Addis Ababa University,
College of Health Sciences,
School of Medicine

Prevalence of Periventricular-Intraventricular Hemorrhage Diagnosed on Transcranial Ultrasound among Preterm Neonates Admitted to the NICU in Tikur Anbessa Specialized Hospital, Ethiopia

Investigator Dr. Aman Getachew, MD., Final year Resident in Radiology, School of Medicine, College of Health Sciences, AAU, Addis Ababa, Ethiopia

A senior paper for Partial Fulfillment of specialty Certificate in Radiology Submitted to Addis Ababa University, College of Health Sciences, School of Medicine, Department of Radiology

September, 2018
Addis Ababa, Ethiopia

Addis Ababa University,
College of Health Sciences,
School of Medicine

Prevalence of Periventricular-Intraventricular Hemorrhage Diagnosed on Transcranial Ultrasound among Preterm Neonates Admitted to the NICU in Tikur Anbessa Specialized Hospital, Ethiopia

Investigator Dr. Aman Getachew, MD., Final year Resident in Radiology, School of Medicine, College of Health Sciences, AAU, Addis Ababa, Ethiopia

A senior paper for Partial Fulfillment of specialty Certificate in Radiology Submitted to Addis Ababa University, College of Health Sciences, School of Medicine, Department of Radiology

Advisors:

Dr. Daniel Zewdneh (MD., MHA, Associate Professor of Pediatric Radiology)
Dr. Yocabel Gorfu (MD., Assistant Professor of Pediatric Radiology)

September, 2018
Addis Ababa, Ethiopia

SUMMARY

Objective: To determine the incidence of PIVH among preterm neonates admitted to TASH NICU using .TCUS.

Method: A hospital-based cross-sectional study was conducted at Tikur Anbessa Specialized Hospital among preterm neonates admitted to the NICU in TASH from November, 2017 to July, 2018. The study population comprised all preterm neonates born 36 weeks and earlier and admitted to NICU in TASH for whom focused trans cranial ultrasound (TCUS) was done. Data were collected from November, 2017 to July, 2018 using structured data collection instrument and it was analyzed by using SPSS 20.0 software, then summarization and comparison of data was done.

Results: In our study, the prevalence of PIVH in preterm infants was 20.7% in the first seven days of postnatal life. Grade I PIVH was the most frequent (42.86%) followed by Grade III PIVH (25.71%), Grade IV (27.5%) and Grade II PIVH (22.86%) respectively. Grade II was the least prevalent. Independent variables significantly associated with presence of PIVH were birth weight (P = 0.001, CI 95%), gestational age (P = 0.001, CI 95%). Other associations were Low 1st minute APGAR (P = 0.021, CI 95%), Prenatal steroid administration (P = 0.215, CI 95%), mode of delivery (P = 0.01, CI 95%) and neonatal sepsis (P = 0.023, CI 95%),

Conclusion: The study found lower overall prevalence of PIVH compared to reports of other studies in Africa and globally, while the frequency of severe PIVH was relatively very high. Variables significantly associated with IVH were birth weight and gestational age. The other associations were Low 1st min. APGAR, mode of delivery and presence of neonatal sepsis. The findings of the study are in keeping with findings of studies from other African and global studies.

ACKNOWLEDGMENT

I would like to express my gratitude to my advisors Dr. Daniel Zewdneh and Dr. Yokabel Gorfu for their constructive comments trough the course of this research.

I would like to thank the Department of Pediatrics NICU unit and Dr. Asrat Demissie and Dr. Goitom G/Yesus for their assistance and feedbacks and Miss Ephrata Melesse from SIPS for helping in patient selection.

I would also like to extend my gratitude to Dr. Hansel Otero from children's hospital of Philadelphia for helping fine tune my TCUS skill and protocol and taking time from his busy schedule to critique the final manuscript.

I would like to thank the department of radiology for providing an opportunity to do this research.

And finally I would like to thank my family and my wife Dr. Elfign Fekadu for their endless support throughout the undertaking of this study.

Table of contents

List of Tables and Figures

List of Abbreviations

AAU	Addis Ababa University
APGAR	Appearance, Pulse Rate, Grimace, Activity, Respiration
CT	Computed Tomography
GMH	Germinal Matrix Hemorrhage
ICH	Intracranial Hemorrhage
MD	Medical Doctor
MHz	Megahertz
MHA	Masters in Hospital Administration
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
PI	Principal Investigator
PIVH	Periventricular-Intraventricular Hemorrhage
PHH	Post Hemorrhagic Hydrocephalus
SPSS	Statistical Package for Social Sciences
TASH	Tikur Anbessa Specialized Hospital
TCUS	Transcranial Ultrasound
WHO	World health Organization

Introduction

1.1 Background

Periventricular-Intraventricular hemorrhage (PIVH) remains one of the most common serious neurologic events of the neonatal period. This lesion has achieved its prominence in large part as a result of the remarkable improvements in neonatal intensive care in recent decades. The greatest improvements in neonatal intensive care have been made in the care of particularly low birth weight (LBW) and preterm infants. It is precisely this group that is at highest risk for intracranial hemorrhage (ICH) and its sequele [1].

The highest incidence of PIVH has been demonstrated by studies in premature infants, who were subjected to CT scan or ultrasound scan routinely in the first week of life, as table 1 below clearly details approximately 35 to 45 per cent of all infants born weighing less than 1500 gram or at gestational age of less than 35 weeks' were found to have PIVH. The incidence is highest among infants born at less than 32 weeks gestation [2, 3]. The high incidence and the severe neurological sequele make PIVH the most important determinant of neurologic morbidity in most neonatal intensive care units (NICUs). So a thorough understanding of the epidemiology as well as the variables associated with PIVH is essential for any NICU care provision especially when dealing with premature neonates.

Table 1. Incidence of PIVH in Premature infants gestational age less than 35 weeks Adopted from reference [2]

REFERENCE NUMBER	CRITERIA FOR INCLUSION	TOTAL NO. STUDIED	IMAGING TECHNIQUE	INCIDENCE OF PERIVENTRICULAR-INTRAVENTRICULAR HEMORRHAGE
61	<1500 gm	46	CT	43%
1	<35 weeks	191	CT	40%
34	<35 weeks	264	Ultrasound	34%
44	<35 weeks	124	Ultrasound	43%

The primary lesion in PIVH is bleeding, principally from small vessels, into the periventricular germinal matrix. A rich arterial supply to this region is derived particularly from the anterior cerebral artery, via Heubner's artery, and the middle cerebral artery, via the deep lateral striate arteries. Wigglesworth has shown that this vascular supply is particularly prominent from 24 to 32 weeks' gestation [4]. In most infants the hemorrhage originates in the germinal matrix overlying the head of the caudate nucleus at the level of the foramen of Monro. Heubner's artery constitutes the major blood supply to this particular region of the germinal matrix. In infants less than 28 weeks' gestation, however, the hemorrhage often originates in the germinal matrix overlying the body of the caudate nucleus in the territory of the anterior choroidal artery and the deep lateral striate arteries [5].

In some cases, periventricular hemorrhage ruptures through the ependyma into the ventricular system. Blood typically spreads throughout the ventricles, and then passes through the medial and lateral apertures of the fourth ventricle to collect in the basal cisterns. Subsequent to the initial hemorrhage an obliterating fibrosing arachnoiditis may develop and cause the obstruction to cerebrospinal fluid (CSF) flow that results in post hemorrhagic hydrocephalus [6]. In particularly severe forms, the periventricular hemorrhage appears to extend into the cerebral parenchyma. In such cases the development of a porencephalic cyst is a frequent sequele, recent neuropathology observations suggest that intraparenchymal hemorrhage most commonly is, in fact, concurrent hemorrhagic venous infarction rather than simple extension of matrix hemorrhage [7].

Although the pathophysiology of PIVH in neonates has not been fully elucidated, it has been observed that elevations in arterial blood pressure, comparable in magnitude to those used in the experimental models of ICH have been observed in the first minutes of life, during episodes of apnea, with spontaneous or handling-induced motor activity, during seizures, during rapid eye movement sleep, during exchange transfusions, during rapid colloid infusions, and as a consequence of asphyxia. This observation correlates with findings that have shown neonates with complications relating to asphyxia and rapid volume colloid infusions having higher incidence of PIVH [8,9,10].

Another important observation is the periventricular germinal matrix is a gelatinous region that appears to provide poor support for the many small vessels that course through it; In addition, the periventricular germinal matrix of the human premature infant has been shown to contain a high level of fibrinolytic activity. This factor may explain why capillary hemorrhage has the capacity to enlarge into a massive lesion that may extend into the ventricular system or dissect into brain parenchyma or both [11].

Finally, it has been suggested that a decreased tissue pressure or a sub atmospheric cerebrospinal fluid pressure may contribute to the occurrence of PIVH [12].

The clinical features of PIVH vary from a catastrophic neurologic event to an extremely subtle, perhaps even silent, course. The time of onset of the lesion is not known with great precision but is most often in the first two days of life. Recent studies using Transcranial ultrasonography (TCUS) have suggested approximately 50 per cent of affected infants exhibited PIVH in the first 24 hours of life [13, 14]. It should be emphasized, however, that a later onset of the initial lesion is not uncommon particularly in premature infants without an initial intraventricular hemorrhage who experience a secondary hypoxic insult [15].

In a prospective study of premature infants subjected to routine CT scans in the first week of life, only about one half of the cases of PIVH hemorrhage were correctly predicted on the basis of clinical criteria. The most reliable sign was an unexplained fall in hematocrit or a failure of the hematocrit to rise following transfusion [16].

The major aim of diagnosis is to direct families of preterm infants toward the most appropriate follow-up facilities, to promote early diagnosis and intervention for chronic neuro-

developmental sequele of hemorrhagic or ischemic brain injury and to support ongoing research activities that are aimed at ensuring the best possible outcomes for all infants [17].

A variety of imaging techniques have been used for diagnosis of PIVH in the neonatal period, Trans-Cranial ultrasound (TCUS) is the imaging modality of choice commonly used in most NICU setups [18]. Non contrast head CT and MRI have also been used for diagnosis in high risk neonates with equivocal TCUS findings and those having long term neurodevelopmental sequele respectively. But the risk of ionizing radiation in case of CT and the need to transport the neonate outside of the NICU, their high cost and technical difficulty including issues of sedation have made CT and MRI less desirable alternatives to TCUS.

The major advantages of TCUS is, its low cost, relative safety and its ability to be performed on the bedside with little manipulation of the neonate. It also can be repeated as often as necessary, thereby enabling visualization of ongoing brain maturation and the evaluation of brain lesion in addition to assessing the timing of brain damage. When TCUS is used repeatedly, its sensitivity and specificity can be very high [18].

Since the late 1970s, TCUS examinations have been performed on preterm infants to provide information about perinatal brain injury for the prediction of long-term outcomes [19].

Classic studies by Papile et al [21] and Slovis & Kuhn [20] reported on the use of real-time linear array and sector scanning to detect intraventricular and parenchymal hemorrhage, ventricular enlargement and other abnormalities. In his famous paper Papile [21] formulated a grading system of PIVH based on the extent of the hemorrhage, associated ventricular distension and parenchymal involvement. The grading although first based on head CT studies currently has been adapted to TCUS. There is a distinct relationship between the severity of the hemorrhage, as assessed by CT scan or ultrasonography and prognosis. The Papile Grading of Severity and short-term outcomes of PIVH is shown in the Tables 2 and 3 below.[21, 22, 23]

Table 2 Severity of intraventricular Hemorrhage on TCUS [23]

Grade	Description on parasagittal view
I	Germinal matrix hemorrhage only or germinal matrix hemorrhage plus intraventricular hemorrhage less than 10 percent of ventricular area
II	Intraventricular hemorrhage, 10 to 50 percent of ventricular area
III	Intraventricular hemorrhage involving more than 50 percent of ventricular area; lateral ventricles are usually distended
IV	Parenchymal bleed in any location and amount

Adapted from: Papile, LA, et al. J Pediatr 1978; 92:529.

Table 3 Short Term Outcome in PIVH with Long Term Morbidity and Mortality Based on Papile Grade [23]

SEVERITY	DEATH	PROGRESSIVE HYDROCEPHALUS
Mild*	~0	0–10%
Moderate†	5–15%	15–25%
Severe‡	50–65%	65–100%

.

*Mild hemorrhage consists of subependymal hemorrhage with less than 10 per cent of the ventricular area at the level of the trigone filled with blood, equivalent to Papile grade I.

+Moderate hemorrhage consists of intraventricular hemorrhage filling 10 to 50 per cent of the ventricular area, equivalent to Papile grade II PIVH.

++Severe hemorrhage consists of intraventricular hemorrhage filling greater than 50 per cent of the ventricular area or of intraventricular hemorrhage with intraparenchymal involvement, Papile grade III and IV respectively..

Over the past several years the outcome of neonatal intraventricular hemorrhage has improved. This change in prognosis relates in considerable part to the detection by CT or ultrasound of small lesions that in the past would have gone undetected, and also the improved outlook for premature infants in general, which is attributed to the improved supportive care provided by current neonatal intensive care units [24].

The most effective strategy to prevent PIVH is prevention of preterm birth. When preterm birth cannot be avoided aim of the current treatment will be centered on preventing the occurrence of Post hemorrhagic hydrocephalus (PHH) and periventricular leukomalacia (PVL), which are the two significant sequele of PIVH. Delivery room interventions which are associated with a reduced risk of PIVH include, Delayed clamping of the umbilical cord (>30 seconds) and early transfer of mothers to a perinatal center in case of preterm labor [25].

Mothers who are at risk for preterm delivery, are recommend to have administration of antenatal corticosteroids, it is also widely accepted that the following general supportive measures reduce risk of PIVH after birth based on the understanding of the pathogenesis (eg, hemodynamic instability) and risk factors (eg, acidosis) associated with IVH [25].

Management hence should be focused on reducing further brain injury through preservation of cerebral perfusion and oxygenation by maintaining mean arterial perfusion and adequate oxygenation and ventilation, and providing appropriate fluid, metabolic, and nutritional support. In addition, seizures are treated in a timely manner to avoid hypoxia or hypotension. Ongoing surveillance that includes daily head measurement, weekly brain imaging and monitoring for signs of increased intracranial pressure (ICP) are used for early detection of PHH. Infants with rapid progression of hydrocephalus or with signs of increased ICP require neurosurgical intervention [25].

1.2 Statement of the Problem and Significance of the Study

According to the 2014 World Health Statistics Report, Ethiopia has achieved MDG 4 target three years earlier by reducing under 5 mortality from an estimated 203.9 deaths/1000 live births in 1990 to an estimated 74.4 deaths/1000 live births in 2013, yielding a total reduction of 64%. The UN Inter Agency Group's 2013 mortality estimate reported that Ethiopia's under-five, infant and neonatal mortality rates were 68, 44 and 28 per 1000 live births respectively. From 1990 to 2000, the average Annual Reduction Rate (ARR) of U5MR was at 2%, which accelerated to 5% since 2000. Notwithstanding the achievement observed in the reduction of under-five mortality rates, about 190,000 children are still dying each year [26].

Moreover, the reduction in mortality in neonatal age groups (48%) is not as impressive as that of childhood mortality. It has fallen only by 42% during the same period; from 54/1000 live births in 1990 to 28/1000 live births in 2013. About 44% of the childhood deaths occur within the first 28 days of life. Neonatal conditions which used to account for a quarter of under-five deaths in 2004 have recently increased to 43% while deaths due to malaria, measles, HIV, diarrhea and pneumonia have declined. Prematurity (37%), infection (28%), and asphyxia (24%) are the most common causes of death in neonates [26].

Approximately half of all neonatal deaths in sub-Saharan Africa are due to complications of prematurity and perinatal asphyxia. Early detection and treatment of brain injuries associated with these conditions is crucial to reduce mortality and long-term cognitive, behavioral, sensory, language and motor sequele in survivors [27].

Unfortunately although there is an abundance of evidence in the western world, the lack of even basic research about the burden of disease and associated factors of one of the major complications of prematurity, PIVH, in an Ethiopian context makes addressing the policy issues of decreasing neonatal mortality in a broader term as well as improving day to day care provision in those neonates suffering from prematurity and PIVH a formidable challenge in our healthcare system.

With every challenge there are opportunities, the TASH NICU, as well as most Ethiopian hospitals tasked with giving care to preterm neonates are equipped with ultrasound machines, which can be used with minimal training to screen and diagnose preterm neonates with PIVH, which will have a definitive impact on improving treatment for the neonate and helping decrease the mortality rates in our neonatal intensive care units.

It's this challenge and the opportunity it presents, which has kindled the interest of the PI to investigate, the soundness of TCUS in evaluating the incidence of PIVH, among Preterm Neonates as well as its associated factors in the NICU of TASH, one of the first and leading teaching hospitals in Ethiopia with the largest NICU in the country.

It is hoped that this crude study will be used as a baseline for future studies and also serve to direct other researchers to undertake further studies and shed light on the relatively unexplored avenue.

1.3 Literature Review

Literature review was made, using search queries on Pubmed and Medline and the AAU repository, with key words, Periventricular Intraventricular Hemorrhagic (PIVH), Germinal Matrix Hemorrhage (GMH), and Periventricular Leukomalacia (PVL). Neonatal Transcranial Ultrasound (TCUS), Post Hemorrhagic Ventricular Dilation (PHVD), Perinatal Risk Factors, Incidence, Prevalence Mortality and Maternal Risk Factors. Papers considered relevant by the PI were cited and used as references.

1.3.1 Epidemiology of PIVH

In the Literature review the PI has not been able to find any published work with regards to the study of prevalence or risk factors of PIVH among preterm neonates in an Ethiopian context in any of the major international journals or in the AAU repository. Furthermore east African studies are also few and far between with most having severe limitations. In a sub-Saharan Africa context researches in Nigeria[28], South Africa [29, 30] and Zambia[31] have been published.

In one such study, the most recent conducted in Zambia in 2012 and published in the Medical Journal of Zambia, titled "The Prevalence of Intraventricular Hemorrhage and Associated Risk Factors in Preterm Neonates in the Neonatal Intensive Care Unit at the University Teaching Hospital, Lusaka, Zambia" [31], a cross sectional study on 298 preterm neonates with birth weight 1.5kg or less admitted to the neonatal intensive care unit at the University Teaching Hospital in Lusaka, Zambia was undertaken with the aims of determining the prevalence and most frequent grade of PIVH as well as associated risk factors, TCUS was done in the first three days of life and on the seventh postnatal day. Data on the risk factors was obtained from the neonatal referral form, maternal records and direct interview with the neonate's mother [31].

In the study, the prevalence of intraventricular hemorrhage in preterm infants with birth weight 1.5kg and less was 34.2% in the first seven days of postnatal life. Grade 1 (mild) PIVH was the most frequent (54.9%) followed by severe PIVH (grade 3 and 4) at 27.5%. The case fatality rate was 85.7% for those with grade 4 in the first three days of life. Grade 2 was the least prevalent at 17.7%. Risk factors significantly associated with PIVH were birth weight [p=0.04, OR= 0.25(0.06-0.98) 95% C.I.] and gestational age [p=0.02, OR= 0.82 (0.69-0.97) 95%C.I.] [31].

The studies concluded that overall prevalence (37.2 %) was similar or even lower to that reported in studies in Africa and globally, while the frequency of severe PIVH was relatively very high (27.5 %) with a high case fatality rate (85.7%) in the first seven days of postnatal life in grade 4 PIVH [31].

Similar studies in South Africa [29, 30] and Nigeria [28], though with fewer subject numbers, have shown much lower rates in the frequency of severe PIVH but higher or similar overall prevalence of PIVH. Over the last two to three decades the rates for severe PIVH which has the worst prognosis both in the short and long term has remained almost unchanged globally and in some instances even increased in the African studies.

1.3.2 Risk Factors for Development of PIVH

A number of risk factors have been proposed for the development of IVH: low birth weight, low gestational age, maternal smoking, breech presentation, gender, premature rupture of membranes, intrauterine infection, mode of delivery, prolonged labor, postnatal resuscitation and intubation, transfer from one unit to another, early onset of sepsis, development of respiratory distress syndrome or pneumothorax, recurrent endo-tracheal suctioning, metabolic acidosis, rapid bicarbonate infusion, and high-frequency ventilation, whereas Pregnancy induced hypertension has been associated with a lower rate of IVH. Several pharmacological interventions have also been proposed for reducing the incidence of IVH, including antenatal steroids, prenatal tocolytic therapy, postnatal administration of low-dose indomethacin, and surfactant [32].

In a study done in South Korea in 2010 and published in the journal of Korean medicine titled "Risk Factors for Periventricular-Intraventricular Hemorrhage in Premature Infants" [32], the authors conducted a retrospective case-control study from preterm infants born at ≤34 weeks of gestation and admitted to Neonatal Intensive Care Units of Seoul National University Children's Hospital and Seoul National University Bundang Hospital between June 2003 and December 2007. Of the 1,044 eligible subjects, PIVH was diagnosed in 290 cases (27.8%); 231 cases (79.7 %) with grade 1, 20 cases (6.9%) with grade 2, 14 cases (4.8 %) with grade 3, and 25 cases (8.6%) with grade 4. The multivariate logistic regression analysis showed that metabolic acidosis (OR: 6.94; 95% CI: 1.12-43.23) and the use of inotropes (OR: 3.70; 95% CI: 1.16-11.84) were associated with an increased risk of PIVH. The use of stepwise logistic regression analysis demonstrated that the use of an umbilical vein catheter was likely to increase the risk of PIVH (OR: 3.28; 95% CI: 0.8-13.44) [32],

Many clinical factors were significantly higher in the case group than in the control group. The factors included the use of mechanical ventilation, the use of umbilical artery catheterization, respiratory distress syndrome, surgery, sepsis, red blood cell transfusion and frequency, platelet transfusion, treatment for acidosis by NaHCO3 administration. Negative associations were observed for the 5-min APGAR score (5.0±2.1 vs. 6.0±1.9 min; *P*=0.001, c2-test), maternal preeclampsia (11.9% vs. 27.1%; *P*=0.021, Chi square-test) and antenatal use of corticosteroids (62.7% vs. 81.4%; *P*=0.007, Chi square-test) for the case group and control group, respectively [32].

In another paper published in the Journal of American Pediatrics in 2003 titled "Risk Factors for Intraventricular Hemorrhage in Very Low Birth Weight Premature Infants"[33]: A Retrospective Case-Control Study", A total of 641 VLBW preterm infants (1500 g) born at the Rabin Medical Center Tel Aviv, Israel, during the 5-year period from January 1, 1995, to December, 31 1999 were studied. From the cohort, 36 premature infants (5.6%) with IVH grades 3 and/or 4 were retrospectively identified, which composed our study group. A control group composed of 2 infants for each case, matched for gestational age and birth weight was selected on the basis of the first compatible live-born infant before and after each study infant [33].

Previous studies have proposed a number of risk factors for IVH; however, lack of adequate matching for gestational age and birth weight may have confounded the results. The purpose of

this study was to identify variables that affect the risk of high-grade PIVH, using a retrospective and case-control clinical study. Results of cranial ultrasound examinations, whether routine or performed in presence of clinical suspicion, were also collected. Univariate analysis and multivariate logistic regression analysis were performed [33].

High fraction of inspired oxygen in the first 24 hours, pneumothorax, fertility treatment (mostly in vitro fertilization), and early sepsis were associated with an increased risk of IVH. Early sepsis was associated with an 8-fold increase in the incidence of IVH, in agreement with previous studies [33].

A higher number of suctioning procedures, a higher first hematocrit, and a relatively low arterial pressure of carbon dioxide during the first 24 hours of life were associated with a lower occurrence. In the multivariate logistic regression model, early sepsis (odds ratio [OR]: 8.19; 95% confidence interval [CI]: 1.55– 43.1) and fertility treatment (OR: 4.34; 95% CI: 1.42–13.3) were associated with a greater risk of high-grade IVH, whereas for every dose of antenatal steroid treatment there was a lower risk of high-grade IVH (OR: 0.52; 95% CI: 0.30–0.90) and each decrease in a mmHg unit of arterial pressure of carbon dioxide during the first 24 hours was associated with a lower risk of IVH (OR: 0.91; 95% CI: 0.83– 0.98). This multivariate model had a sensitivity of 77%, a specificity of 75%, and a positive predictive value of 76% [33].

The paper concluded that the development of IVH is associated with early sepsis and failure to give antenatal steroid treatment. It also proposed that fertility treatment (and especially in vitro fertilization) may be an independent risk factor in the multivariate analysis, something previously unreported in the literature [33].

1.3.3 Diagnosis of PIVH

In low-income countries, basic clinical observations are used to diagnose PIVH and other causes of ventriculomegaly. For example, the rate of head growth and signs of increased intra-cranial pressure, such as persistent bulging and a tense fontanels, can be used to help diagnose PIVH. Unfortunately, the onset of rapid head growth and intra-cranial hypertension are often late indicators, manifesting days to weeks after the onset of ventricular distention, distortion of the parenchyma and possibly mechanisms leading to secondary brain injury [22]. Early detection is crucial as ventriculomegaly in pre-term infants is a strong predictor of cortical and white matter injury [34].

TCUS can facilitate early detection as it provides a means to directly assess ventricular dilation and parenchymal lesions [35]. Currently the increased availability of modern, affordable, user friendly portable ultrasound machines has made neonatal neuroimaging a possibility even in low resource settings like ours.

A paper titled “Evaluating Affordable Cranial Ultrasonography in East African Neonatal Intensive Care Units” [36], published in the international Journal of Ultrasound in Med. & Biol, in 2016, a study was performed on term healthy, pre-term and term asphyxiated neonates in Rwandan and Kenyan hospitals with the aim of evaluating the efficacy of TCUS in NICUs found in low resource settings. The research was performed on a total of 41 newborns who were

recruited and tested by TCUS at Centre Hospitalier et Universitaire de Kigali in Kigali, Rwanda (21 neonates), and Kenyatta National Hospital in Nairobi, Kenya (20 neonates) using both qualitative and quantitative diagnostic tools as criteria for evaluating the neonatal brain,

The study concluded using a portable and affordable ultrasound unit, a novice sonographer obtained reliable, valid measurements of clinically important neonatal brain anatomy including Anterior Horn Width (AHW) and Ventriculo Hemispheric Ratio (VHR) for evaluation of early signs of hydrocephalus, and a novice sonographer had good-to-excellent agreement with an expert in evaluating further neonatal cerebral abnormalities which could be imaged and identified on TCUS [36]. To assess validity, an expert analyzed the images from approximately two-thirds of the TCUS sessions of the novice sonographer. Ninety-eight percent (50/51) of the abnormalities identified by the primary observer (observer 1) were confirmed by the expert. Additionally, the expert observer added only four additional abnormalities, giving a miss rate of 8% for the novice observer [36]. Although the study has limitations because of the small sample size used, it demonstrates that affordable equipment and cranial ultrasound protocols can be used in low-resource settings to assess the newborn brain adequately.

1.4 Conceptual Framework

The following Conceptual Framework was designed, and adopted for the study by the PI after the undertaking of the Review of Literature on the topic of PIVH in preterm neonates.

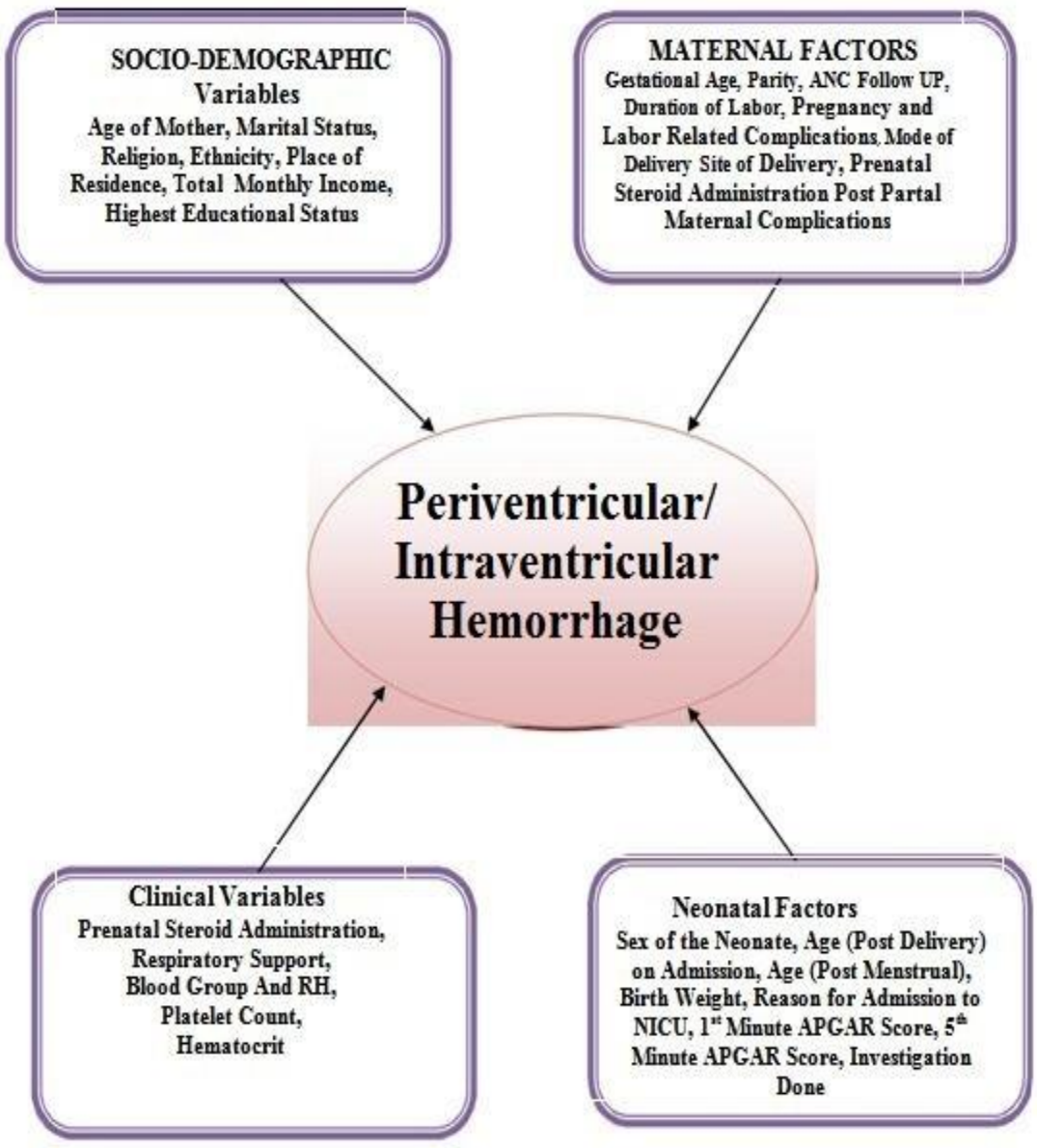


Figure 1 Conceptual frame work for the study on prevalence of neonatal PIVH in preterm neonates admitted to NICU in TASH

1. Objective

2.1 General Objective

- To determine the Prevalence of PIVH among preterm neonates admitted to TASH NICU using TCUS

2.2 Specific Objectives

- To determine the severity of PIVH at time of diagnosis based on TCUS scanning
- To determine patient related risk factors for PIVH
    - To determine demographic factors affecting the distribution of PIVH
    - To determine clinical factors affecting the distribution of PIVH
- To determine maternal and obstetric factors affecting PIVH

2. Materials and Methodology

3.1 Design and Implementation of the study

A Prospective cross sectional hospital based study was done in preterm neonates admitted to the NICU in TASH, Addis Ababa Ethiopia from November, 2017 to July, 2018.

TCUS was performed on all participants after getting informed verbal consent from the legal guardian of the participant of the study by the PI, using a Sonoscape SSI-800 ™ ultrasound machine with L751 10-5MHz ™, linear array high frequency probe and 2P1 4-2MHz™, phased sector array probe. The PI used hand sanitizer before and after each scan and clean disposable gloves were used during each study. The probes were cleaned using 70% alcohol solution before every study. And TASH NICU infection prevention protocols were strictly followed.

The TCUS scanning protocol was adopted from, and was in accordance with the Practice parameters recommended by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society [37], and the anterior fontanel was used as an acoustic window, with coronal and sagittal sequential images taken from anterior to posterior and medial to lateral, taking the midcoronal and midsagittal planes as points of reference respectively,. The scanning protocol was deployed and pretested by the scanner (PI) with the help of an experienced pediatric radiologist (HO) from children's hospital of Philadelphia, U.S.A, and no inter observer variation was seen between HO and PI in the detection and grading of 10 patients scanned during the pretesting.

The PIVH grading was done based on the Papile et al grading system for PIVH [annex 1], and presence or absence of hydrocephalus was assessed using the standardized curve proposed by Levene et al [38, annex 2].The acquired images of participants which had PIVH were saved and transferred to a 1 terabyte Passport WD ™ storage device in JPEG format for later review.

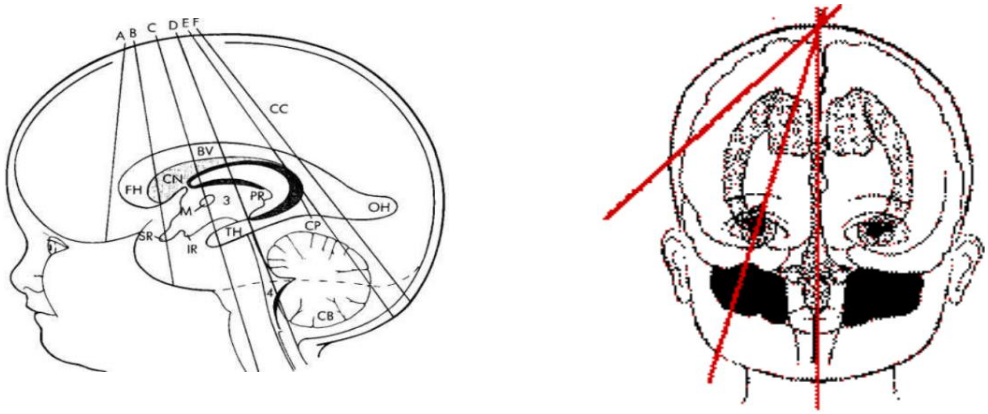


Figure 2a. (Left) Schematic Showing the Six Standard Coronal Planes for TCUS
Figure 2b. (Right) Schematic Showing the Three Left Hemisphere Standard Sagittal Planes for TCUS

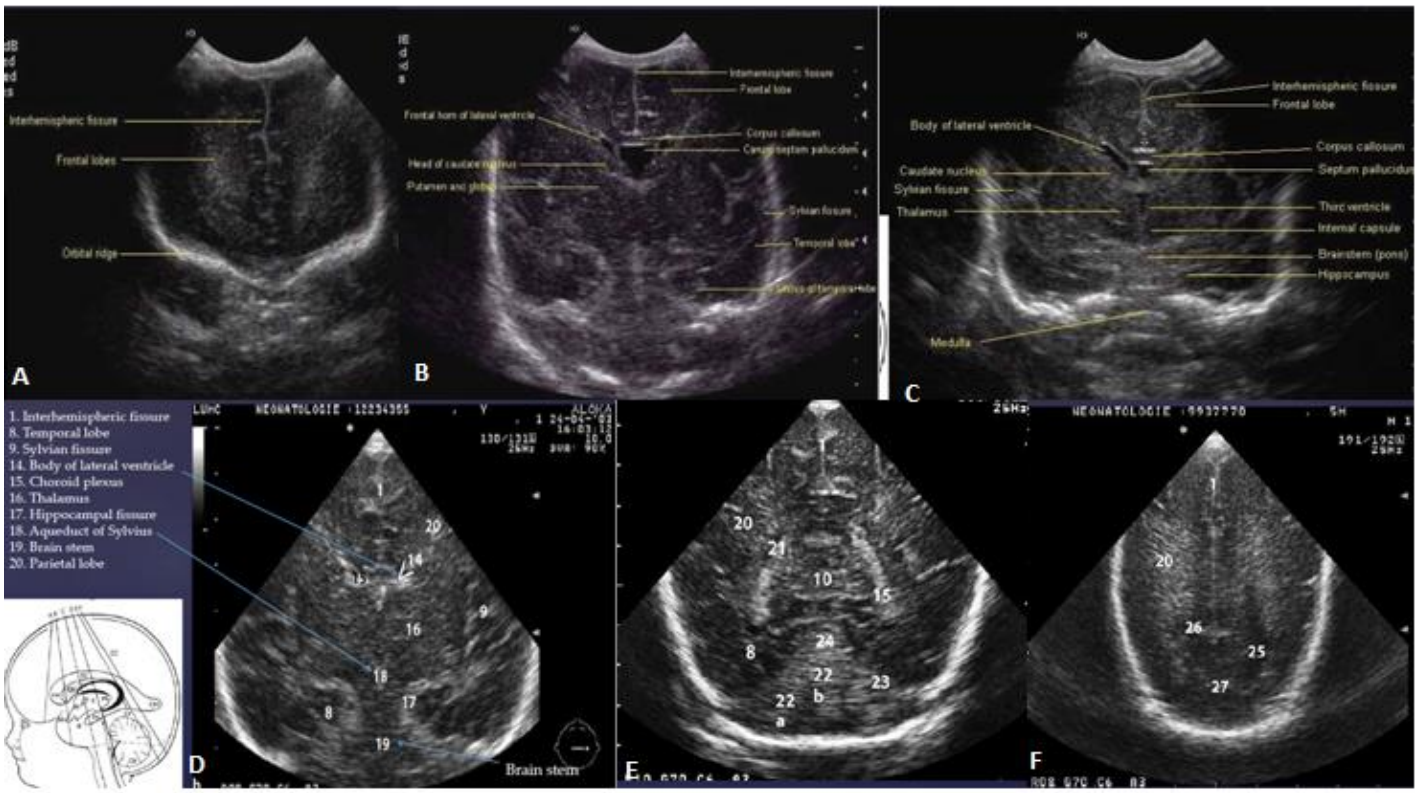


Figure 3. Ultrasound Images Showing the Six Standard Coronal Planes for TCUS

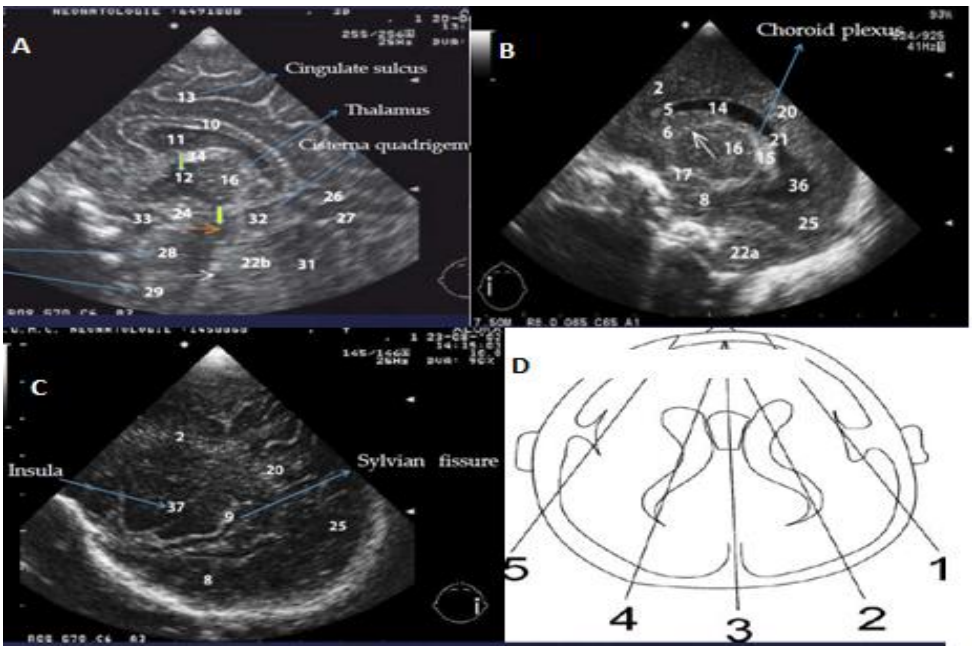


Figure 4. Ultrasound Images Showing the Three Left Hemisphere Standard Sagittal Planes for TCUS

3.2 Study Population

Study population was preterm neonates admitted to the NICU in TASH, Addis Ababa Ethiopia from November, 2017 to July, 2018. Neonates satisfying the inclusion criteria were selected based on convenience method until sample size was achieved

3.3 Inclusion and Exclusion Criteria

3.3.1 Inclusion Criteria

1. Preterm neonates (37 completed weeks or below) admitted to the NICU in TASH, Addis Ababa Ethiopia from November, 2017 to July, 2018
2. Neonates having Transcranial Ultrasound within the first 7 days of Life (168 hrs)
3. Neonates who are willing to participate in the study

3.3.2 Exclusion criteria

1. Neonates with CNS congenital anomalies
2. Neonates with Epidural/ Subdural collections
3. Neonates presenting after first week of life
4. Neonates not willing to participate

3.4 Sampling and Sample Size Determination

169 Preterm neonates who were admitted to the NICU of TASH during the study period were included in the study. Sampling was convenience method with neonates selected every Monday and Thursday until sample size was reached. The sample size was calculated using a Zambian research study as a baseline, which showed prevalence of PIVH of 34 .2 **%** [31]**.** A single population proportion formula with level of significance being 5%, **Z=** confidence level at 95% (standard value of 1.96) and absolute precision (margin of error) at 7.5% (α= 0.075) was used to calculate the sample size as follows:-

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^{2} p(1-p)}{d^2}$$

Where **Z**= The standard normal deviation at 95% confidence interval (1.96)

P= Expected proportion of neonates with PIVH in NICU preterm population (34.2%)

d= Absolute precision or tolerated margin of error (7.5%)

$$\textbf{Sample Size (n)} = \frac{(1.96)^2 \times 0.342 \times (1-0.342)}{(0.075)2}$$

n = 153.6885 rounding n= 154

When contingency of 10% was added to sample size

n = 169

3.5 Data Collection, Management and Safety Consideration

Participants' demographic and clinical variables were tabulated on the structured questionnaire which was prepared by the PI **(annex3)**. Names of participants will not be used and codes given by the PI will be used to identify participants. The questionnaires will be filled from the participants' medical chart by two pre trained NICU staff nurses.

The TCUS structured reports **(annex 4)** were attached to the structured questionnaire checked for quality and kept in plastic folders stacked by month of examination, and stored for later retrieval. The PI entered the data collected into double spread sheet data bases, and the data was analyzed with Statistical Package for Social Sciences (SPSS) version 20 at 5% precision level; the data was cleaned and checked for completeness. Descriptive statistics was used to analyze the data. Percentage, mean, and standard deviation were used to describe the findings. Tables and different graphs were used to assist data presentation.

Additionally association between variables will be determined with Chi-square. P value of < 0.05 will be taken as statistically significant.

. The result will be first presented to Department of radiology AAU as a requirement for partial fulfillment for a specialty certificate in radiology. Further dissemination through oral presentation on different events and publication on national and international peer reviewed journals will be attempted.

3.6 Ethical Consideration

Ethical clearance was obtained from the Research & Ethics Committee of the Department of Radiology, School of Medicine, Addis Ababa University. Verbal informed consent **Annex 6** was obtained from the legal guardian of each study participant and confidentiality was maintained. Names or any other personal identifiers of study participants were not recorded.

3. RESULTS

There were a total of 270 patients admitted to the NICU of TASH during the study period, out of which 169 neonates selected on convenience method, and who fulfilled the inclusion criteria were included in this research. Frequency tables were used to study distribution of variables and cross tabulation with Chi square χ^2 testing was used to identify the association between the independent variables and PIVH.

Out of the 169 neonates 134(79.3%) had no PIVH on TCUS, while 35(20.7%) had PIVH on TCUS. Out of those who had intracranial hemorrhage, 15(8.9%) had grade I, 8 (4.7%) had grade II, 9(5.3%) had grade III and 3(1.8%) had grade IV hemorrhage based on Papile et.al. classification of neonatal IVH. The commonest type of PIVH grade was type I.

Out of the included neonates 103(60.9%) were males and 66(39.1%) were females with a male to female ratio of 1.56:1. 21(20 .4%) of the male neonates had PIVH and 24(21 .2%) of the female neonates had intracranial hemorrhage. There was no association between sex and PIVH observed, χ^2 (1) = 0.017, p = 0.897).

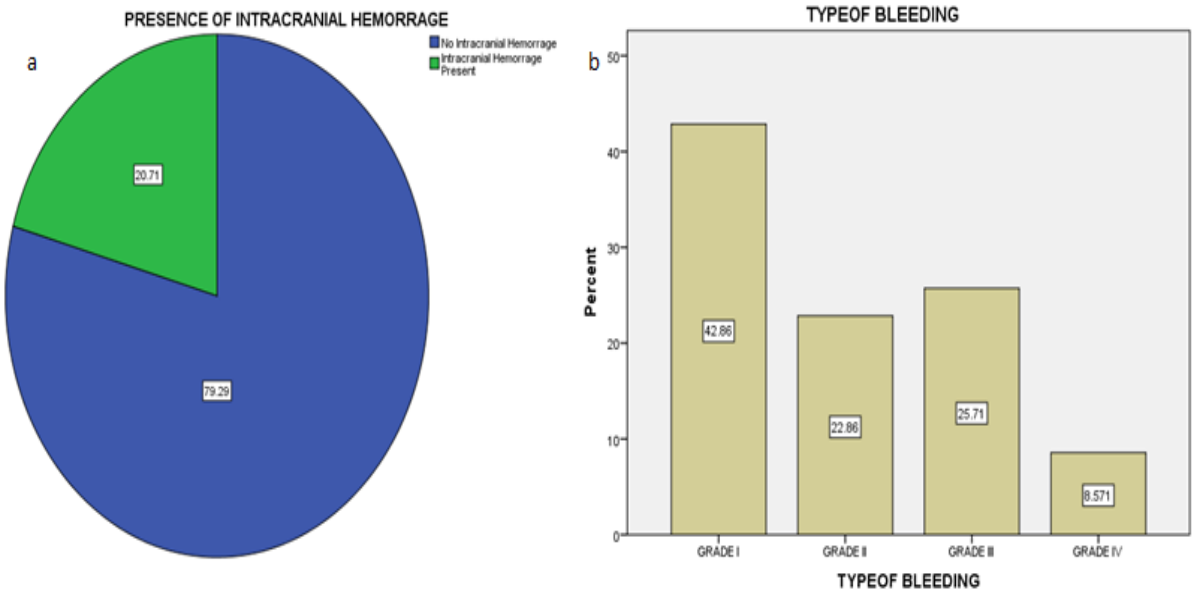


Figure 5a. Prevalence of PIVH in the study population

Figure 5b. Types of PIVH according to Papile grading in the study population

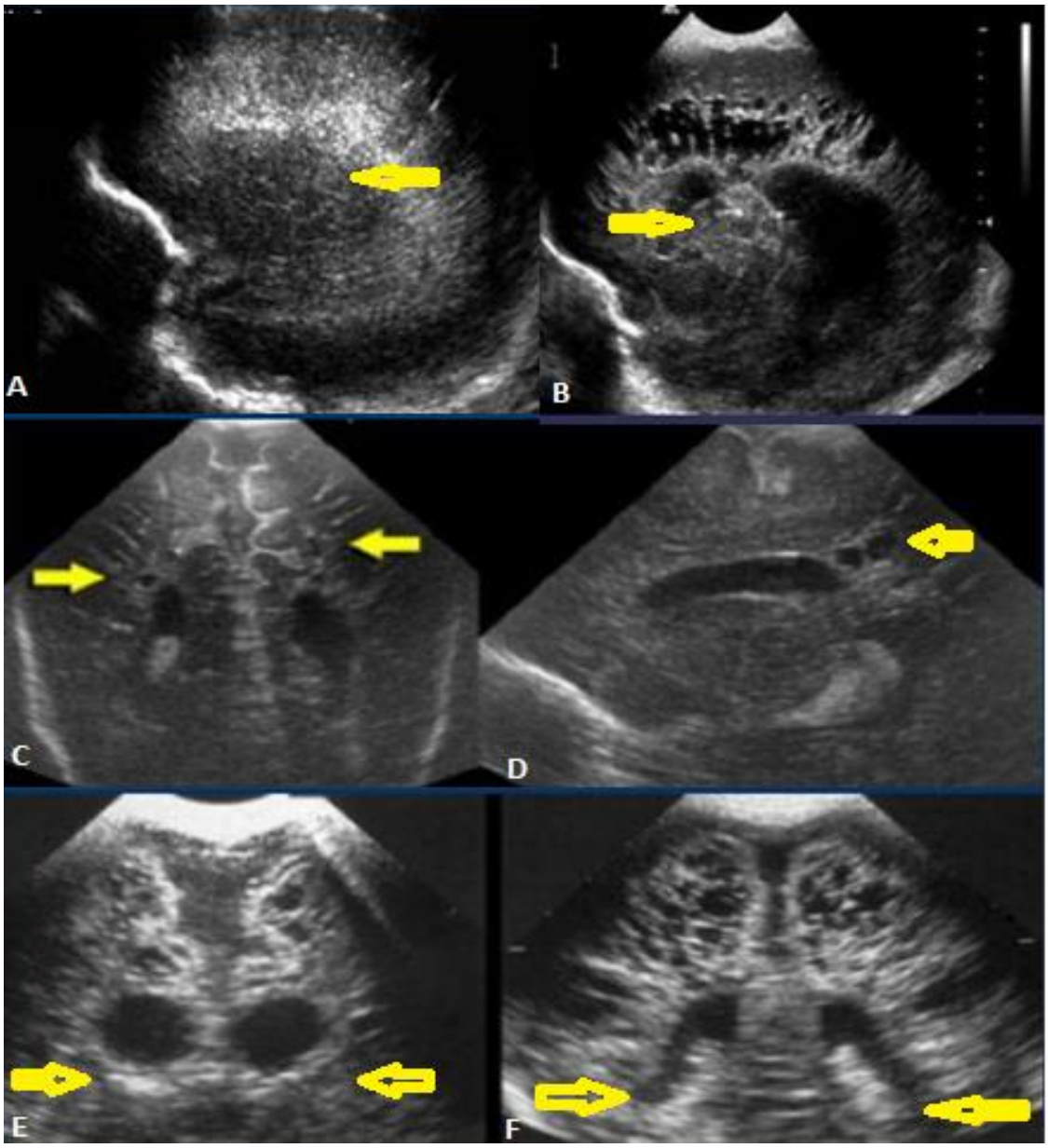


Figure 6(A-E). (A) Parasagittal TCUS Scan Showing Grade I PIVH, (B) Parasagittal TCUS Scan Showing Grade II PIVH, (C) Midcoronal and (D) Parasagittal TCUS Scans Showing Grade III PIVH, (E) Coronal Scan at the Level of the Bodies of the Lateral Ventricles and Midcoronal TCUS Scan Showing Grade IV PIVH.

Table 4. Clinical and laboratory characteristics of the preterm Neonates Admitted to the NICU in TASH and selected for the study

Estimated Gestational Age Mean(SD)		**33.107 weeks (±2.4)**
Category	**Extremely preterm %**	**1.8**
	Very preterm %	**21.3**
`	**Moderate to Late Preterm %**	**76.9**
Sex	**Male %**	**60.9**
	Female%	**39.1**
Birth weight Mean(Grams)		**1677.10**
Category	**ELBW %**	**14.8**
	VLBW %	**21.3**
	LBW %	**59.8**
	NBW %	**4.1**
Place of birth	**Outside TASH%**	**52.1**
	In TASH%	**47.8**
Age at Admission Mean (hours)		**25.94**
Age At Scanning Mean (hours)		**95**
Neonatal Complications	**Sepsis %**	**39.6**
	Hypothermia %	**56%**
	Respiratory Distress %	**69.8**
Respiratory Support Given	**Nasal prong %**	**8.3**
	Bag and mask %	**3.6%**
	CPAP %	**62,7**
	Mask only %	**1.8**
	No support %	**23.7**
Hematocrit Mean (SD) %		**46.059%(**±10.186**)**
Platelet Mean /Ml of blood		**166,905**

The mean gestational age at delivery was 33.1075 weeks, SD of ± 2.4 weeks, with maxim gestational age of 36.29 weeks and minimum of 27 weeks, 3(1.8%) were extremely preterm (less than 28 weeks) out of which all 3(100%) had intracranial hemorrhage, 36(21.3%) were very preterm (between 28 and 32 weeks) out of which 14 (38.9%) had PIVH and 130 (76.9%) were moderate to late preterm's (between 32 and 37 weeks) out of which 18(13.8%) had intracranial hemorrhage. There was significant association between level of prematurity and PIVH observed, χ^2 (2) = 22.460, p = 0.001.

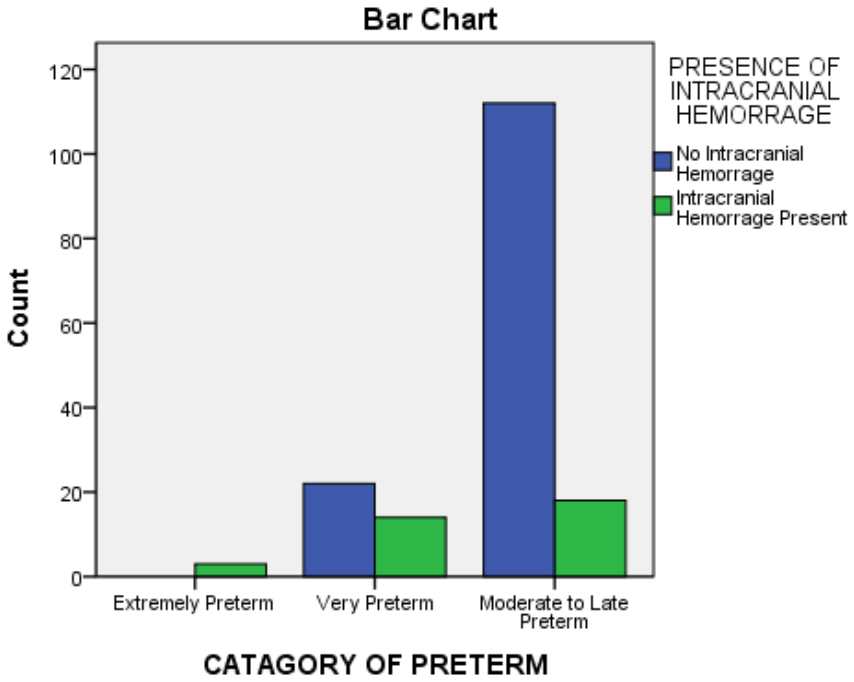


Figure 7. Chart showing prevalence of PIVH cross tabulated with standardized age categories

The mean age on admission was 25.945 hours, with minimum age of 0.1 hrs and the maximum age of 240 hrs, 150 (88.8%) of the neonates presented below 72 hrs of age. TCUS was done at the mean age of 95 hrs after birth with 120(70.8%) of the TCUS done between 48 and 148 hrs of age.

The mean birth weight of the neonates was 1677.10 grams with minimum birth weight of 600.00 grams and maximum birth weight of 3200 grams. Most of the neonates 131(77.5%) had birth weights between 1000.00 gram and 2250 grams. The commonest weight standard in the study was LBW. Out of the 169 neonate 7(4.1%) were standardized as NBW out of which 2(28.6%) had intracranial hemorrhage, 25(14.8%) were standardized as ELBW out of which 13(52.0%) had intracranial hemorrhage, 36(21.3%) were standardized as VLBW out of which 5(13.9%) had intracranial hemorrhage, and 101 (59.8%) were standardized as LBW out of which 15(14.9%) had intracranial hemorrhage. There was significant association between low birth weight and PIVH observed, χ^2 (3) = 18.300, p = 0.001.

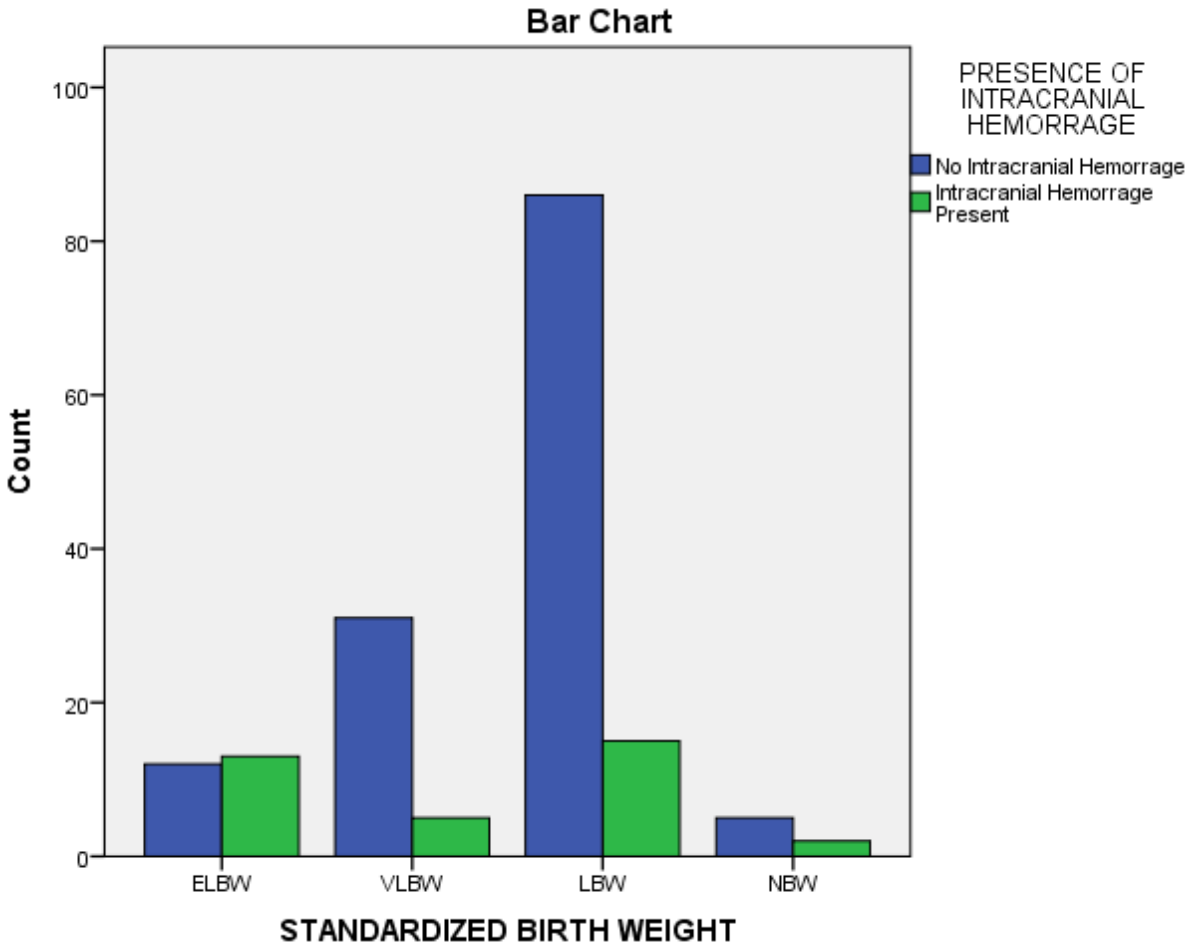


Figure 8. Chart showing prevalence of PIVH cross tabulated with standardized Gestational age categories

The mean 1 and 5th minute APGAR scores were 6.31 (SD ±1.245) and 7.59 (SD ±1.182) respectively. Out of the study population 3(1.8%) had severely depressed 1st minute APGAR score none of whom had intracranial hemorrhage, 86(50.9%) had moderately depressed scores out of which 25 (29.1%) had PIVH and 80(47.3%) had normal APGAR scores out of which 10(12.5%) had intracranial hemorrhage. An association between moderately depressed APGAR scores and PIVH was observed, χ^2 (2) = 7.723, p = 0.021.

The mean maternal age was 27.24 yrs. The youngest mother in the study was 18 yrs and the oldest mother 38 yrs, with 121(71.6%) mothers between 23 yrs and 33 yrs of age. Out of the mothers of the 169 neonates, 3(1.8%) had one ANC follow-up visit during pregnancy, 6(3.6%) had two ANC follow-up visits, 5(3%) had three ANC follow-up, 141(83.4%) had completed four ANC follow-up visits while 3(1.8%) had no ANC follow-up visit and 11(6.5%) had unknown status.

In the study 75 (44.4%) had prenatal steroid administration out of which 13(17.3%) had intracranial hemorrhage, 88(52.1%) had no prenatal steroid administration out of which 22(25%) had PIVH and 6(3.6%) mothers had unknown statues of steroid administration. No significant association between prenatal steroid administration and PIVH was observed, (χ^2 (2) = 3.074, p = 0.215).

The mean parity was 2.09 with 100(59.1%) mothers having parity of 2 to 4 children. 133(78.7%) had no history of abortion while 36(21.3%) had history of one or more abortions. Of the mothers 152(89.9%) suffered from at least one labor or pregnancy related complications while 17(10.1%) didn't have any complications. 61(36.1%) gave history PIH, out of which 12(19.7%) had neonates with intracranial hemorrhage. no association between PIH and PIVH was observed, $\chi^2(1) = 0.063$, p = 0.802, while 18(10.7%) had history of intrauterine infections (chorioamnionitis) during pregnancy out of which none had neonates with intracranial hemorrhage..

Of the 169 mothers 132 (79.1%) were married, 11(6.5%) were single and the rest 26(15.4%) had not disclosed their marital status. The commonest religion of the mother was, Muslim 55 (32.5%), followed by Orthodox Christian 48(28.4%) and protestant 12(7.1%) with 54(32%) having not disclosed their religion. Most mothers 136(80.5%) had a place of residence in Addis Ababa with 33(19.5%) residing outside of Addis Ababa. Total monthly income for the family of the neonates was between 1000 Br-2499 Br for 6 households (3.6%), between 2500 Br- 4999 Br for 12 households (7.1%), while 11 households (6.5%) had incomes equal or greater than 5000 Br. Most of the families 140 (82.8%) in the included study didn't disclose their incomes. In most of the households 123(72.8%) the highest level of educational status (maternal or paternal) was not disclosed with 19 (11.2%) households having tertiary education, 11(6.5%) having secondary level education, 5(3%) primary level education, 5(3%) being able to read and write and 6(3.6%) unable to read and write.

The commonest mode of delivery was SVD accounting for 86(50.9%) of births out of which 30(34.9%) had PIVH and 83(49.1%) were cesarean deliveries out of which 5(6%) had intracranial hemorrhage. In the study SVD was associated with higher rates of neonates with intracranial hemorrhage, χ^2 (1) = 21.423, p = 0.001. out of the neonates 88(52.1%) were delivered in TASH out of which 14(15.9%) had intracranial hemorrhage, 50 (29.6%) were delivered in health centers, 21(12.4%) in government hospitals, 8(4.7%) in private hospitals and 2(1.2%) were delivered in maternal specialty clinics of those delivered outside TASH 21(25.9%) had intracranial hemorrhage. no association between site of delivery and marital status was observed, $\chi^2(1) = 2.577$, p = 0.108.48(28.4%) mothers suffered from postpartum maternal complications, and 112(66.3%) did not suffer from any maternal complications and 9 (5.3%) had unknown status.

Table 5. Maternal Socio demographic and clinical characteristics of the Preterm Neonates Admitted to the NICU in TASH and selected for the study

	Maternal age Mean (SD)	27.24 Yrs()
ANC Follow Up	ANC1 %	1.8
	ANC2 %	3.6
	ANC3 %	3
	ANC4 %	83.4
	Unknown ANC follow-up %	6.5
Mode of Delivery	SVD %	50.9
	Cesarean Section %	49.1
Prenatal Steroid	Administered %	44.4
	Not Administered %	52.1
	Unknown administration status	3.6
	Maternal Parity Mean (SD)	2.09()
Maternal PIH	Present %	36.1
	Absent %	63.9
Maternal Infections	Present %	10.7
	Absent %	89.3
Marital Status	Married %	79.1
	Single %	6.5
	Undisclosed %	15.4
Maternal Place Of Residence	In Addis Ababa %	80.5
	Outside of Addis Abebe %	19.5
Maternal Religion	Islam %	32.5
	Orthodox Christian %	28.4
	Protestant %	7.1
	Others %	32
Household Income	between 1000 Br-2499 Br %	3.6
	between 2500 Br- 4999 Br %	7.1
	Greater than 5000 %	6.5
	Didn't Disclose %	82.4
Highest level of Education in The Household	Tertiary Education %	11.2
	Secondary Education %	6.5
	Primary Education %	3
	Able to Read and Write %	3.6
	Unable to Read and Write %	3.6
	Undisclosed Status %	72.8

On admission to the NICU 96(56%) were diagnosed with hypothermia out of which 13(13.5%) had intracranial hemorrhage, 67(39.6%) were diagnosed with neonatal sepsis out of which 20(20.9%) had PIVH there was strong association between neonatal sepsis and PIVH observed, $\chi^2(12) = 23.57$, $p = 0.023$, and 118(69.8%) had respiratory distress out of which 24(20.3%) had intracranial hemorrhage. no association between respiratory distress and PIVH was observed, $\chi^2(1) = 0.033$, $p = 0.856$. 40(23.7%) of the neonates had no respiratory support, 106 (62.7%) had CPAP administered out of which 26(24.5%) had intracranial hemorrhage, 14(8.3%) had oxygen administered via nasal prong out of which none had intracranial hemorrhage, 6 (3.6%) had bag and mask resuscitation all of whom had PIVH and 3 (1.8%) had oxygen administration via oxygen mask only out of which none had intracranial hemorrhage. no association between type of respiratory support and PIVH was observed, $\chi^2(4) = 9.310$, $p = 0.054$ The mean platelet count for the study population was 166,905.92/ml of blood, with maximum count of 385,000/ml of blood and minimum platelet count of 9000/ml of blood. The mean hematocrit value of the study population is 46.059% with SD of 10.186%, with maximum hematocrit value of 63.65% and minimum hematocrit value of 23.00%. The commonest blood type (ABO) in the study population was type B 62(36.7%) followed by type O 49(29.0%), type A 31(18.3%) and type AB 27 (16%). Out of the neonates 150(88.8%) were RH + and the rest 19(11.2%) were RH negative.

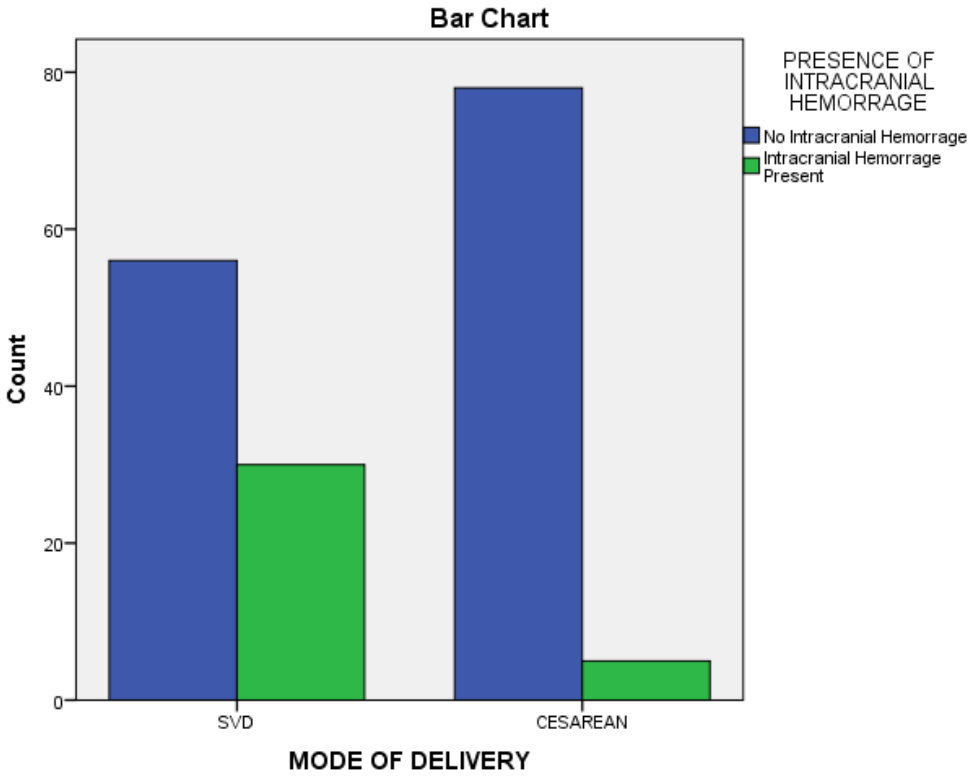


Figure 9. Chart showing prevalence of PIVH cross tabulated with mode of delivery

4. DISCUSSION

This study investigated the prevalence of PIVH in neonates admitted to the NICU at TASH which were less than 37 weeks gestational age and some of the associated factors affecting it. TASH NICU is the oldest and largest government hospital in Ethiopia offering neonatal intensive care services to a country of almost 110 million people[26], hence it was of great importance to have information on the prevalence of PIVH, which has potential to seriously compromise the quality of life of affected surviving neonates as well as cause premature death. The overall prevalence was found to be 20.7%, with mild (grade I) being the most frequent form accounting for 42.86%, while severe PIVH (grade III or grade IV) accounted for 34.2%. Studies in Nigeria[28] and South Africa[29, 30] and Zambia[31] have shown lower rates in the frequency of severe PIVH (27.5% in Zambia) but higher overall prevalence of PIVH (34.2% in the Zambian research). The lower overall prevalence in our study may be explained by the fact that most of the neonates were moderate to late preterm (between 32 and 37 weeks). Over the last decades the rates for severe PIVH, causing both short and long term morbidities has remained almost the same worldwide and in some instances even showed increment. In western countries this may be due to the decrease in the overall death rates of the LBW infants. In resource-limited settings, one may propose the lack of investigation for appropriate risk factors of PIVH and absence of early interventions which may prevent occurrence of severe PIVH or prevent transformation from lower to higher grades, may be the reason for higher prevalence of severe PIVH. This may also be true for the TASH NICU where this study was conducted.

Statistically the most significant factors showing strong associations with PIVH were standardized birth weight category (P =0.001) and standardized estimated gestational age (P =0.001), these factors would be useful to select preterm neonates targeted for intervention for the treatment and or prevention of PIVH in the NICU at TASH. Current studies report the neuroprotective effect of erythropoietin (EPO) in LBW infants with PIVH[33]. This could be one of the possible therapeutic options in the future for the treatment of the at-risk infants.

Other significant associations were between low APGAR (p = 0.021) and neonatal sepsis (p = 0.023), which is in keeping with studies done in South Korea[32] and Israel[33].

No significant associations were observed between sex of neonate, site of delivery, prenatal steroid administration or maternal infections, which could be explained by the fact that our study did not control for confounding factors like gestational age and weight, when comparing, out of hospital referrals and in referrals from TASH maternity ward as well as when comparing those with maternal infections and no maternal infections. It will be important here to mention that in literature some of the above risk factors are reported to be significantly associated with PIVH: findings may be also due to the different study designs employed,

An interesting finding was high prevalence of PIVH observed in SVD as compared to cesarean deliveries (see Figure 5.) which is the opposite of the expected association from the literature review[31]. This could be because most of the SVD neonates were out of TASH deliveries and were referred because of low APGAR scores, or neonatal sepsis and in general more severe illnesses as compared to those internal referrals from TASH maternity ward, which could have confounded the results of our study.

CONCLUSION

The study found lower overall prevalence of PIVH compared to reports of other studies in Africa and globally, while the frequency of severe IVH was relatively very high. Variables significantly associated with IVH were birth weight and gestational age. The other associations were Low 1st min. APGAR, prenatal steroid administration of steroids, mode of delivery and presence of neonatal sepsis. The findings of the study are in keeping with findings of studies from other African and global studies.

.

RECOMMENDATION

- TCUS with limited training and equipment should be routinely used to scan preterm neonates for early detection of PIVH
- There should be more emphasis given for antenatal follow up and perinatal care to prevent adverse pregnancy outcomes like LBW and preterm births and neonatal sepsis
- Further prospective researches with logistic regression and larger study populations should also be undertaken in hospitals which have NICU giving service to preterm neonates to give better evidence for interventions
- Protocols for routine TCUS screening of preterm neonates should be developed and implemented

5. References

1. Volpe, J. J. Neurology of the Newborn. Philadelphia, W. B. Saunders Co., pp. 239-294, 1981.
2. Ahmann, P. A., Lazzara, A., Dykes, F. D., et al.: Intraventricular hemorrhage in the High-risk preterm infant: Incidence and outcome. Ann. Neurol., 7:118, 1980.
3. Papile, L. A., Burstein, J., Burstein, R., and Koffier, H.: Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J. Pediatr., 92:529, 1978.
4. Hambleton, G., and Wigglesworth, J. S.: Origin of intraventricular hemorrhage in the preterm infant. Arch. Dis. Child., 51:651, 1976.
5. Pape, K. E., and Wigglesworth, J. S.: Hemorrhage, Ischemia, and the Perinatal Brain. Philadelphia, Lippincott, 1979.
6. Larroche, J. C.: Developmental Pathology of the Neonate. New York. Excerpta Medica, 1977.
7. G. A. Taylor. New concepts in the pathogenesis of germinal matrix intraparenchymal hemorrhage in premature infants. American Journal of Neuroradiology Feb 1997, 18 (2) 231-232.
8. Goldberg, R. N., Chung, D., Goldman, S. L., and Bancalari, E.: The association of rapid volume expansion and intraventricular hemorrhage in the preterm infant. J. Pediatr., 96:1060--1063, 1980.
9. Fujimura, M., Salisbury, D. M., Robinson, R., et al.: Clinical events relating to intraventricular hemorrhage in the newborn. Arch. Dis. Child., 54:409, 1979.
10. Milligan, D. W. A.: Failure of auto regulation and intraventricular hemorrhage in preterm infants. Lancet, 1:896-898, 1980.
11. Gilles, F. H., Price, R. A., Kevy, S. V., and Berenberg, W.: Fibrinolytic activity in the ganglionic eminence of the premature human brain. Bioi. Neonate, 18:426, 1971.
12. Welch, K.: The intracranial pressure in infants. J. Neurosurg., 52:693, 1980.
13. Tsiantos, A., Victorin, L., Relier, J.P., et al.: Intracranial hemorrhage in the prematurely born infant: Timing of clots and evaluation of clinical signs and symptoms. J. Pediatr., 85:854, 1974.
14. Bejar, R., Curbelo, V., Coen, R. W., et al.: Diagnosis and follow-up of intraventricular and intracerebral hemorrhages by ultrasound studies of infant's brain through the fontanelles and sutures. Pediatrics, 66:661-673, 1980.
15. Hill, A., Perlman, J. M., and Volpe, J. J.: Relationship of pneumothorax to occurrence of intraventricular hemorrhage in the premature newborn. Pediatrics, 69:144, 1982.
16. Lazzara, A., Ahmann, P., Dykes, F., et al.: Clinical predictability of intraventricular hemorrhage in preterm infants. Pediatrics, 65:30, 1980.

17. Routine screening cranial ultrasound examinations for the prediction of long term neurodevelopmental outcomes in preterm infants. Paediatrics & Child Health. 2001;6(1):39-43.
18. Ecury-Goossen GM, Camfferman FA, Leijser LM, Govaert P, Dudink J. State of the Art Cranial Ultrasound Imaging in Neonates. Journal of Visualized Experiments : JoVE. 2015 ;(96):52238.
19. Routine screening cranial ultrasound examinations for the prediction of long term neurodevelopmental outcomes in preterm infants. Pediatrics & Child Health. 2001;6(1):39-43.
20. Slovis TL, Kuhn LR. Realtime sonography of the brain through the anterior fontanelle. Am J Roentgenol 1981; 136: 277–286.
21. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500gm. J Pediatr 1978; 92: 529-534.
22. Volpe JJ. Intracranial hemorrhage: Germinal matrix-intraventricular hemorrhage. In: Neurology of the Newborn, 4th ed, WB Saunders, Philadelphia 2001. p.428.
23. Theodore J. Tarby, Joseph J. Volpe. Intraventricular Hemorrhage in the Premature Infant. In: Pediatric Clinics of North America Volume 29, Issue 5, Pages 1055-1301 (October 1982) Symposium on the Newborn Edited by William Oh.
24. Bassan H. Intracranial hemorrhage in the preterm infant: understanding it, preventing it. Clin Perinatol 2009; 36:737.
25. Volpe JJ. Intracranial hemorrhage: Germinal matrix-intraventricular hemorrhage of the premature infant. In: Neurology of the Newborn, 5th, Saunders, Philadelphia 2008.
26. Federal Democratic Republic of Ethiopia Ministry of Health. HSTP Health Sector Transformation Plan 2015/16 -2019/20 (2008-2012 EFY). 2015.
27. Lawn J, Kerber K, Enweronu-Laryea C, Massee Bateman O. Newborn survival in low resource settings—are we delivering? BJOG 2009; 116 (Suppl. 1):49–59.
28. Ajayi O, Nzeh DA Intraventricular hemorrhage and periventricular leukomalacia in Nigerian infants of very low birth weight. West Africa Journal of Medicine. 2003 Jun; 22(2):164-6.
29. Sandler D. L, Cooper P. A, Bolton K. D, Bental R. Y, Simchowitz I. D: Periventricular-intraventricular hemorrhage in low-birth-weight infants at Baragwanath Hospital. South African medical journal 1994; 84(1):26-9.
30. Ballot E. D, Chirwa F. T and Cooper A. P Determinants of survival in very low birth weight neonates in a public sector hospital in Johannesburg BMC Pediatrics 2010, 10:30.
31. Mulindwa MJ, Sinyangwe S, Chomba E (2014) The Prevalence of Intraventricular Hemorrhage and Associated Risk Factors in Preterm Neonates in the Neonatal Intensive Care Unit at the University Teaching Hospital, Lusaka, Zambia. Med J Zambia 39(1): 16-21.

32. Lee JY, Kim HS, Jung E, Kim ES, Shim GH, Lee HJ, Lee JA, Choi CW, Kim EK, Kim BI, Choi JH. Risk factors for periventricular-intraventricular hemorrhage in premature infants. J Korean Med Sci. 2010; 25:418–424.
33. Nehama Linder, Orli Haskin, Orli Levit, Gil Klinger, Tal Prince, Nora Naor, Pol Turner, Boaz Karmazyn, Lea Sirota. Risk Factors for Intraventricular Hemorrhage in Very Low Birth Weight Premature Infants: A Retrospective Case-Control Study. Pediatrics May 2003, 111 (5) e590-e595.
34. Leviton A , Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatr Res. 1999 Nov; 46(5):566-75.
35. James Barkovich, ed. Philadelphia: Lippincott Williams & Wilkins. Pediatric Neuroimaging, 4th ed. American Journal of Neuroradiology Jan 2007, 28 (1) 192-19.
36. David E. Clay, Annika C. Linke, Daniel J. Cameron, Bobby Stojanoski, Stephen Rulisa, Aggrey Wasunna, Sandrine de Ribaupierre, Rhodri Cusack, Evaluating Affordable Cranial Ultrasonography in East African Neonatal Intensive Care Units, In Ultrasound in Medicine & Biology, Volume 43, Issue 1, 2017, Pages 119-128, ISSN 0301-5629.
37. Practice parameter: Neuroimaging of the neonate: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, L. R. Ment, H. S. Bada, P. Barnes, et al. Neurology 2002; 58; 1726 Information is current as of April 24, 2013.
38. Levene MI. Measurement of the growth of the lateral ventricles in preterm infants with real-time ultrasound. Archives of Disease in Childhood. 1981;56(12):900-904.

6. Annexes

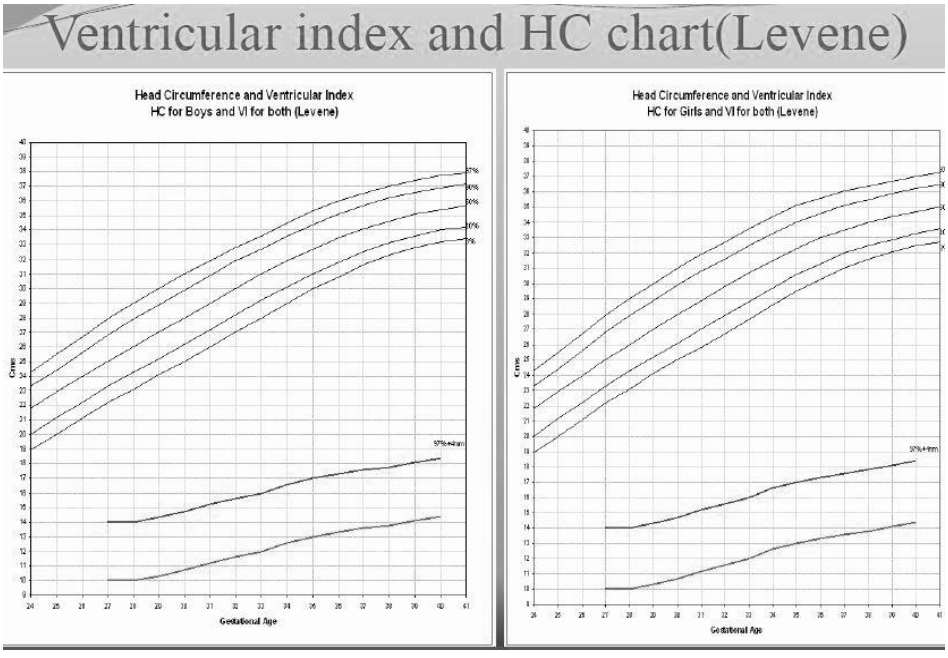
Annex I: Papile et al. Severity Grading of PIVH

Severity of intraventricular hemorrhage on cranial ultrasonography

Grade	Description on parasagittal view
I	Germinal matrix hemorrhage only or germinal matrix hemorrhage plus intraventricular hemorrhage less than 10 percent of ventricular area
II	Intraventricular hemorrhage, 10 to 50 percent of ventricular area
III	Intraventricular hemorrhage involving more than 50 percent of ventricular area; lateral ventricles are usually distended
IV	Parenchymal bleed in any location and amount

Adapted from: Papile, LA, et al. J Pediatr 1978; 92:529.

Annex II: Levene Index for PHH



Annex III: Questionnaires

Addis Ababa University, College of Health Science, School of Medicine,
Department of Radiology
Instruction:
This questionnaire is designed to collect information from records with respect to determination of Periventricular/ Intraventricular Hemorrhage in Preterm Neonates admitted to Tikur Anbessa Specialized Hospital neonatal intensive care unit.

Part A Socio-Demographic data of Parents
Please put a tick (√) in box next to the right response and for a question which has no options, please write the appropriate response in the spaces provided accordingly.

1.0	Phone Number	
1.1	Age of Mother	_____yrs 1. <19 2. 20-24 3. 25-29 4. 30-35 5. >35
1.2	Current Marital Status	1. Married 2. Single 3. Widowed 4. Divorced 5. No Response
1.3	Religion of Mother	1. Orthodox Christian 2. Muslim 3. Protestant 4. Others Specify_____
1.4	Ethnicity of Mother	1. Amhara 2. Oromo 3. Tigre 4. Gurage 5. Others Specify_____
1.5	Place of Residence of Mother	1. In Addis Ababa 2. Outside of Addis Ababa
1.6	Total Monthly Income of Household	1.Mother's Income---------- Eth. Birr

		2.Husband's Income---------- Eth. Birr 3. Other Income Sources.---------- Eth. Birr 4.No Income 5.Doesn't Know Her Own Income 6.Doesn't Know Her Partner's Income
1.7	Highest Educational Status (Maternal/Paternal)	1.Tertiary Education 2.High School 3.Primary Education 4.Able to Read and Write 5.Unable to Read & Write

1.

Part B Clinical Data Maternal **Please put a tick (√) in box next to the right response and for a question which has no options, please write the appropriate response in the spaces provided accordingly.**		
2.1	Gestational Age on Date of Delivery from LNMP	_____Weeks 1. Term 2. Preterm 3. Unknown Date
2.2	Parity	Number_____ Primipara Multipara Grand Multipara
2.3	ANC Follow Up	ANC1 ANC2 ANC3 ANC4 No ANC follow up
2.4	Duration of Labor	1. <6hours 2. 6-12 hours 3. 12-24hours 4. >24 hours
2.5	Pregnancy and Labor Related Complications	1. Pregnancy Induced Hypertension 2. Gestational Diabetes Mellitus 3. Anemia 4. HIV/AIDS 5. Other Infections If yes specify type_____ 6. Non Reassuring Fetal Heart Rate Pattern 7. Obstructed Labor 8. Premature Rupture of Membranes

		9. Meconium Stained Amniotic Fluid 10. Chorioamnionitis 11. Other complications If yes specify type_____
2.6	Mode of Delivery	1. Vaginal 2. C/S If yes indication for C/S _____ 3. Instrumental If yes indication for instrumentation_____
2.7	Site of Delivery	1. In TASH 2. Outside of TASH If Outside 2.1. HC 2.2. Maternal Specialty Clinic 2.3. Private Hospital 2.4. Governmental Hospital 2.5. Home
2.8	Prenatal Steroid Administration	NO Yes
2.9	Post Partal Maternal Complications	No Yes If yes specify_____

2.

Part C Clinical Data Neonatal **Please put a tick (√) in box next to the right response and for a question which has no options, please write the appropriate response in the spaces provided accordingly.**		
3.1	Sex of the Neonate	1. Male 2. Female
3.2	Age (Post Delivery) on Admission	_____Hours 1. <6 Hours 2. 6-12 Hours 3. 12-24 Hours 4. 24-72 Hours 5. >72 Hours
3.3	Age (Post Menstrual)	_____ Weeks 1. >28 Weeks

		2. 28-32 Weeks 3. 32-37Weeks
3.4	Birth Weight	_____ grams 1. ELBW < 1000 Grams 2. VLBW < 1500 Grams 3. LBW < 2500 Grams 4. NBW<= 2500 Grams
3.5	Reason for Admission to NICU	1. LBW 2. Hypothermia 3. Sepsis 4. Respiratory Distress 5. Birth Asphyxia 6. Hypothermia 7. Low APGAR 8. High Risk 9. Observation 10. Others Specify_____
3.6	1st Minute APGAR Score	1. <3 2. 3-7 3. >=7
3.7	5th Minute APGAR Score	1. <3 2. 3-7 3. >=7
3.8	Investigation Done	1. Hematocrit If yes %_____ 2. Platelet If yes_____ 3. Blood Group and RH If Yes_____
3.9	Respiratory Support	1. None 2. Oxygen mask 3. Nasal Prong 4. CPAP 5. Bag and Mask 6.Mechanical Ventilation

Annex IV: Standardized Transcranial Ultrasound Format for the Study

RADIOLOGY DEPARTMENT **_Ç=ÄKAÍ=**
***f*/¡õM**
COLLEGE OF HEALTH SCIENCES **Ö?“ dÃ”e**
¢K?Ï
ADDIS ABABA UNIVERSITY **xÄþS xbÆ**
†nþvRsþtE
☎ 011-515-09-47 ✉ 9086 **Fax No: 251-1-5513099**

Subject Code: _____ **Date of Scanning: _____**
Sex: _____
Post Natal Age _____ hrs
During of Scanning : _____mins

Focused Transcranial Ultrasound Report

FINDINGS:

A. Ventricular Size (Absolute Size) at the level of the choroid plexus of the lateral Ventricles
Rt._____ Lt._____
AHR_____ VHR_____

B. The is Germinal matrix bleeding Present/Absent

If Present Grade _____
Evidence for Grade_____

The ventricles

C. Any other Noted Brain parenchyma echogencity Change
If yes _____

Conclusion: -

Scanned by
Aman G, MD.Radiology resident (R2)
Verified by
Dr Daniel Zewdneh, MD. Consultant Pediatric Radiologist
Dr Yocabel Gorfu, MD. Consultant Pediatric Radiologist

Annex V: Verbal Consent Sheet

Addis Ababa University, College of Health Science, School of Medicine, Department of Radiology

This sheet will be read the legal guardian of the neonate before collecting any information.
Hello. My name is Dr. Aman Getachew and I am a post graduate student in Radiology at Addis Ababa University, college of Health Science School of Medicine, Department of Radiology.
What I will ask you to do: If you agree to do this study, Transcranial Ultrasound will be performed on your preterm child. Ultrasound uses sound waves and will not cause any harm or discomfort to the neonate, I will also collect necessary data from the records and patient file using a check list for research about preterm complications. Hence I would very much appreciate your cooperation in this study.

Risks and benefits: There are no risks associated with the study both to the institution and selected patients. The screening Transcranial ultrasound will improve the care given to your child and the final research outcome will improve the NICU and will benefit the whole community
Confidentiality: All information gathered from the log book and patient file will be kept confidential. Patient's personal information will not be registered. Research records will be kept in a locked file; only the researcher had access to the records.

ይህ ገጽ ለጨቅላ ህጻናቱ ወላጆች ወይም ህጋዊ አሳዳጊዎች ጥናቱ ከመጀመሩ በፊት በቃል የሚነበብ ይሆናል።

ስሜ ዶ/ር አማን ጌታቸው ይባላል፤ በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል በህክምና ኮሌጅ ራድዮሎጂ ትምህርት ክፍል ድህረ ምረቃ ተማሪ ነኝ ። በአሁኑ ሰዓት የመመረቅያ ጥናትዊ ጽሑፌን እያዘጋጀሁ ሲሆን፤ኣሁን የምጠይቆት በዚህ ጥናቴ ላይ ጨቅላ ህጻኖት እንዲሳተፍ ነው።

በጥናቱ ለመሳተፍ ከተስማሙ በጨቅላ ህጻኑ ላይ የጭንቅላት አልትራሳዉንድ ምርመራ ይደረጋል። አልትራሳዉንድ በድምጽ ብቻ የሚሰራ የህክምና መሳርያ ሲሆን ፤በሚያደረገዉ ምርመራ በጨቅላ ህጻኑ ላይ ምንም ዓይነት ቀጥተኛ ወይም የጎንዮሽ ጉዳት አያደርስም። ከምርመራው በተጨማሪ ከጨቅላ ህጻኑ የህክምና ማህደር ላይ አስፈላጊ የሆኑ መረጃዎችን አሰበስባለሁ።

የአልትራሳዉንድ ቅድመ ምርመራዉ የጨቅላ ህጻኑን የህክምና እንክብካቤ የተሻለ ያደርጋል፤እንዲሁም ለአጠቃላይ ማህበረሰቡ የጨቅላ ህጻናት ጽኑ ህክምና መሻሻል ግብዓት ይሆናል። የሚሰበሰቡት የጨቅላ ህጻናቱ የህክምና መረጃዎች በሙሉ ለጥናትዊ ጽሑፉ ብቻ የሚውሉ ሲሆን፤ የህክምና መረጃዎቹ ሚስጥራዊነትም በአግባቡ ይጠበቃል ።