SONOGRAPHIC BRAIN PATTERNS IN NEONATES WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY UNDERGOING THERAPEUTIC HYPOTHERMIA IN MOI TEACHING AND REFERRAL HOSPITAL, ELDORET

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A THESIS SUBMITTED TO MOI UNIVERSITY, SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTERS OF MEDICINE IN RADIOLOGY AND IMAGING.

DECLARATION

I declare that this is my original work and it has not been presented in any other university or institution of higher learning for the award of a diploma, degree, or any other award. This work shall not be reproduced or transmitted without the author's or Moi University's express permission**.**

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DEDICATION

I dedicate this work to my lovely husband, Anthony and my amazing children, Amara, Zara and Thomas, from whom I get the drive to be a better person, and to all the mothers taking care of differently abled children with cerebral palsy, may God continue to give you strength and daily provision.

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ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ADC	Apparent diffusion coefficient
ASL	Arterial spin labelling
ATP	Adenosine triphosphatase
AVD	Assisted Vaginal Delivery
BE	Base excess
CEO	Chief Executive Officer
CS	Caesarean delivery
cUS	Cranial ultrasound
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalogram
EKG	Electrocardiogram
fMRI	Functional Magnetic Resonance Imaging
GM	Grey matter
HIE	Hypoxic Ischemic Encephalopathy
IREC	Institutional Research and Ethics Committee
IVH	Intraventricular Hemorrhage
LMIC	Low Middle Income Countries
MHz	Mega Hertz
MRI	Magnetic Resonance Imaging
MTRH	Moi Teaching and Referral Hospital
NACOSTI	National Commission for Science and Technology
NBU	Newborn Unit

NCC-SIG	Neurocritical Care Interest Group
NICHD	National Institute of Child Health and Human development
NRFS	Non-Reassuring Fetal Status
PET	Positron Emission Tomography
PET	Pre-eclampsia
PVL	Periventricular leukomalacia
RI	Resistive index
Rs-f MRI	Resting state functional Magnetic resonance imaging
SVD	Spontaneous Vertex Delivery
TH	Therapeutic Hypothermia
UNICEF	United Nations Children's Fund
WM	White matter

DEFINITION OF TERMS

Acoustic window -is the location from which the ultrasound probe makes its scan.

Cranial ultrasound- gray scale technique for scanning the brain using high frequency (8-12MHz) sound waves to produce pictures of the brain and inner fluid chambers by use of the open fontanelles as the acoustic windows.

Echogenicity-brightness of an image caused by the reflection of sound waves.

Hyper echogenicity – sonographic image of an area that appears brighter than the surroundings.

Hypoxic ischemic encephalopathy- is a condition characterized by clinical and laboratory evidence of acute or subacute brain injury due to asphyxia.

MRI spectroscopy- a noninvasive diagnostic test for measuring biochemical changes in the brain, especially the presence of tumors.

Periventricular white matter-white matter located immediately adjacent to the fluid-filled ventricles of the brain

Subcortical white matter- primarily white matter composed of myelinated axons with fewer quantities of cell bodies when compared to gray matter

Neonate- a baby in the first 28 days of life.

Therapeutic hypothermia -is a clinical treatment that involves reducing a patient's core body temperature to slow disease progression.

Thompson score- a numerical system and a clinical tool comprising of clinical signs associated with central nervous system dysfunction

Watershed areas- are those border-zone regions in the brain supplied by the major cerebral arteries where blood supply is decreased.

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ABSTRACT

Background: Hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and neurodevelopmental disability. While magnetic resonance imaging (MRI) is considered the gold standard for brain injury assessment, cranial ultrasound (cUS) offers a practical, bedside alternative during therapeutic hypothermia (TH), particularly in resource-limited settings. This study aimed to assess the evolution of sonographic brain injury patterns during TH at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya.

Objective: To describe the evolution of sonographic brain patterns in neonates with HIE undergoing therapeutic hypothermia.

Methods: This was a prospective, census study that recruited 37 neonates (≥36 weeks' gestation) diagnosed with moderate or severe HIE and eligible for TH between August 2023 and February 2024. Approval to conduct the study was obtained from the Institutional Research and Ethics Committee (IREC). Permission to collect data was sought and granted by the Chief Executive Officer, Moi Teaching and Referral Hospital (M.T.R.H.) Further approval to conduct the study was obtained from the National Commission for Science Technology and Innovation (NACOSTI). Cranial ultrasound examinations were performed at the initiation of TH and on day seven of life. Brain regions assessed included periventricular and subcortical white matter, thalami, basal ganglia, and ventricles. Thompson clinical severity scores were recorded. Data were analyzed using STATA version 16, with findings presented as frequencies, medians, and proportions. Associations between cranial ultrasound findings and clinical severity were assessed.

Results: Among the 37 neonates who were recruited, 89.2% had moderate and 10.8% had severe HIE. The median gestational age was 39 weeks, and the median birth weight was 3100 grams. Clinical seizures were present in 43.2%. Pre-treatment cUS findings included periventricular echogenicity (13.5%), subcortical echogenicity (13.5%), intraventricular hemorrhage (8.1%), thalamic hyper-echogenicity (8.1%), and basal ganglia echogenicity (2.8%). Significant associations were found between pre-treatment brain injury patterns and severe Thompson scores (p=0.0019). On day seven after TH, the brain abnormalities on cranial ultrasound scans included increased thalamic echogenicity (17.8%), increased subcortical echogenicity (7.1%), and intraventricular hemorrhage (7.1%). Clinical grading improved significantly post-treatment, with 89.3% of patients classified as having mild HIE.

Conclusion: White matter injury was the predominant early sonographic pattern, whereas thalamic injury became more evident at day 7 of life. Therapeutic hypothermia was associated with substantial improvement in clinical severity scores.

Recommendation: Routine serial cranial ultrasound should be incorporated into the management of neonates undergoing therapeutic hypothermia to identify and follow the evolution of brain injury in order to establish the sonographic biomarkers of HIE that determine prognosis.

CHAPTER ONE: INTRODUCTION

1.1 Background

Hypoxic-ischemic encephalopathy (HIE) in neonates is a major cause of mortality and neurodevelopmental deficits in children. It is a consequence of oxygen deprivation during the perinatal period (Shankaran et al, 2005). HIE is a significant health problem throughout the world, affecting both high- and low-income countries. Neonatal HIE incidence varies, with the highest rate of 1.5 per 1000 live births in developed countries. The burden is especially higher in resource-limited settings, where the incidence ranges from 4.6 to 26 per 1,000 live births, and the case fatality rate can exceed 40% (Bhutta, 2013).The burden of poor obstetric coverage, equity, and quality in Sub-Saharan Africa, particularly in East and Central Africa, is enormous due to gaps in local financing models, socioeconomic norms, low literacy levels, inaccessible health facilities, a shortage of medical personnel and supplies, and inadequate healthcare spending.(Workineh, Semachew, Ayalew, Animaw, Tirfie, et al., 2020) In Kenya, birth asphyxia is the leading cause of neonatal mortality, accounting for approximately 29% of neonatal deaths (Ministry of Health, 2012). At Kenyatta National Hospital, among 119 term neonates admitted, 31% died by day 7, 31.1% remained hospitalized, and 37.8% were discharged, with 6.7% showing neurological sequelae at day 7 of life (Abdisalan, 2011). At Pumwani Maternity Hospital of term neonates with asphyxia,15 % died within seven days,28.5% remained in care,56.4% were discharged of which 14.4 % had neurological impairments. (Kariuki et al., 2022) A significant hurdle in managing HIE is the difficulty in diagnosing it early and implementing timely interventions. This challenge stems from various factors, including the complexity of presentation, the variability in perinatal events, and the need for specialized expertise (S. Kumar & Paterson-Brown,

2010). Early and effective treatment, particularly therapeutic hypothermia, is crucial for optimizing outcomes (Afifi et al., 2024). Therapeutic hypothermia (TH) involves targeted temperature reduction to 33-34 degrees Celsius for 72 hours, then gradual rewarming. Therapeutic hypothermia mitigates secondary energy failure following perinatal asphyxia by reducing the metabolic rate (5-7% per one-degree Celsius decrease), suppressing excitotoxic glutamate release, and attenuating inflammatory cascades. (Gunn et al., 1997) Therapeutic hypothermia, initiated within the first six hours of life, has emerged as the standard of care for neonates with moderate to severe HIE (S. Kumar & Paterson-Brown, 2010). Therapeutic hypothermia has been shown to improve outcomes when combined with supportive measures such as optimal ventilation, fluid management, seizure control, and glucose regulation (Sakr & Balasundaram, 2022). It has demonstrated robust efficacy in improving survival and neurodevelopmental outcomes (Shankaran et al., 2015). Despite this advancement a critical challenge persists: 30-50% of neonates still experience moderate to severe neurodevelopmental impairment, highlighting the need for early prognostic stratification to guide personalized interventions (Merchant & Azzopardi, 2015). Brain imaging plays a major role in the evaluation of neonates with HIE. MRI is the gold standard in assessing term neonates with HIE and has emerged as a pivotal tool for interpreting the nature and extent of brain injury in this population. Advanced MRI techniques, including the diffusion-weighted imaging, magnetic resonance spectroscopy, and volumetric analysis, provide quantitative biomarkers of metabolic distress, white matter injury and cortical/central gray matter damage. These biomarkers correlate strongly with neurodevelopmental outcomes at 18-24 months, offering superior predictive value over clinical assessments alone (Rutherford, Ramenghi, et al., 2010b). For instance, basal ganglia/thalamic lesions on MRI predict

motor deficits with 89% specificity, while reduced N-acetyl aspartate on magnetic resonance spectroscopy correlates with cognitive outcomes. (Lally et al., 2019). While Magnetic Resonance Imaging (MRI) is considered the gold standard for assessing brain injury (Parmentier, de Vries, et al., 2022a), it is often impractical in low-resource settings due to cost, availability, and the clinical condition of critically ill neonates. Cranial ultrasound, by contrast, is widely available, non-invasive, repeatable, and can be performed at the bedside. Recent studies have demonstrated improved diagnostic utility of ultrasound in assessing HIE-related brain injuries. Sonographic brain findings are essential in the early and easy prediction of outcomes and assist as a standard in determining the prognosis and the decision regarding whether to start neuroprotective therapy (Enhesari et al., 2022). Cranial ultrasound can detect evolving brain injuries such as cerebral edema, hemorrhages and focal or diffuse parenchymal abnormalities. A study by Van Laerhoven et al. (2013) highlighted that cranial ultrasound performed during the first week of life in cooled infants showed abnormalities in 62% of cases, with the most common findings being increased echogenicity, suggesting injury. However, the evolution of these patterns during and after cooling may differ from normothermic HIE infants due to neuroprotective effects of hypothermia (Rutherford, Ramenghi, et al., 2010b). Several studies have attempted to correlate specific sonographic patterns with outcomes. For instance, the presence of severe abnormalities on cranial ultrasound, such as bilateral increased echogenicity in the basal ganglia and thalami, has been associated with poor outcomes(De Vries & Groenendaal, 2010) longitudinal studies have also shown that the dynamic changes in cranial ultrasound findings are prognostically significant .Van Laerhoven et al.,(2013) observed that the persistence of abnormal echogenicity beyond the first week was associated with worse outcomes compared to transient

changes. Moreover, the combination of cranial ultrasound with other modalities (like MRI) improves accuracy. For example, Rutherford et al., (2010b) demonstrated that the interrogation of cranial ultrasound findings in cooled infants provided superior outcome prediction than either modality alone. Furthermore, Doppler resistive index > 0.8 in the anterior cerebral arteries post-rewarming correlates with adverse outcomes (Ahmad et al., 2024.) There are several cranial ultrasound scoring systems for infants with HIE available, developed to show association with neurodevelopmental outcome. Annink et al., (2020) developed the system, which included composite scores of white matter and deep grey matter involvements based on the cranial ultrasound obtained between days 3 and 7 after birth. This system was to enhance the interpretation of cranial ultrasound findings and predict clinical outcomes in HIE cases. Others included (Leijser et al., (2007) who scored combinations of white and grey matter involvement and compared cranial ultrasound to MRI. Swarte et al. (2009) defined a combination of patterns including deep gray matter involvement and extensive cortical involvement. Despite some limitations, such as reduced sensitivity for detecting cortical lesions and operator dependency (Bano et al., 2017), cranial ultrasound remains a valuable diagnostic tool in the neonatal intensive care setting. Ultrasound can be utilized before, during, and after therapeutic hypothermia (TH) to monitor the evolution of brain injury (Alfaifi, 2023a). Initial scans help identify pre-existing conditions or pathologies that may mimic or contraindicate TH, such as hemorrhage, stroke, infections, or congenital abnormalities (Salas et al., 2018a). Follow-up scans provide insight into the progression or resolution of injury patterns and may help in prognostication. Studies suggest that ultrasound findings can predict white matter integrity and inform clinical decision-making after therapeutic hypothermia (Salas et al., 2019).

1.2 Problem Statement

Therapeutic hypothermia has become the standard treatment for moderate and severe HIE in near (term)neonates and has been associated with improved survival and neurological outcomes. (S. E. Jacobs et al., 2013) Specifically, it involves cooling the infant to a core temperature of 33-34°C for 72 hours, initiated within 6 hours after birth, and has been proven to reduce mortality and disability (Natarajan et al., 2019).

However, in many low-resource settings, the ability to monitor the progression of brain injury and the neonate's response to treatment remains limited. MRI though ideal for detailed brain assessment, is often unavailable, expensive or impractical for critically ill neonates (Parmentier, de Vries, et al., 2022a). Cranial ultrasound offers a more accessible, bedside imaging modality and can be performed repeatedly throughout the course of therapeutic hypothermia. Despite its widespread use, its role in standardized HIE care protocols remains underutilized. Serial cranial ultrasound studies may be useful in the evaluation of brain injury after neonatal HIE. For example, assessment of cerebral edema or increased echogenicity in vulnerable areas like the basal ganglia may be determined (Chock et al., 2023).

There is a lack of comprehensive data on the specific sonographic brain injury patterns as it evolves during therapeutic hypothermia, and how these relate to clinical severity. Understanding these evolving sonographic patterns is essential for early risk stratification, informed clinical decision-making, and improved long-term care.

1.3 Justification

Therapeutic hypothermia is known to mitigate neuronal injury following perinatal asphyxia, but outcomes can vary significantly. Some neonates still develop substantial neurological impairments despite treatment. Early detection and characterization of brain injury patterns may allow for better risk stratification and targeted intervention (Chock et al., 2023).

MRI is the gold standard for imaging of neonates with HIE (Parmentier, de Vries, et al., 2022a); however cranial ultrasound offers a practical alternative, particularly in settings like Moi Teaching and Referral Hospital (MTRH), where it is readily available and can be repeated as needed without disrupting neonatal care. However, there is limited literature on how brain injury evolves during therapeutic hypothermia and how cranial ultrasound findings correlate with clinical severity.

This study aims to fill that gap by identifying and assessing the sonographic evolution of brain pattern during therapeutic hypothermia treatment in (near) term neonates with HIE. The findings could support the development of localized guidelines, improve prognostication, and ultimately enhance patient care.

1.4 Research Question

What are the sonographic brain injury patterns and clinical severity grades observed in neonates with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia at Moi Teaching and Referral Hospital?

1.5 Objectives

1.5.1 Broad Objective

To describe the evolution of sonographic brain injury patterns in neonates with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia at MTRH.

1.5.2 Specific Objectives

1. To describe the sonographic brain injury patterns in neonates with HIE before/at initiation of therapeutic hypothermia in MTRH newborn unit.
2. To describe the sonographic brain injury patterns in neonates with HIE at day seven of life, after completion of therapeutic hypothermia in M.T.R.H newborn unit.
3. To determine the association between pre-treatment sonographic brain injury patterns and the short term clinical outcomes at MTRH, new born unit

CHAPTER TWO: LITERATURE REVIEW

2.1 Definition and Epidemiology

Hypoxic-ischemic encephalopathy (HIE) represents a complex neurological syndrome resulting from acute or sub-acute brain injury caused by oxygen-depriving events, whether through systemic hypoxemia or reduced cerebral blood flow. This condition may manifest prenatally, during the intrapartum period, or postpartum, representing a critical emergency in neonatal medicine (Allen & Brandon, 2011a). The pathophysiology of HIE involves a cascade of cellular and molecular events triggered by oxygen deprivation, including energy failure, excitotoxicity, oxidative stress, and inflammation, ultimately leading to neuronal death and long-term neurological impairment.

The clinical diagnosis of perinatal asphyxia, which frequently leads to HIE, is established through specific criteria defined by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. These diagnostic criteria include;

i) umbilical cord arterial PH <7

ii) Apgar score of 0-3 for longer than 5min

iii) neonatal neurological manifestations e.g., seizures, coma or hypotonia) and multisystem organ dysfunction.

The severity of HIE is typically classified using the Sarnat staging system, which categorizes encephalopathy into mild, moderate, and severe grades based on clinical neurological findings, electroencephalographic patterns, and duration of symptoms.

The global epidemiological burden of HIE varies significantly between developed and developing nations, reflecting disparities in healthcare infrastructure, obstetric care quality, and resource availability. Internationally, the incidence approximates 1.5 per

1000 live births in developed countries (Kurinczuk et al., 2010). However, this figure represents a substantial underestimate of the global burden, as developing countries experience dramatically higher rates ranging from 4.6 to 26 per 1000 live births, with case fatality rates exceeding 40 percent in many resource-limited settings (Bhutta Z, Manson's tropical diseases, 3rd edition., 2013 p 1200).

According to the World Health Organization (WHO), perinatal asphyxia accounts for four to nine million neonatal deaths annually worldwide and remains a leading cause of neurological disability and developmental impairment in surviving children. The regional distribution of this burden is particularly varied, with Sub-Saharan Africa bearing a disproportionate share of the global mortality. Of the world's newborn deaths, 25% occur in Africa, with birth asphyxia accounting for 24% of these fatalities. In Sub-Saharan Africa specifically, birth asphyxia caused 280,000 newborn deaths on the first day of life, with the incidence in East, Central, and Southern Africa reaching 22%, highlighting the urgent need for improved perinatal care strategies and healthcare system strengthening in these regions (Workineh et al., 2020).

The long-term neurodevelopmental consequences of HIE can be devastating and lifelong, encompassing a spectrum of disabilities including cerebral palsy, epilepsy, cognitive impairments, behavioral disorders, and sensory deficits such as vision or hearing loss. The risk and severity of these outcomes demonstrate a strong correlation with the initial grade of encephalopathy and the timeliness and effectiveness of therapeutic interventions, particularly therapeutic hypothermia. Without prompt and appropriate intervention, moderate to severe HIE frequently results in significant neurodevelopmental disability in survivors, with studies indicating that up to 60% of infants with severe HIE will develop major disabilities (Shankaran et al., 2005).

Recent advances in neuroimaging, particularly magnetic resonance imaging (MRI), have enhanced our understanding of the patterns of brain injury in HIE and improved prognostic accuracy. The pattern of injury often depends on the timing and severity of the hypoxic-ischemic insult, with term infants typically showing injury to the deep gray matter structures, while preterm infants more commonly develop periventricular white matter injury. (De Vries & Groenendaal, 2010) These imaging findings have become increasingly important for counseling families about long-term prognosis and for making decisions about the continuation or withdrawal of intensive care.

2.1.1 Risk Factors and Etiology

The etiology of HIE is multifactorial, involving a complex interplay of maternal, fetal, and intrapartum factors that collectively increase the risk of perinatal hypoxia and subsequent brain injury. Several comprehensive population-based studies have systematically examined these risk factors, providing crucial insights for prevention strategies. Antepartum risk factors include maternal conditions such as hypertension, diabetes mellitus, intrauterine growth restriction, maternal infections including chorioamnionitis, and substance abuse. Intrapartum events that significantly increase HIE risk include prolonged or obstructed labor, uterine rupture, placental abruption, cord prolapse, shoulder dystocia, and abnormal fetal heart rate patterns indicative of fetal distress. Postpartum conditions such as severe meconium aspiration syndrome, persistent pulmonary hypertension, and delayed or inadequate neonatal resuscitation further contribute to the risk profile (Wang et al., 2020).

These findings underscore the multifactorial nature of HIE and emphasize the critical importance of integrated obstetric and neonatal care in prevention strategies. The identification of these risk factors has led to the development of scoring systems and

clinical protocols aimed at identifying high-risk pregnancies and deliveries, enabling proactive management and intervention.

2.1.2 Diagnostic Challenges in Resource-Limited Settings

The diagnosis of HIE in resource-limited settings presents unique challenges that significantly impact both immediate management and long-term outcomes. A prospective observational study conducted by Staunton et al. (2022) examining the challenges in diagnosing common neonatal conditions in Nigeria and Kenya revealed that birth asphyxia diagnosis was primarily based on clinical features suggestive of encephalopathy combined with the exclusion of other causes, rather than relying on standardized laboratory markers or sophisticated diagnostic tools. The study highlighted the use of evidence of organ failure such as acute kidney injury, respiratory distress, circulatory collapse, and disseminated intravascular coagulation as surrogate markers for the diagnosis of HIE.Particularly concerning was the observation that the utilization of cranial ultrasound scanning, a relatively accessible diagnostic tool, varied dramatically across facilities from as low as zero percent to eighty-four percent. This study emphasized the persistent systemic challenges in the diagnosis of birth asphyxia despite the existence of national pediatric diagnostic guidelines. The adherence to these guidelines has been consistently hindered by multiple factors including a lack of skilled workforce, inadequate diagnostic resources, political instability, constant healthcare strikes, and high staff turnover due to poor working conditions and inadequate compensation.

A complementary study by Shikuku et al. (2017) conducted in a peripheral hospital in Kenya further highlighted the gaps in neonatal resuscitation practices. Despite the availability of neonatal resuscitation protocols provided for use in delivery rooms, the research revealed that individual steps were frequently performed incorrectly or

omitted entirely, rendering the protocols ineffective in managing birth asphyxia. This poor adherence to protocols has been directly linked to the persistently high mortality rates related to birth asphyxia within the first hour to twenty-four hours of life.

The study identified specific gaps in healthcare workers' knowledge and skills, particularly in the management of newborns with meconium aspiration. The researchers emphasized the critical importance of investing in strict adherence to the initial steps of neonatal resuscitation within the golden minute to improve neonatal survival rates. They also advocated for regular continuous training and clinical mentorship programs to ensure that essential skills are retained and practiced consistently.

2.1.3 Therapeutic hypothermia and Neuroprotection

The introduction of therapeutic hypothermia has revolutionized the management of HIE and significantly improved the prognosis for neonates with moderate to severe encephalopathy in high-resource settings. When administered within six hours of birth, hypothermia has been demonstrated to reduce mortality and improve neurodevelopmental outcomes at 18 to 24 months of age through multiple mechanisms including reduced metabolic rate, decreased excitotoxicity, and attenuation of inflammatory responses (S. Jacobs et al., 2013). However, the accessibility and implementation of therapeutic hypothermia remain severely limited in many low-income settings due to high costs, lack of specialized equipment, inadequate training of healthcare providers, and insufficient infrastructure to support continuous monitoring and care. (Pauliah et al., 2013).

The mechanism of action of therapeutic hypothermia involves cooling the body temperature to 33-34°C for 72 hours, which interrupts the cascade of cellular injury

that occurs after hypoxic-ischemic events. This intervention must be initiated within a narrow therapeutic window to be effective, requiring rapid diagnosis, decision-making, and access to specialized neonatal intensive care facilities. The complexity of implementing hypothermia therapy in resource-limited settings has led to research into simplified protocols and alternative neuroprotective strategies that might be more feasible in these environments. (Thayyil et al.2021).

2.1.4 Burden and Challenges in Kenya

In Kenya, birth asphyxia represents the leading cause of neonatal mortality, contributing to approximately 29% of all neonatal deaths and making it the single most important cause of early neonatal mortality in the country (Ministry of Health, 2012). This substantial burden reflects both systemic healthcare challenges and significant gaps in perinatal care across Kenyan health institutions. The Kenya Demographic and Health Survey 2022 reported that the national neonatal mortality rate remains alarmingly high at 21 deaths per 1,000 live births, with birth asphyxia identified as a leading contributor to this mortality burden.

A pivotal study conducted by Ayaya et al. (2004) at Moi Teaching and Referral Hospital in Eldoret provided crucial insights into the magnitude of the problem at the tertiary care level. The study found that among all neonatal deaths in the newborn unit, birth asphyxia was the most prevalent underlying cause. This trend has persisted despite numerous interventions aimed at improving obstetric and neonatal outcomes, suggesting the need for more comprehensive and sustained approaches to address the underlying causes.

Local hospital data from M.T.R.H. reveals the ongoing severity of the problem, with 210 neonates admitted with birth asphyxia between January and November 2022 out

of over 2,000 total neonatal admissions. This represents over 10% of all admissions, indicating a substantial local disease burden that requires urgent attention and sustained intervention strategies. The high admission rate for birth asphyxia at tertiary facilities like M.T.R.H. suggests that many cases represent severe disease that has progressed beyond the capacity of lower-level facilities to manage effectively.

While global initiatives have promoted the use of standardized neonatal resuscitation protocols and enhanced intrapartum monitoring, the efficacy of such strategies in resource-limited settings like Kenya remains suboptimal. The disparity between urban and rural healthcare infrastructure further complicates the implementation of these interventions, creating a two-tiered system where urban facilities may have better resources while rural facilities struggle with basic equipment and staffing challenges.

Rural health facilities often lack essential equipment such as bag-mask ventilation devices, suction apparatus, and continuous fetal monitoring systems. Additionally, these facilities frequently experience shortages of trained personnel capable of performing advanced neonatal resuscitation and lack timely referral systems to higher-level facilities. These deficiencies exacerbate the risk of intrapartum hypoxic events that go undetected or are inadequately managed, leading to more severe presentations of HIE when patients eventually reach tertiary care facilities (Ministry of Health, 2022; Workineh et al., 2020).

Despite the availability of advanced obstetric monitoring technologies in some facilities, the incidence of long-term neurological outcomes such as cerebral palsy has remained relatively unchanged globally (G. Kumar et al., 2024). This stagnation is attributed to the multifactorial nature of hypoxic-ischemic encephalopathy, which often involves risk factors that may not be identifiable or preventable even with

vigilant monitoring. Consequently, the focus has shifted toward not only perinatal risk reduction but also early detection and neuroprotective strategies such as therapeutic hypothermia, which has been introduced in tertiary care facilities like M.T.R.H. to mitigate brain injury following hypoxic events.

2.1.5 Healthcare System Challenges and Interventions

Additional systemic challenges contribute significantly to the high incidence of HIE in Kenyan tertiary centers and similar facilities across Sub-Saharan Africa. These challenges include delayed referrals from peripheral facilities, often due to inadequate recognition of high-risk situations or lack of transportation infrastructure. Prolonged second-stage labor remains common due to inadequate monitoring and delayed decision-making for operative interventions. The lack of neonatal intensive care resources in lower-level facilities means that many neonates who might benefit from immediate intensive care are instead transferred to tertiary centers after sustaining severe hypoxic injury, limiting the window for effective therapeutic intervention.

A significant proportion of neonates arrive at referral centers like M.T.R.H. after sustaining severe hypoxic injury during prolonged labor or inadequate resuscitation attempts at referring facilities. This late presentation limits the effectiveness of interventions such as therapeutic hypothermia, which must be initiated within six hours of birth to be optimally effective. The cascade of delays – from recognition of complications to referral decisions to actual transport – often exceeds this critical therapeutic window.

Despite these formidable obstacles, institutions like M.T.R.H. have made significant strides in introducing evidence-based approaches such as therapeutic hypothermia to improve outcomes in neonates with moderate to severe HIE. This strategy has

demonstrated significant benefits in reducing mortality and long-term neurodevelopmental impairment in well-resourced settings (Shankaran et al., 2005). However, the implementation of such advanced interventions requires substantial investment in equipment, training, and ongoing support systems.

The importance of facility-based delivery in mitigating the burden of HIE cannot be overstated, particularly in the context of Sub-Saharan Africa where home deliveries remain common. The Kenya Demographic and Health Survey 2022 reports that while institutional deliveries have improved nationally, reaching approximately 89% of births, significant regional and socioeconomic disparities persist. Some counties continue to report less than 50% of births occurring in health facilities, and even facility-based deliveries may not guarantee access to skilled birth attendance or emergency obstetric care (KNBS and ICF, 2022).

These disparities in access to skilled birth attendance correlate directly with higher neonatal mortality rates and increased incidence of complications like HIE. Therefore, improving access to skilled birth attendance, comprehensive neonatal resuscitation training, and timely obstetric interventions remains a critical national health priority that requires sustained political commitment and resource allocation.

2.1.6 Current Initiatives and Future Directions

Recent collaborative efforts by the Ministry of Health and international partners such as UNICEF and WHO have focused on enhancing neonatal care capacity in high-volume hospitals through initiatives like the Every Newborn Action Plan. This comprehensive strategy emphasizes the critical importance of preventing birth-related brain injuries through improved antenatal care, skilled birth attendance, and enhanced neonatal resuscitation capabilities. The plan also focuses on improving care for affected infants through the introduction of evidence-based interventions such as

therapeutic hypothermia and comprehensive neurodevelopmental follow-up programs.

However, these strategies require consistent implementation, adequate and sustained funding, and comprehensive health system strengthening at all levels of care to translate into measurable reductions in HIE burden. The success of these initiatives depends on addressing the fundamental challenges in healthcare infrastructure, provider training, and health system governance that contribute to the current high burden of HIE in Kenya and similar settings (World Health Organization (WHO), 2023).

The path forward requires a multi-pronged approach that includes strengthening healthcare infrastructure, improving provider training and retention, enhancing referral systems, and implementing evidence-based interventions adapted to resource-limited settings. Only through such comprehensive efforts can the burden of HIE be meaningfully reduced and the long-term outcomes for affected children and families be improved.

2.2 Clinical Presentation of Hypoxic Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) in neonates represents a complex clinical syndrome that results from perinatal asphyxia, leading to impaired cerebral perfusion and oxygenation during the critical peripartum period. The clinical manifestations of HIE reflect not only the severity and extent of cerebral injury but also the dynamic nature of brain damage that typically evolves over time following the initial hypoxic-ischemic insult. The initial presentation often includes altered consciousness, poor muscle tone, feeding difficulties, abnormal reflexes, and seizures, with symptom

severity correlating strongly with long-term neurological outcomes and providing crucial prognostic information for clinical decision-making (Ahearne et al., 2016).

2.2.1 Immediate Postnatal Presentation

In the immediate postnatal period, affected neonates frequently demonstrate significantly low Apgar scores, typically less than 5 at both 1 and 5 minutes, indicating poor cardiopulmonary function at birth and the need for immediate medical intervention. These infants may exhibit a constellation of concerning signs including a weak or absent cry, bradycardia with heart rates below 100 beats per minute, marked hypotonia affecting both axial and appendicular muscle groups, gasping or irregular respirations that may progress to apnea, and frequently require extensive resuscitative measures at birth including positive pressure ventilation, chest compressions, or pharmacological support (ACOG, 2014).

The neurological manifestations in the early hours of life are particularly significant for both diagnosis and prognosis. Early clinical signs include diminished spontaneous movements or complete absence of purposeful motor activity, altered consciousness ranging from hyper alert states where infants appear irritable and overly responsive to stimuli, to obtunded states characterized by reduced responsiveness and poor interaction with the environment. Additional concerning features include poor feeding behaviors with weak or absent suck reflexes, abnormal posturing patterns that may include decerebrate or decorticate positioning, and absent or significantly diminished primitive reflexes such as the Moro reflex, suck reflex, and grasp reflex, which are normally robust in healthy term neonates (Perlman, 2006).

2.2.3 Neurological Manifestations

One of the most clinically significant and hallmark features of moderate to severe HIE is the presence of neonatal seizures, which characteristically occur within the first 6–24 hours of life, coinciding with the secondary energy failure phase of brain injury. These seizures may present in various forms, ranging from subtle manifestations such as eye deviation, sustained eye opening, lip smacking, tongue thrusting, or apneic episodes, to clinically overt presentations including tonic posturing with sustained muscle contractions, clonic movements with rhythmic jerking of extremities, or myoclonic seizures with brief muscle jerks. The seizure pattern and frequency often correlate with the extent and location of brain injury, with more severe and frequent seizures typically indicating more extensive cerebral damage (Glass et al., 2009).

The muscle tone abnormalities in HIE present a complex clinical picture that may evolve over time. Initially, many infants demonstrate hypotonia or flaccidity, particularly in the acute phase following the hypoxic-ischemic insult. However, as the condition progresses, some infants may develop hypertonia, especially those with more severe injury affecting the basal ganglia and thalamus. The pattern of tone abnormalities can provide valuable information about the distribution and severity of brain injury, with diffuse hypotonia often indicating more widespread cortical involvement, while hypertonia may suggest deeper gray matter injury.

2.2.4 Clinical Grading Systems

The severity of HIE is systematically assessed using standardized grading systems that facilitate clinical decision-making, prognostic counseling, and research comparisons. The most widely utilized classification methods include the Thompson score and the Modified Sarnat and Sarnat staging system, both of which have been

validated for their predictive value in determining short-term and long-term neurological outcomes.

2.2.5 Thompson Encephalopathy Score

The Thompson score, developed in 1997, is a simplified numerical clinical tool comprising clinical signs associated with central nervous system dysfunctions. It is based on a set of nine neurological signs: tone, level of consciousness, seizures, posture, Moro reflex, suck reflex, respiratory pattern, fontanelle tension, and abnormal movements such as myoclonus or jitteriness *(Thompson et al., 1997)*. The scoring system is practical in both high-resource and resource-limited settings because it requires no specialized equipment or imaging. with a high predictive value for outcome.

- A score of **0** denotes a normal neurological exam.
- A score between **1–10** indicates **mild HIE**.
- A score between **11–14** indicates **moderate HIE**.
- A score between **15–22** is consistent with **severe HIE**.

Multiple studies have demonstrated the utility of the Thompson score in predicting short- and long-term neurological outcomes in neonates with HIE. For instance, higher Thompson scores in the first 6 hours of life are associated with increased risk of adverse neurodevelopmental outcomes and mortality (Horn & Swingler, 2013).

The Thompson score parameters and scoring. (Thompson et al.,1997)

Score sign	**0**	**1**	**2**	**3**
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyperalert	Lethargic	Comatose
Fits	None	<3/day	>2/day	
Posture	Normal	Fisting/cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent +/-	
Respiration	Normal	hyperventilation	Brief apnea	IPPV (apnea)
Fontanelle	Normal	Full, not tense	Tense	

Prognostic Implications

The severity of clinical presentation is directly correlated with the risk of long-term neurodevelopmental impairments. Infants with mild HIE typically recover without significant long-term sequelae. However, those with moderate HIE are at risk for cognitive deficits, learning disabilities, and mild motor impairments. Severe HIE is associated with poor outcomes, including spastic cerebral palsy, profound intellectual disability, visual and auditory deficits, and in many cases, death during the neonatal period or early childhood (Natarajan et al., 2019). Moreover, early identification and staging of HIE are crucial in determining eligibility for therapeutic hypothermia, which has been shown to reduce mortality and improve neurodevelopmental outcomes when initiated within the first 6 hours of life (S. Jacobs et al., 2013). Thus, systematic and timely clinical assessment using standardized scoring systems remains integral in the management of neonates with suspected perinatal asphyxia. Another classification widely used is the modified Sanart and Sanart based on the following parameters; level of consciousness, tone, seizures, and primitive reflexes and graded into either mild, moderate or severe.

2.2.6 Modified Sarnat and Sarnat Staging System

First described by Sarnat and Sarnat, this classification stratifies HIE into three categories: mild, moderate, and severe, based on clinical features such as level of consciousness, muscle tone, posture, autonomic function, reflex activity, and seizure occurrence (Sarnat and Sarnat, 1976).

- Mild HIE (Stage I) is characterized by hyper alertness, normal muscle tone or mild hypotonia, brisk reflexes, and absence of seizures. Symptoms typically

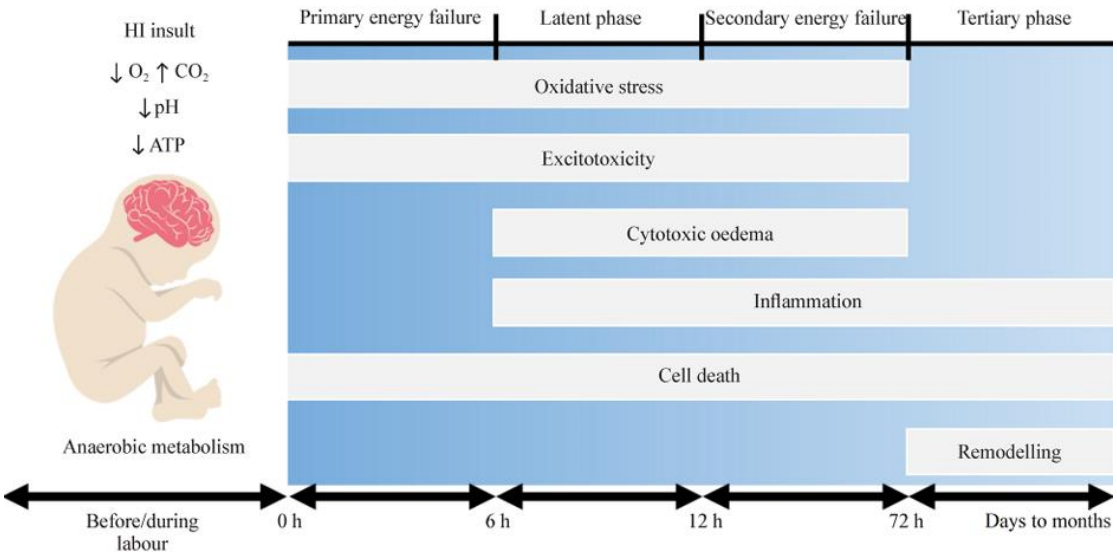
resolve within 24 hours, and neurodevelopmental outcomes are generally favorable.

- Moderate HIE (Stage II) presents with lethargy, hypotonia, weak suck and Moro reflexes, frequent seizures, and abnormal EEG patterns. This stage may persist for several days and is associated with an increased risk of neurodevelopmental delay.
- Severe HIE (Stage III) involves stupor or coma, flaccid tone, absent reflexes, and frequent or refractory seizures. These neonates may exhibit poor spontaneous respiration, requiring mechanical ventilation. The prognosis is generally poor, with high rates of mortality and long-term neurological sequelae, including cerebral palsy, intellectual disability, and epilepsy.

2.3 Pathophysiology

It involves two mechanisms namely primary and secondary energy failure. 1.Primary energy failure occurs as a result of the initial reduction of cerebral blood flow. The impairment of cerebral blood flow leads to decreases in oxygen and glucose, which leads to significantly less energy (adenosine triphosphate (ATP)) and increased lactate production. Most of the effects of the primary energy failure leads to cellular necrosis through impaired cellular integrity, and disruption of the cytoskeleton and cell membrane. If the hypoxic-ischemic insult is severe, neuronal cell death can occur through necrosis. Once blood flow is restored, there is a brief period of recovery. During this brief recovery, the latent period is characterized by normal cerebral metabolism. The latent period is thought to vary depending on the extent of the severity of the hypoxic-ischemic insult. The latent period is considered the optimal timing for therapeutic interventions.

2.The secondary energy failure phase occurs 6 to 48 hours after the initial injury. The exact mechanisms of secondary energy failure remain unclear but appear to be related to oxidative stress, excitotoxicity, and inflammation. The overproduction of free radicals causes damage to neuronal cell membranes and leads to necrosis or apoptosis. Inflammation is also thought to be important in the development of HIE-related brain injury, but the exact mechanism remains unknown. In the tertiary phase, long-term processes such as gliosis, impaired neurogenesis, and remodeling of neural circuits, which can lead to chronic neurological deficits. (Allen & Brandon, 2011b)



2.4 Imaging

Brain imaging represents a cornerstone in the comprehensive evaluation and management of hypoxic-ischemic encephalopathy (HIE), serving as an invaluable workup modality that fundamentally shapes our understanding of injury patterns, treatment strategies, and prognostic outcomes. The correct classification of neurological injury through advanced imaging techniques not only informs immediate treatment decisions but also facilitates the systematic monitoring of therapeutic interventions and provides crucial insights into long-term motor and neurocognitive

outcomes (Salas et al., 2018a). This sophisticated approach to neuroimaging allows clinicians to visualize both the structural and functional consequences of hypoxic-ischemic insults on the developing neonatal brain, thereby guiding both immediate clinical management decisions and comprehensive long-term follow-up planning strategies.

The evolution of neuroimaging in neonatal HIE has been marked by significant technological advances and refinements in imaging protocols. Various imaging modalities have been systematically explored and implemented in the radiological management of neonates with HIE, each offering unique capabilities and clinical applications. The primary modalities that may be utilized in the diagnosis and characterization of brain injury patterns include magnetic resonance imaging (MRI) with its multiple sequences and advanced techniques, computed tomography (CT) scanning, ultrasonography including sophisticated Doppler studies, and positron emission tomography (PET). These imaging techniques have undergone continuous evolution over the past several decades, with each modality offering distinct advantages and inherent limitations that must be carefully considered in the context of clinical scenarios, institutional availability, and optimal timing following the initial hypoxic-ischemic insult.

2.4.1 Comparative utility of MRI and cranial ultrasound in HIE management

The selection of appropriate imaging modality in neonatal HIE requires careful consideration of multiple factors including the neonate's clinical stability, available institutional resources, and the temporal stage of injury evolution. Cranial ultrasound maintains its position as the preferred modality during the immediate postnatal period due to its exceptional safety profile and widespread availability. It demonstrates particular effectiveness in screening for intraventricular hemorrhage, periventricular

leukomalacia, and ventriculomegaly, though its sensitivity for detecting cortical and deep gray matter injury patterns remains limited compared to MRI.

MRI, particularly when performed following the completion of therapeutic hypothermia protocols, provides the most comprehensive assessment of both the extent and distribution of brain injury. This detailed characterization correlates closely with long-term neurodevelopmental outcomes and has become essential for prognostic counseling of families. Multiple studies have demonstrated that specific MRI patterns, including involvement of the basal ganglia, thalamus, and posterior limb of the internal capsule, are strongly predictive of adverse motor and cognitive outcomes (Rutherford, Ramenghi, et al., 2010a; Shankaran, 2015).

Despite its clear advantages in comprehensive injury assessment, MRI's limited accessibility in low-resource settings poses significant challenges for global implementation. In such contexts, cranial ultrasound remains an indispensable tool, providing the capability for repeated assessments over time to monitor the progression or resolution of brain injury patterns. The development of portable ultrasound systems and telemedicine approaches may help bridge this gap in resource-limited settings.

CT scanning, while historically important in neonatal neuroimaging, has become largely obsolete in the routine evaluation of HIE due to its poor sensitivity for detecting the subtle changes characteristic of hypoxic-ischemic injury and the associated radiation exposure risks. Its contemporary role is primarily limited to emergency evaluation of suspected traumatic brain injury and acute intracranial hemorrhage when immediate surgical intervention may be required.

2.5 Cranial Ultrasound: Technique and Findings in Hypoxic-Ischemic Encephalopathy

Cranial ultrasound (cUS) remains a frontline imaging modality in the assessment of hypoxic-ischemic encephalopathy (HIE) due to its non-invasive nature, real-time imaging capacity, and portability. It is particularly advantageous in neonatal intensive care units (NICUs) where critically ill neonates may not be stable enough for transport to radiology suites. The open anterior fontanelle serves as an ideal acoustic window for trans-fontanelle scanning, allowing for visualization of most supratentorial brain structures (Rutherford et al., 2010a; Wezel-Meijler et al., 2010). In the context of HIE, cUS plays a vital role in early brain injury detection, progression monitoring, and prognostication.

The widespread availability of ultrasound equipment in most NICUs, combined with its cost-effectiveness and ability to provide immediate results, makes it an invaluable tool for continuous monitoring of neonates with suspected or confirmed HIE. Unlike computed tomography (CT) or magnetic resonance imaging (MRI), cranial ultrasound can be performed at the bedside without the need for sedation or patient transport, making it particularly suitable for unstable neonates requiring intensive monitoring and life support.

2.5.1 Technique of Cranial Ultrasound

Cranial ultrasound in neonates is typically performed via the anterior fontanelle, which serves as the primary acoustic window. Additional views may be obtained through the posterior, mastoid, and temporal fontanelles to improve visualization of the posterior fossa and cortical structures. The anterior fontanelle typically remains open until 12-18 months of age, providing an excellent acoustic window during the critical neonatal period when HIE-related changes are most dynamic.

High-frequency (7.5–10 MHz) transducers are used for superficial structures, whereas lower-frequency probes (5–7.5 MHz) offer deeper penetration for visualizing subcortical structures (Bano et al., 2017). The choice of transducer frequency represents a balance between resolution and penetration. Higher frequencies provide superior resolution for near-field structures such as the cortical ribbon and superficial white matter, while lower frequencies are necessary to adequately visualize deep structures including the brainstem, cerebellum, and posterior fossa contents.

Scanning is performed in both coronal and sagittal planes, which allows comprehensive assessment of the lateral ventricles, periventricular white matter, basal ganglia, thalami, and brainstem. The coronal plane provides excellent visualization of bilateral structures and allows for symmetry assessment, while sagittal planes offer superior demonstration of midline structures and the relationship between different anatomical regions.

Optimal timing is crucial: baseline scans are ideally performed within the first 24–72 hours of life to identify early changes, and follow-up scans at 5–7 days or later may demonstrate delayed abnormalities, such as evolving periventricular leukomalacia or cyst formation (Martinez-biarge et al., 2011). The temporal evolution of HIE-related changes means that a single scan may be insufficient to fully characterize the extent of injury, necessitating a systematic approach to follow-up imaging.

To reduce artifacts and improve image quality, several technical considerations are important. Scanning should be done when the neonate is calm, ideally post-feeding, as crying and movement can introduce significant artifacts and make detailed assessment difficult. Adequate gel should be used, and probe pressure minimized to avoid discomfort or distortion of underlying structures. Multiple scanning planes should be

used to confirm abnormalities, as artifacts can sometimes mimic pathological changes. The sonographer should be aware of common artifacts such as reverberation, acoustic shadowing, and beam width artifacts that can potentially obscure or mimic pathological findings.

Ultrasound should always be interpreted in conjunction with clinical data and, when available, MRI for correlation and further evaluation. The clinical context, including the severity of encephalopathy, timing of the insult, and response to therapeutic interventions, provides crucial information for accurate interpretation of imaging findings.

2.5.2 Scanning Protocol for Neonates with HIE

The accuracy of cranial ultrasound in detecting HIE-related abnormalities depends heavily on proper technique, operator training, and adherence to standardized imaging protocols. It is essential that the sonographer be adequately trained and competent before independently performing and interpreting scans. This includes understanding normal neonatal brain anatomy, recognizing age-related changes in brain maturation, and being familiar with the spectrum of HIE-related abnormalities.

For term and near-term neonates with encephalopathy, a structured imaging timeline is typically followed. The initial scan is recommended within the first 24 hours of life to detect early abnormalities, though it should be noted that some changes may not be apparent immediately after the insult. A second scan is performed around 3–4 days of life, which captures the evolution of injury, particularly white matter and deep gray matter changes. This timing corresponds to the period when cytotoxic edema is typically most pronounced and when injury patterns become more clearly defined.

A third scan is typically done between 7 and 14 days, which helps evaluate injury resolution, cyst formation, or atrophy. These time points are chosen to track the dynamic nature of hypoxic-ischemic injury, which may be subtle or absent early on but become more conspicuous with time (Martinez-biarge et al., 2011, 2012). Additional scans may be warranted based on clinical evolution, changes in neurological status, or the need to monitor specific abnormalities such as ventricular dilatation or cyst formation.

2.5.3 Image Acquisition Technique

Ultrasound examination must be performed by trained and competent sonographers. Adherence to a standardized image acquisition protocol ensures consistency and diagnostic accuracy. At a minimum, the following views should be included in every examination:

Coronal Views (minimum 6 images):

1. Anterior to the frontal horns of the lateral ventricles, showing the frontal cortex and white matter.
2. At the level of the anterior horns and Sylvian fissures, demonstrating the caudate nuclei and anterior limbs of the internal capsules.
3. Through the third ventricle and thalami, showing the basal ganglia, thalami, and posterior limbs of the internal capsules.
4. Posterior horns of the lateral ventricles showing the choroid plexus and trigone regions.
5. Posterior to the choroids to visualize posterior brain substance, including the occipital cortex and white matter.

6. Additional images if needed to clarify pathology or better demonstrate areas of concern.

Sagittal Views (minimum 5 images):

1. Midline through the corpus callosum, cavum septum pellucidum, and third ventricle, demonstrating midline structures and their integrity.
2. Sagittal view of the cerebellum and fourth ventricle, extending to the foramen magnum for posterior fossa assessment.
3. Sagittal plane through each lateral ventricle capturing anterior and posterior horns and caudothalamic notch.
4. Parasagittal views lateral to the ventricles for deep white matter assessment and evaluation of the cortical-subcortical junction.
5. Optional but recommended: views through the Sylvian fissures and cortical areas for surface injury detection.

Supplementary Views:

- Oblique and surface scans may be needed to visualize cortical lesions or areas of concern that are not well demonstrated in standard planes.
- Axial images can aid in assessing asymmetry and spatial relationships between different structures.
- Posterior fontanelle scans (via the lambdoid-sagittal junction) and mastoid fontanelle scans (via the junction of the parietal, occipital, and temporal bones) are particularly helpful for evaluating the cerebellum and occipital regions, which may not be adequately visualized via the anterior fontanelle.

This systematic approach ensures comprehensive assessment, particularly of structures prone to HIE-related injury such as the basal ganglia, thalami, periventricular white matter, and cortical–subcortical junctions (Blankenberg et al., 2000; Vries et al., 2015).

2.5.4 Sonographic Findings in HIE

The ultrasound features of HIE vary depending on the severity and timing of the insult, and the pattern of injury (deep gray matter vs. watershed injury) is influenced by gestational age and the nature of the hypoxic event (acute profound vs. partial prolonged hypoxia). Understanding these patterns is crucial for accurate interpretation and prognostication.

A. Early Findings (First 3 Days of Life)

Increased echogenicity of the periventricular white matter, thalamus, basal ganglia, and cortical ribbon is the most common early finding. The echogenicity may appear homogeneous or patchy, and tends to become more pronounced over time if injury persists. This increased echogenicity reflects cytotoxic edema and cellular swelling that occurs in the acute phase of hypoxic-ischemic injury.

In severe HIE, the thalamus and basal ganglia appear markedly hyperechoic, often correlating with acute profound hypoxic injury (Wezel-meijler et al., 2010). The loss of normal anatomical landmarks and the appearance of a "bright brain" pattern may indicate extensive injury with poor prognosis. The cortical ribbon may also show increased echogenicity, particularly in watershed zones where blood supply is most vulnerable during hypoxic events.

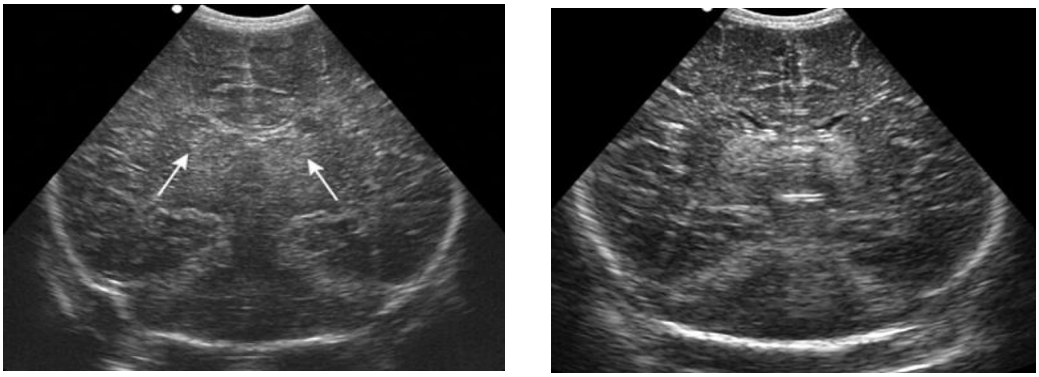


Figure 1: Coronal cUS scans in a full-term neonate with severe HIE. (Left image) subtle echogenicity of the thalami (arrows) and (right image) the echogenicity is now more evident after follow up cUS

B. Subacute to Chronic Findings (Day 4–14 and beyond)

- **Cystic degeneration** (especially in the periventricular regions or parasagittal cortex) may develop within 1–2 weeks after injury and is suggestive of **periventricular leukomalacia (PVL)** or cortical necrosis.
- **Ventriculomegaly** may occur due to brain atrophy or secondary to white matter injury.
- **Loss of normal sulcation** and **cortical thinning** are late features indicating encephalomalacia.

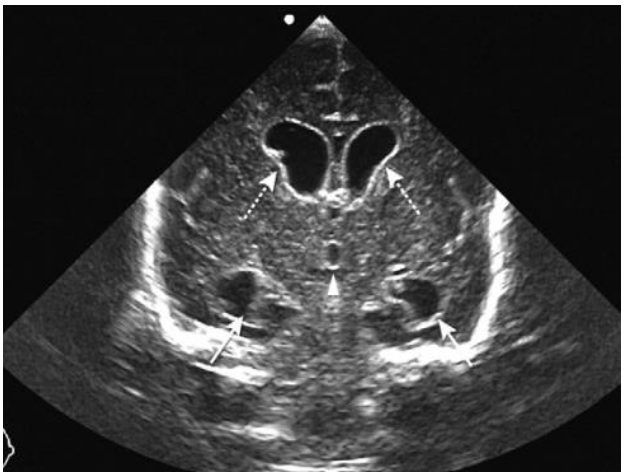


Figure 2: Coronal ultrasound scan in preterm infant with post-hemorrhagic ventricular dilatation, showing dilated frontal (dotted arrows) and temporal (arrows) horns of the lateral ventricles and third ventricle (arrow head). Also, Echogenicity lining the ventricles compatible with ventriculitis.

C. Specific Injury Patterns

1. **Basal Ganglia and Thalamic Pattern** (acute profound hypoxia)
    - Symmetrical hyperechogenicity in thalami, posterior putamen, and perirolandic cortex.
    - Often associated with term infants and sentinel events during delivery.
2. **Watershed Pattern** (partial prolonged hypoxia)
    - Hyper echogenicity in the parasagittal regions (between anterior, middle, and posterior cerebral artery territories).
    - Evolves to cystic encephalomalacia if injury is severe.
3. **Periventricular Leukomalacia (PVL)**
    - More common in preterm neonates, but may occur in term infants with prolonged hypoxia.
    - Early: increased echogenicity in periventricular white matter.
    - Late: periventricular cyst formation.

2.5.5 Advantages of Cranial Ultrasound in Neonatal HIE

- **Bedside Availability:** Enables continuous and repeatable monitoring without the need for transport.
- **Safety:** No ionizing radiation, suitable for repeated use.
- **Cost-effective:** Particularly beneficial in resource-limited settings.
- **Early Detection:** Allows identification of early echogenic changes in brain parenchyma that correlate with HIE severity.

Studies suggest that when performed and interpreted by experienced personnel, **cUS has a sensitivity of over 80%** for detecting moderate to severe HIE (Bano et al., 2017; Rutherford, Ramenghi, et al., 2010a).

2.5.6 Limitations of Cranial Ultrasound

- **Operator dependence** affects consistency and accuracy.
- Limited sensitivity for **cortical injuries**, **posterior fossa**, and **subtle diffuse abnormalities**.
- **Late cystic changes** may be missed if follow-up scans are not done.

2.6 Management of HIE

Treatment of HIE is mainly supportive. Therapeutic hypothermia (TH) has been shown to be a safe and effective method of management of moderate and severe HIE in term infants (Azzopardi et al., 2009) It has been shown to improve the neurodevelopmental outcomes and reduce the severity of imaging findings on MRI (Salas et al., 2018a)

From the pathophysiology, HIE results from reduction in the cerebral blood flow and oxygen delivery to the brain leading to energy failure, excitotoxicity, oxidative stress and cell death. The injury evolves in two phases: the primary energy failure occurring at the time of insult and the secondary energy failure that ensues hours later. (Shankaran, 2009). Therapeutic hypothermia aims to interrupt this cascade by slowing the metabolism reducing free radical production and limiting neuronal injury. The neonate's whole-body temperature is strictly controlled and targeted to the rectal temperature range of 33-34 degrees Celsius. Therapeutic hypothermia is most effective when initiated within the first six hours after birth. Delay beyond this 'therapeutic window' is associated with diminished neuroprotection due to progression of secondary brain injury(Shankaran,2009). Criteria for therapeutic hypothermia includes:

1. $\geq$ 35 weeks of gestation
2. < 6 hours post birth
3. Evidence of asphyxia as defined by 2 or more of the following:

Apgar ≤5 at 10 minutes or continued need for resuscitation with positive pressure ventilation +/- chest compressions at 10 minutes of age

Any acute perinatal event that may result in HIE (i.e. abruption placenta, cord prolapse, severe fetal heart rate abnormality.).

Cord pH <7.0 or base deficit of 12 or more within 60 minutes of birth

If cord pH is not available, arterial pH <7.0 or BE >12 mmol/L within 60 minutes of birth (if available).

4. Assessment of relative contraindications/not moribund
5. Clinically defined moderate or severe HIE (according to the Thompsons score)
6. Moderately to severely abnormal background activity on amplitude-integrated electroencephalography (EEG) i.e., discontinuous, burst suppression or low voltage +/-
7. At the neonatal consultant's discretion to commence therapeutic cooling (Caro-Domínguez et al., 2021)

Equipment required includes a cooling device, disposable esophageal or rectal probe, overhead warming bed with operative skin temperature probe, cardiac monitor, electrocardiogram (EKG) monitor, amplitude integrated EEG and gel pad for head. Preparation of the neonate involves securing the airway, vascular access, Foley's catheter placement to assess strict input and output, pulse oximeter, cardiorespiratory monitor and EKG placement. Baseline laboratory workups (complete blood count, electrolytes, glucose, creatinine, blood urea nitrogen, blood gas, lactic acid, troponin, ammonia and coagulation profile) should also be done.

Therapeutic hypothermia is administered either by selective head cooling or whole-body cooling. Selective head cooling needs a head cap that circulates cold water to decrease the core temperature of the neonate. The head and brain structures reach a cooler temperature than the body. The target temperature is 34 to 35 degrees C. The cooling cap is removed every 12 hours to look for irritative injury of the scalp due to the cap. Whole body cooling needs a special blanket placed that circulates water, which can be cooled or warmed. It achieves uniform cooling of the whole body. The target temperature is 33 to 34 degrees C. This is the more commonly used method. Both cooling devices monitor the neonate's temperature with a probe and maintain the desired target temperature by altering circulating water temperature. Therapeutic hypothermia should last 72 hours, followed by rewarming at a rate of 0.5 degrees Celsius /hour. Passive rewarming will continue for four hours in selective head cooling or six to twelve hours in whole body cooling (Sakr & Balasundaram, 2022) Many randomized controlled trials have established its effectiveness. Some of the studies include the CoolCap trial which demonstrated improved survival without severe neurodevelopmental disability using selective head cooling (Gluckman et al,2005). The NICHD trial showed a significant reduction in death or moderate /severe disability among infants who received whole body cooling (Shankaran et al.,2005). The TOBY trial also supported whole body cooling, reporting improved survival and neurodevelopmental outcomes at 18 months (Azzopardi et al., 2009).

Regarding the long term follow up from major trials has demonstrated that TH improves survival and reduces risk of cerebral palsy, cognitive impairments and motor dysfunction. A study done by Azzopardi et al., (2014) showed that at 6-7 years follow up, children who underwent TH had better motor and cognitive outcomes compared to controls. Meta -analyses confirm that TH significantly reduces the

combined outcome of death or major neurodevelopmental disability (S. E. Jacobs et al., 2013). However, its implementation and effectiveness in low- and middle-income countries remain contentious. The clinical context such as birth practices, availability of neonatal intensive care, infection burden and monitoring capacity-necessitate a critical examination of the role of TH in low and middle income countries. Several observational studies and clinical trials in low and middle income countries have attempted to evaluate the safety and efficacy of TH in these settings with inconclusive or even harmful effects in some cases. The HELIX trial conducted in India, Sri Lanka and Bangladesh reported no benefit of TH in LMICs and showed increased mortality up to 42% in the cooled group verses in the control group. There was also no significant reduction in disability at 18 months. There were also higher incidences of adverse events like coagulopathy, persistent acidosis and sepsis. Potential explanations for the poor outcomes could be the delay of initiation of TH with many patients reaching the referral centers after the critical six hour-window. Presence of higher infection rates such as neonatal sepsis and pneumonia may exacerbate cooling-related complications. In addition, differing etiologies of birth asphyxia as compared to high income countries may potentially alter the HIE pathophysiology. Despite its proven efficacy therapeutic hypothermia is not widely implemented in most Kenyan health facilities due to limited equipment e.g. servo-controlled cooling devices are costly. Lack of trained personnel to initiate and monitor cooling. late presentation of neonates outside the six-hour window and concerns about safety and monitoring capacity in low-resource settings. Some tertiary hospitals have explored the feasibility of cooling therapy. Kenya has no formal national guideline for therapeutic hypothermia. However, the Kenya pediatric association and some hospitals use the adapted World Health Organization or international protocols where resources allow.

Some tertiary hospitals and research collaborations (e.g. the Aga Khan University hospital, Moi Teaching and Referral Hospital) have explored the feasibility of cooling therapy.

2.7 Long-term consequences of epilepsy in HIE

Perinatal hypoxic-ischemic encephalopathy (HIE) represents a critical neurological condition that significantly precedes the development of epilepsy and other long-term neurological complications in affected infants. This birth-related brain injury occurs when oxygen delivery to the brain is compromised during the perinatal period, leading to cellular damage and potential lifelong consequences.

Neonatal seizures emerge as one of the most prevalent and concerning symptoms in infants diagnosed with HIE, affecting approximately 75% of cases. These seizures serve as an early indicator of brain dysfunction and require immediate medical attention and monitoring. Despite this high initial prevalence, the long-term neurological outcomes vary considerably among affected infants.

Remarkably, nearly two-thirds of newborns who experience HIE do not progress to develop post-neonatal epilepsy. Instead, these infants experience self-limiting seizures that are confined to the neonatal period and subsequently resolve without recurring throughout their development. The seizures associated with HIE can manifest in various forms, including generalized seizures that affect the entire brain, focal seizures that originate from specific brain regions, and infantile spasms characterized by sudden muscle contractions.

Therapeutic hypothermia (TH) has been proposed as a potential intervention to reduce epilepsy prevalence following HIE. However, recent research by (Sheng Che Hung et al.,2024) challenges this assumption, demonstrating no significant difference in

epilepsy frequency between newborns who received TH treatment and those who did not.

2.8 Role of Cranial Ultrasound in Therapeutic Hypothermia

2.8.1 Role of cranial ultrasound at or before initiation of therapeutic hypothermia

Cranial ultrasound plays a crucial role in the assessment and management of neonates with hypoxic-ischemic encephalopathy (HIE) who are candidates for therapeutic hypothermia (TH). The diagnostic capabilities of cranial ultrasound performed within the first six hours of birth demonstrate specific limitations, with sensitivity and specificity values of 42% and 60%, respectively (De Vries et al., 1997). Despite these moderate diagnostic parameters, the initial cranial ultrasound examination remains an invaluable tool in the comprehensive evaluation of term neonates presenting with HIE.

The primary importance of performing an initial cranial ultrasound lies in its ability to identify intracranial hemorrhage, which represents a relative contraindication to therapeutic hypothermia (Shah et al., 2025). This screening capability is essential for ensuring patient safety and optimizing treatment outcomes. Beyond hemorrhage detection, the initial ultrasound serves multiple critical functions in the assessment of neonatal encephalopathy. The examination is particularly valuable for identifying abnormalities that may have been acquired in utero, including congenital infections and antenatally acquired lesions, as well as other potential causes of neonatal encephalopathy that may not be related to perinatal hypoxic-ischemic events (de Vries et al., 2022a).

Another fundamental reason for conducting initial screening of term neonates prior to therapeutic hypothermia initiation is to determine the presence of brain injury and establish its timing. The presence of echogenicity observed on admission ultrasound suggests that brain injury is of recent origin but not immediately following delivery (de Vries et al., 2022a). This temporal assessment is crucial for understanding the pathophysiology of the injury and guiding appropriate therapeutic interventions.

Ultrasound examination can be performed at or before the initiation of therapeutic hypothermia to evaluate for the presence of established injury resulting from an insult that occurred before the time of delivery or from a particularly severe perinatal event. The pretreatment ultrasound evaluation should comprehensively assess for brain pathology that clinically mimics HIE or pathology that would constitute a relative contraindication to therapeutic hypothermia, including focal hemorrhage, focal arterial stroke, metabolic diseases, infections, or brain malformations (Salas et al., 2018a).

The triage function of cranial ultrasound is particularly significant in clinical settings where advanced imaging modalities may be limited. Cranial ultrasound assists in identifying neonates who may not be suitable candidates for therapeutic hypothermia, including those with large hemorrhages, congenital malformations, and severe hydrocephalus. This screening capability plays a crucial triage role in determining therapeutic hypothermia eligibility, especially in healthcare settings where magnetic resonance imaging (MRI) is unavailable (Mitra et al., 2020).

Doppler ultrasound parameters provide additional prognostic information that can guide clinical decision-making. The resistive index is regarded as a strong predictor of poor outcomes and mortality before cooling therapy (Alfaifi, 2023b). Research

conducted by Rath et al. (2022) suggested that abnormal resistive index or cerebral blood flow velocity is effective in predicting death or disability in infants with hypoxic-ischemic encephalopathy who are not cooled, and that it may be useful in infants who have undergone therapeutic hypothermia if performed before commencing treatment. Furthermore, a study by Arya et al. (2023) demonstrated that transcranial Doppler findings, including lower resistive index and pulsatility index of the middle cerebral artery within 24 hours of life, were significantly associated with neuromotor outcomes at discharge.

However, the clinical utility of cranial ultrasound before therapeutic hypothermia initiation has been subject to debate within the medical literature. Sanislow et al. (2022) challenged the value of cranial ultrasound before commencement of therapeutic hypothermia, reporting that they could not identify major abnormalities on admission cranial ultrasound that would warrant exclusion of neonates from therapeutic hypothermia treatment. They suggested that cranial ultrasound is used primarily to detect brain hemorrhage, which represents a potential contraindication to therapeutic hypothermia. In their comparative analysis of day 1 cranial ultrasound to day 4 post-therapeutic hypothermia MRIs, they argued that pre-treatment cranial ultrasound is unnecessary as they could not detect any major intracranial hemorrhage.

This perspective was subsequently challenged by de Vries et al. (2022b), who emphasized that the primary purpose of performing cranial ultrasound prior to therapeutic hypothermia extends beyond hemorrhage detection. They insisted that the main rationale for pre-treatment ultrasound is to identify evidence of antenatally acquired lesions, HIE mimics, congenital infections, and malformations. They strongly recommended performing an admission cranial ultrasound for comprehensive

assessment of anatomy, confirmation of absence of evolving acute injury, detection of evidence for antenatal injury, and identification of indicators of underlying problems rather than focusing solely on severe hemorrhage detection.

The timing of ultrasound examinations throughout the therapeutic hypothermia process provides complementary diagnostic information. A second cranial ultrasound performed at the end of therapeutic hypothermia allows for recognition of abnormalities that develop following a peripartum insult and enables valid comparison of cranial ultrasound and MRI findings. This sequential approach to imaging provides clinicians with a comprehensive understanding of the evolution of brain injury and the effectiveness of therapeutic interventions, ultimately contributing to improved patient outcomes and more informed prognostic assessments.

2.8.2 Role of cranial ultrasound during and after therapeutic hypothermia

During therapeutic hypothermia (TH), cranial ultrasound serves as an indispensable bedside monitoring tool that provides real-time insights into evolving brain pathology in neonates with hypoxic-ischemic encephalopathy (HIE). The non-invasive nature, portability, and repeatability of cranial ultrasound make it particularly valuable in the intensive care setting where continuous monitoring of vulnerable neonates is essential. Cranial ultrasound can be used to quickly detect abnormalities, such as an acute hemorrhage, when there is a significant clinical change. When sudden neurological deterioration occurs, including seizure activity or hemodynamic instability, cranial ultrasound can rapidly identify critical abnormalities including acute intracranial hemorrhages, evolving cerebral edema, or expanding ventricular systems. This immediate diagnostic capability is crucial in the intensive care environment where rapid decision-making can significantly impact patient outcomes.

Serial cranial ultrasound examinations during TH allow clinicians to track dynamic changes in brain injury and provide a comprehensive window into the evolving patterns of cerebral pathology. These sequential assessments enable documentation of progressive changes in brain architecture, including the development or resolution of periventricular echogenicity, the evolution of cystic changes in white matter structures, and alterations in ventricular size and morphology. For instance, the progression of periventricular echogenicity or cystic changes may indicate worsening injury, while the temporal progression of these findings often correlates with the severity of the initial hypoxic-ischemic insult. A study by (Parmentier, Steggerda, et al., 2022) found that cranial ultrasound performed at 24-hour intervals during TH helped identify infants at risk of developing severe brain injury, enabling adjustments to clinical care. Their research revealed that systematic monitoring allowed for timely modifications to clinical care protocols, including optimization of cerebral perfusion parameters and early initiation of neuroprotective strategies beyond hypothermia alone.

However, significant limitations persist in cranial ultrasound interpretation during therapeutic hypothermia. Hypothermia itself may transiently alter cerebral blood flow and edema patterns, complicating interpretation and potentially masking evolving injuries. The hypothermic state introduces complex physiological changes that can substantially alter the acoustic properties of brain tissue and modify normal cerebral blood flow patterns. (Wintermark et al., 2011) identified that hypothermia-induced alterations in cerebral hemodynamics and tissue edema patterns can significantly complicate ultrasound interpretation. Wintermark et al. (2014) highlighted that hypothermia-induced reductions in cerebral metabolism and cerebral blood flow can create a "pseudo normalization" effect on cranial ultrasound, masking evolving

injuries. This pseudo-normalization effect can lead to underestimation of injury severity during the acute hypothermia phase, creating falsely reassuring ultrasound appearances. Thus, cranial ultrasound is often supplemented with MRI after rewarming to refine prognostic accuracy and achieve comprehensive injury assessment.

Despite these limitations, cranial ultrasound provides valuable complementary information when properly interpreted. Govaert et al., (2010) noted that cranial ultrasound can capture changes in the basal ganglia and thalami that correlate with later MRI findings, supporting the complementary relationship between these imaging modalities. Serial ultrasound examinations during TH help monitor the progression of brain injury, with appearance of new abnormalities such as increased echogenicity or ventriculomegaly suggesting ongoing hypoxic ischemic damage. The predictive capabilities extend beyond simple injury detection, with quantitative analysis showing promise as early biomarkers for long-term outcomes.

Post-TH cranial ultrasound, usually performed within the first week of life, is useful for identifying complications related to the treatment itself. Some of the notable complications of therapeutic hypothermia include coagulopathy, which can cause intracranial and choroid plexus hemorrhage. These complications may not have been apparent during the cooling phase but become evident following rewarming. Cranial ultrasound is also usually repeated after the TH is completed to assess the persistence of initial indicators of injury or the appearance of new findings. (Salas et al., 2018a) emphasized the importance of this post-treatment monitoring phase for comprehensive patient assessment.

(Martinez-Biarge et al., 2011) highlighted the utility of post cooling cranial ultrasound in identifying late evolving injuries such as cystic periventricular leukomalacia, which may not be visible early in life. These delayed findings often represent the evolution of initially subtle white matter injuries that become more apparent as brain maturation progresses. In a study done by (Salas et al., 2019) demonstrated that the white matter/grey matter ratio on cranial ultrasound performed prior to hypothermia therapy may predict post-hypothermia white matter structural integrity and thus a potential very early and easily obtainable biomarker of severity in HIE. They compared a quantifiable acute cranial ultrasound measure of echogenicity of the brain with diffusion tensor imaging markers of white matter injury in neonates with hypoxic ischemic encephalopathy.

The presence of persistent echogenicity in deep gray matter structures or the development of cystic lesions post TH may indicate worse neurodevelopmental prognosis, making serial cranial ultrasound instrumental in follow up care and rehabilitation planning. This prognostic information directly impacts neurodevelopmental outcome predictions and long-term care planning strategies, proving essential for guiding early intervention services and family counseling. This was emphasized by van Wezel–Meijler et al (2014) who noted that serial cranial ultrasound has good sensitivity for detecting moderate to severe HIE when interpreted by experienced sonographers and plays a complementary role to MRI. Their research validated cranial ultrasound's diagnostic capabilities while acknowledging that optimal clinical care requires integration of multiple imaging modalities for comprehensive brain injury assessment and optimal prognostic accuracy in neonatal neurocritical care.

2.8.3 Global guidelines on cranial ultrasound in HIE during hypothermia treatment

a) The World Health Organization recognizes cranial ultrasound as a vital tool for neuroimaging in resource-limited settings, particularly where magnetic resonance imaging (MRI) facilities are not readily accessible or available. This non-invasive, portable, and cost-effective imaging modality should be systematically integrated as an essential component of the comprehensive neurological assessment protocol for neonates with clinically suspected hypoxic-ischemic encephalopathy (HIE). The primary applications include continuous monitoring of cerebral edema progression, detection of intracranial hemorrhages of varying severity, and real-time assessment of evolving brain injury patterns that may influence treatment decisions and prognostic evaluations. The organization particularly emphasizes its utility in developing nations where advanced neuroimaging resources remain scarce. World Health Organization (2023)

b) The British Association of Perinatal Medicine in the United Kingdom provides comprehensive recommendations emphasizing the critical importance of early cranial ultrasound examination, ideally performed within the first 6 hours of life, to systematically exclude major structural brain abnormalities before initiating therapeutic hypothermia protocols. Their guidelines mandate serial cranial ultrasound examinations throughout the entire therapeutic hypothermia period, including baseline imaging before cooling initiation, regular monitoring during the 72-hour cooling phase, and follow-up studies immediately after rewarming. The protocol concludes with definitive neuroimaging, preferably MRI when available, performed optimally between days 5-14 of life to assess the full extent of brain injury and provide accurate

prognostic information for families and clinicians. (British Association of Perinatal Medicine, 2020)

c) The American Academy of Pediatrics, in conjunction with the Neonatal Resuscitation Program, strongly emphasizes the fundamental importance of early neuroimaging using either cranial ultrasound or MRI in infants diagnosed with moderate to severe HIE. While acknowledging that MRI remains the gold standard imaging modality for accurate prognostic assessment and long-term outcome prediction, they recognize cranial ultrasound as absolutely essential during the active cooling phase for detecting potential complications including intracranial hemorrhages, progressive hydrocephalus, and other acute neurological complications that may contraindicate continued hypothermia treatment. The imaging findings should directly guide critical clinical decision-making processes and facilitate comprehensive, evidence-based parental counseling regarding treatment options and expected outcomes. (American Academy of Pediatrics Committee on Fetus and Newborn, 2014)

d) The Canadian Pediatric Society provides clear recommendations that cranial ultrasound should be systematically performed either before initiating cooling protocols or during the early stages of therapeutic hypothermia, with particular emphasis on its critical importance in clinical settings without immediate access to MRI facilities. This imaging is considered essential for excluding major congenital cerebral malformations, structural abnormalities, or active bleeding that could contraindicate hypothermia treatment or require immediate neurosurgical intervention. Their comprehensive follow-up protocol includes either MRI or serial

cranial ultrasound examinations to monitor treatment response and detect evolving brain injury patterns. (Canadian Pediatric Society, 2018)

e) The European Society of Pediatrics Research and European Academy of Pediatrics have established cranial ultrasound as the recommended first-line neuroimaging modality in neonates with HIE. Their protocol encourages systematic serial ultrasound examinations at specific time points: pre-cooling baseline assessment, during the cooling period (48-72 hours), and post-cooling evaluation. Additionally, they recommend incorporating Doppler ultrasound techniques, which may provide valuable information for evaluating cerebral blood flow patterns, vascular resistance, and overall neurological prognosis. (van Laere, Allegaert, K., Eerdekens, A., & Debeer, A., 2020)

f) The International Liaison Committee on Resuscitation supports the strategic use of cranial ultrasound as an important adjunct neuro-monitoring tool in HIE management during and after hypothermia treatment. They particularly emphasize its crucial importance in low and middle-income countries where MRI facilities may be completely unavailable or significantly delayed. (Wyckoff, M.H., et al., 2020)

g) The National Institute for Health and Care Excellence emphasizes the use of cranial ultrasound as an effective screening tool during cooling protocols, particularly valuable for detecting gross structural abnormalities and guiding critical decisions regarding continuation of hypothermia treatment. (National Institute for Health and Care Excellence, 2010)

Despite this extensive international guidance, there remains a significant gap in documented cranial ultrasound imaging protocols specifically developed for Sub-Saharan and East African healthcare settings.

2.8.4 Gaps in the use of cranial ultrasound in HIE

Cranial ultrasound remains a widely used, cost-effective neuroimaging tool for neonates with suspected hypoxic-ischemic encephalopathy (HIE), especially in low and middle-income countries such as Kenya. However, its application is limited by several diagnostic and operational gaps that affect its sensitivity, prognostic value, and overall clinical utility.

a) Limited sensitivity in early HIE: Cranial ultrasound may not detect early parenchymal changes following hypoxic-ischemic injury, particularly within the first 24-48 hours. Early cellular changes such as cytotoxic edema may not be sonographically apparent, leading to under-diagnosis or delayed diagnosis in the acute phase. This temporal limitation is particularly problematic as the therapeutic window for neuroprotective interventions, such as therapeutic hypothermia, is narrow and requires prompt identification of at-risk infants. The evolving nature of brain injury means that initial normal findings may provide false reassurance, potentially delaying critical interventions (Rutherford, 2008).

b) Suboptimal visualization of deep brain structures: The technique has limited resolution when evaluating deep and peripheral brain regions such as the cerebral cortex, basal ganglia, thalamus, and posterior fossa. These are critical areas in HIE pathophysiology but are often inadequately assessed with ultrasound. The acoustic window limitations inherent to cranial ultrasound mean that watershed zones and cortical-subcortical regions, which are frequently affected in HIE, remain poorly visualized. MRI, particularly diffusion-weighted imaging, is significantly superior in detecting injuries in these locations, offering better contrast resolution and comprehensive brain coverage (Cowan et al., 2003).

c) Operator dependency: Cranial ultrasound is highly dependent on the skill, experience, and interpretation ability of the operator. This variability affects image acquisition and diagnostic accuracy, leading to inconsistent findings, particularly in resource-limited settings where specialized training may be lacking. The subjective nature of image interpretation, combined with inadequate standardization of scanning techniques and protocols, contributes to inter-observer variability. Additionally, the learning curve for acquiring proficiency in neonatal neurosonography is substantial, requiring dedicated training programs that may not be readily available in all healthcare settings (Okere et al., 2021).

d) Poor specificity in prognostication: While certain findings such as periventricular leukomalacia or ventriculomegaly may suggest underlying brain injury, many ultrasound features are non-specific and may not reliably correlate with neurodevelopmental outcomes. Thus, the prognostic value of cranial ultrasound in HIE is relatively limited compared to advanced imaging modalities. The inability to accurately predict long-term neurological outcomes hampers counseling of families and planning of early intervention services. Furthermore, normal ultrasound findings do not exclude the possibility of significant neurodevelopmental impairment, creating challenges in risk stratification and follow-up planning.

e) Limited detection of subtle or diffuse injuries: Cranial ultrasound may fail to detect diffuse white matter injury or subtle cortical abnormalities, which are increasingly recognized as significant predictors of long-term neurodevelopmental impairment. Such injuries are more readily identified on MRI, which can detect microstructural changes and subtle alterations in brain tissue integrity. The predominantly focal nature of ultrasound assessment means that widespread, mild-to-

moderate injury patterns may be missed, potentially underestimating the true extent of brain damage (Rutherford, 2008).

f) Timing and interpretation challenges: Therapeutic hypothermia induces dynamic physiological changes such as reduced metabolic rate and altered cerebral autoregulation, which may transiently mask evolving injury on cranial ultrasound. This pseudo-normalization phenomenon complicates the distinction between genuine neuroprotection and delayed injury progression. Standardized protocols for serial cranial ultrasound timing intervals during cooling versus rewarming phases are still lacking robust validation, making it difficult to optimize the diagnostic yield of the examination.

g) Inconsistent timing and follow-up protocols: In many neonatal units, there is no standardized timing for performing initial or follow-up scans. Given the evolving nature of brain injury in HIE, a single cranial ultrasound may miss delayed manifestations of injury such as cystic encephalomalacia or evolving hydrocephalus. The lack of consensus on optimal imaging schedules means that critical time points for detecting evolving pathology may be missed, potentially affecting clinical management decisions.

h) Lack of standardized reporting systems: The absence of structured protocols and uniform terminology for reporting cranial ultrasound findings can result in miscommunication between neonatologists and radiologists. This inconsistency may hinder timely decision-making and referral for advanced care. Without standardized grading systems or structured reporting templates, the clinical utility of ultrasound findings may be diminished, affecting care coordination and long-term planning.

i) Limited use in clinical research and protocols: Cranial ultrasound is underrepresented in clinical trials evaluating therapeutic interventions for HIE, particularly in LMICs. This limits the integration of cranial ultrasound findings into clinical decision-making algorithms and hinders the development of evidence-based guidelines tailored for resource-limited settings. The relative paucity of research validation means that optimal utilization strategies remain poorly defined (Mwaniki et al., 2010).

j) Operational challenges in LMICs: Despite its affordability and bedside availability, cranial ultrasound use in countries like Kenya is hampered by logistical constraints, including lack of equipment, limited availability of trained personnel, and poor maintenance capabilities. These operational gaps further reduce the potential of cranial ultrasound as a reliable diagnostic and monitoring tool, limiting its clinical impact in settings where it could provide the greatest benefit.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a prospective census study.

3.2 Study area

The study was carried out at the Moi Teaching and Referral Hospital (MTRH), Newborn Unit (NBU), in Eldoret town. M.T.R.H is a level six referral hospital located along Nandi Road in Uasin Gishu County (310 kilometers northwest of Nairobi). It is a multispecialty international teaching and referral hospital serving residents of the Western part of Kenya and the North Rift region with a catchment population of about 13 million. It also serves parts of Eastern Uganda, South Sudan, Northern Tanzania, and the Democratic Republic of Congo with a population of over 25 million. The hospital is affiliated with Moi University College of Health Sciences, making it a key teaching and research institution. It has a bed capacity of over 1000 beds. Its functions are mainly offering clinical services, teaching and training, research and health policy development. M.T.R.H offers both general and specialized services including advanced diagnostics, oncology, renal, neurosurgery and maternal and child health services. The neonatal department is situated in the Riley Mother and Baby maternity wing. It provides level II and level III neonatal care and neonatal intensive care services.it receives neonates for over 20 counties in Western Kenya. It has 110 baby cots,10 functional incubators, and 8 neonatal intensive care beds. The nurse-to-neonate ratio is 1 to 20. It has 2 neonatologists,2 pediatricians,58 nurses, 2 nutritionists, pediatric resident doctors, and clinical officer interns. It provides special neonatal programs such as the therapeutic hypothermia that is selectively practiced for neonates with HIE, Kangaroo Mother Care for stable low birth weight infants and breastfeeding support and neonatal nutritional counselling.

3.3 Target population

The study population consisted of neonates of more than 36-weeks gestation admitted at the NBU at MTRH.

3.4 Study population

The study population consisted of neonates (more than 36 -weeks gestation) admitted to the NBU with a confirmed diagnosis of moderate or severe hypoxic-ischemic encephalopathy made by the pediatrician according to the Thompson score and neonates eligible for therapeutic hypothermia.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

- Neonates (≥ 36 weeks gestation) admitted to NBU with a diagnosis of moderate or severe HIE.
- Eligible for therapeutic hypothermia.

3.5.2 Exclusion criteria

- Neonates with congenital anomalies.

3.6 Sample size and sampling procedure

This study employed a consecutive sampling method, where all eligible neonates more than 36-weeks gestation with moderate or severe hypoxic-ischemic encephalopathy (HIE) undergoing therapeutic hypothermia at Moi Teaching and Referral Hospital (MTRH) during the study period were enrolled.

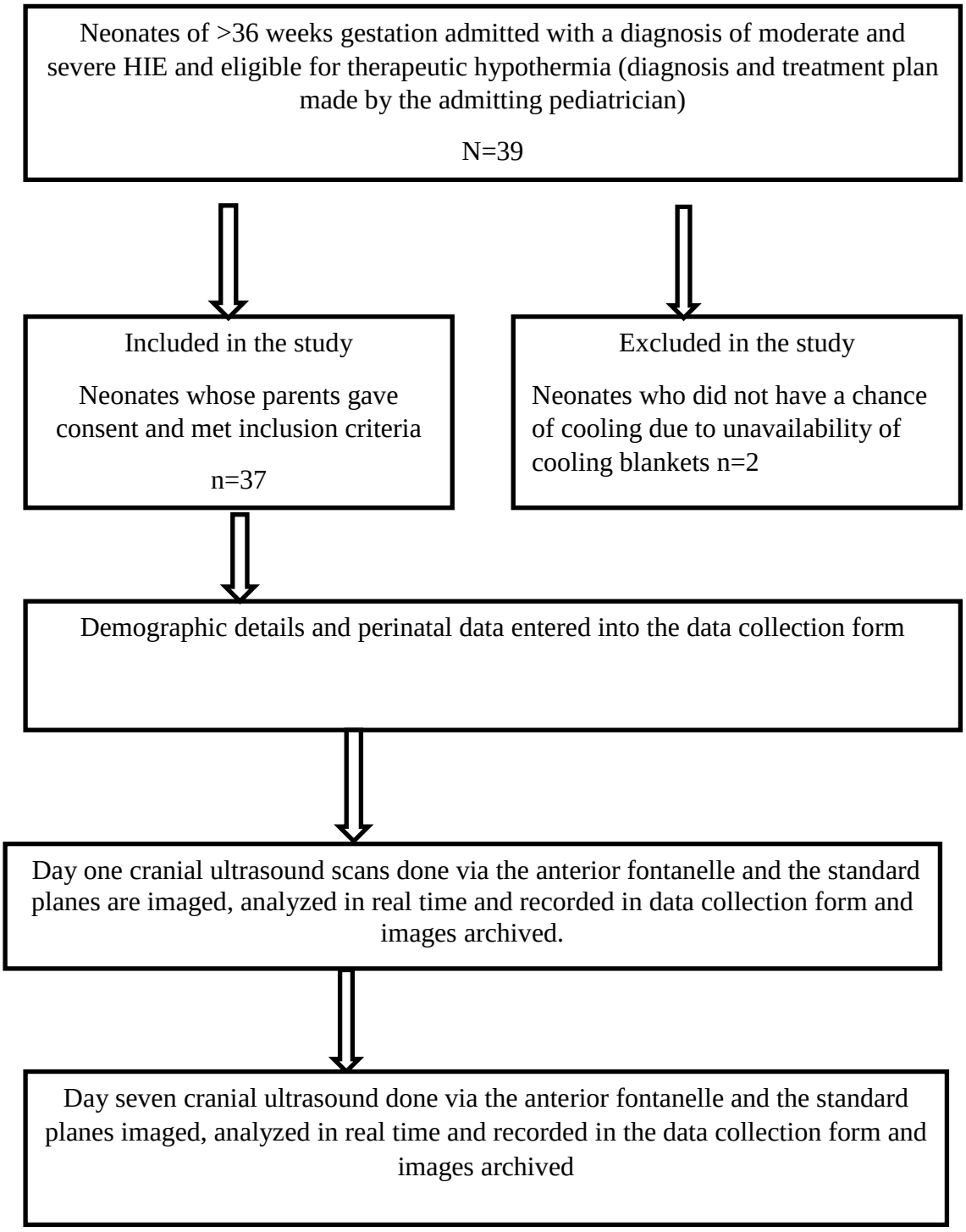


Figure 3: Sampling flowchart and recruitment schema

3.7 Data collection tool

Data was collected using a structured data collection form.

3.8 Study procedure

3.8.1 Planning stage

Upon completion of the concept paper and approval by the faculty in the department of Radiology and Imaging, the principal investigator started experiential learning on the cranial ultrasound procedures, normal brain appearance on cranial ultrasound, and the identification of pathologies in a neonatal brain for nine months.

3.8.2 Execution stage

After approval to conduct the study was granted, training of the research assistant was done by the principal investigator on how to identify, enroll and get consent from the participant's mother/guardian. Posters with the study details and contact information for the principal investigator were displayed in the admission room. Sensitization of the nursing staff was done. After admission, the neonate was reviewed by the admitting pediatrician, assessed and assigned Thompson clinical grading, and assessed for eligibility for therapeutic cooling. Informed consent was obtained by the research assistant from those participants with moderate and severe birth asphyxia and eligible for therapeutic cooling. The research assistant then contacted the principal investigator to perform the cranial ultrasound. The sociodemographic data was taken. Using the Sono scanner ultrasound machine S9 Pro model 2021, with a probe frequency between 7.5 to 8.5MHz, cranial ultrasound was done on day 1 of admission on term neonate with moderate and severe HIE by the principal investigator. Using the scanning protocol, the anterior fontanelle was used as the acoustic window. The gel was warmed. The following parameters were assessed; white matter/gray matter

differentiation, ventricles, periventricular, subcortical and basal ganglia echogenicity. The second cranial ultrasound was taken on day 7 of admission after completion of therapeutic hypothermia and the following parameters were reassessed; white matter/gray matter differentiation, ventricles, periventricular, subcortical, and basal ganglia echogenicity. The severity of HIE was reassessed based on Thompson's score on day 7. The images were analyzed in real-time and stored on a flash disk.

3.9 Data management and analysis

Collected data was coded and entered in Microsoft Excel 2013 spreadsheet database. Data cleaning was conducted before analysis in STATA version 16(Stata Corp, College, Station, Texas 77845 USA). The demographic data such as age was summarized as median and ranges. Quantitative variables were presented as median with interquartile range. Qualitative variables were presented as frequency (percentages). Categorical variables were compared using Fisher's Exact test. Statistical significance level was set to p-value < 0.05.

3.10 Ethical considerations

Before the study was undertaken, approval from Institutional Research and Ethics Committee (IREC) was obtained. Further consent to collect data was sought from the Chief Executive Officer, M.T.R.H. Additional permit to conduct the study was obtained from NACOSTI. The staff at the NBU were sensitized on the study. Notice of the study with the principal investigator's phone number was put on the newborn unit walls. Once a neonate was eligible for cooling, a decision made by the pediatrician, the principal investigator was called. The neonate's mother was traced with the assistance of the nursing staff. The process of consenting was done in the nurse -in-charge's room by the research assistant. The research assistant introduced himself to the neonate's mother. The nature of the study, purpose, benefits and

potential risks of the study was explained in detail to the participant's mother in a simple language either in English or Swahili. It was explained to the participant's mother that their participation was voluntary and that they could refuse to participate or withdraw from the study at any given point. It was explained that full treatment and investigations including the cranial ultrasound were to be done regardless of whether they participated or not. The written informed consent was presented in simple language using non-technical terms and had a Swahili-translated version. The written consent was either signed or thumb printed by the participant's mother. A copy of the informed consent remained with the mother. The participant was made anonymous by use of a serial number. The information obtained was not linked to the participant's name. The consent forms and data collection forms were kept confidential, and safe in a locked cabinet. The study materials will be kept safe for a period of 6 years after which they will be destroyed by shredding them.

CHAPTER FOUR: RESULTS

4.1 Introduction

The study population consisted of neonates more than 36 weeks of gestation admitted to the NBU with a confirmed diagnosis of moderate or severe hypoxic-ischemic encephalopathy made by the pediatrician according to the Thompson score and neonates eligible for therapeutic hypothermia.

4.2 Social demographic characteristics

Majority of the participants were male 23 (62.2%). The median gestational age in weeks was 39.0 with an interquartile range of 38.0 - 40.0. The range was 36 - 42 weeks. Therapeutic hypothermia was started in majority of the neonates at three and four hours of life 11 (29.7%) for both.

The median birth weight was 3100 grams with an interquartile range of 2900 - 3400 grams. The range was between 2615 grams - 4040 grams. Majority of the neonates were born through spontaneous vertex delivery 23(62.2%).

Most neonates had no identifiable risk factors for birth asphyxia at 37.8%. However, meconium aspiration was the commonest identifiable risk factor at 10.8%, followed by non-reassuring fetal status at .1% and pre-eclampsia. The neonates who had convulsions at the time of admission were 43.2% and those without convulsions were 56.7%.

Table 1: General characteristics of the study population

	Total n=37	**Frequency (%)**
Gender		
Male	23	62.2
Female	14	37.8
Gestation by date(weeks)		
Median (IQR)	39.0 [38.0-40.0]	
Range	36 - 42	
Time to cooling in hour		
2	7	18.9
3	11	29.7
4	11	29.7
5	5	13.5
6	2	5.4
7	1	2.7
Birth weight		
Median (IQR)	3100 [2900.0-3400]	
Range	2615 - 4040	
Delivery mode		
SVD/AVD	31	83.8
CS	6	16.2
Risk factor for asphyxia		
NRFS	3	8.1
PET	3	8.1
PROM	1	2.7
Cord compression	1	2.7
Cord around the neck	2	5.4
Breech	1	2.7
Anemia in pregnancy	1	2.7
Delayed 2nd stage	2	5.4
Meconium aspiration	4	10.8
Poor maternal effort	2	5.4
Post date	1	2.7
Shoulder dystocia	2	5.4
None	14	37.8
Seizures at admission		
Yes	16	43.2
No	21	56.7

Objective one: To describe sonographic brain patterns in term neonates with HIE before therapeutic hypothermia.

Table 2: Sonographic brain patterns and clinical severity in neonates with HIE prior to therapeutic hypothermia.

	Total n=37	**Frequency (%)**
White /grey matter differentiation		
Intact	35	94.6
Lost	2	5.4
Periventricular echogenicity		
Increased	4	13.5
Normal	33	86.5
Subcortical echogenicity		
Increased	5	13.5
Normal	32	86.5
Basal ganglia echogenicity		
Increased	1	2.8
Normal	36	97.2
Other brain findings		
IVH	3	8.1
Thalamic hyper echogenicity	3	8.1
Pre-TH Thompson score		
Moderate (11 – 14)	33	89.2
Severe (15 – 22)	4	10.8

The majority of neonates (94.6%) demonstrated intact white/grey matter differentiation, while only 2 cases (5.4%) showed loss of differentiation. Periventricular echogenicity was increased in 4 neonates (13.5%), while 86.5% showed normal echogenicity. There was increased subcortical echogenicity in 5 neonates (13.5%). Basal ganglia echogenicity was increased in only one case (2.8%), whereas 97.2% had normal basal ganglia appearance. Additional sonographic findings included intraventricular hemorrhage (IVH) in 3 neonates (8.1%) and thalamic hyper echogenicity in another 3 cases (8.1%). Clinical severity was assessed using the Thompson score. Most neonates (89.2%) were classified as having moderate HIE

(score 11 - 14), while 4 neonates (10.8%) had severe HIE (score 15 - 22) prior to the initiation of therapeutic hypothermia.

Objective two: To describe sonographic brain patterns and clinical severity post-therapeutic hypothermia treatment in term neonates with H.I.E.

Among the 28 neonates who survived and underwent post-therapeutic hypothermia assessment, all demonstrated intact white/gray matter differentiation (100%). Similarly, no neonate had periventricular increased echogenicity (100%), detected after treatment. Two neonates (7.1%) had increased subcortical echogenicity. None of the neonates had increased echogenicity of the basal ganglia (100%).

Other sonographic findings included intraventricular hemorrhage (IVH) in 2 neonates (7.1%) and thalamic hyper echogenicity in 5 neonates (17.8%).

Pre-therapeutic hypothermia Thompson scores revealed that 25 neonates (89.3%) had mild HIE, and 3 (10.7%) had moderate HIE. None of the neonates in this post-treatment group had a severe Thompson score.

Table 3: Sonographic brain patterns in neonates with HIE post-therapeutic hypothermia.

	n=28	**Frequency (%)**
White /grey matter differentiation		
Intact	28	100.0
Lost	0	0.0
Periventricular echogenicity		
Increased	0	0.0
Normal	28	100.0
Subcortical echogenicity		
Increased	2	7.1
Normal	26	92.9
Basal ganglia echogenicity		
Increased	0	0.0
Normal	28	100.0
Other brain findings		
IVH	2	7.1
Thalamic hyper echogenicity	5	17.8
Pre-TH Thompson score		
Mild (0 -10)	25	89.3
Moderate (11 – 14)	3	10.7
Severe (15 – 22)	0	0.0

Objective three: To determine the association between pre-treatment sonographic brain injury patterns and the short-term clinical outcomes.

Table 4: Association between ultrasound Patterns Before Treatment and short term clinical outcomes.

Ultrasound Pattern	Died n=9(%)	Survived n=28(%)	Total n=37(%)	p-value
White/Gray Matter Differentiation				0.054
Intact	7 (18.9)	28 (75.7)	35 (94.6)	
Lost	2 (5.4)	0 (0.0)	2 (5.4)	
Periventricular Echogenicity				**0.0019**
Increased	4 (10.8)	0 (0.0)	4 (10.8)	
Normal	5 (13.5)	28 (75.7)	33 (89.2)	
Subcortical Echogenicity				**0.0084**
Increased	4 (10.8)	1 (2.7)	5 (13.5)	
Normal	5 (13.5)	27 (73.0)	32 (86.5)	
Basal Ganglia Echogenicity				0.243
Increased	1 (2.7)	0 (0.0)	1 (2.7)	
Normal	8 (21.6)	28 (75.7)	36 (97.3)	
IVH				0.0812
Present	3 (8.1)	2 (5.4)	5(13.5)	
Absent	6 (16.2)	26(70.2)	32(86.6)	
Thalamic hyper echogenicity				**0.0108**
Present	3 (8.1)	0 (0.0)	3 (8.1)	
Absent	6 (16.2)	28 (75.7)	34 (91.9)	
Pre-TH Thompson score				**0.0019**
Moderate (11 – 14)	5 (13.5)	28 (75.7)	33 (89.2)	
Severe (15 – 22)	4 (10.8)	0 (0.0)	4 (10.8)	

Among the 37 neonates included, loss of white/gray matter differentiation was exclusively observed in neonates who died. While these findings showed a trend toward significance ($p = 0.0541$), they did not meet the conventional threshold for statistical significance.

Periventricular echogenicity was significantly associated with mortality. All four neonates with increased periventricular echogenicity died, whereas none of the survivors had this finding ($p = 0.0019$). Similarly, increased subcortical echogenicity

was more frequent in neonates who died (4 out of 9) compared to those who survived (1 out of 28), showing a statistically significant association ($p = 0.0084$).

Additional findings of intraventricular hemorrhage (IVH) and thalamic hyper-echogenicity were also significantly associated with poor outcomes, with both features observed only among neonates who died ($p = 0.0108$ for each). In contrast, basal ganglia echogenicity did not show a significant association with outcome ($p = 0.2432$).

Neonates with a severe Thompson score were significantly more likely to die compared to those with moderate scores.

SAMPLE IMAGES:

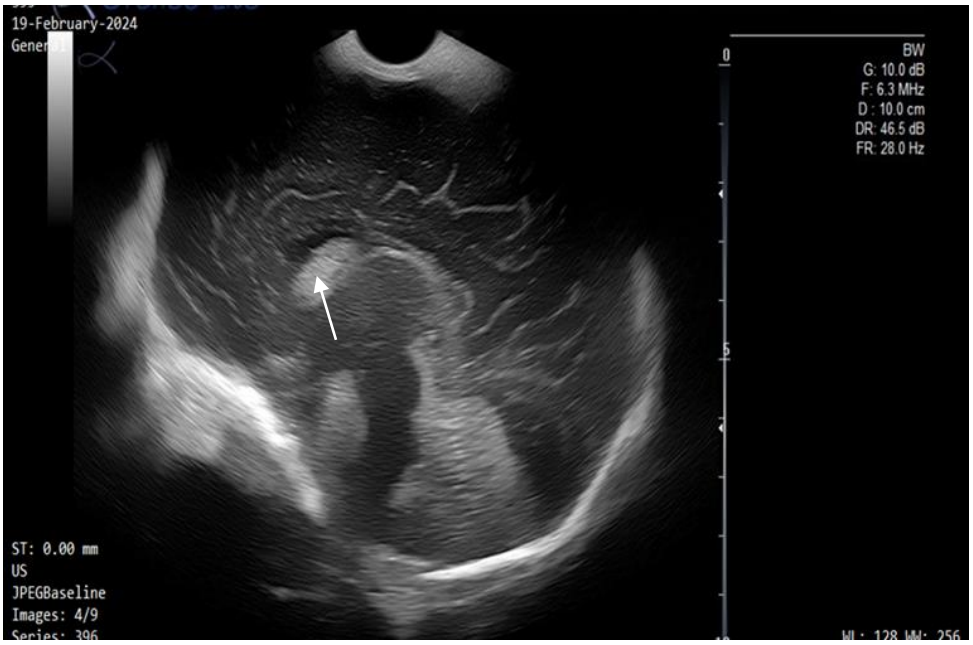


Figure 4: Sagittal plane Male neonate 40 weeks gestation,2820 grams, CS delivery, NRFS Moderate HIE- Day seven cranial ultrasound post cooling showing grade II intraventricular hemorrhage.

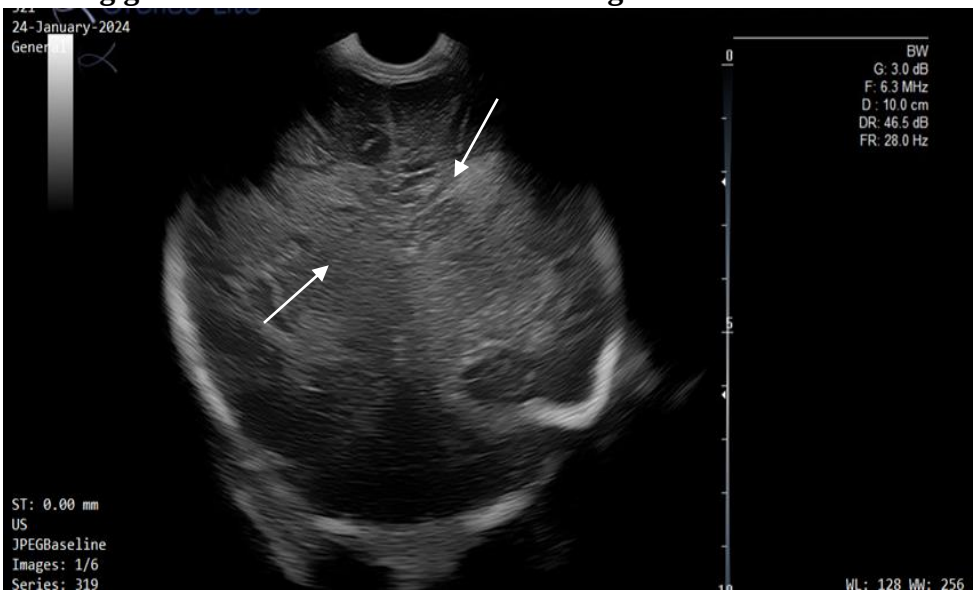
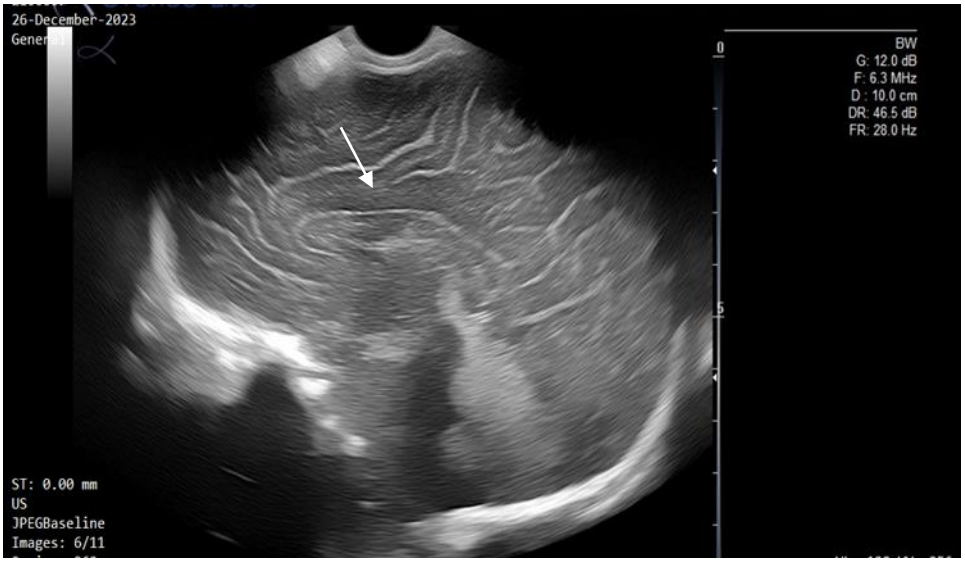
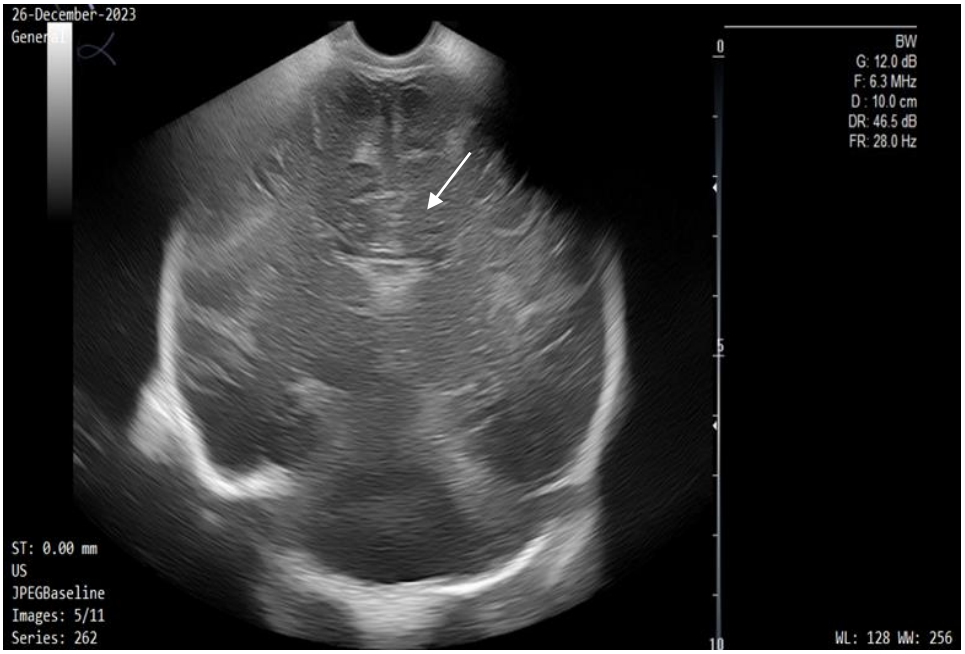


Figure 5: Coronal plane. Male neonate 36 weeks gestation,2800gms, SVD, PET severe HIE day I CU-subcortical echogenicity, loss of grey-white matter differentiation, slit-like ventricles





Figures 6 and 7: Sagittal and coronal plane: Male neonate at 40 weeks gestation 2850grams, SVD, moderate HIE -Day seven CU subcortical and periventricular echogenicity.

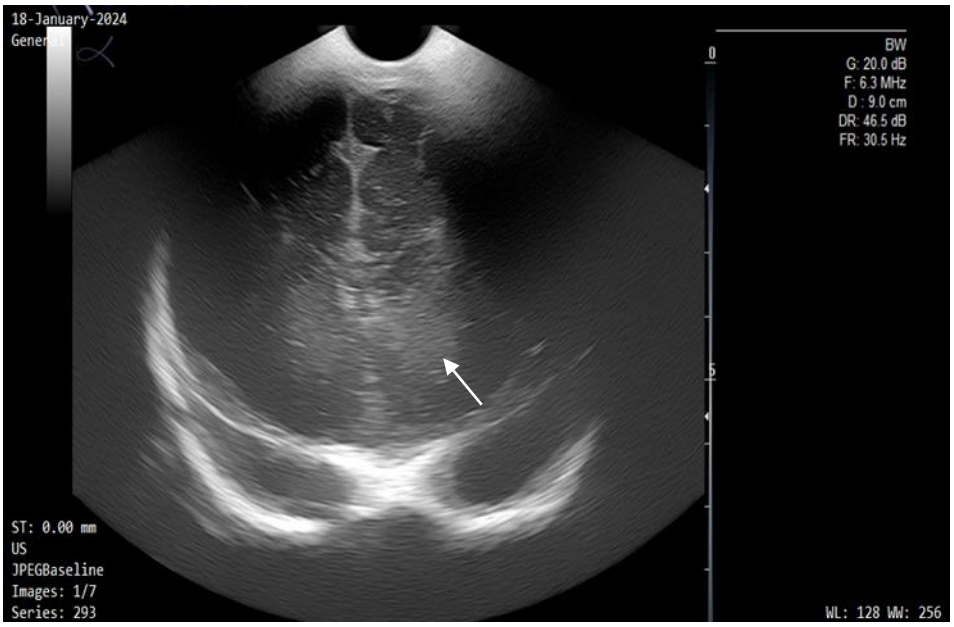
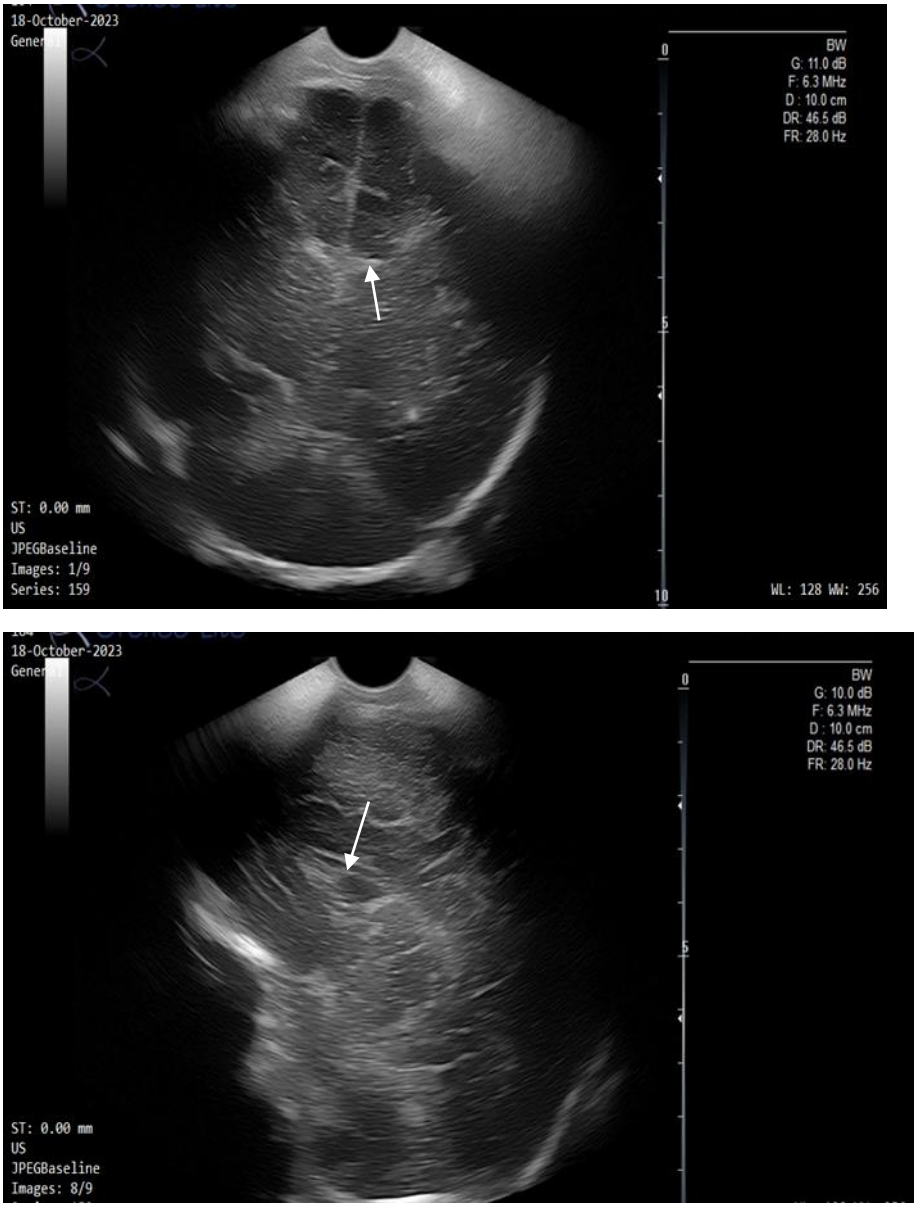


Figure 8: Coronal plane. Female neonate 39 weeks gestation,3100 grams, SVD, moderate HIE. Day seven post cooling CU- Thalamic echogenicity



Figures 9 and 8: Coronal and sagittal plane. Male neonate, at 40 weeks gestation,4025 grams, SVD delivery, history of delayed second stage. Day one cranial ultrasound showing slit ventricles, subcortical and periventricular echogenicity. Neonate succumbed before day seven.

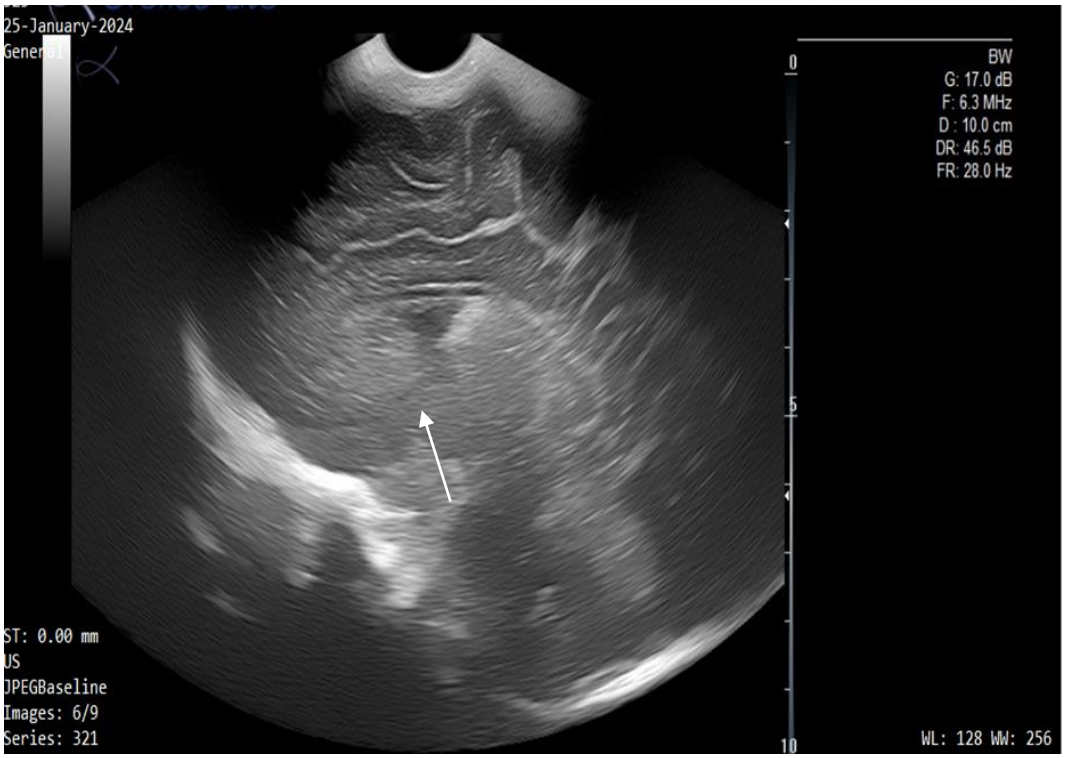


Figure 10: Sagittal plane: female neonate,40 weeks gestation,3035 grams, CS delivery due to NRFS, severe HIE Day cranial ultrasound showed basal ganglia echogenicity, subcortical and periventricular echogenicity.

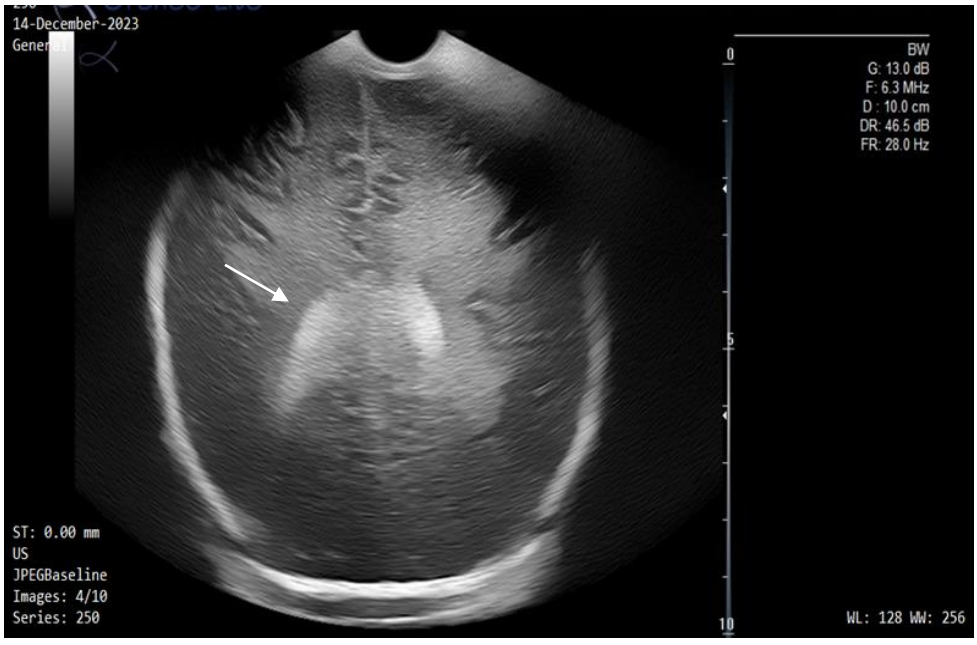


Figure 11: Coronal plane: male neonate, 41 weeks gestation, 3110 grams, CS delivery due to NRFS, moderate HIE. Day one cranial ultrasound shows periventricular echogenicity. Neonate succumbed before day seven.

CHAPTER FIVE: DISCUSSION

5.1 Sonographic brain patterns in term neonates with HIE before therapeutic hypothermia

Majority of the neonates had normal brain findings. This could be because sonographic brain findings may be negative for 24-48 hours following the insult and appearance may vary depending on the severity of injury. (Salas et al., 2018) The abnormal brain patterns encountered included loss of gray/white matter differentiation (5.4%), increased periventricular echogenicity (13.5%), increased subcortical echogenicity (13.5%) increased basal ganglia echogenicity (2.8%) increased thalamic echogenicity (8.1%) and intraventricular hemorrhage (8.1%). Sonographic brain findings may be negative for 24-48 hours following the insult and appearance may vary depending on the severity of injury. (Salas et al., 2018) . In a prospective study done by Bundi et al., (2020), periventricular and subcortical white matter increased echogenicity was observed in 55.6% of neonates admitted to the newborn unit with HIE and 31.1% of the neonates had increased echogenicity within the thalamus and or the basal ganglia. This study agrees with our study in that the most common brain injury pattern observed within the 24 hours of life was the white matter injury. Similarly, Tann et al., (2016) reported white matter abnormalities in 12% of neonates, and no abnormalities 78% of the neonates. In this nested study they concluded that findings of cranial ultrasound done early with a median age of 11 hours could have arose from a recent and evolving brain injury. Increased echogenicity in the basal ganglia and thalami is a common early finding associated with acute profound asphyxia and severe HIE, and often indicates poor prognosis (Bano et al.,2021). Periventricular and subcortical white matter echogenicity is more common in partial prolonged hypoxia and is typically associated with mild to moderate injury but may still result in adverse outcomes depending on the extent (Bano et al.,2021). Loss of

cortical differentiation and compression or dilation of ventricles may also be observed, reflecting cerebral edema or evolving hydrocephalus.

In our study,8.1% of neonates had intraventricular hemorrhage. This agrees with a study done by Gorelik et al., (2016). This was a retrospective study that included neonates of more than 36 weeks gestation, who were treated conventionally and some with TH. Seven percent of the neonates who were treated conventionally had IVH. The pathogenesis of IVH in HIE is still unclear but may be as a result of an altered autoregulation, hemodynamic instability, and immaturity of the capillary bed. IVH hemorrhage is uncommon in term neonates (Gorelik et al., 2016) Intraventricular hemorrhage in HIE may result from hypoxic damage to the fragile periventricular capillaries, particularly in the germinal matrix in preterm neonates. In term neonates, venous congestion following reperfusion, endothelial injury due to oxidative stress, mechanical trauma due during resuscitation or intensive care and coagulation abnormalities following asphyxia can lead to intraventricular hemorrhage(Volpe,2018) Intraventricular hemorrhage is often associated with severe disease. One study found that upto 10-15 % of term neonates with moderate and severe HIE may have some degree of intracranial hemorrhage, including IVH, detectable on MRI. It may occur in a minority of cases but its presence correlates with poor outcome. (Rutherford et al.,2010) In term infants with HIE, the presence of IVH correlates with an increased risk of death or disability at18-24 months. (Shankaran et al.,2012).

5.2 Sonographic brain patterns on day 7 post-therapeutic hypothermia

Following therapeutic hypothermia, cranial ultrasound findings demonstrated substantial preservation of brain architecture in the majority of neonates. In this study, all surviving neonates (n = 28) exhibited preserved WM/GM matter differentiation and normal periventricular and basal ganglia echogenicity on day seven of life. These findings align with the known neuroprotective mechanisms of TH, which mitigates secondary energy failure, cerebral edema, and subsequent structural injury (Shankaran et al, 2005). Increased subcortical echogenicity was noted in two neonates (7.1%). Subcortical white matter regions, especially in the parasagittal watershed zones, are recognized as vulnerable to partial ischemia despite therapeutic intervention. Bano et al. (2017) highlighted that mild to moderate hypoxic insults may selectively impact these areas and that subtle sonographic changes can persist even after apparent clinical recovery.

In addition, thalamic hyper echogenicity was observed in 5 neonates (17.8%). The thalamus, along with the basal ganglia, represents a metabolically active and selectively vulnerable structure in neonatal HIE (Rutherford, Ramenghi, et al., 2010a). Persisting increased thalamic echogenicity may reflect delayed clearance of cytotoxic edema, ongoing metabolic disturbance, or incomplete injury resolution.

While magnetic resonance imaging (MRI) remains more sensitive for detecting deep gray matter injury, studies have shown that cranial ultrasound can reliably detect thalamic abnormalities in moderate to severe cases, particularly when performed

serially (Salas et al, 2020).

In our study, 7.1% of the neonates had intraventricular hemorrhage. This agrees with Gorelik et al., (2016) who found that 10% of the neonates who underwent therapeutic

hypothermia, had intraventricular hemorrhage. However, they could not ascertain whether it was a result of cooling but observed that IVH was more prevalent in the group treated with hypothermia. They advised to perform cranial ultrasound before and during hypothermia to monitor the development of IVH in term neonates with HIE. In a study done by Al Yazidi et al., (2015) reported that 9% of the neonates who had undergone hypothermia treatment developed IVH. In their prospective study, thirty percent of the neonates developed IVH during cooling, thirty percent of the neonates within 24 hours of rewarming, and forty percent developed IVH 24 hours after rewarming. They concluded that IVH seemed to develop during late hypothermia and rewarming; hence, efforts should be directed toward improving and sustaining hemodynamic stability. Therapeutic hypothermia has been associated with significantly increased thrombocytopenia, which is an independent risk factor for IVH. It has also been found to increase hemodynamic instability, a factor that may also predispose to IVH (Germinal Matrix and Intraventricular Hemorrhage (GMH-IVH) in the Newborn: Risk Factors, Clinical Features, Screening, and Diagnosis - UpToDate, n.d.).

The post-TH Thompson clinical scores revealed that 89.3% of neonates were classified as having mild encephalopathy by day seven, and no cases were rated as severe. These findings correspond with evidence from Azzopardi et al. (2009) and Shankaran et al., (2005) studies, which demonstrated that therapeutic hypothermia significantly improves neurological recovery and reduces the severity of brain injury at early follow-up.

5.3 Association between sonographic brain patterns and short-term clinical outcomes

Increased periventricular echogenicity, increased subcortical echogenicity and increased thalamic echogenicity demonstrated statistically significant associations with mortality($p<0.05$). This agrees with a study done by Eken et al, (1995) that neuroimaging performed within six hours of life can predict which neonates will go on to have moderate and severe encephalopathy and subsequently likely to either die or develop adverse neurological sequelae. It also agrees with a study done by Annink et al., who found that on day one only severe hyper echogenicity of the periventricular white matter on cranial ultrasound was significantly associated with adverse outcome. Although the other brain injury patterns in their study such as increased echogenicity of the thalamus did not reach significance, all the infants with thalamic, putamen and with a four-column sign on day one had an adverse outcome. In a study done by Malick et al., found that correlation of initial brain ultrasound grading with mortality and sequelae showed an increasing trend as the ultrasound grading increases. Differences in the timing of cranial ultrasound examinations across studies may influence the visibility and extent of brain lesions. Early imaging within the first 24 hours may underestimate injury severity, as certain lesions, particularly periventricular abnormalities, can evolve over several days (Barkovich et al., 1998).

There was a significant association found between higher Thompsons scores and increased mortality risk. The Thompson score remained a robust clinical predictor of mortality within this cohort. A significant association was found between higher Thompson scores and increased mortality risk ($p = 0.0019$), corroborating earlier studies that validated the Thompson score as a reliable prognostic tool in settings with

limited access to advanced neuroimaging modalities (Horn & Swingler, 2013; Shrestha et al., 2020).

However, it is important to note that not all studies have uniformly supported these associations. For instance, Massaro et al. (2014) found no significant difference in mortality when comparing Thompson scores across groups of neonates who underwent therapeutic hypothermia. This divergence may be explained by the neuroprotective effects of hypothermia, which can alter the natural course of injury and potentially mitigate sonographic abnormalities or clinical deterioration.

5.5 Limitations of the study

The study had several limitations

1. Small sample size hence the study is not powered enough to generalize to a larger population.
2. Severe HIE cases were not prioritized for therapeutic cooling due to the unavailability of cooling blankets hence the smaller number of cases in the study and probably because there would be no much benefit in reversing the brain injury already established.
3. Selection and interobserver bias cannot be ruled out.
4. Different categorization of the brain patterns and timing of cranial ultrasound acquisition in the different studies done on sonographic brain patterns hindered comparison with this study.
5. Inability to correlate cranial ultrasound findings with MRI findings, which is the gold standard due to cost and logistical factors.

5.6 Dissemination of results

The results of this study will be disseminated through a written thesis and an oral defense in a forum that shall be convened by the Moi University, School of Medicine.

The findings of the study will be made known to the MTRH administration and the staff at the new born unit.

A manuscript will be written and submitted for consideration for publishing in a journal.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

1. White matter injury (periventricular and subcortical) was the most common pretreatment sonographic brain injury pattern occurring early in HIE.
2. Deep nuclei injury(thalamus) was the most common brain abnormality at day seven of life/post-therapeutic hypothermia.
3. There was a notable association between severe pre-treatment sonographic brain injury patterns with higher clinical severity scores and poorer short-term clinical outcomes.

6.2 Recommendations

1. Day one cranial ultrasound can identify early brain injury patterns hence all neonates diagnosed with HIE should be subjected to a cranial ultrasound.
2. Post-cooling cranial ultrasound should be done between 4-7 days of life to follow up the evolution of brain injury, especially the thalamic injury, which tends to manifest later.
3. Further clinical studies are required to identify the sonographic biomarkers in HIE that determine prognosis.

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APPENDICES

Appendix I: The Thompson score (Thompson et al.,1997)

Score sign	**0**	**1**	**2**	**3**
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	hyperalert	Lethargic	Comatose
Fits	None	<3/day	>2/day	
Posture	Normal	Fisting/cycling	Strong distal flexion	Decerebrate
Moro	Normal	partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent +/-	
Respiration	Normal	hyperventilation	Brief apnea	IPPV (apnea)
Fontanelle	Normal	Full, not tense	Tense	

Appendix II: Consent form

English version

CONSENT FORM SERIAL NUMBER…….

Study Title: Sonographic brain patterns in term neonates with hypoxemic ischemic encephalopathy post-therapeutic hypothermia and the clinical severity grading in Moi Teaching and Referral Hospital, Eldoret.

Name of Principal Investigator: Maureen Wanjiku Rwengo

Address: P.O Box 4606-30100 Eldoret. Email address-maurinaciku@gmail.com

Telephone Number: 0726529253

Informed Consent Form for Parent to neonates admitted with birth asphyxia

This Informed Consent Form has two parts:

- Part I: Information Sheet [to share information about the study with you]
- Part II: Certificate of Consent [for signatures if you choose to participate]

PART I: INFORMATION SHEET

Introduction: You are being asked to take part in a research study. This information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions.

Taking part in this research study is voluntary. Saying no will not affect your rights to health care or any other services. Your treatment/payment or enrollment in any health plans or eligibility for benefits will not be affected if you decide not to take part. You are also free to withdraw from this study at any time. If after data collection you choose to quit, you can request that information provided by you be destroyed under supervision. This would be before data is de-identified and aggregated. You will be notified if new information becomes available about the risks or benefits of this research. You will receive a copy of this form after it is signed.

Purpose of the study: to describe brain patterns and the clinical severity grade in neonates with birth asphyxia after therapeutic hypothermia treatment.

Study site: newborn unit at Moi Teaching and Referral Hospital.

Study population: term neonates with moderate and severe birth asphyxia.

Study procedures: The neonate admitted with moderate and severe birth asphyxia who fits into the inclusion criteria and for whom the mother has given consent, will be assessed and will undergo cranial ultrasonography. The following parameters will be obtained from the child's mother: age and gender, mode of delivery, residence, gestational age at which the child was born, and birth weight. The brain patterns will be obtained. Data will be collected on data collection forms. Data collecting material will be kept safe by the principal investigator during the study period.

Benefits: There will be no direct benefits to participating in this study. Participants will get the same standard of care /investigation regardless of whether they participate or not.

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

Payments and Reimbursements: there will be no payments or reimbursement.

Confidentiality: All reasonable efforts will be made to keep your protected information (private and confidential). Using or sharing ("disclosure") of such information will follow National privacy guidelines. By signing the consent document for this study, you are giving permission ("authorization") for the use and disclosure of your study information. We may need to share your protected information with the community advisory board, MTRH//MU-IREC, NACOSTI or the healthcare team. We will retain your research records for at least six years after the study is completed. At that time, the research information is destroyed. If you decide to withdraw your permission for use of your personal data, contact the principal investigator in writing and let them know your decision. At that time, we will stop further collection of any information about you. However, the health information collected before this withdrawal may continue to be used for reporting and research quality.

PART II: CONSENT OF PATICIPANT:

I have read or have had someone read to me the description of the research study. The investigator or his/her representative has explained the study to me and has answered all the questions I have at this time. I have been told of the potential risks, discomfort, and possible benefits (if any) of the study. I freely volunteer to take part in this study.

_____ _____

Name of Participant Signature of participant/Thumbprint
Date & Time

_____ _____

Name of the person obtaining consent Signature of person

obtaining consent

_____ _____

Printed name of the investigator Signature of Investigator
Date

Contacts for questions about the study

Questions about the study: kindly contact Rwengo Maureen,0726529253, email address maurinaciku@gmail.com

Questions about your rights as a participant: You may contact the Institutional Ethics and Research Committee (MTRH//MU-IREC) 0787723677 or email irec@mtrh.go.ke or irecoffice@gmail.com. The MTRH//MU-IREC is a group of people that review studies for safety and to protect the rights of participants.

Kiswahili version

FOMU YA IDHINI

NAMBA TAMBULISHI……

Jina la mradi wa utafiti: Mwononekano wa ubongo kwa ultrasonography ya ubongo katika watoto wapya walio na ugonjwa wa kukosa hewa kwa ubongo na wanaopata matibabu ya baridi waliolazwa katika hospitali ya rufaa na mafunzo ya Moi,Eldoret.

Mtafiti mkuu: Maureen Wanjiku Rwengo

Anwani: Sanduku la Posta 4606-30100 Eldoret. Barua pepe - maurinaciku@gmail.com

Nambari ya simu:0726529253

Fomu ya idhini ya: Mama ya mtoto mpya aliyelazwa kwa wadi.

Hii fomu ya idhini ina sehemu mbili:

- Sehemu ya kwanza: Maelezo(kukupa maelezo kuhusu utafiti)
- Sehemu ya pili: Cheti cha idhini

SEHEMU YA KWANZA: MAELEZO

Utangulizi:

Unaulizwa kushiriki katika utafiti. Maelezo haya yametolewa kukuarifu kuhusu utafiti huu. Soma fomu hii kwa umakini. Utapewa nafasi ya kuuliza maswali.

Kishiriki katika utafiti huu ni kaw hiari. Kukataa kuhiriki hakuta zuia haki yako ya matibabu. Pia,uko huru kujiondoa katika utafiti huu wakati wowote. Kama utajiondoa katika utafiti huu baada ya Habari zozote kuchukuliwa,unaweza omba iharibiwe chini ya uangalizi. Utajulishwa kama kutakua na mabadiliko yoyote kuhusiana na faida ama hatari itakayo tokea kuhusu utafati huu. Utapewa nakala ya fomu hii baada ya kutiwa sahihi.

Madhumuni: utafiti unajaribu eleza mwonekano wa ubongo kutumia sonograph kwa watoto wachanga wenye ukosefu wa hewa katika ubongo waliopewa matibabu ya baridi

Mahali ya utafiti : hospitali ya rufaa na mafunzo ya Moi

Wanaohusika: Watoto wapya wenye ugonjwa wa kukosa hewa kwa ubongo

Utaratibu: Watoto wote wapya ambao watakuwa wamelazwa katika wadi ya watoto wapya ambao waliotimiza vigezo kuingizwa kwenye utafiti,na kutathminiwa, watafanyiwa ultrasonograph ya ubongo. Akina mama watahojiwa kuhusu umri na jinsia ya mtoto, jinsi alivyojifungua, makazi,umri wa ujauzito ambao mtoto

alizaliwa,na kilo aliyozaliwa nayo. Takwimu zitakusanywa kwenye fomu kisha kuwekwa katika baraza la mawaziri salama lililofungwa katika ofisi ya mpelelezi mkuu katika kipindi cha utafiti.

Faida:Hakutakuwa na faida moja kwa moja yakushiriki katika utafiti huu. Wahusika watapata huduma ya matibabu bila kujali kama wnamehusika katika utafiti au la.

Hatari: Hakuna hatari yakutarajia kwa washiriki inatokana na utafiti huu.

Malipo/urejeshaji : Hakutakua na malipo au urejeshaji.

Usiri: Habari zote zilizopatikana katika utafiti huu zitahifadhiwa kwa usiri mkubwa, nawala haitatolewa kwa mtu yeyote asiyehusika na utafiti huu.

SEHEMU YA PILI: CHETI CHA IDHINI

Nimesoma au nimesomewa maelezo ya utafiti huu. Mtafiti mkuu/mwakilishi wa mtafiti amenielezea kwa undani kuhusu utafiti huu na amejibu maswali yote. Nimeelezewa hatari na faida zinazowezekana kuhusiana na utafiti huu. Najitolea kwa hiari kuhusuka katika utafiti huu.

Jina la mhusika Tarehe/wakati	Sahihi la mhusika/alama ya kidole
_____ Jina la anaye peana idhini	_____ Sahihi la anaye peana idhini
_____ Jina chapa la mtafiti mkuu	_____ Sahihi la mtafiti mkuu

Kwa maswali kuhusu utafiti:
Wasiliana na Rwengo Maureen,0726529253, barua pepe, maurinaciku@gmail.com.Kwa maswali kuhusu haki yako kama mhusika,unaweza wasiliana na Taasisi za utafiti na Kamati ya Maadili (IREC) 0787723677 ama barua pepe-irec@mtrh.go.ke **ama** irecoffice@gmail.com**.**

Appendix III: Data Collection Form

PART 1: DEMOGRAPHICS

SERIAL NUMBER……

DATE OF ADMISSION……..

TIME OF BIRTH……..

GESTATION BY DATE……

TIME OF COOLING……..

BIRTH WEIGHT…….

GENDER……..

PART 2: BIRTH HISTORY

MODE OF DELIVERY NORMAL DELIVERY SVD……CEASERIAN DELIVERY…….

RISK FACTOR FOR ASPHYXIA …….

PART 3: PATTERNS OF BRAIN INJURY PRE-TREATMENT

WHITE MATTER/GRAY MATTER DIFFERENTIATION INTACT ……. LOST…….

PERIVENTRICULAR ECHOGENICITY

SUBCORTICAL ECHOGENICITY

BASAL GANGLIA ECHOGENICITY

OTHER

PART 4: PRETREATMENT CLINICAL SEVERITY GRADE ACCORDING TO THOMPSON'S SCORE

MODERATE……

SEVERE…….

PART 5: PATTERNS OF BRAIN INJURY POST-TREATMENT

WHITE MATTER/GRAY MATTER DIFFERENTIATION INTACT ……. LOST……..

PERIVENTRICULAR ECHOGENICITY

SUBCORTICAL ECHOGENICITY

BASAL GANGLIA ECHOGENICITY

OTHER…….

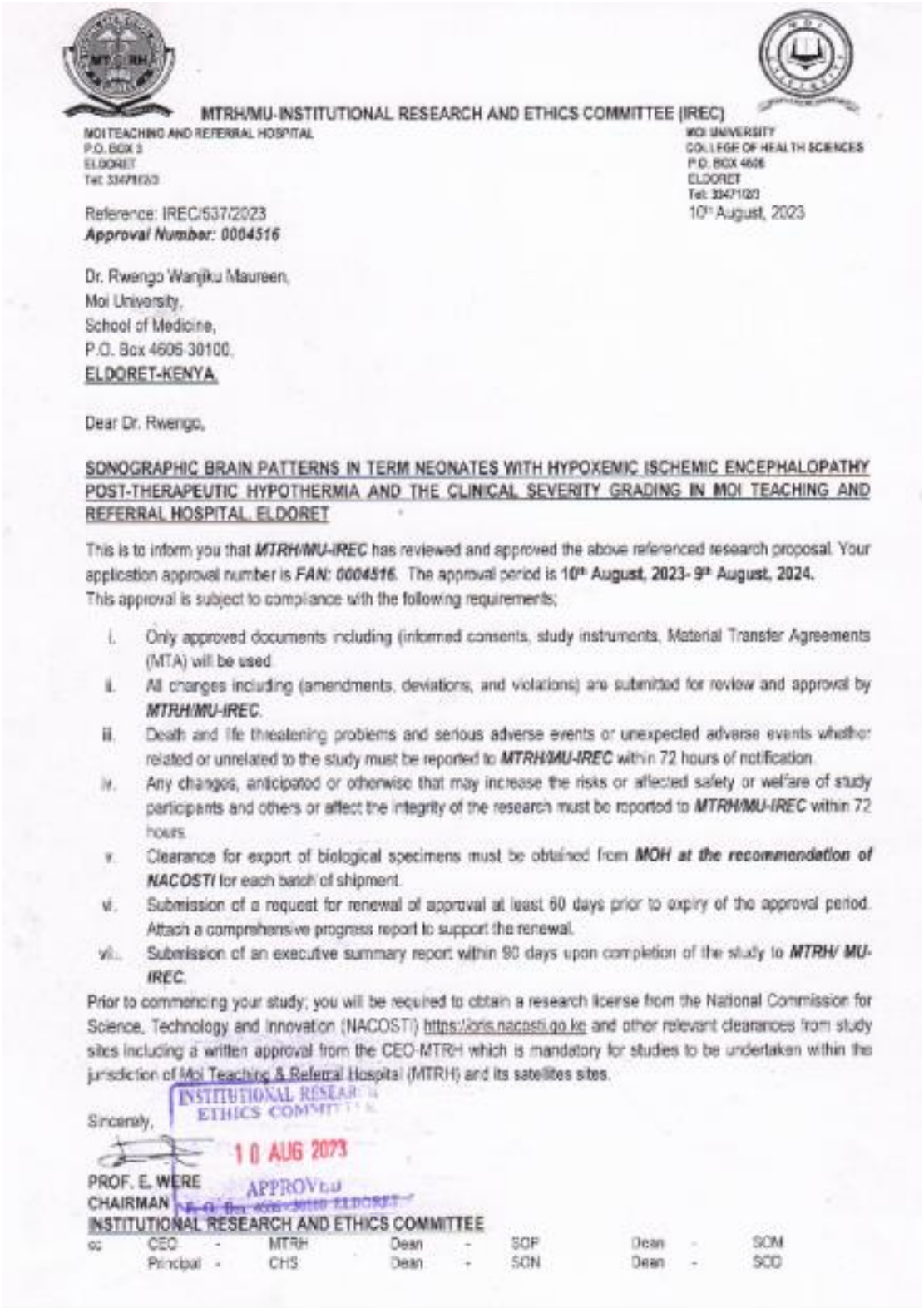
PART 5: POST-TREATMENT CLINICAL SEVERITY GRADE ACCORDING TO THOMPSON'S SCORE

MILD…….

MODERATE……

SEVERE…….

Appendix IV: IREC Approval



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

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471033

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471033

Reference: IREC/537/2023
Approval Number: 0004516

10th August, 2023

Dr. Rwengo Wanjiku Maureen,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Rwengo,

SONOGRAPHIC BRAIN PATTERNS IN TERM NEONATES WITH HYPOXEMIC ISCHEMIC ENCEPHALOPATHY POST-THERAPEUTIC HYPOTHERMIA AND THE CLINICAL SEVERITY GRADING IN MOI TEACHING AND REFERRAL HOSPITAL, ELDORET

This is to inform you that ***MTRH/MU-IREC*** has reviewed and approved the above referenced research proposal. Your application approval number is ***FAN: 0004516***. The approval period is **10th August, 2023- 9th August, 2024.**
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

Sincerely,

10 AUG 2023

APPROVED
P. O. Box 4606-30100 ELDORET

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

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

Appendix IV: MTRH CEO Approval

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: (+254)-(0)3203643/1/2/3/4
Fax: 0532061749
Email: ceo@mtrh.go.ke/ceooffice@mtrh.go.ke

NAIROBI ROAD
P.O. BOX 3-30100
ELDORET,KENYA

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

25th August, 2023

Dr. Rwengo Wanjiku Maureen,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

SONOGRAPHIC BRAIN PATTERNS IN TERM NEONATES WITH HYPOXEMIC ISCHEMIC ENCEPHALOPATHY POST-THERAPEUTIC HYPOTHERMIA AND THE CLINICAL SEVERITY GRADING IN MOI TEACHING AND REFERRAL HOSPITAL, ELDORET

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.

The approval period is 25th August, 2023 – 24th August, 2024.

DR. WILSON K. ARUASA, *MBS, EBS*
CHIEF EXECUTIVE OFFICER

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