

# Short term outcomes of newborn infants with Hypoxic Ischaemic Encephalopathy treated with therapeutic hypothermia in a low resource setting: A retrospective cohort study

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## Research article

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# Abstract

## Background

Hypoxic Ischemic Encephalopathy (HIE) remains a significant cause of death and neuro-developmental deficits among children, especially in resource limited settings. Therapeutic hypothermia which is the mainstay of treatment for moderate to severe hypoxic ischaemic encephalopathy in developed countries, is not widely practiced in low resource settings and the available data is limited. We aimed to determine the short term outcomes and factors associated with survival among newborn infants with moderate to severe hypoxic ischaemic encephalopathy treated with therapeutic hypothermia at St. Francis Hospital, Nsambya.

## Methods

Retrospective cohort study of 81 newborn infants with moderate to severe HIE who were 36 weeks and above that were cooled from June 2016 to February 2019, at St. Francis Hospital, Nsambya, Kampala, Uganda. Data on maternal and infant characteristics, clinical outcomes were extracted from the HIE registry and HIE follow up forms. Descriptive analysis was done to get the patient characteristics. Survival analysis was done to compare outcome among the groups of infants with significant factors at bivariate analysis. Multiple cox proportional hazards regression analysis was done to determine the factors independently associated with survival.

## Results

The proportion of newborn infants who survived was 68/81(84%), (95% CI: 0.74, 0.91).The factors associated with survival were a Thompson score of 7 to10 at initiation of cooling(HR: 0.07, 95% CI: 0.01, 0.94) and at 24 hours of cooling(HR:0.03, 95%CI: 0.004, 0.21), being born within the hospital providing therapeutic hypothermia (HR: 0.26, 95% CI: 0.07, 0.94) and not needing mechanical ventilator (HR: 0.03, 95% CI: 0.01, 0.14) or inotropic support.(HR: 0.13, 95%CI: 0.04, 0.38). The median time to attainment of full cup feeds was 6 days, with the majority 43/68(63%) attaining full feeds from 5 to 8 days. The median time to discharge was 7 days, and the median time to death was 3 days. The median Thompson score at discharge was 1 and at death was 16

## Conclusion

The survival rate of cooled infants in our setting at 84% is comparably high. The majority of infants have normal neurology at discharge.

## Introduction/background

Hypoxic Ischaemic Encephalopathy (HIE) is a significant cause of death and neurodevelopmental deficits among children (1) (2). It is one of the top 20 leading causes of burden of disease in all age groups in terms of disability life adjusted years(1). It is estimated that HIE is 10 to 20 times more common in the developing world compared to the developed world (3). Birth asphyxia which consequently leads to HIE is the major contributor of mortality in Uganda accounting for 28.6% of all the neonatal deaths in Uganda (6). At St. Francis Hospital, Nsambya the incidence of HIE is 30 per 1000 live births (7). This is 10 times higher compared to the developed world. The babies with HIE have an unacceptably high case fatality rate of 23.1% (7).

Therapeutic hypothermia significantly reduces mortality, morbidity and long term disability (8–15) and as such the high income countries recommend it as standard of care for newborn infants with moderate to severe HIE (16, 17). Despite the benefits of therapeutic hypothermia, it is not widely practiced in the low resource setting, and data regarding this intervention is conflicting. (10, 11, 18–20). At St. Francis Hospital, Nsambya, the standard of care for new born infants with moderate to severe HIE is therapeutic hypothermia. However to date, there are no studies that have reported short term outcomes for therapeutic hypothermia among these new born infants with moderate to severe HIE in our setting. We aimed to study the short term outcomes and factors associated with survival of newborn infants with Hypoxic Ischaemic encephalopathy treated with therapeutic hypothermia in a low resource setting.

## Methods

**Study design and setting** This was a retrospective study of newborn infants with hypoxic ischaemic encephalopathy treated with Therapeutic hypothermia at St. Francis Hospital, Nsambya from June 2016 to February 2019. St. Francis Hospital, Nsambya is a 361 bed capacity private-not-for-profit (PNFP) regional referral hospital, in Kampala, Uganda. Its catchment area is Makindye West Health sub district, which has a population of about 250,000. The Hospital also receives referrals from other facilities in and around Kampala. The neonatal unit in St. Francis Hospital, Nsambya is a 50 bed capacity. It has four units, the neonatal intensive care unit (NICU), the high dependency (Baby unit), Kangaroo mother care and the isolation unit. The newborn infants with HIE are admitted in the NICU, which has a bed capacity of 10. The NICU has blended piped oxygen, 8 incubators, 3 servo-controlled radiant warmers under which the new born infants with HIE are cooled, 7 monitors, 2 mechanical ventilators and one arterial blood gas machine. The nurse to patient ratio is 1:4. Ward rounds are done twice a day. Follow up of results and of the morning ward round plan takes place through the course of the day and night as need be. The newborn unit has a total of about 2000 admissions a year of which 400 are critical. In the financial year 2017/2018, the total admission to the NICU was 489 babies. In 2017, 3% of the babies admitted in the NICU had HIE of which 23.1% of them died. (7) Cooling procedure in the Neonatal intensive care unit (NICU) The NICU of St. Francis Hospital, Nsambya admits two to four newborn infants with moderate to severe HIE for therapeutic hypothermia on a monthly basis. The standard of care for these infants is head cooling. Cool gel packs (at 7-10 °C) are applied to the head and upper body and replaced hourly. The core temperature is servo-controlled by an overhead radiant warmer (Servocrib, Servocare Medical Industries cc, Cape Town), capable of controlling to a low target temperature of 34.0 °C. During cooling, the infant

temperature is recorded hourly, and infant clinical details such as clinical seizures, glucose levels, need for CPAP or nasal cannula oxygen, need for mechanical ventilation, presence of hypotension or need for inotropes, sinus bradycardia and any other arrhythmias are recorded. In addition, serum sodium results, presence of bleeding and amount of fluid or feeds are recorded. Presence of seizures or shivering and any medication given for convulsions is recorded as well. The medications that are used for seizure control include phenobarbitone, phenytoin and midazolam which are first, second and third line respectively. Electroencephalogram was not available for monitoring subclinical seizures. All babies are screened for sepsis and managed according to the protocol guidelines. These babies are reviewed daily by the head of the clinical team, resident doctors and the nurses. After 72 hours the cold gel packs are removed and the temperature of the radiant warmer is increased every hour by 0.2°C, until a core temperature of 36.5– 37 °C is achieved. Any other diagnosis during admission for example meconium aspiration, necrotizing enterocolitis and late onset sepsis is recorded. In addition, the time for attainment of full cup feeds or sucking is recorded. Serial Thompson score is also monitored and recorded daily till discharge or death. All the data concerning infant status during and after cooling such as daily feeds and status at discharge is recorded in the HIE follow up form. The resident and the nurse in charge of the HIE register checks for completeness of the register and the HIE follow up form before the baby is discharged. Study procedure Data of all babies who had moderate to severe HIE and had therapeutic hypothermia was extracted from the HIE cooling registry and the HIE follow up forms. From the HIE registry, the names and in patient number of the infants cooled was retrieved. This was correlated to the respective HIE follow up forms. From the HIE follow up forms, we retrieved the patient demographics including referral status, clinical details at birth and at 3-6 hours, cooling details, maternal details including pregnancy and delivery complications, presence of congenital abnormalities. In addition, we also got data on cooling details; this included time of initiation of cooling, presence of seizures, any derangements in the laboratory work up, need for oxygen (nasal cannula, CPAP or mechanical ventilator). From the same HIE follow up form, we also retrieved data on outcome status including death or discharged alive. Lastly we got information on when the new born infant attained full cup feeds or nutritive suckling. Data from the HIE form were then entered in the data extraction tool formulated for this study. Any missing data was retrieved from the maternal and infant charts to ensure completeness of the data extraction tool. Inclusion and exclusion criteria We included records of infants born at St. Francis Hospital, Nsambya or referred in within 6 hours of age with moderate to severe HIE that were cooled and recorded in the HIE registry from 1st June 2016 to 28th February 2019. These infants were 36 weeks of gestation or greater and with birth weight of at least 1800g, ability to start cooling within 6 hours of age. These infants needed to fulfil at least one of the following: need for respiratory support for  $\geq 10$  minutes or Apgar score  $\leq 7$  at 5 minutes or pH  $\leq 7$  or base deficit  $\geq 16$  on cord gas on infant blood within an hour of birth (where available). In addition they had to have either seizures or moderate to severe encephalopathy on clinical grounds based on a Thompson HIE score of  $\geq 7$  within or at 6 hours of life. We excluded infants with missing relevant data and with major congenital anomalies. Variables The primary outcome measure was survival. The secondary outcome measures were duration of hospital stay (time to discharge or death), time to attainment of full cup feeds or nutritive suckling and short term neurological outcome indicated by Thompson score at time of discharge or death. We further analyzed factors associated with survival. Data management and

statistical analysis Using the formula for independent cohort studies by Fleiss (1982), the required sample size for study to take place was 75 newborn infants at 95% confidence interval and power of 80%. Assuming a 10% missing data, the sample size was 83. We managed to retrieve complete records of 81 newborn infants. We used a study by the National Institute of Child health and human development (NICHD), a randomized controlled trial (12, 21) to calculate the sample size. Data was checked for completeness, coded, sorted and entered into the computer using EPI-DATA version 3.1. It was entered by double entry by two independent data entrants and later cleaned, and exported into STATA software version 14.0 (22) for analysis. The data was analyzed in 3 stages. Univariate analysis was done where frequencies and proportions were determined and displayed in form of tables, bivariate analysis to determine association between dependent and independent variables. To determine factors that were independently associated with survival, multivariate analysis was done. A cox regression model was built by including all factors with a P value  $\leq 0.2$  at bivariate analysis. Multicollinearity and interaction of predictor outcomes was checked. Hazard ratios at 95% confidence interval were derived. A log rank test was used to compare the survival rates of the significant factors at bivariate analysis. These were presented on Kaplan-Meier curves. Newborn infants who survived were censored. All factors with a P value of  $\leq 0.05$  were considered significant. Time to full feeds (nutritive suckling and/or breastfeeding), duration of hospital stay and Thompson scores at, initiation of cooling, twenty four hours, forty eight hours, ninety six hours and at discharge were displayed as median, interquartile range, minimum and maximum in tables and graphs.

## Results

### Overview

A total of 87 newborn infants with moderate to severe hypoxic ischaemic encephalopathy (HIE) were cooled from June 2016 to February 2019. However, only 81 records of these infants were included in the analysis. 6 newborn infants were excluded due to missing records. (Fig. 1) .The majority of the newborn infants were male, 54/81(66.7%). A quarter were referrals 17/81(21%). Half of the newborns started cooling between 1 hour and 3.9 hours 41/80(51%); the median time for initiation of cooling of the babies born within the hospital providing cooling being 1 hour compared to 4 hours for those referred in. ( **see supplementary box plot,Additional file 1**) The majority of the infants 50/81(61.7%) had a Thompson score of 7 to 10 at initiation of cooling while 22/81(27.2%) and 9/81(11.1%) had a Thompson score of 11–14 and  $\geq 15$  respectively. The other characteristics of the infants and their mothers are displayed in Table 1 below.

Table 1  
Demographic characteristics of the newborn infants with moderate to severe HIE treated with therapeutic hypothermia

<b>Variables</b>	<b>N(%)</b>
<b>Sex</b>	
Male	54(66.7)
<b>Referral status</b>	
Yes	17(21)
<b>Need for respiratory support at 10 minutes</b>	
Yes	54(68.4)
<b>Gestational age at birth</b>	
37–39	50(62.5)
≥ 40	30(37.5)
<b>5 minute APGAR</b>	
< 5	23(28.7)
<b>Visible seizure</b>	
Yes	51(63)
<b>Thompson HIE score before cooling</b>	
7–10	50(61.7)
10–14	22(27.2)
15	9(11.1)
<b>Thompson HIE score at 24hours</b>	
7–10	63(79.7)
10–14	8(10.1)
> 15	8(10.1)
<b>Age at start of cooling</b>	
< 1hr	25(31.3)
1-3.9hrs	41(51.3)
4-6hrs	14(17.5)
<b>mechanical ventilation</b>	

<b>Variables</b>	<b>N(%)</b>
Yes	16(19.75)
<b>Inotrope</b>	
Yes	10(12.35)
<b>Delivery complications documented</b>	
Yes	53(66.3)
<b>Maternal preexisting medical condition</b>	
Yes	16(20)
<b>Mode of delivery</b>	26(32.1)
Emergency Caesarean section	2(2.5)
Breech	1(1.2)
Instrumental	

## Survival

The proportion of newborn infants that survived to discharge from the hospital was 68/81(84%) (95% CI: 74.1%, 90.6%).

### Factors associated with survival among the participants

At bivariate analysis, newborns with Thompson score of 7–10 before initiation of cooling were 93% less likely to die (HR 0.07, 95%CI: 0.01–0.36) compared to the infants with a Thompson score of  $\geq 15$  at initiation of cooling. Also, infants with a Thompson score 7–10 at twenty four hours of cooling were 97% less likely to die (HR: 0.03, 95%CI: 0.01, 0.11) compared to the newborn infants with a Thompson score of  $\geq 15$  at 24 hours of cooling. Similarly, infants with a Thompson score 11–14 at 24 hours were 94% less likely to die (HR: 0.06, 95%CI: 0.01, 0.48) as compared to infants with a Thompson score  $\geq 15$  at 24 hours. In addition, infants who did not require a mechanical ventilator were 97% less likely to die (HR: 0.03 95%CI: 0.01–0.14) compared to infants who required a mechanical ventilator, while those who did not require inotropic support were 87% less likely to die (HR: 0.13, 95% CI: 0.04–0.38), compared to those who required inotropic support. These factors are shown in Figs. 3 and 4 below

The factors independently associated with survival at multivariate analysis were, being born within the hospital providing cooling, Thompson score of 7–10 before initiation of cooling and at 24 hours of cooling, as well as a Thompson score of 11–14 at 24 hours of cooling. The infants who were born at the hospital providing cooling were 74% less likely to die (HR: 0.26, 95%CI: 0.07, 0.94) compared to the infants who were referred from another health facility. The infants with a Thompson score of 7–10 before initiation of cooling were 93% less likely to die, (HR: 0.07, 95%CI 0.01, 0.94) compared to the

infants with a Thompson score of  $\geq 15$  at initiation of cooling. Similarly, the infants with a Thompson score of 7–10 or 11–14 at 24 hours of cooling were 97% less likely to die (HR: 0.03, 95%CI 0.004, 0.21), (HR:0.03,95% CI:0.003,0.31) respectively compared to the infants with a Thompson score of  $\geq 15$  at 24 hours of cooling. Having a comorbidity, and presence of visible seizures were not associated with survival. These factors are presented on Table 2 **below**

Table 2  
Factors independently associated with survival of cooled newborn infants at multiple cox proportional regression analysis

	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
<b>Referral status</b>				
Yes	1		1	
No	0.19 (0.06, 0.57)	0.003	0.26 (0.07, 0.94)	<b>0.039</b>
<b>Visible seizures documented</b>				
No	1		1	
Yes	0.95 (0.31, 2.91)	0.93	0.23 (0.05, 1.01)	0.052
<b>Co morbidity</b>				
Yes	1		1	
No	0.42 (0.13, 1.38)	0.154	0.68 (0.16, 2.89)	0.604
<b>Thompson HIE Score before cooling</b>				
≥ 15	1		1	
7-10	0.07 (0.01, 0.36)	0.002	0.07 (0.01, 0.94)	<b>0.044</b>
11-14	0.56 (0.16, 1.92)	0.356	0.7 (0.14, 3.49)	0.664
<b>Thompson HIE Score at 24hours</b>				
≥ 15	1		1	
7-10	0.03 (0.01, 0.11)	< 0.001	0.03 (0.004, 0.21)	<b>&lt; 0.001</b>
11-14	0.06 (0.01, 0.48)	0.008	0.03 (0.003, 0.31)	0.004
<b>Mechanical Ventilation</b>				
yes	1			
no	0.03 (0.01, 0.14)	< 0.001		
<b>inotrope</b>				
yes	1			
no	0.13 (0.04, 0.38)	< 0.001		

### Time to attainment of full cup feeds or nutritive suckling

The median time to attainment of full feeds was 6 days, the maximum time being 18 days and the minimum time being 4 days. 11(16%) of the infants attained full feed below the first quartile, while

14(21%) attained above the third quartile. The majority of the infants discharged (43(63%) attained full cup feeds between the first and third centile.

### **Duration of Hospital stay**

The median time to discharge was 7 days (iqr+-4), and the median time to death was 3 days (iqr+-1). 63% of the newborn infants who survived spent 6 to 10 days in the hospital while 50% of those who died spent 1 to 3 days. The last death was recorded on day 6. The longest duration of hospital stay was 34 days and the shortest was 4 days for those who were discharged from the hospital. **(Additional file 2)**

### **Thompson score at time of discharge or at time of death**

The median Thompson score at discharge for those who survived was 1 (iqr+- 2), minimum 0 and maximum was 6, compared to the median before initiation of therapeutic hypothermia that was 9(iqr+-4), minimum 6 and maximum 18. In comparison to those who died, their median Thompson score at death was 16(iqr +-7) minimum being 7 and maximum being 19, while at initiation and 13(iqr +-3, minimum being 8 and maximum 18.

## **Discussion**

Our study aimed at describing the short term outcomes and the factors associated with survival of newborn infants with moderate to severe hypoxic ischemic encephalopathy treated with therapeutic hypothermia at St. Francis hospital Nsambya from June 2016 to February 2019.

### **Survival**

The proportion of 84% newborn infants who were cooled and survived is high especially in a low resource setting. We attribute our high survival rates to the benefit therapeutic hypothermia has on newborn infants with moderate to severe HIE. Therapeutic hypothermia for newborn infants with moderate to severe HIE has been found to reduce mortality by 8-32 % (12, 15). It has also been found to reduce brain metabolic demands, by 5-7% for every 1°C drop in body temperature, reduce biosynthesis and release of excitatory amino acids. Similarly, therapeutic hypothermia has also been found to slow destructive enzymatic reactions, suppress free radical reactions, stabilize the cell membranes, slow deterioration of the blood-brain barrier, and reduce cerebral edema hence reducing intracranial pressure. These mechanisms have been found to reduce brain injury. (23-27). Different studies have shown different survival rates. Our findings are comparable to studies done in South Africa, United Kingdom and India with a survival rate of 89% (11) ,89% (28) and 87% (12, 21), though there was a difference in the cooling devices used and in the neonatal unit equipment.

The survival rate of 67% reported from a similar setting studies ( 30), differ from our findings The difference would be in the monitoring, in our setting the nurse to patient ratio was 1:4 compared to high nurse to patient ratio. Additionally availability of CPAP to appropriately managed respiratory distress and

having mechanical ventilation may have been an added advantage, although very few babies were ventilated. Furthermore screening for infection and appropriate infection controls measures may have improved the outcome for these patients. On the other hand, in the study by Robertson and colleagues, there was an increased rate of sepsis and this could have resulted in higher mortality.

### **Factors associated with survival**

Survival was related to a Thompson score of 7-10 at initiation of cooling and at 24 hours of cooling, Thompson score 11-14 at 24 hours, being born within the hospital providing cooling, and not needing a mechanical ventilator and inotropes. These factors may not be of a surprise for therapeutic hypothermia has been found to be more beneficial for the less encephalopathic babies (8, 9, 12, 15, 21). This could be attributed to the newborn infants in this group being less sick and probably having no multi organ damage due to the effect of hypoxia. It is known that the severity of hypoxia correlate the severity of cellular injury and destabilization of homeostasis hence, greater degree of depolarization leading to cytotoxic edema, increased accumulation of excitatory amino acids, free oxygen radicals, nitric acid and increased cell lysis. This reduces the benefits of hypothermia to avert these derangements. These findings are similar to other studies (8, 9, 11, 12, 31, 32).

The infants born within St. Francis hospital, Nsambya, had a better probability of survival as compared to the infants referred in from other health facilities. This could be attributed to having a neonatal resuscitation team for high risk deliveries and appropriate monitoring of labour and timely intervention in the intrapartum period. Furthermore these infants are born within the hospital providing cooling they are most likely not to suffer the temperature irregularities which worsen outcome following therapeutic hypothermia (27, 33) faced by the referred babies during transport to the hospital providing cooling. Our study showed that the median time to initiation of cooling for the newborn infants born within St. Francis Hospital, Nsambya was 1 hour compared 4 hours for those who were referred in. **(Additional file 1)** Therapeutic hypothermia for newborn infants with moderate to severe HIE started within the first three hours has been associated with a better outcome in some studies.(34, 35). The difference in the outcome of the infants born within the hospital providing cooling and those referred to the cooling centre in the study of Kali and colleagues(11) could be due to the temperature control during transport to the cooling hospital, and initiation of cooling at the referral hospitals before transfer.

### **Duration of hospital stay**

The median time to discharge for those who survived was 7 days, while the median time to death was 3 days. The majority of the infants 43/68(63%) who survived spent 6 to 10 days in the hospital while most infants 8/13(62%) died between the first and the third day of life. The shorter median time to death could have been influenced by the severity of the encephalopathy. Our study found that infants with a higher grade of encephalopathy were more likely to die as compared to infants with a lower grade of encephalopathy at initiation of cooling. On the other hand, the median time to discharge could have been influenced by a lower Thompson score at initiation of cooling for those who survived. Also, our hospital discharge protocol requires that all babies are discharged when either on full cup feeds or breast feeding

and when the infants are clinically well. This could also influence a longer duration of hospital stay. The infant with the longest duration of hospital stay had other comorbidities, and a Thompson score of over 10 at initiation of cooling, hence a longer duration of hospital stay. The duration of hospital stay in our study is comparable to some studies.(28, 30, 36).

### **Return to full cup feeds or nutritive suckling for the participants who survived**

The majority of the surviving infants 43/68(63%) attained full oral cup feeds or nutritive suckling between 5-8 days.

This is comparable to studies done elsewhere (11, 36). This similarity could be due to similarities in the NICU protocols on feeding. Our feeding protocol ensures that the babies are discharged only having attained full cup feeds or nutritive suckling. Therapeutic hypothermia has been found to improve neurological outcome (8-15) of which nutritive suckling is among.

### **Thompson score at discharge**

The median Thompson score at discharge was 1, while the median Thompson score at death was 16. The infant with the Thompson score 7 at the time of death had completed cooling with an improving Thompson score but developed necrotizing enterocolitis with multiple gut perforation and died on day 5, hence a lower Thompson score than the median at death. The findings of our study is comparable to studies that report that most infants had normal neurology at discharge.(11, 28, 37). Similarly, the findings of our study are consistent with studies that have found that therapeutic hypothermia improves neurological outcome for infants with mild to moderate hypoxic ischaemic encephalopathy, but not with those who have severe encephalopathy.(8, 9, 11, 15, 21)

### **Strengths and Limitations of the study**

This is one of the few studies in our setting to look at the short term outcome of newborn infants with moderate to severe HIE treated with Therapeutic hypothermia in our setting. The NICU protocol of St. Francis Hospital Nsambya ensures that newborn infants admitted for therapeutic hypothermia are investigated and managed for infections. This could have reduced the confounders. The protocol also ensures that additional life support like ventilator and inotropes where necessary was accorded to the newborn infant. There was a wide variety of data collection tools hence a minimal likelihood of having missing data.

We acknowledge some study limitations: The study was conducted in a health facility, clinical characteristics of babies referred in and the intrapartum, circumstances were based on the referral notes hence a difficulty in controlling referral bias. Secondly this was a retrospective cohort study with its known study limitations. Metabolic cause of neonatal encephalopathy like some inborn errors of metabolism were not explored, this could have influenced some of the results. Lack of infant seizure monitor whilst being cooled hence infants with subclinical seizures could have been missed. We hence

used a Thompson score of 7 as a cut off since it has been found to be a sensitive predictor of either an abnormal 6-hour EEG or moderate to severe encephalopathy (28).

### **What this study adds**

Therapeutic Hypothermia is feasible in a resource poor setting under strict protocol. As such it can be taken up as a standard of care for all newborns with moderate to severe HIE. We therefore anticipate that the findings of this study could be used to inform clinicians, improve the existing cooling protocols and contribute to policy development regarding the uptake of therapeutic hypothermia for newborn infants with hypoxic ischaemic encephalopathy in low resource settings

## **Conclusion**

The survival and short term outcomes of newborn infants with HIE following therapeutic hypothermia at 84% in our setting is comparably good. The factors associated with survival are, lower grade of HIE at initiation of cooling and at 24 hours, being born within the hospital providing therapeutic hypothermia, not requiring mechanical ventilator and inotropic support. Infants with Thompson score of 7–10 regardless of whether they had a seizure have favorable outcomes.

## **Recommendations**

The factors associated with survival could be considered in the low resource setting when designing management protocols for infants with HIE that require therapeutic hypothermia. There is need to explore the benefit of surrogate markers of outcome such as Thompson score at discharge in neurological assessment of these infants in low resource settings. There is also need to strengthen the current strategies on prevention of hypoxic ischaemic encephalopathy. Lastly, we recommend the long term follow up of these newborn infants.

## **Abbreviations**

aEEG: Amplitude Electroencephalogram, CBC:Complete blood count, CPAP:Continuous Positive Airway Pressure CRP:C-reactive protein, CI:confidence interval, HIE:Hypoxic ischaemic encephalopathy, HR:Hazard ratio, iqr:Interquartile range, IRB:Institutional Review Board, NICU:Neonatal Intensive care unit, NICE:National Institute for health and Care Excellence, NICHD:National Institute of Child health and Human Development.

## **Declarations**

### **Ethical approval and consent to participate**

Approval was sought from St. Francis Hospital, Nsambya Institutional Review Board (IRB) - IRB number: UG-REC-020. Since this was a retrospective study of the existing records, waiver of consent was sought

from the IRB.

### **Consent for publication**

Consent for publication of the information got from this study was sought from the institutional review board of St. Francis, Hospital, Nsambya.

### **Availability of data and materials**

The data sets for this study are available from the corresponding author on request

### **Competing interest**

The authors declare that there is no competing interests

### **Funding**

No funding was available for this study, we had ready data from the neonatal unit and from the hospital records of St. Francis Hospital, Nsambya

### **Authors' contribution**

KJD and NVK conceived the study, designed the research protocol, participated in the study and also drafted the manuscript. NVK and SR, supervised the study and also participated in writing the manuscript. All the authors read and approved the final manuscript.

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## Figures

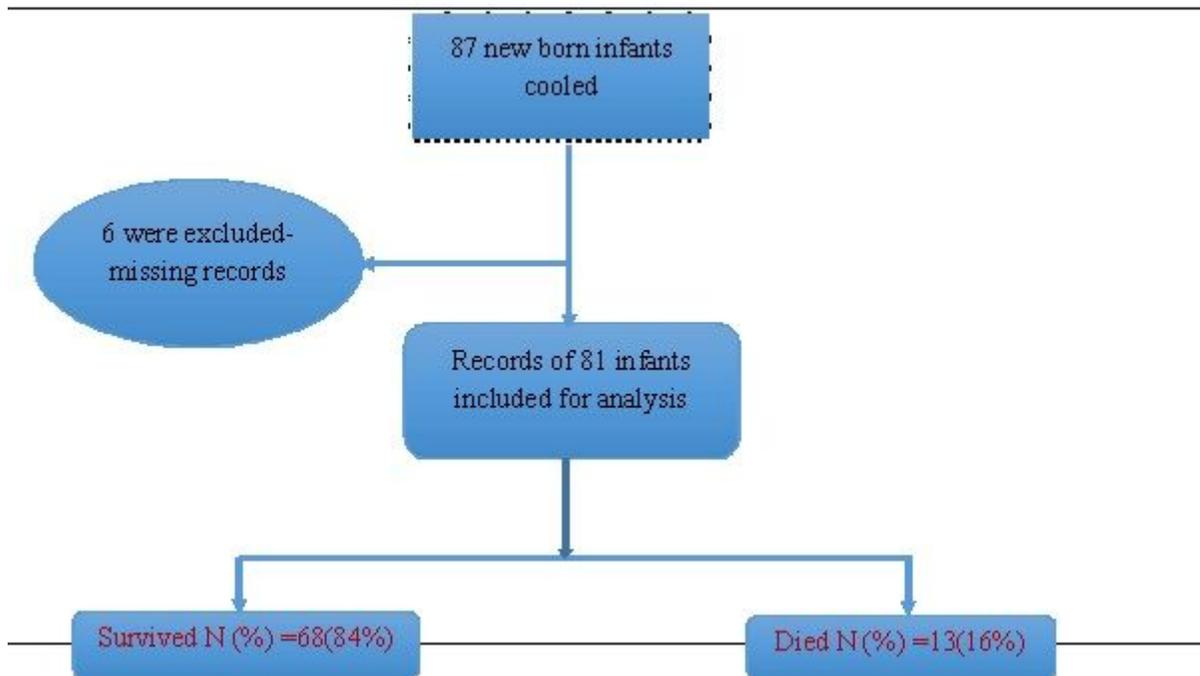


Figure 1

Study profile

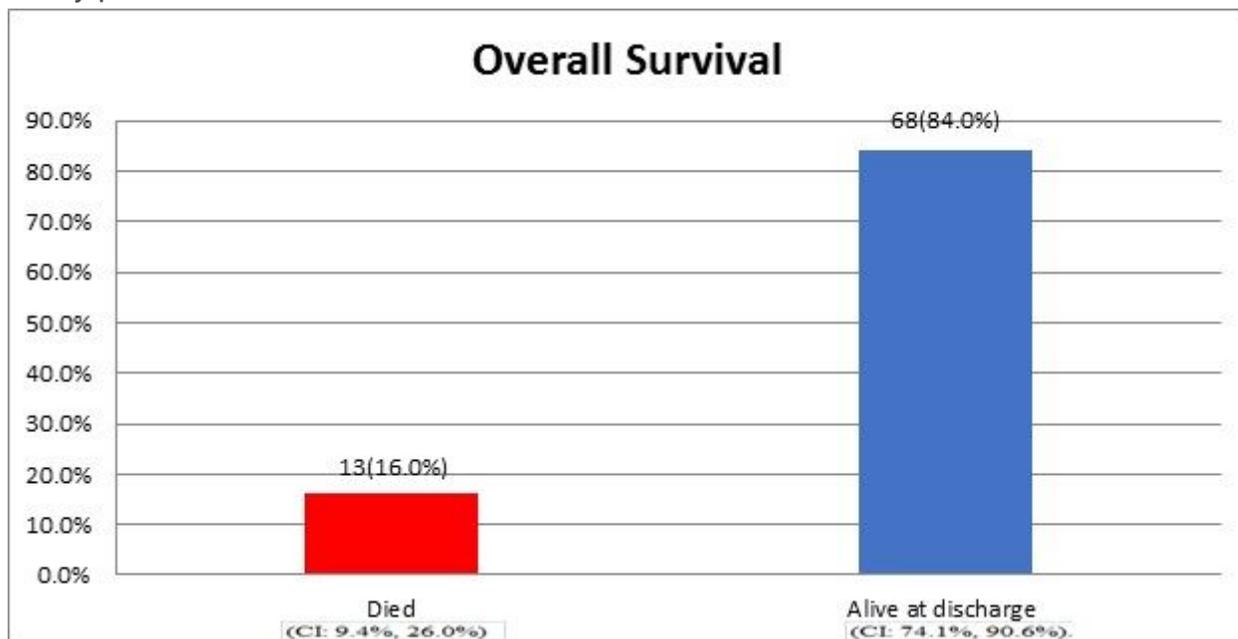


Figure 2

Proportion of newborn infants with HIE cooled that survived to discharge and those who died

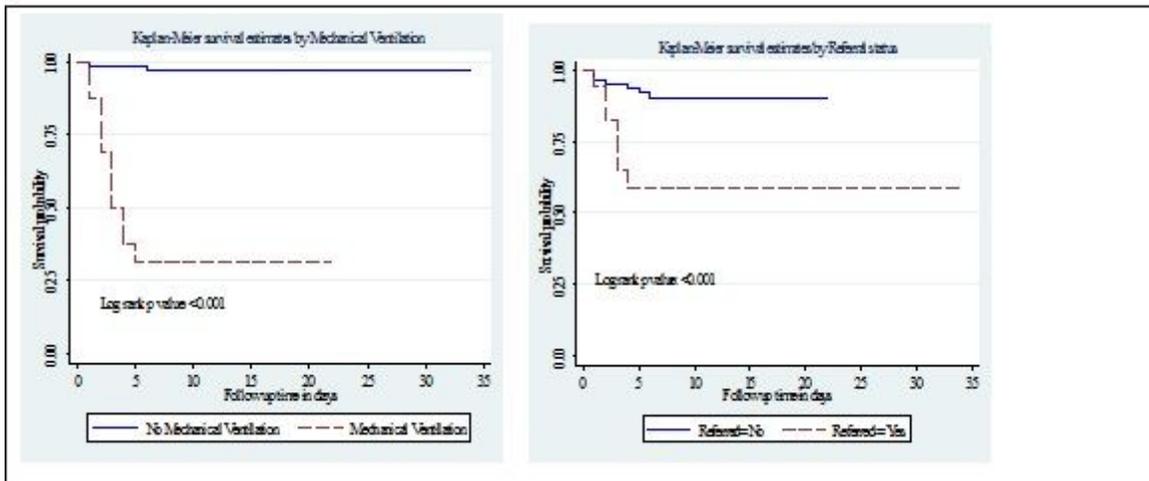


Figure 3

Kaplan Meier curves Comparing survival of new born infants with HIE cooled

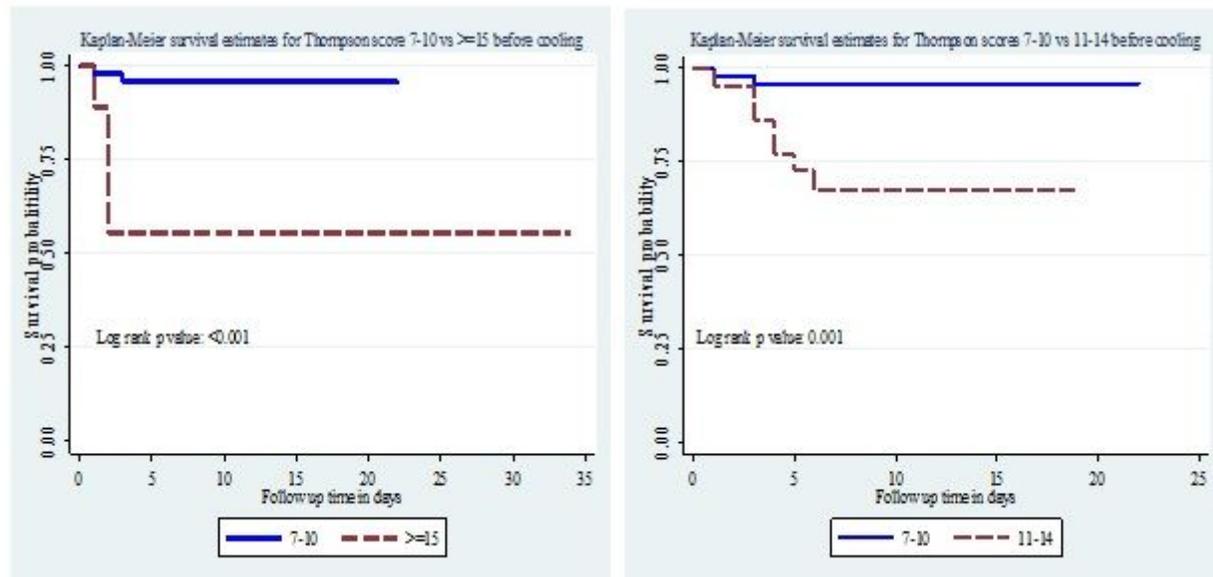
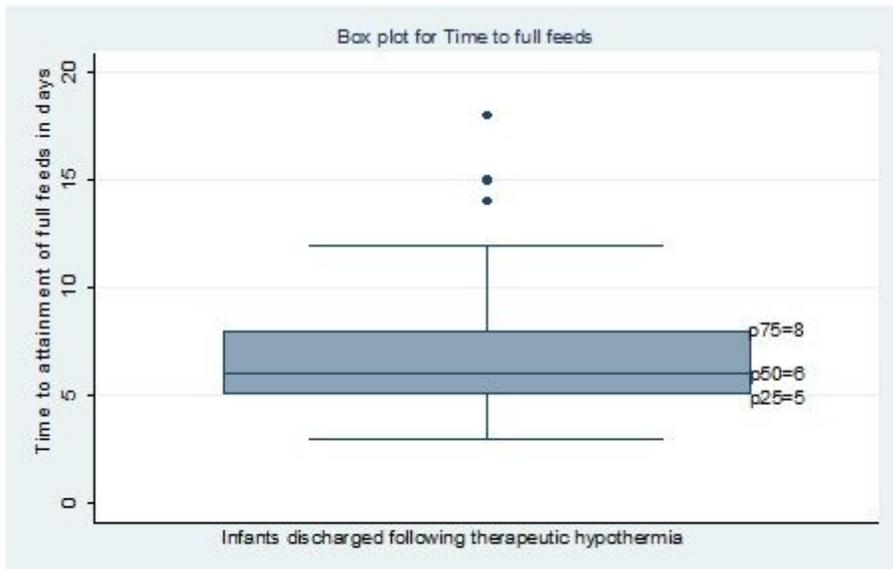


Figure 4

Kaplan Meier curve for infants with HIE cooled based on Thompson score



p75=75<sup>th</sup> percentile,

p50=50<sup>th</sup> percentile, p25=25<sup>th</sup> percentile

Figure 5

Time to attainment of full feeds for newborn infants with HIE cooled who survived



Figure 6

Median Thompson from before initiation of cooling to discharge or death of newborn infants cooled