NONCONTRAST COMPUTED TOMOGRAPHY MARKERS FOR PREDICTING HEMATOMA EXPANSION IN SPONTANEOUS INTRACEREBRAL HEMORRHAGE

THESIS SUBMITTED TO

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

In partial fulfillment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(RADIOLOGY)

JULY, 2020 **DR. ABBU J**

AIIMS, JODHPUR

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CERTIFICATE

This is to certify that the thesis titled "**Noncontrast computed tomography markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage**" is the bonafide work of Dr. Abbu J carried out under our guidance and supervision in the Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur.

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DECLARATION

I hereby declare that the thesis titled "**Noncontrast computed tomography markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage**" embodies the original work carried out by the undersigned in the All India Institute of Medical Sciences, Jodhpur.

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ABBREVIATIONS

SICH: Spontaneous intracerebral hemorrhage.
NCCT: Non contrast computed tomography.
IVH: Intraventricular hemorrhage.
HE: Hematoma expansion.
RHE: Revised hematoma expansion.
HU: Hounsfield unit.
BHS: Blackhole sign.
BS: Blend sign.
IS: Island sign.
SS: Satellite sign.
mRS: Modified Rankin scale.
SAH: Subarachnoid hemorrhage.
SDH: Subdural hemorrhage.
CAA: Cerebral amyloid angiopathy.
CTA: CT angiography.
CTP: CT perfusion.
AHA: American heart association.
ASA: American stroke association.
NIHSS: National institute of health stroke scale.
GCS: Glasgow coma scale.

MRI: Magnetic resonance imaging.
ROI: Region of interest.
CKD: Chronic kidney disease.
IQR: Interquartile range.
CPMS: computerized patient management system.
PPV: Positive predictive value
NPV: Negative predictive value
mAS: milli ampere second
kv: Kilovolt
KFT: Kidney function test
PT: Prothrombin time
INR: International normalized ratio
Vb: Baseline hematoma volume
Vf: Follow up hematoma volume
ml: Millilitres.

INTRODUCTION

"Spontaneous intracerebral hemorrhage" (SICH) is the term for the extravasation of blood into the brain parenchyma in the absence of identifiable structural cause and in absence of significant head trauma. SICH is a type of stroke with a high fatality, accounting for about 10 to 20 percent of all kinds of stroke, with higher incidence rates in Asia. [1]

It is the second most common cause of stroke, with high mortality and morbidity. After SICH, only one-fifth of them become functionally independent, and the remaining four-fifths perish. [2]

Risk factors for SICH are hypertension, smoking, increased alcohol consumption, hypocholesterolemia, and substance use (for example cocaine, heroin, amphetamine, ephedrine, and phenylpropanolamine). Old age, male gender, Asians, chronic kidney disease, cerebral amyloid angiopathy (CAA), and cerebral microbleeds also increase the risk of SICH. [3]

Despite decades of research, we do not have curative treatment for SICH, but recent research has shown that hematoma expansion (HE) is a modifiable and independent predictor of clinical and neurological deterioration in patients with SICH. Prevention of HE has been accepted as the most promising therapeutic strategy in SICH management. [4] A small increase in the size of a hematoma is associated with death and functional dependence, making it a potential therapeutic target. [5, 6] That is why identifying patients with a high risk of developing hematoma expansion becomes a priority. [4]

Considering the poor outcome associated with patients with HE, when identified early patients may benefit from hemostatic therapy, blood pressure reduction, or emergency surgical evacuation. [7, 8, 9] Several scoring systems have been introduced, integrating demographic, clinical, and radiological features to stratify the risk of death in patients with ICH. [10]

Radiological features to predict HE began with the introduction of CT spot sign. Multiple studies have shown that CT spot sign in CT angiography predicted hematoma and poor functional outcome. [10, 11] Although CTA spot sign is a reliable marker for,

HE, only 11-25% of patients undergo CTA in high-income countries [12, 13] and very few would undergo it in low-income countries. Also, in patients with deranged renal function tests, it is unsuitable to get a CTA done. In this context as every suspected stroke patient undergoes a non-contrast CT scan (NCCT), markers from the NCCT which may predict HE are current hot topic for investigation and research. [14]

As per the current literature, the NCCT markers are divided based upon the shape and density. Shape markers include the irregular shape sign, island sign and satellite sign. Density markers include the heterogeneous density sign, swirl sign, hypodensity sign, blackhole sign, blend sign and fluid level sign. Majority of the currently available prediction models which include NCCT markers lack external validation, making it difficult to understand the diagnostic value of every new sign. [14] Hence we intend to carry out further research to say if these NCCT markers have incremental diagnostic value in predicting hematoma expansion and thereby predicting functional outcomes in a patient with SICH.

AIMS AND OBJECTIVES

AIM: To evaluate the noncontrast computed tomography markers for predicting the expansion of hematoma in cases of spontaneous intracerebral hemorrhage.

PRIMARY OBJECTIVE:

To analyse the association between noncontrast CT (NCCT) markers and hematoma expansion (HE) in patients presenting with spontaneous intracerebral hemorrhage (SICH).

SECONDARY OBJECTIVE:

To analyse the association between noncontrast CT (NCCT) markers and functional outcomes in patients presenting with spontaneous intracerebral hemorrhage (SICH).

REVIEW OF LITERATURE

Epidemiology: Stroke is the second leading cause of death and a major cause of long-term disability worldwide [15]. The two main forms of major strokes are ischemic and hemorrhagic. 85% of strokes are ischemic strokes, which are caused by occlusive intra-arterial thrombus leading to abrupt stoppage of blood to an arterial territory. Rest of the stroke are hemorrhagic, of which the intracerebral hemorrhage is major cause. [16].

Over the past few decades, the epidemiology of stroke has witnessed a few changing trends. While the incidence has reduced in developed countries, the middle and low-income countries have shown a hundred percent rise in incidence [17]. While the middle-aged and elderly population is the most inflicted, a rising trend has been studied in the younger population as well which poses serious implications on the individual's functional independence in the prime years of life, economic condition, and longevity [15,17].

Intracranial hemorrhage refers to any bleeding that occurs inside the intracranial vault, while intra-cerebral hemorrhage is defined as intraparenchymal bleeding. Depending on the anatomic location of the hematoma, further kinds of cranial bleeding include subarachnoid (SAH), epidural, intraventricular (IVH), and subdural hemorrhage (SDH). Spontaneous intracerebral hemorrhage (SICH) is hemorrhage without trauma or obvious structural abnormalities, like a cerebral aneurysm, tumor, or an arteriovenous malformation. [18]

The site of the SICH allows for further characterization of the condition. About two-thirds of SICH are deep intracerebral hemorrhages, which include those in the basal ganglia, brainstem, internal capsule, and cerebellum. The remaining one-third of SICH comprise of lobar intracerebral hemorrhages, which are defined as hemorrhages that occur in the cortical-subcortical regions.[18]

Risk factors: High blood pressure, smoking, increasing alcohol usage, hypocholesterolemia, and drug use (for example cocaine, heroin, amphetamine, ephedrine, and phenylpropanolamine). The risk of SICH is also increased by advanced age, male gender, Asian origin, chronic kidney illness, cerebral amyloid angiopathy (CAA), and cerebral microbleeds.[3]

Classification: According to the primary (80%–85%) or secondary (15%–20%) causes of ICH, several categories are used. Hypertensive microangiopathy and CAA constitute the majority and are included under the primary causes. Aneurysms, arteriovenous malformations, venous angiomas, cavernomas, dural arteriovenous fistulas, amyloid angiopathy, stimulant drugs, vascular malformations, coagulopathy (hereditary, acquired, induced by anticoagulants or antiplatelets), neoplasms, trauma, vasculitis, Moyamoya disease, or sinus venous thrombosis are included under secondary causes.[19]

ICH is currently divided into primary and secondary categories based solely on causes (Table 1). However, this classification ignores the fundamental variations in underlying vascular diseases.[19] So based on the underlying illnesses of ICH, Meretoja et al. [20] proposed the SMASH-U classification: Structural lesions (cavernomas and arteriovenous malformations), Medication (anticoagulation), Amyloid angiopathy, Systemic diseases (liver cirrhosis, thrombocytopenia, and various rare conditions), Hypertension, and Undetermined causes. This classification has been demonstrated to be practical and is connected to survival prognosis.[20]

Classification of causes of intracerebral hemorrhage	
Primary causes	Secondary causes
● Hypertension ● Cerebral amyloid angiopathy	● Ischemic stroke hemorrhagic conversion ● Stimulant drugs ● Aneurysms ● Arteriovenous malformation ● Venous angioma ● Cavernoma ● Dural arteriovenous fistula ● Coagulopathy ● Hereditary Acquired Iatrogenic (anticoagulants, antiplatelets) ● Neoplasms ● Trauma ● Vasculitis ● Moyamoya disease ● Sinus venous thrombosis

Table.1. Classification of ICH based on causes [19]

Pathophysiology of SICH:

These seemingly spontaneous hemorrhages are not primary, but rather the outcome of underlying (and sometimes co-occurring) vascular diseases. Arteriolosclerosis and cerebral amyloid angiopathy (CAA) are the two most common cerebral small vessel pathologies, accounting for the vast majority of primary ICH. Arteriolosclerosis (also known as lipohyalinosis) is characterized by concentric hyalinized vascular wall thickening that favors penetrating arterioles in the basal ganglia, thalamus, brainstem, and deep cerebellar nuclei. [21] Lipohyalinosis and degenerative alterations in penetrating arterioles are considered to cause Charcot-Bouchard aneurysms in small arteries serving deep cerebral regions in patients with persistent arterial hypertension.

CAA is characterized by the accumulation of the beta-amyloid peptide primarily in the walls of arterioles and capillaries in the leptomeninges, cerebral cortex, and cerebellar hemispheres (lobar territories).[21]

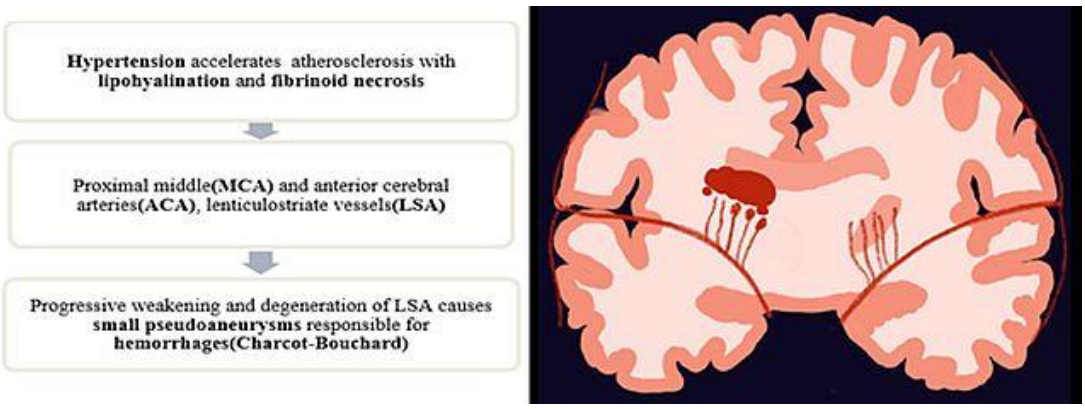

Figure 1: Demonstrating the pathophysiology of hypertensive bleed. [21]

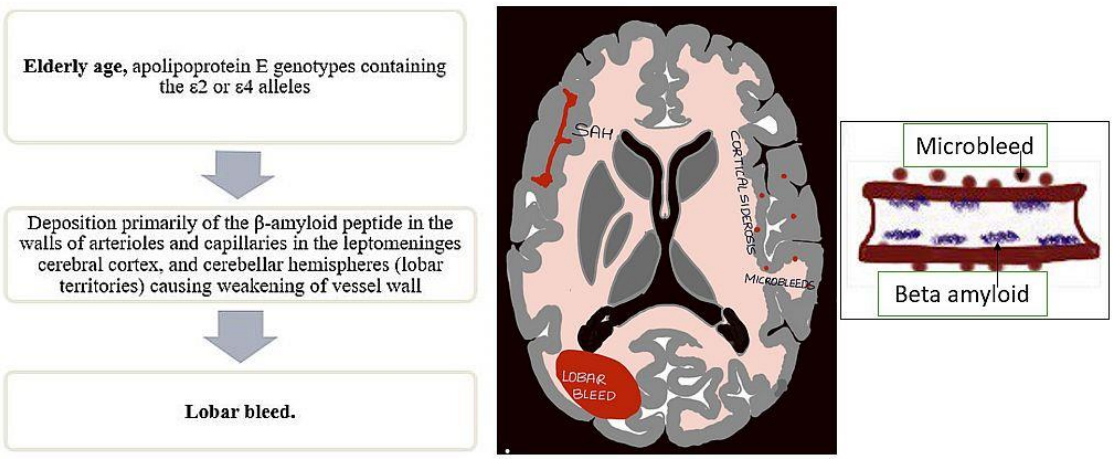

Figure 2. Demonstrating the pathophysiology of bleed in Cerebral amyloid angiopathy.[21]

Clinical presentation and diagnosis of SICH: The clinical manifestations of ICH and ischemic stroke appear similar, with a sudden onset of a localized neurologic impairment. Reduced level of consciousness, vomiting, headache, seizures, and elevated blood pressure all may indicate the presence of ICH. However, none of these symptoms/signs are specific enough to differentiate between hemorrhagic and ischemic stroke, hence the diagnosis of ICH must always rely on neuroimaging. [23]

1.**Clinical assessment**: All patients should have a general physical evaluation and have their vital signs (blood pressure, heart rate, and rate of breathing) recorded. The American Heart Association and American Stroke Association (AHA/ASA) propose using the National Institutes of Health Stroke Scale (NIHSS) score for baseline evaluation of these patients [24] (Table 2). The Glasgow Coma scale (GCS) is the most frequent assessment scale used to define the extent of impaired consciousness in patient with ischemic and hemorrhagic stroke [22] and is classified according to severity as mild (13-15), moderate (9-12) and severe (<8).

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

Table 2: NIHSS stroke severity scale [25]

2.**Blood investigations**: Complete blood count, electrolytes, creatinine, glucose, and coagulation tests should be done in SICH patients.[23] Complete blood count and coagulation tests (prothrombin time/partial thromboplastin time/INR) can assist in determining the type of hemorrhage, such as spontaneous ICH due to extreme thrombocytopenia (e.g., platelets < 10,000, though platelet counts below higher thresholds may also contribute to ICH), anticoagulant-related hemorrhage, or coagulopathy secondary to malignancy or liver failure. Hemorrhages caused by anticoagulants are associated with increased hematoma volume and expansion, as well as increased morbidity and mortality. Anemia at admission is linked to hematoma expansion and poor outcomes, thrombocytopenia is associated with increased mortality in patients receiving antiplatelets. Renal failure on admission is also linked to poor functional outcomes, in-hospital mortality, and 12-month mortality. Admission hyperglycemia is linked to poor short and long-term outcomes after ICH. [21]

3.**Imaging studies:**

A) Non-contrast computed tomography (NCCT): Non-contrast computerized tomography (NCCT) is a quick procedure with high sensitivity for detecting acute ICH and is regarded the gold standard for detecting ICH in the emergency department. [19,24] Apart from diagnosing ICH, NCCT can offer information such as ICH site,

intraventricular extension, hydrocephalus, the presence and severity of edema, and midline shift or compression of the brainstem caused by the hematoma's mass effect. [23] Volume of the hematoma can also be assessed and is a powerful predictor of ICH prognosis. [26]

B) CT angiography (CTA): A CT angiography is invariably done for imaging of patient with suspected secondary causes of ICH [27]. Lobar ICH, considerable IVH, young age, and the absence of established cerebrovascular risk factors may raise the possibility of ICH related to vascular malformation or other cerebral pathology [24,27]. The diagnosis of these lesions as soon as possible is critical and has a substantial impact on patient care.[23] The 1999/2007 AHA/ASA guidelines recommended angiography (DSA or CTA) for all surgical candidates without a clear cause of hemorrhage, particularly young and normotensive patients who are clinically stable.[27]

While CTA is a great non-invasive screening tool, digital subtraction angiography remains the gold standard study for cerebral vascular malformation diagnosis.[26]

C) Magnetic resonance imaging (MRI): The sensitivity of magnetic resonance imaging (MRI) for the diagnosis of ICH is comparable to that of NCCT. MRI can help detect underlying secondary causes of ICH, such as neoplastic tumors or hemorrhagic transformation of ischemic stroke [19]. Finally, in individuals with impaired renal function, contrast allergies, or other contraindications to CTA, brain vascular imaging without contrast can be accomplished via magnetic resonance angiography (MRA). MRI is infrequently used in the emergency department workup of ICH due to the cost, duration of the exam, and poor tolerability for most patients.[24]

Hematoma expansion: What has been discovered till date?

SICH was formerly thought to be a monophasic disease, but new research reveals that it is a dynamic disease with early substantial growth or expansion of hematoma in up to one-third of patients.[28] Continued bleeding in the hematoma causes volume expansion that is hematoma expansion (HE), which can lead to severe neurological impairment and possibly death.[29]

According to recent literature, HE (Hematoma expansion) is a controllable and an independent predictor of clinical and neurological deterioration in SICH patients.[4]

The presence of CTA spot sign, early imaging after symptom onset, substantial baseline hematoma volume and anticoagulant medication, are consistently the most powerful predictors of considerable hematoma expansion. [30] Perihematomal edema, intraventricular extension of the ICH, hydrocephalus, seizures, fever, and infections are all associated with clinical deterioration. [31]

Definition: HE is defined by visibly perceptible hematoma variations between baseline and follow-up CT. The assessment of hematoma volume growth varies across HE-related studies.[4]

There is no uniform terminology for defining HE, Fujii et al. [29], one of the first researchers on HE, defined it as absolute hematoma volume growth of more than 20 ml or relative hematoma volume growth of more than 50%. [4,29] Later, Brott et al. used relative hematoma volume growth of more than 33% which can be discovered by CT to define HE [4,32] To define it, some recently published large clinical studies used relative hematoma growth of more than 33% [4,33], or merged hematoma expansion of 6 mL absolute rise and 33% relative increase [4,12,34].

Recently the term "revised hematoma expansion" (RHE) was created by combining the traditional definition of hematoma expansion with Intraventricular hematoma growth (IVH). [35] IVH growth was defined either as a new IVH on follow-up CT alone without presence of IVH on the initial CT scan (delayed IVH) or an absolute increase of IVH volume >1 mL from the initial CT scan to the follow-up CT scan.[36]

Prevalence: The prevalence rate of HE in under 6 hours of the onset of ICH symptoms ranges from 13 to 38 percent. [4,37] Remarkably, the incidence of HE is highest during the hyperacute stage (within 6 hours of symptom onset), and HE typically occurs in the internal capsule, thalamus, and brainstem. As a result, hematoma surveillance is essential, particularly during the hyperacute phase of ICH. [4,37]

Risk factors: ICH patients with high risk factors for developing HE are predisposed to clinical deterioration, necessitating closer neurological monitoring, whereas the exclusion of the predictors may identify ICH patients with low risk of developing HE. Thus, HE predictors play an important role in identifying high risk ICH patients and facilitating individualized treatment.[4] A number of risk factors/predictors of HE have now been described on basis of clinical, imaging, and lab characteristics.

Clinical predictors:

Blood pressure: In ICH patients, systolic blood pressure (SBP) is positively linked to initial hematoma volume [38], and the probability of HE is higher among patients with post-admission SBP greater than 160.[4]

Anticoagulant therapy/drugs: Antiplatelet or anticoagulant drugs increases the risk of HE. More than a quarter of ICH patients in high-income countries have previously received antiplatelet therapy [4,39].

Others: A higher starting point NIHSS or GCS, men, and older people may be at a higher risk of HE. Increased body temperature, baseline weight, and a history of ischemic stroke or alcohol abuse also increase the risk [4].

Laboratory predictors:

Coagulation studies: In general, coagulation function is altered among those with coagulation impairment due to the blood system ailments and antiplatelet or anticoagulant drug use, rather than hypertension ICH patients; therefore, special attention should be paid to the former. Elevated D-dimer (D-D) levels, decreased fibrinogen, and international normalized ratio (INR) >1.5 were found to be predictors of HE in those patients [4,40]. Furthermore, coagulation factor deficiency caused by liver dysfunction raises the risk of developing HE [4, 41].

Blood glucose: More than half of all stroke patients [42] have admission hyperglycemia because of defective metabolic activities in response to acute ICH. However, regardless of diabetes history, admission hyperglycemia is associated with poor functional recovery and a high mortality rate.[4]

Others: In observational studies, low serum cholesterol, calcium, hemoglobin, or magnesium levels, as well as high serum creatinine levels, have been linked to HE. [4,8]

Imaging predictors:

Some imaging features associated with HE have their origin in pathophysiological processes surrounding the hematoma, such as the breakdown of the blood – brain after ICH, which reflects blood infiltration into peri-hematoma tissues and supplemental damage caused by blood components such as albumin.[4]

CTA predictors: Wada et al. first discussed the spot sign [4,11], as several foci of contrast enhancement in the hematoma that is considered a risk factor for mortality and clinical neurological worsening, based on increased contrast agent permeation. [4,43]

On CTA source images, this sign was defined by Wada et al. "as one or more 1 to 2-mm foci of enhancement within the hematoma. Extravasation associated with this was defined as an increase in contrast density on the follow up CTA scan".[11] Latest definition was given by Demchuk et al [34] in 2012 and was defined as, "one or more foci of contrast enhancement within an acute primary parenchymal hematoma on the source images of CTA".[34]

Spot sign is an independent indicator of HE in various clinical research facilities with 51-62 percent sensitivity and 85-88 percent specificity [4,43] The spot sign has still not been observed in secondary ICH; these findings indicate that spontaneous ICH has some specificity. [27]

Leakage sign was introduced in a study by Orito K, et al. [44] and was defined as a 10% increase in HU in a 1-cm-diameter ROI between the CTA phase and the delayed phase. It was found that the leakage sign outperformed the spot sign in terms of predicting subsequent HE, with higher sensitivity (93.3 %) and specificity (88.9 %). [44]

Fan fu et. al. [45] using gemstone spectral imaging, investigated the relationship between the iodine concentration in the spot sign and HE and found that the iodine content of hematoma was a reliable predictor of HE and was superior to Spot sign.

CT perfusion (CTP) predictors:

Dynamic spot sign: One study recently proposed a dynamic spot sign using CTP, a superior technique that can provide information on the entire blood circulation. When compared to the CTA spot sign, the dynamic spot sign had a better predictive value of HE within 6 hours of symptom onset.[46]

It is defined as "one or more 1- to 2-mm foci of enhancement within the hematoma on CTP source images and is assessed using the CTA spot sign".[46]

NCCT markers: As every suspected stroke patient undergoes a non-contrast CT scan (NCCT), several markers from the NCCT may be used to predict HE because every patient presenting with stroke may not undergo a CTA. [14]

Various NCCT markers may be divided based upon the shape and density (figure 4). Shape markers include the irregular shape sign, island sign and satellite sign. Density markers include the heterogeneous density sign, swirl sign, hypodensity sign, blackhole sign, blend sign and fluid level sign. Even though many NCCT features of acute ICH have been linked to HE and poor outcome, there is a need for further research to determine the diagnostic performance of these markers. [14]

Classification of density and shape markers.	
Density markers	**Shape markers**
Heterogenous density Swirl sign Hypodensity sign Black hole sign Blend sign Fluid level sign	Irregular shape sign Island sign Satellite sign

Table 3. Classification of density and shape markers [14].

Pathophysiology of hematoma expansion:

The avalanche model is the most widely accepted model for HE: The initial vessel rupture is responsible for peripheral vessels shearing, which rupture secondarily and maintain an active source of bleeding. The CT appearance of the hemorrhage in this model is caused by a matrix of acute and subacute blood. Because fresh blood coexists with a more subacute clot, hemorrhage heterogeneity is increased. Lower attenuating regions are more immature, whereas hyperattenuating regions are more stable bleed areas, potentially explaining the higher prevalence of density heterogeneity in cases with subsequent HE. This sequential model is also supported by the observation that growing hemorrhages frequently have irregular shapes and can expand in various axial directions over time. Irregular hemorrhages may thus be in an intermediate stage of development, with persistent bleeding or increased intra-hemorrhage pressure favoring hematoma bulging into surrounding brain structures. [14]

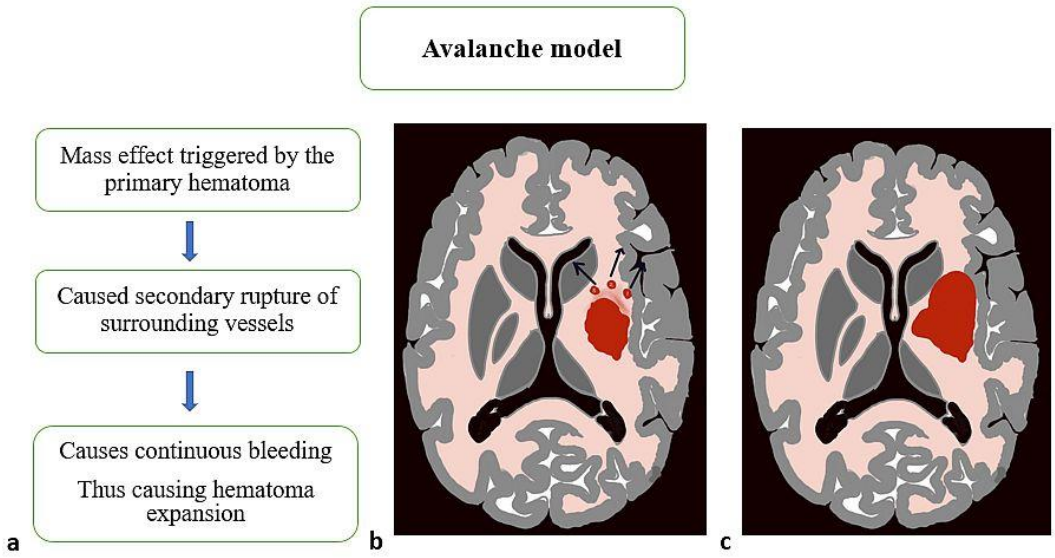

Figure 3: Depicting the avalanche model [14] for hematoma expansion **a)** Flow chart explaining the sequence of hematoma expansion. Diagrammatic representation of **b)** Initial hemorrhage which is surrounded by secondary bleeding sites and edema **c)** Final hemorrhage showing increase in size of the hematoma.

Hematoma volume: The volume of the hemorrhage at presentation is the most basic and well-established predictor of subsequent hemorrhage expansion. Although larger hemorrhages have been shown to be more likely to expand, the inverse is true, with

smaller hemorrhages consistently demonstrating a lower risk of expansion and a notably lower ICH volume increase.[47]

Hematoma volume is thought to be the most accurate predictor of 30-day mortality and functional outcome in ICH patients. Patients with hematoma volumes less than 30 ml have a 30-day mortality rate of less than 20%, whereas volumes greater than 60 ml have a mortality rate of more than 90%. Patients with hematomas larger than 30 mL are more likely to be functionally dependent after 30 days.[26]

Several studies have shown that a baseline hematoma volume of 30 ml or more is a predictor of hematoma expansion and a poor outcome, whereas a hematoma volume of 10 ml or less is associated with a lower likelihood of hematoma expansion and a favorable functional outcome. [26]

Density markers:

Swirl sign: It is defined as "the rounded, streaky, or irregular hypo or isoattenuation region compared to brain parenchyma. It may not be necessary to be encapsulated in the ICH".[14]

Kim et al [48] published the first direct evidence of a link between hemorrhage heterogeneity and expansion in 2008. The authors discovered a univariable link between both the swirl sign and poor prognosis, but no association with hemorrhage growth.[47]

Heterogenous density sign: It is defined as "presence of at least three foci of hypoattenuation compared to the surrounding hematoma, as determined by the axial NCCT density slice with the greatest ICH area. (The Barras density scale is III, IV, or V.)" [14]

Barras et al [49] pioneered the use of a 1 to 5 heterogeneity scale, with 1 representing homogeneous hemorrhages and 5 representing heterogeneous hemorrhages. In this study, heterogeneous hemorrhages at base point (defined as a score of 3) were found to have an association with increased risk of expansion.[47]

Blackhole sign: It is defined as a "hypoattenuating area with a density difference of more than 28HU from the surrounding hematoma. There should be no contact with the surface outside of the hematoma".[14]

Li et al [50] expanded on this in a recent study of the prediction accuracy of the black hole sign. The authors discovered that the existence of a black hole was separately linked with an increased incidence of hemorrhage expansion in this study.[47]

Hypodensity sign: It is defined as "any hypodense region encapsulated within the hemorrhage, regardless of shape, size, or density. It is not necessary to measure the density".[14]

The ability of the above-mentioned signs to capture the presence of hypodense structures within the hemorrhage is described, but it is unclear to what extent the swirl sign, black hole sign, and density heterogeneity scale capture the same phenomenon. There is most likely a significant amount of overlap, particularly because the black hole is a subcategory of the swirl sign and because a significant amount of heterogeneity should capture the presence of all swirls, thus black holes.[47]

A retrospective study conducted by Gregoire Boulouis et al [47] discovered that the specific pattern in hypodensities had no effect on the association with hemorrhage expansion, but these findings were not externally validated.

Blend sign: It is defined as a "relatively hypoattenuating area of the hematoma adjacent to a hyperattenuating area, with a very well margin and a density difference of >18HU between the two areas".[14]

Li et al. [51] described additional unusual patterns of hemorrhage density heterogeneity, including the blend sign. This sign demonstrated a good predictability in hematoma expansion.

Fluid level sign: It is defined as "Regardless of density appearance, the presence of 1 distinct hypoattenuating area (hypodense to the brain) above and 1 distinct hyperattenuating area (hyperdense to the brain) below a discrete straight line of separation".[14]

Similarly, the presence of intra hematoma fluid levels has recently been linked to expansion and a poor clinical outcome. This sign has been linked to anticoagulation treatments and the lobar location of the bleed.[47]

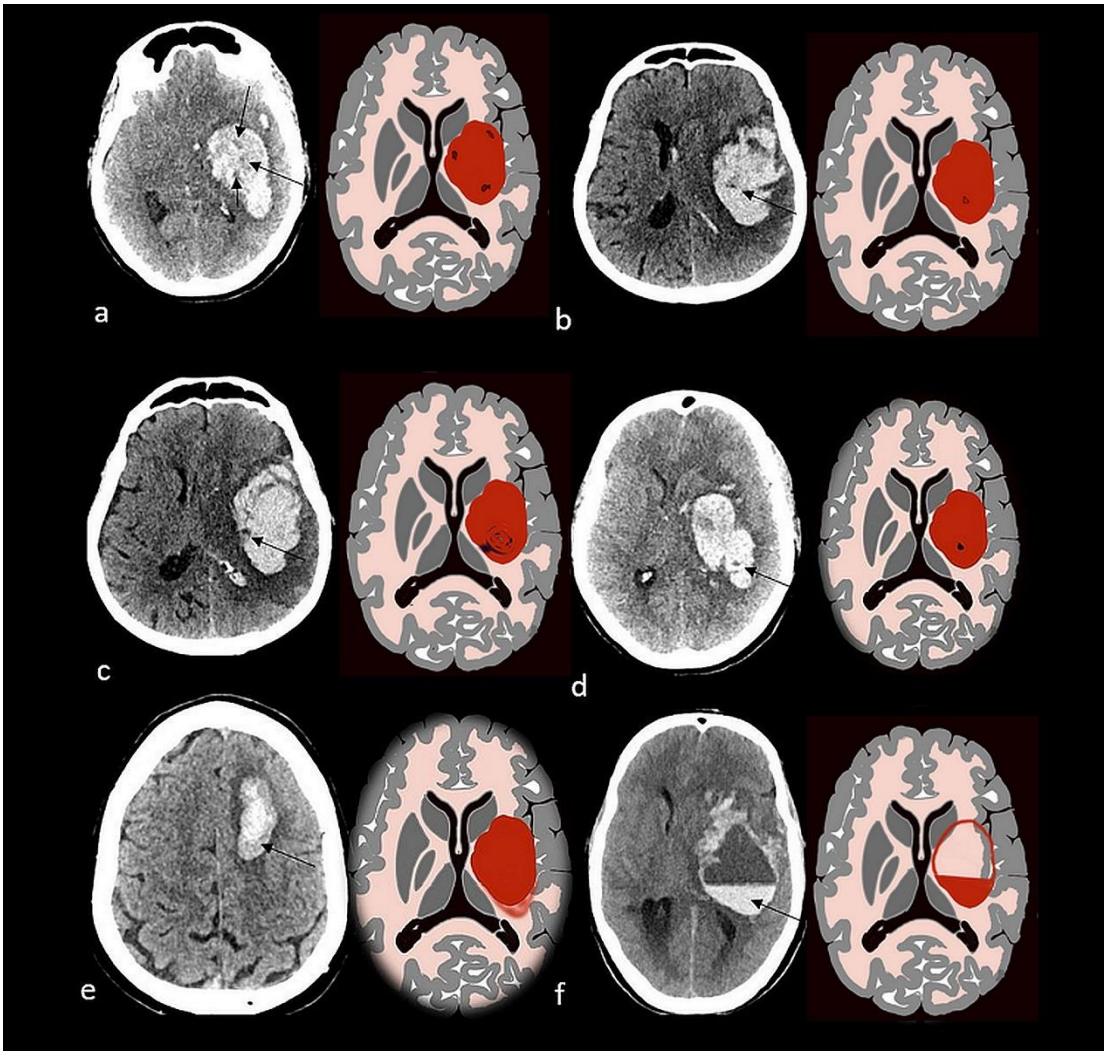

Figure 4: Depicting various density markers on NCCT image(arrows) and pictorial diagram **a)** Heterogenous density sign **b)** Hypodensity sign **c)** Swirl sign **d)** Blackhole sign **e)** Blend sign **f)** Fluid level sign.

Shape markers:

Irregular shape sign: It is defined as "2 or more focal hematoma margin irregularities, joined or separated from the hematoma edge, assessed on the axial NCCT slice containing the most ICH (Barras shape scale = III, IV, or V)".[14]

Fujii et al [29] conducted the first study of the relationship between hemorrhage shape and hemorrhage expansion in 1994. The authors divided hemorrhages into three categories in this study: round, with round and smooth margins; irregular, with irregular, multinodular margins; and divided, with a fluid level in the cavity finally divided into

regular and irregular.[47] Overall, margin irregularity seems to be associated with hemorrhage expansion in various settings investigating hemorrhage expansion [47].

Island sign: It is defined as "at least three scattered small hematomas that are all separate from the main ICH, or at least four small hematomas that may or may not be connected to the ICH".[14]

The island sign is a reliable CT imaging marker that predicts hematoma expansion and poor outcome in ICH patients. The noncontrast CT island sign could be used to guide therapeutic intervention.[51]

Satellite sign: It is defined as a "presence of a small hematoma (diameter 10mm) separated from the main hemorrhage in at least one slice and distinguished from the main hematoma by a distance of 1-20mm".[14]

In spontaneous ICH, the satellite sign is an independent prognostic factor of hematoma expansion. Although spot sign has a higher prediction performance, satellite sign still is a good predictor of hematoma expansion when CTA is not available.[52]

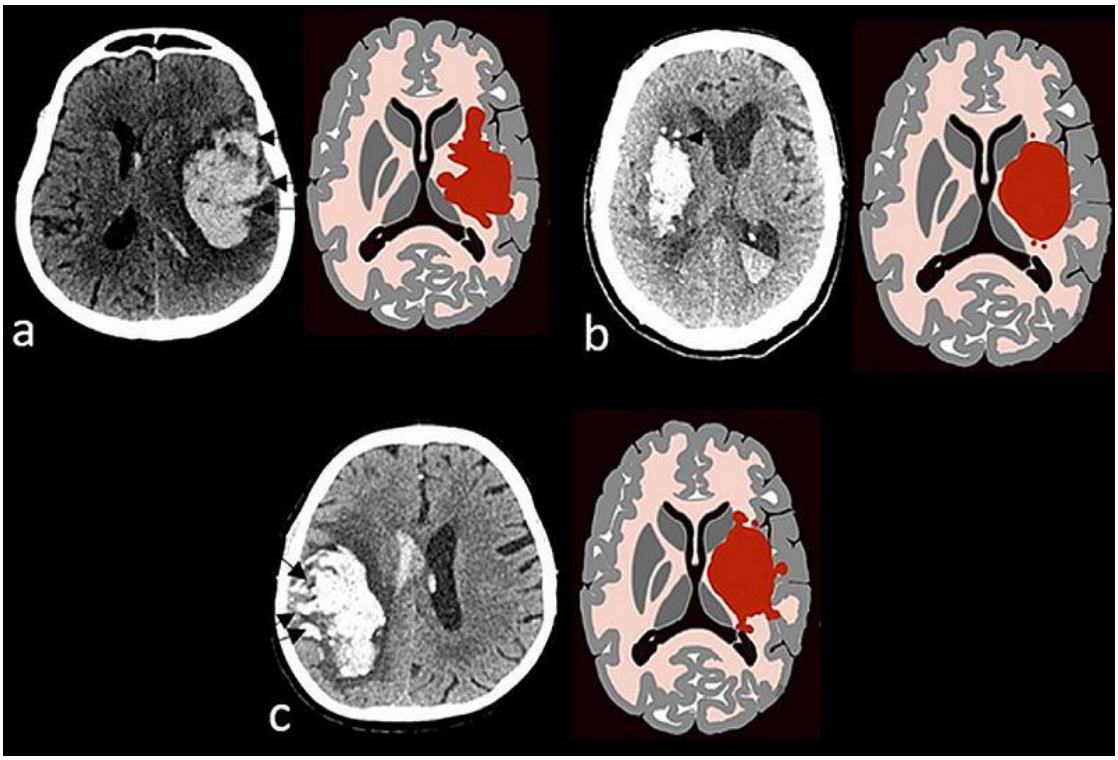

Figure 5: Depicting Shape markers on NCCT image and pictorial diagram a) Irregular shape sign b) Satellite sign c) Island sign.

Overlapping of signs:

Since there are number of defined NCCT signs, for uniformity and better sensitivity there is a need to define a single marker or combination of markers for better prediction of hematoma expansion. That is why it becomes important to study the overlapping of definitions of these markers.

ICH density features that overlap:

- All swirl signs that are not connected to the brain surrounding the hematoma also are termed as hypodensities. [14]
- All black hole indicators are also swirl indicators and hypodensities. The inverse may not be true, because hypodensity-positive regions encapsulated in the hemorrhage do not qualify as black hole signs if the density difference between the hypodense region and the surrounding hemorrhage does not reach the 28HU cut-off. Similarly, hypodense regions that connect to the outer surface are swirl positive but not black hole signs. [14]
- Fluid levels encapsulated in the hemorrhage with no connection to hematoma margins are also considered hypodensities. [14]
- Fluid levels are considered blend sign-positive if the density difference between the two regions exceeds the 18HU threshold proposed for detecting blend signs. [14]
- Hemorrhages with one or two hypodense regions have homogeneous density (Barras grade = I or II), whereas patients with three or more hypodensities (regardless of size or degree of hypoattenuation) have heterogeneous density (Barras grade = III). [14]
- Hemorrhages with only a blend sign should be classified as homogeneous density (Barras grade = I-II with two attenuation regions). The same is true for fluid level. [14]
- **ICH shape features that overlap:**
- Hemorrhages with only one satellite sign are classified as regular shape (Barras grade = II), whereas hematomas with at least two satellites are classified as irregularly shaped (Barras grade = III). [14]

- According to Barras, island signs are always irregular in shape (Barras grade III for the presence of at least three regions of irregularity in shape). [14]
- Hemorrhages with at least three satellite signs are also recognized as island sign-positive. [14]
- ICHs with an island sign do not always have satellite signs. Satellite sign diagnostic criteria require a clear separation from the main hemorrhage, whereas island sign diagnostic criteria allow for multiple small hematomas that are connected and originate from the main hemorrhage. [14]

Expansion prone hematoma:

The presence of one or more of the following imaging markers is defined as an expansion-prone hematoma: blend sign, black hole sign, or island sign. Since the sensitivity of a single marker was relatively low, Li Q et al [53] defined expansion prone hematoma and concluded that it was a better predictor than any single NCCT marker for predicting hematoma expansion and poor outcome.[53] Further Yang et al (2021) [35] concluded that expansion-prone hematoma has a higher predictive accuracy for RHE and poor outcome than any single NCCT marker.

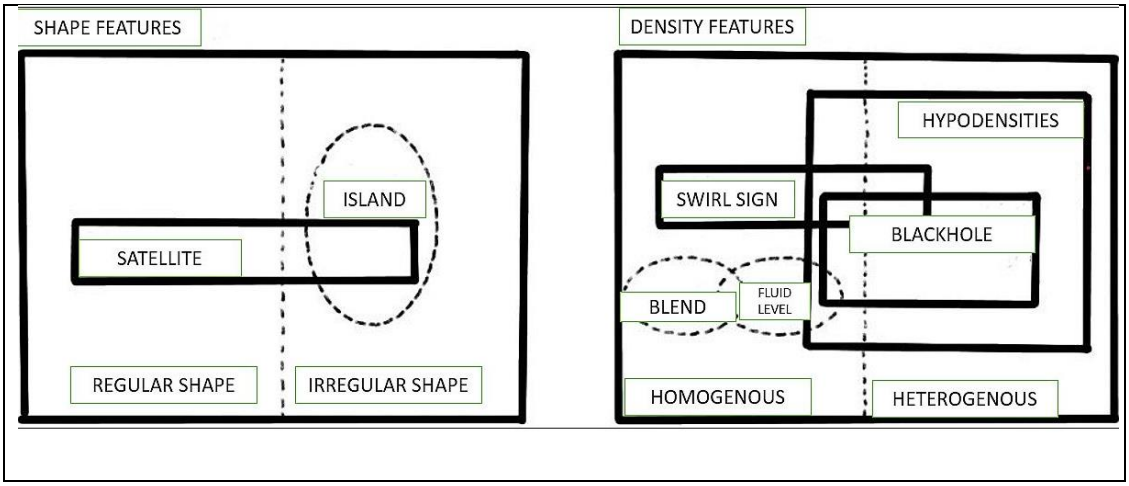

Figure 6: Venn diagram showing potential overlap between various shape and density markers **(Morotti et al 2019) [14]**

Functional outcomes in patients with hematoma expansion: Poor functional outcome was defined as MRS 4-6 at 90 days [54]. All shape-related NCCT markers and all density-related NCCT markers were linked to a poor outcome. [54] In a meta-analysis study by Andrea Morotti et al [54] they found that Black hole sign and swirl sign were associated with poor functional outcome among density related markers, with high statistical heterogeneity for black hole sign and low statistical heterogeneity for swirl sign. Density heterogeneity, hypodensity, and the blend sign were also linked to a poor clinical outcome. Statistical heterogeneity was high for all three density markers on NCCT. The swirl sign was the only NCCT marker for which more than one study's mortality data was available (three studies were included), and it was associated with a more than four-fold risk of death, with high statistical heterogeneity. Among shape-related markers, both island sign and shape irregularity were associated with poor outcomes, with island sign exhibiting no heterogeneity and shape irregularity exhibiting significant statistical heterogeneity.[54]

PUBLISHED LITERATURE

1. Peter B. Sporns, MD et al (2018) [55] in a retrospective study concluded that of 201 patients with spontaneous ICH, 28 (13.9 %) had black hole sign, 38 (18.9 %) had blend sign, 120 (59.7 %) had hypodensities, 97 (48.3 %) had heterogeneous densities, 53 (26.4 %) had island sign, and 45 (22.4 %) had satellite sign. Higher hematoma volume (P=0.001), intraventricular hemorrhage (P=0.002), and the existence of black hole sign/blend sign/hypodensities/island sign/Satellite sign (SS) /heterogeneous density (all P=0.001) on admission CT were all associated with poor outcome in univariable logistic regression. The presence of hypodensities (odds ratio, 2.47; P=0.018), intraventricular hemorrhage (odds ratio, 2.20; P=0.025), and SS (odds ratio, 12.22; P=0.001) were all found to be independent predictors of poor outcome in multivariable analysis.

2. Andrea Morotti, MD et al (2020) [54] in a meta-analysis study including 25 studies with a total sample size of 10650 found black hole sign, swirl sign, heterogeneous density and blend signs, hypodensities, irregular shapes, and island signs and concluded that both the density and shape markers were associated with an increased risk of HE and a poor outcome, respectively.

3. Yang et al (2021) [35] in a study including 314 patients found that 61 (19.4%) had IVH growth, while 93 (23.9%) had Revised hematoma expansion and concluded that the NCCT markers are linked to IVH growth and RHE on their own. Besides this, the expansion-prone hematoma outperforms any single NCCT marker in terms of predicting RHE and poor outcome. These findings could help with the risk stratification of NCCT signs for predicting active bleeding.

4. **D. Ng et al (2018)** [56] in a retrospective study including 212 patients with excellent interobserver agreement, found that the swirl sign was identified in 91 patients. The swirl sign was related to larger initial hematoma and hematoma expansion. If similar initial hematoma volume, onset-to-first scan, and time between CT scans were assumed, the median absolute hematoma growth was 5.77 mL and relative growth was 35.6 percent higher in patients with the swirl sign compared to those without. They concluded that The NCCT swirl sign was consistently identified and is linked to hematoma expansion.

5. **Yilin Chen et al (2020)** [57] in meta-analysis of 6 studies including 1876 patients found out that the pooled sensitivity, specificity, and positive and negative likelihood ratios of black hole sign were 0.30, 0.93, 4.00, and 0.75, respectively. The AUC (area under the curve) was 0.83. The studies were highly heterogeneous (I2=89.00%, 95 percent CI 78.00-100.00). They concluded that in patients with intracerebral hemorrhage, the black hole sign is a useful imaging marker with high specificity for predicting hematoma expansion.

6. **Yu et al (2017)** [58] in a meta-analysis of 5 studies including 2248 patients found the pooled sensitivity, specificity, positive and negative likelihood ratios of blend sign were 0.28, 0.92, 3.4, and 0.78, respectively for hematoma expansion. The AUC (area under the curve) was 0.85. They concluded that blend sign is a useful predictor of hematoma expansion in ICH with a high specificity.

7. **Qi Li et al (2017)** [51] in a study including 252 patients found that on baseline NCCT scans, 41 (16.3 %) patients had the island sign. Furthermore, the island sign was seen in 38 of 85 patients (44.7 %) who had hematoma growth. The time to baseline CT scan, initial hematoma volume, and the presence of the island sign on baseline CT scan all independently predicted early hematoma growth, according to multivariate logistic

regression analysis. The island sign had a sensitivity of 44.7 %, a specificity of 98.2 percent, a positive predictive value of 92.7 %, and a negative predictive value of 77.7 % for predicting hematoma expansion. They concluded that the island sign is a reliable CT imaging marker that predicts hematoma expansion and poor outcome in ICH patients. The noncontrast CT island sign could be used to guide therapeutic intervention.

8. **Shimoda Y et al (2017)** [59] in a study of 153 patients found that Satellite signs were found in 58 (37.91%) of the patients, while spot signs were found in 38 (24.84%) of the patients. There were 22 (59.46%) satellite signs and 23 (62.16%) spot signs among 37 patients with hematoma expansion. The satellite sign's sensitivity and specificity for predicting hematoma expansion were 59.46 percent and 68.97 percent, respectively. Spot sign sensitivity and specificity were 62.16 percent and 87.07 percent, respectively. The satellite sign's area under the curve (AUC) was 0.642, while the spot sign's AUC was 0.746. They concluded that in spontaneous ICH, satellite sign is an independent prognostic factor of hematoma expansion. Although spot sign has a higher predictive ability, satellite sign is still a good predictor of hematoma expansion when CTA is not available.

MATERIALS AND METHODS

Institutional ethics committee approval was obtained, certificate reference number: AIIMS/IEC/2021/3328. This was a prospective observational study conducted in the Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur, and included patients who presented between JAN 2021 to JULY 2022.

Informed written consent was obtained from every patient/guardian after an explanation of all aspects of the study as per the consent form (Annexures).

Inclusion criteria:

1. All patients with intracerebral hemorrhage of nontraumatic origin.

2. ICH diagnosed on baseline CT within 12 h of symptom onset.

3. Follow-up NCCT performed within 48 h after the initial CT.

Exclusion criteria:

1. Secondary causes of ICH such as vascular malformation and tumor, traumatic and aneurysmal bleeding.

2. Hemorrhagic transformation of ischemic stroke.

3. Patients undergoing surgical intervention before the first follow up NCCT scan.

Methods:

1) The study recruited patients presenting to the emergency department with non-traumatic intracerebral bleeds of unknown origin.

2) Patient's clinical history (age, gender, GCS, blood pressure, seizures at presentation, comorbid illnesses like diabetes, hypertension, cardiovascular diseases) and symptoms at presentation were recorded. History of trauma was also taken.

3) Laboratory parameters (HbA1c, Complete hemogram, PT/INR, Lipid profile, KFT) were recorded from the computerized patient management system (CPMS) patient panel.

Imaging protocol:

A baseline NCCT scan was performed within 12 hours of onset of symptoms followed by another scan done within 48 hours.

Siemens Somatom Definition Flash Dual Energy 128*2 Slice Multi Detector CT scanner and Siemens Somatom Drive Dual Energy 128*2 Slice Multi Detector CT Scanner with NCCT settings of 120 kV and 300 mAs were used for scanning and the DICOM images were digitally stored. Images were analyzed using 1mm slice thickness.

Image interpretation and analysis:

The location of the hematoma was assessed and documented. Hematoma expansion was defined as relative hematoma growth >33% over the initial volume identified on CT or an absolute increase in hematoma volume 6 ml over the baseline SICH volume. [4,12,34]

IVH growth was also included under hematoma expansion according to the definition of revised hematoma expansion and was defined either as a new IVH on follow-up CT alone without presence of IVH on the initial CT scan (delayed IVH) or an absolute increase of IVH volume >1 mL from the initial CT scan to the follow-up CT scan.[36]

Volume estimation:

Hematoma volume was measured by semi-automated region growing algorithm implemented in the FDA approved Siemens synovia, since the "ABC/2 formula for the volume estimation of ICH underestimates by 15% compared to the planimetric methods". [60]

Baseline hematoma volume (Vb) and the follow up hematoma volume (Vf) were measured. Absolute (Vf-Vb in ml) and relative values (Vf-Vb/Vb*100 in percentage) were calculated.[14] IVH volumes were separately calculated.

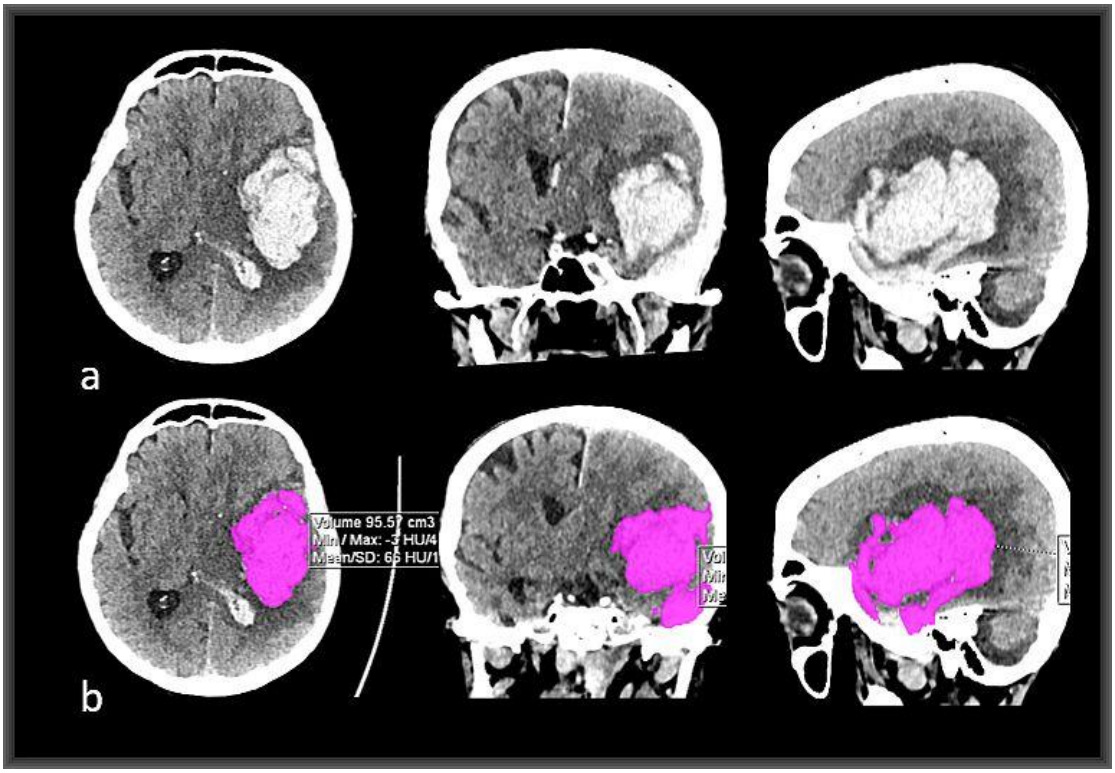

Figure 7: NCCT, MPR image **a)** Showing left gangliocapsular bleed **b)** showing hematoma volume calculation using region growing algorithm in siemens synovia.

NCCT markers:

These were analyzed as per the definitions given by Morotti et al by consensus of two observers.[14] (Table 4 and Table 5).

DENSITY MARKERS:

Blackhole sign (BHS)	Hypoattenuating area with a difference of density >28HU compared with the surrounding hematoma. No connection with surface outside the hematoma.
Blend sign (BS)	A relatively hypoattenuating area adjacent to a hyperattenuating area of the hematoma, with a well-defined margin and a difference of density >18HU between the 2 areas.
Heterogenous density sign	Presence of at least three foci of hypoattenuation compared to the surrounding hematoma, as determined by the axial NCCT density slice with the greatest ICH area (The Barras density scale is III, IV, or V).
Hypodensity sign	Any hypodense region encapsulated within the hemorrhage, regardless of shape, size, or density. It is not necessary to measure the density.
Swirl sign	The rounded, streaky, or irregular hypo or isoattenuation region compared to brain parenchyma. It may not be necessary to be encapsulated in the ICH.
Fluid level sign	Regardless of density appearance, the presence of 1 distinct hypoattenuating area (hypodense to the brain) above and 1 distinct hyperattenuating area (hyperdense to the brain) below a discrete straight line of separation.

Table 4: Definitions of density markers [14].

SHAPE MARKERS:

Island sign	At least three scattered small hematomas that are all separate from the main ICH, or at least four small hematomas that may or may not be connected to the ICH.
Satellite sign	A small hematoma (at least 10mm) separated from the main hemorrhage in at least one slice and separated from the main hematoma by 1-20mm.
Irregular shape sign	2 or more focal hematoma margin irregularities, joined or separated from the hematoma edge, assessed on the axial NCCT slice containing the most ICH (Barras shape scale = III, IV, or V).

Table 5: Definitions of shape markers [14].

Functional outcome:

It was assessed using the **Modified Rankin scale (mRS)** at 90 days. This information was collected telephonically by the contact numbers available on CPMS panel.

mRS is a grading system to evaluate the level of functional independence in post-stroke patients [53]. It is a 6-point scale, ranging from 0 to 6, where 0 stands for no symptoms and 6 stands for deceased status. A score of 0-3 was considered as a favorable outcome, while a score of 4-6 was considered as poor outcome.[54]

Modified Rankin scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help but is able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

Table 6: Modified Rankin Scale

ETHICAL JUSTIFICATION:

Since mandatory NCCT was done in all patients of SICH, there was no additional radiation exposure or financial burden incurred to the patient. No contrast studies were done for the study.

STATISTICAL ANALYSIS:

Data was analyzed using the Statistical Package for Social Sciences Windows, version 25.0 (Armonk, NY: IBM Corp.) Continuous variables were represented as means ± standard deviations and categorical variables as frequency (percentage).For association of continuous variables(Age, GCS, NIHSS, time of onset of symptoms to baseline CT, SBP, DBP, Hb%, Triglycerides, Lipid profile PT, INR and KFT, baseline hematoma volume, Baseline IVH volume) with revised hematoma expansion ,Student t-tests were used. For association of categorical variables (Hematoma location, density markers and shape markers) with revised hematoma expansion and poor outcome, Chi square tests or Fisher exact tests were used. In all cases p value <0.05 was considered to be statistically significant.

OBSERVATIONS AND RESULTS

During the study period a total of 358 patients presented to the emergency of AIIMS, Jodhpur with non-traumatic intracerebral hemorrhage. Out of these, 139 patients presented with secondary intracerebral hemorrhage and were excluded. The remaining 219 patients presenting with no obvious cause, were considered for the study. Out of these 75 patients were finally included and 144 patients were excluded because of unavailability of the follow up CT scan in 74 patients and 70 patients undergoing emergency neurosurgical interventions before the follow up CT.

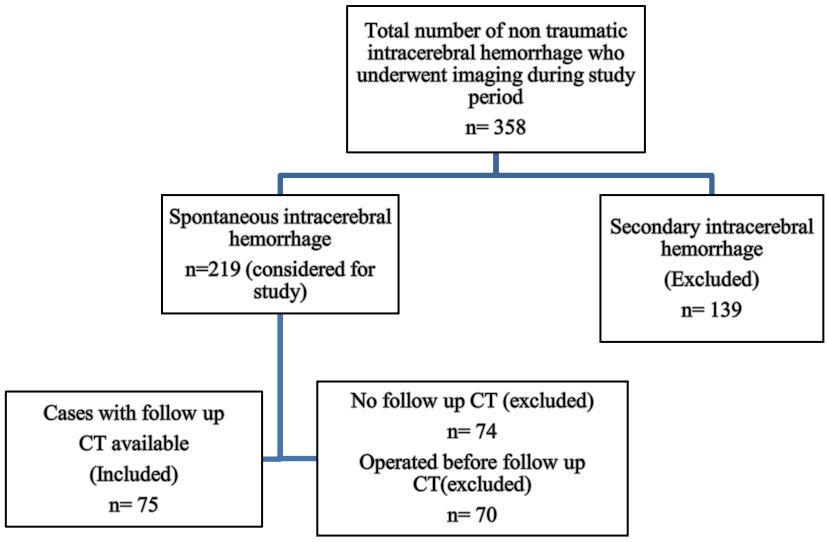

Figure 8: Flow chart showing the distribution of patients excluded and included in the study.

Age distribution:

Out of 75 patients included in study, 3 patients were less than 20 years of age, 1 patient between age 20-30 years, 7 patients between 31-40 years, 16 patients between 41-50 years, 14 patients between 51-60 years, 34 patients were more than 61 years old. The median age was 58 years with IQR of 18.5 years.

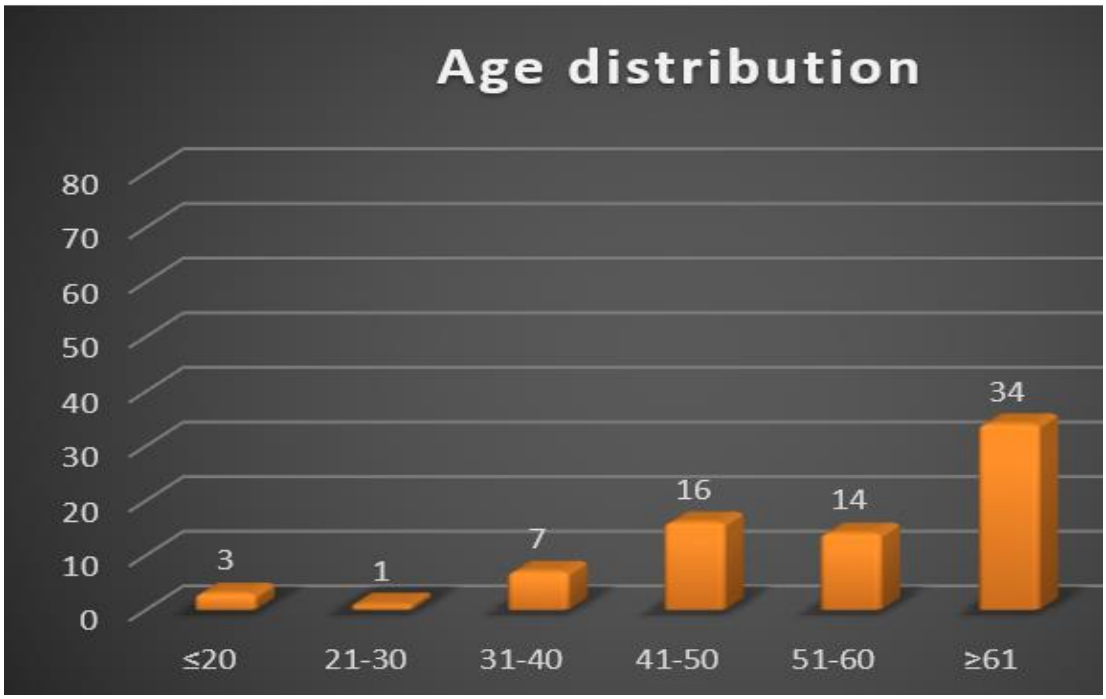

Figure 9: Age distribution

Sex distribution: Out of 75 patients enrolled in our study 44 (59%) patients were males and 31 (41%) were females.

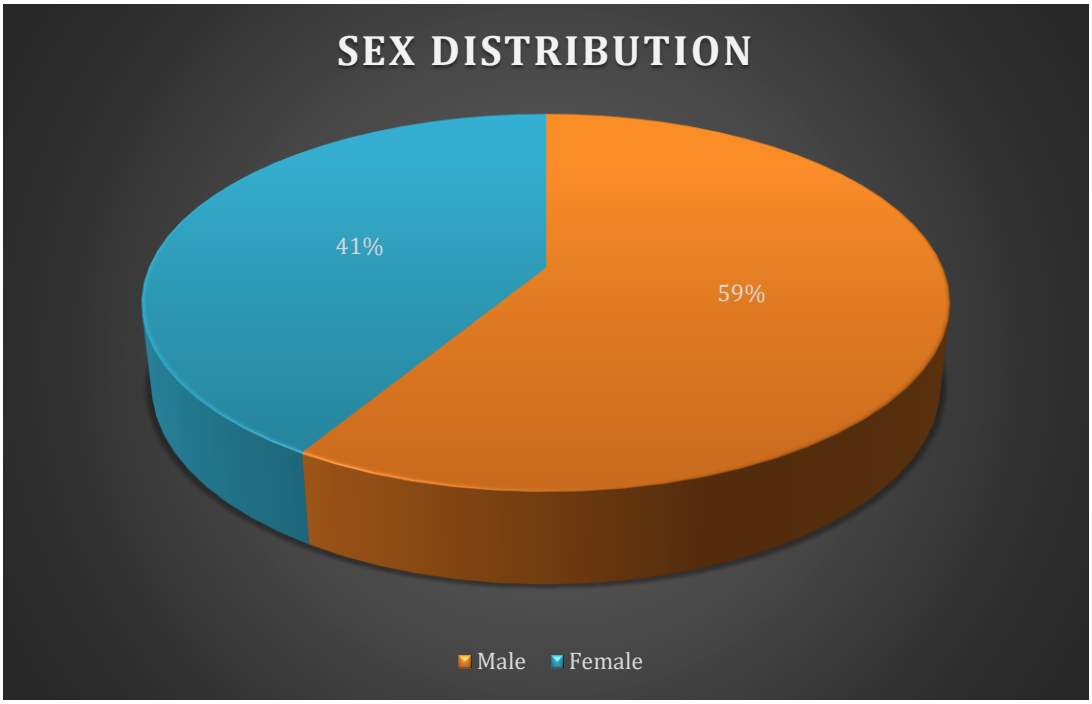

Figure 10: Sex distribution**.**

Clinical data:

NIHSS at presentation: Out of 75 patients, 4 had minor stroke ,9 patients had severe stroke symptoms, 4 patients had moderate to severe, 58 patients had moderate and symptoms

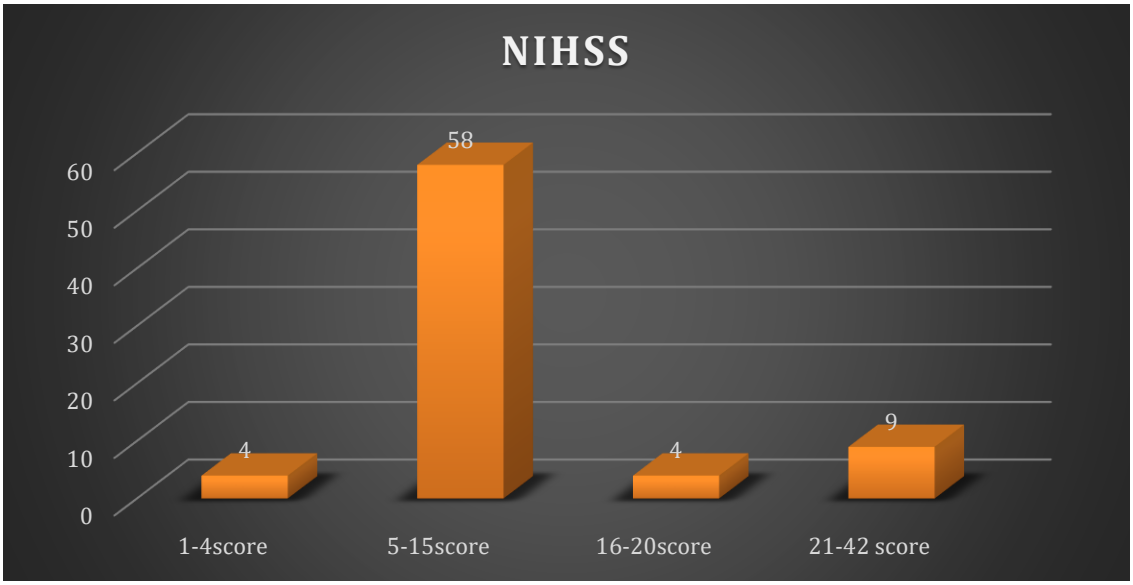

Figure 11: Distribution of NIHSS score.

GCS at presentation: Out of 75 patients, 50 patients had GCS scores between 13-15, 19 patients had GCS score between 9-12 and 6 patients had a score less than 8. Mean GCS score was 13.1+/-2.9SD.

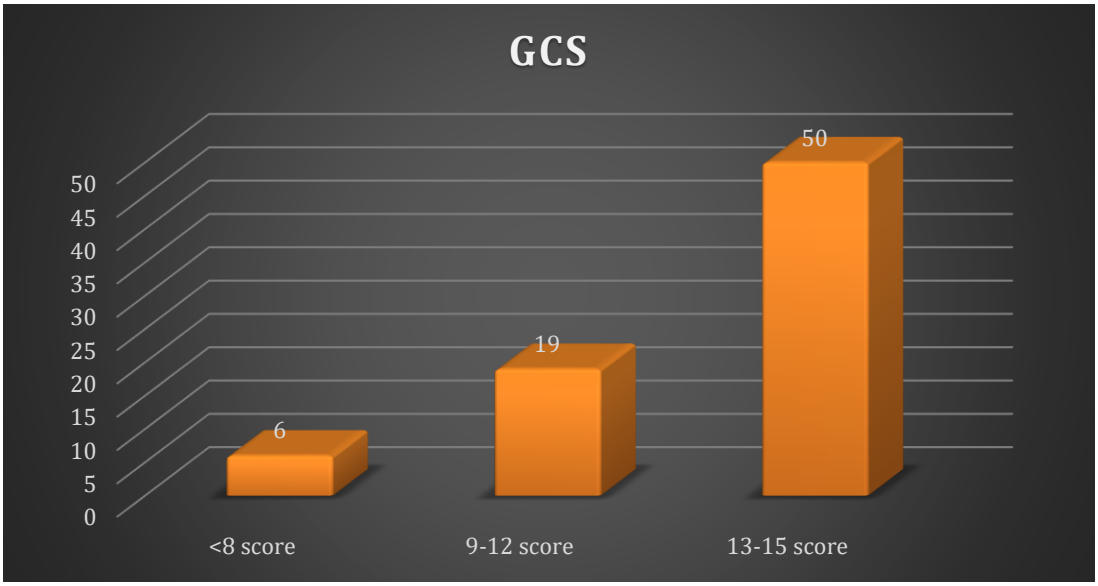

Figure 12: Distribution of GCS score.

Systolic BP: Out of 75 patients, 16 patients had SBP between 100-140 mmHg 28 patients had SBP between range 140-180 mmHg, 21 patients had SBP between 180-200 mmHg and 10 patients had SBP more than 200 mmHg. Mean SBP was 159.7 mmHg.

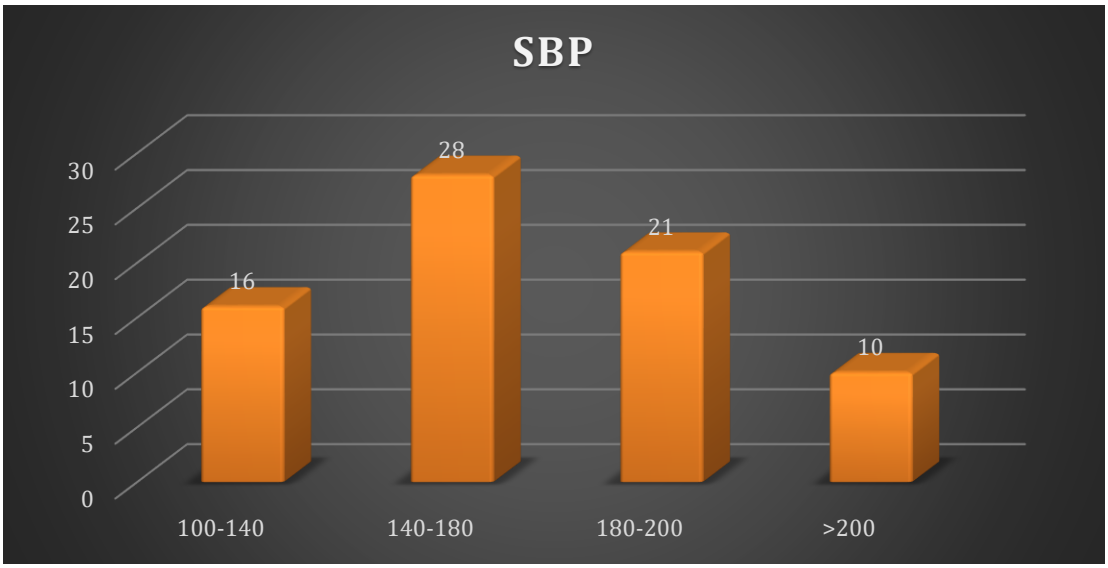

Figure 13: Distribution of Systolic blood pressure.

Diastolic BP:

Out of 75 patients 16 patients had DBP less than 80 mmHg, 31 patients had DBP between 80-100 mmHg and 28 patients had BP of >100 mmHg. Mean DBP was 99.5 mmHg.

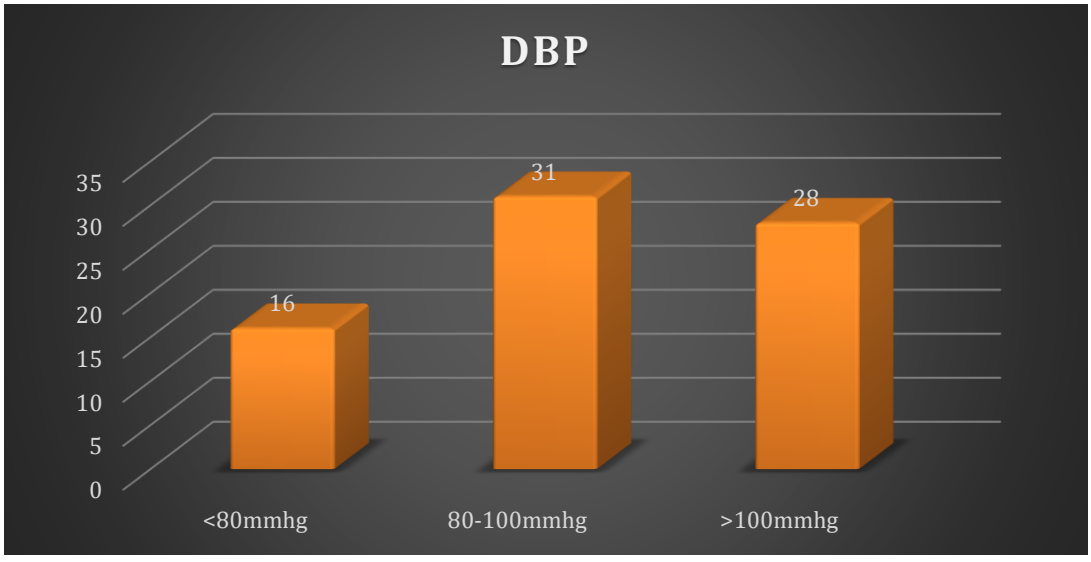

Figure 14: Distribution of Diastolic blood pressure.

Time of symptom onset to baseline CT:

The median time onset of symptoms to baseline CT was 6 hours with an IQR of 3 hours. Majority of the patients (n=29, 38.6%) presented between 4-6 hours from stroke onset.

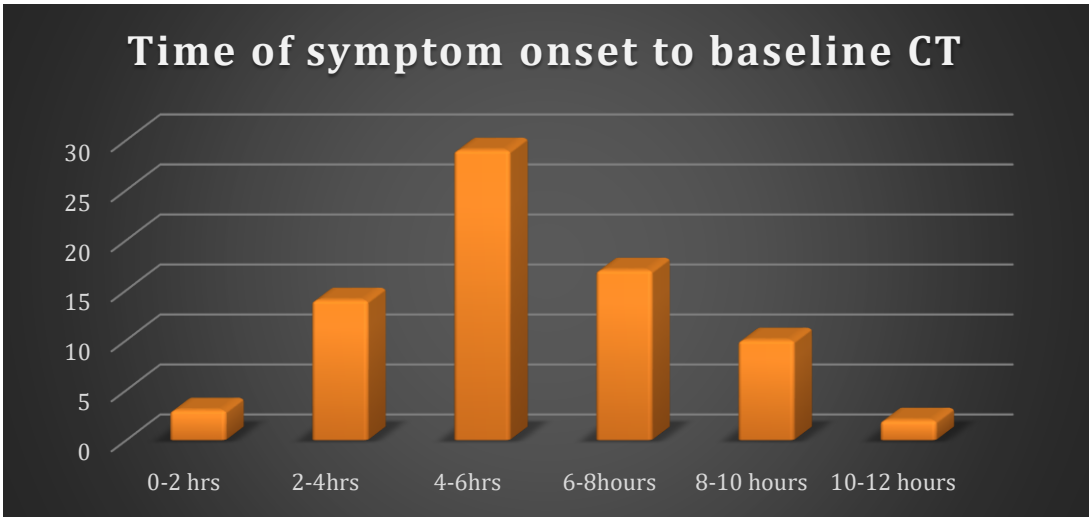

Figure 15: Distribution of duration between time of symptom onset and baseline CT.

Time interval between baseline and follow up CT:

The median time interval between the baseline CT and follow up CT was 16 hours with an IQR of 11 hours. Majority of the patients (n=38, 50.6%) underwent follow up CT scan 12-24 hours after the baseline CT scan.

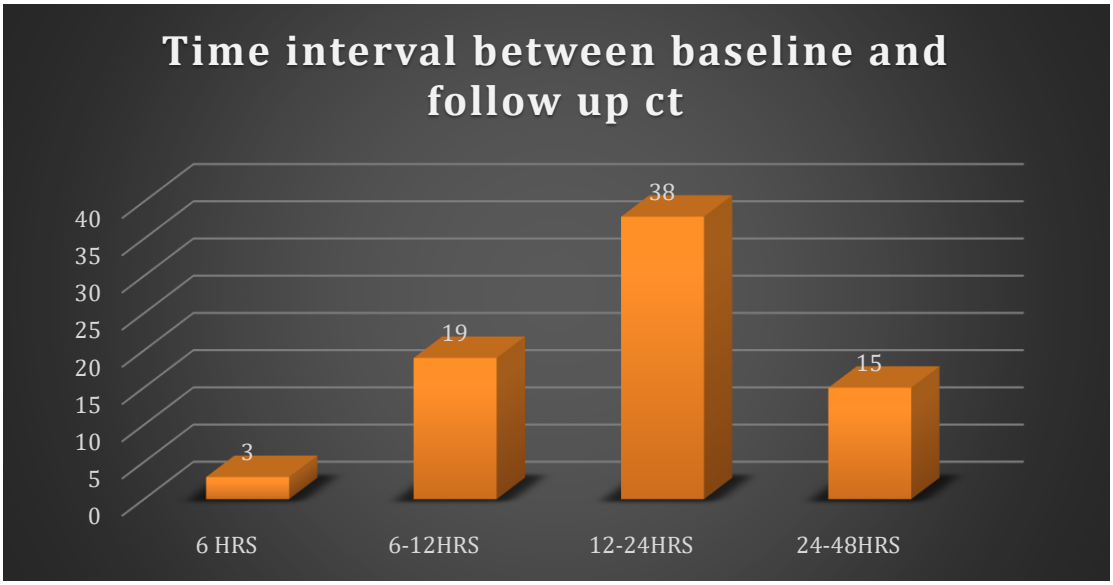

Figure 16: Distribution of duration between time interval between baseline and follow up CT scan.

Comorbidities:

Out of 75 patients 37 patients had no known comorbidities, 27 patients had hypertension, 4 patients had hypertension with diabetes mellitus, 3 patients had hypertension with diabetes mellitus and chronic kidney disease,2 patients had hyperhomocystinemia and 2 patients had hypertriglyceridemia.

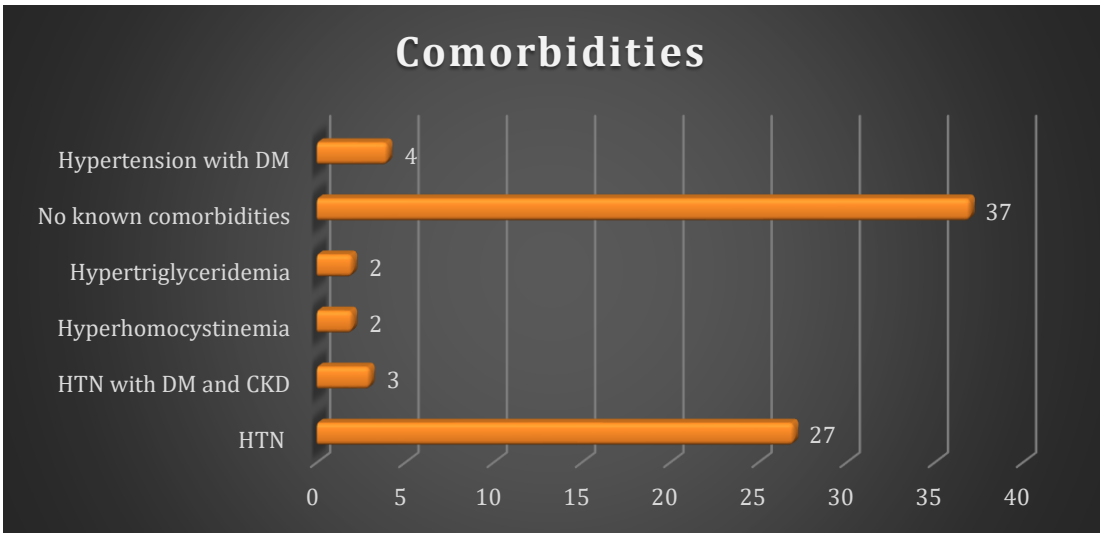

Figure 17: Distribution of comorbidities in patients with SICH

Bleed location:

Thirty-three patients had hemorrhage located in the gangliocapsular region, 19 patients had thalamus involvement, 13 patients had bleed in the lobar region, 6 patients had both thalamus and gangliocapsular involvement, and 4 patients in the infratentorial location.

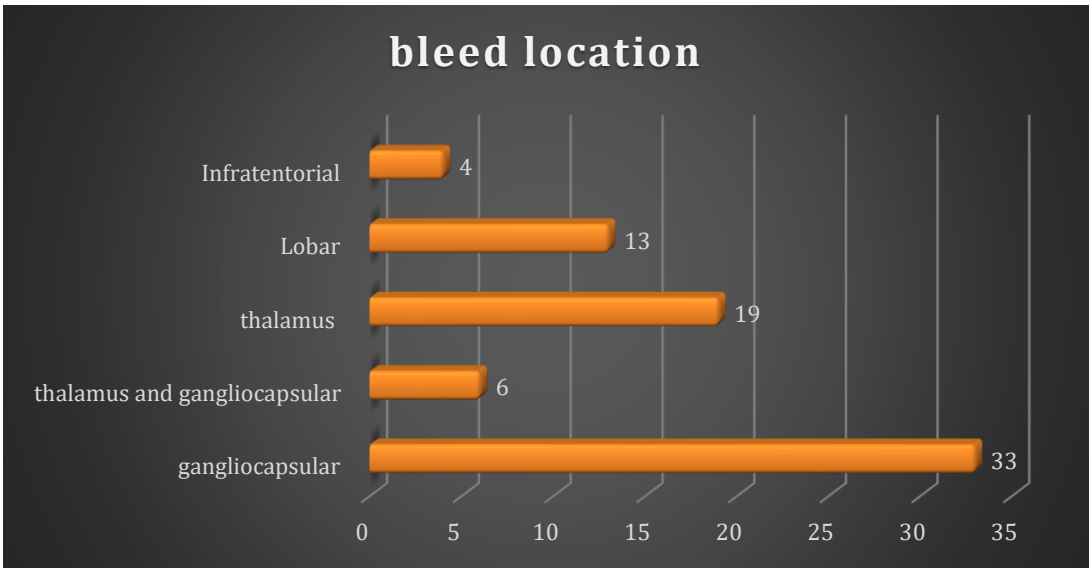

Figure 18: Distribution of bleed location

Revised hematoma expansion (RHE): Out of 75 presenting to the emergency with intracerebral hemorrhage, 18 (24%) patients had hematoma expansion and 57 (76%) patients did not have hematoma expansion.

Association of demographic factors, clinical and laboratory markers with RHE:

Sex: Of the 44 male patients, 10 patients (55.56%) had hematoma expansion and 34 patients (59.65%) did not have hematoma expansion. Out of 31 female patients, 8 patients (44.44%) had hematoma expansion and 23 (40.35%) did not have hematoma expansion. Male or female gender was not associated with hematoma expansion and poor outcome (p values >0.05). Implying that males or females were not separately at risk of hematoma expansion.

Table 7: Association of gender with RHE.

Sex	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Male	10	55.56	34	59.65	44	58.67
Female	8	44.44	23	40.35	31	41.33
Total	18	100.00	57	100.00	75	100.00

Chi square 0.094, p value 0.758

Table 8: Association of gender with poor outcome

Sex	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Male	17	54.84	27	61.36
Female	14	45.16	17	38.64
Total	31	100.00	44	100.00
p value	0.572			

Table 9:

Patient characteristics stratified by Revised hematoma expansion

Variables	Revised hematoma expansion		p value
	Present (Mean±SD)	Absent (Mean±SD)	
Age (years)	49.94±21.91	57.93±14.4	0.161
Time of symptom onset to baseline CT in hours	6.66±2.35	6.35±2.35	0.623
systolic BP	172.72±33.64	168.91±25.45	0.662
diastolic BP	101.5±24.31	99.28±14.37	0.717
NIHSS	13.94±4.9	10.21±5.9	**0.011**
GCS	11.39±3.11	13.68±2.69	**0.009**
HbA1c	5.69±0.76	5.89±1.07	0.400
Hb%	11.3±3.1	13.01±2.32	**0.041**
Platelets	219333.3±168042.3	251789.4±102093	0.446
PT	16.68±4.92	14.57±6.66	0.155
INR	1.3±0.4	1.34±1.87	0.895
Total cholesterol (mg/dl)	160.67±40.73	177.3±45.15	0.151
HDL (mg/dl)	49.83±11.57	54.53±38.76	0.422
LDL (mg/dl)	98.33±36.2	109.95±38.27	0.251
Triglyceride (mg/dl)	117.56±73.26	212.37±293.72	**0.029**
Urea	32.22±17.29	43.28±40.54	0.105
Creatinine	0.96±0.66	1.45±1.55	0.061
Baseline (ml)(Vb)	45.56±31.77	21.13±20.79	**0.005**

NIHSS, GCS score, hemoglobin percentage and triglyceride levels, baseline volume at presentation with a volume of 45.56±31.77 (Mean±SD) at presentation were statistically significant and were associated with RHE.

Table 10:

Patient characteristics stratified by poor outcome at 90 days.

Variables	Poor outcome at 90 days		p value
	Yes (Mean±SD)	No (Mean±SD)	
Age (years)	60.23±19.02	53.05±14.36	0.081
systolic BP	171.06±27.14	168.95±27.93	0.744
diastolic BP	102.52±19.62	97.91±15.05	0.276
NIHSS	11.16±5.37	11.07±6.25	0.645
GCS	12.84±3.13	13.34±2.82	0.479
Hba1c	5.59±1.22	6.02±0.79	0.095
Hb%	11.75±2.51	13.2±2.53	**0.016**
Platelets	213258±97125.3	265659±131645.2	0.051
PT	15.21±3.46	14.98±7.77	0.863
INR	1.15±0.31	1.45±2.12	0.359
Total cholesterol (mg/dl)	171.48±49.65	174.59±40.92	0.775
HDL (mg/dl)	46.35±15.58	58.36±42.26	0.089
LDL (mg/dl)	105.65±42.75	108.23±34.5	0.781
Triglyceride (mg/dl)	201.58±207.21	181.18±295.3	0.726
Urea	46.42±48.57	36.55±24.7	0.304
Creatinine	1.51±2	1.2±0.73	0.415
Baseline volume vb (ml)	30.5±28.08	24.4±24.2	0.316

Hemoglobin percentage with a mean of 11.75±2.51 was statistically significant and was associated with poor outcome at 90 days.

Association of imaging features with RHE and Poor outcome mRS (4-6) at 90 days:

ICH location: Gangliocapsular bleeds with thalamus involvement were statistically significant for hematoma expansion (p value =0.028), however were not statistically significant for poor outcome.

Table 11: Association of bleed location with RHE

Bleed location	Revised hematoma expansion				Total		p value
	Present		Absent				
	N	%	N	%	N	%	
Gangliocapsular	7	38.89	26	45.61	33	44.00	0.616
Infratentorial	0	0.00	4	7.02	4	5.33	0.566
Lobar	5	27.78	8	14.04	13	17.33	0.281
Thalamus	2	11.11	17	29.82	19	25.33	0.133
Thalamus with Gangliocapsular	4	22.22	2	3.51	6	8.00	**0.028***
Total	18	100.00	57	100.00	75	100.00	-

Table 12: Association of bleed location with poor outcome mRS (4-6)

Bleed location	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Gangliocapsular	10	32.26	23	52.27
Infratentorial	2	6.45	2	4.55
Lobar	6	19.35	7	15.91
Thalamus	9	29.03	10	22.73
Thalamus with gangliocapsular	4	12.90	2	4.55
Total	31	100.00	44	100.00
p value	0.436			

Density markers:

Heterogenous density sign: Forty-two patients showed positive heterogenous density sign out of which 17 were present in patients with RHE and 25 in patients without RHE. It was associated with RHE (p value = 0.0002) and was associated with poor outcome at 90 days (p value = 0.007)

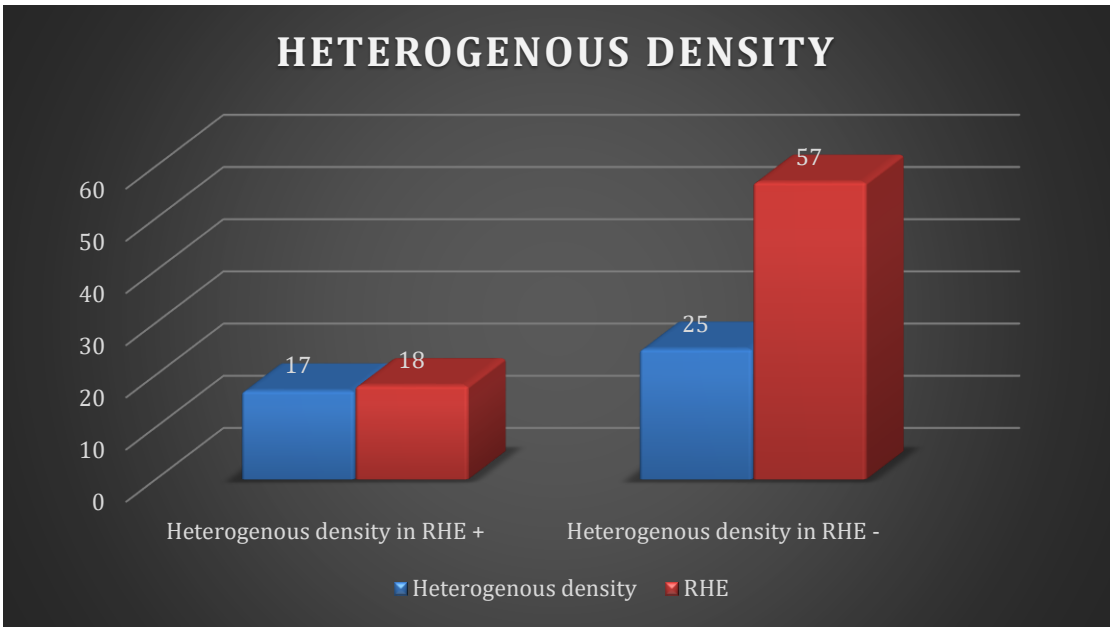

Figure 19: Distribution of heterogenous density sign

Table 13: Association of heterogenous density sign with RHE

Heterogenous density	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	17	94.44	25	43.86	42	56.00
Absent	1	5.56	32	56.14	33	44.00
Total	18	100.00	57	100.00	75	100.00

Chi square 14.20, p value 0.0002

Table 14: Association of heterogenous density with poor outcome

Heterogeneous density	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	23	74.19	19	43.18
Absent	8	25.81	25	56.82
Total	31	100.00	44	100.00
p value	**0.007***			

Black hole sign (BHS): Thirty-nine patients showed positive black hole sign out of which 12 were present in patients with RHE and 27 in patients without RHE**.** It was not associated with RHE (p value =0.153); however, it was associated with poor outcome at 90 days (p value 0.022).

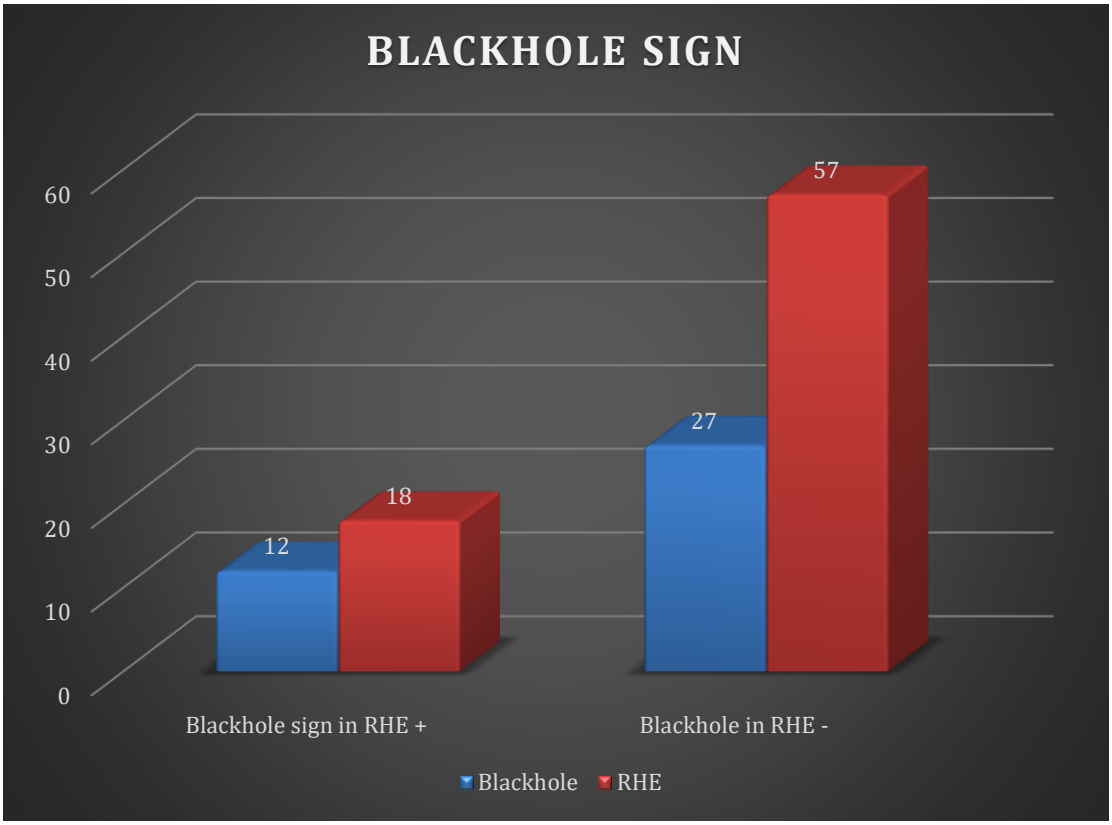

Figure 20: Distribution of Black hole sign**.**

Table 15: Association of blackhole sign with RHE.

Black hole sign	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	12	66.67	27	47.37	39	52.00
Absent	6	33.33	30	52.63	36	48.00
Total	18	100.00	57	100.00	75	100.00

Chi square 2.041, p value 0.153

Table 16: Association of blackhole sign with poor outcome

Black hole sign	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	21	67.74	18	40.91
Absent	10	32.26	26	59.09
Total	31	100.00	44	100.00
p value	**0.022***			

Blend sign: A total of 19 patients showed positive blend sign out of which 6 were present in patients with RHE and 13 in patients without RHE. It was not associated with RHE (p value= 0.153). It was also not associated with poor outcome at 90 days.

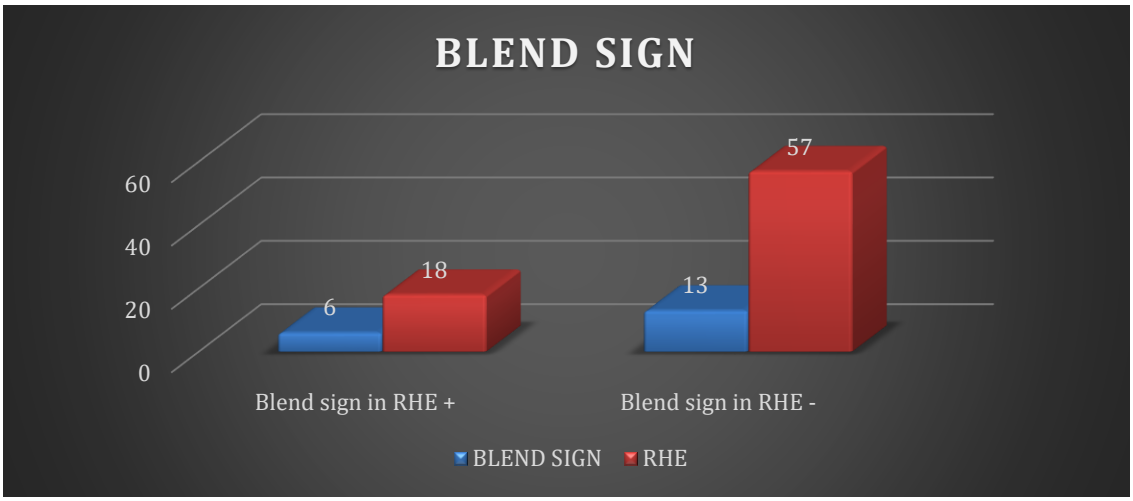

Figure 21: Distribution of blend sign

Table 17: Association of Blend sign with hematoma expansion.

Blend sign	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	6	33.33	13	22.81	19	25.33
Absent	12	66.67	44	77.19	56	74.67
Total	18	100.00	57	100.00	75	100.00

Chi square 2.041, p value 0.153

Table 18: Association of blend sign with poor outcome.

Blend sign	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	6	19.35	13	29.55
Absent	25	80.65	31	70.45
Total	31	100.00	44	100.00
p value	0.317			

Shape markers

Irregular shape sign: Out of 75 patients, 35 patients showed irregular sign 7 patients with irregular shape sign showed RHE while the remaining 28 did not**.**

It was not associated with RHE (p value= 0.448), and showed no association with poor outcome at 90 days (p value=0.103)

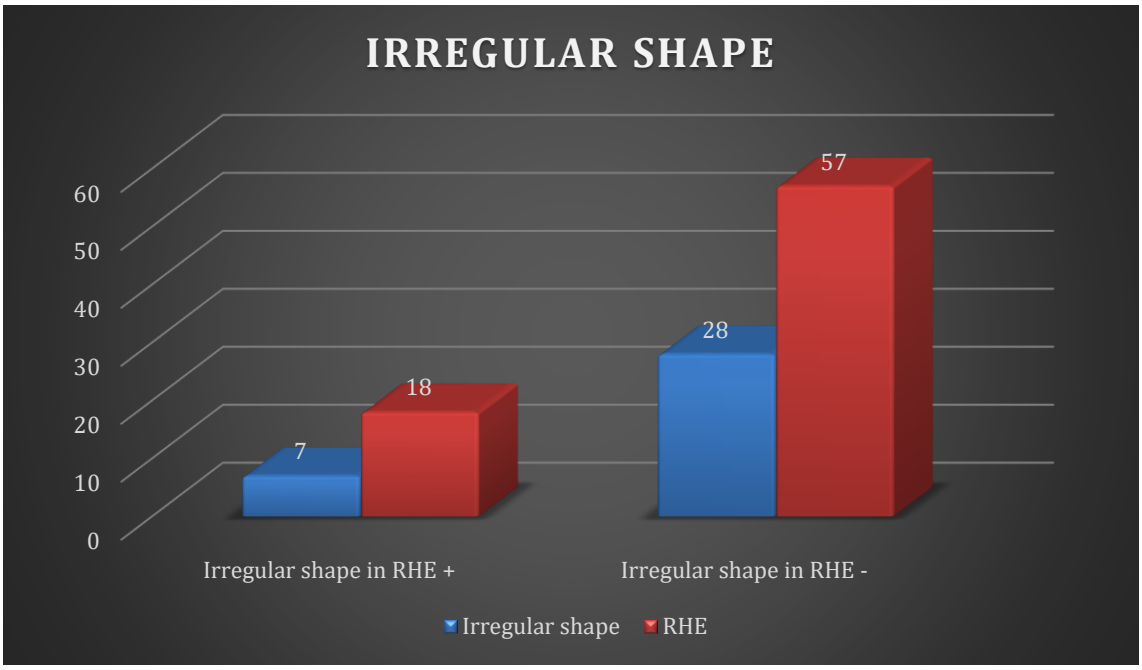

Figure 22: Distribution of irregular shape sign.

Table 19: Association of irregular shape with RHE

Irregular shape	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	7	38.89	28	49.12	35	46.67
Absent	11	61.11	29	50.88	40	53.33
Total	18	100.00	57	100.00	75	100.00

Chi square 0.575, p value 0.448

Table 20: Association of irregular shape with poor outcome

Irregular shape	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	11	35.48	24	54.55
Absent	20	64.52	20	45.45
Total	31	100.00	44	100.00
p value	0.103			

Island sign: A total of 35 patients showed positive island sign out of which 13 were present in patients with RHE and 22 in patients without RHE**.** It was associated with RHE (p value =0.012); however, it was not associated with poor outcome at 90 days (p values >0.05).

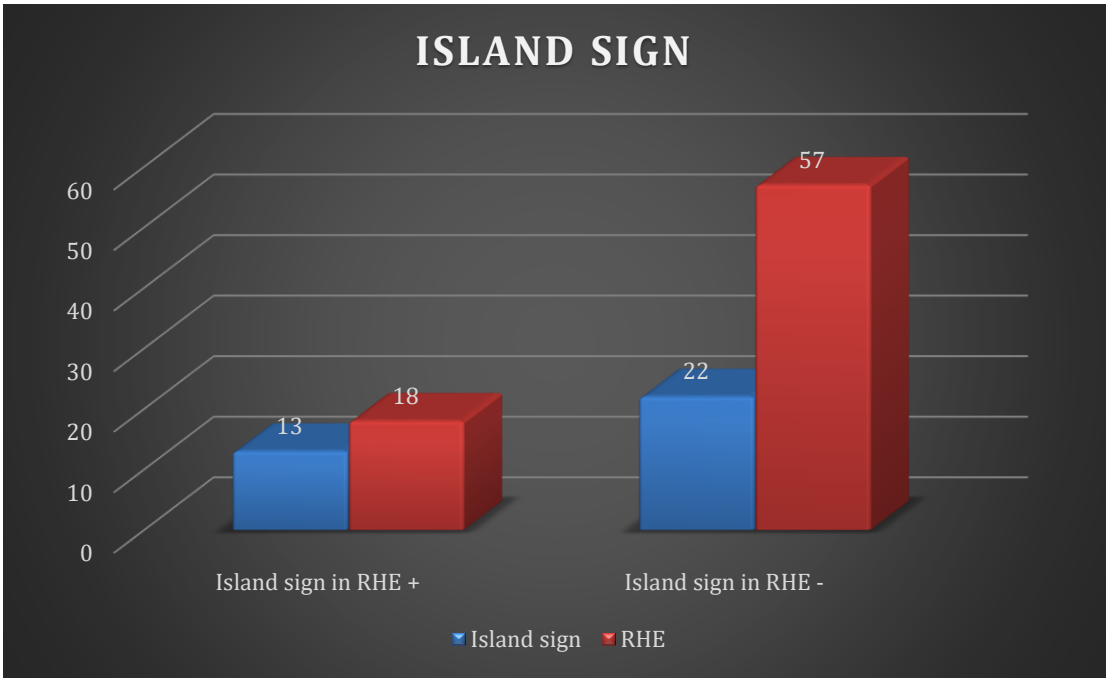

Figure 23: Distribution of island sign

Table 21: Association of island sign with RHE

Island sign	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	13	72.22	22	38.60	35	46.67
Absent	5	27.78	35	61.40	40	53.33
Total	18	100.00	57	100.00	75	100.00

Chi square 6.215, p value 0.012

Table 22: Association of island sign with poor outcome.

Island sign	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	15	48.39	20	45.45
Absent	16	51.61	24	54.55
Total	31	100.00	44	100.00
p value	0.802			

Satellite sign: Thirty-seven patients showed positive satellite sign, 11 were present in patient with RHE and 26 were present in patients without RHE**.** Presence of this sign was not associated with RHE or poor outcome at 90 days (p values>0.05).

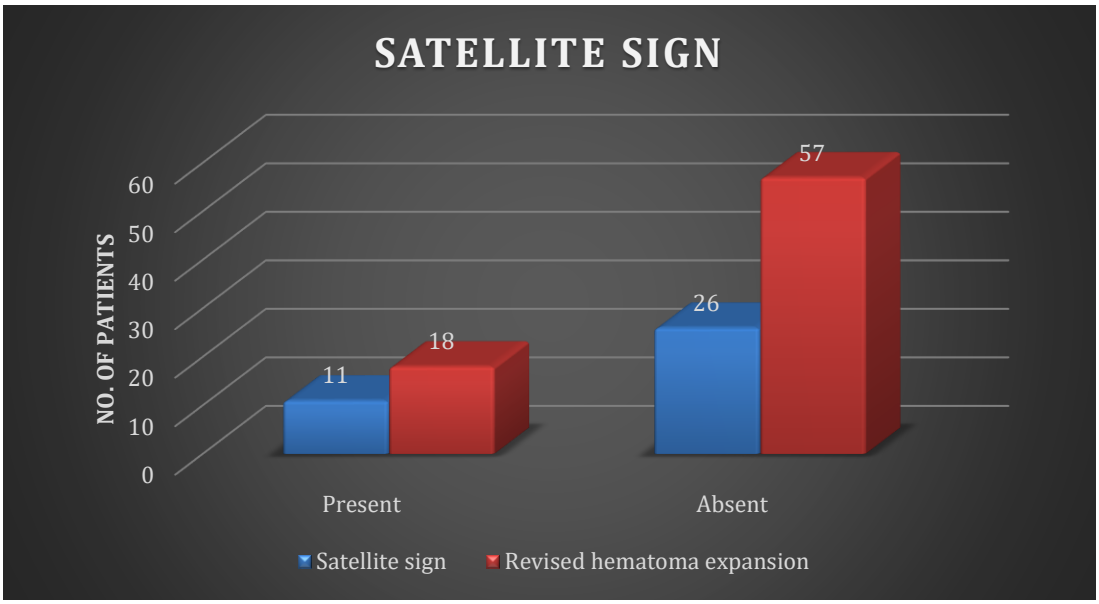

Figure 24: Distribution of satellite sign.

Table 23: Association of satellite sign with RHE

Satellite sign	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	11	61.11	26	45.61	37	49.33
Absent	7	38.89	31	54.39	38	50.67
Total	18	100.00	57	100.00	75	100.00

Chi square 1.314, p value 0.251

Table 24: Association of satellite sign with poor outcome.

Satellite sign	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	18	58.06	19	43.18
Absent	13	41.94	25	56.82
Total	31	100.00	44	100.00
p value	0.204			

One density and shape marker: Presence of one density marker and one shape marker was associated with RHE, however was not associated with poor outcome at 90 days (p values>0.05).

Table 25: **Association of one density and one shape marker with RHE.**

One shape and one density	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	16	88.89	39	68.42	55	73.33
Absent	2	11.11	18	31.58	20	26.67
Total	18	100.00	57	100.00	75	100.00

Fisher exact test, p value 0.007

Table 26: Association of baseline one shape and one density marker with poor outcome

One shape and one density	Poor outcome at 90 days			
	Yes		No	
	N	%	N	%
Present	22	70.97	33	75.00
Absent	9	29.03	11	25.00
Total	31	100.00	44	100.00
p value	0.697			

IVH in baseline scan: Presence of IVH in baseline scan was not associated with RHE

Table 27: Association of baseline IVH with RHE

IVH (Baseline Scan)	Revised hematoma expansion				Total	
	Present		Absent			
	N	%	N	%	N	%
Present	10	55.56	23	40.35	33	44.00
Absent	8	44.44	34	59.65	42	56.00
Total	18	100.00	57	100.00	75	100.00

Chi square 1.284, p value 0.257

Table 28: Summary of various NCCT markers with RHE and poor outcome.

Marker	RHE n=18	No RHE n=57	p value	Poor outcome at 90 days n=31	Good outcome at 90 days n=44	p value
Heterogenous density	17	25	**0.0002***	31	23	**0.007***
Black hole	12	27	0.153	21	18	**0.022***
Blend sign	6	13	0.153	6	13	0.317
Irregular shape	7	28	0.448	11	24	0.103
Island sign	13	22	**0.012***	15	20	0.802
Satellite	11	26	0.251	18	19	0.204
One shape and one density	16	39	**0.007***	22	33	0.697

***Denotes statistical significance p value <0.05**

Table 29: Summary of sensitivity, specificity, PPV* and NPV* of NCCT markers for RHE.

Variables	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Heterogeneous density	94.44	56.14	40.48	96.97	65.33
Black hole	66.67	52.63	30.77	83.33	56
Blend	33.33	77.19	31.58	78.57	66.67
Island	72.22	61.40	37.14	87.50	64
Irregular shape	38.89	50.88	20	72.50	48
Satellite	61.11	54.39	29.73	81.58	56
One shape and one density marker	88.89	31.58	29.09	90	45.33

***Positive predictive value and negative predictive value**

DISCUSSION

Since the concept of hematoma expansion in spontaneous intracerebral hemorrhage (SICH) was introduced, there have been many attempts to find association of various clinical and radiological markers to predict the hematoma growth and thereby prognosticate patient outcome. Imaging markers such as spot sign on CTA is well established as reliable indicator of hematoma expansion in patients with SICH. In the recent past there has been considerable increase in the literature to find association of NCCT markers for predicting hematoma expansion. Research so far has suggested that heterogeneous or irregularly shaped hematomas in the intraparenchymal tissue may reflect active bleeding.[14] Many NCCT markers, including the blend sign, black hole sign, CT hypodensities, and island sign, have been linked to HE and have been validated in multiple studies.[35] Finding associations between these markers and hematoma expansion becomes important for stratifying patients at risk of hematoma expansion and selecting them for early medical and neurosurgical interventions , thereby preventing poor outcome, considering the mortality rate of patient with SICH.

In 2019 the International NCCT ICH Study Group's standards published the standard reporting guidelines for detecting NCCT markers of HE, summarized practical standards for detecting NCCT markers and encouraged future clinical investigators to include NCCT markers in HE studies. [14]

Our study included 75 patients presenting to AIIMS Jodhpur with spontaneous intracerebral hemorrhage. We aimed at establishing association between various NCCT markers with hematoma expansion and functional outcome in patients with spontaneous intracerebral hemorrhage.

Patient demographics:

1. Age: Median age of patients included in our study was 58.0 years with IQR of 18.5. It was similar in comparison with the previous published studies such as **Yang et al (2021) [35], Qi Li et al (2017) [51] and Peter B. Sporns, MD et al (2018) [55]**, implying that the patients presenting with ICH were between 50-70 years of age. Age was not associated with hematoma expansion. Similar results were seen in the study done by **Li Q et al [36].**

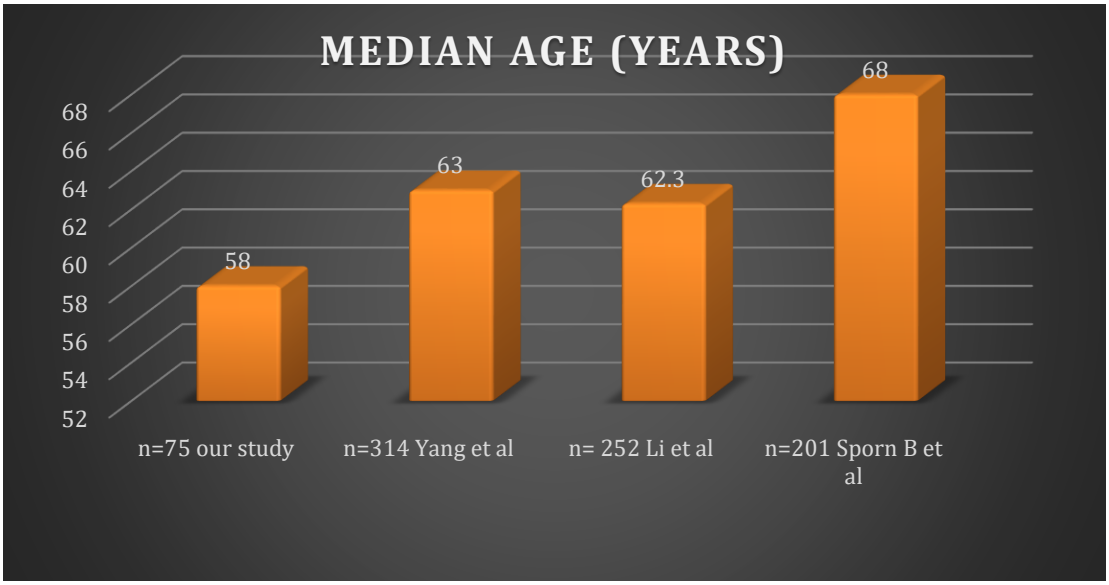

Figure 25: Age distribution across different studies.

2. Sex: Out of 75 patients, 44 (59%) were males and 31 (41%) were females compared to the study by **Yang et al (2021) [35], Qi Li et al (2017) [51] and Peter B. Sporns, MD et al (2018) [55]**. Both the studies show male predominance for SICH. The possible reason for this observation is a higher incidence of hemorrhagic stroke in male patients.[61] Our study did not show association of gender with hematoma expansion which is similar to the study by **Li Q et al [36] and Yang et al (2021) [35].**

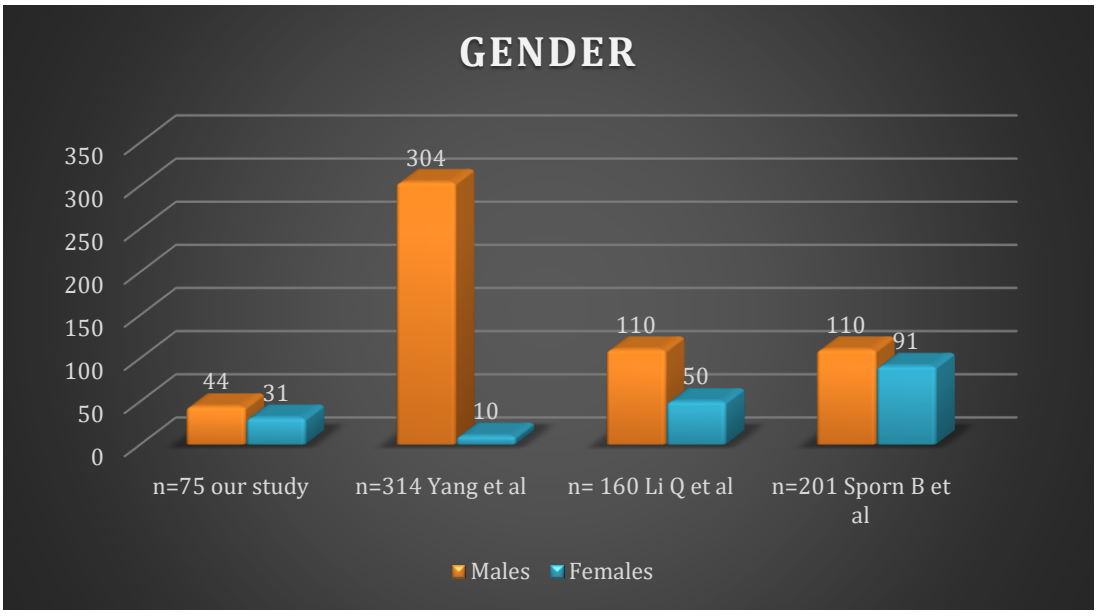

Figure 26: Gender distribution of patients with SICH among different studies.

Clinical features:

1.GCS: Patients presenting with SICH had mild to moderate GCS similar to previously published studies by **Hemphill et al [62].** Our study found association of GCS with revised hematoma expansion similar to study by **Yang et al (2021) [35],** implying that patients at who had hematoma expansion had moderate impairment in the GCS (score of 9-12). Similar results were also seen in the study published by **Li Q et al [53].**

2.NIHSS: Majority of the patients presenting with SICH had moderate stroke (NIHSS 5-15) similar to previously published study by **Sakuta K et al [63].** Our study found association of NIHSS score at presentation with hematoma expansion. There are very few studies that are published which describe the association of NIHSS score with hematoma expansion, because of the fact that patients with low GCS are taken up immediately for neurosurgical interventions, where NIHSS was not calculated most of the times [63]. Implication of our study in comparison to the previously published studies by **Sakuta K et al [63] and Elkhatib THM et al [64]** was that the patients presenting with moderate stroke symptoms (NIHSS 5-15) were associated with hematoma expansion.

3.**Blood pressure:** Majority of the patients included in our study had elevated blood pressure at presentation which is comparable to previously published studies by **Qureshi et al [65]**. Implying that patients with SICH had high blood pressure at presentation. Our study showed no association with elevated SBP at presentation with hematoma expansion, supported by the study by **Fujii et al [66]** who discovered a link between hematoma expansion and high SBP after admission. They hypothesized that the link between elevated blood pressure after admission and hematoma enlargement was more likely caused by increased intracranial pressure.[66]

4.**History of hypertension:** Our study had a lower fraction of patients with hypertension (27.3%) as compared to the previously published studies by **Dong H et al** [67], the possible cause for this discrepancy could be attributed to a higher population of subclinical and undiagnosed hypertension in our study population, which was mostly rural who does not undergo routine health evaluation.

Imaging features:

Time of symptom onset to baseline imaging: In our study the Median time between symptom onset to baseline imaging was 6 hours with IQR of 3 hours in comparison to the studies by **Yang et al (2021) [35] and Jinjin Liu et al [68]** which showed a median time of 2 hours. The discrepancy could be attributed to a higher population living in rural areas in our study area where transport time to the hospital is increased. The time of onset to baseline imaging was not associated with hematoma expansion in our study compared to **Yang et al (2021) [35] and Jinjin Liu et al [68]** who found significant association, this implies that patients who arrived at the emergency room first at 6 hours may have already had hematoma expansion.[66]

Hematoma location: Our study found that gangliocapsular bleeds were more common, followed by thalamus, lobar, gangliothalamic, and infratentorial bleeds, similar to the bleed locations found out in previous study by **Yang et al. (2021) [35]**. Our study also found that gangliothalamic bleeds were more likely to expand in comparison to the studies by **Lei Song et al [69]**. **David Roh [70] et al** and **Yang et al. (2021) [35]** which found that lobar bleeds were more likely to expand. This may be due to ethnic differences and differences in risk factors between the study population. It has already been published by **Kurabe et al. [71]** that basal ganglia bleeds, especially in the posterior limb of the internal capsule, are more likely to expand; however, the precise mechanism underlying the association between posterior limb involvement of the internal capsule, and HE remains unknown. It is possible that specific anatomic features lay the groundwork for hemorrhagic progression. Because projection fibres are primarily found in the internal capsule and are most abundant in the posterior limb of the internal capsule, blood is supplied to the posterior limb of the internal capsule region by branches from multiple arteries and is more prone for bleed.[71]

Our study did not find significant association between bleed location and poor outcome, however patients with gangliocapsular bleeds had slightly poorer outcome compared to other locations similar to a study by **Yang et al. (2021) [35].**

Hematoma volume: Our study found out that baseline hematoma volume of 45.56+/-31.77ml (Mean±SD) was associated with hematoma expansion compared to the previously published studies by **Brouwers HB et al [30]** and **Yang et al (2021) [35]** who

had similar results and implied that hematoma volume >30ml were more likely to expand and were associated with poor outcome [30].

IVH: Presence of baseline IVH was not associated with hematoma expansion in our study in comparison to study by **Li Q et al [36].** Association with hematoma expansion was noted by **Yaghi et al [72].** Discrepancy in the results might be due to differences in time to baseline scan and the time interval between baseline and follow up CT scans.

Association of NCCT markers with revised hematoma expansion.

We found that 18 patients out of 75 (24%) had revised hematoma expansion which supports the already existing literature on the prevalence of hematoma expansion by **Li Z et al [4] and Brott et al [37]** to be 13-38%.

Previous research has suggested that heterogeneous or irregularly shaped hematomas in the intraparenchymal tissue may reflect active HE bleeding [47]. Many NCCT markers, including the blend sign [58] black hole sign [57], island sign [51] and satellite sign [59] have been linked to HE and have been validated in multiple studies.

Density markers:

We found an association of heterogenous density sign with revised hematoma expansion. A study by **Ji et al [73]** suggested that heterogenous density in a hematoma in SICH patient could predict hematoma expansion. In 2009 **Barras et al [49]** introduced a novel 5-point categorical scale for heterogenous density grade and found that, heterogenous density sign could independently predict HE. **Takeda et al [74]** also found association of heterogenous density with HE. **Boulouis et al [75]** in a study found out that the sensitivity and specificity of heterogenous density to predict hematoma expansion was 50% and 78%. Our study showed a sensitivity and specificity of 94.4% and 56.1% which had a better sensitivity than the study by **Boulouis et al [75].** Implication of our study was that heterogenous density sign had a better sensitivity and good predictor for HE even after including IVH growth in the definition of HE. It adds to the pathophysiology of the heterogenous density sign that it reflects active bleeding, with various stages of bleed giving its morphological appearance and thus hematoma expansion. Thus, concluding that the more the heterogenous the bleed was the more risk associated with hematoma expansion.

Previously published studies have shown that the blend sign [58] and the black hole [57] are heterogeneity signs associated with HE, however, our study did not show a significant association. This can be because of our small sample size, the ethnic difference and absence of studies published in India. Before concluding that blend or black hole sign might not be associated with hematoma expansion, large multicentric study need to be carried out in Indian Subcontinent.

Shape markers:

In our study we found that irregular shape sign was not associated with hematoma expansion similar to the study by **Takeda et al [74]**. Previously published studies by **Fuji et al [66], Barras et al [49] and Huttner et al [76]** have found an association between irregular shape with hematoma expansion. Implying that the differences might be due to a lack of standard definition of irregular shape sign. In most previous studies, the shape of the hematoma was categorized as round or irregular. Hematoma shape is extremely variable, and the definition of irregularly shaped hematoma is subjective. Our study included the latest definition given by **Morotti et al (2019) [14]** for the identification of irregular shape sign.

We found an association in our study between island sign and hematoma expansion which shows similar results to previously published study by **Qi Li et al [51] and Wei Y et al [77].** According to **Morotti et al (2019) [14]**, island sign was a subset of irregular shape signs, where more bubble like and spike like small hemorrhagic foci were connected to the main hematoma. The implication of this is that not all the bleeds with irregular shapes will expand rather bleeds which have bubble like and spike hematomas connected to the main hematoma or three bleed foci that are disconnected to the main hematoma were likely to expand.

We didn't find an association between satellite sign with hematoma expansion. Previously published studies by **Yu et al [52] and Deng et al [78]** found association of satellite sign with hematoma expansion**.**

One shape and one density marker:

When compared to the predictive ability of each individual marker, we found that combining imaging markers in baseline non-contrast CT can improve prediction in patients with ICH. Patients with hematoma expansion had more irregular and heterogeneous bleeds, according to our findings. This is most likely due to ongoing intra-hematoma bleeding (heterogenous density of the bleed) and secondary bleeding (shape feature of a bleed) from a shear injury to surrounding arterioles caused by a rapidly expanding hematoma ('avalanche model') [14]. This is a newer topic in the literature, with only a few studies published by **Katsanos AH et al [79] and Li Q et al [53]**. They concluded that a combination of signs provided a good accuracy for predicting hematoma expansion compared to any other single marker. Because definitions of various density and shape markers are overlapping, when a combination of signs is used the association with hematoma expansion gets stronger. Thus, there is a need for further research to find out a model of combination of signs that best predicts hematoma expansion.

Table 30: Reference Study characteristics of NCCT markers with hematoma expansion.

Study	Year	Sample size	HE criteria	Results
Ji et al [73]	2009	126	>20ml absolute increase or 33% relative increase	Heterogenous density positive
Barras et al [49]	2009	90	>12.5ml growth or 33% increase	Heterogenous density and irregular shape positive
Takeda et al [74]	2012	201	>12.5ml growth or 33% increase	Heterogenous density positive
Boulouis et al [75]	2016	784	>6ml growth or 33% increase	Heterogenous density and irregular shape positive Blend negative
Fuji et al [66]	1998	627	>20ml increase or 50% increase	Irregular shape positive
Qi Li et al [51]	2017	252	>6ml growth or 33% increase	Island positive
Wei Y et al [77]	2020	4310	>6ml growth or 33% increase	Island positive
Yu et al [52]	2017	153	>12.5ml growth or 33% increase	Satellite sign positive
Deng et al [78]	2019	307	>6ml growth or 33% increase	Satellite and island sign positive
Katsanos AH et al [79]	2022	79	>6ml growth or 33% increase	Combination of NCCT markers is associated with HE
Li Q et al [53]	2018	282	>6ml growth or 33% increase	Expansion prone hematoma, that is presence of more than 1 NCCT marker was associated with HE
Yang et al [35]	2021	314	>6ml growth or 33% increase or >1ml IVH increase or presence of new IVH	Blackhole, blend and Island sign positive.

NCCT markers with poor outcome:

Previous research has established association of both the density and shape markers with poor functional outcome [54]. Our study showed that the heterogenous density sign and the black hole sign were associated with poor outcome mRS (4-6) at 90 days supporting the previously published research [54]. However, our study didn't show association of blend sign, irregular density sign, island sign and satellite sign with hematoma expansion contradicting the previously published research (a meta-analysis study by **Morotti et al [54]**). A possible explanation for this is that, while hematoma expansion increased the risk of poor functional outcome, other factors such as perihematomal edema and mass effect might also have resulted in poor functional outcome, acting as confounding factors for poor outcome prediction. Because majority of the patients presenting to our emergency department with SICH had to be excluded due to them undergoing emergency neurosurgical intervention for significant mass effect before the follow up CT scan, it is possible that a few of the signs associated with poor outcome in previously published studies were influenced by sampling bias in our study. Our study also didn't find any association with poor outcome when signs were combined in contradiction to the study conducted by **Katsanos AH et al [79]**. With only few studies being published on combination model of markers with hematoma expansion with poor outcome we need further studies to validate association of combination of markers with poor outcome.

CONCLUSION

1. Heterogenous density sign and island sign are associated with hematoma expansion.
2. Presence of at least one density marker and one shape marker in SICH is associated with hematoma expansion.
3. Heterogenous density sign and blackhole sign are associated with poor outcome at 90 days.

These findings are important because:

1. NCCT is uniformly performed at all imaging centers in patients with SICH, establishing association of NCCT signs with predicting hematoma expansion can be helpful in early medical or surgical managements to prevent adverse outcomes and might reduce the overall mortality rate of the disease.
2. The learning curve for interpretation of NCCT signs is short and hence easy to interpret.
3. This study further solidifies the importance of NCCT markers for predicting hematoma expansion, replacing the need for CTA to see the highly reliable spot sign.

FUTURE DIRECTIVES

1. Compare the diagnostic performance of different NCCT markers.
2. To create a simplistic diagnostic module which comprises of combination of signs or one ideal sign which strongly predicts hematoma expansion.
3. Application of artificial intelligence in automated calculation of hematoma volume and automated sign identification softwares.
4. To carry out further research on NCCT markers and their association with hematoma expansion as a prospective multicentric study.

LIMITATIONS

1. Many of the patients were referred to other centers because of the unavailability of hospital beds, so had to be excluded before the follow up CT scan resulting in very small sample size.
2. Sample size was affected by patient's deterioration before the follow up CT scan who had to undergo emergency neurosurgical interventions.
3. The second wave of the COVID 19 pandemic contributed to less sample size.

REFERENCES

1. Macellari F, Paciaroni M, Agnelli G, Caso V. Neuroimaging in intracerebral hemorrhage. *Stroke*. 2014 Mar; 45(3):903-8.

2. Hegde A, Menon G, Kumar V, Lakshmi Prasad G, Kongwad LI, Nair R, et al. Clinical profile and predictors of outcome in spontaneous intracerebral hemorrhage from a tertiary care center in South India. *Stroke Res Treat.* 2020 Jan 27; 2020.

3. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke*. 2017 Jan;19(1):3.

4. Li Z, You M, Long C, Bi R, Xu H, He Q, et al. Hematoma Expansion in Intracerebral Hemorrhage: An Update on Prediction and Treatment. *Front Neurol*. 2020 Jul 17; 11:702.

5. Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology*. 2011 Apr 5;76(14):1238-44.

6. Steiner T, Bösel J. Options to restrict hematoma expansion after spontaneous intracerebral hemorrhage. *Stroke*. 2010 Feb 1;41(2):402-9.

7.Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010 Feb 1;41(2):307-12.

8. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, et al. Determinants of intracerebral hemorrhage growth: an exploratory analysis. *Stroke*. 2007 Mar 1;38(3):1072-5.

9. Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet*. 2013 Aug 3;382(9890):397-408.

10. Romero JM, Brouwers HB, Lu J, Almandoz JE, Kelly H, Heit J, et al. Prospective validation of the computed tomographic angiography spot sign score for intracerebral hemorrhage. *Stroke*. 2013 Nov;44(11):3097-102.

11.Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke*. 2007 Apr 1;38(4):1257-62.6.

12. Sprigg N, Flaherty K, Appleton JP, Salman RA, Bereczki D, Beridze M, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018 May 26;391(10135):2107-15.

13.Morotti A, Brouwers HB, Romero JM, Jessel MJ, Vashkevich A, Schwab K, et al. Intensive blood pressure reduction and spot sign in intracerebral hemorrhage: a secondary analysis of a randomized clinical trial. *JAMA Neurol*. 2017 Aug 1;74(8):950-60.

14. Morotti A, Boulouis G, Dowlatshahi D, Li Q, Barras CD. Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. *Ann Neurol*. 2019 Oct;86(4):480-92.

15. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol*. 2018;38(02):208–11.

16. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. *Int J Mol Sci.* 2020;21(20):7609.

17 Knight-Greenfield A, Nario JJQ, Gupta A. Causes of Acute Stroke A Patterned Approach. *Radiol Clin North Am.* 2019;57(6):1093–108.

18. Aguilar MI, Freeman WD. Spontaneous intracerebral hemorrhage. *Semin Neurol*. 2010 Nov;30(05):555-564.

19. Macellari F, Paciaroni M, Agnelli G, Caso V. Neuroimaging in intracerebral hemorrhage. *Stroke*. 2014 Mar;45(3):903-8.

20. Meretoja A, Strbian D, Putaala J, Curtze S, Haapaniemi E, Mustanoja S, et al. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. *Stroke*. 2012 Oct;43(10):2592-7.

21. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke*.:10-161.

22. Ziai WC, Carhuapoma JR. Intracerebral hemorrhage. *Continuum (Minneap Minn)*. 2018 Dec 1;24(6):1603-22.

23. Morotti A, Goldstein JN. Diagnosis and management of acute intracerebral hemorrhage. *Emerg Med Clin North Am*. 2016 Nov 1;34(4):883-99.

24. Hemphill III JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015 Jul;46(7):2032-60.

25. Kogan E, Twyman K, Heap J, Milentijevic D, Lin JH, Alberts M. Assessing stroke severity using electronic health record data: a machine learning approach. *BMC Med Inform Decis Mak*. 2020;20(1):8.

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

27. Khosravani H, Mayer SA, Demchuk A, Jahromi BS, Gladstone DJ, Flaherty M, et al. Emergency noninvasive angiography for acute intracerebral hemorrhage. *AJNR Am J Neuroradiol*. 2013 Aug 1;34(8):1481-7.

28. Brouwers HB, Greenberg SM. Hematoma expansion following acute intracerebral hemorrhage. *Cerebrovasc Dis*. 2013;35(3):195-201.

29. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J Neurosurg*. 1994 Jan 1;80(1):51-7.

30. Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, et al. Predicting hematoma expansion after primary intracerebral hemorrhage. *JAMA neurol*. 2014 Feb 1;71(2):158-64.

31. Lord AS, Gilmore E, Choi HA, Mayer SA. Time course and predictors of neurological deterioration after intracerebral hemorrhage. *Stroke*. 2015 Mar;46(3):647-52.

32. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1–5.

33. He GN, Guo HZ, Han X, Wang EF, Zhang YQ. Comparison of CT black hole sign and other CT features in predicting hematoma expansion in patients with ICH. *J Neurol*. 2018; 265:1883–90.

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

35. Yang WS, Zhang SQ, Shen YQ, Wei X, Zhao LB, Xie XF, et al. Noncontrast Computed Tomography Markers as Predictors of Revised Hematoma Expansion in Acute Intracerebral Hemorrhage. *J Am Heart Assoc*. 2021 Feb 2;10(3):e018248.

36. Li Q, Li R, Zhao LB, Yang XM, Yang WS, Deng L, et al. Intraventricular hemorrhage growth: definition, prevalence and association with hematoma expansion and prognosis. *Neurocrit Care*. 2020;33:732–739.

37. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*.1997;28:1–5.

38. Rodriguez-Luna D, Rodriguez-Villatoro N, Juega JM, Boned S, Muchada M, Sanjuan E, et al. Prehospital systolic blood pressure is related to intracerebral hemorrhage volume on admission. *Stroke*. 2018;49:204–6.

39. Lovelock CE, Molyneux AJ, Rothwell PM. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurol.* 2007;6:487–93.

40. Huynh TJ, Aviv RI, Dowlatshahi D, Gladstone DJ, Laupacis A, Kiss A, et al. Validation of the 9-point and 24-point hematoma expansion prediction scores and derivation of the PREDICT A/B scores. *Stroke*. 2015;46:3105–10.

41. Schindlbeck KA, Santaella A, Galinovic I, Krause T, Rocco A, Nolte CH, et al. Spot sign in acute intracerebral hemorrhage in dynam T1-weighted magnetic resonance imaging. *Stroke*. 2016;47:417–23.

42. Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Prevalence of admission hyperglycaemia across clinical subtypes of acute stroke. *Lancet*. 1999;353:376–7.

43. Xu X, Zhang J, Yang K, Wang Q, Xu B, Chen X. Accuracy of spot sign in predicting hematoma expansion and clinical outcome: a meta-analysis. *Medicine.* 2018;97:e11945.

44. Orito K, Hirohata M, Nakamura Y, Takeshige N, Aoki T, Hattori G, et al. Leakage sign for primary intracerebral hemorrhage: a novel predictor of hematoma growth. *Stroke*. 2016 Apr;47(4):958-63.

45. Fu F, Sun S, Liu L, Gu H, Su Y, Li Y. Iodine sign as a novel predictor of hematoma expansion and poor outcomes in primary intracerebral hemorrhage patients. *Stroke*. 2018 Sep;49(9):2074-80.

46. Sun SJ, Gao PY, Sui BB, Hou XY, Lin Y, Xue J, et al. "Dynamic spot sign" on CT perfusion source images predicts haematoma expansion in acute intracerebral haemorrhage. *Eur Radiol*. 2013 Jul;23(7):1846-54.

47. Boulouis G, Morotti A, Charidimou A, Dowlatshahi D, Goldstein JN. Noncontrast computed tomography markers of intracerebral hemorrhage expansion. *Stroke*. 2017 Apr;48(4):1120-5.

48. Kim J, Smith A, Hemphill JC 3rd, Smith WS, LuY, Dillon WP, et al. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. *AJNR Am J Neuroradiol*. 2008;29:520–525.

49. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke.* 2009;40:1325–1331.

50. Li Q, Zhang G, Xiong X, Wang XC, Yang WS, Li KW, et al. Black hole sign: novel imaging marker that predicts hematoma growth in patients with intracerebral hemorrhage. *Stroke*. 2016;47:1777–1781.

51. Li Q, Liu QJ, Yang WS, Wang XC, Zhao LB, Xiong X, et al. Island sign: an imaging predictor for early hematoma expansion and poor outcome in patients with intracerebral hemorrhage. *Stroke*. 2017;48:3019–3025.

52. Yu Z, Zheng J, Ali H, Guo R, Li M, Wang X, et al. Significance of satellite sign and spot sign in predicting hematoma expansion in spontaneous intracerebral hemorrhage. *Clin Neurol Neurosurg*. 2017 Nov 1;162:67-71.

53. Li Q, Zhang G, Xiong X, Wang XC, Yang WS, Li KW, et al. Expansion-Prone Hematoma: Defining a Population at High Risk of Hematoma Growth and Poor Outcome. *Neurocrit Care*. 2019 Jun;30(3):601-608.

54. Morotti A, Arba F, Boulouis G, Charidimou A. Noncontrast CT markers of intracerebral hemorrhage expansion and poor outcome: a meta-analysis. *Neurology*. 2020 Oct 6;95(14):632-43.

55. Sporns PB, Kemmling A, Schwake M, Minnerup J, Nawabi J, Broocks G,et al . Triage of 5 noncontrast computed tomography markers and spot sign for outcome prediction after intracerebral hemorrhage. *Stroke*. 2018 Oct;49(10):2317-22.

56. Ng D, Churilov L, Mitchell P, Dowling R, Yan B. The CT swirl sign is associated with hematoma expansion in intracerebral hemorrhage. *AJNR Am J Neuroradiol*. 2018 Feb 1;39(2):232-7.

57. Chen Y, Tian L, Wang L, Qin Y, Cai J. Black hole sign on noncontrast computed tomography in predicting hematoma expansion in patients with intracerebral hemorrhage: a meta-analysis. *Curr Med Imaging*. 2020 Aug 1;16(7):878-86.

58. Yu Z, Zheng J, Guo R, Ma L, Li M, Wang X, et al. Performance of blend sign in predicting hematoma expansion in intracerebral hemorrhage: a meta-analysis. *Clin Neurol Neurosurg*. 2017 Dec 1;163:84-9.

59. Shimoda Y, Ohtomo S, Arai H, Okada K, Tominaga T. Satellite sign: a poor outcome predictor in intracerebral hemorrhage. *Cerebrovasc Dis*. 2017;44(3-4):105-12.

60. Maeda AK, Aguiar LR, Martins C, Bichinho GL, Gariba MA. Hematoma volumes of spontaneous intracerebral hemorrhage: the ellipse (ABC/2) method yielded volumes smaller than those measured using the planimetric method. *Arq Neuropsiquiatr*. 71(8):540–544.

61. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke*. 2009;40(4):1082–90.

62. Hemphill III JC, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001 Apr;32(4):891-7.

63. Sakuta K, Yaguchi H, Sato T, Mukai T, Komatsu T, Sakai K, et al. The NAG scale can screen for hematoma expansion in acute intracerebral hemorrhage–a multi-institutional validation. *J Neurol Sci*. 2020 Jul 15; 414:116834.

64. Elkhatib THM, Shehta N, Bessar AA. Hematoma Expansion Predictors: Laboratory and Radiological Risk Factors in Patients with Acute Intracerebral Hemorrhage: A Prospective Observational Study. *J Stroke Cerebrovasc Dis*. 2019 Aug;28(8):2177-2186.

65. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, et al. Prevalence of elevated blood pressure in 563 704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007 Jan 1;25(1):32-8.

66. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke.* 1998;29:1160 –1166.

67. Dong H, Liu S, Jing L, Tian M, Sun J, Pang Y, et al. Hypertension among hemorrhagic stroke patients in northeast China: A population-based study 2017–2019. *Med Sci Monit.* 2020;26:e926581-1.

68. Liu J, Xu H, Chen Q, Zhang T, Sheng W, Huang Q, et al. Prediction of hematoma expansion in spontaneous intracerebral hemorrhage using support vector machine. *EBioMedicine.* 2019 May;43:454-459.

69.Song L, Qiu XM, Guo TT, Zhou H, Tang DF, Wang LS, et al. Association Between Anatomical Location and Hematoma Expansion in Deep Intracerebral Hemorrhage. *Front Neurol*. 2022 Feb 2;12:749931.

70. Roh D, Sun CH, Murthy S, Elkind MSV, Bruce SS, Melmed K, et al. Hematoma Expansion Differences in Lobar and Deep Primary Intracerebral Hemorrhage. *Neurocrit Care*. 2019 Aug;31(1):40-45.

71.Kurabe S, Okamoto K, Suzuki K, Matsuzawa H, Watanabe M, Suzuki Y, et al. The posterior limb of the internal capsule as the subcortical transitional zone of the anterior and posterior circulations: insights from human 7T MRI. Cerebrovasc Dis. (2016) 41:256–64.

72. Yaghi S, Dibu J, Achi E, Patel A, Samant R, Hinduja A. Hematoma expansion in spontaneous intracerebral hemorrhage: predictors and outcome. Int J *Neurosci*. 2014 Dec;124(12):890-3.

73. Ji N, Lu JJ, Zhao YL, Wang S, Zhao JZ. Imaging and clinical prognostic indicators for early hematoma enlargement after spontaneous intracerebral hemorrhage. *Neurol Res*. 2009 May;31(4):362-6.

74. Takeda R, Ogura T, Ooigawa H, Fushihara G, Yoshikawa S, Okada D, et al. A practical prediction model for early hematoma expansion in spontaneous deep ganglionic intracerebral hemorrhage. *Clin Neurol Neurosurg*. 2013 Jul;115(7):1028-31.

75. Boulouis G, Morotti A, Brouwers HB, Charidimou A, Jessel MJ, Auriel E, et al. Association Between Hypodensities Detected by Computed Tomography and Hematoma Expansion in Patients with Intracerebral Hemorrhage. *JAMA Neurol*. 2016 Aug 1;73(8):961-8.

76. Huttner HB, Steiner T, Hartmann M, Köhrmann M, Juettler E, Mueller S, et al. Comparison of ABC/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. *Stroke*. 2006;37:404–408.

77. Wei Y, Zhu G, Gao Y, Chang J, Zhang H, Liu N, et al. Island Sign Predicts Hematoma Expansion and Poor Outcome After Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis. *Front Neurol*. 2020 Jun 4;11:429.

78. Deng L, Zhang G, Wei X, Yang WS, Li R, Shen YQ, et al. Comparison of Satellite Sign and Island Sign in Predicting Hematoma Growth and Poor Outcome in Patients with Primary Intracerebral Hemorrhage. *World Neurosurg*. 2019 Jul;127:e818-e825.

79. Katsanos AH, Gupta H, Morotti A, Beshara S, Patil T, Al-Zahrani S, et al. Increased Prognostic Yield by Combined Assessment of Non-Contrast Computed Tomography Markers of Antithrombotic-Related Spontaneous Intracerebral Hemorrhage Expansion. *J Clin Med*. 2022 Mar 14;11(6):1596.

IMAGE GALLERY

DENSITY MARKERS:

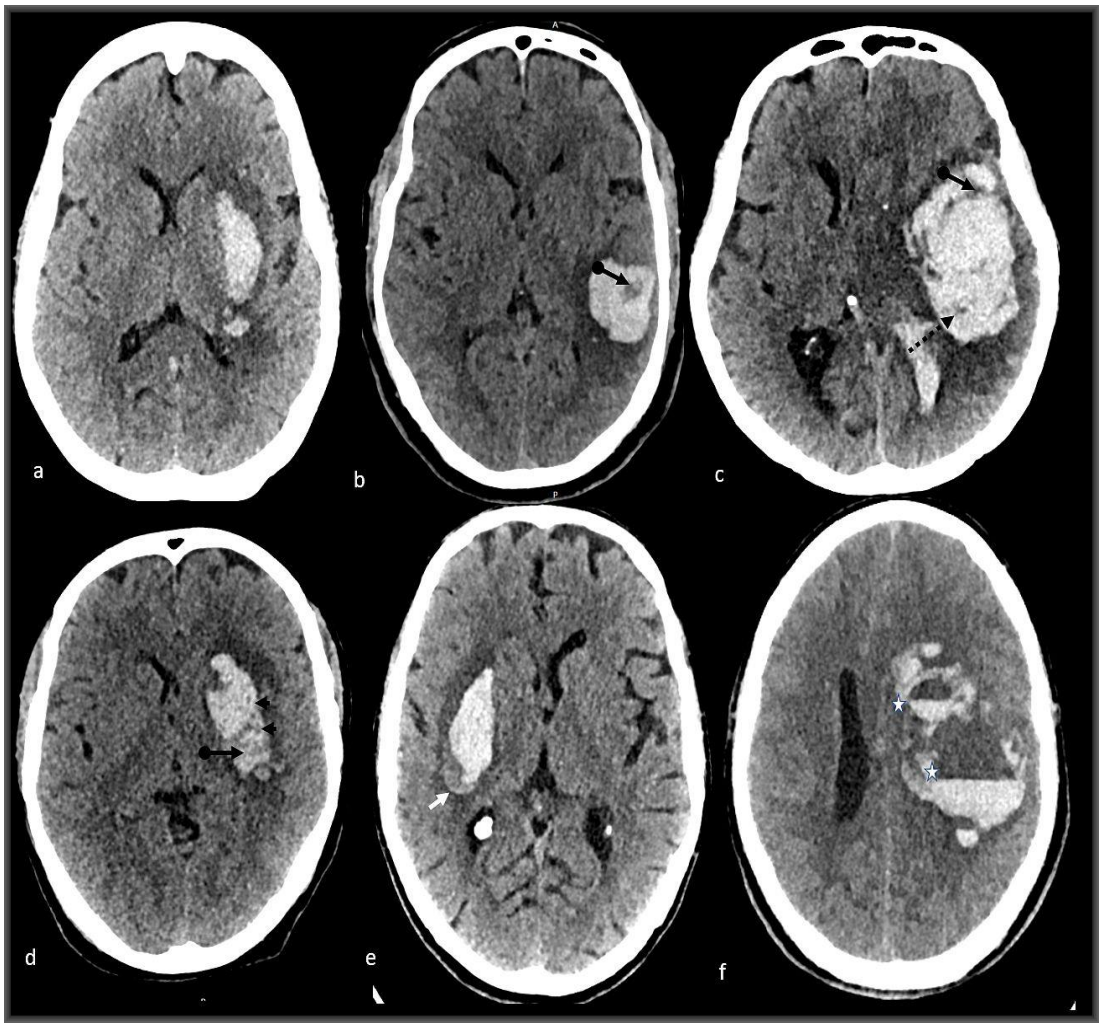

Figure 27 : NCCT axial section images (density markers) a) Shows left gangliopcapsular bleed with homogenous density and regular shape b) Left lobar bleed showing a blackhole sign (round ended black arrow) with a density difference of at least 28HU with the surrounding hematoma c) Left gangliocapsular bleed , showing a swirl sign; hypodensity connecting to the surface (round ended black arrow) and a black hole (dashed black arrow) sign d) Left gangliocapsular bleed showing three hypodensities in a section of maximum bleed area consistent with a heterogenous density sign (black arrow heads) e) Right gangliocapsular bleed showing a blend sign with a density difference of 18HU with the main hematoma (white arrow) f) Left lobar bleed showing fluid levels (white stars).

SHAPE MARKERS:

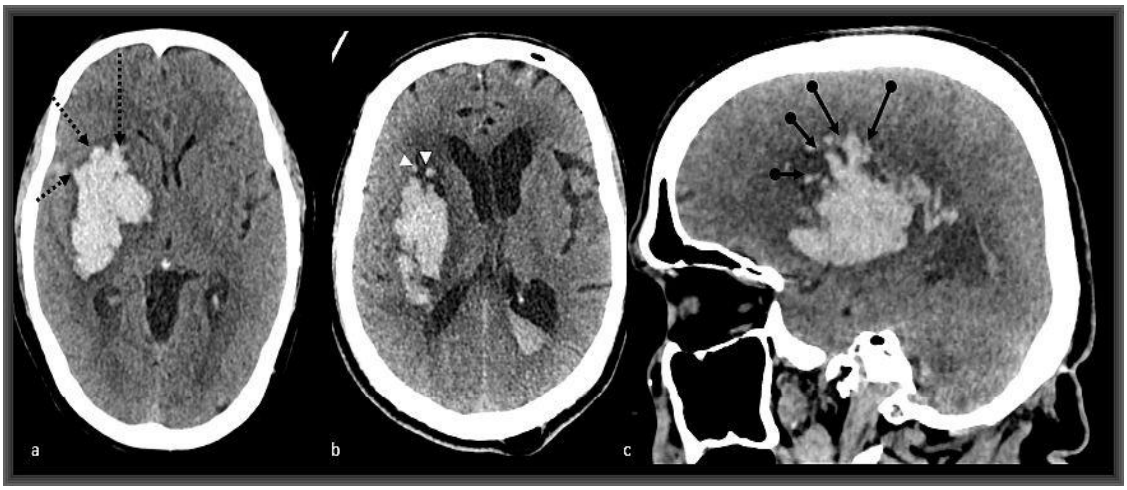

Figure 28: NCCT images (shape markers) a) Axial section image showing right gangliocapsular bleed with showing at least three margin irregularities consistent with irregular shape sign (dashed black arrows) b) Axial section image showing right gangliocapsular bleed with two foci of hemorrhages separated from the main hematoma consistent with satellite sign (white arrow heads) c) Sagittal section image showing at least four scattered hematomas connected to the main hematoma consistent with island sign (round ended black arrows).

REPRESENTATIVE CASES

Case 1:

A 58-year-old male patient presented to the emergency with complaints of left sided upper and lower limb weakness for 6 hours. NIHSS score was 12 and blood pressure was recorded as 200/110 mmHg. NCCT head showed hemorrhage in right thalamus with intraventricular extension. Baseline volume of the hematoma was 9.18cc. A follow up NCCT was done after 7 hours of baseline NCCT scan due to dip in the sensorium of the patient. Follow up NCCT showed increase in the volume of the hematoma ~51.61cc. Patient died after 4 days of admission (mRS =6)

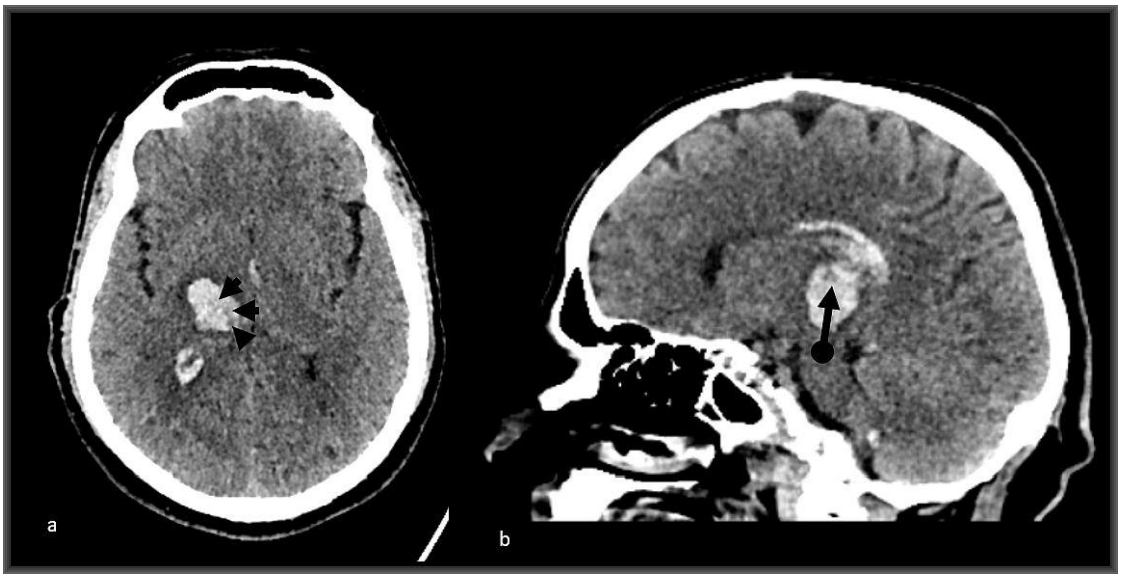

Figure 29.1: NCCT images (Imaging markers) a) Axial section showing right thalamic bleed with showing heterogenous density sign (black arrow heads) b) Sagittal section image showing swirl sign, hypodensity extending to the surface (round ended black arrows).

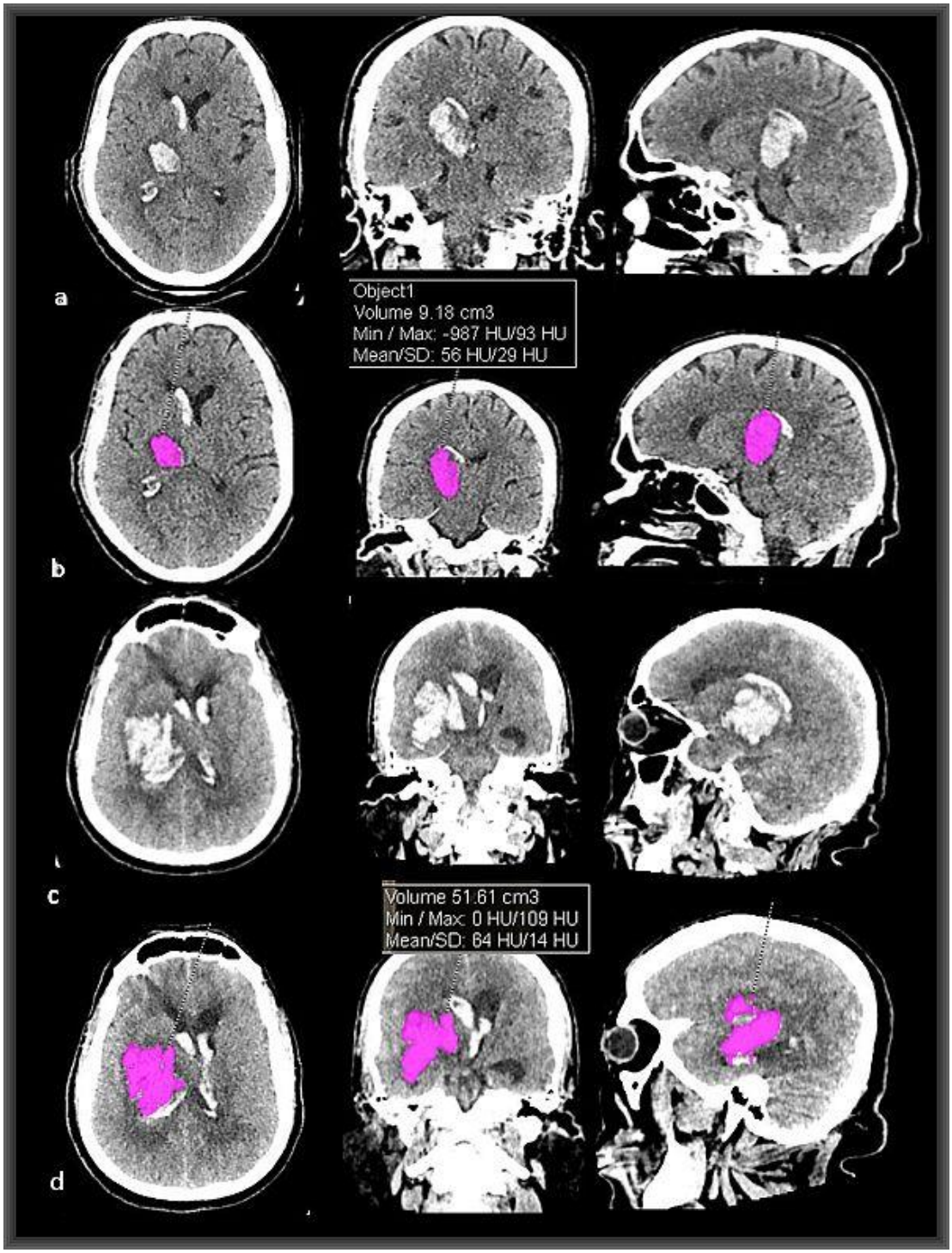

Figure 29.2: NCCT images with volume estimation a) and b) Baseline NCCT showing right thalamic bleed with intraventricular extension and volume calculated using region growing algorithm in Siemens synovia respectively c) and d) Follow up CT showing visually perceptible increase in the hematoma size and with volume estimation respectively.

Case 2:

A 55-year-old male patient presented with complaints of left sided upper and lower limb weakness for 2 hours. NIHSS was 10 with recorded blood pressure of 210/100 mmHg. NCCT head showed hemorrhage in right gangliocapsular region. Baseline volume of the hematoma was 80.5cc. Patient underwent a follow up NCCT after 8 hours. Follow up NCCT showed increase in the volume of the hematoma ~86.19cc. Patient died within 1 month of presentation (mRS =6).

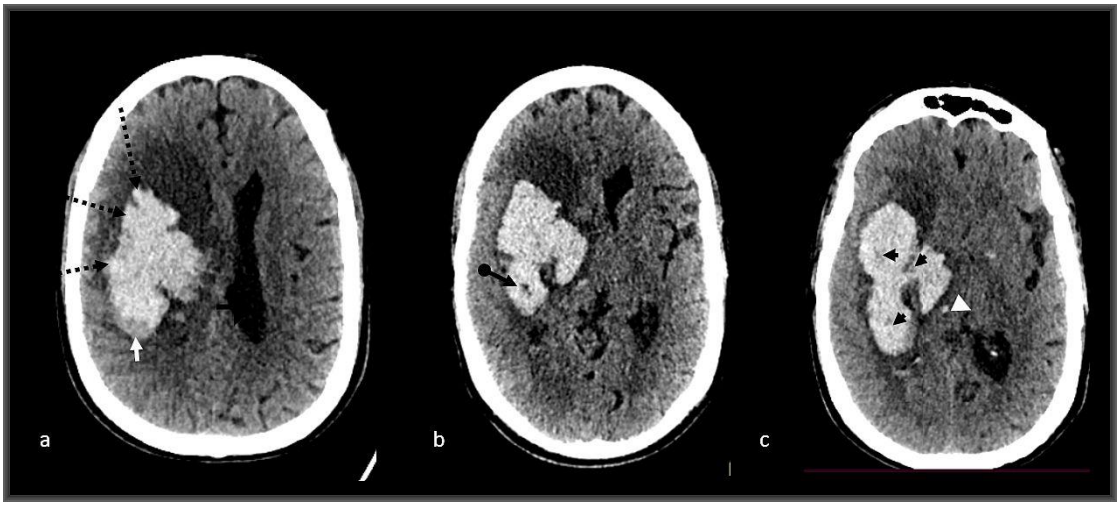

Figure 30.1: NCCT axial section images (imaging markers) a) Right gangliocapsular bleed with irregular shape sign (dashed black arrows) and blend sign (white arrow) b) Showing blackhole sign (round ended black arrow) c) Showing heterogenous density sign (black arrow heads) showing and showing a satellite sign (white arrow head).

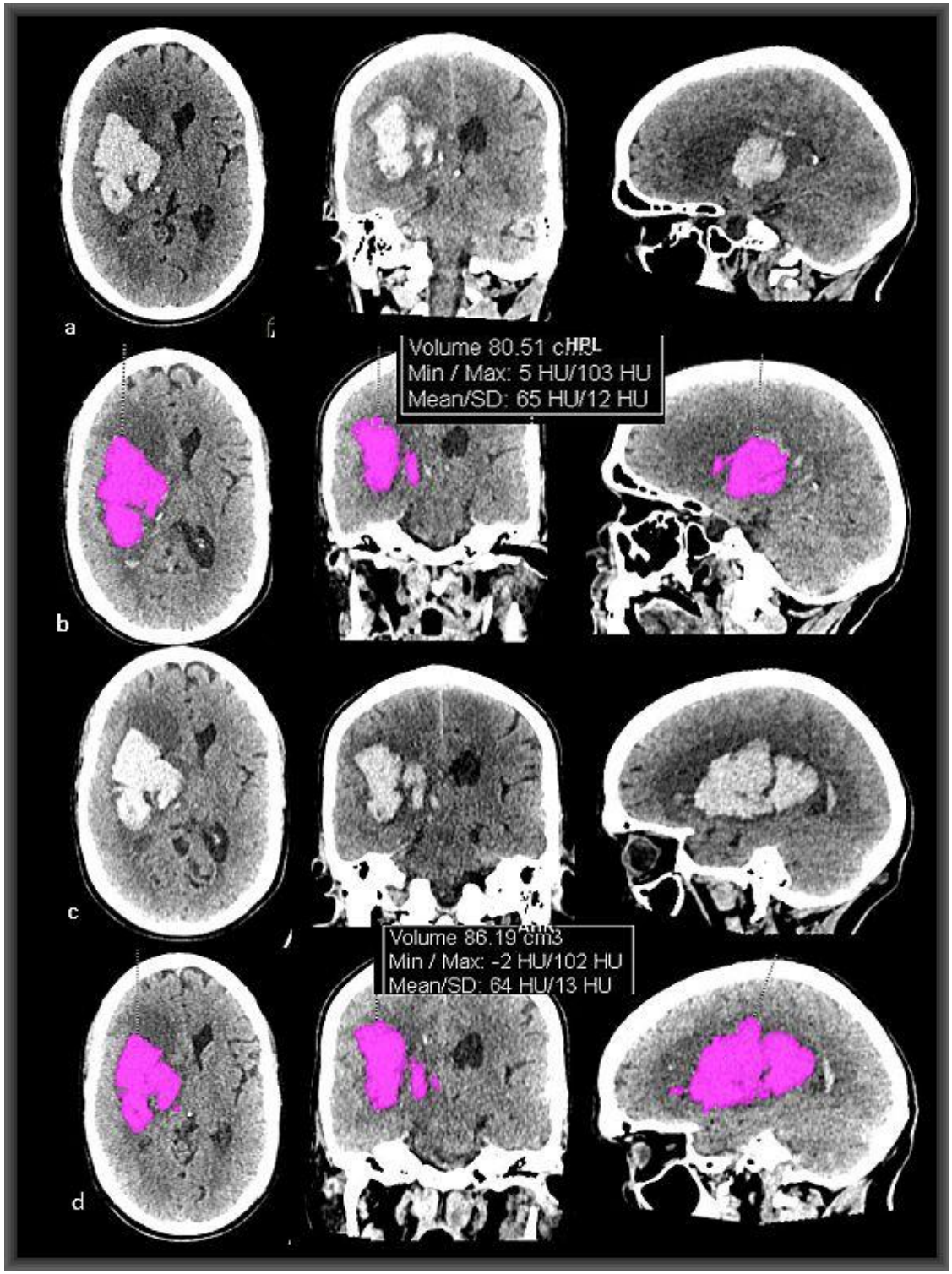

Figure 30.2: NCCT images with volume estimation a) and b) Baseline NCCT showing gangliocapsular bleed and volume calculated using region growing algorithm in Siemens synovia respectively c) and d) Follow up CT image showing increase in the hematoma size on plain scan and with volume estimation of the hematoma respectively.

Case 3:

A 34-year-old male patient presented with complaints of right sided upper and lower limb weakness for 4 hours. NIHSS was 10, BP was 190/100mmhg.NCCT head was done which showed hemorrhage in the left high parietal region. Baseline CT shows bleed volume of 30.08cc follow up CT shows a bleed volume of 36.61cc fitting under the definition of hematoma expansion. Patient died after 2 months of presentation (mRS =6).

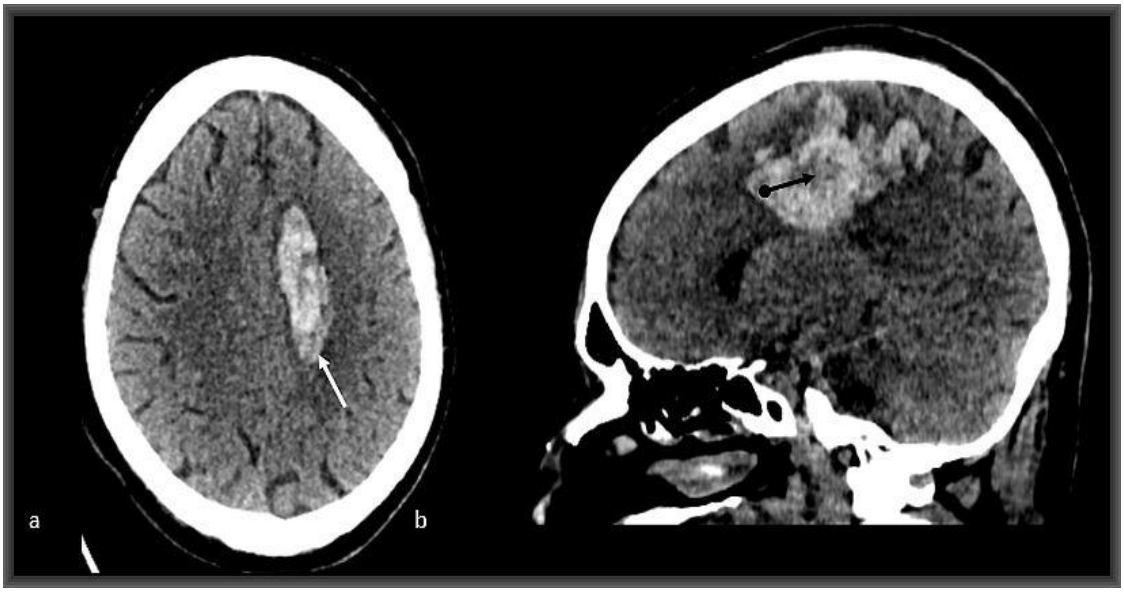

Figure 31.1: NCCT images (imaging markers) a) Axial CT image showing a blend sign (white arrow) in a left parietal bleed b) Sagittal CT image with a swirl sign (round ended black arrow).

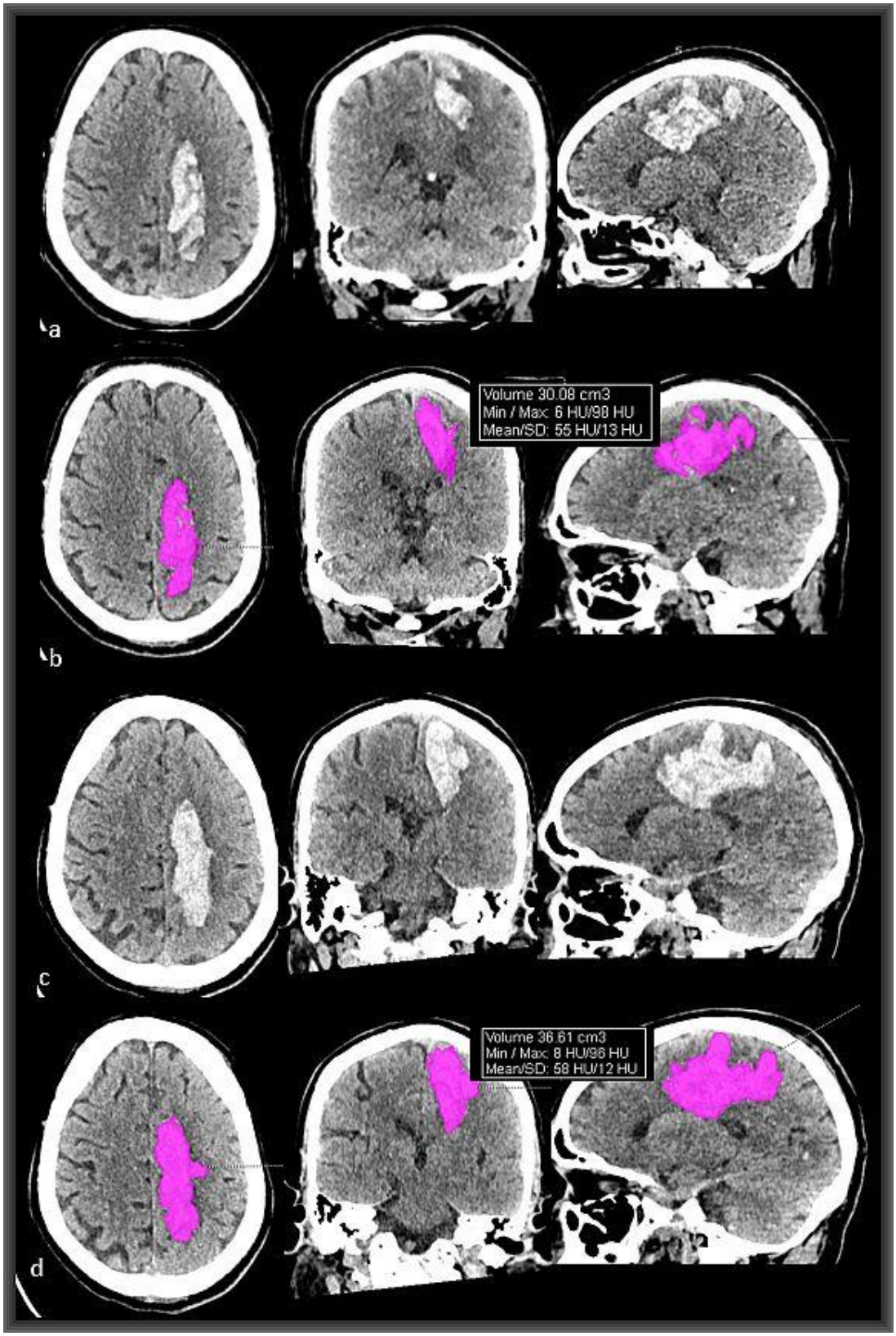

Figure 31.2: NCCT images with volume estimation a) and b) Baseline NCCT showing left lobar bleed and volume calculated using region growing algorithm in Siemens synovia respectively c) and d) Follow up CT image showing increase in the hematoma size on plain scan and with volume estimation of the hematoma respectively.

Case 4:

An 83-year-old female presented to emergency with acute onset right upper limb and lower limb weakness for 6 hours. Baseline NCCT showed a left thalamic bleed which was homogenous in density and shape and showed no expansion on follow up CT done after 24 hours. mRS at 90 days was 3.

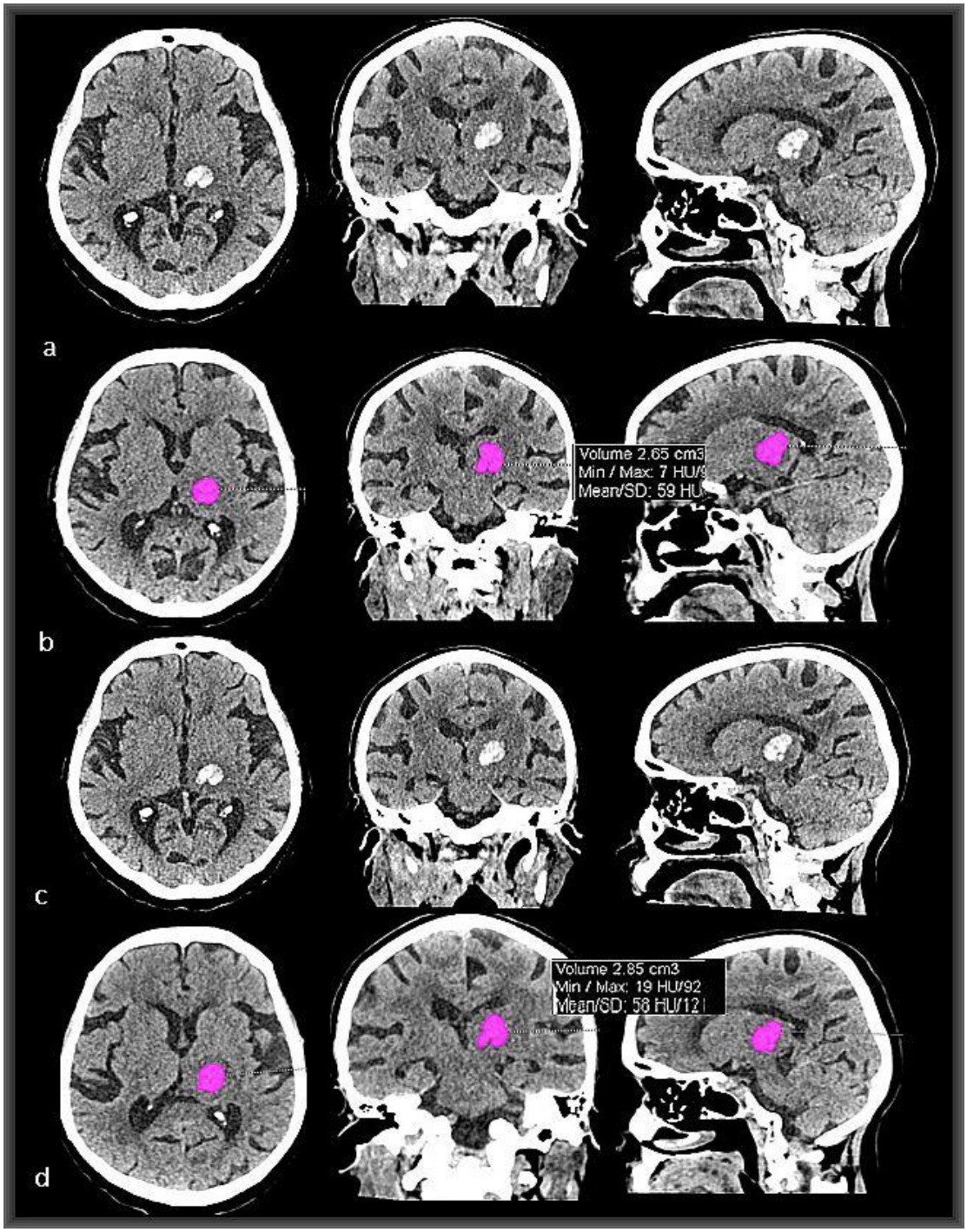

Figure 32: NCCT images with volume estimation a) and b) Baseline NCCT shows left thalamic bleed and volume calculation respectively. c) and d) Follow up CT shows hematoma without visually perceptible increase in volume on plain scan and on volume calculation respectively.

Annexure –I Ethical Clearance Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/ 3493 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3328**

Project title: **"Non contrast computed tomography markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Abbu**
Guide:	**Dr. Sarbesh Tiwari**
Co-Guide:	**Dr. Pushpinder S. Khera, Dr. Taruna Yadav, Dr. Suryanarayanan Bhaskar, Dr. Samhita Panda & Dr. Mayank Garg**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

ANNEXURE II

All India Institute of Medical Sciences Jodhpur, Rajasthan

Informed Consent Form

Title of the project: **Non contrast Computed Tomography Markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage.**

Name of the Principal Investigator: Dr. Abbu J Tel. No. 7892906308

Patient/Volunteer Identification No. : _____

I, _____ S/o or D/o _____

R/o _____

give my full, free, voluntary consent to be a part of the study " **Noncontrast Computed Tomography Markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage.**", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions. I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____(Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date : _____ _____

Place : _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date : _____ _____

Place : _____ Signature of Principal Investigator

Witness 1

_____

Signature

Name: _____

2. Witness 2

_____

Signature

Name: _____

All India Institute of Medical Sciences, Jodhpur, Rajasthan

informed consent form(hindi)

- थीसिस / निबंध का शीर्षक:
- पी. जी. छात्रकानाम: ABBU J टेल. न: :7892906308
- रोगी / स्वयंसेवक पहचान संख्या: _____

मैं, _____ पुत्र/पुत्री_____

निवास_____

अध्ययन "**Noncontrast Computed Tomography Markers for predicting hematoma expansion in spontaneous intracerebral hemorrhage** " मे भाग लेने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिकसहमतिदेताहूँ, जिसकी प्रक्रिया और प्रकृति मुझे अपनी पूरी संतुष्टिशह अपनी भाषा में समझाई गई है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है। मुझे बिना कोई कारण प्रकाशित कि ये किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार की जानकारी है।

मैं समझता हूं कि मेरे और मेरे मेडिकल रिकॉर्ड के बारे में एकत्रित की गई जानकारी को _____ (कंपनी नाम) या विनियामक प्राधिकरणों से जिम्मेदार व्यक्ति देख सकता है। मैं इन व्यक्तियों को अपने अभिलेखों कि जांच के लिए अनुमति देता हूं।

तारीख : _____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का

छाप_____

यह प्रमाणित किया जाता है कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है।

तारीख : _____

ANNEXURE III

PATIENT INFORMATION SHEET

1. Risks to the patients: There's no risk of death or any disability resulting directly due to imaging. No interventions or life-threatening procedures will be done. CT is a non-invasive modality.
2. Confidentiality: Your participation will be kept confidential. Your medical records will be treated with confidentiality and will be revealed only to doctors/ scientists involved in this study. The results of this study may be published in a scientific journal, but you will not be identified by name.
3. Provision of free treatment for research-related injury: Not applicable.
4. Compensation of subjects for disability or death resulting from such injury: Not applicable.
5. You have complete freedom to participate and to withdraw from the research at any time without penalty or loss of benefits to which you would otherwise be entitled, including subsequent medical treatment or relationship with the treating physician.
6. Your participation in the study is optional and voluntary.
7. The copy of the results of the investigations performed will be provided to you for your record.

रोगी सूचना पत्रक

1. मरीजों के लिए जोखिम इमेजिंग के कारण मौत या किसी भी विकलांगता का कोई खतरा नहीं है। कोई हस्तक्षेप या जानलेवा प्रक्रिया नहीं की जाएगी।
2. गोपनीयता आपकी भागीदारी गोपनीय रखी जाएगी। आपके मेडिकल रिकॉर्ड का उपयोग गोपनीयता के साथ किया जाएगा और इस अध्ययन में शामिल डॉक्टरों / वैज्ञानिकों के लिए ही खुलासा किया जाएगा। इस अध्ययन के परिणाम वैज्ञानिक पत्रिका में प्रकाशित किए जा सकते हैं लेकिन आपको नाम से पहचाना नहीं जाएगा।
3. अनुसंधान से संबंधित चोट के लिए नि:शुल्क उपचार की व्यवस्था लागू नहीं है।
4. ऐसी चोट से होने वाली विकलांगता या मृत्यु के लिए मुआवजा लागू नहीं है।
5. आपके पास किसी भी समय जुर्माना या नुकसान के बिना अनुसंधान से वापसी की पूर्ण स्वतंत्रता है।
6. अध्ययन में आपकी भागीदारी वैकल्पिक और स्वैच्छिक है।
7. किए गए जांच के परिणामों की रिकॉर्ड आपको प्रदान की जाएगी

PATIENT PROFORMA

Date: _____ Patient ID: _____

Name: _____

Age: _____ Mobile number: _____

Address: _____

CLINICAL DETAILS.

Presenting complaints:

Comorbidities: Hypertension ☐ Diabetes mellitus ☐

History of trauma: Yes ☐ No ☐

History of Surgery for Intracranial bleed : Yes ☐ No ☐

Recent NCCT head done (if so when?)_____

IMAGING FINDINGS

<table>
<tr><th>BASELINE SCAN(<12hrs)</th><th>FOLLOW UP SCAN(<48hrs)</th><th>FUNCTIONAL OUTCOME</th></tr>
<tr>
<td>DENSITY MARKERS:

Swirl sign ☐
Black hole sign ☐
Blend sign ☐
Fluid level ☐
Others ☐
1._____
2._____
3._____

SHAPE MARKERS

Irregular shape ☐
Island sign ☐
Satellite sign ☐
Others ☐
1._____
2._____
3._____

HEMATOMA VOLUME(V_b):
_____ml</td>
<td>HEMATOMA VOLUME(V_f)

_____ml

HEMATOMA EXPANSION:

1.Absolute increase = V_f-V_b
_____ml

2.Relative increase = V_f-V_b/V_b
_----------%</td>
<td><table><tr><th>1 Month</th><th>3 Months</th></tr><tr><td>MRS score</td><td>MRS score</td></tr></table></td>
</tr>
</table>