ASSOCIATION BETWEEN BRAIN COMPUTER TOMOGRAPHY FINDINGS AND FUNCTIONAL OUTCOMES AMONG ADULTS WITH NON-TRAUMATIC INTRACRANIAL HEMORRHAGE AT MOI TEACHING AND REFERRAL HOSPITAL

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A research thesis submitted to the School of Medicine in partial fulfillment of the award of the degree of Master of Medicine in Radiology and Imaging of Moi University.

DECLARATION

I declare that this is my original work, and it has not been presented in any other university or institution for an award of a degree or any academic credit. No part of this work may be reproduced or transmitted in any form without prior permission from the author or Moi University.

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DEDICATION

I dedicate this work to my two beautiful daughters Alexina and Angel who have not enjoyed the presence of their mother for many years. As you grow up, I hope you will one day understand I had to do this and that I love you so much despite never being there most of the time to watch you grow.

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ABBREVIATIONS

CT	Computer Tomography
CTA	Computer Tomography Angiography
NECT	Non-Enhanced Computer Tomography
DALYs.	Disability Adjusted Life Years
DSA	Digital Subtraction Angiography
dIVH	Delayed Intraventricular Hemorrhage
GCS	Glasgow Coma Scale
HIC	High Income Countries
ICH	Intracerebral Hemorrhage
IVH	Intraventricular Hemorrhage
LMIC	Low- and Middle-Income Countries
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified RANKIN Scale
MTRH	Moi Teaching and Referral Hospital
pHE	Perihematomal Edema
WHO	World Health Organization

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OPERATIONAL DEFINITION OF TERMS

Adult in this study will be defined as any person above the age of 18 years according to (WHO, 2020).

ICH in this study refers to intracerebral hemorrhage which is parenchymal.

Functional outcomes are defined as patients 'ability to perform their day-to-day activities and is measured using the modified Rankin scale.

Non-traumatic ICH any intracerebral hemorrhage not associated with trauma.

ABSTRACT

Background: Intracranial hemorrhage (ICH) is an important medical event associated with stroke globally. Worldwide the incidence and mortality of ICH is increasing in the low- and middle-income countries as compared to the high-income countries. Non-contrast computerized tomography (CT) is the most widely used and readily available tool for diagnosis of intracranial hemorrhage. It has a rapid acquisition of images and high accuracy for detecting intracranial hemorrhage. The modified Rankin Scale is a reliable, easy to use tool for assessing the functional outcomes of post-stroke cases. There is paucity of data on the association of brain CT findings and functional outcomes in our setting. Therefore, this study seeks to describe brain CT findings and functional outcomes among adults with non-traumatic intracranial hemorrhage.

Objectives: To describe brain CT findings, functional outcome and determine their associations among adults with non-traumatic intracranial hemorrhage at MTRH.

Methods: This study was a prospective cohort study conducted among adult patients at MTRH from December 2021 to November 2022. A census sampling was used to recruit 97 participants who were eligible. A data collection tool was used to record age, gender, brain CT findings and outcomes at 30 days. The modified Rankin Scale was used to score the 30-day functional outcome. The participants were scanned using the Siemens 32 slice CT. Continuous variables were analyzed using mean, median, and their corresponding standard deviation and interquartile ranges while categorical variables were summarized as proportions and percentages. The Mood's median test, Chi square test and the logistics regression models were used to test for association between Brain CT findings and functional outcomes. A P-value of less than 0.05 was considered significant.

Results: Most of the study participants were male at 52.6%, aged more than 50 years with a mean age 59.09 (±14.43). Intracerebral hemorrhage was supratentorial on brain CT in 84 (85.7%) study participants. ICH was observed in the lobar (44.3%), deep lobar (41.2%), cerebellar (9.3%), brain stem (3.1%) and the 4^{th} ventricle (2.1%). 73.2% of the study participants had hematoma volume of less than 30ml, 69.1%, 89.7% and 17.5 % had associated mass effect, edema, and cerebral herniation respectively. The median modified ranking score was 4 (IQR: 3-6) and 57.7% of the participants had poor outcome. On multivariable analysis, the presence of mass effect (OR=40.06, CI: 1.61 - 994.90, p-value=0.024) and cerebral herniation (OR= 81.79 CI: 8.25 - 810.62, p-value <0.001) were statistically significant predictors of 30-day mortality.

Conclusion: Majority of the patients had intracerebral hemorrhage in the supratentorial region and less than 30 ml hematoma volume. The median modified ranking score was 4 and slightly more than half of the participants had poor functional outcome. Hematoma volume more than 30 ml, presence of mass effect and herniation were significantly associated with poor outcome and higher odds observed with mass effect and herniation.

Recommendation: A longer duration study with more participants to ascertain the strength of association.

CHAPTER ONE: BACKGROUND

1.1 Introduction

Intracranial hemorrhage is defined as the accumulation of blood within the cranium that could either be within the cerebrum/brain parenchyma (intracerebral hemorrhage) or within the meningeal spaces. Intracranial hemorrhage can either be secondary to trauma or non-traumatic causes. Non-traumatic intracranial hemorrhage is also known as spontaneous intracerebral hemorrhage, it may occur as intra-axial (intracerebral/parenchymal) or extra-axial (epidural, subdural or arachnoid) hemorrhage. Non-traumatic hemorrhage is caused by several pathologies, including hypertension, cerebral aneurysms, cerebral amyloid angiopathy, hemorrhagic conversion of ischemic infarction, cerebral vascular malformations, vasculitis, and venous sinus thrombosis among many others (Heit et al., 2017).

Intracerebral hemorrhage is an important medical event that accounts for up to 15 % of strokes (C. J. van Asch et al., 2010) and other acute neurological deficiency with associated significant morbidity and mortality (Heit et al., 2017). Over the last 20 years, stroke has been the second leading cause of death and disability globally with the global numbers of deaths and disability adjusted life years (DALYs) due to hemorrhagic stroke being higher than those of ischaemic stroke. According to the global burden of disease (GBD), stroke was responsible for 116.4 million DALYs and 5.5 million deaths globally in 2016 (C. O. Johnson et al., 2019). These has recently increased to 143 million DALYs and 6.55 million deaths and an increase in the stroke due to intracerebral hemorrhage to 27.9% (Feigin et al., 2021).

There were about 80 million prevalent cases with 13.7 million new cases of stroke globally in 2016 and approximately 41 million were women. Of the total number of prevalent strokes, 84·4% were ischaemic strokes. Globally, the age-standardized rate

of deaths due to stroke decreased by approximately 36% from 1990 to 2016. The largest decrease was noted among the high-income Asia Pacific region and no significant change among the southern sub-Saharan Africa. Similar results were seen for DALYs, hemorrhagic and ischaemic stroke (C. O. Johnson et al., 2019). In 2019, a lower global incidence of 12.2 million stroke cases was reported in the period 1990 to 2019. In addition, it was reported that deaths from stroke increased by 43% while DALYs increased by 32% (Feigin et al., 2021).

Stroke incidence and mortality rates have been decreasing in the high-income countries as compared to the middle- and low-income countries. The burden of stroke in Africa is high. Southern sub-Saharan Africa was one of the 2 regions with increasing stroke incidence, increasing mortality rates and increasing DALYs. Much of the increasing incidence and persistent mortality in this region is due to higher rates of intracerebral hemorrhage (ICH) in Africa than in the rest of the world (Krishnamurthi et al., 2013).

Hemorrhagic stroke is associated with a higher morbidity and mortality than ischemic stroke, with hemorrhagic stroke accounting for 35% of all strokes in Africa, as compared to 10%–20% in higher-income regions of the world (Saylor & Vora, 2020). The stroke epidemic in Africa needs to be addressed for better understanding of the disease, identify its primary drivers and design effective interventions to both prevent stroke and improve its outcomes in this region (W. Johnson et al., 2016).

A comparative retrospective study conducted in Belgium and Guinea showed that the patients with spontaneous intracerebral hemorrhage were younger and had larger hematoma volumes as compared to those in Belgium with an associated higher mortality rate (Damien et al., 2021).

Ndubuisi et al (2019) in Nigeria conducted a retrospective analysis of patients with spontaneous intracerebral hemorrhage where a good GCS at admission and young age were predictors of good outcome. Unlike in other studies, anatomical location of the hemorrhage did not have any impact on 6 months' mortality (Ndubuisi et al., 2019).

In prospective hospital-based study conducted in Mulago national referral and teaching hospital, Uganda showed high early mortality rates and poor functional outcomes associated with acute stroke. The independent predictors of mortality and poor functional outcome in this study were severe stroke at admission, unconsciousness, high fasting blood sugar, old age and history of hypertension (Nakibuuka et al., 2015).

Functional outcome can be defined as patients' ability to perform their day-to-day activities and does not imply clinical or symptom resolution.

Studies have been conducted to assess functional outcome of stroke patients before and after a neurological event (Quinn et al., 2017). This has been done widely using the modified Ranking scale. The Rankin scale was first introduced in 1957 by Dr John Rankin and later modified in the 1980s by Charles Warlow. It's a validated, easy to use tool that has 7 main parameters that assess the functional outcomes. These range from no symptoms to death. Neuroimaging findings in the acute phase of stroke has an influence on the functional outcomes and disability of patients with stroke.

Neuroimaging is essential in the diagnosis, treatment, prevention of complications and follow-up of patients who present with intracranial hemorrhage (Merhemic et al., 2018). It is also important for the health care provider to identify the cause of hemorrhage and to understand the location and severity of hemorrhage, the risk of impending cerebral injury, and to guide often emergent patient treatment.

Several imaging modalities are used in the diagnosis of intracranial hemorrhage. Brain computer tomography and Magnetic resonance imaging are the first and widely used modalities for the diagnosis of intracranial hemorrhage. Other modalities that can be used include: Computer Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) and Digital subtraction angiography (DSA) (C. J. J. van Asch et al., 2015).

Non-contrast computerized tomography is the most widely used and readily available tool for diagnosis of intracranial hemorrhage (Kranz et al., 2018). Generally, CT is associated with rapid acquisition of images, with minimal contraindications and high accuracy for detecting intracranial hemorrhage. It also gives the basic characteristics of the hematoma and a quick assessment of the age of the hematoma.

The appearance of intracranial hemorrhage on non-contrast enhanced CT changed with the age of the hematoma. Initially the hematoma appears as a homogenous hyper-attenuation NECT. The hyper-attenuation results from the increasing protein density within the hematoma. As the hematoma matures, there is progressive clot formation and retraction with fluid loss, which then causes the hyper-attenuation to increase from a range of 40–80 HU to 80–100 HU (Parizel et al., 2001).

In the acute phase, the presence of fluid-fluid levels and/or hypo-attenuated areas inside the hematoma may represent a hyperacute hematoma, active bleeding (with the new incoming blood corresponding to these hypoattenuating areas), and/or the presence of coagulation disorder (acquired or congenital).

Typically, clots become isodense to brain on CT images at 8–14 days after hemorrhage, then progressively hypodense after 2–4 weeks and, finally, at the late

subacute and chronic phases, they are usually hypodense approaching the attenuation of cerebrospinal fluid (CSF).

The changes seen on brain CT or MRI are attribute to hemoglobin products, mainly hemosiderin and hematoidin. The hemosiderin forms within histiocytes that have phagocytized red blood cells (RBCs) and takes the form of ferritin granules that stain positively for iron. As oxyhemoglobin is liberated from the RBCs and becomes deoxygenated, methemoglobin appears. This begins within a few days and imparts a brownish hue to the periphery of the hematoma. Phagocytosis of red cells begins within 24 h, and hemosiderin is first observed around the margins of the hematoma in 5 to 6 days. The hematoma then changes color gradually over a few weeks from dark red to pale red, and the border of golden-brown hemosiderin widens. In 2 to 3 months, larger clots are filled with a chrome-colored thick fluid, which is slowly absorbed, leaving a smooth-walled cavity or a yellow-brown scar. The iron pigment (hematin) becomes dispersed and studs' adjacent astrocytes and neuron. This may persist well beyond the border of the hemorrhage for years (Ropper et al., 2014).

Over time, the surrounding edema and mass effect increases. Edema is worse in the first 48 -72 hours and increases over the first two weeks with activation of the inflammatory reaction. (Vilela & Wiesmann, 2020)

In the subacute phase, there is a thin, irregular ring enhancement seen on contrast enhanced images. This feature is seen due to disruption of the blood brain barrier and inflammation. Edema and mass effect begin to decrease in the third week or sub-acute phase.

In the late and chronic phase of the hematoma, there is reduction in edema and mass effect. As the blood ages, a hemosiderin scar is seen as a hypodense lesion on CT.

Chronic hematomas are associated with brain atrophy and ex vacuo dilatation of the ventricles. There may be calcifications and peripheral gliosis.

In this study, the patients included were in the acute phase hence a non-contrast enhanced CT will be used for assessment. (Vilela & Wiesmann, 2020)

As the hematoma ages the density decreases because of clot lysis and liquefaction. These process occurs in a centripetal manner at an estimated rate of 0.7 -1.5 HU per day (Parizel et al., 2001).

Computerized tomography angiography is also increasingly being used as a diagnostic tool for diagnosis in the acute setting. CTA aids in ruling out vascular abnormalities and secondary causes of intracranial hemorrhage. Approximately 15% of patients with ICH will show any underlying vascular etiology on CTA and this will change the acute management of these patients. With CTA one can demonstrate if there is ongoing bleeding with the help of the “spot sign” that is due to extravasation of contrast, and this helps to identify patients at risk of hematoma expansion, poor outcome, and mortality.

MRI works in a similar manner to CT in an acute setting. It aids in detecting the underlying secondary causes such as tumours, hemorrhagic transformation of ischaemic stroke. MRI can also be used for patients with a poor renal function since one can use the Time-of-Flight MR angiography for cerebral vascular analysis. The outcomes of intracranial hemorrhage vary greatly and depend on the location of the hematoma, the volume of the hematoma, extension into ventricles, presence of increased intracranial pressure and other factors. Early detection of patients at risk of developing worse outcomes is crucial in directing the management and follow-up of these patients (Al-Mufti et al., 2018).

Initial hemorrhage may cause extravasation of blood leading to localized edema. Progressive bleeding causes hematoma expansion and edema which greatly determine the patient outcome. Hematoma expansion may lead to increased intracranial pressures and tissue displacement with subsequent potential herniation. These contribute to increased morbidity and mortality of these patients and neuroimaging can play a great role in follow up and contribute to better outcomes.

1.2 Problem Statement

Intracranial hemorrhage is a major contributor of the global incidence of stroke accounting for about 15% of the cases (Steiner et al., 2014). It estimated that in the last two decades, there was a potential 400% increase in the burden of stroke in Africa compared to economically rich countries (Connor, 2004). In addition, despite a declining trend of stroke incidence and death rates in the developed world there is an increasing trend in Africa (Feigin, 2005; Moran et al., 2013). However, these reported disease burden measures are mainly model based estimates used to attain the global burden of disease. In Kenya, it was estimated that stroke had a prevalence of 0.6% to 7.1% of which ischemic strokes account for 48% to 85% of the stroke cases (Waweru & Gatimu, 2021).

For Africa to realize reductions of stroke and specifically non-traumatic ICH, in line with sustainable development goals (SDG) number 3, it is important to obtain accurate disease burden estimates and patterns of non-traumatic ICH that would inform policy and patient care. However, there exists paucity of surveillance data specifically on stroke from Africa (Kengne & Anderson, 2016). This could be partially linked to the continuous battle against communicable diseases in the

continent, hence limited allocation of the existing constrained resources to non-communicable diseases (Bonita & Truelsen, 2003; Unwin et al., 2001).

ICH is a high burden condition that needs multispecialty approach to management. Patients with ICH need prompt imaging services, urgent neurosurgical care and even ICU/HDU care in the severe cases. It also has the potential to bring about lifetime disability and hence cause great financial and emotional strain and burden to the patient and caregivers. Early diagnosis and identification of ICH and prompt management has the potential of mitigating the disability or death brought about by this condition. Therefore, there is limited understanding of the burden, patterns, and patient outcomes of non-traumatic intracranial hemorrhage in Africa.

This study therefore seeks to describe the brain CT findings of the patients presenting with ICH and to determine the CT features associated with poor outcomes thereby guide management protocols.

1.3 Justification

Reviewed literature has shown that stroke, specifically intracranial hemorrhage, is scarcely reported from Africa (Feigin et al., 2009; Kengne & Anderson, 2016; Mensah, 2008). In addition, the role played by neuroimaging in the management of the acute phase of intracerebral hemorrhage cannot be understated (Macellari et al., 2014). Specifically, radiology is used in the diagnosis, management and follow up of patients with ICH (Hegde et al., 2020). Therefore, using radiology to describe the patterns and outcomes of non-traumatic ICH in Kenya will contribute to the body of knowledge and provide additional data from Africa which is currently scarce. Such information can be used to greatly improve patient care, giving patients an opportunity for better outcomes hence achievement of SDG 3 target on reduction of

premature mortality from non-communicable diseases through prevention and treatment is facilitated.

Moreover, clinical scales such duration of hospitalization, Glasgow Coma Scale (GCS) and ranking score play an important contributory role to the patient assessment and management (J. Claude Hemphill et al., 2001). This study proposes to evaluate radiological findings of patients with intracranial hemorrhage at MTRH while referring to their clinical grading scales and make follow up assessments.

Therefore, this study will offer comparative data on patterns of intracranial hemorrhage among patients hence contribute to the generalizability of findings from Africa, and more specifically Kenya. The results from my study will enable us to know the brain CT findings that are probable predictors of poor outcomes, with this knowledge, radiologists are able to report on these findings and clinician should pay attention to the same findings and make follows to ensure the patients have the best outcomes possible.

1.4 Research Question

What are the brain CT findings and associated functional outcome among adults with non-traumatic intracranial hemorrhage at Moi Teaching and Referral Hospital.

1.5 Objectives

1.5.1 Broad objective

To describe brain CT findings and functional outcome among adults with non-traumatic intracranial hemorrhage at Moi Teaching and Referral Hospital.

1.5.2 Specific objectives

1. To describe the brain CT findings among adults with non-traumatic intracranial hemorrhage at Moi Teaching and Referral Hospital.
2. To describe the functional outcomes among adults with non-traumatic intracranial hemorrhage at Moi Teaching and Referral Hospital.
3. To determine the association between brain CT findings and functional outcomes among adults with non-traumatic intracranial hemorrhage at Moi Teaching and Referral Hospital.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

2.1.1 Burden of Disease

According to WHO stroke is the second leading cause of death globally after ischemic heart disease and the third leading cause of disability ("WHO | Global Health Estimates," 2018). Stroke can either be hemorrhagic, which account for 15% of all strokes, or ischemic. Globally there are 87% stroke related deaths and of these, 70% occur in the low and middle-income countries (LMIC) (Owolabi et al., 2015). The stroke incidence in LMIC is increasing while that in high-income countries is decreasing (Krishnamurthi et al., 2020; Owolabi et al., 2015).

The 2019 GBD analysis showed that 27.9% of the stroke case were attribute to intracerebral hemorrhage with an increase in stroke prevalence and incidence rates among people younger than 70 years of age (Feigin et al., 2021).

According to a systematic review done by Owolabi et al., (2015), 34% of strokes in the LMIC are hemorrhagic. In LMIC, 84% of patients diagnosed with stroke die within three years of diagnosis and 16% in HIC. In a systematic review and metanalysis conducted to assess the functional outcome, case fatality and incidence of intracerebral hemorrhage in relation to sex, age and ethnic origin found an overall incidence of 24.6 per 100,000 person years (95% CI 19.7 – 30.7), the incidence had no sex predilection. The study showed an increase of incidence ratio with age from 0.1for those less than 45 years of age to 9.6 for those more than 85 years of age. This study also shows a difference in incidence of intracerebral hemorrhage per 100,000 person years with regards to ethnicity as follows 24.2 in whites, 22.9 in blacks, 19.6 in Hispanics and 51.8 in Asians (Asch et al., 2010).

In a population-based study conducted among white, black and Hispanic Americans to evaluate the incidence of deep vs lobar intracerebral hemorrhage found that the Blacks and Hispanics had a greater risk of primary intracerebral hemorrhage than whites. In this study the annual incidence of intracerebral hemorrhage was 30.9 per 100,000 with men having a higher risk than women (Labovitz et al., 2005).

The term spontaneous ICH was preceded by the terms, secondary and primary intracranial hemorrhage, which were used to denote whether the etiology of the hemorrhage could be detected or not. Traditionally, primary ICHs are attributed to vascular changes due to hypertension, atherosclerosis, and cerebral amyloid angiopathy. Secondary intracranial hemorrhages are hematomas caused by: cerebral arteriovenous malformations, cavernous malformations, and arterial aneurysms, intracranial venous thrombosis or hemorrhagic transformation of cerebral infarction, cerebral tumors, and illicit drug use. Additionally, hemorrhages caused by coagulation deficiencies secondary to anticoagulant/thrombolytic therapy are sometimes regarded as secondary intracranial hemorrhage (Qureshi et al., 2001).

It is estimated that early mortality due to spontaneous intracranial hemorrhage is about 40% at 1 month, which is relatively high, and further increases to about 60% at year 1 (Sacco et al., 2009). Results from previous studies have indicated that the following factors contributing to increased spontaneous intracranial hemorrhage mortality include increasing age, low Glasgow Coma Scale (GCS) score, infratentorial intracranial hemorrhage, larger hematoma volume and intraventricular hemorrhage (Fallenius et al., 2017; Meretoja et al., 2012; Mustanoja et al., 2015; Reinikainen et al., 2012). However, most of these studies focused on short-term mortality.

High blood pressure, body mass index (BMI), Plasma glucose level, smoking and air pollution are the five leading risk factors for stroke as outline by Feigin et al (2021).

2.1.2 Causes of Intracranial Hemorrhage

Non-traumatic intracranial hemorrhage also known as spontaneous intracranial hemorrhage is mostly intracerebral but may also involve the intraventricular, subarachnoid, and subdural spaces like traumatic intracranial hemorrhage. Rarely does it involve the epidural space (Caceres & Goldstein, 2012; Rajashekar & Liang, 2021).

Some of the causes of non-traumatic intracranial hemorrhage include:

- Hypertension
- Aneurysms
- Cerebral amyloid angiopathy
- Cerebral vascular malformations such as:
    - Arteriovenous malformations
    - Arteriovenous fistulas
    - Cavernous malformations
    - Capillary telangiectasis and
    - Developmental venous malformations
- Hemorrhagic infarction (venous sinus thrombosis)
- Brain tumors
- Bleeding disorders
- Central nervous system infections (e.g., herpes simplex encephalitis)
- Vasculitis
- Drugs such anticoagulants.

Typically, damage to the walls of small cerebral blood vessels located in the deep brain structures lead to occurrence of spontaneous intracerebral hemorrhage. These small arteries and arterioles are in most cases branches of large vessels of the circle of Willis that supply blood to the basal ganglia, thalamus, pons, and deep portions of the cerebellum. In most cases the occurrence of intracerebral hemorrhage has been linked to hypertensive cerebral vasculopathy and cerebral amyloid angiopathy which preferentially affect vessels of this size (Aguilar & Freeman, 2010).

Hypertension is one of the leading causes and main risk factors for the development of spontaneous ICH. Specifically, uncontrolled hypertension is the most common risk factor for spontaneous intracranial hemorrhage (Ariesen et al., 2003; Meretoja et al., 2012). Hypertension causes damage to the arterial wall which leads to either ischaemic or hemorrhagic stroke. The commonly affected locations are the basal ganglia, pons, thalami, and cerebellum. Hypertensive intracranial hemorrhage or intraparenchymal hemorrhage affects older patients aged 60-70 years (Qureshi et al., 2001; Wekesa et al., 2012).

For a long period of time, spontaneous intracerebral hemorrhage has been attributed to the rupture of microaneurysms on small, deep vessels. C.M. Fisher termed “lipohyalinotic change” as a combination of hyalinization and lipid deposition in the vessel wall due to the pathophysiological mechanism by which hypertension causes putamen and thalamic hemorrhage. He further observed that these are sites of vessel rupture and not microaneurysms that also result from chronic hypertension was only apparent after painstaking examination of hundreds of microscopic serial sections (Fisher, 1971).

These aneurysms are referred to as Charcot–Bouchard aneurysms, they have been identified as the cause of bleeding. In recent years, intracerebral hemorrhage has been mostly observed to occur in the lobar region, whereby the hematoma is located in the white matter of the frontal, parietal, temporal, or occipital lobes as compared to the deep intracerebral regions. Chronic hypertension is also a risk factor for lobar hemorrhage, albeit to a lesser degree than for deep hemorrhage; anticoagulation and rupture of arteriovenous malformations account for a larger proportion of lobar hemorrhages than of basal ganglia hemorrhages (Biffi et al., 2015).

A prospective cohort study was conducted in Egypt on 252 consecutive patients with acute first-ever spontaneous intracranial hemorrhage within 24 hours of onset. In the study, the authors noted that elevated systolic blood pressure after 6 hours of admission to hospital was associated with increased risk (OR=2.2, 95% CI: 1.86-2.87, p-value=0.005) of intracranial hemorrhage (Esmael et al., 2020). In the United States, Biffi et al., (2015) conducted an observational study at a single-site tertiary center on 1145 patients with intracranial hemorrhage from July 1964 to December 2013. The 1145 patients were those who had survived at least 90 days following intracranial hemorrhage out of a total of 2197 patients who were initially recruited. Blood pressure measurements were taken at 3,6,9 and 12 months and every 6 months thereafter, leading to a median follow-up duration of 36.8 months. Systolic BP during follow-up was associated with increased risk of recurrence of both lobar and non-lobar intracranial hemorrhage with hazard ratios (HR) of 1.33 (95% CI: 1.02-1.76) and 1.54 (95% CI: 1.03-2.30) per 10-mm Hg increase respectively. In addition, diastolic blood pressure was associated with increased risk of non-lobar ICH recurrence (HR=1.21, 95% CI: 1.01-1.47) per 10-mm Hg increase but not with recurrence of lobar intracranial hemorrhage (HR=1.36, 95% CI:0.90-2.10). The

authors therefore concluded that inadequate blood pressure control during follow-up was associated with recurrence of both lobar and non-lobar intracranial hemorrhage.

In its guidelines for the management of spontaneous intracranial hemorrhage, the American Heart and Stroke association recommended that early and intensive blood pressure lowering in patients with acute intracranial hemorrhage and raised BP between 150 and 220 mmHg is safe and can be effective in improving patient outcomes (Hemphill et al., 2015). However, the optimal strategy to lowering high blood pressure during the hyper-acute stage of intracerebral hemorrhage remains debatable and controversy surrounds the idea that aggressive treatment could be better. Specifically, the acute hypertensive response is considered protective by preserving the cerebral blood flow in the setting of raised intracranial pressure and prevent occurrence of ischemic injury. On the contrary, high blood pressure levels lead to increased risk of edema formation and hematoma enlargement by enhancing ongoing bleeding and re-bleeding (Lattanzi & Silvestrini, 2015).

Aneurysm is an abnormal focal dilatation of an artery. There are four main types of intracranial aneurysms: saccular, fusiform, dissecting, and mycotic. Aneurysms may rupture causing subarachnoid hemorrhage (SAH) which accounts for about 85% of all SAH (Rabinstein & Lanzino, 2018). Once a cerebral aneurysm ruptures, the risk of morbidity and mortality exponentially rises whereby about 25% of the cases die within the first 24 hours and 50% die within the next three months (Ajiboye et al., 2015; Jersey & Foster, 2023).

Several factors have been identified as important risk factors of cerebral aneurysms are hypertension, smoking, chronic alcohol consumption, family history of

intracranial aneurysms in first-degree relatives (Ellamushi et al., 2001; International Study of Unruptured Intracranial Aneurysms Investigators, 1998; Lee et al., 2018). Other factors include age, cocaine use, tumors and certain embolic-forming infections like endocarditis (Lee et al., 2018).

In Germany, a study was conducted on six hundred and thirty-two consecutive patients with aneurysmal ASH over a period of 8 years. The study reported occurrence of ICH in one hundred and fifty patients 25% of the study participants using computed topography. In the study, the investigators looked at the correlation and association between a host of factors and volume of intracranial hemorrhage. Occurrence and volume of ICH were associated with the location (distal anterior or middle cerebral artery >proximal anterior cerebral or internal carotid artery >posterior circulation, P-value < .001 v/s P-value < .001) and size (>12 mm, p-value = .026 versus p-value < .001) of the ruptured aneurysm (Jabbarli et al., 2016).

Current guidelines recommend screening with intracranial magnetic resonance angiography for people with at least two close relatives with intracranial aneurysms and for patients with autosomal dominant polycystic kidney disease (Williams & Robert D. Brown, 2013).

Cerebral amyloid angiopathy (CAA) causes spontaneous lobar hemorrhage affecting the cortical and subcortical white matter and spares the white matter, deep grey matter and brainstem. The prevalence of CAA increases with age and 80-90% of the cases are associated with Alzheimer's disease (Masuda et al., 1988; Yamada, 2015).

Approximately 2 percent of primary hemorrhages are multiple. Multiple nearly simultaneous intracerebral hemorrhages raise the possibility of amyloid angiopathy or a bleeding diathesis but may occur when one conventional hypertensive intracerebral hemorrhage causes hypertension, which in turn leads to one or more additional hemorrhages (Ropper et al., 2014).

CAA is characterized by the accumulation of amyloid beta-peptide within the leptomeninges and small/medium cerebral blood vessels resulting in fragile vessels that may lead to lobar intracranial hemorrhage. In addition, CAA may also present with cognitive impairments, incidental microbleeds, hemosiderosis or transient neurological symptoms (Charidimou et al., 2012; Viswanathan & Greenberg, 2011). Cerebral amyloid angiopathy (CAA) is also predominantly associated with lobar intracerebral hemorrhage or hemorrhage into the cerebellum. In addition, the deposition of result of β-amyloid in arterioles and capillaries emanating from the leptomeninges and cortical vessels has been associated with occurrence of Cerebral amyloid angiopathy. However, the safety of continued anticoagulation remains unclear in patients who have received anticoagulant therapy. This is most common in those with lobar intracerebral hemorrhage attributable to cerebral amyloid angiopathy (Itoh et al., 1993; Pasi et al., 2019).

The major contributing factors to deposition of β-amyloid in the vascular regions (arterioles and capillaries) have been identified as old age (60 years or more) and the presence of apolipoprotein (Apo) E2 and ApoE4. The ApoE2 and ApoE4 alleles confer a risk for intracerebral hemorrhage that is three to five times that in persons with the more common ApoE3 genotype (Biffi et al., 2010; Charidimou et al., 2017). When a patient presents with cerebral hemorrhage from amyloid angiopathy, results

from the magnetic resonance imaging of the brain often reveals multiple tiny asymptomatic hemorrhages of different ages, dilated perivascular spaces, and superficial siderosis of the cortex owing to deposition of blood breakdown products from previous episodes of bleeding (Charidimou et al., 2013).

Cerebral vascular malformations are a group of vascular malformations related to the vessels of the brain. They are classified either histopathologically or by function. Interventional neuroradiologist and neurosurgeons prefer the functional classification where CVM are divided into (1) those with arteriovenous shunting – Arteriovenous malformations, arteriovenous fistulas and (2) those without arteriovenous shunting – Cavernous malformations, capillary telangiectasis (Macellari et al., 2014).

CNS vasculitis is the inflammation of blood vessels wall supplying the brain. CNS vasculitis can be the cause of systemic autoimmune diseases such as Systemic Lupus Erythematous (SLE), Dermatomyositis and Rheumatoid Arthritis or by infections; bacterial or viral. Vasculitis confined to the brain, or the spinal cord is referred to as primary angiitis of the CNS (PACNS).

Venous sinus thrombosis occurs when the dural venous sinuses are occluded. This is a rare cause of ICH and is more prevalent in females (Fischbein & Wijman, 2010).

Brain neoplasms (primary or metastatic) may be associated with ICH as a complication and not the main presenting complain.

2.2 Radiological Findings of Patients with Non-Traumatic Intracranial Hemorrhage.

Radiology plays an important role in the diagnosis of intracranial hemorrhage and its underlying cause. In addition, imaging plays an important role in establishing patient prognosis, stratification of patients for subsequent treatment and gives a treatment guide (Hegde et al., 2020). In an emergency, computed tomography (CT) is the modality of choice used to evaluate patients with suspected or known to have intracranial hemorrhage. This is because CT is widely available, images are rapidly acquired and is highly accurate in depicting intracranial hemorrhage.

A Non-contrast Enhanced Computerized Tomography (NECT) is the most widely used tool that is very informative in the diagnosis and evaluation of intracranial hemorrhage. Hemorrhage appears differently on CT depending on time of occurrence; hence the hematoma evolves and appears different with time on CT images**.** NECT are useful in defining the hematoma location, hematoma volume, hematoma expansion, spot sign, swirl sign, perihematomal edema (PHE), intraventricular hemorrhage (IVH), brain herniation (coning) and hydrocephalus (Panagos et al., 2002).

Hematoma location: These can either be deep or lobar hemorrhages. Deep hemorrhages are located within the basal ganglia, thalami, internal capsule, cerebellum, and brain stem while lobar hemorrhages are within the cortical and subcortical white matter.

A Norwegian population based retrospective study demonstrated the most common location of hemorrhage was as follows deep lobar 44.9%, followed by lobar 40.9%, cerebellar 8.2% and brainstem 5.1% (Øie et al., 2018). A prospective observational

study conducted in the western part of India showed that the most common site of ICH was basal ganglia (49%) followed by lobar (21%) and thalamus (14%) (Suthar et al., 2016).

A hospital based retrospective cohort study done in a Sub-Saharan tertiary hospital found the most common location of intracerebral hemorrhage to be basal ganglia 85.1%, lobar 10.7%, brain stem 2.7% and cerebellar 1.5% (Doumbe et al., 2020a). In a cross-sectional descriptive study by Adeleye et al it was shown that the most common location was supratentorial (90.5%) mainly within the ganglionic thalami (58.1%) (Adeleye et al., 2015a). A review done in South East Nigeria demonstrated the most common site to be the deep 53.2%, lobar 46.8%, and cerebellum 5% (Ezeala-Adikaibe & Ohaegbulam, 2016). These studies show varying common locations among different populations.

Hematoma volume has been shown to be an important predictor of mortality in patients with ICH. This can be calculated accurately from the initial CT images using the ABC/2 method. In this method, A is the greatest hemorrhage diameter on the axial plane, B is the hemorrhage diameter perpendicular to A on the axial plane, and C is the number of axial slices with bleeding multiplied by the slice thickness. (Broderick et al., 1993)

Hematoma expansion is defined as an increase in hematoma volume of > 33%. Spot sign and swirl sign are signs of hematoma expansion seen on contrast enhanced and non-contrast enhanced CT scan respectively and can be used to identify patients at risk of developing hematoma expansion and poor outcome (Al-Mufti et al., 2018).

Ropper et al., (2014) stated that the extravasation of blood into the substance of the brain forms a roughly circular or oval mass that disrupts the tissue and can grow in

volume if bleeding continues. As the hematoma expansion continues it distorts and compresses adjacent brain tissue.

Perihematomal edema may develop within hours after ICH, double within 7 to 11 days and last for weeks after the insult. The mass effect created by the edema may contribute to the increased mortality rate and is associated with worse outcomes. Perihematomal edema is inversely related to ICH volume (Al-Mufti et al., 2018; Staykov et al., 2011)**.**

Perihematomal edema formation has also been attributed to early neurologic deterioration beyond that caused by the hematoma, and these changes can evolve for days. The volume of perihematomal edema varies, but the ultimate edema volume may be as large as the initial hematoma. Increased edema volume by as little as a milliliter has been shown to increase the odds of poor functional outcome (Murthy et al., 2015; Urday et al., 2016).

As the hematoma volume expands with the associated perihematomal edema, the midline strictures are displaced to the contralateral side causing a midline shift of the septum pellucidum.

Brain herniation is defined as displacement of brain tissue from one brain compartment to another. Generally, the brain is divided into the right and left hemispheres by the falx cerebri and into supratentorial and infratentorial regions by the tentorium cerebelli.

As brain herniates it compresses crania nerves, blood vessels and vital brain structures leading to neurological morbidity, coma or even death.

There are different types of brain herniations broadly classified as into intracranial and extracranial herniations.

Intracranial herniations include: Subfalcine, Uncal, Tonsilar and Central transtentorial herniation (Gilardi et al., 2019).

Subfalcine herniation is the most common type of herniation. It refers to a shift in cingulate gyrus under falx cerebri, which results in the compression of the ipsilateral corpus callosum, contralateral cingulate gyrus, obstruction of the foramen of Monro resulting in contralateral ventricular dilatation and compression of ipsilateral lateral ventricle due to mass effect. Compression of the pericallosal branch of the anterior cerebral artery may result in the infarction of the frontal lobe.

Uncal herniation (lateral transtentorial herniation) refers to lateral suprasellar cistern effacement, widening of ipsilateral ambient and lateral pontine cistern. In the later stage, the midbrain is compressed and elongated in the anteroposterior diameter. In coronal section, obliteration of the choroid fissure and perimesencephalic cistern is also noted. Posterior cerebral artery compression may result in infarction.

Central transtentorial herniation refers to a decent in the brainstem leading to effacement of basal cisterns, flattening of the pons against the clivus and infero-posterior displacement of the quadrigeminal plate. In the later stage, there is deformity and buckling of the brainstem. Aqueduct obstruction may result in bilateral hydrocephalus.

Tonsillar herniation refers to inferior displacement of the cerebellar tonsil. The brain tissue herniates into the foramen magnus causing crowding at the craniocervical junction. This results in medullary compression and could be associated with cerebellar infarction due to occlusion of the posterior inferior cerebellar artery.

Transtentorial herniation is considered the most sever consequence of the mass effect of an intracerebral clot and surrounding edema. Studies have shown that surgical removal of the clot, undertaken in an attempt to alleviate transtentorial herniation, has had inconsistent or generally negative results. These findings have led to variations in practice with regard to the performance of craniotomy for clot removal. The Surgical Trial in Intracerebral Hemorrhage II (STICH II) trial examined the role of early clot-removal surgery in 601 patients with intracerebral hemorrhage. This trial was conducted in 27 countries tested the hypothesis that early surgery could improve patient outcomes compare to the conservative initial treatment. Therefore, patients were assigned either to early surgery or initial conservative treatment; the primary outcome was a prognosis-based binary (favourable or unfavourable) outcome using the 8-point extended Glasgow outcome scale (GOSE) at 6 months. Results from this study showed that early surgery did not increase the rate of unfavourable outcomes at 6 months (OR=0.86, 95% CI: 0.62 to 1.20, p-value=0.367) though with a small but clinically relevant survival advantage for patients with spontaneous superficial intracerebral haemorrhage without intraventricular haemorrhage (Mendelow et al., 2013).

Randomized trials are not available to gauge the effect of surgical treatment for cerebellar intracerebral hemorrhage. However, based on large observational studies, the general practice has been to remove the hematoma if clinical or imaging signs of brain-stem compression are present or if the hematoma volume is greater than 15 ml. Kuramatsu et al., (2019) conducted a meta-analysis of 4 studies that recruited 6580 patients from 64 hospitals across the United states and Germany for a period of 10 years. The primary outcome of interest was a dichotomized modified ranking score at 3 months; 0 to 3 was classified as favorable while 4 to 6 was classified as

unfavourable. At 3 months, surgical hematoma evacuation was not significantly associated with better functional disability (OR=0.94, 95% CI: 0.81 to 0.91, p-value-0.43) but was significantly associated with greater probability of survival at 3 months (OR=1.25, 95% CI: 1.07 to 1.45, p-value=0.005) and at 12 months (OR=1.21, 95% CI: 1.03 to 1.42, p-value=0.02).

Hydrocephalus may occur with intracerebral hemorrhage. This can be caused by extravasation of the hematoma into the adjacent ventricle causing expansion of the ventricle or occlusions of the flow of the CSF by mass effect or blood products.
Cerebellar hemorrhage commonly causes obstruction of the fourth ventricle that leads to hydrocephalus, which requires placement of an external ventricular drain. Osmotherapy is typically used to treat acute neurologic deterioration that is secondary to the mass effect or edema associated with intracerebral hemorrhage, but the results have been uncertain. Raised intracranial pressure is usually treated with mannitol or a bolus of hypertonic saline. However, there is a huge inadequacy of data to support prophylactic infusion of hypertonic saline or administration of glucocorticoids for conditions caused by the mass effect of an intracerebral hemorrhage (Ropper, 2012).

It is estimated that Intraventricular hemorrhage occurs in 30 to 50% of patients with intracerebral hemorrhage. In addition, the resultant hydrocephalus owing to the added volume to the ventricular space, obstruction of cerebrospinal fluid (CSF) flow, and inflammation-stimulated secretion of CSF leads to a decreased level of arousal and poor outcome (Karimy et al., 2017).

Hydrocephalus that results in decreased wakefulness is usually treated by the placement of an external ventricular drain to divert CSF and reduce intracranial pressure. In a clinical trial called the Clot Lysis Evaluation of Accelerated Resolution

of Intraventricular Hemorrhage (CLEAR III) trial, 500 patients with hydrocephalus after intracerebral hemorrhage were evaluated. The trial was a double-blinded placebo controlled whereby participants with a routinely placed extra-ventricular drain, in the intensive care unit with stable, non-traumatic intracerebral haemorrhage volume less than 30 mL, intraventricular haemorrhage obstructing the 3rd or 4th ventricles, and no underlying pathology were recruited. The patients were randomly assigned to receive a maximum of 12 doses of 1 mg of alteplase (n=249) that were timed 8 hours apart or 0.9% saline with extra-ventricular drain. The primary outcome was good functional outcome defined by modified Rankin score of <=3 at 190 days. Results from the trial showed that the treatment group had lower case fatality rate (18%) compared to the saline group (29%). In addition, alteplace did not significantly improve functional outcomes of the patients (Hazard Ratio=0.60, 95% CI: 0.41 – 0.86, p-value =0.006). However, the treatment group had a higher proportion of patients with modified Rankin score of 5 (17% versus 9%) and a higher risk (Relative risk= 1.99, 95% CI: 1.22-3.26, p-value=0.007) of the same outcome of mRS=5 (Hanley et al., 2017). Although the overall comparison between groups showed no difference in functional outcomes, thrombolysis might have been associated with improved survival (Kuramatsu et al., 2022). Patients who survive intraventricular hemorrhage typically have substantial disability at 6 months.

2.3 Outcomes of Patients with Intracranial Hemorrhage

Intracranial hemorrhage is associated with long term functional dependence and increased mortality. These outcomes depend on severity of patient clinical presentation at the time of diagnosis, the time taken to make a diagnosis and the timeliness of any intervention (Caceres & Goldstein, 2012; Panagos et al., 2002). Some of the short term outcomes that have been assessed in literature include 30-day

mortality rate, GCS at one-month, functional outcome using several validated tools such as the modified Rankin Scale, presence of hydrocephalus and finally length of hospital stay (Hegde et al., 2020).

The outcomes of patients with intracranial hemorrhage can be predicted radiologically. These radiological predictors of outcome that have been studied widely include haematoma volume and location, haematoma expansion, presence of perihematomal edema and presence of intraventricular hemorrhage with associated hydrocephalus. Some of these radiological predictors of outcome can be used to identify high risk patients and aid in decision-making of their management and eventually lessen the impact of intracranial hemorrhage on morbidity and mortality.

Many scoring systems have been introduced and modified to predict the outcome of patients with spontaneous intracerebral bleeding, these include the modified Rankin Scale (mRS) that measures functional outcomes among post-stroke patients, the Intracerebral Hemorrhage (ICH) score which was developed to estimate the 30-day mortality, the FUNC score which estimates the functional independence at 90 days and the Intracerebral hemorrhage grading scale (ICH-GS) that was designed to predict the outcome and mortality at 30 days (Safatli et al., 2016).

Functional outcomes assessed on admission is a strong predictor of 30-day mortality and disability. The mean length of hospital stay was 9.0 ± 7.7 days in a hospital-based retrospective cohort study conducted among patients admitted for spontaneous intracerebral hemorrhage. The duration was attributed to the size of hematoma and severity. A long hospital stay was due to presence of complications such as chest infections (Doumbe et al., 2020a).

In another prospective hospital based cohort study done in Uganda among patients with both ischemic and haemorrhagic stroke showed that a shorter length of hospital stay of <14 days was associated with reduced 30 day mortality (Namale et al., 2020). Glasgow coma scale is a tool used to measure the level of consciousness among patients and studies have shown that a GCS of <9 on admission is a predictor of mortality (Doumbe et al., 2020a; Namale et al., 2020). A study in India showed that a GCS of <8 was a statistically significant predictor of poor outcome.

2.4 Associations between CT findings and outcomes of patients with Intracranial Hemorrhage

Studies have shown an association between CT findings and outcomes of patients with non-traumatic intracranial hemorrhage. Hematoma volume is an important radiological finding that has been shown to predict patient outcome. First a hematoma volume of more than 30ml is associated with a poorer outcome as compared to smaller volumes (Broderick et al., 1993). Secondly, an increase of hematoma volume also leads to an increase in the risk of mortality. As hemorrhage volume increased, the patients' 30-day mortality rates were significantly worse ($p < 0.0001$), indicating a strong predictive value of hemorrhage volume at presentation (Al-Mufti et al., 2018).

Hematoma expansion, initial large ICH volume is likely to be associated with hematoma expansion unlike smaller volumes. The higher the volume of hematoma expansion the poorer the outcome and this can be assessed radiographically using the spot sign and swirl sign. Some studies have shown that an increase in baseline hematoma volume by 1ml results in increase in mortality by 1% (Suthar et al., 2016).

Hematoma location is also an important predictor of outcome. Infratentorial hematomas, especially brain stem hematomas, are known to carry a poor outcome

compared to supratentorial hematoma. Cerebellar ICH was the highest predictor of 30-day mortality rate, considering the limited space in the posterior fossa and higher risk of herniation (Al-Mufti et al., 2018). About 50% of patients with ICH have intraventricular extension which is an important predictor of 30-day mortality and long-term functional outcome. Delayed Intraventricular hemorrhage too is known to adversely affect the outcome. In the INTERACT 2 study, dIVH had greater odds of 90-day death or major disability versus initial IVH (Suthar et al., 2016).

In a study conducted in DRC by Lelo et al, it was reported that an ICH volume >25ml was an independent predictor of mortality. In this study there were more fatalities associated with males, younger age, ICH volume of more than 25 ml , midline shift of more than 7mm, location within left hemisphere and the presence of coma (Tshikwela & Longo-Mbenza, 2012). Small hematoma volumes are associated with more perihematomal edema than large ICH. However, large hematomas cause significant mass effect with subsequent worsening of morbidity and mortality. With this information, perihematomal edema is not a good parameter for assessing outcome (Staykov et al., 2011).

Multiple logistic regression revealed increase in absolute PHE volume in the first 3 days after ICH as an independent predictor of in-hospital mortality together with initial ICH volume. Other known predictors of poor prognosis after ICH, including age and presence of intraventricular hemorrhage, or hemorrhage growth were not significantly predictive for in-hospital mortality. In conclusion, they found that PHE develops early after ICH and increases within the first 7 to 11 days after the initial bleeding event. At this time, PHE reaches a volume of approximately 2 times of the initial ICH volume. This additional mass effect may contribute to secondary clinical

deterioration and mortality, especially in larger ICH. Therefore, PHE may represent a treatment target in such patients. However, the clinical importance of PHE has not been sufficiently documented yet. Because of its inverse correlation with ICH volume, relative PHE may not be suitable for analyses considering the clinical impact of PHE (Staykov et al., 2011)**.**

2.5 Diagnosis and Assessment of ICH

In the diagnosis of intracerebral hemorrhage, CT and MRI have been established to be both sensitive and specific diagnostic tools which establish the location and volume of the clot (Kidwell et al., 2004). During the initial imaging examination, a CT angiogram may detect an underlying aneurysm or vascular malformation which would be critical in informing the care provided to the patient. However, these findings are not common if the hematoma/bleed is contained entirely within the brain substance. The American Heart Association provided guidelines on intracerebral hemorrhage suggesting that CT angiography can be performed in patients who are younger than 70 years of age and have lobar intracerebral hemorrhage, in those who are younger than 45 years of age and have deep or posterior fossa intracerebral hemorrhage, and in those who are 45 to 70 years of age and have no history of hypertension. The Association further recommends early assessment of the severity of intracerebral hemorrhage with the use of one of several validated scales (Greenberg et al., 2022).

The Intracerebral Hemorrhage (ICH) score is one of the most used scales that is used in patient assessment. The scale incorporates Glasgow Coma Scale score, the patient's age, the presence of infratentorial hemorrhage or intraventricular hemorrhage, and clot volume (J. Claude Hemphill et al., 2001). The initial ICH score estimates the risk of early death and death at 12 months as well as functional outcome. However, the

primary purpose of the tool is for quality improvement and to provide health care workers with an avenue to discuss clinical severity of the assessed patients (Hemphill et al., 2009).

Clinical evaluation alone is insufficient to differentiate ICH from other stroke subtypes, and to determine the characteristics and possible cause of ICH. Thus, imaging of the brain is needed, and the diagnostic study of choice in ICH at first place is usually non-contrast brain computed tomography (CT). It provides a significant amount of information about the size and location of the hemorrhage, presence of intraventricular, subarachnoid, or subdural blood, and about the presence of mass effect with threatening herniation or hydrocephalus (Diringer et al., 1998; Ropper, 1986, 2012).

CT differentiates ICH from cerebral infarction with high sensitivity – an imperative matter in the management of acute stroke, given the availability of thrombolytic therapy. Hemoglobin displays bright on non-contrast head CT (Manno et al., 2005). CT may also enable the prediction of hematoma expansion based on pattern of bleeding. Magnetic resonance imaging (MRI) is as sensitive in detecting ICH as is CT, but superior in identifying perihematomal edema, arteriovenous malformation (AVM), amyloid angiopathy, or underlying neoplasm (Kidwell et al., 2004). MRI may provide important hints regarding underlying pathology, such as microbleeds, lacunar infarcts, and chronic white-matter change, which all suggest microangiopathy. It can also provide information about the time course of ICH. Compared to CT, shortcomings of MRI include longer scanning time, and limited possibilities to monitor and treat critically ill patient while in scanner. CT remains, therefore, as the gold standard,

but MRI is the first-line imaging method for all younger ICH patients (Fan et al., 2004; Marsh et al., 2014; Pasi et al., 2019).

Location of a hemorrhage may provide information about the etiology. Deep subcortical structures (putamen, caudate, thalamus), pons, cerebellum, and periventricular deep white matter are typical locations for hypertensive small-vessel disease, whereas single or multiple lobar hemorrhages in the cortical surface are often caused by CAA. These assumptions may, however, be incorrect: majority of patients with lobar ICH have a history of hypertension, and vascular malformations may also be the cause of deep or lobar hemorrhages (Feigin et al., 2021; Marsh et al., 2014; Ropper, 2012).

According to one study, in 48% of normotensive patients younger than 45 years, in 49% of patients with lobar hemorrhage, and 65% of cases with isolated intraventricular hemorrhage, there are abnormalities on angiography, such as aneurysm or AVM (Fang et al., 2007). CT-angiography (CTA), MR-angiography (MRA), or digital subtraction angiography (DSA) should be performed in all young patients due to the high likelihood of underlying vascular abnormality. Angiography should also be performed in other patients without obvious risk factors or cause of ICH, if intraventricular, subarachnoid, peri-sylvian, or interhemispheric fissural blood is present, if abnormal calcification or prominent draining vein is present, if hematoma shape is unusual (noncircular), if edema is out of proportion to the early time the ICH is first imaged, if location of ICH is unusual, and if abnormal structure in the brain is visible (Anderson et al., 2008; Flint et al., 2008).

The need of angiography also depends on whether patient is candidate for neurosurgery, and angiography timing depends on urgency of surgery (Flint et al., 2008; Qureshi et al., 2001; Ropper et al., 2014) . If a suspicion of a structural abnormality remains after a negative CTA or MRA, an adjunct DSA is highly recommended after two to four weeks after the resolution of the hematoma, when vascular anomalies may become visible. In contrast to younger individuals, elderly patients with a history of hypertension and a thalamic, putaminal, or posterior fossa ICH are less likely to benefit from angiography (Qureshi et al., 2001). Both contrast extravasation into the hematoma and presence of tiny enhancing foci, "spot sign" predict hematoma expansion and poor outcome. MRI with gadolinium as a contrast medium also gives insight to structural causes underlying ICH, such as a tumor. In general, an angiographic study is strongly recommended in ICH cases except in patients who are not candidates for active surgery or active treatment (Davis et al., 2006; Han et al., 2014; Havsteen et al., 2014) .

A detailed patient history and clinical examination are necessary in every ICH patient. A thorough examination should be conducted to detect signs of external trauma, pressure sores, and rhabdomyolysis, particularly in patients with depressed level of consciousness. A comprehensive laboratory evaluation covering a complete blood cell count, prothrombin time, activated partial thromboplastin time, serum electrolytes, liver function tests, glucose, glycosylated hemoglobin, C-reactive protein, creatinine, creatinine kinase, troponin-T, and coagulation profile, urea, nitrogen, and INR, is needed to detect underlying or complicating pathologies, such as infection, electrolyte disturbance, renal failure, rhabdomyolysis, or myocardial ischemia that are frequently treatable. Urine analysis, urine culture, and pregnancy test should be conducted in a woman of childbearing age, and toxicology screening should be executed in young

and middle-aged patients to detect illicit drug use. Routine electrocardiography is also needed, for it may reveal prior cardiac injury indicating poor cardiac function, or left ventricular hypertrophy, an evidence of chronic hypertension, and chest radiograph, for it may reveal aspiration or other pulmonary process suffered, or an enlarged heart (Havsteen et al., 2014; Hemphill et al., 2015; Qureshi et al., 2001).

ICH is a medical emergency and therefore any delays in treatment may result in worse outcomes. Initial prehospital care should focus on ventilatory and cardiovascular management by maintaining airways, breathing, and circulation to prevent hypoxia and limit hematoma growth while maintaining cerebral perfusion (Flower & Smith, 2011). Quick delivery to the nearest emergency department (ED) is imperative in patients with abrupt neurological focal deficit, such as hemiparesis, impaired consciousness, or severe headache, which is presumed to be of vascular origin until proven otherwise (Flower & Smith, 2011; Greenberg et al., 2022; Hemphill et al., 2015). Finally, an advance notice to the ED of the forthcoming potential stroke patient by emergency medical service providers is of great value, since it shortens the time to CT in the ED (Abdullah et al., 2008; Qureshi et al., 2001).

It is of utmost importance that ED is prepared to treat patients with ICH or has a plan for swift transfer to a tertiary center. Majority of ICH patients are unstable in the acute phase and require close monitoring, particularly on cardiovascular, respiratory, and neurologic status. Respiratory and hemodynamics may be compromised in patients with impaired consciousness. Cardiovascular instability associated with increased ICP needs immediate attention to avoid the damage caused by hypertension or hypotension in a patient with limited autoregulation (Feigin et al., 2003, 2021).

Initial management should focus on stabilization of cardiorespiratory function and treatment of intracranial complications. Intubation is needed, if other measures are insufficient to protect airways and sustain adequate ventilation in patients with decreasing consciousness (GCS≤8) or impairment of reflexes protecting the airways. Approximately 30% of patients with supratentorial ICH and majority of patients with infratentorial ICH require intubation. Low GCS has been identified as a factor predicting a need for tracheostomy in two studies. One of them also described hydrocephalus, midline-shift, thalamic location of hematoma, large hematoma volume, and intraventricular hemorrhage factors to associate with tracheostomy.

Initiation of tracheostomy early could reduce the length of stay in hospital. Elective tracheostomy should be performed after intubation of 2 weeks at the latest. Urgent brain CT scanning upon arrival to the ED is vital to differentiate between ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage, and to evaluate the characteristics of hemorrhage, such as location and volume, as well as to detect presence of IVH, edema, increased ICP, obstructive hydrocephalus, and imminent brain herniation (Davis et al., 2006; Hemphill et al., 2015; Murthy et al., 2015).

2.6 Treatment options after occurrence of intracranial hemorrhage

The focus for treatment of patients is prevention of secondary brain damage following intracerebral hemorrhage. The elements of secondary damage that have attracted the most attention and respond to treatment are clot enlargement, secondary brain edema, and intraventricular hemorrhage. Hematoma expansion causes tissue destruction beyond that caused by the initial clot. Though this type of damage is not always present, it is identified on serial imaging and typically occurs in the first 6 hours after the onset of symptoms. There are a number of hemostatic treatment options that are used to limit ongoing bleeding (Flibotte et al., 2004; Morotti & Goldstein, 2016).

A phase 3 clinical trial was conducted to investigate the impact of recombinant activated factor VII (rFVIIa) reduced growth of the hematoma and improved survival and functional outcomes. In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, patients were randomized in a treatment arm to receive one of two dose levels of recombinant factor VIIa or placebo within 4 hours after the onset of symptoms of intracerebral hemorrhage. The increase in clot size at 24 hours was 15 percentage points less in the group that received the highest dose of factor VIIa; however, there was no difference between the patient groups in the incidence of severe disability or death (Mayer et al., 2008).

Patients with intracerebral hemorrhage that is associated with anticoagulant use have been identified to have an increased risk of three to six times higher for hemorrhage expansion, neurologic deterioration, and poor outcome compared to patients with intracerebral hemorrhage in the absence of anticoagulation (Flibotte et al., 2004). In a trial of patients with intracerebral hemorrhage who had received vitamin K antagonists and who had an international normalized ratio (INR) that was greater than 1.9, four-factor prothrombin complex concentrate was found to be superior to fresh frozen plasma for normalizing the INR and reducing the incidence of hematoma expansion (Steiner et al., 2016).

The American Stroke Association provided further guidelines recommending intravenous vitamin K and prothrombin complex concentrate over fresh frozen plasma if the INR is elevated owing to the use of vitamin K antagonists (Greenberg et al., 2022). The reversal agents idarucizumab and andexanet alfa are available for use in the treatment of patients with intracerebral hemorrhage that is associated with direct oral anticoagulants in the form of direct thrombin and factor Xa inhibitors; however,

clinical trials are needed to determine their effect, and it has been suggested that prothrombin complex concentrate can be substituted if reversal agents are not available (Greenberg et al., 2022).

A randomized clinical trial was conducted to compare platelet transfusion versus Standard Care after Acute Stroke due to Spontaneous Cerebral Haemorrhage. Patients in the treatment arm received platelet transfusions while the rest formed the control group. Results from the trial showed that the treatment arm had higher odds of death or disability at 3 months (OR= 2·05, 95% CI 1·18–3·56; p-value =0·0114) compared to the control arm. The authors concluded that platelet transfusion cannot be recommended in practice for acute stroke due to spontaneous ICH (Baharoglu et al., 2016). Consequently, guidelines from the American Heart Association suggested that platelet transfusion should only be used in patients receiving aspirin therapy following intracerebral hemorrhage and have undergone surgical procedures (Greenberg et al., 2022)

In addition, two separate trials tested the hypothesis that lowering of blood pressure would improve clinical outcomes in patients with intracerebral hemorrhage. In the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial, 1000 patients were recruited in the double-blinded study with supratentorial intracerebral hemorrhage (volume <60 cm^3) and a Glasgow coma scale (GCS) score of 5 or more (from a scale of 3 to 15 whereby lower scores indicated worse conditions). The intensive-treatment arm received parenteral nicardipine to maintain a target range for systolic blood pressure of 110 to 139 mm Hg (intensive treatment) while the control group were intended to maintain to a target range of 140 to 180 mm Hg using standard treatment for 24 hours. Results from the trial showed that the primary

outcome of death or disability was observed in 38.7% of patients in the intensive-treatment arm and 37.3% of those in the standard treatment arm. Further results showed that after 90 days post randomization, intensive treatment did not result in lower rate of death or disability (Relative risk=1.04, 95% CI: 0.85 to 1.27) compared to standard treatment (Qureshi et al., 2016).

In the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2), 2783 patients with spontaneous intracerebral hemorrhage were randomly assigned to the same blood-pressure target ranges as were those patients in the ATACH-2 trial. However, in this trial the intervention period was extended by 7 days and the choice of the anti-hypertensive medication was the prerogative of the treating clinicians. Similarly, the primary outcome or event was death or major disability defined by a modified Rankin scale of 3 to 6 at 90 days. Results from this study showed that intensive treatment (OR=0.87, 95% CI: 0.75 to 1.01, p-value=0.06) did not significantly reduce the rate of primary outcome (Anderson et al., 2013).

Intensive Care Treatment

Despite the inherent appeal of admitting patients with cerebral hemorrhage to an ICU, whether intensive monitoring improves clinical outcome in intracerebral hemorrhage is not clear, and a trial to test this question seems unlikely to be conducted. Seizures after intracerebral hemorrhage can occur, although the role of prophylactic antiseizure drugs in patients with intracerebral hemorrhage is unclear (Gilmore et al., 2016). In patients with a depressed level of consciousness after intracerebral hemorrhage, continuous electroencephalography may detect inapparent seizures that require the initiation of antiseizure drugs (Vespa et al., 2003). Routine care in the intensive care unit includes airway protection and adequate pulmonary gas exchange for mitigation

of secondary brain injury from hypoxemia, but the effectiveness of these measures is difficult to prove. Assessment of swallowing, maintenance of normothermia and normal glucose levels, and prophylaxis for deep-vein thrombosis (a therapy that is considered to be safe despite the presence of intracerebral hemorrhage) reduce additional morbidity.

Systems for early prognostication may not have adequate predictive ability to direct the withdrawal of life-sustaining treatments after intracerebral hemorrhage (Hwang et al., 2016). Patients who might otherwise have survived may succumb if life-sustaining treatments are withdrawn too early (Gilmore et al., 2016). Several studies suggest that withholding the determination of prognosis in the first few days after hemorrhage is appropriate, and these findings are consistent with American Heart Association guidelines (Greenberg et al., 2022; Urday et al., 2016; Woo et al., 2022). Shared decision making to gauge the previously expressed wishes of the patient and family is a fruitful approach. Fewer than half the patients who survive intracerebral hemorrhage have adequate blood pressure control after discharge. Poorly controlled blood pressure is associated with adverse events such as recurrent stroke and death and is more common among Black persons than among non-Black persons. In addition to recurrent intracerebral hemorrhage, survivors are at risk for thrombotic events both in the brain and in the cardiovascular system (Murthy et al., 2015, 2021).

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Study Design

A hospital based prospective cohort study.

3.2 Study Setting

The study was conducted at the Radiology and Imaging directorate, medical wards and clinics at Moi Teaching and Referral Hospital (MTRH). MTRH is the second largest referral hospital in Kenya and is located along Nandi Road in Eldoret town. The catchment area of these hospitals encompasses counties within the Western and North Rift regions of Kenya as well as neighboring countries of Uganda, Rwanda, and Burundi. The hospital serves some of the highest populated counties such as Kakamega and Bungoma as seen in the 2019 Kenya population Census survey. MTRH has a bed capacity of 991 patients an average number of 1200 of inpatients at any given time and about 1500 outpatients.

3.3 Study Population

The study population consisted of all adults with brain CT findings of intracranial hemorrhage at MTRH.

3.4 Target population

The target population in this study were patients aged 18 years and above with features of non-traumatic intracranial hemorrhage on brain CT at MTRH.

3.5 Sample Size Determination

As per the Fisher et.al (1998) formula

$$n = Z^2 \frac{p\,(1-p)}{d^2}$$

n = desired sample size.

z = Standard normal variance corresponding to 1.96

p = 0.3 is estimated from Nakibuuka et al., 2015

d= 7% is the margin of error.

When this formula is applied at d = 0.05, z = 1.96, and p = 0.087

$$n = \frac{(1.96)2 \times 0.3\ (1-0.3)}{(0.07)^2}$$

Therefore n = 165

3.6 Sampling Technique

A review of the previous two year's registry records showed that about 100 patients with non-traumatic intracranial hemorrhage were served by the radiology department annually. Therefore, a census survey was conducted on patients presenting at the radiology departments of MTRH. This census approach was adopted due to the anticipated small target population of patients demonstrating signs of non-traumatic intracranial hemorrhage and sent to radiology department for imaging. The study was conducted for a period of 1 year from December 2021 to November 2022.

3.7 Eligibility Criteria

3.7.1 Inclusion criteria

1. Patients aged 18 years and above with a brain CT diagnosis of intracranial hemorrhage.
2. Patient who accepted to be included into the study and gave informed written consent.

3.7.2 Exclusion criteria

1. History of trauma associated with the presented case of intracranial hemorrhage.
2. Patients with pre-existing neurological events.
3. Patients with prior history of brain surgery and hemorrhagic metastasis.

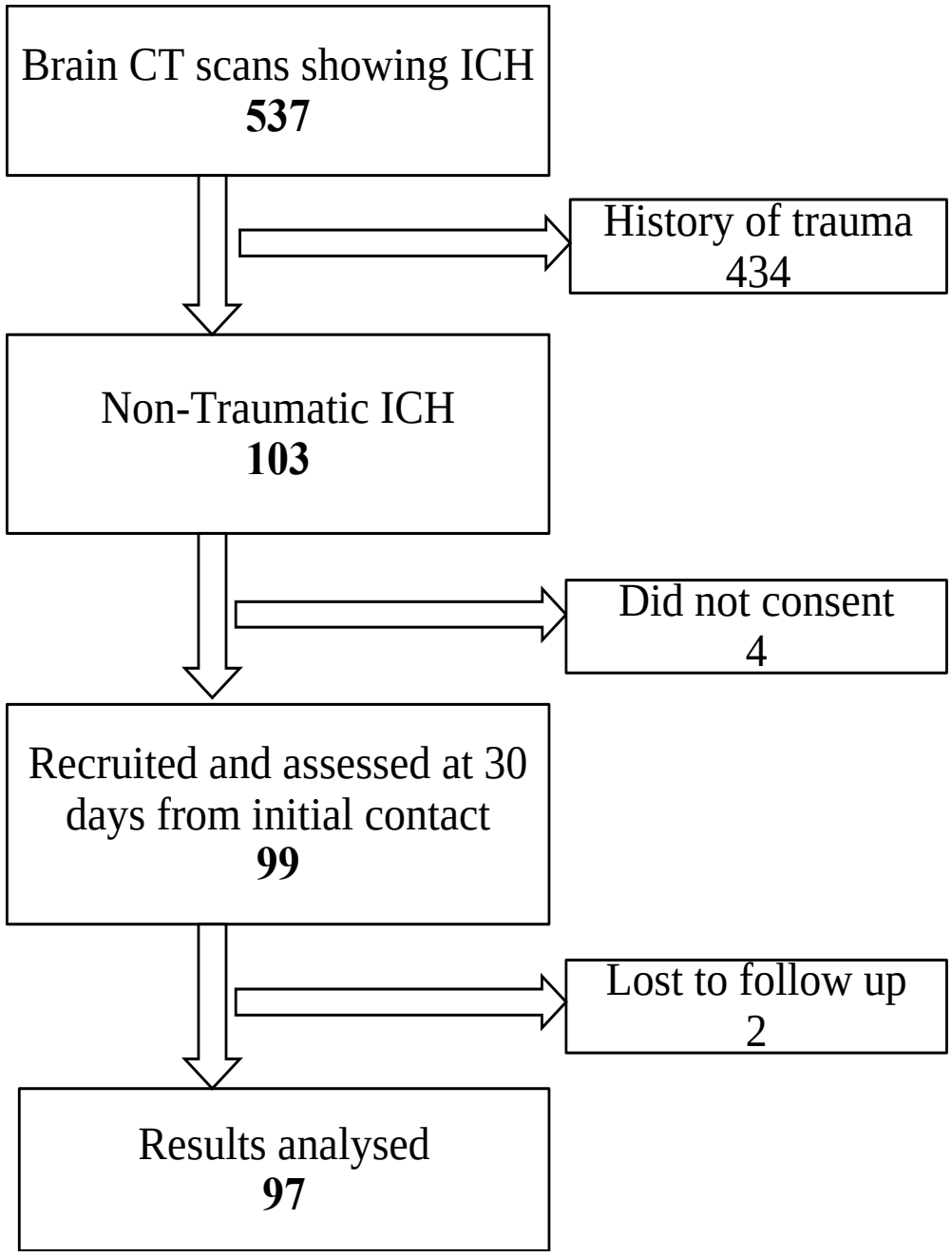
3.8 Data collection procedures

Clinicians and radiographers were sensitized about this study to enable them to identify potential study participants among patients sent to the departments for non-contrast enhanced brain CT. The radiographers were requested to inform the principal investigator (PI) on patient who presented at the department with requisition for suspected stroke. The PI then reviewed the images at the console to ascertain presence of intracranial hemorrhage. Upon confirmation of intracranial hemorrhage, the researcher contacted the patient within 24 hours for screening based on the eligibility criteria of this study. All eligible patients and their primary care givers were extensively informed of the study and written informed consent/assent sought from the participant or caregiver of participant. The primary care giver was allowed to sign the consent form on behalf of the patient in scenarios whereby the patient agreed to participate in the study but was too incapacitated to append their signature on the consent.

An interviewer administered questionnaire (Appendix 3) was used to collect data on patients' demographics. The premorbid modified Rankin scale was determined based on evaluation of the patient at the time of the interview. The researcher then reviewed the CT scan images and wrote a detailed report that included the following: hematoma location, hematoma volume, intraventricular extension of hematoma, perihematomal edema and mass effect (midline shift, herniations). As part of quality control process, the images were reviewed by two consultant radiologists to confirm the findings and cross checked with the report from the researcher. Elaborate discussions between the researcher and the qualified radiologists were conducted in case different reports were produced by the two until a consensus was reached. If the two-consultant radiologist did not come to a consensus, a third consultant radiologist reviewed the images.

A second review was conducted on the patients 30 days after the initial contact with the study. Patients who were admitted and were still in the wards after the 30 days window were reviewed in the wards. Appointments with patients discharged within 30 days of initial contact were made via phone and a date of visiting the hospital given to them. The study reimbursed transport costs to all patients who visited the hospital for day 30 review. This second review primarily focused on the functional outcomes using the modified Rankin scale (mRS). In the unfortunate demise of a patient prior to day 30 review, the primary care giver was contacted. He/she was requested to provide the investigator with the patient's date of death, and additional information regarding type of intervention given prior to their demise will be sort from the patients' records.

Study schema



3.8.1 Image acquisition

Helical scanning was performed with the Siemens 32 Slice CT scanner. First a scout was obtained on anteroposterior and lateral views. The scan start location was required to be just below the skull base with the end location just above the vertex.

The scan parameters for the non-contrast brain CT were expected to be identical for each phase: 1:1pitch, 80 -120 kVp, 150 – 250 mAs and 3-5-mm slice thickness with a slice interval of 1.5 mm. The window settings were as follows for the brain and bone windows respectively: Brain window width –140, window level – 40, Bone window width – 4000, window level – 400. The non-enhanced CT images were uploaded and archived to the picture archive and communication system (PACS).

3.8.2 Image evaluation

Soft copy images of brain CT were read by the principal investigator and reviewed by two qualified consultant radiologists who was unaware of patient history. The non-contrast brain CT images were viewed for the presence intracranial hemorrhage. The hemorrhage was characterized in terms of hematoma location, hematoma volume, presence of surrounding edema, extension into the ventricular system and any mass effect or midline shift was also documented. This information was then documented in the data collection tool.

The hematoma volume was obtained using the ABC/2 method by Kothari et al where A is the maximum anteroposterior length on axial plane, B is the maximum width that is perpendicular to A on the same CT slice and C is the number of slices with hemorrhage multiplied by the slice thickness (*Image 1*).

The measurements were taken in centimeters (cm) and the obtained volume was in cubic centimeters (cm3) or milliliters (mL).

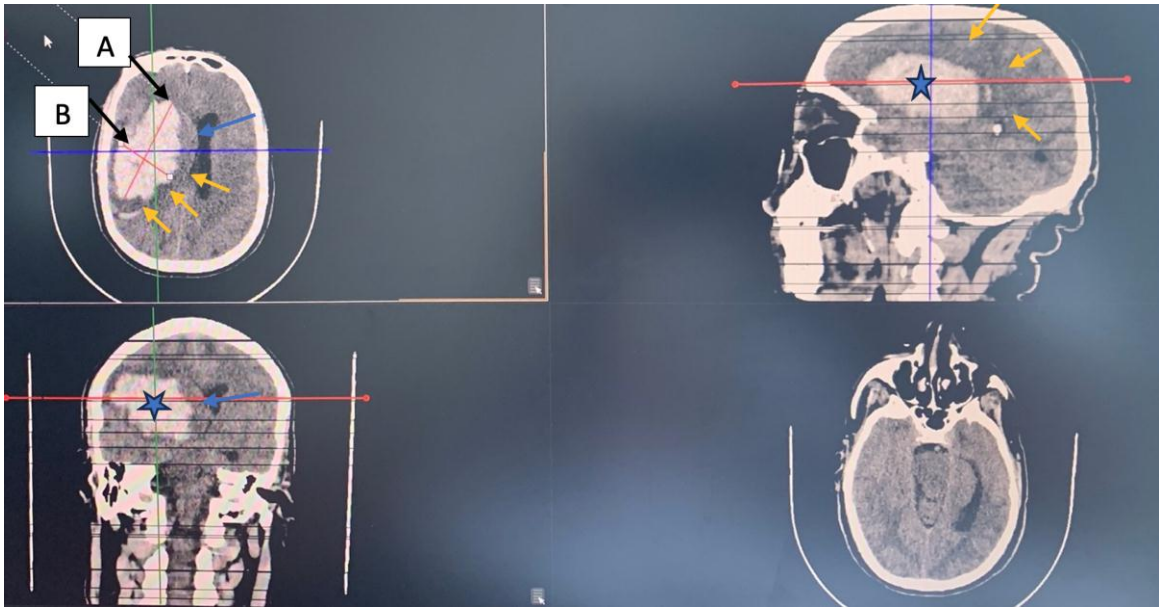


Image 1: **Multiplanar non-contrast Brain CT images of a 62 yr M with frontal-parietal ICH (blue star), perihematomal edema (yellow arrows), mass effect and midline shift (blue arrows).**

Hematoma volume calculation using the ABC/2 method by Kothari et al (1996): A= 8.6 cm, B= 5.3 cm and C= 3.9 cm /2. Calculated volume 88.9 mL.

The midline shift was obtained by drawing a line connecting the anterior-most and posterior-most point of the falx on axial plane and measuring the distance between this line and the septum pellucidum (*Image 2*).

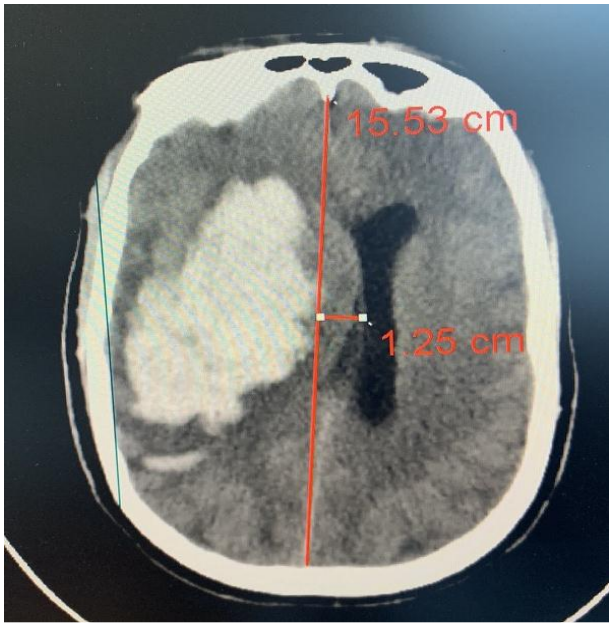


Image 2: **Demonstrates left midline shift of 12.5mm in a patient with right frontal - parietal intracerebral haemorrhage.**

3.9 Data Management and Analysis

Data entry was made in a data sheet and later transferred to a computer database. Double entry was used to ensure accuracy of the data. All patient details were kept confidential, and data were only available to the investigator and the supervisors via password access. Patients were provided a copy of their results and had complete autonomy over who else could view their scan results. Study generated serial numbers were used to protect patients' identity. At the end of each day data collection forms were verified for completeness and coded.

Data analysis results were presented using descriptive and inferential statistics. Continuous variables were presented using measures of central tendency (mean, and median) and measures of dispersion (standard deviation, interquartile range). Categorical variables were presented using frequencies and proportions. After performing descriptive analysis on the functional outcome and CT finding variables, some functional outcomes were recategorized based on the numbers observed. For instance, the modified ranking score scale was recategorized into good (modified ranking score = 1 and 2) and poor outcomes (ranking scale score = 3, 4 and 5). The Mood's median test was used to test for equality of medians for continuous variables between two groups. The chi square test of association was used to investigate the association between CT findings and brain functional outcomes. In addition, logistic regression models were used to estimate the effect of the different CT findings on the brain functional outcomes at 30 days. Data analysis was conducted using STATA version 17.0.

3.10 Ethical Considerations

The research ethics approval to conduct this study on human subjects was sought from the Institutional Research and Ethics Committee (IREC) of Moi University. In addition, permission was also obtained from the Chief Executive Officer (CEO) MTRH. All patients and their care givers were exhaustively informed about the study, its procedures and all potential risks and benefits of the study. Failure to give consent or withdrawn consent did not in any way interfere with the quality of care that the patient was entitled at any time. No incentives or inducements were used to convince the patients to participate in the study.

Strict confidentiality was maintained throughout the study. Personal identifying information such as names, physical address, phone numbers and national identification numbers were captured in the data collection form. All data collection materials were kept in a locked cabinet during the study period.

The results of the research will be available for academic reference at the College of Health Sciences Resource Centre and the Moi university thesis repository. In addition, findings from this study shall be published in a peer reviewed scientific journal.

CHAPTER FOUR: RESULTS

4.1 Introduction

This study collected data on the brain functional outcomes of patients with non-traumatic intracranial hemorrhage at the Moi Teaching and Referral Hospital. The study was conducted from December 2021 to November 2022. This chapter presents the findings of the brain CT examinations conducted on the study participants and the association between the findings and patient outcomes.

4.2 Demographics

A total of 97 study participants with brain CT showing intracerebral hemorrhage were recruited into the study of which majority 51 (52.6%) were male. The overall mean and median ages were 59 (± 14) and 61 (IQR: 48-71) years respectively. Majority of the participants (71%) were aged above 50 years while a smaller proportion of 29% were aged 50 years or less. Specifically, in descending order of the ages, the age distributions were above 70 years (25.8%), 61-70 years (27.8%), 51-60 years (17.5%), 41-50 years (18.6%) and 10.3% aged 40 years and below. Majority of the participants (86.6%) were admitted in hospital while 13.4% were not admitted. In addition, 43.9% and 64.9% of the participants received surgical and physiotherapy interventions respectively. These results are presented in table 4.1 below.

Table 4.1: General characteristics of the study participants

Demographic Characteristic		Overall
		n(%)
Age (years)	Mean (±SD)	59.09 (±14.43)
	Median (IQR)	61.0 (48.0-71.0)
Age (Categorical)	≤ 40 yrs	10 (10.31)
	41-50 yrs	18 (18.56)
	51-60 yrs	17 (17.53)
	61-70 yrs	27 (27.84)
	> 70 yrs	25 (25.77)
Sex	Female	46 (47.42)
	Male	51 (52.58)
Hospital admission	No	13 (13.40)
	Yes	84 (86.60)
Surgery	No	54 (56.1%)
	Yes	43 (43.9%)
Physiotherapy	No	34 (35.1%)
	Yes	63 (64.9%)

4.3 CT Findings

Brain CT findings of 97 study participants were analyzed at the end of the study. A total of 84 (85.7%) study participants had intracerebral hemorrhage at the supratentorial region while 14 (14.3%) had intracerebral hemorrhage occurring at the infratentorial region. Specifically, the proportion of the exact location where intracerebral hemorrhage was observed in the participants included lobar (44.3%), deep lobar (41.2%), cerebellar (9.3%), brain stem (3.1%) and the 4^{th} ventricle (2.1%). Table 4.2 provides a summary of the frequencies and proportions of the intracerebral hemorrhage locations.

Out of the 40 intracerebral hemorrhage that occurred in the deep lobar region, 63.4% occurred in the basal ganglia while 36.6% occurred in the thalamus. There were 43 brain CT showing intracerebral hemorrhage in the lobar region of which 39.5%, 32.6% and 18.6% occurred in the parietal, temporal and the frontal lobes while the occipital and parieto-occipital accounted for 7% and 2.3% of the hemorrhages in the lobar region.

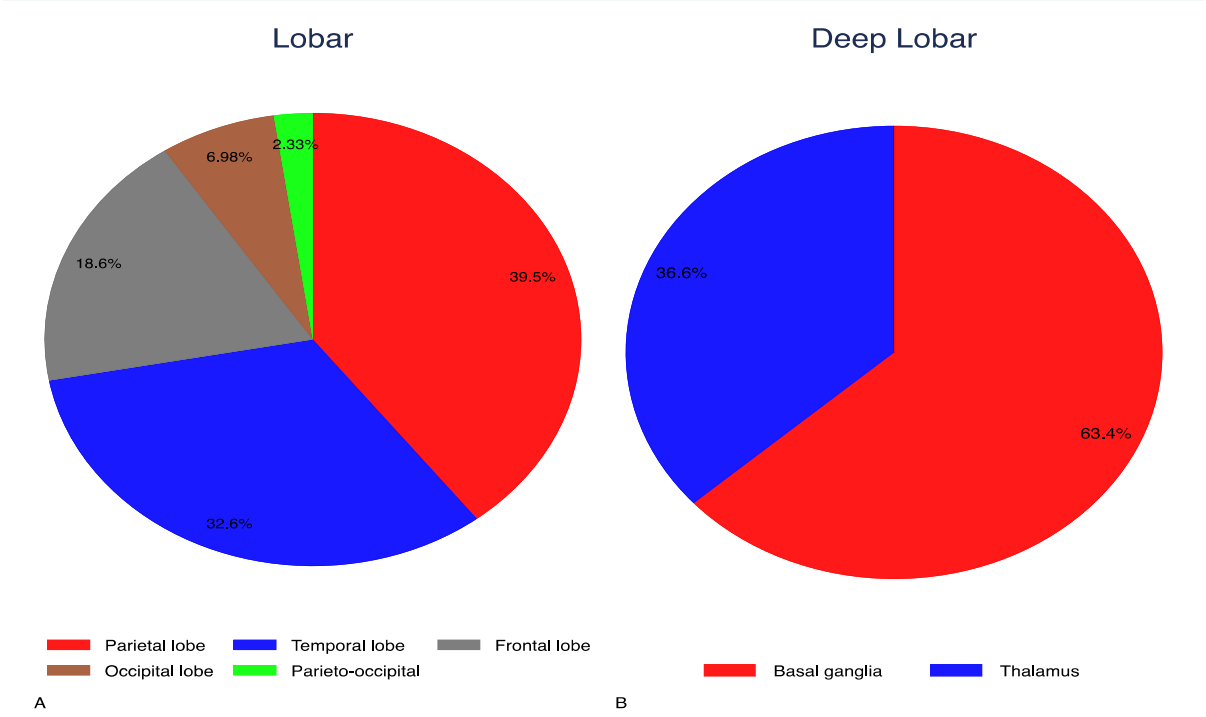


Figure 4.1: Distribution of intracerebral hemorrhage in the lobar (A) and the deep lobar (B) regions of the brain.

The mean and median hematoma volume were 22.8 ml (±23.1) and 16.1ml (IQR: 4.4-30.2) respectively. In addition, majority (n=71, 73.2%) of the study participants had hematoma volume of less than 30ml compared to 26 (26.8%) of the participants whose hematoma volume was greater than or equal to 30ml. The mean and median midline shift were 3.60 (±4.64) mm and 0.0 (IQR: 0.0-6.6) mm respectively. In addition, 33 (33.7%) of the participants had midline shift values of greater than or equal to 5mm.

Further findings showed presence of mass effect and edema in 67 (69.1%) and 87 (89.7%) study participants respectively. On the contrary, in most the patient's brain CT findings there was absence of Intra ventricular extension, hydrocephalus and herniation in 61 (62.9%), 65 (67%) and 80 (82.5%) of the study participants respectively. Summary statistics of CT findings is presented in table 4.2 below.

Table 4.2: Summary statistics of CT findings (n=97)

CT Finding		**Overall**
		n (%)
Hematoma volume (ml)	Mean (±SD)	22.79 (±23.08)
	Median (IQR)	16.1 (4.4-30.2)
Hematoma volume (ml)	< 30 ml	71 (73.20)
	≥ 30 ml	26 (26.80)
Hematoma location	Deep lobar	40 (41.24)
	Lobar	43 (44.33)
	Brainstem	3 (3.09)
	4th Ventricle	2 (2.06)
	Cerebellar	9 (9.28)
Mass effect	Absent	30 (30.93)
	Present	67 (69.07)
Intra ventricular extension	No	61 (62.89)
	Yes	36 (37.11)
Middle shift (mm)	Mean (±SD)	3.60 (±4.64)
	Median (IQR)	0.0 (0.0-6.6)
Hydrocephalus	No	65 (67.01)
	Yes	32 (32.99)
Edema	No	10 (10.31)
	Yes	87 (89.69)
Herniation	Absent	80 (82.47)
	Present	17 (17.53)

4.4 Functional Outcomes

The median modified ranking score was 4 (IQR: 3-6) at day 30 of assessment. Out of the 97 participants with brain CT findings and whose modified ranking score was established, participants with moderate disability were the most predominant (28.9%) while 5 (5.2%) of the participants had no significant disability upon assessment. About 22.7% of the participants were established to have moderately severe disability, 9.3% had slight disability and 6.2% had severe disability. In addition, 27.8% of the participants died within 30 days following CT scan examination. The ranking scale scores were grouped into two broad categories: good outcomes (modified ranking score = 1 and 2) and poor outcomes (ranking scale score = 3, 4 and 5). At day 30, majority of the study participants had poor outcomes (57.7%) compared to 14.4% who had good outcomes.

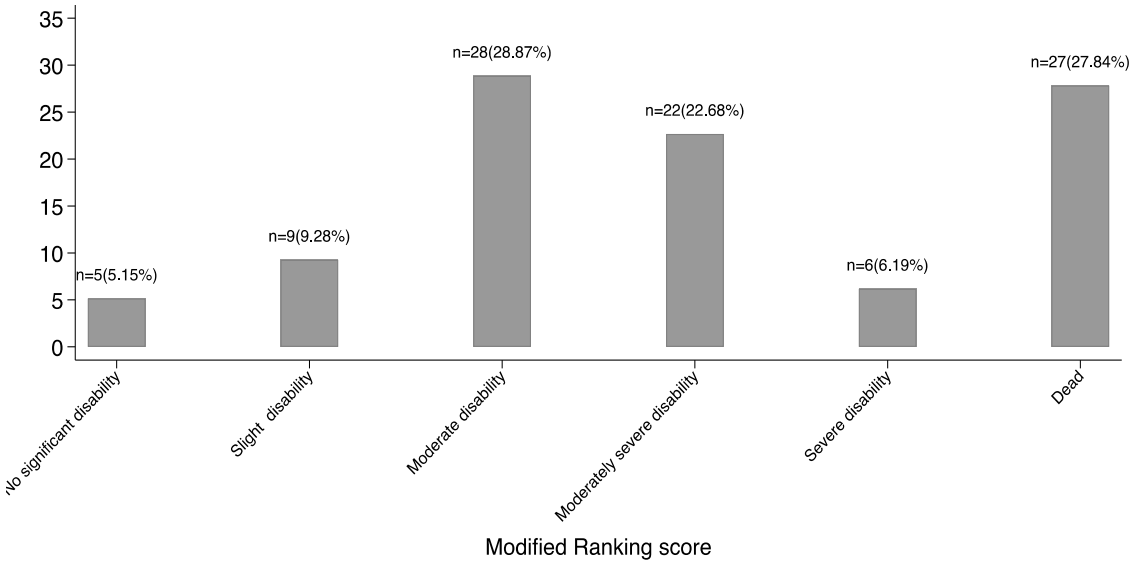


Figure 4.2: Distribution of functional outcomes for all study participants

4.4.1 Surgery

A total of 43 (43.9%) of the participants underwent surgical procedures of which 2.3% had slight disability, 23.3% had moderate disability, 31.9% had moderately severe disability, 11.6% had severe disability and 20.9% died within 30 days after CT scan examination of their intracranial hemorrhage episodes. Among those who did not undergo surgery, the highest proportion of disability was observed among those with moderate disability (40.9%), followed by slight disability (18.2%), death (18.2%), no disability (11.4%), moderately severe disability (9.1%) and severe disability (2.3%). These results are presented in figure 4.3 below.

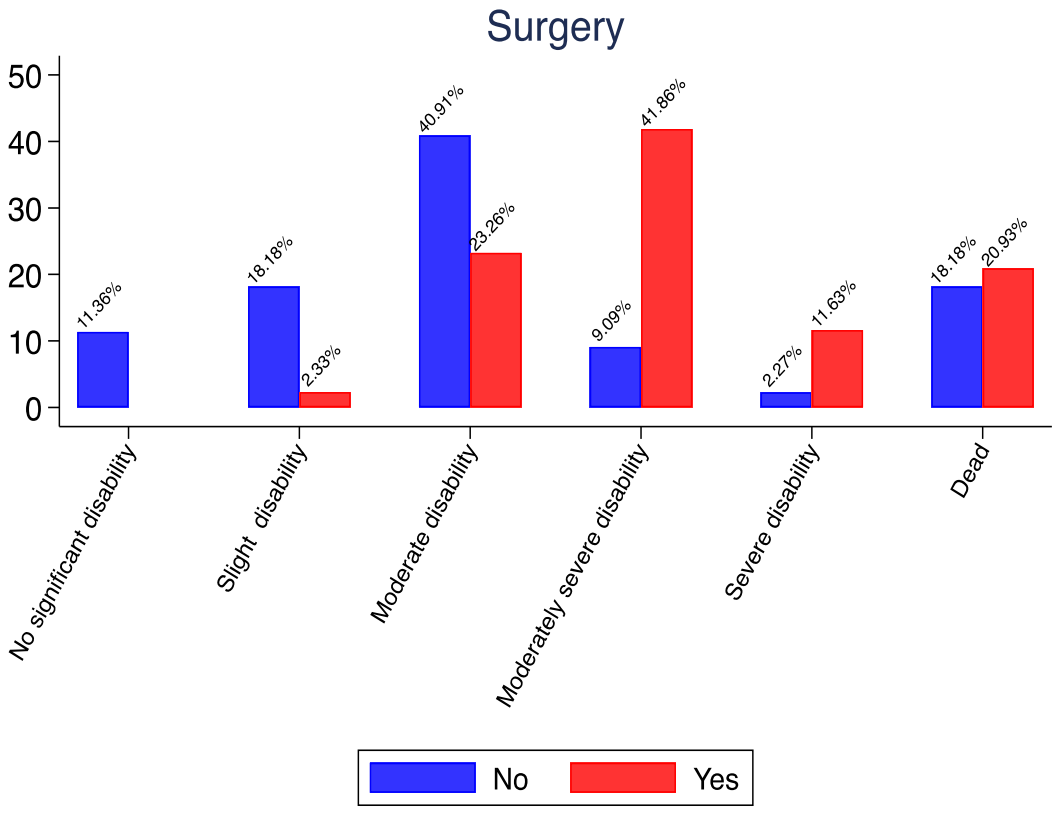


Figure 4.3: Distribution of functional outcomes for all study participants by surgical intervention

4.4.2 Physiotherapy

The proportion of participants who underwent physiotherapy was 64.9% of which the highest proportions had moderate and moderately severe disabilities at 37.1% and 32.3% respectively. Individuals with slight disability, severe disability and death had the same proportion of 9.7% each while 1.6% had no significant disability. On the other hand, among individuals who did not have physiotherapy the highest proportion (44.4%) died within 30 days of CT examination and 22.2% did not have any significant disability.

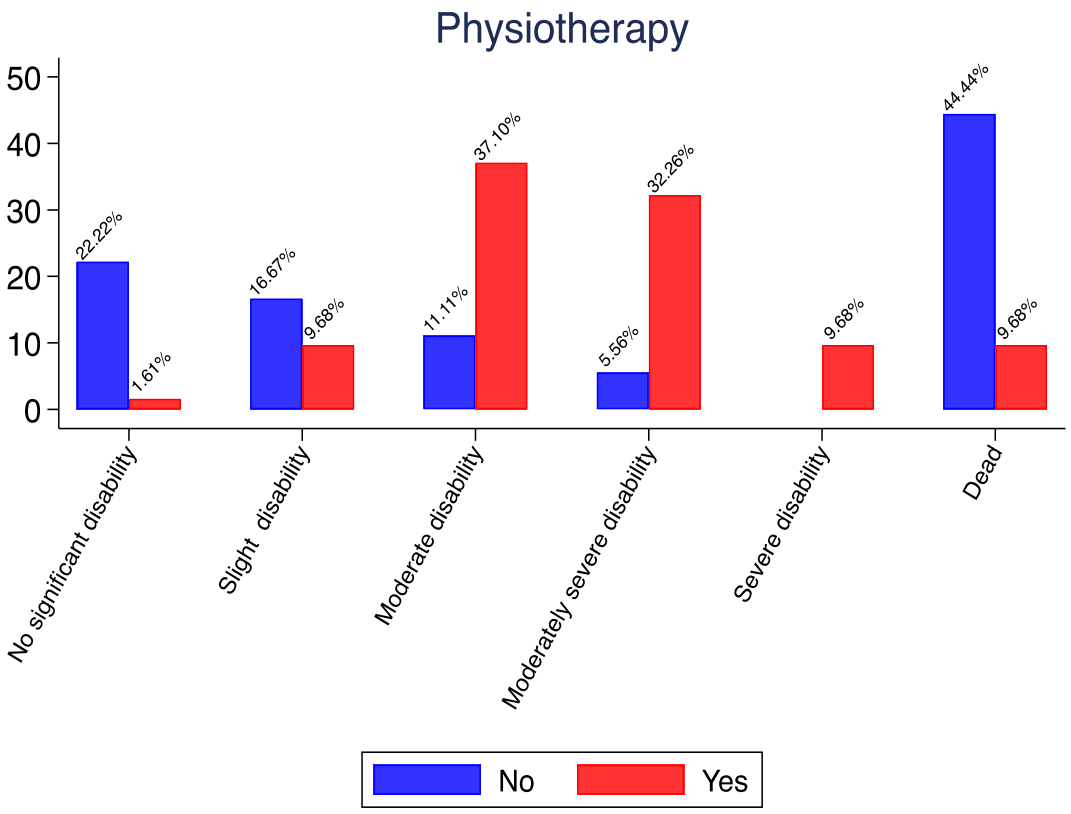


Figure 4.4: Distribution of functional outcomes for all study participants by physiotherapy intervention

4.4.3 ICU admission

Less than a quarter of the study participants (19.4%) were admitted into the intensive care unit (ICU) following intracranial hemorrhage episodes. Majority (36.8%) of those who were admitted in the ICU were deceased within 30 days post CT scan examination. This was followed by individuals with moderate, moderately severe and severe disabilities at 21.1%, 26.3% and 15.8% respectively. Among study participants who were not admitted at the ICU, the majority were deceased (36.8%), moderate disability (35.3%) and moderately severe disability (25%). These findings are presented in figure 4.5 below.

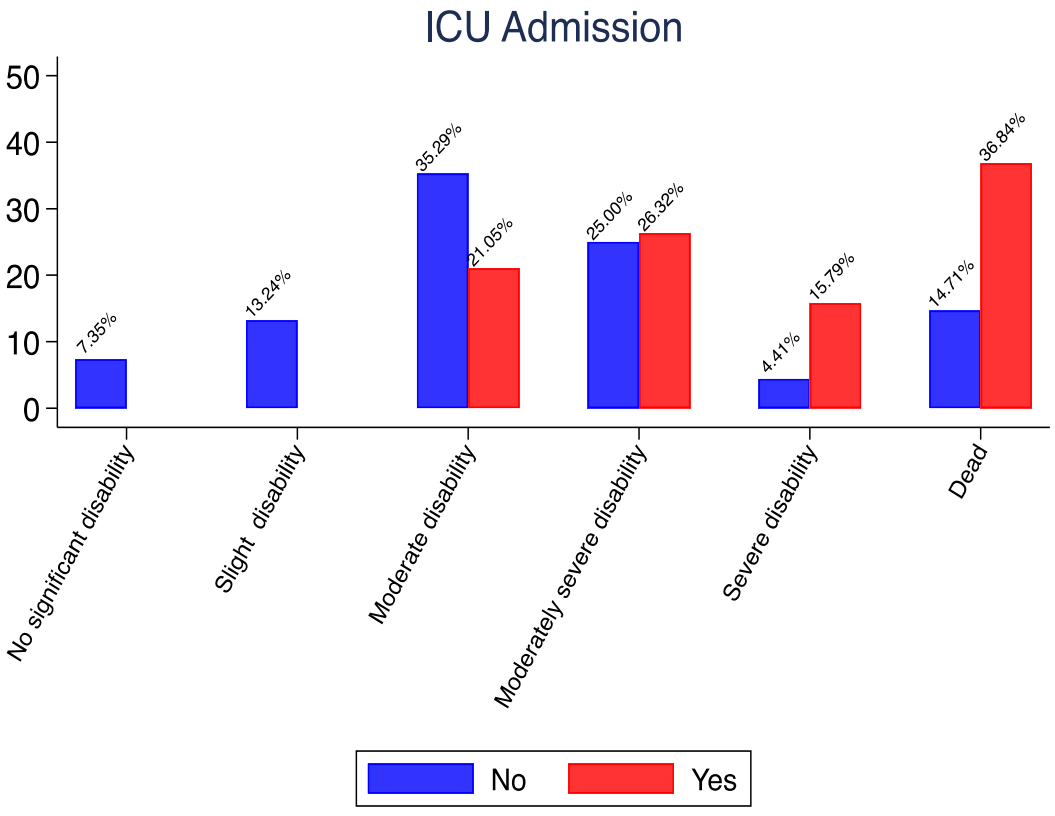


Figure 4.5: Distribution of functional outcomes for all study participants by ICU admission status.

4.5 Association between brain CT findings and functional outcome

Study participants who died within 30 days of CT evaluation had higher mean and median values of hematoma volume and middle shift values. Specifically, the median hematoma volume for individuals who died was 29.8 (IQR: 15.8-67.1) compared to those who were alive at 10.7 (IQR: 4.1-24.6). This difference in median hematoma volume was found to be statistically significant by the Mood's median test $\chi^2_{(1)}$=9.050, p-value= 0.0026. Similarly, the median middle shift was 7.8 (IQR: 0-12) mm and 0 (IQR: 0-4.6) mm for alive and dead study participants respectively. This difference was also found to be statistically significant $\chi^2_{(1)}$=4.419, p-value= 0.0355.

Using the Chi-square test of association, statistically significant effects of CT findings on functional outcomes (Alive/ Dead) were observed on hematoma volume ($\chi^2_{(1)}$=8.69, p-value=<0.001), location ($\chi^2_{(9)}$=15.14, p-value=<0.001), mass effect ($\chi^2_{(1)}$=12.98, p-value=<0.001), hydrocephalus ($\chi^2_{(1)}$=3.89, p-value=0.0486) and herniation ($\chi^2_{(1)}$=37.44, p-value=<0.001). However, statistically significant association between CT findings and functional outcome (Alive/ Dead) was not observed for Intra ventricular extension ($\chi^2_{(1)}$=1.95, p-value=0.1624) and edema ($\chi^2_{(1)}$=0.34, p-value=0.5594). The results of the Moods median test and Chi square test of association are presented in table 4.3 below.

Table 4.3: Test of association/ difference of median between CT findings and functional outcome (Alive/Dead).

CT Finding		Alive	Deceased	Overall	
		n (%)	**n (%)**	**n (%)**	
Hematoma volume (ml)	Mean (±SD)	15.92 (±15.30)	40.46 (±30.25)	22.79 (±23.08)	$\chi^2_{(1)}$=9.050, p-value= 0.0026#*
	Median (IQR)	10.7 (4.1-24.6)	29.8 (15.8-67.1)	16.1 (4.4-30.2)	
Hematoma volume (ml)	< 30 ml	57 (81.43)	14 (51.85)	71 (73.20)	$\chi^2_{(1)}$=8.69, p-value=<0.01*
	≥ 30 ml	13 (18.57)	13 (48.15)	26 (26.80)	
Hematoma location	Deep lobar	37 (52.86)	3 (11.11)	40 (41.24)	$\chi^2_{(9)}$=15.14, p-value=<0.001*
	Lobar	26 (37.14)	17 (62.96)	43 (44.33)	
	Brainstem	2 (2.86)	1 (3.70)	3 (3.09)	
	4th Ventricle	1 (1.43)	1 (3.70)	2 (2.06)	
	Cerebellar	4 (5.71)	5 (18.52)	9 (9.28)	
Mass effect	Absent	29 (41.43)	1 (3.70)	30 (30.93)	$\chi^2_{(1)}$=12.98, p-value=<0.001*
	Present	41 (58.57)	26 (96.30)	67 (69.07)	
Intra ventricular extension	No	47 (67.14)	14 (51.85)	61 (62.89)	$\chi^2_{(1)}$=1.95, p-value=0.1624
	Yes	23 (32.86)	13 (48.15)	36 (37.11)	
Middle shift (mm)	Mean (±SD)	2.38 (±3.34)	6.90 (±5.92)	3.60 (±4.64)	$\chi^2_{(1)}$=4.419, p-value= 0.0355#*
	Median (IQR)	0.0 (0.0-4.6)	7.8 (0.0-12.0)	0.0 (0.0-6.6)	
Hyrocephalus	No	51 (72.86)	14 (51.85)	65 (67.01)	$\chi^2_{(1)}$=3.89, p-value=0.0486*
	Yes	19 (27.14)	13 (48.15)	32 (32.99)	
edema	No	8 (11.43)	2 (7.41)	10 (10.31)	$\chi^2_{(1)}$=0.34, p-value=0.5594
	Yes	62 (88.57)	25 (92.59)	87 (89.69)	
Herniation	Absent	68 (97.14)	12 (44.44)	80 (82.47)	$\chi^2_{(1)}$=37.44, p-value=<0.001*
	Present	2 (2.86)	15 (55.56)	17 (17.53)	

*** Statistically significant (p-value <=0.05), # Moods median test**

Results from the adjusted logistic regression model showed that individuals who were admitted in hospital had lower odds of death compared to those who were not admitted (OR=0.04, p-value=0.002 - 0.42, p-value= 0.008). The results from the model also showed that the odds of death were higher in participants with mass effect (OR=40.06, 95% CI: 1.61 - 994.90, p-value=0.024) and those with edema (OR=81.79,

95% CI:8.25 - 810.62, p-value <0.001) compared to those without mass effect and edema respectively (Table 4.4).

Table 4.4: Logistic regression model results for alive/dead functional outcome

		Unadjusted Models		Adjusted Model	
		OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Sex	**Female**	Ref			
	Male	0.52 (0.21 - 1.27)	0.150	0.25 (0.56 – 1.12)	0.069
Age (in years)		0.98 (0.95 - 1.01)	0.226	1.03 (0.98 - 1.09)	0.230
Admission	**No**	Ref		Ref	
	Yes	0.39 (0.12-1.29)	0.122	0.04 (0.002 - 0.42)	0.008*
Hematoma volume	**< 30 ml**	Ref		Ref	
	≥ 30 ml	4.07 (1.55 - 10.69)	0.004*	1.45 (0.26 - 8.16)	0.672
Mass Effect	**Absent**	Ref		Ref	
	Present	18.39 (2.36 - 143.30)	0.005*	40.06 (1.61 - 994.90)	0.024*
Intraventricular Extension	**No**	Ref		Ref	
	Yes	1.89 (0.77 - 4.69)	0.165	2.77 (0.59 - 13.04)	0.197
Hydrocephalus	**No**	Ref		Ref	
	Yes	2.49 (0.99 - 6.26)	0.052*	1.05 (0.18 - 6.18)	0.960
Edema	**No**	Ref			
	Yes	1.61 (0.32 - 8.13)	0.562	_	
Herniation	**No**	Ref		Ref	
	Yes	42.5 (8.60 - 210.07)	<0.001*	81.79 (8.25 - 810.62)	<0.001*
Surgery	**No**	Ref			
	Yes	1.19 (0.41 – 3.44)	0.747	-	

*** Statistically significant (p-value <=0.05)**

Further analysis on the association between functional outcome based on functional outcome status i.e. (good or poor) and CT findings were also conducted using logistic regression model. Results showed that the individuals who were recommended hospital admission had lower odds of poor outcomes (OR=0.057, 95% CI: 0.01 - 0.51, p-value=0.011). In addition, presence of mass effect and herniation each had higher odds of poor outcomes with OR= 21.59 (95% CI: 1.27-368.24, p-value=0.034) and OR=58.80 (95% CI: 6.83 - 505.91, p-value<0.001) respectively with reference to

absence of mass effect and absence of herniation. These results are presented in table 4.5 below.

Table 4.5: Logistic regression model results for CT findings on functional outcome (Good v/s poor outcomes)

		Unadjusted Models		Adjusted Model	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Sex	**Female**	Ref			
	Male	0.69 (0.20 - 2.32)	0.547	_	
Age (in years)		1.00 (0.96 - 1.04)	0.837	_	
Admission	**No**	Ref		Ref	
	Yes	7.01 (1.37 - 36.52)	0.020*	0.057 (0.01 - 0.51)	0.011*
Hematoma volume	**< 30 ml**	Ref		Ref	
	≥ 30 ml	3.55 (0.42 - 29.89)	0.245	1.22 (0.22-6.82)	0.824
Mass Effect	**Absent**	Ref		Ref	
	Present	3.24 (0.95 - 10.10)	0.059	21.59 (1.27-368.24)	0.034*
Intraventricular Extension	**No**	Ref		Ref	
	Yes	3.6 (0.73 - 17.68)	0.115	2.50 (0.57-10.91)	0.223
Hydrocephalus	**No**	Ref		Ref	
	Yes	6.16 (0.75 - 50.78)	0.091	1.01 (0.18-5.80)	0.989
Edema	**No**	Ref			
	Yes	0.54 (0.06 - 4.78)	0.578	_	
Herniation	**No**	Ref		Ref	
	Yes	4.23 (2.31 - 7.74)	<0.001*	58.80 (6.83 - 505.91)	<0.001*
Surgery	**No**	Ref			
	Yes	18.65 (2.27-152.7)	0.006	0.36 (0.04 -3.21)	0.361

*** Statistically significant (p-value <=0.05)**

SAMPLE IMAGES

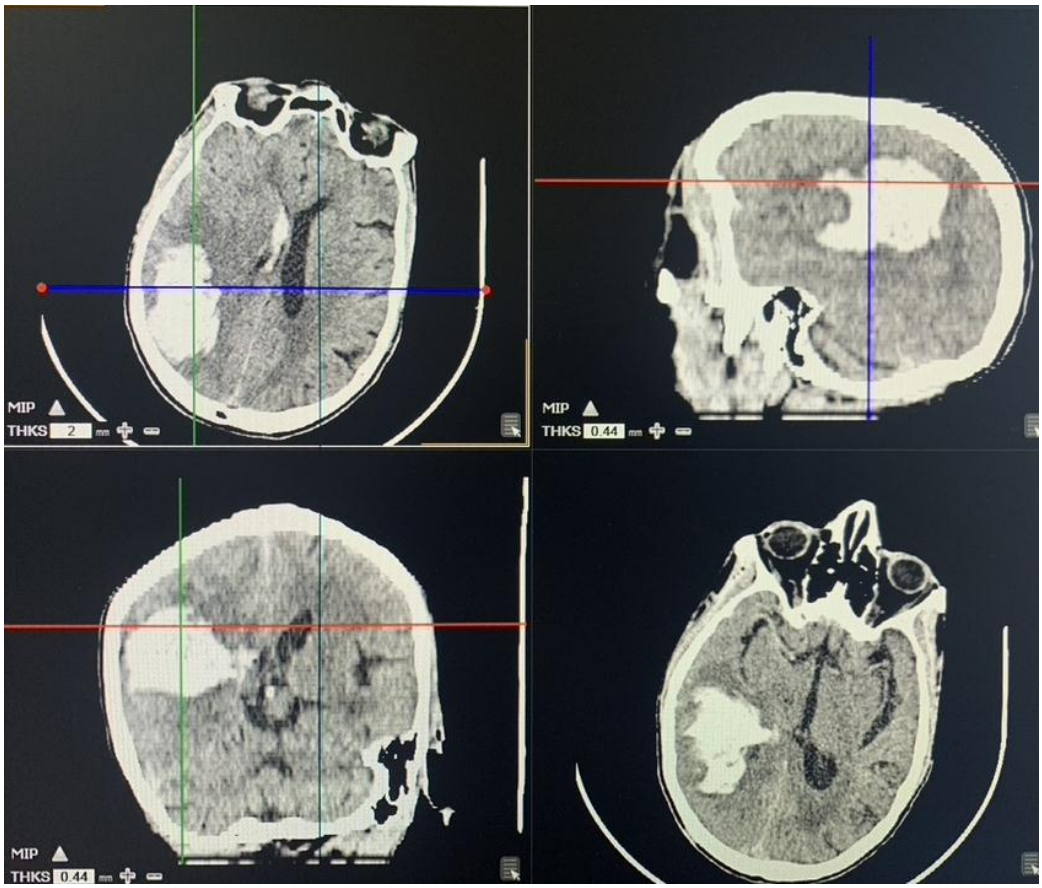


Image 3: **Multiplanar Non-enhanced Brain CT of a 55-year-old male in axial, sagittal and coral planes. The images demonstrate a right parietal temporal hyperdense lesion with surrounding hypodense area, midline shift and intraventricular hemorrhage.**

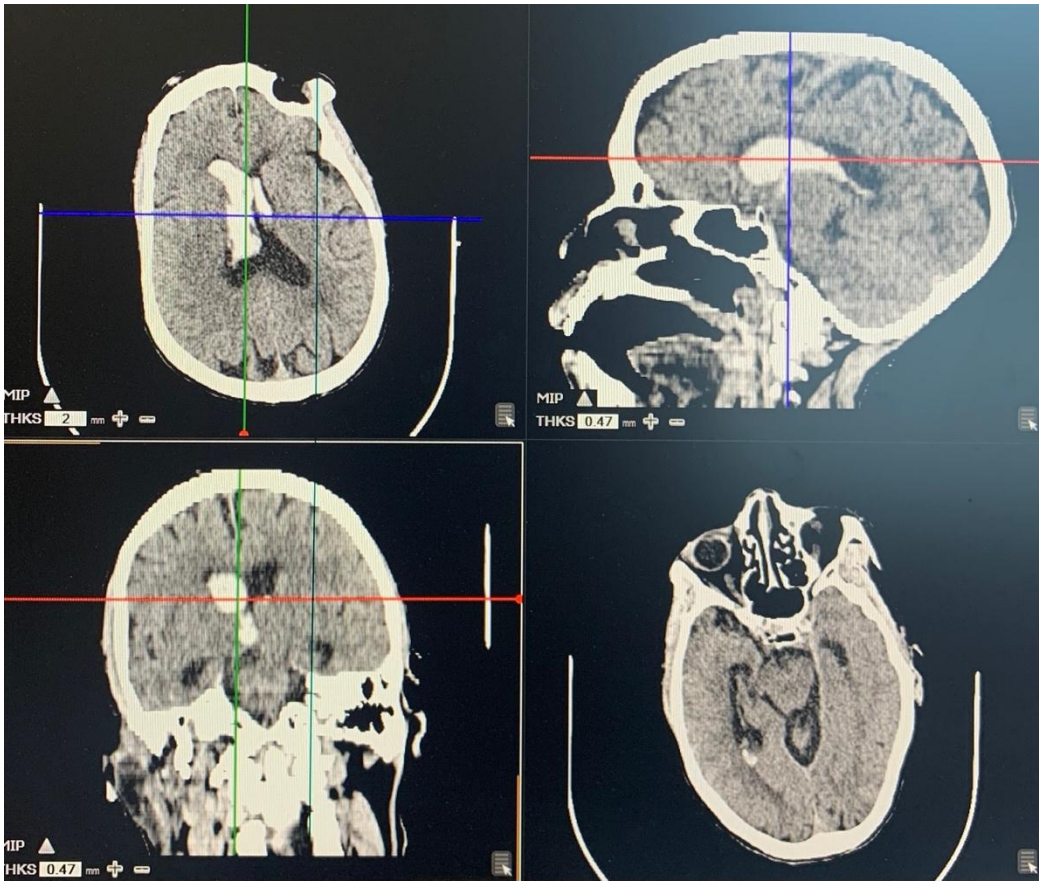


Image 4: **Multiplanar non-enhanced Brain CT of a 76-year-old male in axial, sagittal and coral planes. The images demonstrate a hyperdense lesion in the right caudate nucleus with intraventricular extension of the ipsilateral lateral ventricle and the third ventricle.**

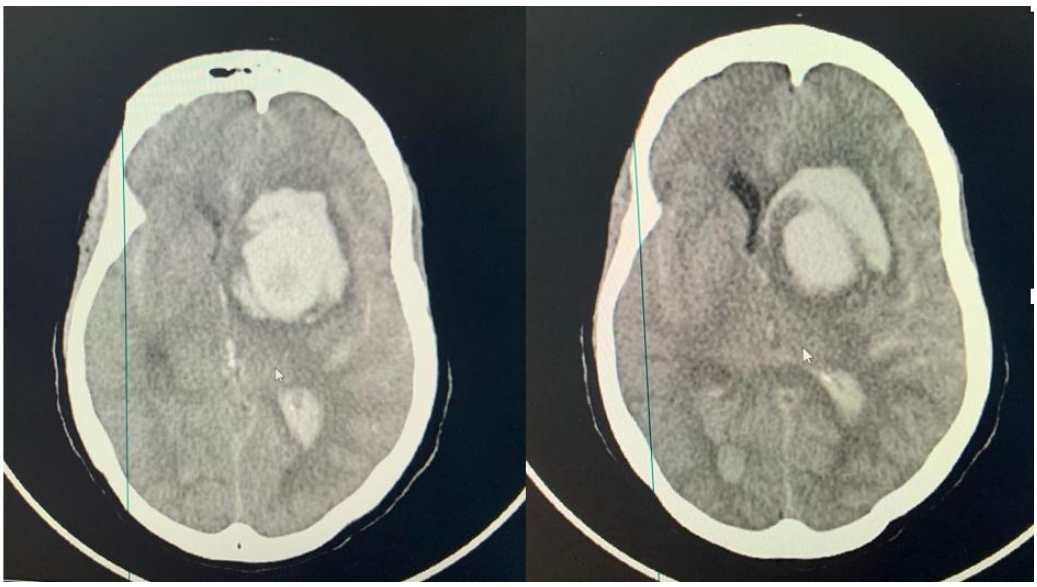


Image 5: **Non-enhanced Brain CT of a 44-year-old female in axial plane. The images demonstrate a hyperdense lesion in the right basal ganglia. There is perilesional hypodense area that depicts edema and midline shift due to mass effect. Intraventricular hemorrhage is seen in the ipsilateral lateral ventricle and subarachnoid hemorrhage.**

CHAPTER FIVE: DISCUSSION

5.1 Introduction

Globally, intracranial hemorrhage is a major contributor to the burden of strokes and has greater morbidity and mortality compared to ischemic strokes (An et al., 2017; Asch et al., 2010). Africa is faced by a huge paucity of data on non-traumatic intracranial hemorrhage, the available treatment options and the role played by neuro-imaging in patient care and management (Feigin et al., 2009; Hegde et al., 2020; Kengne & Anderson, 2016; Mensah, 2008; Nakibuuka et al., 2015; Namale et al., 2020). This study therefore aimed to describe the patterns and non-traumatic intracranial hemorrhage at MTRH.

Results from this study showed that study participants had a mean age of 59 years, and the majority (71%) were aged above 50 years. Similar findings have showed that patients with spontaneous intracranial hemorrhage have a high mean age of 56 years in Cameroon and Nigeria and 62 years in Turkey (Adeleye et al., 2015a; Celikbilek et al., 2013; Doumbe et al., 2020a). Similar findings to those from MTRH indicating that majority of the participants were aged above 50 years were reported as 66.7% of participants were above 50 years and 50.6% were aged above 55 years in Nigeria and Cameroon respectively (Adeleye et al., 2015b; Doumbe et al., 2020a). In a tertiary hospital in southern Ghana, Edzie et al., (2021) reviewed patient charts of 435 patients diagnosed with spontaneous intracranial hemorrhage and reported a mean age of 61 years with the predominant age band being those aged above 60 years (56.8%). In central Africa, a study conducted on 185 patients with known hypertensive with intracerebral hemorrhage reported a mean age of 53.7 (±9.2) years (Tshikwela & Longo-Mbenza, 2012). In a 7 years retrospective population-based study, the reported mean age was 74.8 (±12.1) years and 56.6% were aged above 76 years from a total of

452 patients with spontaneous intracerebral hemorrhage in Norway (Øie et al., 2018). In south India, from a total of 905 patients with spontaneous intracerebral hemorrhage were recruited in a 3-year prospective study, the reported mean age was 58.10 (±12.8) years and 70.6% of the participants were aged at least 50 years (Hegde et al., 2020).

There were more males (53%) than females (47%) recruited into this study at MTRH. Adeleye et al., (2015a) also reported more males (60.3%) than females (39.7%), though the difference of proportions between the two genders was larger than that observed in this study. Similarly, Doumbe et al., (2020a) reported more male (64%) than female (36%) participants with spontaneous intracerebral hemorrhage. A separate study on 435 participants in southern Ghana also reported a higher proportion of spontaneous intracranial hemorrhage in males (51.5%) compared to females (48.5%) (Edzie et al., 2021). Outside the African continent, a higher proportion of 56.6% was males compared to females (43.4%) by Celikbilek et al., (2013) in Turkey. Similarly in Malaysia, out of 160 patients with spontaneous intracranial hemorrhage 58% were males and 42% were females (Rathor et al., 2012). In the United States, the gender distribution was 50% for each gender in a study of 67 patients with spontaneous supratentorial intracranial hemorrhage who underwent two or more CT scans (Zazulia et al., 1999). In the Norwegian population based retrospective study, the majority of the patients were males (54.4%) out of a total of 452 patients (Øie et al., 2018). Additional results from south India also reported that males (70.5%) were the predominant gender out of 905 patients recruited from a tertiary hospital (Hegde et al., 2020).

At MTRH, about 44% and 65% of the study participants underwent surgical procedures and physiotherapy respectively as part of their therapy. Adeleye et al., (2015b) reported a lower proportion of patients who were surgically treated (36.5%) compared to findings from MTRH. In addition, about a quarter (25.8%) of 186 participants in Spain and 22.4% of 905 patients in south India were treated operatively following spontaneous intracerebral hemorrhage (Ferrete-Araujo et al., 2015; Hegde et al., 2020).

5.2 CT findings of spontaneous intracranial hemorrhage

Findings from MTRH showed that out of the 97 spontaneous intracranial hemorrhage episodes that were reported, majority 84 (85.7%) occurred in the supratentorial regions while 14 (14.3%) occurred at the infratentorial regions. These findings are consistent with those from Nigeria whereby out of 63 participants, 90.5% of the spontaneous intracerebral hemorrhage occurred in the supratentorial regions, 7.9 in the infratentorial region and 1.6% in supra- with infratentorial component (Adeleye et al., 2015a).

Findings from MTRH also showed that the proportion of location of bleeds were lobar (44.3%), deep lobar (41.2%), cerebellar (9.3%), brain stem (3.1%) and the 4th ventricle (2.1%). These findings were contrary to those from Nigeria whereby out of 50 supratentorial bleeds, 17.5%, 23.8% and 50.8% occurred in the superficial lobar, deep lobar and ganglionic regions respectively (Adeleye et al., 2015b). At the Douala General Hospital in Cameroon, out of 261 patients with spontaneous intracerebral hemorrhage the observed bleeds occurred in the basal ganglia (85.1%), lobar (10.7%), brainstem (2.7%) and cerebellar (1.5%) parts of the brain (Doumbe et al., 2020a). Out of 905 patients at a tertiary hospital in south India, the majority of bleeds were

observed in the basal ganglia (52.8%), thalamus (22.3%), lobar (11.7%), cerebellar (6.7%), brainstem (3.4%) and the 3.0% at the primary intraventricular hemorrhage (Hegde et al., 2020).

Out of 76 patients in the United States, the distribution of bleeding locations were 51.3%, 23.7% and 25% in the basal ganglia, thalamus and lobar respectively (Zazulia et al., 1999). Øie et al.,(2018) reported CT findings for 451 (99.8%) of the patients recruited in the study. Reported results from this Norwegian study showed the distribution of the location of bleeds as; lobar (40.9%), deep lobar (44.9%), brain stem (5.1%), cerebellum (8.2%) and strict intraventricular hemorrhage (0.7%) (Øie et al., 2018). These hemorrhage locations in descending order of proportions were similarly reported in this study at MTRH at the lobar and deep lobar locations. In Spain, a prospective observational study was conducted on 186 patents with severe spontaneous intracerebral hemorrhage the reported bleeding locations as; cerebral hemorrhage (40.3%), cerebellar hemorrhage (15.6%), intraventricular hemorrhage (75.3%), basal ganglia (53.2%) and brainstem (10.8%) (Ferrete-Araujo et al., 2015).

At MTRH, over 73% of the participants had hematoma volume of less than 30ml and 27% had hematoma volume of greater than or equal to 30ml. These findings are consistent with those from Turkey where Celikbilek et al., (2013) reported that 82% of the participants had hematoma volume of less than 30ml. In addition, a study conducted in Finland reported that 77% of 972 participants with spontaneous intracerebral hemorrhage had less than 30ml hematoma volume (Fallenius et al., 2019). However, the Finnish study was a retrospective multicenter study using the Finnish intensive care database from 2003 to 2013 compared to this study which was prospective and conducted at a single site (MTRH). In addition, Fallenius et al.,

(2019) used a follow-up duration of 12 months compared to a 30 day follow-up duration used in this study at MTRH. In Norway, 65.9% of the patients had hematoma volume of less than 30ml, 14.8% had 30-60 ml and 18.1% had hematoma volume greater than 60 ml (Øie et al., 2018). Similarly, out of 905 patients with spontaneous intracerebral hemorrhage in south India, majority (74.1%) had a hematoma volume of less than 30 ml (Hegde et al., 2020).

Further analysis showed that there was mass effect in 69% of 97 participants with spontaneous intracranial hemorrhage. Similar findings of mass effect in majority of the patients was observed in the United states whereby 88% of 67 patients had mass effect (Zazulia et al., 1999). Contrary findings by Doumbe et al., (2020a) indicated presence of mass effect in a quarter (25.7%) of 261 patients with spontaneous intracerebral hemorrhage. Ferrete-Araujo et al., (2015) reported presence of mass effect in 69.4% of 186 patients recruited in the study; 84.6% and 85.1% presence of mass effect in patients admitted in the ICU (n=65) and general hospital admission (n=87) respectively.

Midline shift (>=5 mm) was noted in about a third (33.7%) of the study participants at MTRH compared to 88% of participants in the study by Zazulia et al., (1999). Similar findings were observed in Finland where 33% of 972 patients under intensive care experienced midline shift of >=5mm (Fallenius et al., 2019). In the Turkish study, midline shift was observed in 41.5% of 106 patients in a retrospective study of patients with spontaneous intracerebral hemorrhage (Celikbilek et al., 2013). However, Celikbilek et al., (2013) did not specify the cutoff value used to define midline shift unlike in this study and those reported in the united states and Finland (Fallenius et al., 2019; Zazulia et al., 1999). Tshikwela & Longo-Mbenza (2012)

reported presence of midline shift in 44.9% of 185 hypertensive patients with spontaneous intracerebral hemorrhage in the Democratic Republic of Congo (DRC). However, Tshikwela & Longo-Mbenza (2012) used a midline shift cutoff of greater than or equal to 7 mm rather than 5mm as discussed in this study at MTRH.

About 37.1% of the study participants in this study had intraventricular extension. These findings are similar to those reported in the Turkish study whereby intraventricular extension was reported 36.8% of 135 patients (Celikbilek et al., 2013). A slightly higher proportion of intraventricular extension (47%) was reported in south India from a total sample size of 905 patients (Hegde et al., 2020).

At MTRH, hydrocephaly was observed in a third of the participants in this study. In Germany, a study on spontaneous intracerebral hemorrhage with ventricular extension reported an overall hydrocephalus proportion of 92% in 155 patients (Stein et al., 2010). Stratified results by Stein et al., (2010) reported presence of hydrocephalus in 89.4% and 98% in the retrospective (n=104) and prospective (n=51) cohorts respectively. Hegde et al., (2020) reported hydrocephalus in over a quarter (26.1%) of the 905 study participants recruited in India.

In this study, edema was observed in 89.7% of the study participants which was contrary to a small proportion of 8.8% that was observed in Cameroon (Doumbe et al., 2020a). Results from Spain by Ferrete-Araujo et al., (2015) also showed a slightly lower proportion of edema (70.4%) compared to findings from MTRH. In China, 59 patients were admitted with spontaneous intracerebral hemorrhage of which edema was observed in 36 (61%) of the patients on day 3 MRI examination (Li et al., 2013). In contrast to this study conducted at MTRH, Li et al., (2013) examined presence of

edema on day 3 using MRI compared MTRH where edema was evaluated within 24 hours.

Herniation was observed in 17.5% of the 97 patients recruited in the MTRH study. This proportion was relatively lower than those observed in India whereby herniation was reported in 46% of a relatively smaller sample size of 24 patients (Kalita et al., 2009). In Cameroon, Doumbe et al., (2020a) observed herniation in 5% from a total of 704 patients which was considerably a lower proportion of herniation compared to results from MTRH.

5.3 Functional Outcomes

In this study, 67.0% of the study participants had a modified ranking score of greater than 2 and a fatality of 27.8%. Similarly, 61.5% of 261 patients at the Doula General Hospital in Cameroon had a modified ranking score of >2 and 46% fatalities were observed in the first month of evaluation (Doumbe et al., 2020). Contrary to this study at MTRH, Doumbe et al., (2020) further reported the proportion of patients ranking score >2 at the third month (50%) and case fatalities at the third (59.8%) and sixth (63.2%) months. Stein et al., (2010) reported an overall 30-day mortality of 28.4% for all patients; 29.8% in the retrospective cohort (n=104) and 25.5% in the prospective cohort (n=51).

In a study conducted on 411 patients in central Finland, 7.3% died prior to admission and 50.6% died within the first 28 days of spontaneous intracerebral hemorrhage diagnosis. In addition, 87.3 % of the patients were conservatively treated and 6.3% required surgical evacuation of the hematomas (Fogelholm et al., 2005). In Norway, Øie et al., (2018) conducted functional outcome assessments using the modified ranking score at 3 and 12 months after Spontaneous intracerebral hemorrhage.

Results from Norway showed that the overall median modified ranking scale score at both 3 and 12 months was 5 compared to a median score of 4 from this study at MTRH. However, the Norwegian study conducted patients' functional outcome assessments after a longer period (3 and 12 months) compared to the 30-day period used in this study at MTRH.

In south India, Hegde et al., (2020) reported an overall mortality at discharge of 12.8%, 3-month mortality of 30.1%, favorable outcomes (ranking scale score = 0 to 3) of 45.5% and poor outcomes (ranking scale score = 4 to 5) of 22.9%. Compared to findings from this study at MTRH, the proportion of patients stratified by ranking scale score by Hegde et al.,(2020) were; No significant disability (7.2% v/s 5.2%), Slight disability (14.4% v/s 9.3%), Moderate disability (21.9% v/s 28.9%), Moderately severe disability (17.7% v/s 22.7%) and Severe disability (5.5% v/s 6.0%). In general, the comparison between the two studies shows that the proportions of 30-day good outcomes (No to slight disability) were lower at MTRH compared to the 90-day good outcomes from south India. However, the proportions of poor outcomes (moderate to severe disability) were higher at MTRH compared to south India. Such results are expected due to the difference in times (30-day v/s 90-day) that functional outcomes assessments were conducted in the two studies.

Further findings from Norway showed the proportion of severe disability and fatalities at 3 months were 18.9% and 39.2% respectively and 4.8% and 44.9% respectively at 12 months (Øie et al., 2018). In Spain, the median modified ranking scale score was 5 (IQR: 4-6) at 6 months of follow-up, following spontaneous intracerebral hemorrhage. (Ferrete-Araujo et al., 2015). Further results by Ferrete-Araujo et al., (2015) that out of the 186 patients recruited in the Spanish study, 99

were alive at 6 months of which 20.4 had good functional outcomes (ranking scale score = 1 and 2) and 32.8% had poor functional outcomes (ranking scale score = 3, 4 and 5).

5.4 Association between CT findings and functional outcome

In this study, there was statistically significant association between functional outcomes (Alive or Dead) and CT findings on hematoma volume, location, mass effect, hydrocephalus, and herniation. Results from the adjusted regression model showed that individuals who were hospitalized had lower odds of death (OR=0.04, 95% CI: 0.002 - 0.42, p-value=0.008) compared to those who were not admitted in hospital. Presence of mass effect (OR=40.06, 95% CI: 1.61 - 994.90, p-value=0.024) and herniation (OR= 81.79 95% CI: 8.25 - 810.62, p-value <0.001) were associated with higher odds of death. Further analysis was used to investigate the association between CT findings and functional outcomes classified as poor (ranking scale score = 1 and 2) or good (ranking scale score = 3, 4 and 5) outcomes. In this analysis, results showed that the odds of good outcomes were lower among those who were admitted in hospital (OR=0.057, 95% CI: 0.01 - 0.51) compared to those who were not. In addition, presence of mass effect (OR=21.59, 95% CI:1.27-368.24, p-value=0.034) and herniation (OR=58.80, 95% CI: 6.83 - 505.91, p-value<0.001) were associated with higher odds of poor outcomes at day 30 of evaluation. It is worth noting that there were instances of very wide confidence intervals in the estimates obtained from this study. This is attributed to the low sample size (n=98) obtained from MTRH.

Similar to findings from MTRH, Doumbe et al., (2020b) reported that presence of mass effect (OR=3.6, 95% CI: 1.2 – 10.4, p-value=0.020) using a multivariate model was associated with poor functional outcomes. The authors also reported hyperthermia (OR=4.6, 95% CI: 1.3 – 16.1, p-value = 0.015) as an important predictor of poor outcomes. However, hyperthermia was not collected in the MTRH study.

In South India, Hegde et al., (2020) reported unadjusted results showing that age above 70 years (OR 4.806, 95% CI: 3.064 - 7.54, p-value <0.001), hematoma volume (OR= 2.45, 95% CI: 1.626 – 3.691, p-value <0.001) and hydrocephalus (OR=1.78, 95% CI:1.12 – 2.81, p-value = 0.014) were independent predictors of mortality at three months. In addition, the authors identified intraventricular extension (OR= 1.69, 95% CI: 1.11- 2.89, p-value=0.015) and hematoma volume >30 ml (OR= 4.26 95% CI: 2.66 – 6.84, p-value < 0.001) as important predictors with increased odds of poor outcomes at 3 months. These reported results from India are consistent with findings from the unadjusted models at MTRH. However, there was a difference in the assessment period between the two studies whereby evaluation of functional outcomes was conducted at 3 months in India compared to 30 days at MTRH.

Araujo et al., (2015) used cox proportional hazards model to model the risk of death using hazard ratios (HR). In their results, the authors reported an increased risk of fatality for patients with intraventricular extension in the ICU (HR=2.36, 95% CI: 1.32 – 6.35, p-value=0.047) and those in hospital wards (HR=3.21, 95% CI: 1.55 – 6.67, p-value=0.002). In addition, there was increased risk of death for those in the ICU that experienced increased hematoma volume in cubic centimeters was (HR=1.99, 95% CI: 1.14 – 3.46, p-value=0.014). The authors further reported

increased risk of poor clinical outcomes (ranking score >=3) for intraventricular extension (RR=1.67, 95% CI: 1.13 – 2.48, p-value=0.010), increasing age (RR=1.02, 95% CI: 1.01 – 1.03, p-value=0.007) and increasing hematoma volume in cubic centimeters (RR=1.007, 95% CI: 1.002 – 1.011, p-value = 0.002). Although the statistical methodology is different from that used in this study, results from both studies are consistently indicative of increased risk/ odds of mortality or poor outcomes with selected CT findings.

5.5 Limitations of the study

The following section highlights several limitations faced during the execution of the study:

There was potential intra-observer bias in reading the CT images of the patients. To mitigate against such biases, the images were read by the principal investigator and later reviewed by two consultant radiologists who were blinded from the patients' history.

CHAPTER SIX: CONCLUSIONS AND RECOMMEDATIONS

6.1 Conclusion

This study examined brain CT findings and investigated their effect on functional outcomes following non-traumatic intracerebral hemorrhage. Therefore, the following conclusions are made:

1. Non-traumatic intracerebral hemorrhage predominantly occurred in the supratentorial region and more specifically in the lobar and deep lobar regions. Further CT findings observed on majority of the participants showed presence of hematoma volume of less than 30ml, mass effect and edema. The other parameters assessed in this study namely: Intra ventricular extension, hydrocephalus and herniation were seen in minority of the cases.
2. The 30-day case fatalities were over a quarter of the study participants, majority had poor outcomes with a median modified ranking score of 4.
3. The hematoma volume more than 30 ml, the presence of mass effect and herniation were observed as independent predictors of functional outcomes and higher odds observed with mass effect and herniation among participants with non-traumatic intracerebral hemorrhage.

6.2 Recommendations

Based on the findings of this study, the following recommendations are made:

A larger study with a longer follow up and outcome evaluation at 3 months or more be conducted at MTRH to allow directed comparison of results between MTRH and other settings.

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APPENDIX

Appendix1: Consent form

Investigator: My name is Zipporah Mwebi, I am a qualified doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a master's degree in Radiology and Imaging at Moi University. I would like to recruit you into my research which is to study **Brain computer tomography findings and outcomes of patients with non-traumatic intracranial hemorrhage in major hospitals within Eldoret, Kenya.**

Purpose:

Procedure: All patients sent to the radiology and imaging department of the major hospitals in Eldoret with imaging findings of non-traumatic intracranial hemorrhage will be recruited into the study. An interviewer administered questionnaire will be used to collect data. Data collecting material will be kept in a locked cabinet in the office of the principal investigator during the study period.

Benefits: There will be no direct benefits of participating in this study. Study subjects will be accorded same quality of management as non-study subjects. The feedback from my findings will be shared with you and the institution and this will help in management of the patients.

Risks: There are no anticipated risks to the participants attributable to this study.

Confidentiality: All information obtained in this study will be treated with utmost confidentiality and shall not be divulged to any unauthorized person

Rights to Refuse: Participation in this study is voluntary, there is freedom to decline to take part or withdraw at any time. This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital and other major hospitals in Eldoret.

Sign or make a mark if you agree to take part in the study.

Parent/Guardian
Signature……. Date……..

Investigator
Signature……. Date……..

Consent form (Swahili)

MOI TEACHING & REFERRAL HOSPITAL / MOI UNIVERSITY
COLLEGE OF
SAYANSI YA AFYA -UTAFITI WA TAASISI NA
KAMATI YA MAADILI(MTRH/MU-IREC)

FOMU YA RIDHAA INAYOFAHAMISHWA

Kichwa cha Utafiti**: MATOKEO NA MATOKEO YA TOMOGRAFI YA UBONGO NA MATOKEO YA WAGONJWA WA KUTOKWA NA MADHARA NDANI YA UPYA ISIYO NA MSITUKO KATIKA HOSPITALI YA MAFUNDISHO NA RUFAA MOI ELDORET, KENYA.**

Jina la Mpelelezi Mkuu: ZIPPORAH MWEBI

Fomu ya Idhini Iliyoarifiwa kwa:

Wagonjwa na walezi wa wagonjwa ambao hawawezi kutoa kibali.

Fomu hii ya Idhini yenye Taarifa ina sehemu mbili:

• Sehemu ya I: Karatasi ya Taarifa [kushiriki nawe taarifa kuhusu utafiti]

• Sehemu ya II: Cheti cha Idhini [kwa saini ukichagua kushiriki]

SEHEMU YA I: KARATASI YA HABARI

Utangulizi:

Unaombwa kushiriki katika utafiti wa utafiti. Taarifa hii imetolewa ili kukuambia kuhusu utafiti. Tafadhali soma fomu hii kwa makini. Utapewa nafasi ya kuuliza maswali.

Kushiriki katika utafiti huu ni kwa hiari. Kusema hapana hakutaathiri haki zako za utunzaji wa afya au huduma zingine zozote. Matibabu/malipo au uandikishaji wako katika mipango yoyote ya afya au ustahiki wa manufaa hautaathiriwa ukiamua kutoshiriki. Pia uko huru kujiondoa kwenye utafiti huu wakati wowote. Ikiwa baada ya kukusanya data utachagua kuacha, unaweza kuomba kwamba maelezo uliyotoa yaharibiwe chini ya usimamizi. Hii itakuwa kabla ya data haijatambuliwa na kujumlishwa. Utaarifiwa iwapo taarifa mpya itapatikana kuhusu hatari au manufaa ya utafiti huu. Utapokea nakala ya fomu hii baada ya kusainiwa

Madhumuni ya utafiti:

Madhumuni ya utafiti ni kutathmini matokeo ya kazi mwanzoni na mwisho wa siku 30 na kulinganisha na matokeo ya CT ya wagonjwa wenye kutokwa na damu isiyo ya kiwewe ya ndani.

Tovuti ya masomo:

Kitengo cha Radiolojia ya Hospitali ya Kufundisha na Rufaa ya Moi, wodi za Neurology na wagonjwa wa nje.

Idadi ya watu waliosoma:

Idadi ya waliotafitiwa itajumuisha watu wazima wote walio na matokeo ya CT ya ubongo ya kuvuja damu ndani ya fuvu katika idara za radiolojia za MTRH.

Taratibu za masomo:

Huu utakuwa utafiti wa kikundi unaotarajiwa wa hospitali uliofanywa katika kipindi cha mwaka mmoja. Mshiriki/walezi wote wa washiriki wanaokidhi vigezo vya ujumuishi watahitajika kujaza fomu hii ya idhini. Baada ya hapo, dodoso linalosimamiwa na mhojaji litatumika kukusanya data na tathmini ya utendaji itafanywa wakati wa kuajiri na mwisho wa siku 30. Ubongo wa CT unaofanywa utaangaliwa na PI na mtaalamu wa radiolojia wawili waliohitimu na ripoti itatolewa kwa mtoaji wako wa huduma ya msingi.

Ukikubali utafanya yafuatayo:

Mshiriki/mlezi kwa mshiriki atahitajika kusaini kibali na kutoa mawasiliano kwa ajili ya ufuatiliaji.

Faida:

Hakutakuwa na manufaa ya moja kwa moja ya kushiriki katika utafiti huu. Masomo ya masomo yatapewa ubora sawa wa usimamizi kama masomo yasiyo ya masomo.

Hatari/Masumbuko:

Hakuna hatari/ usumbufu unaotarajiwa kwa washiriki kutokana na utafiti huu.

Malipo na Marejesho:

Iwapo mshiriki hatakuwa ndani ya MTRH mwishoni mwa siku 30, utawasiliana na mtoaji na kuombwa kuja kliniki kwa uchunguzi upya. Gharama ya hii itatozwa na PI lakini risiti na ushahidi wa malipo lazima itolewe kwa ajili ya kurejesha. Gharama itatosheleza mshiriki na mlezi mmoja.

Usiri:

Juhudi zote zinazofaa zitafanywa ili kuweka maelezo yako yaliyolindwa (ya faragha na ya siri). Kutumia au kushiriki (“kufichua”) kwa maelezo kama haya kutafuata miongozo ya faragha ya Kitaifa. Kwa kutia sahihi hati ya idhini ya utafiti huu, unatoa ruhusa ("idhini") kwa matumizi na ufichuaji wa maelezo yako ya utafiti. Huenda tukahitaji kushiriki habari zako zinazolindwa na bodi ya ushauri ya jamii, MTRH//MU-IREC, NACOSTI au timu ya afya. Tutahifadhi rekodi zako za utafiti

kwa angalau miaka sita baada ya utafiti kukamilika. Wakati huo, taarifa za utafiti huharibiwa [Mfahamishe mshiriki jinsi rekodi zitakavyoharibiwa]. Ukiamua kuondoa ruhusa yako ya kutumia data yako ya kibinafsi, wasiliana na [PI] kwa maandishi na uwajulishe uamuzi wako. Wakati huo, tutasimamisha mkusanyiko zaidi wa taarifa yoyote kukuhusu. Hata hivyo, maelezo ya afya yaliyokusanywa kabla ya uondoaji huu yanaweza kuendelea kutumika kwa madhumuni ya kuripoti na ubora wa utafiti.

[SI LAZIMA]: Kwa tafiti zinazohusisha wagonjwa, eleza kuwa maelezo yao yataongezwa kwenye rekodi zao za matibabu na kwamba taarifa yoyote ya utafiti itakayowekwa kwenye rekodi zao za matibabu itawekwa kwa muda usiojulikana.

SEHEMU YA PILI: RIDHAA YA MGONJWA:

Nimesoma au kuna mtu amenisomea maelezo ya utafiti huu. Mpelelezi au mwakilishi wake amenieleza utafiti na amejibu maswali yote niliyo nayo kwa wakati huu. Nimeambiwa kuhusu hatari zinazoweza kutokea, usumbufu, na manufaa yanayoweza kutokea (ikiwa yapo) ya utafiti. Ninajitolea kwa hiari kushiriki katika utafiti huu.

Mshiriki/mlezi anapaswa kusaini au kutoa alama ya kidole gumba iwapo atakubali kushiriki katika utafiti.

_____ _____ _____

Jina la Mshiriki /mlezi Sahihi/Alama ya kidole gumba Tarehe & Saa

_____ _____

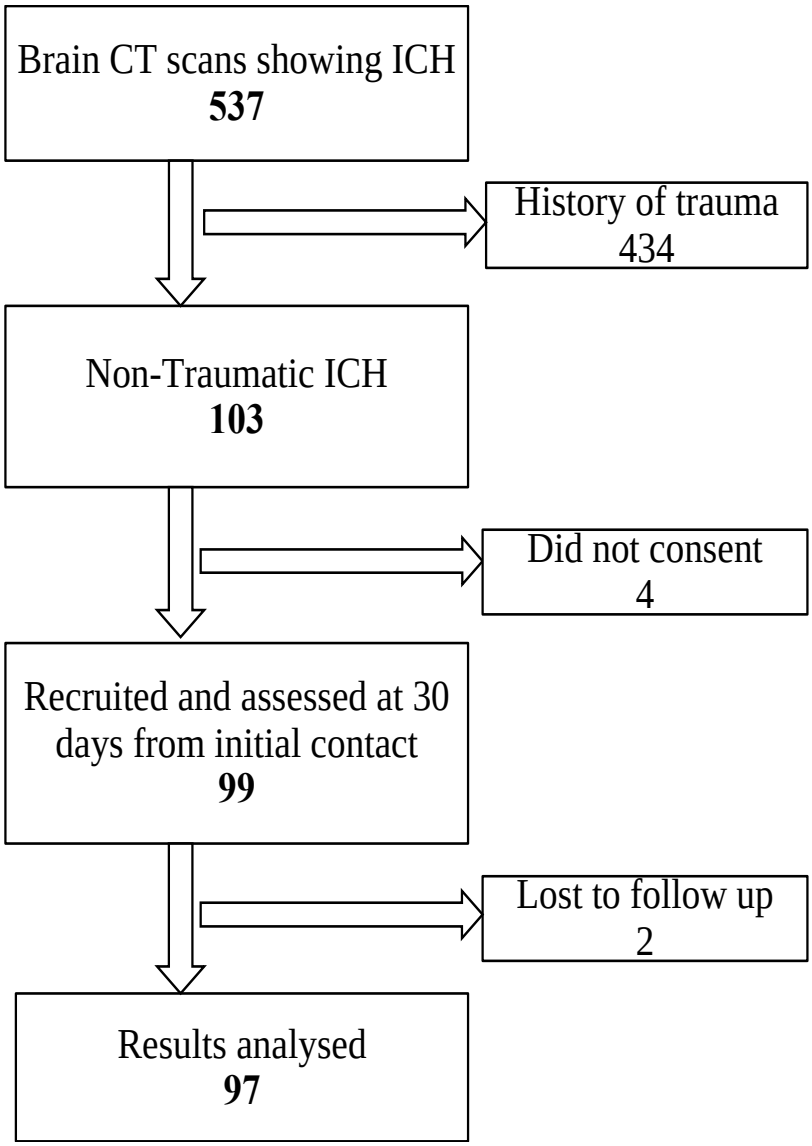
Jina lililochapishwa la mpelelezi Sahihi ya Tarehe ya Mpelelezi

Anwani kwa maswali kuhusu utafiti

Maswali kuhusu utafiti: PI Maelezo ya Mawasiliano ZIPPORAH MWEBI (0714096188)

Maswali kuhusu haki zako kama mshiriki: Unaweza kuwasiliana na Kamati ya Maadili na Utafiti ya Kitaasisi (MTRH//MU-IREC) 0787723677 au barua pepe irec@mtrh.go.ke au irecoffice@gmail.com. MTRH//MU-IREC ni kundi la watu wanaopitia tafiti kwa ajili ya usalama na kulinda haki za washiriki.

Appendix 2: Study Schema



Appendix 3: Data Collection Form

Study Identification code: …….
Telephone number of the participant and caregiver……...

I. Demographics

(i) Date of interview | DD | MM | YYYY |

(ii) Date of birth: | DD | MM | YYYY |

(iii) Sex | M | F |

(iv) Admission | Yes | No |

(v) If yes, Date of admission | DD | MM | YYYY |

(vi) Date of discharge | DD | MM | YYYY |

II. Initial clinical review

a) Functional outcome

Ranking score…….

III. Brain computer tomography findings

Date of Brain CT | DD | MM | YYYY |

a) Hematoma volume ☐

b) Hematoma location ☐

c) Mass effect | Present | Absent |

Middle shift _____mm to right ** or left **

Any other findings suggestive of the mass effect.

……

……

……

d) Intra ventricular extension Yes ☐ No ☐

Indicate location within the ventricles.

☐ Lateral ventricle ☐ Anterior ☐ Body ☐ Posterior

☐ Temporal

e) Hydrocephalus | Yes | No |

f) Pre-hematomal edema | Yes | No |

g) Herniation | Present | Absent |

If present state, the location

☐ Trans tentorial
☐ Uncal herniation
☐ Transtentorial central herniation
☐ Subfalcine herniation.
☐ Cerebellar tonsillar herniation
☐ Other:
……

IV. 30 day follow up

b) Functional outcome at 30 days

Ranking score…….

c) Medical interventions conducted on the patient:

i. ICU admission/care | Yes | No |

ii. Surgery | Yes | No |

iii. If yes, type of surgery…….

iv. Physiotherapy | Yes | No |

v. If yes, what was the intensity of the physiotherapy.

☐ Once daily
☐ Twice or thrice a week
☐ Once weekly
☐ Once in two weeks

Appendix 4: The Modified Rankin Scale

SCORE	DESCRIPTION
0	No symptom
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 able to walk unassisted.
4	Moderately severe disability. Unable to attend own bodily needs without assistance, and unable to unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

(Rankin, 1957)

Appendix 5: Time Frame

Proposal Concept Development	Feb 2019	May 2019
Proposal Writing	June 2019	August 2021
IREC Approval	August 2021	August 2021
Research	September 2021	August 2022
Data Analysis and Thesis Writing	August 2022	September 2022

Appendix 6: BUDGET

PARTICULARS	**QUANTITY**	**UNIT COST (Kshs.)**	**TOTAL COST (Kshs.)**
Research assistants	1	6,000/month @ 9months	60,000
Biostatistician	-	-	50,000
Box files	5	350	1,750
Paper punch	1	500	500
Stapler	1	250	250
Staples	2packets	100	200
Marker pens	5	50	250
Biro pens	2 dozen	250	500
Pencils	1 dozen	250	250
Laptop	1	65,000	65,000
Printer	1	18,000	18,000
Photocopy charges	-	-	30,000
Internet Access	Monthly	3,000/Month	27,000
Weighing scale/ height meter	1	18,000	18,000
Printing costs	-	-	50,000
Thesis Writing	1	30,000	30,000
Binding of Thesis	6	400	2,400
Correspondence with Publishing Journal			10,000
Contingency (10%)			**36,410**
Total			**400,510**

Appendix 7: IREC Approvals

MTRH/MU-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2021/116
Approval Number: 0004038

9th December, 2021

Dr. Mwebi K. Zipporah,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Mwebi,

ASSOCIATION BETWEEN BRAIN COMPUTER TOMOGRAPHY FINDINGS AND FUNCTIONAL OUTCOME AMONG ADULTS WITH NON-TRAUMATIC INTRACRANIAL HEMORRHAGE IN MOI TEACHING AND REFERRAL HOSPITAL

This is to inform you that ***MTRH/MU-IREC*** has reviewed and approved the above referenced research proposal. Your application approval number is ***FAN: 0004038.*** The approval period is **9th December, *2021- 8th December, 2022.***
This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, Material Transfer Agreements (MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MTRH/MU-IREC***.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MTRH/MU-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MTRH/MU-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from ***MOH at the recommendation of NACOSTI*** for each batch of shipment.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MTRH/ MU-IREC.***

Prior to commencing your study; you will be required to obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and other relevant clearances from study sites including a written approval from the CEO-MTRH which is mandatory for studies to be undertaken within the jurisdiction of Moi Teaching & Referral Hospital (MTRH) and its satellites sites.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
09 DEC 2021
APPROVED
P. O. Box 4606 - 30100 ELDORET

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 8: Hospital Approvals (MTRH)

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

15th December, 2021

Dr. Mwebi K. Zipporah,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET- KENYA.

ASSOCIATION BETWEEN BRAIN COMPUTER TOMOGRAPHY FINDINGS AND FUNCTIONAL OUTCOME AMONG ADULTS WITH NON-TRAUMATIC INTRACRANIAL HEMORRHAGE IN MOI TEACHING AND REFERAL HOSPITAL

You have been authorised to conduct research within the jurisdiction of Moi Teaching and Referral Hospital (MTRH) and its satellites sites. You are required to strictly adhere to the regulations stated below in order to safeguard the safety and well-being of staff, patients and study participants seen at MTRH.

1. The study shall be under Moi Teaching and Referral Hospital regulation.
2. A copy of MTRH/MU-IREC approval shall be a prerequisite to conducting the study.
3. Studies intending to export human bio-specimens must provide a permit from MOH at the recommendation of NACOSTI for each shipment.
4. No data collection will be allowed without an approved consent form(s) to participants unless waiver of written consent has been granted by MTRH/MU-IREC.
5. Take note that data collected must be treated with due confidentiality and anonymity.

The continued permission to conduct research shall only be sustained subject to fulfilling all the requirements stated above.

for

DR. WILSON K. ARUASA, *MBS, EBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

CHIEF EXECUTIVE OFFICER
15 DEC 2021
MOI TEACHING & REFERRAL HOSPITAL

c.c. - Senior Director, Clinical Services
- Director of Nursing Services
- HOD, HRISM