	51.2 (43.4 – 58.9)	80.7 (70.9 – 88.3)
4-6	**40.2 (31.6 – 49.2)**	**88.4 (81.6 – 93.3)**	**52.0 (42.9 – 60.9)**	**83.7 (76.2 – 89.6)**	**60.6 (51.6 – 69.2)**	**79.8 (71.9 – 86.4)**
5-6	49.4 (37.8 – 61.0)	84.4 (78.2 – 89.4)	58.4 (46.6 – 69.6)	76.5 (69.6 – 82.5)	66.2 (54.6 – 76.6)	70.9 (63.7 – 77.5)
6	55.9 (42.4 – 68.8)	83.2 (77.3 – 88.2)	66.1 (52.6 – 77.9)	75.6 (69.0 – 81.5)	74.6 (61.6 – 85.0)	70.1 (63.1 – 76.4)
C-Statistic*	0.64		0.68 (p=0.036) †		0.70 (p=0.0062) †	

*For Primary Outcome (mRS4-6)

†Non-parametric comparison to Conventional Definition

Abbreviations: IVH: intraventricular hemorrhage; CI: confidence intervals

Table 4: Univariate Predictors of Poor Outcome, n=256

Baseline Characteristics	**mRS 4-6 (N = 127)**	**mRS 0-3 (N =129)**	**P**
Age, years (median; IQR)	75 (17)	62 (20)	<0.001
Male Sex (n, %)	72 (56.7%)	83 (64.3%)	0.211
Medical History (n, %)			
Hypertension	97 (76.4%)	93 (72.1%)	0.433
Coronary Artery Disease	13 (10.2%)	11 (8.5%)	0.639
Congestive Heart Failure	2 (1.6%)	2 (1.6%)	0.987
Hypercholesterolaemia	26 (20.5%)	32 (24.8%)	0.408
Diabetes Mellitus	25 (19.7%)	23 (17.8%)	0.704
Antiplatelet Usage	12 (9.4%)	11 (8.5%)	0.797
Anticoagulant Usage	14 (11.0%)	6 (4.7%)	0.057
Previous Stroke	16 (12.6%)	7 (5.4%)	0.045
Prior Hemorrhage	5 (3.9%)	2 (1.6%)	0.242
Baseline Clinical Information (median; IQR)			
Systolic Blood Pressure, mmHg	174 (43)	170 (43)	0.650
Diastolic Blood Pressure, mmHg	93 (24)	92 (27)	0.220
Glucose, mmol/L	7.3 (3.3)	6.8 (2.9)	0.074
National Institute of Health Stroke Scale	17 (6)	7 (10)	<0.001
premorbid modified Rankin Score	0 (0)	0 (0)	0.137
International normalized ratio > 2, (n, %)	14/125 (11.2%)	5/128 (3.9%)	0.028
Partial Thromboplastin Time, seconds	28 (6)	29 (4)	0.456
Platelets, $x10^9$ cells per L	212 (107)	224 (85)	0.591
Time to CT, min	131 (119)	143 (149)	0.286
Imaging (mean; Standard deviation)			
Baseline ICH Volume, mL	26.7 (19.9)	11.24 (11.4)	<0.001
ICH Change, mL	12.8 (22.4)	2.7 (6.8)	<0.001
Baseline IVH Volume, mL	4.6 (9.4)	1.6 (4.0)	<0.001
IVH Change, mL	3.8 (11.8)	0.4 (2.9)	<0.001
Lobar Hemorrhage (n,%)	47/126 (37.3%)	27 (20.9%)	0.004
Spot Sign Positive (n,%)	44/126 (34.9%)	23/127 (18.1%)	0.002

Abbreviations: ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; IQR: interquartile range

Table 5: Multivariable Logistic Regression Models of Revised and Conventional Definitions for the Prediction of Primary (Bolded) and Secondary Outcomes (n=256) [a]

Outcome Range (mRS)	Conventional Definition aOR (95% CI)	IVH Expansion ≥ 1mL aOR (95% CI)	Any IVH Expansion aOR (95% CI)
≥ 6mL or ≥ 33%			
2-6	1.01 (0.44-2.32)	0.99 (0.45-2.18)	0.86 (0.40-1.86)
3-6	2.08 (0.94-4.62)	1.98 (0.95-4.14)	1.91 (0.94-3.88)
4-6	**2.36 (1.16-4.80)**	**2.47 (1.27-4.82)**	**2.58 (1.33-4.99)**
5-6	2.62 (1.30-5.27)	2.12 (1.06-4.22)	1.82 (0.89-3.72)
6	3.41 (1.59-7.29)	3.25 (1.51-6.98)	3.44 (1.54-7.66)
≥ 6 mL			
2-6	1.34 (0.52-3.46)	1.44 (0.63-3.29)	0.83 (0.36-1.90)
3-6	1.91 (0.77-4.73)	1.79 (0.80-4.00)	1.64 (0.78-3.45)
4-6	**2.58 (1.17-5.67)**	**2.61 (1.29-5.29)**	**2.71 (1.38-5.33)**
5-6	3.30 (1.57-6.91)	2.30 (1.14-4.65)	1.94 (0.95-3.97)
6	3.81 (1.75-8.31)	3.24 (1.51-6.94)	3.39 (1.54-7.49)

[a]Adjusted for Age, Baseline Intracerebral Hemorrhage Volume, Baseline National Institute of Health Stroke Scale (0-5, 6-13, 14+)

Abbreviations: IVH: intraventricular hemorrhage; aOR: adjusted odds ratio; CI: confidence intervals

CHAPTER EIGHT: THESIS SUMMARY and DISCUSSION

This chapter provides a summary of thesis findings, highlights strengths and limitations, and outlines the next steps for future research including knowledge translation and dissemination.

In this thesis, we sought to advance the current understanding of hematoma expansion, one of the major pathological events that can determine outcome after acute intracerebral hemorrhage. We first began with a review of hematoma expansion in Chapter 2, discussing its pathophysiology, reviewing the major clinical and radiological predictors associated with expansion, and finally, exploring the historical development of determining what amount of hematoma growth is clinically significant. Through this process we identified several knowledge gaps in the literature and explored these gaps further in the subsequent chapters of this broad thesis.

In Chapters 3 and 4, we performed a scoping review to assess the current state of hematoma expansion prediction scores in the literature. Our review identified ten scores built from varying combinations of clinical and radiological variables. We observed significant heterogeneity in variable selection, and we hypothesize this may be the result of the derivation process using cohort samples of modest to moderate size. Our hypothesis is supported by the fact that while most scores reported moderate performance with c-statistics ranging from 0.72-0.92 during the derivation process, scores that underwent external validation reported modest performance with c-statistics as low as 0.62. The most glaring observation from our analysis was the lack of mainstream adoption of prediction scores in general. Beyond the original derivational study and the occasional external validation study, we did not find many examples of scores being used in trials, prospective cohorts, or in guideline recommendations. This is unfortunate, as although

imperfect, scores such as BRAIN, 9-point, and BAT possess more consistent predictive capability than single variables alone.

This begs the larger question: why are these scores not being used? Complexity in use, limited imaging expertise, or limited access to contrast may play all play a role, but ultimately, the cause(s) is not clear. A potential way to clarify this is to ask clinicians (neurologists, neurosurgeons, intensivists, emergency physicians) directly, through the use of a structured survey. The range of responses may be heterogenous, but first understanding what pieces of clinical information are being most commonly utilized at the bedside by clinicians may assist us in developing prediction tools that are practical and accessible. In addition, investigators hoping to develop future scores should only do so in a large cohort of patients, and should consider pre-selecting variables: time to CT, baseline hemorrhage volume, anticoagulant use, and antiplatelet use. These four variables stood out in a recently performed large individual patient data meta-analysis[62] and the first three were the most consistently observed between prediction scores in our review.

Only half of the scores in our review had undergone necessary external validation. In light of this fact, we attempted to independently validate the Hematoma Expansion Prediction (HEP) score using a multicenter, prospective hemorrhage cohort. Our validation analysis (Chapter 5) showed that the HEP score performed modestly with an AUC of 0.64 but was independently associated with significant expansion (≥6mL or ≥33%) and performed similarly to the spot sign (AUC of 0.65). We chose to evaluate the HEP score because unlike the other scores assessed in Chapter 4, the HEP score requires the least amount of neuroradiological knowledge and is more dependent

on clinical data. As such, this score may be more appealing for use in centers where contrast access or radiological expertise is limited. While far from being the most superior prediction tool, the HEP score has the potential to assist clinicians with predicting expansion and deterioration when used in the right context.

In Chapters 7 and 8, we shifted our focus from predicting hematoma expansion to re-examining how we define significant expansion. Dichotomous definitions of hematoma expansion are used extensively in the literature as an outcome measure in both clinical trials and observational studies. We hypothesized that the use of total blood volume in a definition of hematoma expansion would better predict long-term outcome. In the first phase of this study we first sought to understand the relationship between ventricular hemorrhage expansion and long-term outcome and used a data driven approach, comparing changes in intraventricular hemorrhage volume over 24 hours and using fractional polynomials to characterize the non-linear relationship between IVH expansion and outcome (Chapter 7). We found that even minimal increases in ventricular hemorrhage at 24 hour follow-up was strongly associated of death and disability at 90 days. We therefore selected two thresholds, IVH expansion ≥ 1mL and any IVH expansion, and validated these in a separate hemorrhage cohort. Our selected thresholds performed similarly in the validation cohort and were deemed appropriate to use in the second phase of this study. In Chapter 8 we integrated these thresholds into conventional definitions of hematoma expansion already widely in use, creating a revised definition of significant hematoma expansion:

- ≥6 mL or ≥33% or IVH expansion ≥ 1mL
- ≥6 mL or ≥33% or any IVH expansion

We chose this approach as we felt that integrating ventricular thresholds into pre-established definitions would be easily accessible and still adequately incorporate the influence of IVH hemorrhage expansion. When compared to their conventional counterparts both revised definitions exhibited higher sensitivities with only minimal decreases in specificity. The overall diagnostic accuracy (represented as an c-statistic) of the revised definitions were significantly improved to the conventional definitions. These findings support our original hypothesis and provide an argument that IVH expansion is an additional factor that should be accounted for when we assess hematoma expansion.

Our study is strengthened by the use of a multi-center prospectively collected intracerebral hemorrhage cohort. However, this was a retrospective analysis and our cohort was only moderate in sample size. Several incremental steps are therefore recommended to further validate our revised definitions:

1) Validation Analysis with multiple hemorrhage datasets (retrospective).
2) Perform a prospective observational study (preferably multi-center).
3) Broaden outcome measures – consider assessing shorter and longer term outcomes (one month mortality, one year mRS etc.)
4) Assess the performance of the definitions with both research staff and bedside clinicians

Once validated and refined, we intend to advocate for the definition's widespread adoption as a preferred outcome measure in future treatment trials.

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet (London, England)* [Internet]. 2009;373:1632–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19427958

2. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet. Neurol.* [Internet]. 2012;11:101–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22172625

3. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. *Cerebrovasc. Dis.* [Internet]. 2013;35:195–201. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23466430

4. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet. Neurol.* [Internet]. 2010;9:167–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20056489

5. Gokhale S, Caplan LR, James ML. Sex differences in incidence, pathophysiology, and outcome of primary intracerebral hemorrhage. *Stroke* [Internet]. 2015;46:886–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25657181

6. Ovesen C, Christensen AF, Havsteen I, Krarup Hansen C, Rosenbaum S, Kurt E, et al. Prediction and prognostication of neurological deterioration in patients with acute ICH: a hospital-based cohort study. *BMJ Open* [Internet]. 2015;5:e008563. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26220872

7. Fan J-S, Huang H-H, Chen Y-C, Yen DH-T, Kao W-F, Huang M-S, et al. Emergency department neurologic deterioration in patients with spontaneous intracerebral hemorrhage: incidence, predictors, and prognostic significance. *Acad. Emerg. Med.* [Internet]. 2012;19:133–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22320363

8. Leira R, Dávalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, et al. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology* [Internet]. 2004;63:461–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15304576

9. Lim-Hing K, Rincon F. Secondary Hematoma Expansion and Perihemorrhagic Edema after Intracerebral Hemorrhage: From Bench Work to Practical Aspects. *Front. Neurol.* [Internet]. 2017 [cited 2017 Aug 24];8:74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28439253

10. Schlunk F, Greenberg SM. The Pathophysiology of Intracerebral Hemorrhage Formation and Expansion. *Transl. Stroke Res.* [Internet]. 2015 [cited 2017 Aug 24];6:257–263. Available from: http://link.springer.com/10.1007/s12975-015-0410-1

11. Auriel E, Greenberg SM. The pathophysiology and clinical presentation of cerebral amyloid angiopathy. *Curr. Atheroscler. Rep.* [Internet]. 2012;14:343–50. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22565298

12. Brouwers HB, Falcone GJ, McNamara KA, Ayres AM, Oleinik A, Schwab K, et al. CTA spot sign predicts hematoma expansion in patients with delayed presentation after intracerebral hemorrhage. *Neurocrit. Care* [Internet]. 2012;17:421–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22878870

13. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J. Neuropathol. Exp. Neurol.* [Internet]. 1971;30:536–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4105427

14. Greenberg SM, Nandigam RNK, Delgado P, Betensky RA, Rosand J, Viswanathan A, et al. Microbleeds versus macrobleeds: evidence for distinct entities. *Stroke* [Internet]. 2009;40:2382–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19443797

15. Greenberg CH, Frosch MP, Goldstein JN, Rosand J, Greenberg SM. Modeling intracerebral hemorrhage growth and response to anticoagulation. *PLoS One* [Internet]. 2012;7:e48458. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23119028

16. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke* [Internet]. 2009;40:1325–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19286590

17. Boulouis G, Morotti A, Brouwers HB, Charidimou A, Jessel MJ, Auriel E, et al. Noncontrast Computed Tomography Hypodensities Predict Poor Outcome in Intracerebral Hemorrhage Patients. *Stroke* [Internet]. 2016;47:2511–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27601380

18. Dowlatshahi D, Smith EE, Flaherty ML, Ali M, Lyden P, Demchuk AM, et al. Small intracerebral haemorrhages are associated with less haematoma expansion and better outcomes. *Int. J. Stroke* [Internet]. 2011;6:201–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21557804

19. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke.* 1993;24:987–993.

20. Dowlatshahi D, Smith EE, Flaherty ML, Ali M, Lyden P, Demchuk AM, et al. Small intracerebral haemorrhages are associated with less haematoma expansion and better outcomes. *Int. J. Stroke* [Internet]. 2011;6:201–206. Available from: http://dx.doi.org/10.1111/j.1747-4949.2010.00563.x

21. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J. Neurosurg.* [Internet]. 1994;80:51–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8271022

22. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J. Neurosurg.* 1994;80:51–7.

23. Blacquiere D, Demchuk AM, Al-Hazzaa M, Deshpande A, Petrcich W, Aviv RI, et al. Intracerebral Hematoma Morphologic Appearance on Noncontrast Computed Tomography Predicts Significant Hematoma Expansion. *Stroke* [Internet]. 2015;46:3111–

6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26451019

24. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast Computed Tomography Markers of Intracerebral Hemorrhage Expansion. *Stroke* [Internet]. 2017;48:1120–1125. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28289239

25. Al-Nakshabandi NA. The swirl sign. *Radiology* [Internet]. 2001;218:433. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11161158

26. Selariu E, Zia E, Brizzi M, Abul-Kasim K. Swirl sign in intracerebral haemorrhage: definition, prevalence, reliability and prognostic value. *BMC Neurol.* [Internet]. 2012;12:109. Available from: http://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-12-109

27. Kim J, Smith A, Hemphill JC, Smith WS, Lu Y, Dillon WP, et al. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. *Am. J. Neuroradiol.* 2008;29:520–525.

28. Li Q, Zhang G, Xiong X, Wang X-C, Yang W-S, Li K-W, et al. Black Hole Sign: Novel Imaging Marker That Predicts Hematoma Growth in Patients With Intracerebral Hemorrhage. *Stroke* [Internet]. 2016;47:1777–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27174523

29. Li Q, Zhang G, Huang Y-J, Dong M-X, Lv F-J, Wei X, et al. Blend Sign on Computed Tomography: Novel and Reliable Predictor for Early Hematoma Growth in Patients With Intracerebral Hemorrhage. *Stroke* [Internet]. 2015;46:2119–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26089330

30. Li Q, Liu Q-J, Yang W-S, Wang X-C, Zhao L-B, Xiong X, et al. Island Sign: An Imaging Predictor for Early Hematoma Expansion and Poor Outcome in Patients With Intracerebral Hemorrhage. *Stroke* [Internet]. 2017;48:3019–3025. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29018128

31. Shimoda Y, Ohtomo S, Arai H, Okada K, Tominaga T. Satellite Sign: A Poor Outcome Predictor in Intracerebral Hemorrhage. *Cerebrovasc. Dis.* [Internet]. 2017;44:105–112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28605739

32. Yu Z, Zheng J, Ma L, Guo R, Li M, Wang X, et al. The predictive accuracy of the black hole sign and the spot sign for hematoma expansion in patients with spontaneous intracerebral hemorrhage. *Neurol. Sci.* [Internet]. 2017;Available from: http://www.ncbi.nlm.nih.gov/pubmed/28577268

33. Morotti A, Boulouis G, Romero JM, Brouwers HB, Jessel MJ, Vashkevich A, et al. Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. *Neurology* [Internet]. 2017;89:548–554. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28701501

34. Du F-Z, Jiang R, Gu M, He C, Guan J. The Accuracy of Spot Sign in Predicting Hematoma Expansion after Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis. *PLoS One* [Internet]. 2014;9:e115777. Available from:

http://dx.plos.org/10.1371/journal.pone.0115777

35. Dowlatshahi D, Wasserman JK, Momoli F, Petrcich W, Stotts G, Hogan M, et al. Evolution of computed tomography angiography spot sign is consistent with a site of active hemorrhage in acute intracerebral hemorrhage. *Stroke.* [Internet]. 2014 [cited 2014 Nov 11];45:277–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24178918

36. Goldstein J, Fazen L, Snider R, Schwab K, Greenberg S, Smith E, et al. Contrast Extravasation on CT Angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology*. 2007;68:889–894.

37. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA. Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. *Stroke* [Internet]. 1999;30:2025–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10512902

38. Murai Y, Takagi R, Ikeda Y, Yamamoto Y, Teramoto A. Three-dimensional computerized tomography angiography in patients with hyperacute intracerebral hemorrhage. *J. Neurosurg.* [Internet]. 1999;91:424–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10470817

39. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007;38:1257–1262.

40. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina C a, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol.* [Internet]. 2012;11:307–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22405630

41. Huynh TJ, Aviv RI, Dowlatshahi D, Gladstone DJ, Laupacis A, Kiss A, et al. Validation of the 9-Point and 24-Point Hematoma Expansion Prediction Scores and Derivation of the PREDICT A/B Scores. *Stroke* [Internet]. 2015;46:3105–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26463691

42. Falcone GJ BA. PRedictors of hematoma volume in deep and lobar supratentorial intracerebral hemorrhage. *JAMA Neurol.* [Internet]. 2013;1–7. Available from: http://dx.doi.org/10.1001/jamaneurol.2013.98%5Cnhttp://archneur.jamanetwork.com/data/Journals/NEUR/0/jamaneurol.2013.98.pdf

43. Yao X, Xu Y, Siwila-Sackman E, Wu B, Selim M. The HEP Score: A Nomogram-Derived Hematoma Expansion Prediction Scale. *Neurocrit. Care* [Internet]. 2015;23:179–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25963292

44. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P, CHANT Investigators. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke* [Internet]. 2008;39:2993–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18703803

45. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology* [Internet].

2004;63:1059–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15452298

46. Di Napoli M, Parry-Jones AR, Smith CJ, Hopkins SJ, Slevin M, Masotti L, et al. C-reactive protein predicts hematoma growth in intracerebral hemorrhage. *Stroke* [Internet]. 2014;45:59–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24262327

47. Naidech AM, Jovanovic B, Liebling S, Garg RK, Bassin SL, Bendok BR, et al. Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke* [Internet]. 2009;40:2398–401. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19443791

48. Sansing LH, Messe SR, Cucchiara BL, Cohen SN, Lyden PD, Kasner SE. Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. *Neurology* [Internet]. 2009;72:1397–1402. Available from: http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000342709.31341.88

49. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* [Internet]. 2007;38:1072–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17290026

50. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* [Internet]. 2004;35:1364–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15118169

51. Sakamoto Y, Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. *Stroke* [Internet]. 2013;44:1846–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23704107

52. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet. Neurol.* [Internet]. 2008;7:391–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18396107

53. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N. Engl. J. Med.* [Internet]. 2016;375:1033–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27276234

54. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke* [Internet]. 1996;27:1783–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8841330

55. Newman GC. Clarification of abc/2 rule for ICH volume. *Stroke* [Internet]. 2007;38:862. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17255550

56. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* [Internet]. 1997;28:1–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8996478

57. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology* [Internet]. 2011;76:1238–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21346218

58. Chang EF, Meeker M, Holland MC. Acute traumatic intraparenchymal hemorrhage: risk factors for progression in the early post-injury period. *Neurosurgery* [Internet]. 2006;58:647–56; discussion 647-56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16575328

59. Delcourt C, Huang Y, Arima H, Chalmers J, Davis SM, Heeley EL, et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. *Neurology* [Internet]. 2012;79:314–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22744655

60. Rodriguez-Luna D, Boyko M, Subramaniam S, Klourfeld E, Jo P, Diederichs BJ, et al. Magnitude of Hematoma Volume Measurement Error in Intracerebral Hemorrhage. *Stroke* [Internet]. 2016;47:1124–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26892283

61. Kosior JC, Idris S, Dowlatshahi D, Alzawahmah M, Eesa M, Sharma P, et al. Quantomo: validation of a computer-assisted methodology for the volumetric analysis of intracerebral haemorrhage. *Int. J. Stroke* [Internet]. 2011;6:302–305. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21609412

62. Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet. Neurol.* [Internet]. 2018;17:885–894. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30120039

APPENDIX I: HEMATOMA EXPANSION SCORE SCOPING REVIEW – Protocol

Publication: Yogendrakumar V, Moores M, Sikora L, Ramsay T, Fergusson D, Dowlatshahi D. Evaluating the Predictive Capabilities of Hematoma Expansion Scores in Patients with Acute Intracerebral Hemorrhage: Protocol for a Scoping Review. *BMJ Open.* 2019;9:e024744.

Contents:

Review/Publication History

- Submitted to *BMJ Open*: June 11, 2018
- Revised (Major Revision): September 7, 2018
- Accepted for Publication: October 31, 2018
- First Published: January 21, 2019

BMJ Open

Evaluating the predictive capabilities of haematoma expansion scores in patients with acute intracerebral haemorrhage: protocol for a scoping review

Vignan Yogendrakumar,[1] Margaret Moores,[1] Lindsey Sikora,[2] Tim Ramsay,[3] Dean A Fergusson,[3] Dar Dowlatshahi[1]

To cite: Yogendrakumar V, Moores M, Sikora L, *et al*. Evaluating the predictive capabilities of haematoma expansion scores in patients with acute intracerebral haemorrhage: protocol for a scoping review. *BMJ Open* 2019;**9**:e024744. doi:10.1136/bmjopen-2018-024744

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-024744).

Received 11 June 2018
Revised 7 September 2018
Accepted 31 October 2018

[1]Ottawa Stroke Program, The Ottawa Hospital: Division of Neurology, University of Ottawa, Ottawa, Ontario, Canada
[2]Health Sciences Library, University of Ottawa, Ottawa, Ontario, Canada
[3]Ottawa Methods Center, Ottawa Hospital Research Institute, University of Ottawa School of Epidemiology, Public Health and Preventative Medicine, Ottawa, Ontario, Canada

Correspondence to
Dr Vignan Yogendrakumar;

ABSTRACT

Introduction Patients presenting with acute intracerebral haemorrhage are at a high risk of exhibiting haematoma expansion, a phenomenon that can significantly worsen long-term functioning. Numerous clinical and radiological factors are associated with expansion. In a bid to better select patients at increased risk of expanding, these factors have been collated together into clinical scores. Several clinical scores have been developed, but comparisons of diagnostic potential between these scores are limited and the frequency of use in clinical trial enrolment is unknown.

Objective To perform a scoping review of haematoma expansion scores and explore numerous factors such as the methodology of development and diagnostic capabilities.

Methods and analysis MEDLINE, PubMed, EMBASE, CENTRAL and ClinicalTrials.gov will be searched with assistance from an experienced information specialist. Eligible studies will involve adults presenting with spontaneous intracerebral haemorrhage who received baseline assessments, follow-up imaging and risk stratification through a haematoma expansion score. Reviewers will independently extract data from the included studies and will collect data on patient demographics and medical history, details on score development, diagnostic capabilities and usage proportions. Analysis of extracted data will focus on comparing the predictive capability of each score and similarities/differences in score development. The exact analysis technique will be dictated on the type of data extracted.

Ethics and dissemination Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through conference presentations and peer-reviewed publications.

Strengths and limitations of this study

- This review will perform a detailed assessment of prediction scores in their current form which has not been conducted previously.
- The use of a scoping review methodology allows flexibility in assessment and may assist in the preparation of a formal diagnostic test accuracy systematic review.
- Quality of evidence will not be evaluated in this scoping review.
- Limitations in this study include heterogeneity in the primary outcome measure (several definitions of haematoma expansion exist in the literature, not all studies may use the same definition) and changes in the overall management of intracerebral haemorrhage that may limit the extent of haematoma expansion observed.
- This study may highlight unexpected strengths, weaknesses and areas requiring increased focus for future prediction tool development.

INTRODUCTION

Intracerebral haemorrhage and haematoma expansion

Spontaneous intracerebral haemorrhage, the non-traumatic rupture of cerebral blood vessels, is the most devastating stroke subtype and is a major cause of morbidity and mortality across the world.[1] One-month mortality can be high as 55% and a large proportion of survivors often suffer severe long-term disability.[2] The high morbidity and mortality associated with intracerebral haemorrhage is secondary to the dynamic nature of the disease. The size of an intracerebral haemorrhage is rarely a static fixture: it can change after initial presentation, often enlarging in size. This enlargement of haematoma volume, formally termed as haematoma expansion, is a major cause of the poor long-term outcome.[3] It occurs early in the presentation, and has become the therapeutic target of choice in recent clinical trials.[4–6]

Unfortunately, therapies that are designed to mitigate haematoma expansion date have been largely unsuccessful at improving patient outcomes.[6–8] An inability to precisely select the patients most at risk of expansion, and therefore most likely to benefit from therapy, has been considered a potential reason for this lack of success. As such, investigation into the predictors of haematoma expansion has been a major research focus

for intracerebral haemorrhage experts worldwide. It is the hope that by accurately selecting patients who are at the highest risk of expansion, future trials will be better able to evaluate the effectiveness of their respective treatments.

Predicting haematoma expansion

Given that the diagnosis of intracerebral haemorrhage is confirmed with imaging, the majority of expansion predictors are radiological. A multitude of imaging variables has been identified as potential predictors.[9 10] Certain clinical variables, such as concomitant antithrombotic use and time of presentation, also play a significant role in influencing expansion.[11] These factors are used together in combination to develop predictive models designed to optimise patient selection accuracy. These models are subsequently simplified into clinical scores for ease of use in day-to-day practice. In the past 5 years alone, several prediction scores were created.[12–14] While the diagnostic capabilities of each score have been assessed by the creating teams on an individual basis, there is no clear consensus of which tool has the best predictive capability. No in-depth or comparative analysis of the scores has been performed and no systematic or scoping review has been conducted to date. It is also unclear whether these tools have been used in recent or ongoing clinical trials.

Objective

Perform a scoping review of the literature assessing the predictive capabilities and extent of use of haematoma expansion scores developed for use in clinical treatment trials. Using the population, concept, context (PCC) elements our clinical objectives are as follows:

1. Describe the characteristics of each score and how each score was developed.
2. Outside of the original derivation studies, have scores been externally validated, used in recent randomised controlled trials or been proposed for use in upcoming studies?
3. Collate and compare the diagnostic capabilities between scores (discrimination, calibration, sensitivity, specificity, positive predictive, negative predictive values).

METHODS

Study registration

This study will be conducted based on the guidelines of the Joanna Briggs Institute (JBI) Methodology for Scoping Reviews.[15] The findings of this study will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of Scoping Reviews (PRISMA). This protocol will be reported, using PRISMA-Protocols and JBI guidelines.[15 16]

Inclusion/exclusion criteria

Eligibility criteria were established using the PCC framework. Studies will be selected according to the following criteria:

Participants

Included studies will involve adult patients (≥18 years of age) presenting with spontaneous intracerebral haemorrhage (haemorrhagic stroke), confirmed with either CT or MRI. Eighteen is the threshold age for adulthood used in the majority of haemorrhage trials. Paediatric intracerebral haemorrhage is more often secondary to intravascular lesions and malignancy and hence will not be included in this review. Patients presenting solely with a haemorrhage of another type (subarachnoid, subdural, epidural) with not be included in this review. Haemorrhages with a known secondary aetiology (tumour, vascular malformation, trauma) will also be excluded.

Concept

The major concepts we hope to explore in this scoping review are haematoma expansion and the predictive models, haematoma expansion scores, that have been developed to try and accurately predict this phenomenon in patients presenting with acute intracerebral haemorrhage. An expansion score is defined as a collection of variables, clinical, radiological or both, that have been identified and weighted in a way such that patients presenting with higher cumulative scores are at a higher risk of exhibiting an expansion of their baseline haematoma. We aim to look at the original studies which derived a respective score, subsequent studies that validated and compared different scores to each other, and clinical trials or observational cohorts which used these scores as a clinical tool. Because our primary objective is to learn about both the diagnostic capability and prevalence of use of these scores, we will be evaluating original research contributions, systematic reviews, meta-analysis and guideline documents where appropriate. Studies focused solely on a single clinical or radiological predictor (eg, blend sign) will be excluded from our analysis. There is clear evidence to show that no single variable adequately predicts haematoma expansion.[9 17]

Haematoma expansion acts as the outcome of interest in this scoping review. Expansion is evaluated by assessing the change in haematoma volume at initial presentation to follow-up imaging usually performed at the 24–48 hours mark. Expansion can be reported as the net change in volume or as a dichotomous outcome via a predetermined definition of haematoma expansion (eg, haematoma enlargement >6 mL). There are several definitions of haematoma expansion in current use today and we will use whichever definitions have been decided on by the study authors. However, only studies that provide a dichotomous definition of haematoma expansion would be used in any subsequent summary analysis.

Context

There is no restriction on healthcare locations, although we expect most studies will involve patients who were treated in an emergency room, intensive care unit or neurological/neurosurgical ward. We also have no restrictions on country of study, ethnicity, gender or socioeconomic status.

Information sources and search strategy

For the purposes of our scoping review, we will include data from primary research studies (with no limitation to study design), previously published systematic reviews, meta-analysis and guidelines that pertain to the topics of haematoma expansion and predictive scores. We will only include studies that are presented in the English language due to constraints in translational resources. A search strategy was developed (see online supplementary appendix) using keywords and Medical Subject Headings (MeSH) terms relating to intracerebral haemorrhage and haematoma expansion. This search strategy will be used on the following four databases: MEDLINE (via Ovid), Embase (via Ovid), PubMed, Cochrane CENTRAL (via Ovid), from date of inception to June 2018. Supplementary searches will include scanning the reference list of included studies and reviews identified through the primary search. Released abstracts from the last 10 years in the International Stroke Conference, European Stroke Organisation Conference or American Academy of Neurology Annual Meeting that have not been published in full manuscript form will also be screened to ensure completeness. Study authors will be contacted for further information as required.

Study records

Data management

Database search results will be downloaded and imported to EndNote Reference Manager Software (Clarivate Analytics, Philadelphia, Pennsylvania, USA) and then transferred to Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). After removal of duplicate results, citation titles and abstracts will be screened.

Selection process

At least two reviewers will independently screen articles in a two-level process. Level 1 will involve a title and abstract screening for potentially eligible studies. Studies that score a 'yes' or 'unsure' in this phase will be brought forward for full-text (level 2) evaluation. Full-text screening will use a precreated article screening form. In the event of a disagreement between the two authors in either stage, a third party neurologist will adjudicate. The process of study selection will be described using a PRISMA flow diagram.

Data extraction process and summarisation of results

Reviewers will independently extract data from the included studies using an a priori designed data extraction form. We will collect basic publication data (eg, year and journal of publication, authorship list, funding), study population information (demographic and medical history measures), details on score development (variables involved, development or validation methodology), definition of haematoma expansion used and markers of diagnostic accuracy (c-statistic, calibration, sensitivity/specificity/positive and negative predictive values). The basic make-up of each score will be compared side to side in a tabular format. The underlying methodology used to develop each score will be described descriptively. Study authors will be contacted for further information on score development if deemed necessary.

The analysis of diagnostic summary markers will ultimately be dependent on the data we are able to extract from each study. If possible, we aim to compare the accuracy of each score through multiple pairwise comparisons. Because each score is reported on a continuous scale, multiple positivity thresholds may exist. In this case, we would aim to make comparisons based on the summary reciever operating characteristic (ROC) curves. Due to the potential concern of data paucity, we plan to use test accuracy data from all eligible studies that have evaluated one or more of these scores and will include data from both derivation and validation cohorts. If possible, data from validation cohorts will be examined separately in a sensitivity analysis. To account for changes in clinical practice and intracerebral haemorrhage management, studies published in differing time periods or studies with significant differences in baseline populations may be assessed separately in sensitivity analysis. If the data extracted makes meta-analysis not possible, we will compare the diagnostic summary markers descriptively. As data synthesis is not the primary aim of a scoping review, a formal assessment of the methodological quality of the included studies will not be performed.

Patient and public involvement

Because the collected data within this scoping review originates from previously published studies, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

Dissemination

The findings of this review and analysis may aid scientists in future clinical trial development and guide future research endeavours, including the development of a formal diagnostic test accuracy systematic review. We will, therefore, disseminate the findings of our work through conference presentations, the popular press and a peer-reviewed publication.

CONCLUSION

Early haematoma expansion presents a compelling therapeutic target for spontaneous intracerebral haemorrhage. Optimal patient selection is critical to identify those at highest risk of expansion for enrolment into future

intracerebral haemorrhage trials. Expansion scores have been proposed as a method to improve patient selection. Our study will inform future clinical trials by systematically assessing the literature to identify, and analyse, the diagnostic abilities and potential limitations of existing haematoma expansion scores.

Contributors VY is the guarantor. VY, MM, TR, DAF and DD drafted the manuscript protocol. VY, DAF and DD contributed to the development of the selection criteria, article screening strategy and data extraction criteria. VY and LS developed the search strategy. All authors read, provided feedback and approved the final protocol.

Funding This study did not receive any specific funding or sponsor supports. DD is supported by a Heart and Stroke Foundation New Investigator Award and a University of Ottawa Department of Medicine Clinician-Scientist Chair.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study does not require primary data collection and no local research ethics board approvals were acquired.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet* 2009;373:1632–44.
2. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol* 2012;11:101–18.
3. Dowlatshahi D, Demchuk AM, Flaherty ML, *et al*. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology* 2011;76:1238–44.
4. Mayer SA, Brun NC, Begtrup K, *et al*. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777–85.
5. Anderson CS, Huang Y, Wang JG, *et al*. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008;7:391–9.
6. Mayer SA, Brun NC, Begtrup K, *et al*. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;358:2127–37.
7. Qureshi AI, Palesch YY, Barsan WG, *et al*. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016;375:1033–43.
8. Sprigg N, Flaherty K, Appleton JP, *et al*. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* 2018;391:2107–15.
9. Boulouis G, Morotti A, Charidimou A, *et al*. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. *Stroke* 2017;48:1120–5.
10. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, *et al*. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol* 2012;11:307–14.
11. Broderick JP, Diringer MN, Hill MD, *et al*. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke* 2007;38:1072–5.
12. Yao X, Xu Y, Siwila-Sackman E, *et al*. The hep score: a nomogram-derived hematoma expansion prediction scale. *Neurocrit Care* 2015;23:179–87.
13. Huynh TJ, Aviv RI, Dowlatshahi D, *et al*. Validation of the 9-point and 24-point hematoma expansion prediction scores and derivation of the predict A/B Scores. *Stroke* 2015;46:3105–10.
14. Wang X, Arima H, Al-Shahi Salman R, *et al*. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. *Stroke* 2015;46:376–81.
15. Institute TJB. *Methdology for Scoping Reviews: Joanna Briggs Institute Reviewers' Manual: 2015 edition / Supplement*. Adelaide: The Joanna Briggs Institute, 2015.
16. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
17. Dowlatshahi D, Brouwers HB, Demchuk AM, *et al*. Predicting intracerebral hemorrhage growth with the spot sign: the effect of onset-to-scan time. *Stroke* 2016;47:695–700.

APPENDIX II: HEMATOMA EXPANSION SCORE SCOPING REVIEW

Publication: Yogendrakumar V, Moores M, Sikora L, Shamy M, Ramsay T, Fergusson D, Dowlatshahi D. Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review. *Stroke.* Under Review (May 2019).

Contents:

Review/Publication History

- Submitted to *Stroke*: May 27, 2019

Yogendrakumar, Vignan

From:
Sent: Monday, May 27, 2019 5:34 PM
To: Yogendrakumar, Vignan
Subject: STROKE/2019/026467 Approved MS Received

MS ID#: STROKE/2019/026467
MS TITLE: Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review
AUTHORS: Vignan Yogendrakumar, Margaret Moores, Lindsay Sikora, Michel Shamy, Timothy Ramsay, Dean Fergusson, and Dar Dowlatshahi

Dear Dr. Yogendrakumar,

On May 27, 2019, the manuscript entitled "Evaluating Hematoma Expansion Scores in Acute Intracerebral Hemorrhage: A Systematic Scoping Review" was approved for submission by the corresponding author. The manuscript will be checked in by staff. Manuscripts that do not pass the initial review by the editorial office staff will be returned to the corresponding author for correction PRIOR to review. It is possible that you may receive another notification if the manuscript has been corrected and submitted again.

The manuscript has been assigned the number STROKE/2019/026467.

Sincerely,

Rebecca Seastrong
Managing Editor

APPENDIX III: INDEPENDENT VALIDATION OF A NON-CONTRAST HEMATOMA EXPANSION PREDICTION SCORE

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Selim M, Dowlatshahi D. Independent Validation of the Hematoma Expansion Prediction Score: A Non-Contrast Score Equivalent in Accuracy to the Spot Sign. *Neurocritical Care.* Published ahead of print: May 2019. doi.org/10.1007/s12028-019-00740-5

Contents:

Review/Publication History

- Submitted to *Neurocritical Care:* January 16, 2019
- Revised (Major Revision): February 28, 2019
- Revised (Minor Revision): April 11, 2019
- Accepted for Publication: May 6, 2019
- First Published: May 23, 2019

Neurocrit Care
https://doi.org/10.1007/s12028-019-00740-5

NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Independent Validation of the Hematoma Expansion Prediction Score: A Non-contrast Score Equivalent in Accuracy to the Spot Sign

Vignan Yogendrakumar[1*], Tim Ramsay[2,3], Dean A. Fergusson[2,3], Andrew M. Demchuk[4], Richard I. Aviv[5], David Rodriguez-Luna[6], Carlos A. Molina[6], Yolanda Silva Blas[7], Imanuel Dzialowski[8], Adam Kobayashi[9,10], Jean-Martin Boulanger[11], Cheemun Lum[12], Gord Gubitz[13], Padma Srivastava[14], Jayanta Roy[15], Carlos S. Kase[16], Rohit Bhatia[14], Michael D. Hill[4], Magdy Selim[17] and Dar Dowlatshahi[1,3] on behalf of the PREDICT/Sunnybrook CTA Study Group

Abstract

Background and Purpose: The computed tomography angiography (CTA) spot sign is widely used to assess the risk of hematoma expansion following acute intracerebral hemorrhage (ICH). However, not all patients can receive intravenous contrast nor are all hospital systems equipped with this technology. We aimed to independently validate the Hematoma Expansion Prediction (HEP) Score, an 18-point non-contrast prediction scale, in an external cohort and compare its diagnostic capability to the CTA spot sign.

Methods: We performed a retrospective analysis of the predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT (PREDICT) Cohort Study. Primary outcome was significant hematoma expansion ($\geq$ 6 mL or $\geq$ 33%). We generated a receiver operating characteristic (ROC) curve comparing the HEP score to significant expansion. We calculated sensitivity, specificity, positive and negative predictive values (PPV/NPV) for each score point. We determined independent predictors of significant hematoma expansion via logistic regression.

Results: A total of 292 patients were included in primary analysis. Hematoma growth of $\geq$ 6 mL or $\geq$ 33% occurred in 94 patients (32%). The HEP score was associated with significant expansion (adjusted odds ratio [aOR] 1.14, 95% confidence interval [CI] 1.01–1.30). ROC curves comparing HEP score to significant expansion had an area under the curve of 0.64 (95% CI 0.57–0.71). Youden's method showed an optimum score of 4. HEP Scores $\geq$ 4 ($n = 100$, sensitivity 49%, specificity 73%, PPV 46%, NPV 75%, aOR 1.99, 95% CI 1.09–3.64) accurately predicted significant expansion. PPV increased with higher HEP scores, but at the cost of lower sensitivity. The diagnostic characteristics of the spot sign ($n = 82$, Sensitivity 49%, Specificity 81%, PPV 55%, NPV 76%, aOR 2.95, 95% CI 1.61–5.42) were similar to HEP scores $\geq$ 4.

Conclusion: The HEP score is predictive of significant expansion ($\geq$ 6 mL or $\geq$ 33%) and is comparable to the spot sign in diagnostic accuracy. Non-contrast prediction tools may have a potential role in the recruitment of patients in future intracerebral hemorrhage trials.

†Cheemun Lum: Deceased.
[1]Ottawa Stroke Program, Division of Neurology,
Full list of author information is available at the end of the article

Keywords: Intracerebral hemorrhage, Hematoma expansion, Prediction, Computed tomography, Computed tomography angiography

Introduction

Hematoma expansion is a major contributor to the morbidity and mortality associated with intracerebral hemorrhage (ICH) [1]. Current therapeutic approaches have had limited success in preventing hematoma expansion and improving outcomes. As only a proportion of patients experience hematoma expansion, optimizing patient selection to identify those at highest risk of expansion can increase the success of future trials [2].

Several baseline variables are associated with hematoma expansion and have been incorporated into prediction scores for bedside use [3–6]. Prediction scores allow selection of high-risk patients for enrollment in treatment trials and can also help clinicians identify patients at highest risk of deterioration. However, many scores require the use of intravenous (IV) contrast [5]. While the use of computed tomography (CT) has increased worldwide, access to IV contrast remains limited in certain jurisdictions. Most scores also require an accurate measurement of baseline ICH volume, which is a limiting factor for primary stroke centers that may not have 24-h access to neuro-radiological expertise [5–7]. As a result, the wide-spread implementation of these scores for trial recruitment or bedside practice is not always possible, and potentially limited to comprehensive care centers with advanced stroke expertise. An easy-to-use non-contrast prediction tool could be used to improve trial recruitment and may significantly improve triaging and resource allocation for primary stroke centers and acute stroke-ready community hospital systems.

The Hematoma Expansion Prediction (HEP) Score is an 18-point nomogram-derived non-contrast scale based on patient characteristics that can be easily acquired at the bedside [8]. We aimed to independently validate this tool, and to evaluate its predictive potential against the spot sign, a CT-angiogram (CTA) marker of hematoma expansion currently used in ongoing ICH treatment trials [9].

Subjects and Methods

Patients were participants in the predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT (PREDICT) study [10]. Local research ethics board approval was obtained at all enrolling sites, and written informed consent was obtained from all participants. The dataset is available for access to all PREDICT investigators and qualified researchers trained in human subject confidentiality protocols collaborating with PREDICT investigators.

Patients

Patients were participants consecutively enrolled from June 2006 to July 2012 into PREDICT, a prospective multicenter observational study of patients presenting with spontaneous ICH under 6 h. Patients had baseline CT and CTA, follow-up imaging at 24 h post-event, and serial clinical assessments. Exclusion criteria was ICH > 100 mL, known renal impairment precluding CTA, baseline modified Rankin scale > 3, or terminal illness. For this study, patients who lacked follow-up imaging or information related to HEP scoring were excluded. Also excluded were patients who received recombinant Factor VIIa or had craniotomy for hematoma evacuation or ventricular drainage prior to repeat imaging, as these interventions directly affect final hemorrhage volume at follow-up assessment.

Primary Exposure and Primary Outcome

The primary exposure was the HEP score at initial presentation. The HEP score is an 18-point nomogram that is dependent on six variables: (1) time to CT, (2) dementia history, (3) smoking status, (4) antiplatelet use, (5) Glasgow Coma Scale (GCS), and (6) presence of subarachnoid hemorrhage [8]. The points allocated to each variable are highlighted in Table 1. Five of the six variables were originally collected by PREDICT-ICH investigators during primary data collection at the time of first presentation (time from symptom onset to CT, dementia status, smoking status, antiplatelet use, baseline GCS). Dementia status was not distinguished by sub-type. Authors VY and DD assessed subarachnoid hemorrhage by reviewing baseline imaging data of all enrolled patients. Subarachnoid hemorrhage was defined as the presence of subarachnoid blood either adjacent or distinct to the primary hematoma. HEP scores were then calculated for each patient. The primary outcome of this study was significant hematoma expansion, defined as an absolute ICH growth of ≥ 6 mL or a relative growth of ≥ 33% on follow-up imaging [11]. Because varying definitions of hematoma growth may be used, the performance of the HEP score was also tested with another commonly used definition of hematoma expansion (≥ 12.5 mL or ≥ 33%) in a sensitivity analysis.

Table 1 Summary of the Hematoma Expansion Prediction Score

Risk factor	Categories	Point	Occurrence in PREDICT cohort ($n = 292$) (%)
Time to baseline CT < 3 h	No	0	34.9
	Yes	3	65.1
Diagnosis of dementia	No	0	94.5
	Yes	4	5.5
Current smoker	No	0	88.4
	Yes	3	11.6
Antiplatelet drug use	No	0	90.1
	Yes	3	9.9
GCS Score at presentation	3–5	3	0.3
	6–8	2	3.1
	9–11	1	14.7
	12–15	0	81.8
SAH at baseline	No	0	81.2
	Yes	2	18.8

CT computed tomography, *GCS* Glasgow coma scale, *PREDICT* predicting hematoma growth and outcome in intracerebral hemorrhage using contrast bolus CT, *SAH* subarachnoid hemorrhage

Statistical Analysis

A receiver operating characteristic (ROC) curve was generated by comparing HEP scores of each patient to the primary outcome. An area under the curve (AUC) with 95% confidence intervals (95% CI) was computed using stratified bootstrap replicates. We calculated the sensitivity, specificity, positive and negative predictive values (PPV/NPV) for each score point. In addition, the method of Youden was used to derive a mathematically optimal threshold score. Because the optimal cut-point derived from Youden's method is not an integer, several score thresholds were selected for further analysis. Multivariable logistic regression was used to adjust for potential confounding. Candidate covariates were derived with exploratory univariate analysis. Fisher's exact test, ANOVA, or Mann–Whitney *U* tests were used as appropriate ($p < 0.10$). Continuous variables that did not conform to the linearity assumption were re-categorized into dichotomous or ordinal variables [12]. Potential interactions were assessed using Wald or likelihood ratio testing. Baseline ICH volume, anticoagulant use, and spot sign are known major predictors of hematoma expansion [13] and were therefore forced into multivariable models a priori. Dichotomous threshold scores and the overall score (as a continuous variable) were both evaluated. Competing model accuracies expressed as AUCs were compared using deLong's method [14]. To further investigate the generalizability of the HEP score, the occurrence of each individual variable that makes up patient's individual HEP scores was calculated and the associations between each individual variable and hematoma expansion were also explored.

In post hoc analysis, spot sign was compared to the HEP score further by assessing the differences in predictive capability of patients who were spot sign positive but did not have sufficiently high HEP scores, to patients who were HEP ≥ 3 or HEP ≥ 4 and spot sign negative. We looked for a potential biological interaction (synergism) when combining spot sign with high threshold HEP scores through testing of relative excess risk due to interaction, attributable proportion due to interaction, and synergy index measures. In addition, both HEP score (as an ordinal variable) and spot sign were entered into linear regression models to better determine whether either variable is associated with hematoma growth that may be below pre-determined thresholds. Statistical analysis was performed using SPSS v24.0 (IBM, Armonk, NY) and SAS v9.4 (SAS Institute Inc, Cary, NC).

Results

The PREDICT study prospectively enrolled 390 patients presenting with spontaneous ICH. Of these, 98 were excluded from our study: 17 patients were excluded due to delayed presentation or having an alternative diagnosis other than spontaneous ICH (e.g., tumour). Twenty-four patients did not receive baseline or follow-up imaging. Thirty-one patients were treated with recombinant FVIIa treatment or surgical intervention prior to follow-up imaging, and 26 patients lacked data on GCS or subarachnoid hemorrhage status. Our primary analysis population included 292 patients. The occurrence of each variable associated with the HEP score is outlined in Table 1. Presentation within 3 h of symptom onset was observed in 65% of the primary analysis cohort. The presence of the other variables only ranged from 3 to 19%. Baseline patient characteristics are outlined in Table 2. Those excluded were similar to the primary analysis cohort on measured baseline factors. However, patients excluded from this study had larger baseline ICH and intraventricular (IVH) volumes.

Thirty-two percent (94/292) of the PREDICT cohort exhibited significant hematoma expansion. Exploratory analysis revealed associations between the primary outcome and anticoagulant use, history of previous stroke, baseline National Institute of Health Stroke Scale (NIHSS), partial thromboplastin time (PTT), serum creatinine, HEP score, baseline ICH volume, and spot sign status ($p < 0.1$, online-only data supplement). PTT, baseline ICH volume, and baseline NIHSS did not meet linearity assumptions. As such, PTT was re-categorized as a dichotomous variable, >35 s. Baseline ICH volume was re-categorized as: <10, 10–30, >30 mL, reflecting

Table 2 Baseline patient characteristics of the primary analysis cohort

Characteristics	Included (*N* = 292)	Excluded (*N* = 98)	*p*
Age, years (median; IQR)	71 (57–80)	68 (56–78)*	0.47
Male sex (*n*, %)	174 (60%)	55/97 (57%)	0.61
Medical history (*n*, %)			
Hypertension	218 (75%)	59/97 (61%)	0.01
Coronary artery disease	30 (10%)	7/52 (14%)	0.49
Congestive heart failure	5 (2%)	0/52 (0%)	0.34
Atrial fibrillation	29 (10%)	6/52 (12%)	0.83
Hypercholesterolaemia	62 (21%)	15/52 (29%)	0.22
Diabetes mellitus	54 (19%)	7/52 (14%)	0.38
Anticoagulant usage	26 (9%)	11/97 (11%)	0.48
Previous stroke	26 (9%)	8/52 (15%)	0.15
Prior hemorrhage	11 (4%)	3/52 (6%)	0.50
Baseline clinical information (median; IQR)			
Systolic blood pressure (mmHg)	173 (150–196)	172 (147–200)[‡]	0.89
Diastolic Blood Pressure (mmHg)	93 (80–109)	82 (81–110)[‡]	0.43
Glucose (mmol/L)	7 (6–9.1)*	7 (6–8.6)[§]	0.99
National Institute of Health Stroke Scale	14 (7–18)[†]	14 (7–20)[†]	0.33
Premorbid modified Rankin Score	0 (0–0)[‡]	0 (0–0)[#]	0.18
International normalized ratio	1.0 (1.0–1.1)[§]	1.0 (0.9–1.2)[§]	0.92
Partial thromboplastin time (s)	29 (27–32)|	30 (28–34)**	0.02
Platelets ($\times 10^9$ cells per L)	221 (180–272)[‡]	241 (203–299)[h]	0.06
Creatinine (μmol/L)	77 (65–92)[‡]	80 (65–93)[i]	0.39
Hematoma Expansion Scale characteristics			
Time to CT (min) (median; IQR)	142 (90–223)	130 (80–257)*	0.91
Dementia (*n*, %)	16 (6%)	0/52 (0%)	0.08
Current smoker (*n*, %)	34 (12%)	8/52 (15%)	0.45
Antiplatelet usage (*n*, %)	29 (10%)	10/97 (10%)	0.91
Glasgow Coma Scale (median, IQR)	15 (13–15)	14 (10–15)[j]	0.02
Subarachnoid hemorrhage (*n*, %)	55 (19%)	25/93 (27%)	0.09
HEP Score (median; IQR)	3 (2–5)	4 (3–6)[k]	0.03
Imaging (median; IQR)			
ICH volume (mL)	12.1 (6.1–25.9)	18.7 (9.9–44.6)[l]	< 0.01
IVH volume (mL)	0.0 (0–1.9)	1.0 (0.0–8.4)[l]	< 0.01
Spot sign positive	82/290 (28%)	34/96 (35%)	0.19

Equal variances not assumed for students *t* tests

CT computed tomography, *HEP* Hematoma Expansion Prediction Score, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *IVH* intraventricular hemorrhage

*Missing 1 value, [†]Missing 2 values, [‡]Missing 3 values, [§]Missing 4 values, |Missing 7 values, [#]Missing 49 values, **Missing 11 values, [h]Missing 5 values, [i]Missing 50 values, [j]Missing 51 values, [k]Missing 55 values, [l]Missing 8 values

past ICH analysis by Dowlatshahi et al. [15, 16] and large meta-analysis findings by Al-Shahi et al. [13]. Baseline NIHSS was re-categorized as ≤ 5, 6–13, ≥ 14 [17]. Adjusting for the relevant covariates, including spot sign, each 1-point increase in the HEP score was associated with a 14% increased odds of significant hematoma expansion (Table 3). Similar results were observed in a sensitivity analysis using ≥ 12.5 mL or $\geq 33\%$ as the definition of significant expansion (83 expansion events, adjusted odds ratio (aOR) 1.13 per 1-point increase, 95% CI 0.99–1.29). A ROC curve comparing HEP score to significant expansion possessed an AUC of 0.64 (Fig. 1). The discriminative capability of the HEP score was similar to the spot sign (AUC = 0.65, $p = 0.68$).

The calculated sensitivities, specificities, PPV/NPV of each HEP score point are summarized in the online-only data supplement. PPV increased with increasing scores, and sensitivity decreased correspondingly. As per the method of Youden, the mathematically optimal HEP threshold score was at 3.5. This clinically

Table 3 Multivariable-adjusted relationship between HEP Score (as a continuous variable) and significant hematoma expansion

Variable	Adjusted OR	95% CI
HEP Score	1.14	1.01–1.30
Spot Sign	2.71	1.47–5.00
Anticoagulant use	5.01	1.96–12.78
Creatinine	1.01	1.00–1.02
National Institute of Health Stroke Scale		
≤ (Ref)	–	–
6–13	1.44	0.55–3.79
≥ 14	2.93	1.11–7.08
Baseline intracerebral hemorrhage volume		
< 10 mL (Ref)	–	–
10–30 mL	1.13	0.54–2.35
> 30 mL	1.07	0.44–2.57

C-statistic: 0.77, Hosmer and Lemeshow goodness of fit: $p = 0.76$

CI confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio

corresponds to HEP scores of 3 or 4. Two hundred and nineteen (75%) patients had HEP scores ≥ 3. One hundred patients (34%) had HEP scores ≥ 4. After adjusting for the relevant covariates, threshold scores of ≥ 3 and ≥ 4 were associated with significant hematoma expansion (HEP ≥ 3: aOR 2.13, 95% CI 1.04–4.37//HEP ≥ 4: aOR 2.13, 95% CI 1.19–380). The diagnostic performance of spot sign was marginally better than that of the threshold scores (Table 4). The model c-statistics of both HEP ≥ 3 and HEP ≥ 4 were similar to the spot sign (0.73 vs. 0.76, $p = 0.16$; 0.74 vs. 0.76, $p = 0.44$). There was no clear difference in predictive performance when patients who were solely spot sign positive were directly compared to spot sign negative patients with HEP scores ≥ 4 in regression modeling (Table 5). Combining spot sign with the HEP score did not appear to have a synergistic effect on predicting significant hematoma expansion. In a univariate linear model, HEP score was significantly associated with any hematoma expansion (Parameter estimate: 0.88; $p = 0.03$). After adjusting for the relevant covariates, HEP score was not significantly associated with any hematoma expansion. In contrast, spot sign presence was associated

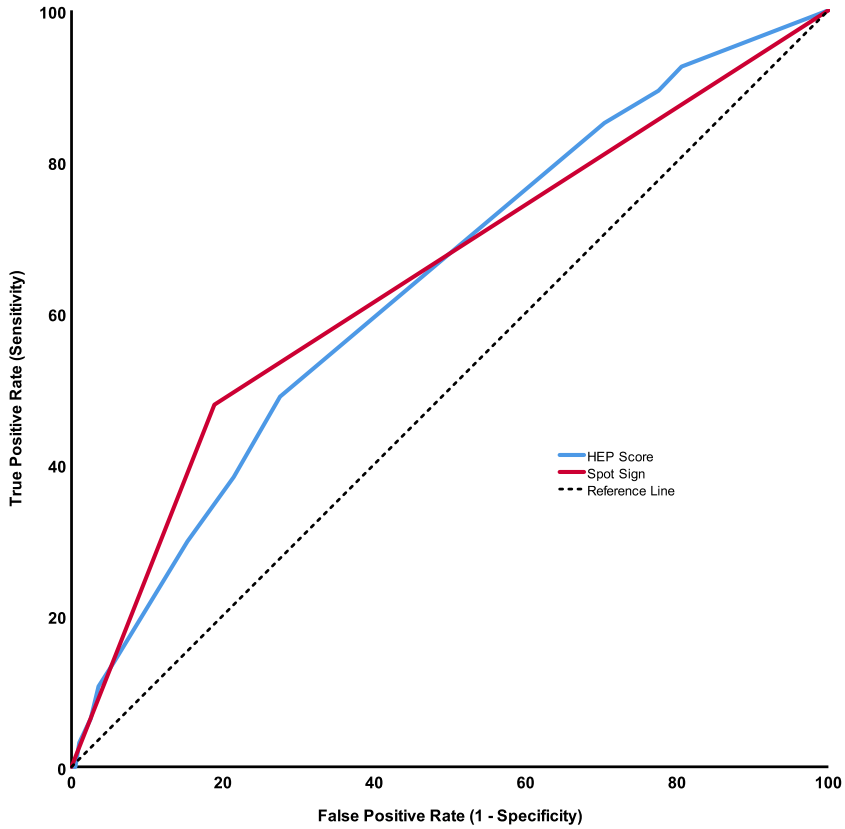


Fig. 1 Receiver operating characteristic curve comparing Hematoma Expansion Prediction (HEP) score and spot sign to significant hematoma expansion (≥ 6 mL or ≥ 33%). HEP Score, area under the curve (AUC): 0.64 (95% CI 0.57–0.71). Youden's Index: 3.5. Spot Sign, AUC: 0.65 (95% CI 0.58–0.72)

Table 4 Diagnostic capabilities of spot sign and HEP Score

	Frequency	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Adjusted OR (95% CI)*	Model C-statistic
Spot Sign	82 (28.3%)†	47.9	81.1	54.9	76.4	2.95 (1.61–5.42)	0.76
HEP ≥ 3	219 (75.0%)	85.1	29.8	36.5	80.8	2.14 (1.04–4.41)	0.73
HEP ≥ 4	100 (34.2%)	48.9	72.7	46.0	75.0	1.99 (1.09–3.64)	0.74

CI confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10–30 mL, > 30 mL), and baseline National Institute of Health Stroke Scale (≤ 5, 6–13, ≥ 14)

† Missing 2 values

Table 5 Direct comparisons of Hematoma Expansion (HEP) Score and spot sign

	Adjusted OR (95% CI)*		Adjusted OR (95% CI)*
Spot Sign − & HEP < 3	Ref	Spot Sign − & HEP < 4	Ref
Spot Sign − & HEP < 3	13.38 (2.33–77.01)	Spot Sign + & HEP < 4	3.79 (1.68–8.59)
Spot Sign − & HEP ≥ 3	3.06 (1.22–7.73)	Spot Sign − & HEP ≥ 4	2.56 (1.19–5.51)
Spot Sign + & HEP ≥ 3	7.08 (2.62–19.16)	Spot Sign + & HEP ≥ 4	5.86 (2.45–14.08)
Additive measures (95% CI)			
RERI	− 8.37 (− 30.42 to 13.69)	RERI	0.51 (− 4.43 to 5.36)
AP	− 1.18 (− 4.21 to 1.85)	AP	0.09 (− 0.70 to 0.87)
S Index	0.42 (0.09–1.89)	S Index	1.12 (0.40–3.16)

AP attributable proportion, *CI* confidence interval, *HEP* Hematoma Expansion Prediction Score, *OR* odds ratio, *RERI* relative excess risk due to interaction

*Adjusted for anticoagulant use, serum creatinine, baseline intracerebral hemorrhage volume (< 10 mL, 10–30 mL, > 30 mL) and baseline National Institute of Health Stroke Scale (≤ 5, 6–13, ≥ 14)

with any hematoma expansion, even after adjusting for the relevant covariates (Parameter estimate: 9.86; $p < 0.05$).

Discussion

We aimed to independently validate the HEP score and compare its predictive potential to the commonly used CTA spot sign. Our study used a real-world, pragmatic, observational ICH population with study subjects originating from 6 different countries (Canada, USA, Germany, Poland, Spain, and India) and data collected prospectively at the time of presentation. Our findings show that the HEP score independently predicts significant hematoma expansion and has similar test characteristics to the spot sign.

Our base findings reflect that of Yao and colleagues' original study on the HEP score [8]. Baseline patient characteristics between the development cohort and the primary analysis population were largely similar. There was a higher proportion of warfarin use and a higher median ICH volume reported in the development cohort [8], which is likely due to the exclusion of patients with hemorrhage volumes > 100 mL in the PREDICT study. Thirty-two percent of patients exhibited significant expansion, which is in keeping with prior reports and with the original development cohort [8, 18–20]. We found that HEP scores > 3 were at highest risk of expansion and our calculated c-statistics were similar to that of the development cohort [8]. The consistency in these findings supports the generalizability of the HEP score.

By using the PREDICT study, we were able to compare the performance of HEP to that of the CTA spot sign. Table 4 highlights our key findings and highlights that HEP scores ≥ 4 exhibited similar sensitivities/specificities to that of the spot sign. Spot sign had an improved specificity, but the discriminative capacity, indicated by the model c-statistics, was virtually identical. In addition, our post hoc analysis did not show a superiority in predictive performance between spot sign and HEP score in direct comparison. These findings are in keeping with previous studies [4, 7] and lend support to the notion that non-contrast predictive models have the capability of predicting hematoma expansion with an accuracy that can match the spot sign. Moreover, the proportion of patients observed with HEP scores ≥ 4 was greater than those observed with spot sign (34.2% vs 28.3%, respectively). Given spot sign ICH trials have experienced recruitment challenges (the spot sign for predicting and treating ICH growth study [STOP-IT], NCT00810888/"Spot Sign" selection of intracerebral hemorrhage to guide

hemostatic therapy [SPOTLIGHT], NCT01359202), non-contrast tools such as HEP may be a compelling alternative.

Al-Shahi et al. [13] recently identified baseline hemorrhage volume, time to CT, antiplatelet and anticoagulant use, and spot sign, as predictors of hematoma expansion in a large individual patient data meta-analysis. The HEP score complements these findings by utilizing two of the four major variables (antiplatelet use and early time to CT). As baseline hematoma volume assessment and IV contrast use may be challenging in primary stroke centers, the HEP score may act as a suitable substitute tool to use in these particular scenarios. Our findings show that the HEP score was predictive of significant expansion, independent of anticoagulant use. Anticoagulant use is well associated with hematoma expansion, and rapid reversal has already been shown to improve outcomes [21].

The components of the HEP score can be automatically calculated using information available in modern electronic medical records (EMR). This allows for its use as an EMR-based clinical decision rule or an automated clinical support application, analogous to VIZ.ai and MaxQ AI. Such applications can facilitate acute care decision making in the neurocritical care setting.

Our study has several limitations. Unlike the development cohort used by Yao et al. [8], the PREDICT cohort reported significantly lower rates of dementia and antiplatelet use. The former may be explained by the fact that the majority of ICH in the PREDICT cohort were non-lobar (70%), and therefore less likely to be associated with conditions such as amyloid angiopathy or dementia [22, 23]. The incidence of subarachnoid hemorrhage was comparable, but the number of patients with a time to CT < 3 h was significantly higher in the PREDICT population. Further work in a larger dataset is warranted to ensure generalizability. In addition, data around the early withdrawal of care were not available in this cohort. This introduces the potential for bias as these patients can be excluded from analysis due to lack of follow-up imaging. We also could not rule out a selection bias when excluding patients who underwent surgery or received hemostatic agents. Indeed, the primary difference between those included versus excluded from primary analysis was the higher ICH and IVH volumes observed in those, which is an independent predictor of hematoma expansion [13, 15, 24, 25]. Finally, while our study validates the use of HEP score to predict pre-specified hematoma expansion definitions, it does not imply that its components are directly related to the mechanistic aspects or pathophysiology of hematoma expansion. We see evidence of this in our post hoc linear regression analysis, where after adjusting for confounding, the HEP score is not associated with a range of hematoma growth. The HEP score, and the majority of other scores developed, was primarily designed to assess a threshold of hematoma expansion, and these findings provide useful information regarding the limitations of this type of predictive modeling.

Conclusion

In an independent, real-world cohort we confirmed that the HEP score is predictive of significant hematoma expansion. The HEP score is comparable to the spot sign in diagnostic accuracy and frequency when a threshold of significant expansion is used and may have a role in recruitment for future ICH treatment trials. However, the HEP score is limited in predictive capabilities when assessing lesser amounts of hematoma expansion.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-019-00740-5) contains supplementary material, which is available to authorized users.

Author details

[1] Ottawa Stroke Program, Division of Neurology, Department of Medicine (Neurology), University of Ottawa, Rome C2182, The Ottawa Hospital: Civic Campus, 1053 Carling Avenue, Ottawa, ON K1Y4E9, Canada. [2] Ottawa Methods Center, University of Ottawa, Ottawa, Canada. [3] Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada. [4] Calgary Stroke Program, Department of Clinical Neurosciences, Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada. [5] Division of Neuroradiology and Department of Medical Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada. [6] Department of Neurology, Hospital Universitari Vall d'Hebron, Barcelona, Spain. [7] Department of Neurology, Dr. Josep Trueta University Hospital, Institut d'Investigació Biomèdica Girona (IDIBGi) Foundation, Girona, Spain. [8] Department of Neurology, Elblandklinikum Meissen Academic Teaching Hospital of the Technische University, Dresden, Germany. [9] 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland. [10] Department of Experimental and Clinical Pharmacology, Institute of Psychiatry and Neurology, Warsaw, Poland. [11] Department of Medicine, Charles LeMoyne Hospital, University of Sherbrooke, Longueuil, Canada. [12] Department of Diagnostic Imaging (Neuroradiology Section), University of Ottawa, Ottawa, Canada. [13] Department of Neurology, Dalhousie University, Halifax, Canada. [14] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India. [15] Apollo Gleneagles Hospitals, Kolkata, India. [16] Department of Neurology, Boston Medical Center, Boston, USA. [17] Department of Neurology, Beth Israel Deaconess Medical Centre, Boston, USA.

Author contributions

This manuscript complies with the instructions provided by ***Neurocritical Care.*** All authors meet the requirements for authorship. Their roles and contributions to this manuscript are listed below: VY and DD were involved in protocol/project development, data analysis, and manuscript writing/editing. TR contributed to data analysis and manuscript writing/editing. AMD, RIA, DR-L, CAM, YSB, ID, AK, J-MB, CL, GG, PS, JR, CSK, RB were involved in data collection or management. MDH contributed to data collection or management and manuscript writing/editing. DF contributed to manuscript writing/editing. MS was involved in protocol/project development and manuscript writing/editing.

Source of support

There was no support for this work.

Conflicts of Interest

Andrew M. Demchuk reports grants from NovoNordisk Canada, during the conduct of the study; Jean-Martin Boulanger reports other from Pfizer, other from Novartis, outside the submitted work; Cheemun Lum has deceased;

Michael D. Hill reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, grants from Covidien (Medtronic), grants from Boehringer-Ingleheim, grants from Stryker Inc., grants from Medtronic LLC, grants from NoNO Inc., outside the submitted work; In addition, Hill has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, National Institutes of Neurological Disorders and Stroke; Magdy Selim reports grants from NIH/NINDS, during the conduct of the study and the remaining authors have nothing to disclose.

Ethical approval/Informed consent
Local research ethics board approval was obtained at all enrolling sites, and written informed consent was obtained from all participants.

Published online: 23 May 2019

References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet (London, England). 2009;373(9675):1632–44.
2. Gonzales NR. Ongoing clinical trials in intracerebral hemorrhage. Stroke. 2013;44(6 Suppl 1):S70–3.
3. VanDerWerf J, Kurowski D, Siegler J, Ganguly T, Cucchiara B. Combination of intra-hematomal hypodensity on CT and BRAIN scoring improves prediction of hemorrhage expansion in ICH. Neurocrit Care. 2018;29:40–6.
4. Morotti A, Dowlatshahi D, Boulouis G, et al. Predicting intracerebral hemorrhage expansion with noncontrast computed tomography: the BAT Score. Stroke. 2018;49(5):1163–9.
5. Huynh TJ, Aviv RI, Dowlatshahi D, et al. Validation of the 9-point and 24-Point Hematoma Expansion Prediction Scores and derivation of the PREDICT A/B Scores. Stroke. 2015;46(11):3105–10.
6. Delgado Almandoz JE, Yoo AJ, Stone MJ, et al. The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. Stroke. 2010;41(1):54–60.
7. Wang X, Arima H, Al-Shahi Salman R, et al. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. Stroke. 2015;46(2):376–81.
8. Yao X, Xu Y, Siwila-Sackman E, Wu B, Selim M. The HEP Score: a nomogram-derived Hematoma Expansion Prediction Scale. Neurocrit Care. 2015;23(2):179–87.
9. Meretoja A, Churilov L, Campbell BCV, et al. The spot sign and tranexamic acid on preventing ICH growth–AUStralasia Trial (STOP-AUST): protocol of a phase II randomized, placebo-controlled, double-blind, multicenter trial. Int J Stroke. 2014;9(4):519–24.
10. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. Lancet Neurol. 2012;11(4):307–14.
11. Dowlatshahi D, Demchuk AM, Flaherty ML, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology. 2011;76(14):1238–44.
12. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol. 1999;28(5):964–74.
13. Al-Shahi Salman R, Frantzias J, Lee RJ, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol. 2018;17(10):885–94.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
15. Dowlatshahi D, Smith EE, Flaherty ML, et al. Small intracerebral haemorrhages are associated with less haematoma expansion and better outcomes. Int J Stroke. 2011;6(3):201–6.
16. Dowlatshahi D, Yogendrakumar V, Aviv RIRI, et al. Small intracerebral hemorrhages have a low spot sign prevalence and are less likely to expand. Int J Stroke. 2016;11(2):191–7.
17. Schlegel D, Kolb SJ, Luciano JM, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. Stroke. 2003;34(1):134–7.
18. Balami JS, Buchan AM. Complications of intracerebral haemorrhage. Lancet Neurol. 2012;11(1):101–18.
19. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke. 1996;27(10):1783–7.
20. Brott T, Broderick J, Kothari R, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28(1):1–5.
21. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015;313(8):824–36.
22. Cordonnier C, Leys D, Dumont F, et al. What are the causes of preexisting dementia in patients with intracerebral haemorrhages? Brain. 2010;133(11):3281–9.
23. Rodrigues MA, Samarasekera N, Lerpiniere C, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. Lancet Neurol. 2018;17(3):232–40.
24. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. Stroke. 2017;48(4):1120–5.
25. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24(7):987–93.

APPENDIX IV: REDEFINING HEMATOMA EXPANSION – Understanding Ventricular Expansion

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Warren AD, Anderson CD, Gurol ME, Greenberg SM, Viswanathan A, Rosand J, Goldstein JN, Dowlatshahi D. New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage. *Neurology*. Accepted, in press: April 2019.

Contents:

Review/Publication History

- Submitted to *Neurology*: December 18, 2018
- Revised (Major Revision): February 28, 2019
- Revised (Minor Revision): March 11, 2019
- Accepted for Publication: April 4, 2019

NEUROLOGY MS ID#: NEUROLOGY/2018/961243
MS TITLE: New and Expanding Ventricular Hemorrhage Predicts Poor Outcome in Acute Intracerebral Hemorrhage
Vignan Yogendrakumar, Tim Ramsay, Dean A Fergusson, Andrew Demchuk, Richard I Aviv, David Rodriguez-Luna, Carlos A. Molina, Yolanda Silva, Imanuel Dzialowski, Adam Kobayashi, Jean-Martin Boulanger, Cheemun Lum, Gord Gubitz, Padma Srivastava, Jayanta Roy, Carlos S Kase, Rohit Bhatia, Michael D. Hill, Andrew Warren, Christopher D. Anderson, M. Edip Gurol, Steven Greenberg, Anand Viswanathan, Jonathan Rosand, Joshua Goldstein, and Dar Dowlatshahi

Dear Dr. Yogendrakumar:

We are pleased to accept your paper for publication in NEUROLOGY.

Embargo Policy
Your paper and its findings are embargoed. Prior to publication, authors may not reveal that the paper is under consideration when presenting at scientific meetings, or release information to the press. News media and institutional public relations departments must not publicize the paper or its findings until 4:00PM Eastern the day of online publication. *Consequences for an embargo break are serious*: Neurology.org/research-policies-and-guidelines.

Embargo policy/press release inquiries—*only after receipt of the Welcome to Production email*

Embargo lift date inquiries—*only when returning proofs*

Please Note: If you or a coauthor are contacted by representatives from the AAN's *Neurology Today* or *Brain & Life,* you may communicate with them for coverage of your paper. However, please do not directly engage with any other news source prior to embargo lift.

Production Timeline
The corresponding author will receive a **Welcome to Production** email from our publisher (Wolters Kluwer) 24 hours after the paper is transmitted by the journal (in 5–12 weeks).

Print publication date inquiries—*no sooner than* 4 weeks *after receipt of this email*

The corresponding author will receive proofs approximately 15 business days after the **Welcome to Production** email is received. The proof will come via email from wolterskluwer.com. The subject line will read **Please Pick Up Your Proofs for Your Article in Neurology**.

Proof inquiries—*only after receipt of the Welcome to Production email*

The corresponding author must be available to review proofs within 48 hours (2 business days). If necessary, please arrange to have

proofs sent to a coauthor for review and notify REDACTED. We are not able to modify the production schedule to accommodate author absences.

Reader Comments

Readers may comment on your published article via *Disputes & Debates: Rapid online correspondence* (the letters-to-the-editor section of NEUROLOGY). The corresponding author of your paper will be notified via email 1 day prior to online posting of reader comments. Authors are expected to respond promptly to comments (within 10 business days). Comments of great interest will be chosen for print (*Disputes & Debates: Editors' Choice)* and indexed in PubMed.

Corresponding Author from UKB institution in the Netherlands

If the corresponding author is from a UKB institution in the Netherlands, please contact your library (http://www.openaccess.nl/en/references/contacts) for information on their open access requirements.

Many thanks for your contribution to NEUROLOGY. As a valued author, we are pleased to offer you a 20% discount on any LWW book. Please go to http://journals.lww.com/dm/Pages/BookDiscountMedical.aspx for details.

American Board of Psychiatry and Neurology (ABPN) diplomates

NEUROLOGY is a peer-reviewed journal indexed in the MEDLINE database. Therefore, ABPN diplomates who have published an article in NEUROLOGY may self-report the non-CME self-assessment activity to waive 8 self-assessment CME credits. Contact the ABPN directly for details: mquestions@abpn.com or tel: (847) 229-6500.

Sincerely,

Robert A. Gross, MD, PhD, FAAN
Editor-in-Chief, NEUROLOGY

APPENDIX V: REDEFINING HEMATOMA EXPANSION – Creation and Comparative Analysis of A Refined Definition Of Hematoma Expansion

Publication: Yogendrakumar V, Ramsay T, Fergusson D, Demchuk AM, Aviv RI, Rodriguez-Luna D, Molina CA, Blas YA, Dzialowski I, Kobayashi A, Boulanger J, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Bhatia R, Hill MD, Goldstein JN, Dowlatshahi D. Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth. *Neurology*. Under Review (May 2019).

Contents:

Review/Publication History:

- Submitted to *Neurology*: May 31, 2019

Yogendrakumar, Vignan

From:
Sent:
To:
Cc: [redacted]

Subject:

NEUROLOGY MS ID#: NEUROLOGY/2019/001214
MS TITLE: Redefining Hematoma Expansion with the Inclusion of Intraventricular Hemorrhage Growth

Dear Dr. Yogendrakumar:

The above mentioned manuscript has been submitted to NEUROLOGY by the Corresponding Author. If you did not approve the submission, please contact the Editorial Office immediately at journal@neurology.org.

Please use the assigned manuscript number in all further correspondence. We will contact you once the review process has been completed.

Be sure to visit NPub.org/submit and log in to your Author Area. Once logged in, you may check on the status of your manuscript.

If you have any questions or concerns about your paper, do not hesitate to contact us by e-mail: journal@neurology.org or by phone: (612) 928-6400.

If you've uploaded figures for which you indicated that you do not own the copyright, you will be required to obtain permission to reprint the figure(s) from the current copyright holder before publication.

FOR FULL-LENGTH ARTICLE SUBMISSIONS ONLY, PLEASE NOTE:

Short Article in Print/Full Article Online Pilot for Research Articles in 2018: All Articles that are ultimately accepted and scheduled to be published in the January-December 2018 issues will appear in a short, one-page format in print. The full article, the version of record, will be published online. We are piloting this electronic-long, paper-short to further assess reader preference. The first issue containing short-form articles in print, the January 2, 2018 issue, will be published on December 26, 2017. Please review an example of the short-form article, published in the September 6, 2016 issue as a pilot: http://www.neurology.org/content/suppl/2016/09/01/WNL.0000000000003078.DC4/kappos.pdf.

The short-form article places the research in context by summarizing the study question and answer, what is known and what the paper adds, design and setting, primary outcomes or main results, confounding factors, and generalizability to other populations. Authors will not be requested to write the short article (this will be done by a medical writer after acceptance), but will have the opportunity to edit and proof the short article.

Thank you for giving NEUROLOGY this opportunity to consider your work.

Sincerely,

NEUROLOGY Editorial Office

APPENDIX VI: INTRODUCTION CHAPTER

Publication: Yogendrakumar V, Goldstein JN, Dowlatshahi D. "Expansion of Intracerebral Hemorrhage." *Complications of Acute Stroke: A Concise Guide to Prevention, Recognition, and Management*. Ed: R Behrouz, L Birnbaum. New York: Springer Publishing Company, 2019.

Dr. Yogendrakumar drafted the manuscript. Drs. Goldstein and Dowlatshahi provided critical revisions of the manuscript for intellectual content.

Contents:

1. Title Page and Table of Contents of Textbook

Complications of Acute Stroke

A Concise Guide to Prevention, Recognition, and Management

Editors

Réza Behrouz, DO
Associate Professor
Division of Cerebrovascular Diseases
Department of Neurology
School of Medicine
University of Texas Health San Antonio
San Antonio, Texas

Lee A. Birnbaum, MD
Associate Professor
Division of Cerebrovascular Diseases
Department of Neurology
Division of Endovascular Neurosurgery
Department of Neurological Surgery
Department of Radiology
School of Medicine
University of Texas Health San Antonio
San Antonio, Texas

demosMEDICAL
An Imprint of Springer Publishing

Contents