Diagnosis and Acute Management of Intracerebral Haemorrhage

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Acknowledgments

Abstract

Intracerebral haemorrhage is a form of haemorrhagic stroke that is associated with significant morbidity and mortality. Its clinical course can be fulminant, meaning that the early diagnosis and management of this condition is particularly time critical. Early diagnosis through computed tomography (CT) imaging and implementation of interventions such as blood pressure control and reversal of coagulopathy can improve outcomes in this patient cohort. Prolonged time to hospital presentation or imaging diagnosis can delay delivery of appropriate care. Factors associated with delays to care are not currently well defined, and identification of a modifiable factor could enhance management of patients with this condition.

An increase in the volume of haematoma following initial diagnosis can be associated with precipitous neurological decline, and occurs in a significant subset of patients. The presence of a spot sign on CT angiography imaging represents a site of active contrast extravasation and is associated with an increased risk of haematoma expansion. More recently, the presence of spot signs on delayed contrast imaging sequences such as post contrast CT and CT perfusion have emerged as alternate predictors of haematoma expansion, as have certain non contrast CT imaging signs. It is currently not clear which is the imaging sign with the greatest level of diagnostic accuracy in predicting haematoma expansion in patients with intracerebral haemorrhage.

Aims of this thesis:

To characterise through a systematic review the diagnostic accuracy of various types of delayed CT spot signs in predicting rates of haematoma expansion in patients with intracerebral haemorrhage.

To characterise in patients with intracerebral haemorrhage the average time taken from ictus to hospital presentation and diagnosis, along with factors associated with delayed presentation.

To directly compare the diagnostic accuracy of non contrast, first pass angiography and perfusion CT signs in predicting haematoma expansion.

1.1 Definition

The term stroke encompasses a heterogeneous collection of vascular disorders of the brain which affects a significant proportion of the Australian population and people worldwide. In 2016, stroke accounted for 5% of all deaths, and nearly 1% of Australians live with a disability as a result of a stroke (Australian Bureau of Statistics, 2016). Stroke is classically delineated into the 2 broad categories of ischaemic stroke (IS) and haemorrhagic strokes (HS). IS is defined as 'an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction' and HS is defined as haemorrhages that are 'nontraumatic, caused by a vascular event, and result in injury to the CNS'[1].

HS subtypes include intracerebral haemorrhage (ICH), subarachnoid haemorrhage and intraventricular haemorrhage, with haemorrhages from trauma being excluded from this classification. The most common subtype of HS is ICH, which can further be delineated into spontaneous ICH and ICH that is secondary to a macroscopic vascular anomaly such as an arteriovenous malformation, intracranial aneurysm or cerebral cavernous malformation. Spontaneous ICH will be the focus of the remainder of this thesis.

1.2 Epidemiology of Spontaneous Intracerebral Haemorrhage

Ten percent of all strokes occur secondary to ICH, with the incidence being higher in low to middle income countries[2]. Incidence varies according to ethnic origin, with rates per 100,000 person years ranging from 52 in Asians to 24 in Whites[3]. In recent decades, the age adjusted incidence of ICH has decreased in Australia and other high income countries, likely due to improved control of vascular risk factors at the population level[4,5]. However, incidence in those over 75 has remained relatively stable, hypothesised to be due to increased rates of

amyloid angiopathy and antithrombotic medication-associated ICH[6,7]. This means that as the Australian population ages in the coming years, overall incidence of ICH may increase.

HS occurs approximately 10 times less frequently than ischaemic stroke but is associated with higher rates of mortality[8]. Because of high mortality rates, HS (on a global level) causes more death worldwide than IS[9]. One year mortality of ICH approaches 50%, with a 1 month mortality rate of 40%[3,10]. In those that survive, only between 12-39% of patients are functionally independent[3]. HS in total accounts for 62% of disability adjusted life years due to stroke world-wide[9,11]. Though it is evident that ICH is associated with significant morbidity and mortality, there is some evidence that case fatality rates in high income countries have decreased over the last few decades[12,13]. This improvement in outcome has been attributed to generalised improvements in the quality of critical and stroke-unit care given the paucity of novel effective ICH therapies over that time period[14,15].

1.3 Aetiology of and Risk Factors for ICH

ICH most commonly occurs in the deep grey matter of the brain (basal ganglia and thalamus), but can also occur in the cerebral lobes, cerebellum and pons[16]. ICH is thought to originate as a result of rupture of small perforating arteries at their point of bifurcation, and is most commonly secondary to 'arteriolosclerosis' for which the main risk factor is chronic hypertension[17,18]. Pathological studies of patients with ICH have demonstrated significant degeneration of the tunica media at these anatomical sites, presumably as a result of prolonged increased tension in the vessel wall[19]. Rupture at one point in these arteries results in extravasation of blood that compromises the structural integrity of similarly diseased adjacent blood vessels and results in a cascading domino-like expansion of the haemorrhage until haemostatic mechanisms and tamponade arrest further growth[20].

The second most common cause of spontaneous ICH is cerebral amyloid angiopathy (CAA)[21]. This condition is characterised by the deposition of amyloid in vessel walls, which when stained with Congo red has yellow green birefringence under polarised light[22]. Amyloid deposition causes vascular fragility and predisposes to rupture. In contradistinction to arteriolosclerosis, it is the longer vessels which are most likely to be affected, rather than the short penetrating arteries. Thus, haemorrhages have a predilection for the lobar areas of the brain, sparing the brainstem and deep nuclei[23].

Antiplatelet and anticoagulant medication increases with risk of ICH. Anticoagulants are associated with up to 20% of all ICH[24]. Rather than experiencing a novel mechanism of haemorrhage, anticoagulant use is thought to exacerbate the risk in patients who already have arteriolosclerosis or CAA[25,26]. Rarer causes include rupture of arteriovenous malformations[27], intracranial aneurysms[28] or cerebral cavernous malformations[29]. ICH can be a sequela of cerebral venous sinus thrombosis[30]. Other causes of ICH include trauma (though excluded by definition from 'stroke'), thrombolysis, non-medication related coagulopathies, Moyamoya disease, reversible cerebral vasoconstriction syndrome, vasculitis, radiotherapy and genetic disorders (for instance COL4A1 gene mutations)[31-36]. Intratumoural haemorrhage is an infrequent complication of neoplasms of the brain, with melanoma metastases having a particular propensity to bleed[37].

Increasing age is a risk factor for ICH, with risk increasing considerably after the age of 75[38,39]. This is presumably due to cumulative hypertension-mediated damage to vessel walls, along with increased prevalence of cerebral amyloid angiopathy in this age group[40]. Hypertension itself is the most significant risk factor for the occurrence of ICH, increasing the relative risk by 50% when compared to people without hypertension[41]. The relationship between blood pressure and haemorrhage risk appears to be 'dose dependent' to an extent, as patients with

SBP greater than 160mmHg are nearly 6 times more to experience ICH[42]. Every 10mmHg systolic blood pressure decrease reduces the risk of ICH by a third, with this relationship being true as low as a systolic blood pressure of 115mmHg[43]

The presence of microbleeds in locations suggestive of CAA is associated with increased risk of subsequent ICH[44]. At particularly elevated risk are those patients who demonstrate convexity SAH or superficial siderosis on MR images[45,46]. CAA associated ICH tends to recur at a rate of 7% per year, significantly higher than the recurrence rate of 1% seen in ICH unrelated to CAA[47].

Other identified risk factors for ICH include diabetes mellitus[48], heavy alcohol intake[49], obstructive sleep apnoea[50] and smoking[51]. High levels of low density lipoprotein and triglycerides appear to protect against ICH[42,52]. Conversely, high dose statin therapy following ischaemic stroke has been identified as a risk factor for subsequent development of ICH[53].

The genetic profile of an individual is an important component in determining their risk of ICH. ICH in a first degree relative increases one's own risk of developing ICH sixfold[54]. The most significant gene identified thus far is Apolipoprotein E (APOE). APOE is involved in lipid metabolism, and the ε2 and ε4 alleles of this gene are associated with increased risk of ICH in patients with CAA[55]. Further study has shown that the ε4 allele is associated with the development of CAA, which presumably explains the increased ICH risk in these patients[56]. In addition, variations in multiple other genes involved in vessel wall integrity (COL4A2), blood pressure control (angiotensin converting enzyme gene) and inflammation (MTHFR 677 T variant allele) are risk factors for ICH[57-59]. Acquired proinflammatory somatic mutations in lymphocytes – so-called clonal haematopoiesis of undetermined significance (CHIP) – is a recently identified risk factor[60].

1.4 Prognostic Factors

Multiple factors have been identified as predicting poor outcome in ICH, including older age, lower admission Glasgow Coma Scale (GCS) , infratentorial location, larger volume and intraventricular haemorrhage[61]. The ICH score is a composite of the aforementioned factors and gives the likelihood of mortality at 30 days post ictus[61,62]. Haematoma volume is an especially powerful predictor of outcome, with a volume of >60mL at presentation associated with a 90% risk of death[63]. ICH volume can be quickly calculated using simple measurements of the various planes of head CT scans[64].

In addition to the aforementioned prognostic factors, in recent decades haematoma expansion (HE) has emerged as a marker of poor prognosis[65,66]. While most other prognostic factors in ICH are non modifiable and fixed, HE is a dynamic process and represents a target for novel therapeutic interventions. The pathology, prediction and treatment of HE is discussed later in this introduction.

1.5 Pathophysiology of ICH

The events that initiate ICH have been described in the preceding section. To summarise, rupture of a small perforating artery weakened by chronic hypertensive angiopathy or distal CAA-affected vessel occurs. Subsequent events can be classified as an initial growth phase of the haematoma where extravasated blood compresses and destroys surrounding brain parenchyma. This is followed by a secondary phase where either cessation of haemorrhage occurs, or there is a prolonged or intermittent period of secondary expansion due to ongoing bleeding. Other secondary pathological events that occur include intraventricular extension, hydrocephalus, and perihaematomal events such as cerebral oedema and delayed cellular

death. Neurological deterioration occurs in a subset of patients with ICH, and represents the clinical correlate of one of the secondary mechanisms of brain injury discussed above.

1.5.1 Pathophysiology of ICH: Primary Injury

Primary injury refers to the local anatomical destruction and mass effect that occurs as a result of initial haemorrhage. Our understanding of the immediate dynamics of haematoma growth in the aftermath of vessel rupture is limited because neuroimaging does usually occur in the hyperacute period of clinically encountered ICH. However, animal studies have provided some insight into the events that occur in this critical period. In 2015, Liu and colleagues used focused ultrasound to induce ICH in pigs, then took MR images of their brain at 10 second intervals to characterise the evolution of the haematoma in the first seconds to minutes after ictus[67]. They determined that on average, haematomas had reached nearly 90% of their final size within 3 minutes[67]. One case report has described a patient who sustained an ICH while in an MRI scanner, with the haemorrhage reaching 20% of its final volume within 2 minutes, and 50% of its final volume within 10 minutes[68].

These findings imply that the rate of bleeding is most rapid immediately following rupture as the perforating artery decompresses into surrounding neural tissue. As the haematoma grows, local pressure may rise to the point where the extravasated blood tamponades the ruptured artery, precluding the escape of any further blood. This mechanism, aided by the activation of the various haemostatic pathways of body terminates the initial growth phase of ICH.

1.5.2 Pathophysiology of ICH: Secondary Pathological Events

The structural damage caused acutely by the initial haemorrhage may be intractable, however several other pathophysiological mechanisms subsequently exacerbate brain injury. Further

bleeding into the haematomal cavity can occur, expanding the haematoma and worsening clinic outcomes[65]. Intraventricular haemorrhage can occur secondary to decompression into the ventricular system, and can contribute to the development of hydrocephalus[69]. Furthermore, toxic components of extravasated blood can induce oedema and cellular death in the already vulnerable perihaematomal region of brain parenchyma[70]. This mass effect of this cerebral oedema can have further pathological consequences. These events are discussed in the following sections.

Haematoma Expansion:

Definition and pathology

By definition all patients with ICH have some haematoma expansion from the point of arterial rupture to the time the ICH is diagnosed. In the majority of patients haematoma volume quickly attains a stable volume, however in a subset of patients ICH is not a rapidly monophasic event, with follow up neuroimaging demonstrating an increase in the volume of extravasated blood, often with deleterious clinical consequences. It can directly compress surrounding neurological structures, cause a generalised raise in ICP and leads to the liberation of more toxic thrombin and iron.

Studies on haematoma expansion typically report it in a dichotomous manner, requiring either an absolute volume increase (eg. >6mL) or a proportionate increase in the size of the haematoma (eg >33%)[66]. There is however some variation across studies in the exact parameters used to define haematoma enlargement[71,72]. It has been postulated that this secondary haematoma expansion is a result of the pressure of the initial haematoma rupturing other adjacent small vessels which then contribute further volume to the haemorrhage[20,73].

Analysis of histological sections of pontine haemorrhages have supported this theory, with multiple ruptured small arteries identified at the periphery of the haematoma cavity[20]. Further support of this 'avalanche' or 'domino' model of ICH and haematoma expansion is that MRI studies have shown a dichotomy between cerebral microbleeds and macrobleeds[74]. This tends to suggest that a singular bleed can either commence a chain reaction of further vessel haemorrhage or remain sufficiently small to be clinically silent. The theory that secondary shearing of vessels contributes to haematoma expansion finds further support in the fact that multiple CTA spot signs are commonly seen in ICH, and are harbingers of haematoma expansion[75,76].

Frequency of haematoma expansion

There is significant heterogeneity in the reported rates of haematoma expansion in ICH, with figures ranging from 15-30% in patients undergoing their first CT scan within 6 hours of ictus[66]. This variation is presumably at least in part attributable to different definitions of HE used in the literature. Rates of haematoma expansion are also strongly influenced by the length of time after ictus the initial CT scan is performed. The earlier the scan is performed after haemorrhage onset the more likely haematoma expansion will be seen, with up to 70% of patients scanned within 3 hours of onset demonstrating haematoma expansion on later scans[65]. Though less common, haematoma expansion does occasionally occur in patients presenting 6-24 hours post symptom onset[77]. Enlargement rarely occurs after the 24 hour mark[78].

Predictors and Significance of Expansion

Multiple factors associated with haematoma expansion have been described in the literature. Male sex is an independent risk factor for expansion[79]. As discussed previously, haematoma expansion is more common in patients who present early post ictus[77,80]. Larger haematomas

expand more commonly, with haematomas under a size of 10mL having the lowest propensity to expand[81,82]. Antiplatelet and in particular anticoagulant therapy is associated with higher risks[83]. Concurrent use of warfarin is associated with increased risk of haematoma expansion[84]. Though initial animal models suggested that use of direct acting oral anticoagulants did not increase the risk of haematoma expansion[85], clinical evidence currently suggest that the risk is similar to that of warfarin[86].

In recent years CT imaging features that predict haematoma expansion have been the subject of considerable research. The first of these was the CT angiogram (CTA) spot sign, first described in 2007 and subsequently repeatedly shown to predict both haematoma expansion and poor neurological outcome in ICH[87,88]. The use of post contrast CT and CT perfusion source images to capture a more prolonged period of time has been shown to improve sensitivity and specificity, presumably by identifying lower-rate arterial, capillary and venous sources of bleeding that contribute to haematoma expansion[89,90] and by better excluding CTA spot sign mimics (such as focal vascular ectasia). Finally, over the last five years certain non contrast CT imaging findings have been shown to predict expansion in ICH[91-93]. The imaging features that can be used to determine those at risk of expansion are discussed in depth in a later section of this thesis.

Haematoma expansion is correlated to poorer outcome, with each 10% increase in haematoma volume increasing mortality by 5%[65]. Similarly, expansion in haematoma volume is associated with poorer functional outcome post ICH[65]. Subsequent studies have reinforced the dose dependent influence of haematoma expansion on outcome, with Delcourt and colleagues demonstrating that every 1mL of volume increase was associated with a 5% increased risk of dependency or death[94].

Intraventricular Haemorrhage and Hydrocephalus

Intraventricular haemorrhage (IVH) is may be seen in ICH as a result of the developing haematoma decompressing into the ventricular system, and occurs in around 40% of cases[95,96]. IVH is more common in thalamic ICH due to the close proximity of this structure to the ventricular system[97]. The presence of IVH confers a poorer prognosis, with outcomes worsening as the volume of IVH increases[96,98]. IVH expansion is a risk factor for poor outcome additional to presence or absence at baseline[99]. The association of IVH with poorer prognosis is believed to be related to damage to vital periventricular brain structures, the inflammatory response induced by intraventricular blood, and the subsequent hydrocephalus that may develop[95,100,101].

Hydrocephalus occurs in 50% of patients with intraventricular extension of ICH, and is one likely cause for the increased mortality in this cohort[95]. Acute hydrocephalus is commonly due to obstruction of the interventricular foramens or cerebral aqueduct by thick blood clots[102]. Additionally, inflammation and fibrosis of the arachnoid granulations following IVH may result in the delayed onset of communicating hydrocephalus[103]. The development of hydrocephalus post IVH has been identified as an independent predictor of poor outcome in ICH, and commonly requires some form of cerebrospinal fluid diversion procedure to treat[102,104].

Perihaematomal Cerebral Oedema

Perihaematomal oedema develops in the aftermath of all ICH cases[105]. This volume of this oedema can dramatically increase in the first 24 hours following haemorrhage, inducing mass effect on surrounding structures, raising intracranial pressure and potentially causing hydrocephalus and herniation syndromes[106]. Perihaematomal expansion develops in three phases. The first phase occurs with clot retraction of the main haematoma, and takes place in

the first 3 hours following ictus[107]. This first phase really represents a reduction in haematoma volume rather than an increase in perihaematomal oedema, and may paradoxically be associated with improved outcome[108].

Oedema volume develops rapidly in the second phase, which lasts for the first 3 days following ICH[109]. Progression is especially prominent in the first 24 hours post injury, with oedema volumes doubling in this time[106]. This phase is thought to be mediated by the toxic effects of thrombin[110]. Studies have associated the progression of oedema in this period with neurological deterioration[109,111]. Delayed exacerbations in perihaematomal oedema are thought to relate to the toxic effects of iron, and there is evidence in preclinical models that the administration of iron chelators such as deferoxamine can decrease the volume of surrounding oedema[112].

1.5.3 Pathophysiology of ICH: Secondary Injury and its Mediators

Neurological deficits in ICH can therefore be progressive, due to heterogenous pathophysiological mechanisms[113]. It was initially theorised that the local pressure of the haematoma created an area of ischaemic penumbra in the perihaematomal tissue, with perfusion studies demonstrating decreased cerebral blood flow in these regions [114]. However, more sensitive imaging studies and laboratory evidence suggest that the blood flow does not decrease to a point sufficient to cause ischaemia and infarction[115,116].

In the absence of ICH expansion and secondary hydrocephalus, other processes must mediate the pathological perihaematomal cerebral oedema and cell death that occurs in the aftermath of ICH. Rather than being of ischaemic aetiology, secondary injury appears to be predominantly due to the cerebral toxicity of extravasated substances, in particular

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thrombin[117] and the breakdown products of lysed red blood cells[70,118]. These substances contribute to the development of cerebral oedema at different times and in different ways and they are briefly discussed below.

Thrombin is a serine protease involved in the clotting cascade, and has been shown to be a potent neurotoxic agent [119]. Large quantities of thrombin are liberated following ICH[110], and direct injections of thrombin into brain parenchyma has been shown to produce early oedema and cellular death within the first 24 hours of ictus[117,120]. Thrombin's central role in the development of cerebral oedema has been affirmed by the fact that administration of specific thrombin inhibitors attenuates the oedema response post ICH[117]. Furthermore, decreased perihaematomal oedema has been shown in patients with ICH that occurs while on medications such as warfarin that decrease the total amount of thrombin produced[108].

From the above paragraph, it is evident that residual haematomal thrombin contributes negatively to the disease course in ICH. Thereby medical therapies that decrease or inhibit its action, or surgical techniques to reduce the total burden of thrombin could potentially alleviate some of the toxic effects and improve clinical outcomes in ICH patients.
Lysis of extravasated red blood cells (RBC) begins 24-48 hours after ICH, and continues for up to 2 weeks[121]. While whole red blood cells do not appear to be toxic initially[122], their degradation products induce marked brain oedema[123]. The prolonged period that cell lysis occurs over may explain the delayed and progressive perihaematomal oedema that first occurs 24 hours after first injury and can continue for up to 14 days following initial haemorrhage[109]. Multiple erythrocyte-derived substances may provoke the oedema that develops during this period, including haemoglobin, heme, bilirubin and ferrous iron[70]. The toxicity of these substances is mediated by the generation of potent free radicals which induce oxidative injury

in a variety of cellular components[124]. The synergistic action of thrombin and RBC lysis products in causing brain injury has been demonstrated experimentally[125].

Several factors protect the brain from the toxic effects of lysed RBCs. Haptoglobin, a molecule that binds free haemoglobin and neutralises it, is upregulated in perihaematomal tissue post ICH and deficiencies in this protein are associated with increased susceptibility to oxidative injury[126]. Heme oxygenase (HO) is an enzyme responsible for the catabolism of free heme and the release of iron. Deficiency in the HO1 isoenzyme has been shown to reduce brain injury following ICH, presumably due to decreased liberation of free iron[127]. Similarly, iron chelation therapies such as deferoxamine have shown promise as a treatment for ICH, with animal studies demonstrating consistent benefits[128]. However, there is no high quality evidence to support this practice in human patients; a recent randomised, double blinded phase II clinical trial showing that while deferoxamine was safe in this setting, a clinical benefit was not realised, and a pre-specified futility threshold was met [129,130].

1.6 Computed Tomography in Intracerebral Haemorrhage: Predictors of Haematoma Expansion

1.6.1 Non Contrast Head CT

Excepting rare centres which use MRI as a primary imaging modality, non contrast head CT (NCCT) imaging is ubiquitous in the diagnostic work up of patients with ICH. The use of CTA and delayed phase imaging in the setting of ICH is less routine. Patients with contraindications to contrast administration the NCCT may be the only CT modality available to review. These facts underline the usefulness of determining features of NCCT scans that can predict haematoma expansion.

As previously discussed, initial size of haematoma determines risk of subsequent expansion. Volume divided by time can estimate 'ultra early haematoma growth', which predicts further growth, and can be easily calculated through the use of the ABC/2 method[64]. Though validated in subsequent studies, this method may lose accuracy when describing ICH that is irregular in shape, lobar or very large[131]. Recently studies have identified that certain novel NCCT features such as irregular margins and increased heterogeneity of haematoma density predict an increased risk of haematoma expansion[91-93,132]. These novel imaging features are discussed below.

Haematoma irregularity is typically graded from 1 to 5, with the presence of each additional lesion edge irregularity adding a point, as described by Barras and colleagues[133]. Haematomas with an irregular, nodular margin undergo expansion at a higher rate than regular margin haematomas[132,134]. In addition, the presence of irregular margins has been shown to correspond with poorer functional outcome and mortality[135,136]. Several possible explanations exist for why margin irregularity predicts expansion. Irregular spots may represent new haemorrhage from vessels sheared by haematoma expansion, as per Fisher's avalanche model[20]. There is some evidence that haematoma expansion occurs preferentially in a manner so that the haematoma most closely approximates the shape of a sphere[137]. This would imply that haematomas with irregular margins have been imaged in a growing phase that predates their final shape, and would thus explain why they are more liable to expand. Alternately, an irregular haematoma shape may be a marker of underlying pre-existing cerebral injury. Finally, irregular margins may increase post-ICH oedema, potential due to a greater surface area interface with oedema producing cells or mediators[138].

Haematomas with heterogenous densities, seen as regions of hypoattenuation within the hyperattenuating ICH, are more likely to expand that haematomas with homogenous

densities[139]. These hypodensities are theorised to represent regions of hyperacute, active haemorrhage[140].Various subcategories of these signs have been described including the swirl sign[141], black hole sign[93] and heterogeneity measurements which encompass the entire haematoma[133]. A definition of what exactly constitutes a sign varies across studies. The swirl sign has been defined in later papers as a region hypointense or isointense to brain parenchyma (Hounsfield units 30-50) completely surrounded by haematoma, and is associated with haematoma expansion[142]. The black hole sign is similar to the swirl sign, but the region of hypodensity has a border that clearly demarcates it from the surrounding haematoma[93]. Barras graded haematomas based on how many different hypodensities appeared within them[133].

The multiplicity and subjectivity of reported non contrast markers of CT hinders their application in clinical practice. Recent evidence has suggested that the presence of an encapsulated hypodensity within the haematoma is more important in predicting expansion rather than its exact pattern[139]. The presence of these hypodensities is also associated with increased risk of poor outcome[143]. The presence of a fluid level within the haematoma is another rare imaging feature most commonly seen in anticoagulated patients that is associated with haematoma expansion and mortality[135,144].

Though useful, the sensitivity of NCCT signs in predicting haematoma expansion tends to be slightly inferior to the CTA spot sign. Zheng and colleagues compared the blend sign and the CTA spot sign and found that while the specificity of the presence of the 2 signs was similar, the sensitivity of the CTA spot sign was superior[145]. Similar results have been found when comparing the accuracy of the black hole sign and spot sign in predicting expansion[146]. These findings suggest that in the setting of ICH additional predictive power is gained by the acquisition of some form of contrast imaging.

1.6.2 The Spot Sign on Computed Tomography Angiography:

Computed Tomography Angiography (CTA) has several uses in the setting of ICH. It has shown utility in identifying the underlying vascular lesions in cases where the ICH is secondary to ruptured intracranial aneurysms[147] or arteriovenous malformations[148]. Furthermore, in 2007 Wada and colleagues reported on the CTA 'spot sign' in a cohort of patients with spontaneous ICH, a finding associated with increased risk of haematoma expansion and worse clinical outcomes[87].

The CTA spot sign was defined by the authors as "1 or more 1- to 2-mm foci of enhancement within the hematoma"[87]. Subsequent authors have refined the definition of a spot sign, stipulating that the foci of enhancement not be contiguous with any larger vessel traversing the haematoma, and that there should be no hyperattenuation (indicative of calcification) at the site on non contrast CT[149,150]. In addition, some authors have taken a more quantitative approach to identification of the spot sign specifying that the spot sign should have a Hounsfield unit density of at least 1.5 times that of surrounding haematoma[150].

Factors associated with the presence of the spot sign include early presentation post ictus, low admission GCS, coagulopathy, IVH and increased haematoma volume at admission[80,151,152]. Spot signs are seen in 24% of patients presenting within 6 hours post symptom onset[153]. Rates approach 40% in those presenting within 3 hours, and drop to 10% in patients that present >6 hours post symptom onset[154]. Multiple meta-analyses have demonstrated the accuracy of the CTA spot sign in predicting HE, with a pooled sensitivity of 60% and a specificity approaching 90%[155,156]. Multiple meta-analyses have also shown that the presence of the spot sign is associated with increased mortality and poorer functional outcomes following ICH[88,156].

While the specificity of the spot sign in predicting HE is relatively high, the sensitivity is moderate. In general, studies reporting on the spot sign on first pass CTA have generally reported delays of 5 – 40 seconds from time of contrast administration to time of imaging acquisition[80,87]. This has been theorised to be insufficient period of time to allow spot opacification in all cases due to variations in blood pressure and intrahaematomal pressure[89,155]. Delayed imaging techniques such as post contrast CT (PCCT) that acquire images at times greater than 2 minutes post contrast administration could potentially capture a greater number of spot signs, and are discussed in the next section.

1.6.3 The Delayed Spot Sign:

As discussed above, the CTA spot sign does not predict all instances of HE, probably because it does not image instances where spot sign opacification is more delayed. In 2009, Ederies demonstrated that the sensitivity of first pass CTA and PCCT was superior to the use of isolated first pass CTA[90]. The extra spot signs detected with the use of PCCT tended to have smaller initial haematoma volume, and demonstrated less absolute volume growth[90]. Further subsequent studies have confirmed the use of PCCT in predicting HE[157,158]. Delayed phase CTA, performed in the late arterial phase has also shown to have improved accuracy when compared to first pass CTA[159,160].

Of particular promise is the use of CT perfusion source images to capture a 'dynamic' spot sign. This imaging modality continually images a contrast bolus over a period of 120 seconds and represents a hybrid that does not adhere to traditional definitions of early (CTA) or late acquisitions (dCTA or PCCT). Koculym was the first to show that the sensitivity of the CTP spot sign was superior to that of the CTA spot sign[89]. Spots that were identified on CTP but not on CTA typically had maximum attenuation at a time point of 30-70 seconds post contrast administration, after when CTA images are usually captured[89]. CTP was also more sensitive

than PCCT in detecting a spot sign, theorised to be because some spot signs may appear and then disperse prior to the usual imaging time of 360 seconds post contrast in PCCT[89].

Subsequent studies have confirmed the accuracy the CTP spot sign in predicting haematoma expansion, with sensitivity and specificity of around 90%[161,162]. Spot signs occurring prior to 23 seconds post contrast administration have the highest specificity for predicting HE[162]. The use of CTP therefore represents an attractive means of assessing for the spot signs in patients with ICH. The additional radiation dose incurred by patients is potentially concerning, but ICH is generally a disease of the more elderly who will likely not experience the full stochastic effects of the radiation exposure.

The routine use of CTP helps streamline acute stroke imaging in general. Ancillary benefits from performing CTP may include delineation of small arteriovenous malformations and better detection of venous sinus thrombosis as a cause of ICH, by examination of the later phases (CT venography).

However, few studies have been performed on the use of CTP in this context, and those studies have been on limited numbers of patients. Furthermore, no studies have been performed that compare the accuracy of NCCT imaging predictors of HE with the CTP spot sign. An advantage of CTP over delayed imaging techniques such as PCCT or delayed CTA is that it allows accurate assessment of the rate of growth and time to maximum attenuation of the spot sign. Brouwers and colleagues have previously determined that rate of contrast extravasation predicts haematoma expansion and outcome[163]. However, this paper calculated rates on the basis of scan appearance at 2 separate time points (first pass CTA and 90 second delayed post contrast CT)[164]. CTP imaging would theoretically allow more accurate measurements of growth as images of the haemorrhage would be available at far more time

points. However there is limited data currently on what the significance of the rate of growth of the CTP spot sign is.

1.6.4 Implications for Future Studies:

ICH is currently a disease that is bereft of highly effective treatments. The prevention of HE in ICH patients is an enticing therapeutic target. However, most patients with ICH will not undergo HE. Inclusion of these patients in trials may dilute the effect size of therapies assessed. A means of predicting which patients will undergo HE is therefore valuable when developing a clinical trial as it allows a selection of a population that is highest risk. Previous studies on the efficacy of tranexamic acid in limiting HE have used the presence of the CTA spot sign as a requirement for inclusion[149]. The limited sensitivity of the CTA spot sign has been discussed above, and it is possible that a more accurate imaging modality such as CTP could be utilised in future studies selecting patients on the basis of imaging parameters.

1.7 Clinical Interventions in Intracerebral Haemorrhage

ICH is currently a disease with a limited number of effective therapeutic interventions. Initial management is centred on early control of blood pressure, reversal of coagulation deficits and early neurosurgical consultation if appropriate. Admission to specialised neurological intensive care units and stroke units has been associated with improved prognosis in ICH patients[15,165,166]. The literature on clinical interventions in ICH is discussed below.

1.7.1 Blood Pressure Control

Patients who have had a haemorrhagic stroke commonly present with hypertension, with one study of 45000 patients showing that 75% of patients presented with a systolic blood pressure of over 140 mmHg[167]. Intuitively, elevated blood pressure in these patients should carry a risk

of further bleeding, haematoma expansion and worse clinical outcome. Early studies did find

an association between hypertension and poorer clinical outcomes, though several studies also

demonstrated a U shaped relationship between blood pressure and outcome, with significant

hypotension also being associated with worse clinical outcomes[168,169]. Control of hypertension

was therefore identified as potentially significant therapeutic target in the acute stages of

spontaneous ICH.

In 2005, Qureshi et al. demonstrated in a non randomised study that in patients with

spontaneous ICH targeting a SBP below 160 mmHg was associated with decreased haematoma

expansion and did not precipitate neurological decline[167]. Subsequently the INTERACT 1 trial

attempted to more closely examine the benefit of aggressive early control of SBP in

spontaneous ICH. INTERACT 1 was a randomised, multicentre outcome blinded pilot trial of

404 patients with one group having a target SBP of <140mmHg, and the other having a target

SBP of <180mmHg[170]. It found that aggressive pharmacological SBP control was well tolerated,

with a trend towards decreased haematoma expansion in the intensively treated group[170].

The main phase component of the study, INTERACT2, randomised 2839 patients to intensive

SBP control (<140mmg) or standard care (<180mmHg)[71]. This study again showed that

intensive blood pressure control was well tolerated, but failed to demonstrate a significant

decrease in the number of patients experiencing death or major disability, though a trend

towards decreased mortality was demonstrated[71]. However, an ordinal analysis of patient mRS

scores showed improved functional outcome in those patients in the intensive blood pressure

control group[71]. These findings are similar to the findings of the ATACH-2 study, another

randomised trial which showed that while intensive blood pressure control was safe, it did not

improve rates of good functional outcome (although the achieved BP in the control group of

ATACH-2 was identical to the actively treated group in INTERACT-2)[71]. However, a subgroup

analysis of patients with deep (thalamic or basal ganglia) ICH showed that intensive blood pressure control was associated with reduced rates of haematoma expansion,[172] and an individual patient meta-analysis of the BP-lowering trials suggested decreased mortality and ICH expansion with an achieved BP of 140[173]. Given the safety of intensive SBP control and the trends towards improved mortality and functional outcomes, current guidelines recommend aiming for a SBP of <140mmHg in patients similar to those enrolled in the INTERACT trials[174]. There is, however a suggestion of harm if BP is lowered too far (i.e. to 120mm Hg) or too fast (>60mm Hg in an hour)[173], possibly due to increased microinfarction risk in the setting of impaired autoregulation[175].

1.7.2 Haemostatic Therapies and Reversal of Coagulation Defects

The effectiveness of several haemostatic agents in preventing HE and improving outcomes in patients without pre-existing coagulopathy have been assessed. Recombinant factor VIIa is a theoretically attractive means of attaining haemostasis in the acute setting of ICH, with initial studies showing a reasonable safety profile[176]. However, a meta-analysis of studies of recombinant VII has demonstrated that while it may reduce HE, it does not reduce it sufficiently to reduce mortality or morbidity, and is associated with an increased risk of thromboembolic events[177]. Tranexamic acid (TXA) is another agent that has been shown in the CRASH-3 trial to improve outcomes when given to traumatic brain injury patients with 3 hours of initial trauma, an effect presumably related to its ability to retard growth of intracranial bleeds[178]. The TICH-2 randomised controlled trial found that treating ICH patients with TXA was associated with a minor reduction in ICH expansion and a trend towards improved functional outcomes at 90 days post ictus but did not reach statistical significance[179]. The STOP-AUST trial gave a similar result, with a trend towards reduced expansion, especially in the group treated ultra-early, but without a functional outcome benefit[180]. Both TXA and rFVIIa are being tested in an ultra-early (<2 hour) cohort[181].

Patients with anticoagulant associated ICH comprise a distinct clinical subset. The relationship between anticoagulants and ICH is reflected in the fact that while only 1.5% of the population takes an oral anticoagulant[182], 15% of ICH is associated with medications such as warfarin or direct acting oral anticoagulants[183]. Even more patients are taking antiplatelet agents such as aspirin at the time of ICH. The influence antithrombotic medications have on risk of ICH and clinical outcomes will be discussed in the following paragraphs, as will the role of coagulation reversal.

Long term aspirin use is associated with an absolute risk increase of 12 episodes of ICH per 10000 persons, or in other words a risk of 0.12 events per 1000 patient years[184,185]. Whether aspirin use is associated with poorer clinical outcomes in ICH is controversial. Roquer and colleagues recognised aspirin as a predictor of mortality in patients sustaining spontaneous supratentorial ICH[186]. However, some subsequent studies did not find an association between prior antiplatelet use and haematoma expansion or outcome in ICH[187]. Despite this, a subsequent meta-analysis of all trials has identified a significant association between antiplatelet use and instances of haematoma expansion[83].

The antiplatelet effects of aspirin can vary between different subjects, and it has been shown that patients with reduced platelet activity on admission with ICH had increased instances of haematoma expansion, and worse functional outcomes[188]. A later paper from the same group demonstrated in a small cohort that platelet transfusion improved platelet activity, decreased haematoma expansion and was associated with improved functional outcomes[189]. However, a randomised controlled trial comparing platelet transfusion with standard of care in antiplatelet associated ICH showed that platelet transfusion was associated with increased mortality and worse functional outcomes[190]. Due to the findings of this trial, reversal of

antiplatelet therapy with platelet transfusion is not currently standard practice in the setting of ICH. This trial did not utilise measures of platelet activity to select patients, which may represent a possible avenue of further research. It should be noted that if craniotomy is being performed to evacuate antiplatelet associated ICH, platelet transfusion should be strongly considered. A randomised controlled trial on this topic demonstrated that patients who received peri operative platelet transfusions achieved lower post operative haemorrhage rates; lower volumes of residual haematoma and lower mortality at 6 months post operatively[191].

There is convincing evidence that patients with vitamin K associated ICH have increased initial haematoma volume, greater rates of haematoma expansion and increased rates of mortality [192-194]. Current guidelines endorse rapid reversal with vitamin K and prothrombin complex concentrates (PCC), along with cessation of warfarin in the short term [195]. Reversal of anticoagulation is imperative if surgical intervention is planned. Vitamin K is essential to ensure reversal of the coagulation deficiencies is prolonged so that a rebound coagulopathy does not occur following initial reversal [196]. PCC is generally preferred to reversal with fresh frozen plasma (FFP), as reversal of elevated INRs occurs more quickly, without the concern of volume overload in the patient [197]. A randomised controlled trial by Steiner and colleagues comparing FFP with PCC reversal of warfarin associated ICH demonstrated that PCC was associated with faster normalisation of INR and reduced rates of haematoma expansion[198]. The administration of PCC in warfarin associated ICH has been shown to be associated with improved clinical outcomes compared to no patients receiving no reversal [199]. Similarly, other studies in addition to the Steiner trial have shown that reversal with PCC is superior to reversal with FFP [200].

In recent years, direct acting oral anticoagulants (DOACs) such as apixaban, dabigatran and rivaroxaban have become more common in clinical practice. These drugs are associated with a

decreased risk of ICH when compared with warfarin [201]. When first introduced, concerns existed regarding the lack of reversal agents available in the event of DOAC associated ICH. Use of a DOAC agent is associated with increased mortality when compared with no anticoagulation [202]. However, DOAC associated ICH has not been shown to have poorer outcomes than warfarin associated ICH, and may even be associated with superior outcomes and mortality [86,202].

Idarucizumab, a monoclonal antibody that rapidly and durably reverses the anticoagulant effects of dabigatran has subsequently been released, allaying some of the fears associated with its use [203]. Evidence of the utility of idarucizumab in the setting of dabigatran associated ICH is mainly limited to small case series and case reports, but a recent systematic review of 23 cases showed it was safe to use with some trend towards therapeutic benefit [204,205]. These findings were reinforced by a larger cohort study that demonstrated the efficacy and safety of idarucizumab reversal in 98 patients with intracerebral haemorrhage[203]. Though there is no commercially available reversal agent for factor Xa inhibitors such as apixaban and rivaroxaban, andexanat alfa has recently been shown to be potentially efficacious and safe in the treatment of factor Xa inhibitor associated bleeding [206] and is undergoing evaluation in a phase-3 trial[207].

1.7.3 Surgical Intervention

Surgery for infratentorial ICH has been generally accepted as indicated in instances where the patient is deteriorating neurologically, developing brainstem compression or obstructive hydrocephalus [174]. Multiple previous studies have suggested improvements in mortality with surgical evacuation in these circumstances [208,209]. A lack of equipoise has to date precluded the possibility of a randomised controlled trial to examine the question, although a recent

individual patient meta-analysis suggests that the benefit may not be clear-cut[210]. However, whether surgery is beneficial in supratentorial ICH is controversial.

Surgical evacuation of supratentorial ICH allows removal of the CNS clot burden, therefore minimising the toxic effects of residual thrombin and iron. However, this is balanced by the need to disrupt intact parenchyma and vasculature en route to the haematoma, which can potentially result in new neurological deficits. This possible complication is coupled with the attendant risks of any surgical procedure, which include infection, bleeding and the risks of administering an anaesthetic.

The first prospective RCT to compare surgical and conservative treatments in supratentorial ICH was performed in 1961, and demonstrated worse outcomes in surgically treated patients [211]. Further trials failed to demonstrate improved outcomes with open evacuation of ICH [212,213]. A meta-analysis performed at the turn of the millennium assessed all of the RCTs assessing the issue and was unable to show whether surgery for supratentorial ICH was clearly beneficial or detrimental [214]. However, when only modern studies were included the study found a trend towards improved outcomes with surgical treatment. This raised the question as to whether advances in neuroimaging, surgical techniques and anaesthesia had progressed to the point where surgical evacuation was superior to conservative management of supratentorial ICH.

The ongoing confusion regarding the benefit of surgery in the treatment of supratentorial ICH predicated the need for a larger RCT to examine the question. The international surgical trial in intracerebral haemorrhage (STICH) randomised 1033 patients with supratentorial ICH to conservative management or early surgery and demonstrated that early surgery was overall not associated with improved outcomes [215]. This trial has been criticised due to inclusion only on the basis of 'clinical equipoise' and the high rates of surgical cross-over in the conservative

arm. Even with these caveats, subgroup analysis of STICH trial patients suggested that patients with superficial lobar ICH without intraventricular extension had better outcomes than those with ICH situated in the basal ganglia with intraventricular extension [95].

Therefore the STICH 2 study assessed whether surgery was superior to conservative management in patients with superficial (<1cm from a cortical surface) lobar ICH without intraventricular extension, but again failed to demonstrate improved outcomes in those undergoing surgery [216]. The findings of the STITCH 2 study have tempered support for surgical evacuation of supratentorial ICH, at least via traditional means. A meta-analysis of all RCTs performed prior to the publication of STITCH 2 suggested that some sub groups may benefit from haematoma evacuation [217]. These subgroups included patients undergoing surgery within 8 hours of symptom onset, those with GCS 9-12, haematoma volume 20-50mL and age 50-69 [217]. Therefore although traditional open evacuation lacks a clear evidence base, the findings of this meta-analysis are useful in that may help guide inclusion criteria for future surgical trials of ICH.

The major early ICH trials which failed to show clear benefit incorporated traditional open surgical techniques to access and evacuate the haematoma. Minimally invasive surgical (MIS) techniques have gained greater recognition in recent years, and represent a means of surgically treating neurosurgical pathology with less disruption of normal anatomical structures than traditional open approaches. The incorporation of MIS in the treatment of supratentorial ICH evacuation may be associated with a decreased surgical and anaesthetic risk profile, therefore tilting the balance in favour of surgical intervention. Hersch and colleagues have divided MIS techniques into 2 broad categories; that of 'stereotactic aspiration with thrombolysis' compared with 'active evacuation' [218]. Both approaches are discussed in the following paragraphs.

The 'MISTIE' trial investigated the potential benefits of stereotactic aspiration with thrombolysis [219]. In brief, following initial stabilisation of the ICH, a drainage catheter is inserted into the region of the haematoma using stereotactic guidance. Following gentle aspiration, tissue plasminogen activator is administered into the cavity, with further gentle aspiration of the haematoma. This process is repeated several times, with the results monitored by serial CT scan. This procedure is safe, but unfortunately the phase 3 trial (MISTIE 3) of this technique failed to show evidence of improved functional outcomes when compared with conservative therapy [220]. A possible benefit was seen in the pre-specified subgroup of patients with 'effective removal' (defined as residual ICH volume <15ml). Craniopuncture followed by infusion of thrombolytic drugs represents a similar therapeutic intervention, with a meta-analysis of 4 RCTs demonstrating decreased rates of death and dependence when compared with traditional craniotomy [221]. These findings suggest that while aspiration with thrombolysis may be superior to traditional open evacuation of ICH, there is little evidence to suggest it is a superior alternative to best medical therapy.

Active evacuation of ICH via an endoscopic technique was described in 1989 in ICH patients with altered conscious state, with investigators able to achieve a significant reduction in haematoma volume, along with favourable mortality outcomes when compared with medically managed patients [222]. In 2016, Vespa and colleagues assessed the utility of CT guided endoscopic drainage of 20 patients with a haematoma volume >20mL, GCS >5 and National Institute of Health Stroke Scale (NIHSS) score of >5 [223]. Outcomes of these patients were compared with those of the medically managed MISTIE 3 patients, with surgical therapy being associated with improved neurological outcomes at 12 months [220].

The promising results of this trial have been followed by technical advances that potentiate the ability of the operating surgeon to effectively and safely evacuate the ICH. The stereotactic intracerebral underwater blood aspiration (SCUBA) system is an endoscopic technique of ICH evacuation that initially evacuates in a dry field, but then irrigates the haematoma cavity, allowing visualisation and treatment of residual bleeding spots [224]. The system was able to achieve an average evacuation percentage of nearly 90% in a cohort of 47 patients, and treated bleeding found intra operatively in 23 cases [224]. Similar results were seen in a recent, updated report of 100 patients[225], and a recent meta-analysis of minimally invasive surgical trials suggests benefit[226].

There are multiple ongoing registered trials of minimally invasive active haematoma evacuation in ICH. These include the MIND (Artemis in the removal of ICH) trial, the ENRICH (Early minimally invasive removal of ICH) trial, the INVEST (Minimally invasive endoscopic surgery with Apollo in patients with brain haemorrhage) trial and the EVACUATE (Ultra-early minimally invasive ICH evacuation versus standard treatment) trial. Findings from these trials may provide further information on the role MIS plays in the treatment of ICH. The advent of more accurate predictors of haematoma expansion could help identify patients with the potential to rapidly deteriorate, thereby allowing prioritisation of these patients for emergent surgery.

Chapter 2: The predictive accuracy of the delayed spot sign for haematoma expansion in spontaneous supratentorial intracerebral haemorrhage: A systematic review and analysis

2.1 Introduction

Spontaneous intracerebral haemorrhage (ICH) is the most common type of haemorrhagic stroke, and has a 1 year mortality rate approaching 50% [10]. Neurological deterioration frequently occurs in the first 24 hours following ictus, and is commonly caused by haematoma expansion (HE) [65]. HE is associated with poor outcome, and is unique in that it represents a potentially modifiable prognostic marker [66]. The ability to accurately predict which patients will experience HE would improve prognostication, and help identify appropriate candidates for future trials aimed at mitigating HE.

The presence of a spot sign on first pass computed tomography angiography (CTA) has been shown to predict HE in multiple previous meta-analyses, but with limited sensitivity [88,156]. Delayed spot signs seen on CT perfusion (CTP), delayed phase CTA (dCTA) and post contrast CT (PCCT) reportedly have greater ability to predict HE than the first-pass CTA spot sign [89,90,227]. The delayed spot sign may therefore represent the most accurate imaging predictor of HE.

Studies reporting on the delayed spot sign have varied in imaging modality, definition of spot sign and definition of haematoma expansion. This systematic review and meta-analysis reports the combined accuracy of the delayed spot sign in predicting haematoma expansion.

2.2 Methods

2.2.1 Search Process

Our search adhered to PRISMA guidelines [228] (See supplementary appendix 1 for checklist). The protocol for this systematic review has been registered on PROSPERO. Pubmed, Excerpta Medica Database (EMBASE), and the Cochrane library were searched from January 2000 until July 2020. The search strategy utilised the following terms and their synonyms: CT angiography OR post contrast CT OR CT perfusion OR CT AND intracerebral haemorrhage OR haemorrhagic stroke OR hypertensive intracranial haemorrhage AND spot sign OR delayed spot sign OR dynamic spot sign. These search terms were adapted to the search engines of the other databases. The reference lists of studies identified in this search were also screened.

2.2.2 Definitions

In all studies spot signs were accepted as enhancing foci within the haematoma that were not continuous with an extra haematomal vessel on CTA and were not hyper intense on non contrast imaging [150]. Delayed spot signs were defined as those captured on dCTA, PCCT, CTP or CT venography (CTV). Studies solely assessing spot signs captured on first pass CTA were not included. Haematoma expansion was defined as an absolute volume increase of >6ml or relative increase of >30% at time of follow up scan [82,87]. Small variations from this definition were accepted.

2.2.3 Inclusion and Exclusion Criteria

Authors CO and AH independently screened studies. Titles and abstracts were reviewed to determine if the article could be excluded. If the article could not be excluded on the basis of title and abstract review, full text review occurred and a final decision made. In the event reviewers disagreed, discussion occurred with resolution by consensus.

To be included in the study, articles needed to: (1) Report on human patients with spontaneous intracerebral haemorrhage (2) Include patients with delayed CTA, CT venography, CTP or post contrast CT scans performed at time of diagnosis with reporting of spot sign presence (3) Include follow-up imaging to determine whether HE had occurred. Follow-up imaging time-frame was not pre-defined. Studies had to contain sufficient information to determine the diagnostic odds ratio, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio of the presence of the delayed spot sign in predicting HE. Studies allowed included randomised controlled trials, retrospective studies, cohort and case control studies. Case reports, systematic reviews and narrative reviews were excluded. Exclusion criteria included studies reporting on ICH secondary to trauma, neoplasms, aneurysms or vascular malformations. Studies reporting on the use of MRI to diagnose spot signs were excluded.

2.2.4 Data Extraction and Quality Assessment

Data was extracted from the studies and recorded in a standardised table. Information extracted included year of publication, study design, sample size, imaging modality used, scan timing, HE definition, time from symptom onset to diagnosis, time from initial CT scan to follow up CT scan, whether study was blinded, effective dose of radiation. For studies assessing CTP, it was determined whether whole brain acquisition had occurred. In addition for every study raw data of spot sign presence/absence and HE presence/absence was extracted into a 2 by 2 table. Assessment of study quality was performed using the QUADAS-2 tool [229].

2.2.5 Statistical Analysis

Statistical tests were performed using R studio version 1.2.5033, and the packages 'meta' and 'mada' as described by Shim and colleagues [230]. Measurements of pooled sensitivity, specificity,

diagnostic odds ratio (DOR), positive likelihood ratio (PLR) and negative likelihood ratio

(NLR) were calculated using the DerSimonian-Laird approach [231]. PLR values of >10 with a NLR

of <0.1 were taken to denote outstanding accuracy, with PLR values of >0.5 with a NLR of <0.2

taken to denote good accuracy, as previously described in the literature [232].

The area under the summary of receiver operating curves (AUC) for diagnostic accuracy of

delayed spot sign in predicting HE was calculated using bivariate random effects meta-analysis

as described by Reitsma et al. [233]. Interpreting an AUC follows the standard approach used in

previous similar meta-analyses, with values from 0.8-0.89 designating good accuracy and

values >0.9 denoting excellent accuracy [88]. The impact of publication bias was assessed

through visual assessment of a funnel plot and Deek's test [234].

Heterogeneity was assessed through the use of the I^2 measure [235]. Prior to data collection,

possible sources of heterogeneity were identified, which included whether the study was

prospective or retrospective, whether sample size was >70 or <70 and whether assessment of

imaging was blinded. The subgroups chosen mirror those identified previously as possible

sources of heterogeneity in a systematic review of the diagnostic accuracy of first pass CTA [236].

2.3 Results

Our initial search returned 501 articles. Following removal of duplicates, 321 studies remained.

311 of these studies were excluded, leaving 10 studies remaining [89,157-162,237-239]. Reason for

exclusion was due to an excluded study format in 153, only studying first pass CTA in 94,

reporting on secondary ICH in 44, not reporting HE rates in 20, incomplete data for analysis in

6 studies and 1 study was excluded as it reported on the same data set. The article selection

process is summarised in figure 1 (Figure 1) [228]. Details of the study characteristics can be found

in table 1 (Table 1), with 5 prospective studies and 5 retrospective studies. The studies included

711 patients overall, with 272 (38%) demonstrating a spot sign. Study quality was assessed

using the QUADAS-2 tool, with studies assessed as high quality with a relatively low risk of bias [229].

2.3.1 Diagnostic Accuracy of Delayed Spot Sign: All Modalities

Ten studies were identified, with 1 study assessing 2 different delayed imaging modalities. Summarised findings are presented in table 2 (table 2). The presence of a delayed spot sign was associated with HE with a diagnostic odds ratio (DOR) of 25.4 (12.7-50.9). Pooled sensitivity was 0.81 (0.72-0.88), with a pooled specificity of 0.82 (0.76-0.88). Forest plots for sensitivity can be found in figure 2 (Figure 2) and for specificity in figure 3 (Figure 3). Pooled positive likelihood ratio (PLR) was 4.30, with a pooled negative likelihood ratio (NLR) of 0.26. Significant heterogeneity was present in all of the above results. The area under the receiver operating curve (AUC) was 0.88 (Figure 4).

There was no evidence of publication bias on visual inspection of the funnel plot, and Deek's test did not indicate publication bias. Prespecified subgroup analyses showed no statistically significant relationship that could explain the heterogeneity.

2.3.2 Diagnostic accuracy of individual delayed spot sign modalities

Diagnostic Accuracy of Delayed Spot Sign: Delayed CT Angiography

4 studies were identified that assessed accuracy of dCTA. The presence of a delayed sign was associated with HE with a DOR of 17.3 (7.3-41.0). Pooled sensitivity was 0.81 (0.64-0.91), with a pooled specificity of 0.79 (0.72-0.85). Pooled PLR was 3.83, with a pooled NLR of 0.25.

Diagnostic Accuracy of Delayed Spot Sign: Post Contrast CT

3 studies were identified that assessed accuracy of post contrast CT. The presence of a delayed sign was associated with HE with a DOR of 84.1 (18.1-390.5). Pooled sensitivity was 0.84 (0.4-

0.98), with a pooled specificity of 0.92 (0.80-0.97). Pooled PLR was 8.79, with a pooled NLR of 0.18.

Diagnostic Accuracy of Delayed Spot Sign: CT Perfusion

3 appropriate studies assessed the diagnostic accuracy of the spot sign on CTP source images. The presence of a delayed sign was associated with HE with a DOR of 41.7 (6.9-251.9). Pooled sensitivity was 0.82 (0.72-0.90), with a pooled specificity of 0.89 (0.66-0.97). Pooled PLR was 7.18, with a pooled NLR of 0.22.

Diagnostic Accuracy of Delayed Spot Sign: CT Venography

Only one study was found on the diagnostic accuracy of the spot sign on CTV which precluded meta-analysis. This study found a sensitivity of 0.8, a specificity of 0.74, a PLR of 3 and a NLR of 0.14.

2.4 Discussion

Multiple systematic reviews have been performed of the diagnostic accuracy of first-pass CTA spot sign [88,155,156,240]. However, to our knowledge only one systematic review and meta-analysis performed in 2014 has assessed the diagnostic accuracy of the spot sign on delayed imaging modalities in predicting haematoma expansion [155]. Our updated review includes numerous studies published since then, focusing on those explicitly reporting delayed spot sign association with haematoma expansion. In Du's prior systematic review, the limited number of studies reviewed precluded meta-analysis. The inclusion of more recently published papers on this topic has allowed for the first meta-analysis of the diagnostic accuracy of the CTP spot sign in predicting haematoma expansion [161,162].

The presence of the spot sign on CTA imaging is known to be associated with HE [87]. However previous meta-analyses of the ability of the CTA spot sign to predict HE has shown a sensitivity of only 50-60% [155,156]. CTA usually captures images at a point shortly after bolus arrival in the carotids, which may be an insufficient period of time for some spot signs to opacify [153]. Spot signs on modalities that image a greater length of time after contrast administration such as PCCT, dCTA or CTP have been shown to have greater sensitivity in predicting HE [89,157,159]. This is presumably due to their ability to visualise late opacifying spot signs which may still signal extravasation of blood at sufficient rate to cause HE.

Our studies show a pooled sensitivity of 81% for the spot sign on delayed imaging modalities predicting HE, indicating a significant improvement over use of the traditional spot sign on first pass CTA. Specificity of the spot sign on delayed imaging modalities was 83%, slightly inferior to the 88% reported in prior meta-analyses for first pass CTA [155,156]. Spot signs occurring after 23 seconds have been shown to be less predictive of HE than early opacifying signs, which may explain lower specificity [162].

The spot sign can predict patients that are more likely to experience HE, and who therefore may be more likely to benefit from mitigating interventions. For example, several previous studies assessing the effect of haemostatic therapies have used a spot sign as an inclusion criterion [180,241]. However, recruitment to these studies were slow. Use of CTP in such studies may increase both recruitment and generalisability. The high accuracy of the dynamic spot sign in predicting HE could help identify patients that may benefit from more aggressive blood pressure control [172]. Finally, the presence of a dynamic spot sign may warn of potential sites of intraoperative bleeding in patients being considered for minimally invasive haematoma evacuation [224].

There are several limitations of our study. The sample sizes of included studies were generally quite small. Many studies did not assess spot signs across a variety of imaging modalities, which would have allowed a comparison of diagnostic accuracy within the same cohort. In addition, the presence of the spot sign is not the sole predictor of haematoma expansion. Haematomas with a larger volume at initial diagnosis are more likely to expand, as are haematomas in patients on oral anticoagulant medications [66,84]. Studies included in our analysis generally did not control for these factors, and these variables could potentially explain some of the heterogeneity present in our results. Another possible explanation for the heterogeneity of our findings was the variation or uncertainty in imaging technique that existed even within the same imaging modality. Timing of imaging post contrast administration was not consistent, or in some cases not reported at all. An issue exclusive to CTP was that only one study used whole brain acquisition techniques [162]. A lack of WBA could mean insufficient visualisation of the ICH and allow the spot sign to elude detection, underestimating the potential sensitivity of CTP.

2.5 Conclusion

The delayed spot sign imaged by a variety of techniques appears to have superior diagnostic accuracy in predicting HE than first pass CTA. Further work is needed to determine the most accurate delayed imaging technique. The delayed spot sign may have a role in identifying the subset of patients most likely to benefit from therapies aimed at reducing HE.
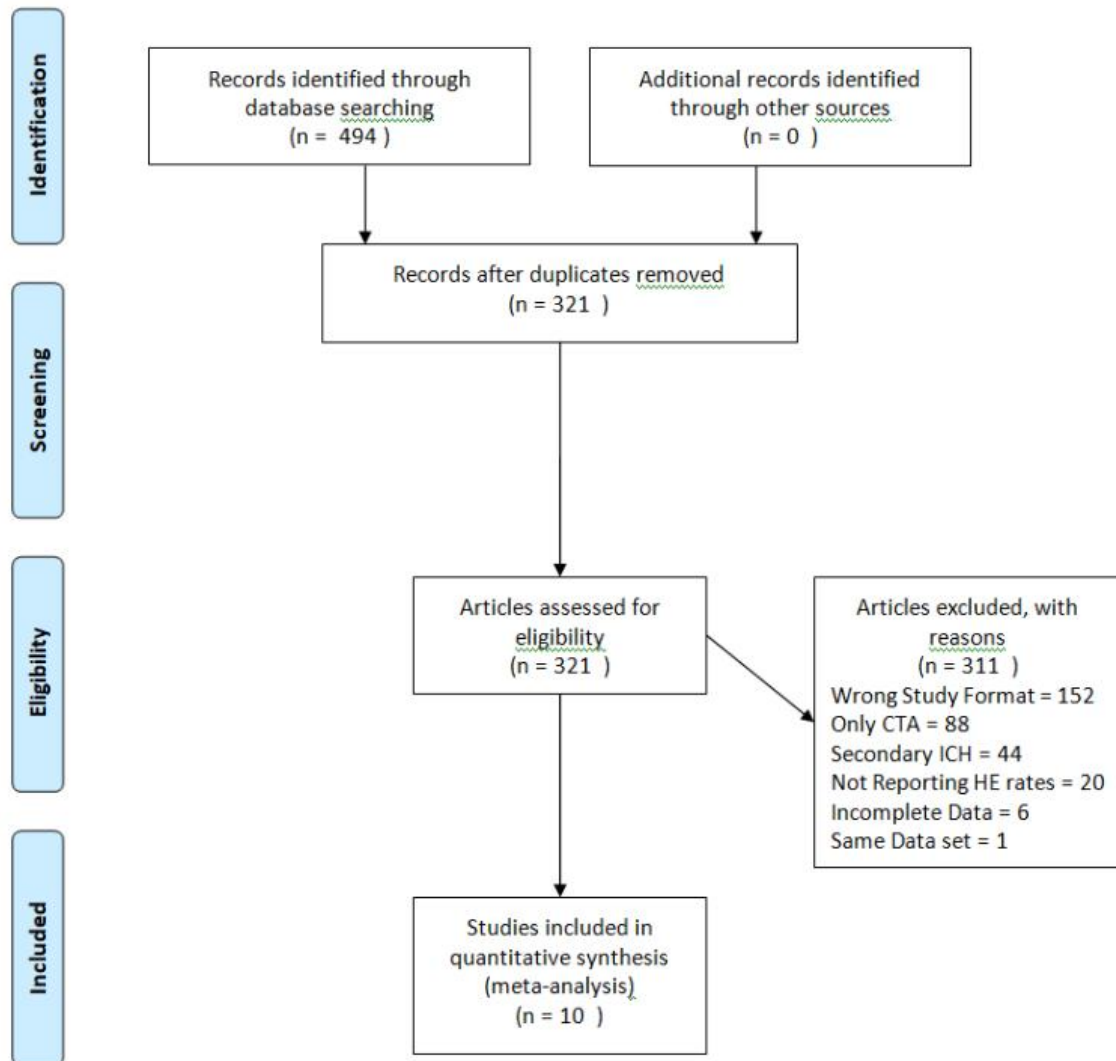
Figure 1: Flow diagram for study inclusion with reasons for exclusion.
Image sourced from: Moher, D., et al. (2009). "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." PLoS Med **6**(7): e1000097[228].

Study	Events	Total		Proportion	95%-CI
g = DCTA					
Ciura	7	11		0.636	[0.308; 0.891]
R–L 2014	10	14		0.714	[0.419; 0.916]
Tsukabe	25	27		0.926	[0.757; 0.991]
Wu	23	26		0.885	[0.698; 0.976]
Random effects model		78		0.812	[0.643; 0.912]
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 0.3910$, $p = 0.12$					
g = PCCT					
Hallevi	16	16		1.000	[0.794; 1.000]
Kocylym (same study)	9	18		0.500	[0.260; 0.740]
Orito	21	23		0.913	[0.720; 0.989]
Random effects model		57		0.844	[0.400; 0.978]
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 2.6433$, $p < 0.01$					
g = CTP					
Kocylym	14	18		0.778	[0.524; 0.936]
Sun	25	28		0.893	[0.718; 0.977]
Wang	20	25		0.800	[0.593; 0.932]
Random effects model		71		0.824	[0.715; 0.898]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.53$					
g = CTV					
R–L 2017	20	25		0.800	[0.593; 0.932]
Random effects model		25		0.800	[0.600; 0.914]
Heterogeneity: not applicable					
Random effects model		**231**		**0.808**	**[0.716; 0.876]**
Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.3601$, $p = 0.03$					
Residual heterogeneity: $I^2 = 61\%$, $p = 0.01$					

Sensitivity

Figure 2 Sensitivity Forest Plot

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Study	Events	Total	Proportion	95%-CI
g = DCTA				
Ciura	55	63	0.873	[0.765; 0.944]
R−L 2014	39	54	0.722	[0.584; 0.835]
Tsukabe	42	56	0.750	[0.616; 0.856]
Wu	61	74	0.824	[0.718; 0.903]
Random effects model		247	0.794	[0.719; 0.853]
Heterogeneity: $I^2 = 41\%$, $\tau^2 = 0.0716$, $p = 0.17$				
g = PCCT				
Hallevi	12	12	1.000	[0.735; 1.000]
Kocylym (same study)	10	10	1.000	[0.692; 1.000]
Orito	25	28	0.893	[0.718; 0.977]
Random effects model		50	0.916	[0.796; 0.968]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$				
g = CTP				
Kocylym	10	10	1.000	[0.692; 1.000]
Sun	79	84	0.940	[0.867; 0.980]
Wang	35	47	0.745	[0.597; 0.861]
Random effects model		141	0.888	[0.656; 0.971]
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 1.1181$, $p < 0.01$				
g = CTV				
R−L 2017	49	70	0.700	[0.579; 0.804]
Random effects model		70	0.700	[0.583; 0.796]
Heterogeneity: not applicable				
Random effects model		**508**	**0.824**	**[0.756; 0.876]**
Heterogeneity: $I^2 = 60\%$, $\tau^2 = 0.2418$, $p < 0.01$				
Residual heterogeneity: $I^2 = 55\%$, $p = 0.03$				

Figure 3 Specificity Forest Plot

Figure 4 SROC for diagnostic accuracy of delayed spot sign

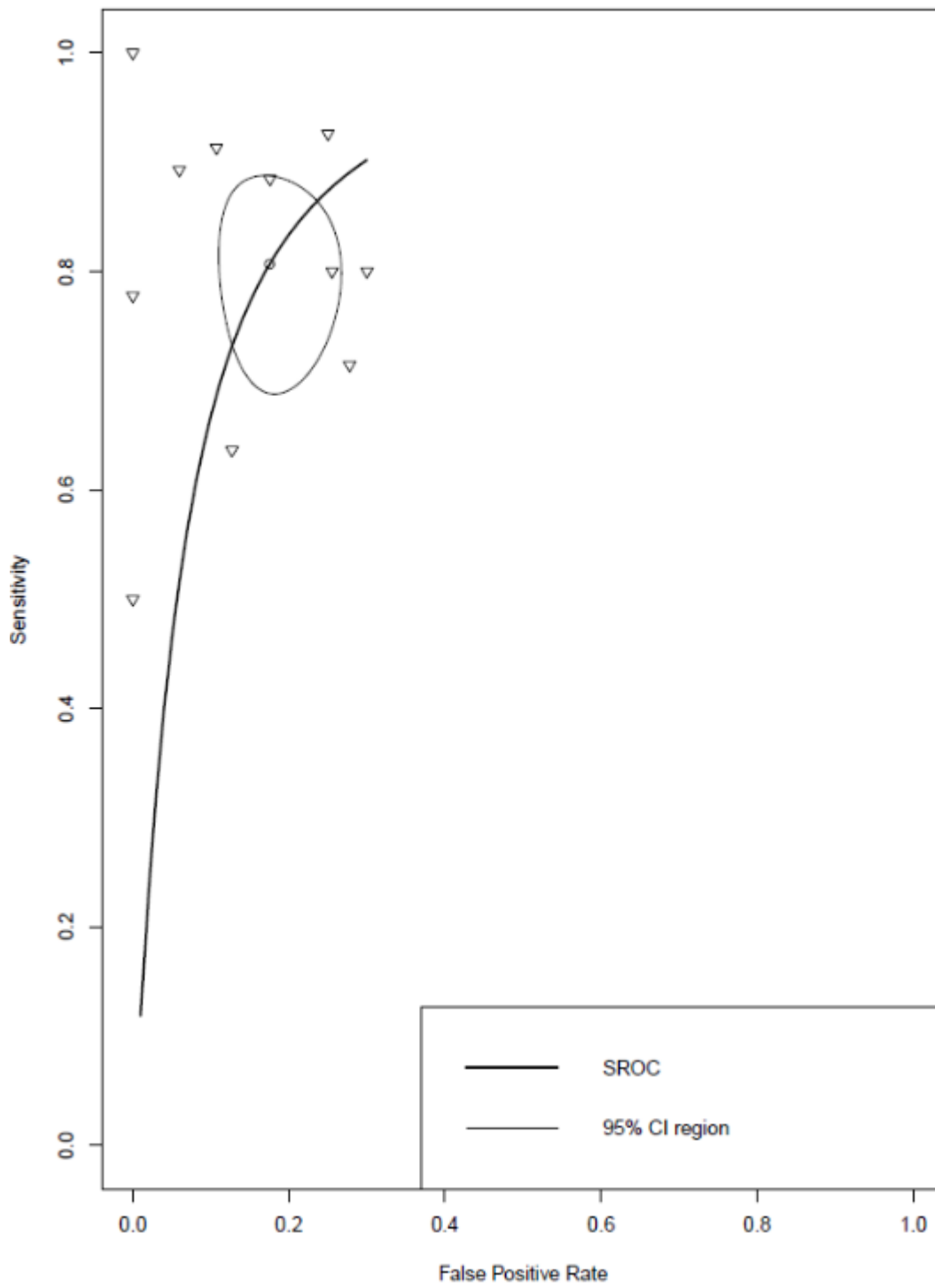| Author (Year)	Design	Sample Size	Imaging Modality	Timing of acquisition (seconds)	HE definition	Time from ictus to scan (hours)	Time from first scan to HE assessment (hours)	Blinded	Effective dose mSv	Whole Brain Acquisition
Hallevi 2009	P	28	First pass CTA, PCCT	NA	>20%	Mean 2.5	Mean 11.5	Yes	NA	Y
Koculym 2013	R	28	First pass CTA, PCCT, CTP	CTP: 90	>30% or 6mL	<6	24	No	NA	N
Sun 2013	P	112	First pass CTA, CTP	NA	>30% or 6mL	<6	24	Yes	CTP: 3.5	N
Ciura 2014	P	74	dCTA	dCTA: 90	>33% or 6mL	No limit	24	No	NA	Y
Rodriguez-Luna 2014	R	371	CTV	NA	>33% or 6mL	<6	24	No	NA	Y
Tsukabe 2014	R	188	First pass CTA, dCTA	NA	>30% or 6mL	<6, mean 2	24	Yes	NA	Y
Orito 2016	P	80	first pass CTA, dCTA	dCTA: 300	>10%	No limit	24	Yes	NA	Y
Wang 2016	R	83	CTP	CTP: 74	>33% or 6mL	<6	24	Yes	CTP: 5.94	Y
Wu 2017	R	100	dCTA	dCTA: 75	>33% or 6mL	<24	24	Yes	NA	Y
Rodriguez-Luna 2017	P	123	dCTA	NA	>33% or 6mL	<6	24	Yes	NA	Y

Table 1: Included study characteristics

Imaging Modality	DOR	Sensitivity	Specificity	PLR	NLR
dCTA	17.3 (7.3-41.0)	0.81 (0.64-0.91)	0.79 (0.72-0.85)	3.83	0.25
PCCT	84.1 (18.1-390.5)	0.84 (0.4-0.98)	0.92 (0.80-0.97)	8.79	0.18
CTP	41.7 (6.9-251.9)	0.82 (0.72-0.90)	0.89 (0.66-0.97)	7.18	0.22
Combined Delayed Studies	25.4 (12.7-50.9)	0.81 (0.72-0.88)	0.82 (0.76-0.88)	4.30	0.26
First pass CTA (Du et al. 2014)	11.84 (7.35–19.05)	0.53 (0.49-0.57)	0.88 (0.86-0.89)	4.70	0.44
First Pass CTA (Phan et al. 2019)	NA	0.57 (0.49–0.64)	NA	4.85	0.49

Table 2: Summarised Ability of Spot Signs Across Different Imaging Modalities to Predict Haematoma Expansion

Chapter 3: Time to hospital presentation following intracerebral haemorrhage: Proportion of patients presenting within eight hours and factors associated with delayed presentation

3.1 Introduction

Intracerebral haemorrhage (ICH) causes significant mortality and morbidity[10]. It is well recognised that interventions in the setting of acute ischaemic stroke, such as intra-arterial thrombolysis and endovascular thrombectomy, are time critical[242,243]. Concordantly, time to presentation and its associations has been precisely delineated in patients with ischaemic stroke[244,245]. However, the absence of similarly effective therapies for ICH has resulted in the time to presentation being less well characterised. The majority of patients with ICH present within 24 hours of ictus, however the distribution of presentation time within this period has not previously been completely elucidated[246,247]. However, the benefits of coagulopathy reversal and achievement of goal blood pressure are probably time-dependent[248] and benefits of surgical intervention for ICH may also be limited to early time-frames (surgery within 8 hours of ictus is shown to be associated with improved patient outcomes)[173,217,248].

Current guidelines recommend a target systolic blood pressure of around 140mmHg in patients with ICH[174]. Earlier recognition of ICH allows timely implementation of treatments to control blood pressure, facilitating optimal management in the acute stages of the disease.

This study seeks to determine the time to presentation and time to diagnosis for a cohort of ICH patients treated at a single stroke centre. Secondary aims comprise the determination of factors associated with delayed presentation.

3.2 Methods

3.2.1 Methodology

Ethics approval for this study was obtained from the Royal Adelaide Hospital ethics review board. A stroke database of a single metropolitan hospital was retrospectively reviewed to identify patients presenting to the emergency department with ICH from January 2017 until December 2018. Data collected included demographics (age and sex), comorbidities, anticoagulation status, clinical scores (NIHSS, GCS), and imaging (anatomical site, haematoma size). ICH scores were calculated for each patient[61]. It was noted whether the patient's initial presentation was to our hospital or whether they were transferred to our centre from another institution. Patients with ICH secondary to vascular causes (i.e aneurysm or vascular malformation) were excluded, as were ICHs due to tumour or venous sinus thrombosis.

Time of symptom onset was defined as the time when the patient reported experiencing symptom onset, or the time when the patient was last seen well if they were unable to communicate. Time from symptom onset to hospital presentation and time from hospital presentation to imaging diagnosis were also recorded. In cases where the patient was transferred from another hospital to the institution for management, time of presentation was considered to be the time of patient arrival at that first institution. Delayed presentation was defined as duration of greater than 8 hours from ictus to hospital presentation.

3.2.2 Statistical Analysis.

Only cases presenting initially to our hospital (i.e. not transferred) were assessed for factors predictive of delayed presentation. Univariate binary logistic regressions were performed using student t tests, Chi-Squared or Fisher's Exact Test P value (for sparse data) was calculated as appropriate.

Using the model described by Heinze and colleagues,[249] predictors with P value <0.2 on univariate regression were included in an initial multivariable binary logistic model with

outcome of delay from ictus to hospital. Backwards elimination was performed, removing the predictor with the highest P value one model at a time, until all predictors had a P value <0.2 – this is the final multivariable model.

A comparative analysis of the patients who initially presented to our institution and those who were transferred from another hospital was performed. As no continuous time nor baseline variable was normally distributed median and interquartile ranges (IQR) were presented and Wilcoxon Rank Sum Test P values were calculated. Cross tabulations were performed for transfer versus all categorical baseline variables, and frequency and percentage for transfer and non-transfer cases were presented for each value. A Chi-Squared or Fisher's Exact Test P value (for sparse data) was calculated as appropriate. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3.3 Results

During the study period, 235 patients with ICH meeting study inclusion criteria were identified (72 ICH cases were excluded as defined above). 125 of the included patients (53%) were male. Of these, 35 patients (15%) did not initially present to the study centre, leaving 200 primary presenter patients. Baseline characteristics of both transfer and non-transfer patients are displayed in Table 1.

For the 200 primary presenters, median time to hospital presentation was 179 minutes (IQR 77-584 minutes), and median time from ictus to non-contrast CT imaging was 268 minutes (IQR 114-717). 139 (70%) patients presented within 8 hours of symptom onset, and 129 (65%) patients had imaging of the brain performed within 8 hours of symptom onset.

Variable associations with time from ictus to hospital presentation >8 hours on the multivariable analysis are displayed in Table 3; significant associations were found for older age (p = 0.0108) and wake up stroke (p<0.0001). The presence of hemiplegia was associated with earlier presentation (p =0.0142).

A comparison was performed between the 200 patient who initially presented to the study hospital and the 35 patients who were transferred (Table 1). Significantly greater median minutes from ictus to diagnosis were found in the transferred group (p = 0.0047), in addition to a significantly lower median age (p = 0.0120) and significantly lower percentage of patients with hemiplegia (p = 0.0051). All other comparisons were not statistically significant at the 0.05 level of comparison.

3.4 Discussion

Our study retrospectively reviewed time to presentation and time to diagnosis in a population of patients with intracerebral haemorrhage treated at a tertiary stroke centre. 70% of patients who presented first to our hospital presented within 8 hours of symptom onset, with a median presentation time of 179 minutes. 65% of patients had brain imaging within 8 hours of symptom onset. The time taken to present to hospital following ICH is similar to a previously reported Australasian study, though the time to CT brain is far less in our study[247]. Our findings correlate well with the median time taken to present following the onset of stroke symptoms in patients with ischaemic stroke, which describes that 30-50% of patients present within 3 hours[245,250,251].

In ischaemic stroke, time is brain[252], as the time critical nature of early interventions is well recognised[242,243]. However there is also some evidence that outcomes following acute therapy in ICH may be dependent on the timing of the intervention. Kuramatsu and colleagues found that in patients on oral anticoagulation therapy, achieving an INR of <1.3 and systolic blood

pressure of <160mmHg within 4 hours of admission was associated with improved outcomes, [248] with evidence of further trends of improvement if treated successfully even earlier. In the individual patient meta-analysis of surgical craniotomy trials, only patients randomised to surgery within 8 hours of symptom onset had a decreased likelihood of an unfavourable outcome (OR 0.59, 95% CI 0.42-0.84)[217]. Based on this evidence of a surgical time-window, several early-window ICH surgical trials are underway[253]. Successful recruitment will be contingent on patient presentation volume within an early time-frame. Our study demonstrates that a significant majority of ICH patients present within this 8 hour window.

The presence of hemiplegia was associated with presentation within 8 hours of symptom onset (OR 0.41, 95% CI 0.21, 0.84), a finding which correlates with previous studies of patients with ischaemic stroke[254]. Interestingly, neither presentation NIHSS, GCS or ICH score was found to be associated with earlier timing of presentation to hospital. These scores act as surrogates for the severity of the insult to the brain, and previous studies in ischaemic stroke have shown that patients with more significant neurological symptoms tend to present to hospital earlier[255]. The presence of 'wake up stroke' was an unsurprising predictor of delayed presentation (OR 5.31 (95% CI 2.36, 11.96)). Stroke onset during sleep may occur later in the sleep cycle, and delayed recognition of stroke symptoms and emergency response teams occurs. Our findings correlate with previously reported studies of ischaemic stroke[255,256]. However recent data suggests that unclear symptom onset patients presenting with ICH have similar rates of haematoma expansion to patients with known onset, and that perhaps time of onset in these cases may be (in the majority of cases) close to the time of symptoms discovery[257].

As expected patients with ICH being transferred from another institution to our hospital had significantly delayed onset-presentation to our hospital[258]. Despite this, the median time from

symptom onset to presentation to our hospital was 322 minutes (IQR 160-612), well within a theoretical 8 hour window for surgery[217]. The age of patients transferred from another hospital was significantly lower than in those who presented initially to our hospital, and is presumably related to surgical treatments being less likely under consideration in younger patients.

Our study has limitations. First, the retrospective nature of the study may be associated with data imprecision – however data were obtained from a prospectively-maintained stroke-specific database. Second, the relatively small cohort precludes the identification of less prevalent predictive factors. Last, as a single centre study with disparate and unique geographical catchment, generalisation to other stroke centres may be limited.

A major strength of this study is the non-biased inclusion of consecutively presenting ICH patients. The robust and comprehensive nature of our hospital's prospectively collected stroke database allows for inclusion in the analysis of all major variables most likely to influence the timing of presentation to hospital. The use of a multivariable analysis to assess predictors of delayed presentation mitigates the effect of possible confounding variables on that outcome. The majority of previous studies on delay to presentation following stroke has focused on ischaemic strokes, and this study assesses a cohort solely made up of patients with primary ICH, allowing for an assessment of factors that may uniquely be related to timing of presentation in this stroke subtype.

This research has several significant implications. The majority of patients who sustained primary ICH in the study period presented to the emergency department within 3 hours of symptom onset. This means a significant majority of patients presenting to hospital with primary ICH would meet the time criteria for new studies assessing the efficacy of ultra-early (within 8 hours) surgical evacuation of ICH. The findings of our study show that in patients transferred from another institution the majority also presented within an 8 hour window,

meaning they would also be potentially eligible for enrolment in a surgical trial of early

haematoma evacuation. The significant delays in this population to presentation of these

patients to tertiary care imply that such patients may benefit from introduction of a large

vessel occlusion screening tool[259], as many patients will likely be positive. Such patients may

benefit from earlier reversal of coagulopathy and hypertension, as well as potentially earlier

surgical treatment.

3.5 Conclusion

Our study defines time to presentation in a cohort solely made up of ICH patients. The

median time to presentation was less than 3 hours. Predictors of delayed presentation

included increasing age, wake up stroke and need to transfer to our hospital from another

institution. Hemiplegia predicted earlier presentation. In characterising time to presentation

in ICH, our study helps establish the feasibility of early haematoma evacuation trials.

	Primary (n = 200)	Transfer cohort (n = 35)	p value
Age	77 (70 - 85)	71 (59 - 81)	0.003
Sex: male	106 (53%)	19 (54%)	0.888
Prior stroke	36 (18%)	7 (20%)	0.778
Obesity	12 (6%)	2 (6%)	0.947
Hypertension	156 (78%)	29 (83%)	0.517
Diabetes mellitus	40 (20%)	10 (29%)	0.253
Dementia	26 (13%)	3 (9%)	0.462
Pre-existing antithrombotic	91 (46%)	14 (40%)	0.546
Minutes from ictus to hospital	179 (77 - 584)	322 (160 - 612)	0.715
Minutes from ictus to diagnosis	268 (114 - 717)	422 (221 - 1053)	0.515
NIHSS initial	15 (5 - 24)	10 (4 - 20)	0.199
GCS	12 (9 - 15)	14 (11 - 15)	0.175
Wakeup stroke	35 (18%)	8 (23%)	0.450
Able to walk	46 (23%	11 (31%)	0.283
Hemiplegic	135 (68%)	15 (43%)	0.005
Alertness			0.745
Alert	96 (48%)	20 (57%)	
Drowsy	54 (27%)	7 (20%)	
Obtunded	22 (11%)	3 (9%)	
Comatose	28 (14%)	5 (14%)	
Code stroke called	122 (61%)	16 (46%)	0.078
Haemorrhage volume	12 (5 - 45)	12 (4 - 31)	0.421
Stroke side: left	102 (51%)	16 (46%)	0.390
Stroke aetiology			0.430
Amyloid	78 (39%)	9 (26%)	
Hypertension	122 (61%)	26 (74%)	

ICH score	2 (1 - 3)	1 (0 - 3)	0.244
Decompressive hemicraniectomy	5 (3%)	3 (9%)	0.068
Surgery performed	6 (3%)	3 (9%)	0.113
Palliated	82 (41%)	10 (29%)	0.165

Values presented are n (%) or median (IQR)

Students t and χ^2 tests were used as appropriate

Table 3: Baseline characteristics of patients presenting with intracerebral haemorrhage

Predictor	Global P value
Wakeup stroke	<.0001
Can walk	0.1496
Sex	0.4737
Hemiplegia	0.0443
Alertness	0.7264
Code stroke called	0.2080
Discharge destination	0.9129
Discharge mRS	0.4302
Palliation	0.9883
Stroke side	0.5105
Stroke type	0.3129
Intraventricular extension	0.9389
ICH location	0.3355
Prestroke mRS	0.8297
Prior stroke	0.4205
Obesity	0.8261
Hypertension	0.1865
Diabetes mellitus	0.3997
Dementia	0.9745
Preexisting antithrombotic	0.7011
ICH surgical evacuation	0.1804*
Age	0.0095
NIHSS initial	0.0294
Haemorrhage volume	0.5231
GCS	0.9943
ICH score	0.5946

Table 4. Univariate binary logistic regressions of ictus to hospital delay (0-8 hours versus >8 hours) versus various predictors

Predictors	Comparison	Odds Ratio* (95% CI)	Global P value
Wakeup stroke	Yes vs No	5.31 (2.36, 11.96)	<.0001
Hemiplegia	Yes vs No	0.41 (0.21, 0.84)	0.0142
Hypertension	Yes vs No	0.57 (0.26, 1.23)	0.1529
Age	per 1 year increase	1.04 (1.01, 1.08)	0.0108

*Modelling the probability that delay between ictus and hospital is greater than 8 hours

Table 5. Multivariable binary logistic regression of delay from ictus to hospital versus significant predictors (P<0.2)

Chapter 4: Comparison of non contrast CT signs, the CT angiography spot sign and CT perfusion dynamic spot sign in predicting haematoma expansion

4.1 Introduction

Intracerebral haemorrhage is a disease that commonly results in death, with a mortality rate approaching 50% [10]. Haematoma expansion occurs in a subset of patients, and is associated with clinical deterioration, increased mortality and poorer functional outcomes [65,66]. CTA may demonstrate a region of active contrast extravasation into the haematoma, this is known as the spot sign and is a predictor of both haematoma expansion and mortality [87,260]. Despite its utility in predicting haematoma expansion, the CTA spot sign is imperfect. One prospective study identified that 22% of patients had haematoma expansion despite being spot sign negative [260]. This may represent later phase arterial bleeding, or bleeding from capillary or venous sources that the CTA spot sign will not assess, and prior studies have indeed shown that post contrast extravasation is associated with haematoma expansion in spot sign negative patients [90].

CTP scanning involves the administration of a contrast bolus followed by a more prolonged period of image acquisition. Use of the source images of CTP scans to assess a 'dynamic spot sign' addresses some of the issues with the CTA spot sign raised above. The prolonged period over which images are gathered means non arterial foci of extravasation may be identified, potentially identifying a greater percentage of patients at increased risk of haematoma expansion. In addition, CTP images allow for the assessment of a further parameter, that of rate of growth of the spot sign which may represent a more rapid, torrential source of bleeding. Several small prior studies have demonstrated that the CTP dynamic spot sign is a sensitive marker of haematoma expansion [89]. In addition, in recent years certain NCCT imaging features have been described that may also have the ability to predict haematoma

expansion [91-93,132]. To our knowledge, no direct comparisons between these NCCT imaging signs and the CTP spot sign currently exist in the literature.

The advent of novel imaging predictors necessitates assessment of their relative accuracy. Our study compares the diagnostic accuracy of NCCT signs, the CTA spot sign and the dynamic spot sign on CTP imaging in predicting haematoma expansion in patient with spontaneous ICH.

4.2 Methodology

4.2.1 Patient Selection

Ethics approval for this study was obtained from our local institutions ethics review board (Reference number 12425). Retrospective review of patients with supratentorial ICH on NCCT brain presenting to our tertiary stroke centre from the period of September 2019 to June 2021 were reviewed. To be eligible, patients had to have NCCT, CTA and CTP imaging performed at the time of diagnosis, along with interval imaging that could be used to assess the presence of haematoma growth. Our site routinely performs complete multimodal imaging on all 'code stroke' patients unless contraindicated. Cases of secondary ICH where tumour, vascular lesions (arteriovenous malformation, aneurysms, cavernous malformations, dural arteriovenous fistula), post thrombolysis, venous sinus thrombosis, non medication related coagulopathy, reversible cerebral vasoconstriction syndrome, post radiotherapy, vasculitis, Moya Moya syndrome, trauma was deemed to be the cause of the haemorrhage were excluded. Patients who had surgery or died prior to progress CT were excluded from the haematoma expansion analysis.

4.2.2 Clinical Data

Our hospital's prospectively collected stroke database was reviewed, and missing data was identified by retrospective chart review. Information recorded included demographic data, time from ictus to initial imaging, National Institute of Health Stroke Scale (NIHSS) score, admission blood pressure, medical history (use of antithrombotic medication, previous stroke, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, alcohol use), blood tests (platelet count, coagulation studies, serum glucose), need for haematoma evacuation, in hospital mortality and modified Rankin Score on discharge.

4.2.3 Imaging Acquisition

All images were acquired using the 320-detector Aquilion ONE CT Scanner (Canon Medical Systems, Otawara, Japan) with whole brain coverage (16cm). 50mL of contrast is injected at a rate of 6mL/sec. Over 60 seconds 19 images are acquired (radiation dose 4.7 milliSieverts), with manual over-ride for more prolonged acquisition (4x5 seconds) if cardiac output causes delayed bolus transit. CTP source image analysis was performed using the MiSTAR imaging platform (Apollo, Melbourne, Australia) following 3D motion artefact correction. Follow up NCCT was obtained at 24 hours post initial scan.

4.2.4 Imaging Analysis

Initial NCCT was reviewed by 2 assessors for the presence of the black hole sign. As previously described, this is defined as a well encapsulated region of hypoattenuation within the haematoma (with a density difference between the two regions of >28 Hounsfield units) [93]. The presence of the island sign was assessed as per the criteria set out by Li et al.[91]. A haematoma was considered to be irregular if the haematoma had a shape that was Barras category 3-5[133]. The presence of a blend sign was defined as previously defined by Li and associates[92]. The presence of a clear fluid-fluid level within the haematoma was used to determine the presence of a fluid level. CT perfusion source images and CTA images were

reviewed by two assessors to identify the presence of spot signs, with disagreements resolved by consensus. The spot sign was defined as a region of hyper density within the haematoma with a density of >120 Hounsfield units. The region could not be visible on NCCT, and could not be contiguous with a vessel on CTA. This corresponds to definitions used in previous studies of the CTP spot sign[89,162]. For CTP spot signs, time to appearance of spot sign and time to maximum attenuation from contrast bolus injection were recorded. Volume of the spot sign at time of maximum attenuation was calculated, and time from appearance to maximal volume was used to calculate immediate rate of growth of the spot sign.

The abc/2 method was used to calculate haematoma volume on both initial and repeat NCCT [64]. Haematoma expansion was defined as an increase of > 6mL or >30%, which corresponds to the definitions used in previous studies of the CTP spot sign [89,261]. Imaging analysis was performed blinded to haematoma expansion status.

4.2.5 Statistical Analysis

Haematoma expansion was defined as the primary outcome. Univariate analysis was performed to identify the relationship between clinical data variables, imaging variables and the aforementioned primary outcome. Relationships between categorical data were tested with the Fischer exact test, and relationships between continuous variables were assessed using the Wilcoxon rank sum test. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of the various imaging signs in predicting the haematoma expansion were calculated. Area under the receiver operating curve for imaging signs in predicting haematoma expansion and the primary outcome will be calculated. Univariate linear regression was performed to determine spot sign characteristics associated with either absolute or percentage haematoma growths. For above statistical tests, a value of <0.05 was

considered significant. The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

4.3 Results

Table 1 demonstrates the characteristics of the general study population. A total of 85 patients had a CTP scan performed at time of initial diagnosis, with 55 patients having a 24 hour follow up CT available to assess for the presence of haematoma expansion. For the 30 patients who did not have a 24 hour CT brain available, the reason was palliation/death in 17, need for emergent surgery in 3, enrolment in clinical trial assessing early surgery in 7 and repeat scan not performed for no clear reason in 3. Of the 55 patients with a follow up scan, 18 had haematoma expansion. In these patients initial haematoma volume was a median of 29.1mL (IQR 7.1- 51.9mL), follow up haematoma volume was a median of 52.4mL (IQR 15.8-78.5mL) with a median absolute volume increase of 15.1mL (IQR 7.4-23.8mL) and a median percentage increase of 52.2 (IQR 40.9-77.1). Table 1 also describes the characteristics of patients who had haematoma expansion, along with patients who did not. Greater NIHSS score on presentation, pre-existing use of anti-thrombotic, greater initial haematoma volume, presence of irregular margins, island sign, CTA spot sign or CTP spot sign were associated with haematoma expansion.

Table 2 presents the results of binary logistic regression analysis of factors associated with haematoma expansion in the 55 patients that had follow up imaging available. Pre-existing anti-thrombotic medications (OR 6.40, 95% CI 1.71-23.95), higher initial NIHSS (OR 1.10, 95% CI 1.01-1.20), presence of IVH (OR 4.24, 95% CI 1.29-14.00), initial ICH volume, presence of irregular margins (OR 3.27, 95% CI 1.01-10.56), presence of the island sign (OR 4.07, 95% CI 1.07-15.50), presence of the CTA spot sign (OR 11.33, 95% CI 2.53-50.74) or presence of the CTP

spot sign (OR 126.00, 95% CI 12.93-1227.68), were significant associated with haematoma expansion.

Table 3 details the sensitivity, specificity, positive predictive value and negative predictive value of the various imaging signs in predicting haematoma expansion. The sign with the lowest sensitivity was the island sign (0.39; 0.17-0.64), with the highest being the CTP spot sign (0.78; 0.52-0.94). The sign with the lowest specificity was the presence of irregular margins (0.68; 0.50-0.82), with the highest being the CTP spot sign (0.97; 0.86-1.00). The sign with the lowest positive predictive value was the black hole sign (0.48; 0.26-0.70), with the highest being the CTP spot sign (0.93; 0.68-1.00). The sign with the lowest negative predictive value was the fluid level sign (0.66; 0.52-0.78), with the highest being the CTP spot sign (0.90; 0.76-0.97).

Of the 14 patients with haematoma expansion who had a positive CTP spot sign, the median time of appearance of the spot sign was 22.8 seconds (14.6-25.3), with a median maximum attenuation of 192 HU (151-255) and a median volume at time of maximum attenuation of 9.5mm^3 (3.6-17.9). Median velocity of spot sign size growth was 1mm^{3}s^{-1} (0.3-1.7). The CTA spot sign was present in nine patients who did not experience haematoma expansion. In the five patients who had a CTP spot sign but not a CTA spot sign, the median time for maximum attenuation was 38.3 seconds (35.1-52.9). Table 4 demonstrates the associations between CTP spot sign characteristics and the percentage or absolute growth of haematoma on progress scan. The only significant association was between absolute growth and time to maximum attenuation (p=0.0429). For every one unit increase in time to maximum attenuation, mean absolute growth increased by 1.34 units (Mean difference=1.34, 95% Confidence Interval (CI): 0.04, 2.64). However, there was no significant association between later time to max

attenuation of the spot sign and greater percentage growth of the haematoma (MD 2.65, 95% CI (-0.75, 6.06), p =0.13).

Table 5 demonstrates the area under the curve univariate binary logistic model for each imaging signs' ability to predict haematoma expansion. The CTP spot sign had an AUC of 0.88 (0.77-0.98) denoting good predictive accuracy. The CTA had an AUC of 0.71 (0.58-0.84) denoting fair predictive accuracy. The remaining imaging signs had poor or failed predictive accuracy.

4.4 Discussion

In a consecutive cohort of patients with ICH who received both CTP at baseline and follow-up imaging, the CTP spot sign had greater accuracy in predicting haematoma expansion than NCCT imaging signs and the CTA spot sign. CTP source images were able to identify more spot signs than CTA images. Spot signs identified by CTP but missed by CTA had a median time to max attenuation (38.3 seconds) - that is after the time post contrast administration that CTA images are acquired. Though NCCT imaging findings such as the black hole sign, island sign and irregular margins were associated with haematoma expansion, their predictive accuracy was poor relative to both the CTA spot sign and particularly the CTP spot sign.

Prior studies of the CTP spot sign have demonstrated a sensitivity of predicting haematoma expansion of 74-89%[89,161,162], similar to the sensitivity of 78% identified in our study. This compares favourably with the sensitivity of the CTA spot sign in predicting haematoma expansion, with systematic reviews finding a sensitivity of 53-57%[88,155], a finding that corresponds well with the sensitivity of 50% found in our study. The ability of CTP images to capture spot signs that opacify and reach maximum attenuation later than the acquisition time of CTA is the likely explanation for the greater sensitivity of the CTP spot sign. In

patients with haematoma expansion who were CTP spot sign positive but CTA spot negative, the timing of maximum attenuation of the spot sign was a median of 38.3 seconds, well after the acquisition time of the CTA images. This is a similar finding to Koculym et al., who found that spot signs identified by CTP but missed by CTA reached maximum attenuation at a time of 30-70 seconds[89]. Spot signs with a later time to maximum attenuation may represent bleeding from a capillary or venous source, explaining why they are not captured on CTA imaging.

Haematoma expansion is a significant complication of ICH that is associated with significant neurological morbidity and mortality[65]. There is no currently available therapy that has conclusively been shown to decrease rates of haematoma expansion. The ability to identify patients at high risk of this complication allows the ability to enrol those most likely to benefit from therapies aimed at reducing instances of haematoma expansion. Previous randomised controlled trials assessing the utility of tranexamic acid or recombinant activated factor VII in reducing rates of haematoma expansion have utilised the presence of a CTA spot sign as a criteria for enrolment in the study[180,262]. However, as noted above, the low sensitivity of the CTA spot sign limits the number of patients identified for such studies, and utilising the presence of the CTP spot sign instead may allow for improved patient selection in future trials of therapies aimed at reducing instances of haematoma expansion, including expedited surgery to directly achieve haemostasis.

NCCT imaging signs such as irregular haematoma margins, fluid levels, black hole signs, blend signs and black hole signs have previously been shown to be associated with haematoma expansion[91,93,133,144]. Our study is the first to compare the predictive accuracy of the CTP spot sign with NCCT imaging signs, and has demonstrated that while the CTP spot sign has good accuracy in predicting haematoma expansion, NCCT have poor to failed predictive accuracy.

These findings support the role of CTP imaging as the primary means of assessing for haematoma expansion. NCCT imaging findings do provide utility in instances where contrast imaging is unavailable or the patient is unable to tolerate the contrast agent.

No one CTP spot sign characteristic was found to be associated with both absolute and percentage increase in haematoma volume. However, greater time to maximum attenuation was associated with increased absolute growth of haematoma volume. Prolonged time to reach maximum attenuation may represent progressive and continuing contrasting extravasation representing more significant ongoing bleeding, possibly explaining this finding. Our findings that maximum axial dimensions and maximum density of spot sign are not significantly associated with haematoma expansion correspond to the findings of Wang and colleagues[162]. However, their study showed a relationship between earlier appearing spot signs and haematoma expansion, whereas our study did not[162].

The majority of previous studies assessing the predictive accuracy of the CTP spot sign have utilised CTP imaging techniques that do not allow whole brain acquisition and complete imaging of the haematoma[89,261]. This issue has explicitly been identified as a source of 'false negatives' where a spot sign that can be visualised on CTA imaging was unable to be visualised on CTP source images[89]. CTP studies performed on patients in our cohort were whole brain acquisition images removing the possibility of detection of a spot sign secondary to inadequate spatial coverage of the scan. This technique of imaging acquisition allows for more accurate determination of the presence of a spot sign and could prevent instances of false negatives which could depress the accuracy of the CTP spot sign. Even with whole brain acquisition techniques, our study and others have shown that some patients may have a negative CTP scan but still experience haematoma expansion[162]. This is probably related to imaging being performed at a time when haemostasis has transiently been achieved,

temporarily limiting further extravasation into the haematoma, with subsequentk haemostasis failure leading to further growth[162].

Our study has some limitations. Our sample size was too small to adequately assess the relation between the various imaging signs and outcomes, and this was reflected in our study design which focused on the presence of haematoma expansion as an outcome. Inherent limitations of retrospective studies such as selection bias are present in our study, though data being collected from a prospectively maintained stroke database acts to mitigate some sources of bias. Concerns may be raised about the additional radiation dose incurred by the CTP scan, but the cohort of ICH patients is typically of an age that is unlikely to fully incur the stochastic effects of ionising radiation.

4.5 Conclusion

The CTP spot sign has a superior predictive accuracy when compared with both the CTA spot sign and NCCT imaging markers of haematoma expansion. Future trials assessing medical and surgical interventions aiming to reduce haematoma expansion could consider the use of CTP source images to identify patients who would be most likely to receive benefit.

		Patients with follow up imaging N=55 n (%)	Haematoma expansion patients N=18 n (%)	Non haematoma expansion N=37 n (%)	P values
Age		74 (66, 82)*	77 (66, 82)	73 (66, 78)	0.2396***
Sex	Males	29 (53%)	8 (44%)	21 (57%)	0.3908
NIHSS score		11 (6, 17)*	14 (10, 20)	10 (5, 14)	0.0388***
Cause	Amyloid	20 (36%)	8 (44%)	12 (32%)	0.3849
	Hypertensive	35 (64%)	10 (56%)	25 (68%)	
Initial systolic BP	<=140	12 (22%)	2 (11%)	10 (27%)	0.2983**
	>140	43 (78%)	16 (89%)	27 (73%)	

Hypertension	Yes	35 (64%)	11 (61%)	24 (65%)	0.7860
Pre-existing antithrombotic	Yes	14 (25%)	9 (50%)	5 (14%)	0.0036
Presence of IVH	Yes	21 (38%)	11 (61%)	10 (27%)	0.0146
ICH location	Lobar	23 (42%)	9 (50%)	14 (39%)	0.7597**
	Putamen/caudate	15 (27%)	4 (22%)	11 (31%)	
	Thalamic	16 (29%)	5 (28%)	11 (31%)	
Stroke territory	Left	27 (49%)	8 (42%)	19 (53%)	0.5637
	Right	28 (51%)	11 (58%)	17 (47%)	
Median initial ICH volume (mL)		15.2 (6.4, 30.2)*	29.1 (7.1, 51.9)*	8.5 (5.4, 17.8)*	0.0350***
Black hole sign	Yes	21 (38%)	10 (56%)	11 (30%)	0.0643
Irregular margins	Yes	33 (60%)	11 (61%)	12 (32%)	0.0431
Blend sign	Yes	21 (38%)	10 (56%)	11 (30%)	0.0643
Fluid level	Yes	2 (4%)	0 (0%)	2 (5%)	1.0000**
Island sign	Yes	12 (22%)	7 (39%)	5 (14%)	0.0325
Presence of spot sign CTA	Yes	12 (22%)	9 (50%)	3 (8%)	0.0009**
Presence of spot sign CTP	Yes	15 (27%)	14 (78%)	1 (3%)	<0.0001
Number of spot signs CTA		0 (0, 0)*	1 (1, 1.5)	0 (0, 0)	0.0010***
Number of spot signs CTP		0 (0, 1)*	1 (1, 1)	0 (0, 0)	0.0007***

*Median (Interquartile range)

**Fisher's Exact Test P value

***Wilcoxon Rank Sum Test P value

Table 6. Descriptive statistics of all variables in study by presence of haematoma expansion

Predictor	Comparison	Odds Ratio** (95% CI)	Comparison P value	Global P value
ICH Location	Lobar vs Putamen/caudate	1.77 (0.43, 7.30)	0.4310	0.7141
	Lobar vs Thalamic	1.41 (0.37, 5.45)	0.6144	
	Putamen/caudate vs Thalamic	0.80 (0.17, 3.80)	0.7789	
Sex	F vs M	1.64 (0.53, 5.10)		0.3924

Predictor	Comparison	Odds Ratio** (95% CI)	Comparison P value	Global P value
Cause	Amyloid vs Hypertensive	1.67 (0.52, 5.30)		0.3868
Initial SBP greater than 140	BP>140 vs BP<=140	2.96 (0.58, 15.26)		0.1941
Hypertension	Yes vs No	0.85 (0.27, 2.72)		0.7861
Pre-existing antithrombotic	Yes vs No	6.40 (1.71, 23.95)		0.0058
Stroke territory	Right vs Left	1.40 (0.45, 4.35)		0.5643
IVH	Yes vs No	4.24 (1.29, 14.00)		0.0176
Black hole sign	Yes vs No	2.95 (0.92, 9.49)		0.0688
Irregular margins	Yes vs No	3.27 (1.01, 10.56)		0.0472
Blend sign	Yes vs No	2.95 (0.92, 9.49)		0.0688
Island Sign	Yes vs No	4.07 (1.07, 15.50)		0.0395
CTA Spot sign	Yes vs No	11.33 (2.53, 50.74)		0.0015
CTP spot sign	Yes vs No	126.00 (12.93, 1227.68)		<.0001
Fluid level		Yes – 0%, No-34%		1.0000*
Age		1.04 (0.98, 1.09)		0.2103
NIHSS score		1.10 (1.01, 1.20)		0.0226
Number of spot signs CTA		0 - 0%, >0 - 100%		0.0006*
Number of spot signs CTP		72.28 (3.85, 1358.55)		0.0042
Haematoma Volume				0.0350

*Fisher's Exact Test P value

**Modelling the probability that Haematoma expansion=Yes

Table 7. Univariate binary logistic regression of predictors of haematoma expansion

Predictor	Sensitivity (95% CI*)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Black hole sign	0.56 (0.31, 0.78)	0.70 (0.53, 0.84)	0.48 (0.26, 0.70)	0.76 (0.59, 0.89)
Irregular margins	0.61 (0.36, 0.83)	0.68 (0.50, 0.82)	0.48 (0.27, 0.69)	0.78 (0.60, 0.91)
Blend sign	0.56 (0.31, 0.78)	0.70 (0.53, 0.84)	0.48 (0.26, 0.70)	0.76 (0.59, 0.89)
Fluid Level	NA**	0.95 (0.82, 0.99)	NA**	0.66 (0.52, 0.78)
Island sign	0.39 (0.17, 0.64)	0.86 (0.71, 0.95)	0.58 (0.28, 0.85)	0.74 (0.59, 0.86)
CTA spot sign	0.50 (0.26, 0.74)	0.92 (0.78, 0.98)	0.75 (0.43, 0.95)	0.79 (0.64, 0.90)
CTP spot sign	0.78 (0.52, 0.94)	0.97 (0.86, 1.00)	0.93 (0.68, 1.00)	0.90 (0.76, 0.97)

*95% confidence interval

**Not available as there is a zero in the contingency table

Table 8. Sensitivity, Specificity, Positive Predicted Value (PPV) and Negative Predicted Value (NPV) for various predictors of Haematoma expansion

Outcome	Predictor	Mean difference (95% CI)	Global P value
Percentage growth	Time to max attenuation	2.65 (-0.75, 6.06)	0.1264
Percentage growth	Growth Velocity	2.59 (-28.52, 33.70)	0.8702
Percentage growth	Peak contrast value	-0.05 (-0.75, 0.66)	0.8979
Percentage growth	Time spot sign appeared	3.20 (-4.05, 10.45)	0.3874
Percentage growth	Volume spot sign max att	3.08 (-1.94, 8.11)	0.2293
Absolute growth	Time to max attenuation	1.34 (0.04, 2.64)	0.0429
Absolute growth	Growth Velocity	-4.19 (-16.53, 8.14)	0.5054
Absolute growth	Peak contrast value	-0.02 (-0.30, 0.27)	0.9010
Absolute growth	Time spot sign appeared	1.43 (-1.47, 4.33)	0.3338
Absolute growth	Volume spot sign max att	0.02 (-2.10, 2.15)	0.9833

Table 9. Univariate linear regression results for haematoma expansion subgroup (N=18)

Predictor	Area under Curve	95% Confidence Interval	Interpretation
Black hole sign	0.63	0.49, 0.77	Poor
Irregular margins	0.64	0.50, 0.78	Poor
Blend sign	0.63	0.49, 0.77	Poor
Fluid level	0.53	0.49, 0.56	Failed
Island sign	0.63	0.50, 0.76	Poor
Presence of Spot Sign CTA	0.71	0.58, 0.84	Fair
Presence of Spot Sign CTP	0.88	0.77, 0.98	Good

Table 10. Area under curve of univariate binary logistic models predicting haematoma expansion
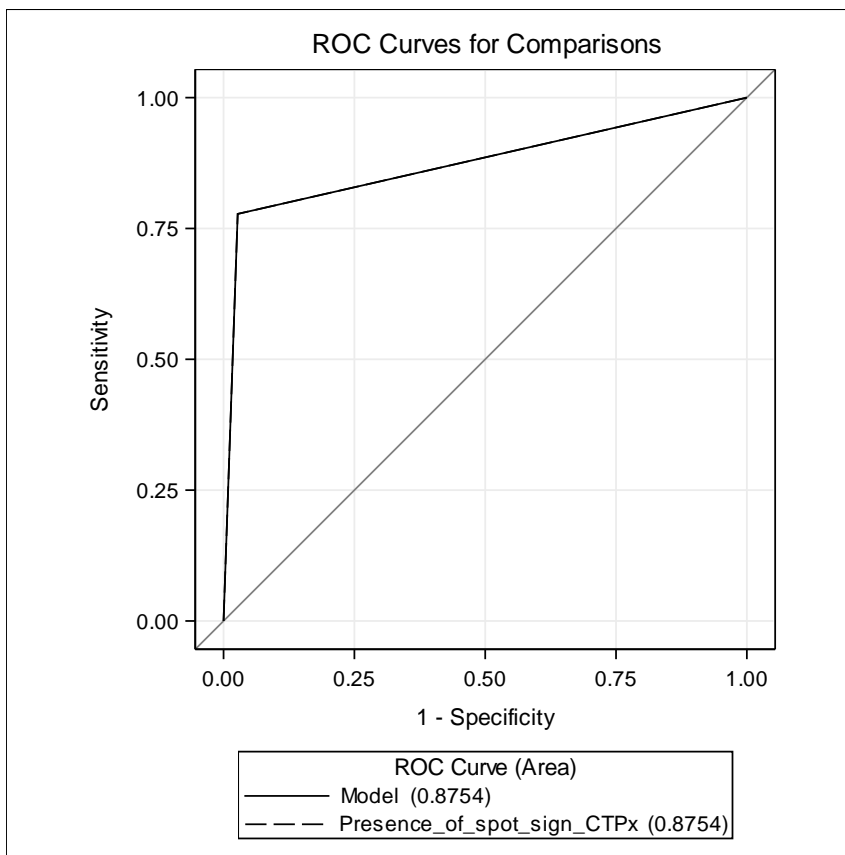

Figure 5. ROC curves of predictive accuracy of CTP spot sign in predicting haematoma expansion

Chapter 5: Thesis summary and Conclusion

This thesis has focused on the acute diagnosis and management of patients with spontaneous intracerebral haemorrhage (ICH), in particular factors related to the timing of patient presentation to hospital and diagnosis, along with the role advanced imaging techniques may play in the diagnosis, management and prognostication of ICH. ICH is a disease with few effective interventions, but optimising diagnosis allows optimal care to rapidly be implemented. In addition, clearly delineating those patients at risk for haematoma expansion through advanced imaging techniques allows for risk stratification and allocation of patients to trials assessing novel treatments for this condition.

ICH remains a major cause of death and disability worldwide[10]. The first hours following ICH area key period during which diagnosis can be established and treatments initiated. Delays to hospital presentation and similar delays to imaging diagnosis can hinder attempts to deliver best practice care to patients. Chapter three characterises the average time taken for patients to present following ICH, demonstrates that most patients present within a time-frame possibly suitable for 'ultra-early' surgical intervention and identifies factors that may be associated with delayed presentation. These findings presented may enhance and expedite the early management of patients with this devastating condition.

Furthermore, our work highlights the utility of CT perfusion imaging in patients with ICH, with the CTP spot sign being a valuable prognostic tool. Chapter two evaluated via systematic review the diagnostic accuracy of various delayed spot signs in predicting haematoma expansion. The diagnostic accuracy of these signs compared favourably with that of the traditional first pass CTA spot sign. With a pooled sensitivity of 0.81 (0.72-0.88), and a pooled specificity of 0.82 (0.76-0.88) delayed spot signs represent a potentially more accurate means of identifying and predicting which patients are likely to experience haematoma expansion.

This would thereby potentiate selection of patients for trials assessing the utility of interventions aimed at decreasing instances of haematoma expansion.

Chapter four further explored the utility of various imaging predictors of haematoma expansion by measuring the diagnostic accuracy of non contrast CT, CTA and CTP spot signs in the same cohort. Our study demonstrated that the CTP spot sign had the greatest diagnostic accuracy, followed by the CTA spot sign and then the non contrast CT imaging predictors. Though the impact characteristics of individual spot signs had on growth was assessed, none of these variables was shown to consistently be associated with increased risk of haematoma expansion. Nonetheless, our work makes a strong case for CTP to be the imaging modality to be used to identify patients at high risk of haematoma expansion.

In conclusion, the acute stage of ICH diagnosis and management is a critical juncture in the course of the disease. More accurate identification of patients at risk of haematoma expansion allows for improved prognostication in this patient subset, and helps identify patients who would be most likely to benefit aimed at interventions aimed to decrease instances of haematoma expansion. Recognition of factors associated with delays to presentation could facilitate approaches aimed at mitigating these factors. Together, action on these issues could lead to improved morbidity and mortality in patients suffering from this condition.

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