Neonatal hypothermia: A retrospective study on association between admission temperature and mortality and major morbidity in Very Low Birth Weight (VLBW) neonates at day seven of life in Kenyatta National Hospital New Born Unit.

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2022

DECLARATION

This work is authentic and has not been presented to any learning institution that I know of for award of diploma or degree certification.

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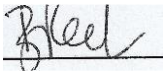
Signature:  **Date: 29/04/2022**

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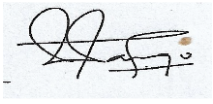
Signature:  **Date: _29/04/2022**

DEDICATION

I devote this proposal to my lovely family for being my pillar always. This would not have been possible without the help of my wife Nelly Gichunge and my children Kendi and Mwenda. Thank you very much for motivating me always.

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Firstly, I thank God for the enormous gifts and opportunities He has accorded to me.

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ABBREVIATIONS AND ACRONYMS

%: Percent

<: less than

>: more than

≥: more or equal to

≤: less or equal to

aPTT: activated Partial Thromboplastin Time.

AOR: Adjusted Odds Ratio.

°C: degrees Celsius

CPR: cardiopulmonary resuscitation.

C/S: Caesarean Section.

INR: International Normalized Ratio.

KNH: Kenyatta National Hospital.

LBW: Low Birth Weight.

Mmol/l : Millimoles per liter.

MTRH: Moi Teaching and Referral Hospital

NBU: Newborn Unit

NICU: Neonatal Intensive Care Unit

NMR: Neonatal Mortality Rate.

NNS: Neonatal sepsis

OR: Odds Ratio.

PT: Prothrombin Time.

RBS: Random Blood Sugar

RDS: Respiratory Distress Syndrome

RR: Relative Risk.

SPSS: Statistical Product and Service Solutions

SVD: Spontaneous Vertex Delivery.

UON: University of Nairobi

VLBW: Very Low Birth Weight

WHO: World Health Organization.

OPERATIONAL DEFINITIONS

Hypothermia: Hypothermia in this study was defined as axillary temperature of less than 36.5◦ C, sub divided into: mild/cold stress = 36.0◦ C – 36.4◦ C , moderate = 32.0◦ C– 35.9◦ C, severe = < 32.0◦ C)(1)(2)

Normothermia: Normal temperatures denoted as axillary temperature between 36.5◦ C to 37.5◦ C.(1)(2)

Hyperthermia: High temperatures defined as axillary temperatures more than 37.5C ◦.(1)(2)

VLBW: Birth weight between 1000 - 1499grams

Admission temperature: Initial axillary temperature taken at first contact with health care professional on neonates at admission in Newborn unit.

Neonate: Chronological age less than 28 days.

Inborn: Study subject born in study facility (KNH)

Out-born: Study subject born outside study facility; either a referral or home delivery.

Hypoglycemia: RBS < 2.6 Mmol/l (3)

Neonatal sepsis: positive blood culture for either bacteria or fungus. Late-onset sepsis will be sepsis after 72 hours of life(4)

Necrotizing enterocolitis: Abdominal distension, Absent bowel sounds, radiographic findings of dilatation of intestines, ileus, or pneumatosis intestinalis(5).

: Modified Bell stage II and above(5).

RDS: Silverman Anderson Score (SAS) ≥ 4 (6)or features of RDS on chest radiograph.

Intraventricular hemorrhage: Any stage of intraventricular bleed confirmed by cranial ultrasound.

Resuscitation after birth: CPR offered after delivery (labor ward or maternity theatre)

ABSTRACT

Study Background

Neonatal hypothermia prevalence is high as shown by studies both locally and internationally. Studies showing the incidence and associated factors of neonatal hypothermia have been conducted, however, there has been no study in our setting to describe the associations between neonatal hypothermia and short-term outcomes in Kenya. This study aims to compare the outcomes of VLBW neonates admitted with hypothermia with those admitted with normal body temperatures at seven days of admission. The study outcomes will include: Late onset neonatal sepsis, intraventricular hemorrhage, respiratory distress syndrome, necrotizing enterocolitis hypoglycemia, and mortality within seven days of admission.

Broad objective.

To evaluate the correlation of admission hypothermia with mortality and major morbidity at day seven of life among VLBW neonates admitted at KNH NBU

Study design and site

The study was a retrospective cohort study on VLBW neonates admitted to KNH NBU from January 2019 to December 2019.

This retrospective study was conducted in Kenyatta National Hospital (KNH) health records department.

Study materials and methods

This study was a retrospective cohort study. A data abstraction tool was developed that was used to extract data of interest from records of VLBW neonates admitted to KNH NBU in the year 2019.

The VLBW neonates with admission hypothermia were the exposed cohort while those with normal temperatures at admission were the unexposed cohort. At seven days post-admission, the outcomes of interest were assessed in both cohorts and odds ratios were calculated. The results are presented in tables and box plots.

Data management

Once the data abstraction tools were completed, the information was filled in an excel spreadsheet. The data was manually cleaned and then exported to SPSS version 25 software for further analysis. We ran a bivariate analysis using odds ratios to assess the association between temperature and the development of comorbidities during the first 7 days of admission in the neonatal unit

Descriptive statistics were used to calculate the results in mean, mode and median, and frequencies. Logistic regression in SPSS will be run on outcomes whose statistical p-value will be <0.05 to determine their odds ratio of association with admission hypothermia. The results were presented in odds ratios and p values. The significance of the statistical tests was considered if they lie within the 5 % significance level.

Results

Admission hypothermia was associated with an increased risk of developing late-onset neonatal sepsis (LONNS) by 11 times OR-11.35 (95% CI, 6.14, 20.96 p<0.01) among the very low birth weight neonates within the first 7 days of admission. Moderate hypothermia increased the risk of LONNS by 19 times OR -19.3 (95% CI, 10, 36.8) while mild hypothermia at admission increased the risk fourfold. Neonates with very low birth weight admitted with hypothermia were 13 times more likely to develop at least one episode of hypoglycemia within the first 7 days of admission (OR-13 p<0.01). Admission hypothermia was not found to be associated with the development of

IVH and NEC within the first seven days of admission. Very low birth weight neonates admitted with hypothermia were 7 times more likely to have RDS persist to seven days post-admission as compared to those who have normal temperatures at admission ($p< 0.01$). Moderate hypothermia increased the risk of death twofold among the study population (AOR- 2.01, p-0.05)

Conclusion

There is an association between hypothermia at admission with comorbidities: late-onset neonatal sepsis, hypoglycaemia, and persistent RDS within the first 7 days after admission. There is no association between the admission hypothermia with NEC and IVH within the first 7 days after admission.

Moderate hypothermia is associated with an increased risk of death among very low birth neonates within the first 7 days after admission**.**

CHAPTER 1: INTRODUCTION

Hypothermia in neonates is delineated as the axillary temperature below 36.5 degrees Celsius in newborns below 28 days of life(1). It is further subdivided into 3 subclasses:

- Cold stress /Mild hypothermia – axillary temperatures between 36.0° Celsius to 36.4° Celsius.
- Moderate hypothermia – axillary temperatures between 32.0° Celsius to 35.9° Celsius.
- Severe hypothermia - axillary temperatures less than 32.0° Celsius.

The prevalence of neonatal hypothermia is high. An unpublished study by S. Ocharo in KNH found a prevalence of 67% among neonates admitted to KNH NBU(unpublished). In MTRH, Nyandiko et al found a prevalence of 73.9% of neonatal hypothermia among neonates admitted in NBU(8). They also found that those with hypothermia at admission were seventeen times likely to die and hypothermia was noted in 98% of the neonates who died within the first day of admission(8).

Neonatal hypothermia has been linked to hypoglycemia(3), late onset neonatal sepsis(9)(10)(11), increased risk of death(12)(8), Respiratory Distress Syndrome(11)(13),necrotizing enterocolitis(5)(11),coagulation defects(14)(15) and increased incidence of intraventricular hemorrhage(16)(11)

With this high prevalence of neonatal hypothermia in our setting, it is imperative to assess the outcomes of these neonates who have admission hypothermia in comparison with those who have normal temperatures at admission.

CHAPTER 2: LITERATURE REVIEW

Definition of neonatal hypothermia

World Health Organization (WHO)(1),has defined neonatal hypothermia as axillary temperatures less than 36.5◦ Celsius in newborns less than 28 days of age.

Hypothermia is sub-classified into:

Mild hypothermia/cold stress: Temperatures: 36.0 – 36.5◦ Celsius.

Moderate hypothermia: 32 – 35.9◦ Celsius.

Severe hypothermia : < 32 ◦Celsius.

Pathophysiology of neonatal hypothermia

Hypothermia in neonates results from an increased heat loss in comparison to heat production. In neonates, heat is generated through a nonshivering mechanism of heat production(17). This occurs in brown fat tissue that is stored in the scapular region, mediastinum, neck region, and axilla. Brown fat is stored in these areas at about 26 to 28 weeks gestation. Brown fat tissue is highly differentiated and has a large number of sympathetic nerve fibers and is richly perfused. Exposure to reduced temperatures stimulates adrenergic nerve fibers which release noradrenaline which binds to sympathomimetic receptors on brown fat cells leading to a release of heat energy(17).

White fat is found in the subcutaneous layer under the dermis and is normally deposited during the final weeks of gestation(12). Neonates born before term have minimal white fat. Premature neonates are at a higher risk of hypothermia because they have minimal brown fat deposited. Thermoregulatory mechanisms are not fully developed in newborns thus making them prone to hypothermia. The average surrounding temperature of the delivery room is about 25 degrees

Celsius in comparison to the temperature of amniotic fluid of about 35 degrees Celsius(1). This change in temperatures during delivery increases the risk of neonatal hypothermia.

In comparison to older children, newborns are at a greater risk of hypothermia because of the huge surface area to body mass ratio, having a large head compared to the body, and a thinner layer of skin. This risk is even higher in preterm and low birth weight neonates(16).4 mechanisms are involved in the loss of heat in neonates: conduction, radiation, convection, and evaporation(18)(19).

Neonates lose body heat to surrounding cool areas that are far from their body surface through radiation. It is the main process of heat loss in preterm neonates born above 28 weeks of pregnancy(18)(19). Preterms born below 28 weeks gestation lose heat majorly by evaporation because of the thin epidermis and the poorly developed subdermal layer. Conduction is the loss of heat from the body to cooler surfaces that are in immediate contact with the body such as wet clothing, cold cots, or cold resuscitation equipment. Convection involves the loss of heat energy from the body to the atmospheric cold air(18).

Sepsis and severe hypoxia reduce nonshivering thermogenesis by preventing the breakdown of brown fat(2).

Complications of neonatal hypothermia

Neonatal sepsis

It is defined as a clinical syndrome manifested by signs and symptoms of infection and isolation of bacteria in the blood in a neonate(4). It is classified into early and late-onset sepsis. Early-onset neonatal sepsis occurs from birth to ≤ 72 hours of life while late-onset neonatal sepsis occurs in

neonates older than 72 hours of life to 28 days(4). Hypothermia increases the risk of developing late-onset neonatal sepsis(9).

In retrospective research by Laptook et al in 2006 on predictors and outcomes of admission temperatures among low birth neonates, they found an inverse relationship between admission temperatures and late-onset neonatal sepsis where the risk of sepsis increased by 11% for a fall of temperature by 1◦ Celsius(10).

Hypoglycemia

Hypoglycemia in neonates is defined by WHO as blood glucose less than 2.6 mmol/l(3).

Hypothermic neonates have increased basal metabolic rates to generate heat. This exhausts glucose and glycogen stores leading to hypoglycemia.

A retrospective study conducted by Chia Saw et al in Western Australia on risk factors of hypoglycemia and hypothermia in neonates found that 49.5% of neonates with hypoglycemia had hypothermia. (3)

Coagulopathy

Studies on asphyxiated neonates who have been managed with therapeutic hypothermia have shown an increased risk of bleeding in hypothermic infants (14)(20). Reduced temperatures slow down the enzymatic activity in the clotting cascade leading to increased INR and aPTT(14)(21).

Respiratory distress syndrome (RDS)

Hypothermia in neonates is associated with pulmonary vascular vasoconstriction and reduced surfactant production(11)(22)(23). This can worsen RDS, especially in premature infants who already have reduced surfactant levels.

Hyperbilirubinemia

Hypothermia causes increased release of catecholamine causing uncoupling of beta-oxidation and release of free fatty acids (FFAs).FFAs displace bilirubin from albumin leading to an increase in unbound bilirubin.

Risk of mortality in neonates with hypothermia

A study by Nyandiko et al in MTRH found that neonates with hypothermia at admission were seventeen times more likely to die with hypothermia being noted in almost all (98%) of the neonates who died within 24 hours of admission(8).

A study by C Mullany et al in Nepal showed that a fall in neonates' temperature by 1◦C increases the risk of death by 80%(24) and the risk of death is highest within the first seven days of life.

Laptook et al, 2006 conducted a retrospective study on predictors and outcomes of admission temperature among low birth weight neonates. 1◦ C decrease in temperature was shown to increase the risk of death by 28%(10).

Hung-Yang Chang1 2015 carried out a retrospective study on short-term and long-term outcomes of neonatal hypothermia in very low-birth neonates at the NICU of MacKay Children's Hospital in Taiwan(11). They studied medical records of 341 very low birth weight infants (< 1500gms) who were admitted to the facility between January 2007 and December 2010. The short outcomes studied were neonatal sepsis, RDS that required surfactant, retinopathy of prematurity, intraventricular hemorrhage, neonatal sepsis, necrotizing enterocolitis, and neonatal mortality. The long-term effect studied was neurodevelopmental Impairment at 24 months corrected age.

Other complications associated with neonatal hypothermia are Necrotizing enterocolitis (NEC)(11)(16), Intraventricular Hemorrhage (IVH)(11)(16), and pulmonary hemorrhage(11).

Research title/author	Study design	Results.
Prevalence of Neonatal hypothermia and adherence to World Health Organization thermal care Guidelines among newborns at Moi Teaching and Referral Hospital, Kenya.2016.(8) Winstone Mokaya Nyandiko, Paul Kiptoon, Florence Ajaya Lubuya	Cross-sectional study. 372 neonates.	Prevalence of neonatal hypothermia – 74% Neonates admitted with hypothermia were seventeen times more likely to die.98% of the neonates who died within the first day of admission had hypothermia. WHO warm chain steps were not adhered to among 92.2% of the participants.
Admission temperature of low birth weight infants: predictors and associated morbidities (10) Abbot R Laptook, Walid Salhab, Brinda Bhaskar.	Cross-sectional study. 5277 low birth weight infants	There was an inverse relationship between admission temperature and risk of mortality. (28% increase for a decrease of temperature by 1◦C) There was an inverse association between admission temperature and late-onset sepsis (11% increase in the incidence of sepsis for 1◦ C decline in temperature. The temperature at admission was not associated with the length of

		conventional ventilation, intraventricular hemorrhage, or necrotizing enterocolitis.
Neonatal hypothermia in low-resource settings(25)Luke c Mullany, 2010	Prospective cohort 23240 infants	Axillary temperatures of the neonates in rural Nepal were taken for 28 days. The incidence of hypothermia was found to be 10%. The risk of hypothermia was inversely related to the weight of the neonate.
Short- and Long-Term Outcomes in Very Low Birth Weight Infants with Admission Hypothermia. Hung-YangChang1,Yi-Hsiang Sung et al, 2015(11)	Retrospective study. 341 Participants	Moderately hypothermic infants had significantly higher incidences of 1-min Apgar score < 7 (63.6% vs. 31.6%, *P* < .001), respiratory distress syndrome (RDS) (58.0% vs. 39.2%, *P* = .006), and mortality (18.5% vs. 5.1%, *P* = .005) when compared to normothermic babies Moderate hypothermia was found not to affect developmental milestones at 24 months corrected age.

		Mild hypothermia was found to have no association with short or long-term outcomes.
Hypothermia in very low birth infants: Distribution, risk factors, and outcomes SS Miller et al, 2011(16)	Cohort study. 8782 very low birth infants	Above half of all the infants had hypothermia (56.2%). Moderate hypothermia increased the risk of intraventricular hemorrhage (OR 1.3) Moderate and severe hypothermia increased the risk of death(OR 1.5 and 5.6 respectively)
Prevalence and risk factors of hypothermia at admission to the Newborn unit in Kenyatta National Hospital. Sharon Ocharo,2021	Cross-sectional study 268 neonates	Prevalence of admission hypothermia was 67.2%.The risk factors associated with hypothermia were VLBW (p=0.003), gestation <37 weeks (p=0.001) and age <1 day(p=0.002)

Table 1: Summary of studies

Study justification

Admission neonatal hypothermia is common among neonates admitted into KNH Newborn Unit (NBU). In KNH, a recent study conducted by Sharon Ocharo,2021(unpublished), revealed a prevalence of admission hypothermia of 67%.In this study, VLBW neonates were found to have a

significant risk of developing hypothermia (p-0.003).In MTRH, Nyandiko et al,2016 found a prevalence of hypothermia of 73.9%(8).In these studies, the risk factors of developing hypothermia were assessed. The studies done however did not specifically assess the effects of admission hypothermia. In KNH the newborn unit is about 200 meters from the labor ward and maternity theatre. This exposes the neonates that are admitted in NBU to low temperatures during transport to the unit. This study aims to compare VLBW neonates who are admitted with hypothermia with those with normal temperatures at admission. It will attempt to determine whether having hypothermia at admission has an effect on survival to seven days and if there is an association between the admission temperatures and major morbidities at day seven of life. If found that hypothermia is associated with adverse outcomes in our facility we will emphasize on the need to maintain a warm chain during handling of the neonates and the need to have a Newborn unit in close proximity with the labor ward and the maternity theatres.

Research objectives and study questions

Broad objective

To evaluate the association of admission hypothermia with mortality and major morbidity at day seven of life among VLBW neonates admitted at KNH NBU.

Specific objectives

1. To evaluate the association of admission hypothermia with late onset neonatal sepsis, hypoglycemia, persistent RDS, Necrotizing enterocolitis and Intraventricular haemorrhage at day seven of life among VLBW neonates admitted at KNH NBU.
2. To quantify the neonatal mortality and admission hypothermia relationship at day seven of life among VLBW neonates admitted in KNH NBU.

Research questions

1. What is the association between admission hypothermia and neonatal morbidities within seven days of admission at KNH NBU?
2. What is the risk of mortality associated with admission hypothermia among VLBW neonates admitted at KNH NBU within seven days of admission?

CHAPTER 3: STUDY METHODS

Design

This study was a retrospective cohort study on VLBW neonates admitted to KNH NBU from January 2019 to December 2019.It was a comparison between two cohorts, those neonates with hypothermia at admission and those with normal temperatures. The exposure was hypothermia at admission and outcomes were morbidities and mortality within seven days of admission.

Study setting

This retrospective study was conducted in Kenyatta National Hospital (KNH) Newborn Unit (NBU). KNH is a national teaching and referral Hospital located in Nairobi, Kenya. The Newborn unit admits an average of 100 neonates every month. The neonates are admitted from the KNH labor ward, maternity theatres, home deliveries, and referrals from other facilities. The neonates progress while in the ward is recorded in a file that bears their names or mothers name for identification. While in the ward, they are reviewed daily by the pediatrics registrars, neonatology fellows and consultant neonatologists. The files are taken to the records department after the neonate has been discharged or has died and these files can be assessed for study after permission from KNH research department and an approval letter from the KNH-UON Ethics and Research Committee.

Study population

VLBW neonates admitted in KNH NBU from January 2019 to December 2019.Neonates whose birth weight was between 1000-1499 grams were studied. Both inborns and outborns were enrolled. The exposed group were the neonates whose admission temperature was less than 36.5 degrees Celsius (hypothermia) while the non-exposed group were those with admission temperature between 36.5 -37.5 degrees Celsius(normothermia)

Inclusion criteria

Neonates were admitted to KNH NBU from January 2019 to December 2019. Neonates born in KNH (Inborn) and those referred to KNH (Outborn) will be included.

Neonates with birth weight 1000 - 1499 grams.

Neonates with admission temperature of less than 37.5 degrees Celsius, those with hypothermia and normothermia at admission.

Exclusion criteria

Incomplete records: Those whose admission temperatures were not recorded.

Those with hyperthermia on admission (temperatures above 37.5◦C)

Follow up times

The neonates medical records were each studied for the first seven days of admission or up to neonate's death if it occurs before seventh day of admission.

Outcome case definitions

1. **Late onset neonatal sepsis -:** positive blood culture for either bacteria or fungus after 72 hours of life.
2. **Persistent RDS** –Silverman Anderson Score (SAS) ≥ 4 at day seven of life / a neonate requiring NCPAP or Mechanical ventilation beyond seven days of admission.
3. **NEC** - Abdominal distension, Absent bowel sounds, radiographic findings of dilatation of intestines, ileus, or pneumatosis intestinalis
4. **Hypoglycemia** – at least one random blood sugar of < 2.6 mmol/l during the first 7 days of admission.
5. **IVH** - Any stage of intraventricular bleed confirmed by cranial ultrasound.

6. **Mortality** – In this study, mortality was death of neonate within the first seven days of admission.

Sample size

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$$n = \frac{z^2 \times p(1-p)}{MOE^2}$$

n = minimum sample size

z = z score, 1.96 at 95% confidence interval

MOE= Margin Of Error = 0.05

p=estimated proportion of neonates admitted with hypothermia who develop Late Onset Neonatal Sepsis- 29%.(11)

$$n = \frac{1.96^2 \times 0.29(1-0.29)}{0.05^2}$$

$$n = \frac{3.84 \times 0.206}{0.0025}$$

n= 316

Therefore, the minimum sample size was 316 neonates. The admissions in 2019 that fit our inclusion criteria and files found were 384 neonates. They were all included in the study

This sample size is comparable to sample size in a study on Short- and Long-Term Outcomes in Very Low Birth Weight Infants with Admission Hypothermia, Hung-YangChang1 et al, 2015(11) where a sample size of 341 VLBW neonates were used.

Sampling methods

Data abstraction from records of VLBW neonates admitted in the year 2019. Total population sampling was done on the records of the neonates that fit the inclusion criteria. The study subjects were then categorized as exposed (hypothermia at admission) or non-exposed (normothermia at admission)

Study variables

Conceptual framework

Independent outcome at 7 days of admission

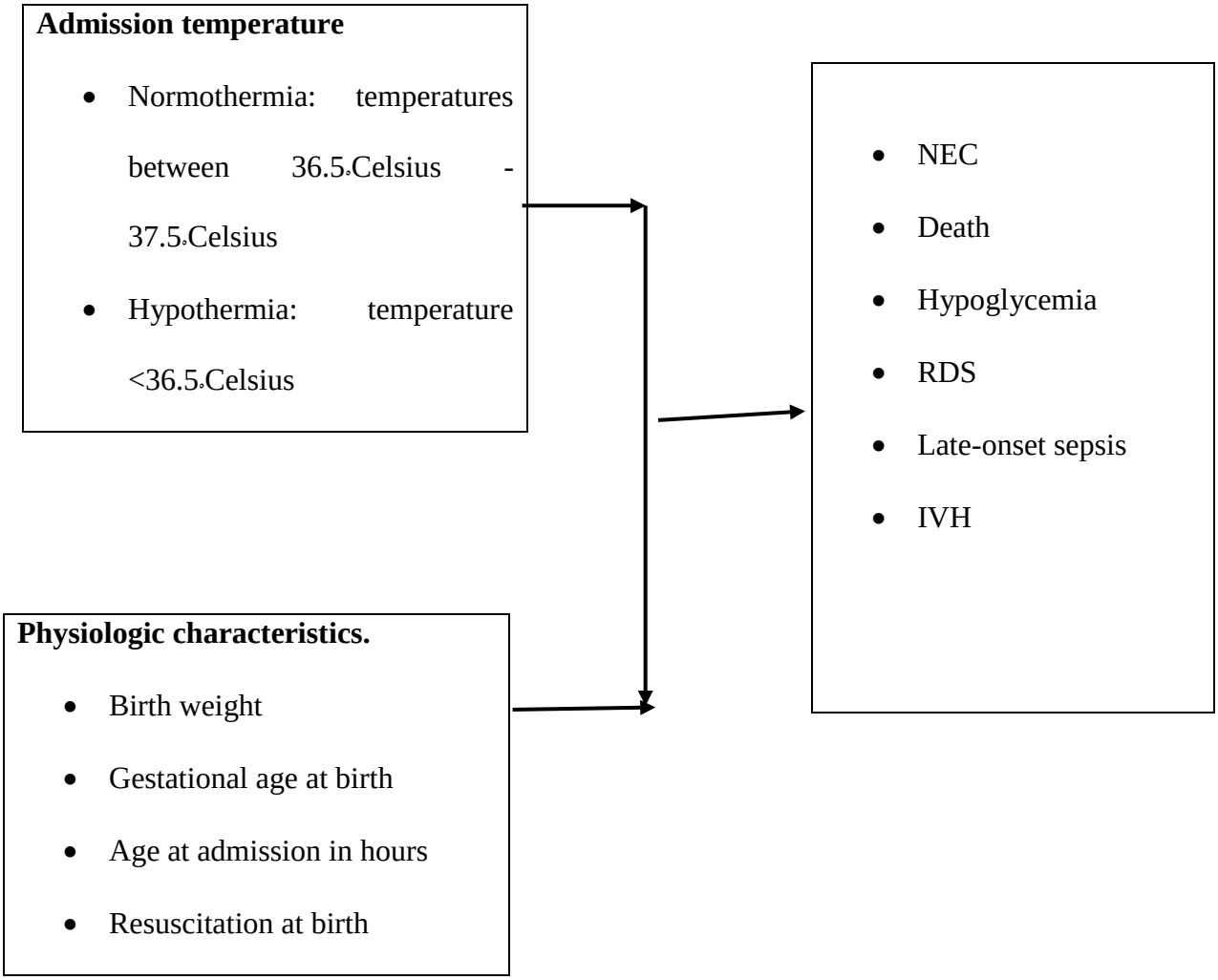


Figure 1: Conceptual Framework

Data collection tool

A tool was developed to be used for data abstraction from medical records of identified neonates that fit the inclusion criteria. The data collection tool is attached as appendix 1

Study procedure

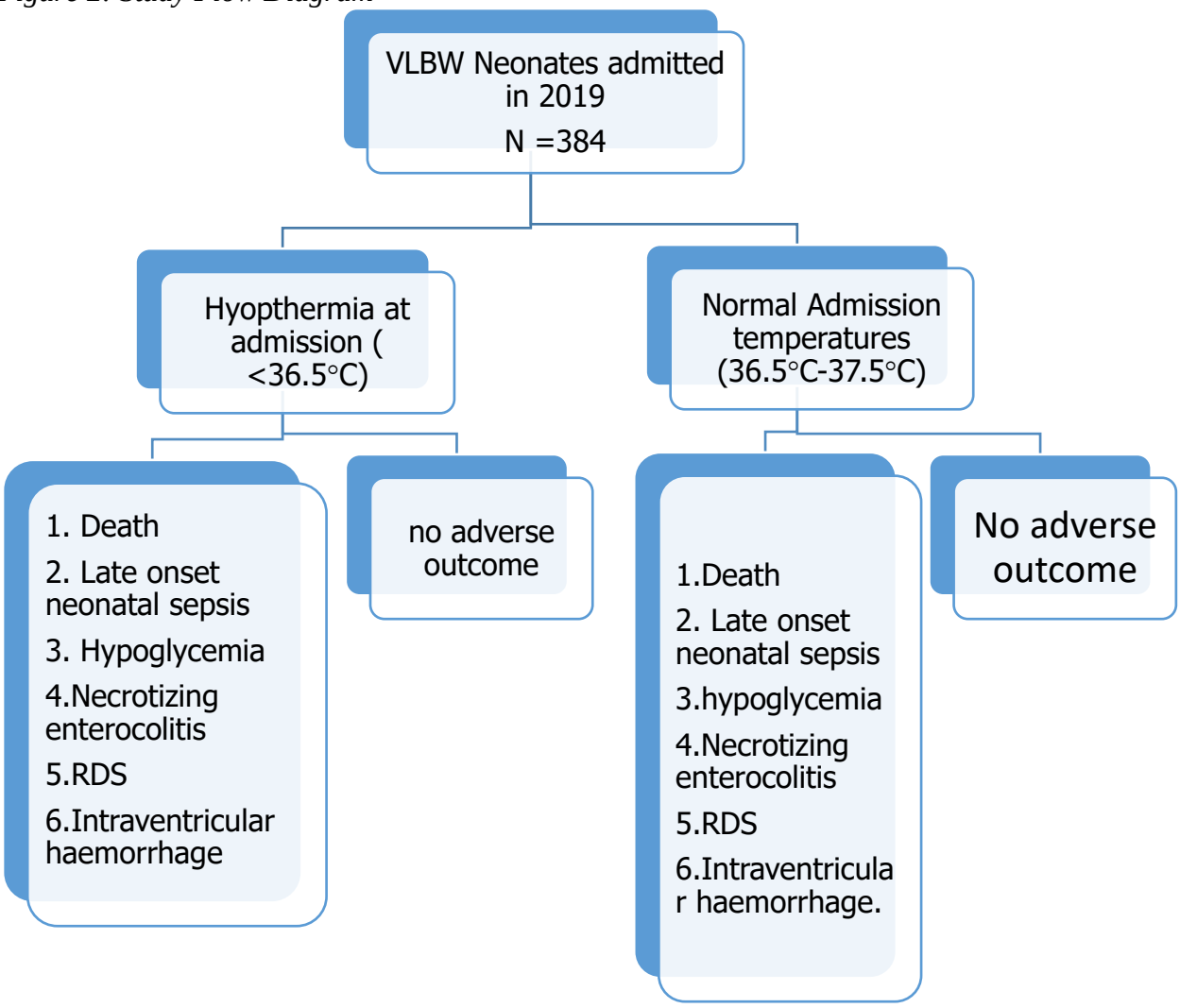
Data was collected from medical records in the KNH medical records department from the files of neonates admitted to NBU in the year 2019. A data collection tool attached was used to collect the

medical information (appendix 1). The temperature of interest was the first temperature taken on admission. The temperature was categorized into normal, mild, moderate and severe hypothermia.

The study aimed to identify if admission temperature affects outcomes at day seven post-admission. Other parameters that were taken were demographic data and clinical characteristics of the neonates at admission: gender, birth weight, gestational age, resuscitation after birth, age at admission, and diagnosis at admission.

At seven days of life, the neonate's records were assessed for comorbidities that have been diagnosed during the stay in the ward, whether alive, dead, or discharged. The morbidities that were assessed were late-onset sepsis, Respiratory Distress Syndrome (RDS), hypoglycemia, necrotizing enterocolitis, and Intraventricular Hemorrhage (IVH).

Figure 2: Study Flow Diagram



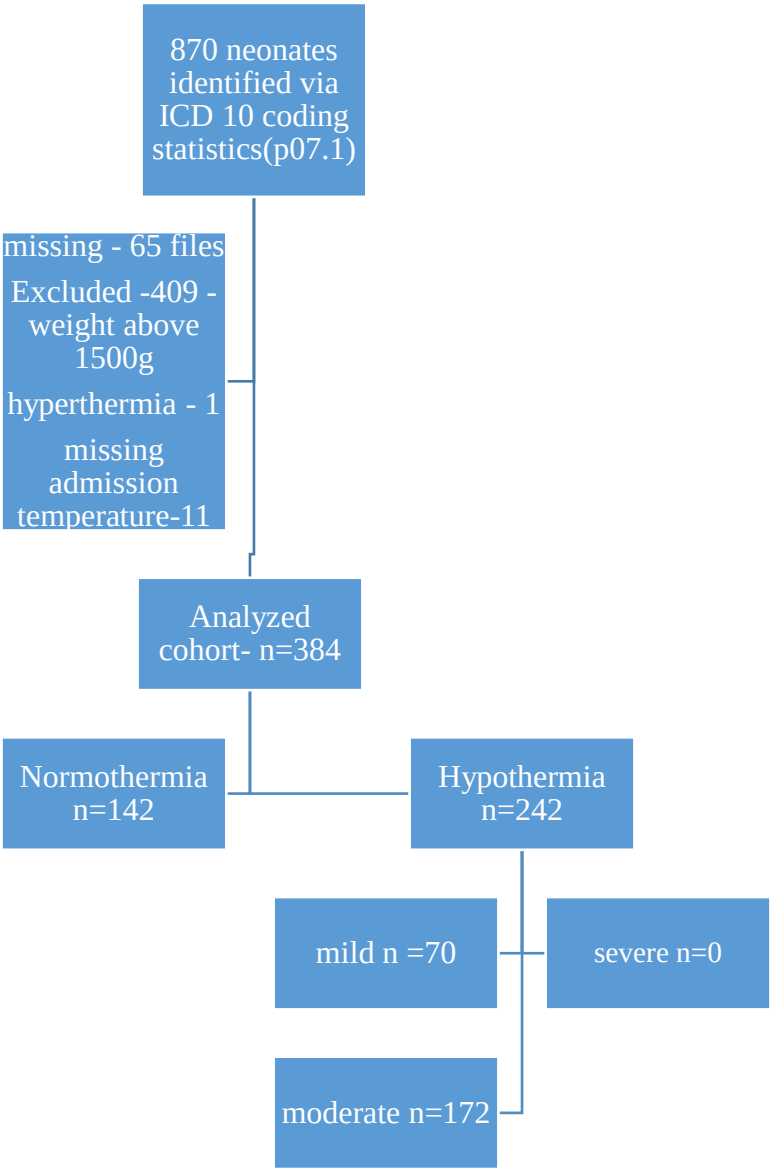


Figure 3: Flow diagram of study participants

Data analysis and protection.

Once the data abstraction tools were completed, the information was filled in an excel spreadsheet. The abstraction tools were stored safely and were not released to third parties. The tools had serial numbers instead of the neonates' names or hospital identification numbers. The data will be manually cleaned and then exported to SPSS version 25 software for further analysis. We ran a bivariate analysis using odds ratios to assess the association between temperature and the

development of comorbidities during the first 7 days of admission in the neonatal unit. The p-values were computed using the Chi-square test and Fisher's exact test. Fisher's test was used where tables have more than 20% of cells with counts less than 5 . Odds ratios were tabulated to determine whether admission hypothermia increased the risk of the comorbidities among the neonates. Those with admission hypothermia were further sub-classified into mild, moderate, and severe hypothermia. The significance of the statistical tests was considered if they lie within the 95 confidence interval. The relative risk of mortality and major morbidity (RDS, Late-onset NNS, NEC, Hypoglycemia, IVH) within the first seven days of admission comparing the exposed and the non-exposed groups. Descriptive statistics were used to calculate the result in mean, mode and median, and frequencies. Logistic regression in SPSS was run on outcomes whose statistical p-value was <0.05 in bivariate analysis to determine their odds ratio of association with admission hypothermia.

Results were presented by the use of tables, box plots, and density plots.

Ethical consideration

Approval to conduct the study was requested from the KNH/UON Ethics and Research Committee and the study was approved (P777/09/2021). Permission was sought from the KNH records department for the retrieval of the medical records. There was no contact with the actual patient therefore no informed consent was sought. The data abstraction tools were serialized and did not bear the neonate's names or inpatient hospital numbers.

CHAPTER 4: RESULTS

This was a retrospective study on neonatal hypothermia and its effect on mortality and morbidity among neonates within the first 7 days of admission. We assessed the effect of admission temperature and whether it would determine the outcomes; mortality and morbidity within the said admission period. The primary morbidity was late onset neonatal sepsis and was used in sample size calculation. The minimum sample size was 316 neonates. We managed a sample size of 384 neonates which translates to 121%.

The majority of the participating babies were males at 53.6% (n = 206) while the rest were females. Age-wise, the babies were categorized as either above 1 hour or 1 hour and below. There was an equal number of babies in the two age categories i.e., 50% each (n = 192). The minimum weight of the participants was 1000 grams and a maximum of 1495 grams. The median weight was 1350 grams with an interquartile range of 222 grams. The mean weight was 1350 grams.

Table 2: Demographic characteristics of the participants and hypothermia vs. normal temperature

Variable	Frequency (%) /Median (IQR) N = 384	Temperature		Crude OR (95% CI)	p-value
		Hypothermia (ref) N = 242	Normothermia N = 142		
Gender: Female (**ref**)	178 (46.4%)	131	47		
Male	206 (53.6%)	111	95	2.39 (1.5, 3.67)	<0.01
Age < = 1 hour (**ref**)	192 (50%)	116	76		
> 1 hour	192 (50%)	126	66	0.80 (0.53, 1.21)	0.29
Weight in grams	1350 (1218,1440)				
Weight in grams					
1000-1249 (**ref**)	106 (27.6)	83	23		
>1249	278 (72.4)	159	119	2.70 (1.61, 4.54)	<0.01
Gestational age	32.0 (30, 33)				
Gestational age					
<28 weeks (**ref**)	10 (2.6%)	6	4		
28-32 weeks	261 (68.0)	192	69	0.54 (0.15, 1.97)	0.34

32 weeks	113 (29.4%)	44	69	2.35 (0.62, 8.81)	0.19
Referral: No (**ref**)	251 (65.4%)	156	95		
Yes	113 (34.6%)	86	47	0.90 (0.58, 1.39)	0.63

The minimum gestational age at birth among the participants was 26 weeks while the maximum was 37.0 weeks. The median gestational age was 32.0 weeks with an interquartile range of 3 weeks. The mean gestational age was 31.3 weeks. The majority of the babies were born between 28 and 32 weeks, 68.0% (n = 261) followed by those born above 32 weeks gestation 29.4% (n = 113). The rest were born below 28 weeks gestation. 65.4% (n = 251) of the babies were born at Kenyatta National Hospital while the rest were referrals. Temperature was significantly associated with weight and gender p-values <0.01 at significance level 0.05. The odds of having normal temperatures given that gender was male were 2.39 times those of females. The odds of temperatures being normal for babies with weights of 1249 grams and above were 2.70 times those of babies below 1249 grams. (Table 2).

Clinical characteristics

Table 3: Clinical characteristics and hypothermia vs. normal temperature

Variable	Frequency (%) /Median (IQR) N = 384	**Hypothermia (ref) N = 242**	**Normothermia N = 142**	Crude OR (95% CI)	p-value
Mode of delivery:					
C-section **(ref)**	186 (48.4%)	117	69		
SVD	198 (51.6%)	125	73	0.99 (0.64, 1.50)	0.96
Baby resuscitated:					
Yes **(ref)**	37 (9.6%)	33	4		
No	347 (90.4%)	209	138	5.45 (1.89, 15.7)	<0.01
RDS at admission:					
Yes **(ref)**	298 (77.6%)	207	91		
No	86 (23.4%)	35	51	3.31 (2.02, 5.44)	<0.01
Risk of neonatal sepsis:					
Yes **(ref)**	23 (6.0%)	15	8		
No	361 (94.0%)	227	134	1.11 (0.46, 2.68)	0.82
Perinatal asphyxia:					
Yes **(ref)**	25 (6.5%)	23	2		
No	359 (93.5%)	219	140	7.35 (1.76, 31.67)	<0.01
Temperature:	36.2 (35.2, 36.7)				

The majority of the babies in this study 51.6% (n = 198) were delivered normally while the rest were delivered via C-section. 9.6% (n = 37) of the babies underwent resuscitation while the rest did not. Most of the babies 77.6% (n = 298) had respiratory distress syndrome at admission while the rest did not. 6.0% (n = 23) had a risk for neonatal sepsis and 6.5% (n = 25) had neonatal asphyxia.

The temperature at admission was recorded in degrees centigrade. In the analysis, babies have been classified into 4 temperature categories i.e., severe hypothermia < 32.0 degrees Celsius, moderate hypothermia 32.0 – 35.9 degrees Celsius, mild hypothermia 36.0 – 36.4 degrees Celsius, and normal temperature 36.5 – 37.5 degrees Celsius.

There were no babies with severe hypothermia, 44.8% (n = 172) had moderate hypothermia, 18.2% (n = 70) had mild hypothermia while the rest had normal temperatures.

Temperature was significantly associated with resuscitation at birth, RDS at admission and perinatal asphyxia with p-value <0.01for the three factors at significance level 0.05. Babies who were not resuscitated at birth were 5.45 times more likely to have normal temperatures compared to those who were not resuscitated. The odds of normal temperature for the babies who were not admitted with RDS were 3.31 times those of the babies who were admitted with RDS. The odds of normal temperature for the babies who did not get perinatal asphyxia were 7.35 times those of the babies who got perinatal asphyxia (Table 3).

Objective 1: To assess the association of admission hypothermia with morbidity within the first 7 days of admission among VLBW neonates admitted at KNH NBU.

Temperature distribution

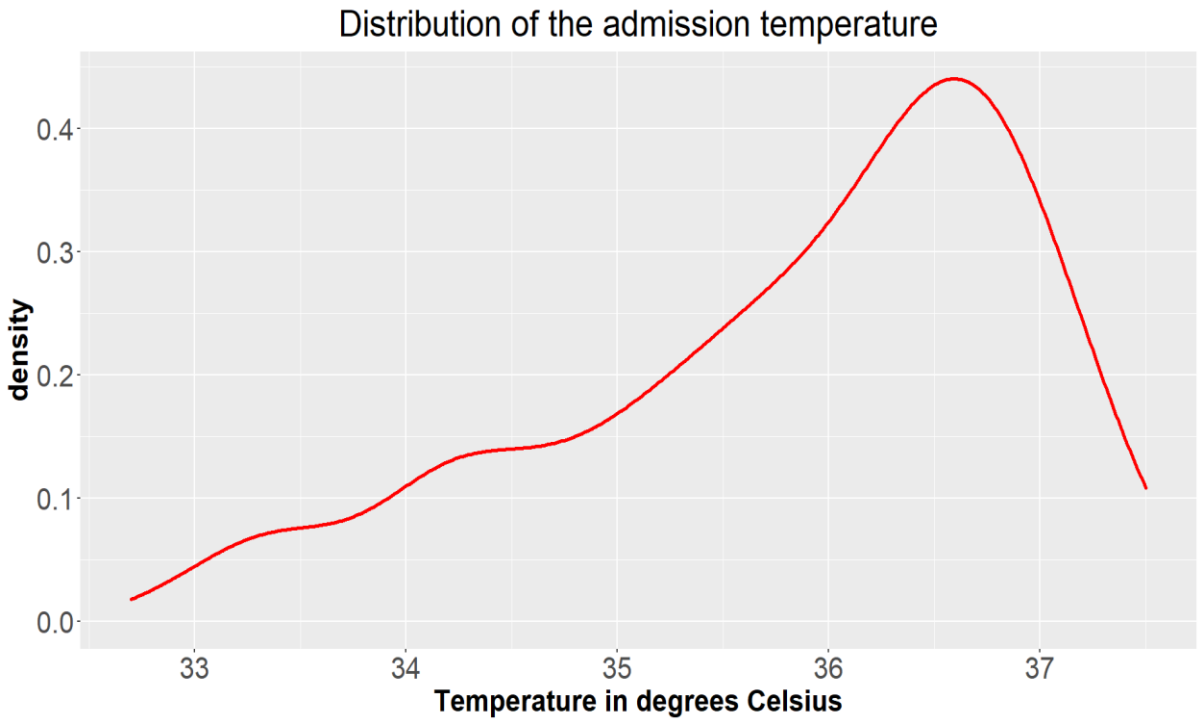


Figure 4: Density plot of the admission temperature

Figure 1 above shows that the temperature of the babies at admission was negatively skewed with the majority having temperatures of below 36.0 degrees Celsius. The median temperature at admission was 36.2 degrees Celsius with an interquartile range of 1.5 degrees Celsius. The mean temperature was 35.8 degrees Celsius. The maximum temperature was 37.5 with a minimum of 32.7 degrees Celsius.

Factors associated with morbidities

Bivariate analysis

We ran a bivariate analysis using odds ratios to assess the association between temperature and development of comorbidities during the first 7 days of admission in the neonatal unit. The p-values were computed using Chi square test and Fisher's exact test. Fisher's test was used where tables have more than 20% of cells with counts less than 5 (table 3).

From the results, temperature, weight, age of the child and referral status were associated with development of late onset neonatal sepsis p-values <0.01, 0.021, 0.02 and 0.04 respectively at 5%

significance level. Babies who were admitted with hypothermia were 11.35 times more likely to develop late onset neonatal sepsis compared to those who were admitted with normal temperatures while. Weights of less than 1249 grams increased the odd of a baby developing late onset neonatal sepsis by 75% while babies who were less than or equal to 1 hour were 41% less likely to develop late onset neonatal sepsis compared to those who were above 1 hour. The babies who were born within the facility were 37% less likely to develop late onset neonatal sepsis compared to the referrals from other hospitals (table 4).

Table 4: Factors associated with late onset neonatal sepsis

Factor	Frequency (%)/ Median (IQR)	**Late onset neonatal sepsis**		Crude OR (95% CI)	P value
	N = 384	Yes N = 137	No (ref) N = 220		
Temperature: Normal (ref)	142 (37.0%)	14	124		
Mild	70 (18.2%)	19	48	3.5 (1.6, 7.6)	<0.001
Moderate	172 (44.8%)	104	48	19.3 (10.0, 36.8)	<0.001
Hypothermia	242 (63%)	123	96	11.35 (6.14,20.96)	<0.01
Normothermia (ref)	142 (37.0%)	14	124		
Gender: Female	178 (46.4%)	69	98	1.26 (0.82, 1.94)	0.28
Male (ref)	206 (53.6%)	68	112		
Weight: <1249	106 (27.6%)	45	48	1.75 (1.09, 2.83)	0.021
>=1249 (ref)	278 (72.4%)	92	172		
Gestation:<28 (ref)	10 (2.6%)	5	5		
28-32	261 (68.0%)	103	134	0.77 (0.22, 2.70)	0.68
>32	113 (29.4%)	29	81	0.36 (0.10, 1.33)	0.11
Age: <=1 hour	192 (50.0%)	58	122	0.59 (0.38, 0.91)	0.02
>1 hour (ref)	192 (50.0%)	79	98		
Referral: No	251 (65.4%)	81	153	0.63 (0.41, 0.99)	0.04
Yes (ref)	133 (34.6%)	56	67		

Table 5:Factors associated with hypoglycemia

Factor	Frequency (%)/ Median (IQR)	**Hypoglycaemia**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 70	No (ref) N = 313		
Temperature: Normal (ref)	142 (37.0%)	4	138		
Mild	70 (18.2%)	7	63	3.8 (1.1, 13.6)	0.04
Moderate	172 (44.8%)	59	112	18.2 (6.4,51.6)	<0.001
Hypothermia	242 (63%)	66	175	13.0 (4.63, 36.58)	<0.01
Normothermia (ref)	142 (37.0%)	4	138		
Gender: Female	178 (46.4%)	22	155	0.47 (0.27,0.81)	<0.01
Male (ref)	206 (53.6%)	48	158		
Weight: <1249	106 (27.6%)	33	72	2.99 (1.74, 5.11)	<0.01
>=1249 (ref)	278 (72.4%)	37	241		
Gestation:<28 (ref)	10 (2.6%)	2	8		
28-32	261 (68.0%)	58	202	1.15 (0.24, 5.55)	1.00
>32	113 (29.4%)	10	103	0.39 (0.07, 2.08)	0.25
Age: <=1 hour	192 (50.0%)	41	151	1.52 (0.90, 2.56)	0.12
>1 hour	192 (50.0%)	29	162		
Referral: No	251 (65.4%)	46	205	1.01 (0.59, 1.74)	0.97
Yes (ref)	133 (34.6%)	24	108		

For factors associated with development of hypoglycaemia; temperature, gender and weight were statistically associated with the development of hypoglycaemia, p-values <0.01 at 5% significance level. Babies who were admitted with hypothermia were 13.0 times more likely to develop hypoglycaemia compared to those admitted with normal temperatures. Female babies were 53% less likely to develop hypoglycaemia compared to male babies while babies with weights of <1249 grams were 2.99 times more likely to develop hypoglycaemia compared to those with weights of above 1249 grams (table 5).

Table 6: Factors associated with necrotizing enterocolitis

Factor	Frequency (%)/ Median (IQR)	**Necrotizing enterocolitis**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 19	No (ref) N = 333		
Temperature: Normal (ref)	142 (37.0%)	5	131		
Mild	70 (18.2%)	2	63	0.83 (0.16, 4.4)	1.00
Moderate	172 (44.8%)	12	139	2.26 (0.78, 6.60)	0.14
Hypothermia	242 (63%)	14	202	1.82 (0.64, 5.16)	0.26
Normothermia (ref)	142 (37.0%)	5	131		
Gender: Female	178 (46.4%)	10	155	1.27 (0.51,3.22)	0.61
Male (ref)	206 (53.6%)	9	178		
Weight: <1249	106 (27.6%)	9	80	2.85 (1.11, 7.24)	0.03
>=1249 (ref)	278 (72.4%)	10	253		
Gestation:<28 (ref)	10 (2.6%)	2	8		
28-32	261 (68.0%)	16	216	0.30 (0.06, 1.51)	0.16
>32	113 (29.4%)	1	109	0.04 (0.003, 0.45)	0.02
Age: <=1 hour	192 (50.0%)	11	166	1.38 (0.54, 3.35)	0.50
>1 hour (ref)	192 (50.0%)	8	167		
Referral: No	251 (65.4%)	12	219	0.89 (0.34, 2.33)	0.82
Yes (ref)	133 (34.6%)	7	114		

Only one factor, weight was found to be associated with necrotizing enterocolitis p-value 0.03 at 5% significance level. The third level of gestational age >32 weeks was also associated with development of necrotizing enterocolitis, p-value 0.02. Weights of less than 1249 grams increased the odds of developing necrotizing enterocolitis by 2.85 while gestation age of >32 weeks reduced the odds of developing necrotizing enterocolitis by 96% OR 0.04 (0.003, 0.45) (table 6).

Table 7: Factors associated with persistent RDS

Factor	Frequency (%)/ Median (IQR)	**Persistent RDS**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 127	No (ref) N =232		
Temperature: Normal (ref)	142 (37.0%)	15	122		
Mild	70 (18.2%)	28	38	6.0 (2.90, 12.37)	<0.001
Moderate	172 (44.8%)	84	72	9.5 (5.1, 17.7)	<0.001
Hypothermia	242 (63%)	112	110	8.28 (4.55,15.05)	<0.01
Normothermia (ref)	142 (37.0%)	15	122		
Gender: Female	178 (46.4%)	66	102	1.38 (0.89, 2.13)	0.14
Male (ref)	206 (53.6%)	61	130		
Weight: <1249	106 (27.6%)	60	33	5.4 (3.25, 8.97)	<0.01
>=1249 (ref)	278 (72.4%)	67	199		
Gestation:<28 (ref)	10 (2.6%)	8	2		
28-32	261 (68.0%)	100	138	0.12 (0.04, 0.87)	<0.01
>32	113 (29.4%)	19	92	0.05 (0.01, 0.26)	<0.01
Age: <=1 hour	192 (50.0%)	58	125	0.72 (0.47, 1.11)	0.14
>1 hour (ref)	192 (50.0%)	69	107		
Referral: No	251 (65.4%)	82	155	0.91 (0.57, 1.42)	0.67
Yes (ref)	133 (34.6%)	45	77		

Three factors were found to be associated with persistent respiratory distress syndrome; temperature, weight and gestation, p-values <0.01 for the three factors at 5% significance level. Babies who were admitted with hypothermia were 8.28 times more likely to have persistent RDS compared to those admitted with normal temperature OR 8.28 (4.55, 15.05). Weights of <1249 grams increased the odds of persistent RDS 5.4 times (table 7).

Table 8: Factors associated with intraventricular hemorrhage

Factor	Frequency (%)/ Median (IQR)	**Intraventricular haemorrhage**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 16	No (ref) N = 336		
Temperature: Normal (ref)	142 (37.0%)	0	136		
Mild	70 (18.2%)	3	62	NA	0.03
Moderate	172 (44.8%)	13	138	NA	<0.001
Hypothermia	242 (63%)	16	200	NA	<0.01
Normothermia (ref)	142 (37.0%)	0	136		
Gender: Female	178 (46.4%)	6	159	0.67 (0.24, 1.88)	0.44
Male (ref)	206 (53.6%)	10	177		
Weight: <1249	106 (27.6%)	8	81	3.15 (1.15, 8.66)	0.02
>=1249 (ref)	278 (72.4%)	8	256		
Gestation:<28 (ref)	10 (2.6%)	0	10		
28-32	261 (68.0%)	16	216	NA	1.00
>32 (ref)	113 (29.4%)	0	110	NA	1.00
Age: <=1 hour	192 (50.0%)	11	166	2.25 (0.77, 6.62)	0.13
>1 hour (ref)	192 (50.0%)	5	170		
Referral: No	251 (65.4%)	16	215	NA	<0.01
Yes (ref)	133 (34.6%)	0	121		

For factors associated with intraventricular haemorrhage; temperature, weight and referral status were found to have a significant association with this outcome, p-values <0.01, 0.02 and <0.01 respectively at 5% significance level.

The babies admitted with weights of <1249 grams were 3.15 times more likely to develop IVH compared to those with weights of 1249 grams and above (table 8).

Multivariable analysis

To develop the multivariable model, we selected factors that were significantly associated with the outcomes under the bivariate analysis p-values <0.05 at 5% significance level. These variables were then fitted in a binary logistic regression model and p-values and odds ratios generated.

Table 9: Factors associated with late onset neonatal sepsis

Factor	Frequency (%)/ Median (IQR)	**Late onset neonatal sepsis**		Adjusted OR (95% CI)	P value
	N = 384	Yes N = 137	No (ref) N = 220		
Hypothermia Normothermia (ref)	242 (63%) 142 (37.0%)	123 14	96 124	11.0 (6.10, 21.35)	<0.01
Weight: <1249 >=1249	106 (27.6%) 278 (72.4%)	45 92	48 172	1.19 (0.69, 2.04)	0.523
Age: <=1 hour >1 hour	192 (50.0%) 192 (50.0%)	58 79	122 98	0.72 (0.37, 1.39)	0.324
Referral: No Yes	251 (65.4%) 133 (34.6%)	81 56	153 67	0.77 (0.39, 1.55)	0.46

After adjusting for other variables, only temperature was found to be significantly associated with the development of late onset neonatal sepsis, p-value <0.01 at 5% significance level. The odds of developing late onset neonatal sepsis were increased 11.0 times for those babies who were admitted with hypothermia. Babies who were admitted with weights of less than 1249 grams were 1.19 times more likely to develop late onset neonatal sepsis compared to those who had weights of 1249 grams and above (table 9).

Table 10: Factors associated with hypoglycemia

Factor	Frequency (%)/ Median (IQR)	**Hypoglycaemia**		Adjusted OR (95% CI)	p-value
	N = 384	Yes N = 70	No (ref) N = 313		
Hypothermia Normothermia (ref)	242 (63%) 142 (37.0%)	66 4	175 138	15.32 (5.97,52.18)	<0.01
Gender: Female	178 (46.4%)	22	155	0.28 (0.15, 0.51)	<0.01

Male (ref)	206 (53.6%)	48	158		
Weight: <1249 >=1249	106 (27.6%) 278 (72.4%)	33 37	72 241	2.48 (1.37, 4.48)	<0.01

Three factors were found to be associated with hypoglycaemia after adjustment. These were temperature, gender and weights, p-values <0.01 at 5% significance level. The odds of developing hypoglycaemia for babies admitted with hypothermia were increased 15.32 times the odds of those with normal temperatures. Female patients were 72% less likely to develop hypoglycaemia after adjusting for temperature and weight (table 10).

Table 11: Factors associated with necrotizing enterocolitis

Factor	Frequency (%)/ Median (IQR)	**Necrotizing enterocolitis**		Adjusted OR (95% CI)	p-value
	N = 384	Yes N = 19	No (ref) N = 333		
Weight: <1249 >=1249	106 (27.6%) 278 (72.4%)	9 10	80 253	1.61 (0.56, 4.47)	0.08
Gestation:<28 (ref) 28-32 >32	10 (2.6%) 261 (68.0%) 113 (29.4%)	2 16 1	8 216 109	 0.40 (0.08, 2.97) 0.06 (0.002, 0.81)	 0.30 0.04

Despite weight being associated with development of necrotizing enterocolitis independently, the association became insignificant after adjusting for gestational age. The third level of gestational age provided information on development of enterocolitis p-value 0.04 at 5% significance level. Babies who were born above 32 weeks gestation were 94% less likely to develop necrotizing enterocolitis after adjusting for weight (table 11).

Table 12: Factors associated with persistent RDS

Factor	Frequency (%)/ Median (IQR)	**Persistent RDS**		Adjusted OR (95% CI)	p-value
	N = 384	Yes N = 127	No N =232		
Hypothermia Normothermia (ref)	242 (63%) 142 (37.0%)	112 15	110 122	7.49 (4.00, 15.02)	<0.01
Weight: <1249 >=1249	106 (27.6%) 278 (72.4%)	60 67	33 199	3.62 (2.01, 6.64)	<0.01
Gestation:<28 (ref) 28-32 >32	10 (2.6%) 261 (68.0%) 113 (29.4%)	8 100 19	2 138 92	 0.21 (0.03, 1.08) 0.16 (0.02, 0.88)	 0.09 0.05

Temperature and weight were significantly associated with persistent RDS p-values <0.01 each at 5% significance level. Babies admitted with hypothermia were 7.49 time more likely to have persistent RDS compared to those who had normal temperature. Babies with weights <1249 grams were 3.62 times more likely to have persistent RDS compared to those with normal temperature (table 12).

Table 13: Factors associated with intraventricular hemorrhage

Factor	Frequency (%)/ Median (IQR)	**Intraventricular haemorrhage**		Adjusted OR (95% CI)	p-value
	N = 384	Yes N = 16	No (ref) N = 336		
Hypothermia Normothermia (ref)	242 (63%) 142 (37.0%)	16 0	200 136	NA	<0.01
Weight: <1249 >=1249 (ref)	106 (27.6%) 278 (72.4%)	8 8	81 256	2.51 (0.86, 7.35)	0.09
Referral: No Yes (ref)	251 (65.4%) 133 (34.6%)	16 0	215 121	NA	1.00

After adjusting for weight and the referral status, only temperature was found to be significantly associated with development of intraventricular haemorrhage at 5% significance level (table 13).

Temperature categorized as mild hypothermia, moderate hypothermia and normothermia

Table 14: Factors associated with late onset neonatal sepsis

Factor	Frequency (%)/ Median (IQR)	**Late onset neonatal sepsis**		Adjusted OR (95% CI)	P value
	N = 384	Yes N = 137	No (ref) N = 220		
Temperature: Normal (ref)	142 (37.0%)	14	124		
Mild	70 (18.2%)	19	48	2.83 (1.27,6.41)	0.01
Moderate	172 (44.8%)	104	48	18.67 (9.94, 37.3)	<0.001
Weight: <1249	106 (27.6%)	45	48	1.97 (1.08, 3.68)	0.03
>=1249 (ref)	278 (72.4%)	92	172		
Age: <=1 hour	192 (50.0%)	58	122	0.78 (0.39, 1.57)	0.49
>1 hour (ref)	192 (50.0%)	79	98		
Referral: No	251 (65.4%)	81	153	0.83 (0.39, 1.73)	0.62
Yes (ref)	133 (34.6%)	56	67		

On factors associated with late onset neonatal sepsis, temperature (normothermia, mild hypothermia, and moderate hypothermia) and weight were found to be significantly associated with development of late onset neonatal sepsis at 5% significance level. Babies who were admitted with moderate hypothermia were 18.67 times more likely to develop latte onset neonatal sepsis compared to those with normal temperatures after adjusting for weight, age and the referral status. The odds of developing late onset neonatal sepsis among the babies with mild hypothermia were 2.83 times those of babies with normothermia (table 14)

Table 15: Factors associated with hypoglycemia

Factor	Frequency (%)/ Median (IQR)	**Hypoglycaemia**		Adjusted OR (95% CI)	p-value
	N = 384	Yes N = 70	No (ref) N = 313		
Temperature: Normal (ref)	142 (37.0%)	4	138		
Mild	70 (18.2%)	7	63	3.3 (0.91, 13.55)	0.08
Moderate	172 (44.8%)	59	112	22.51 (8.62, 77.64)	<0.001
Gender: Female	178 (46.4%)	22	155	0.31 (0.16, 0.57)	<0.001
Male (ref)	206 (53.6%)	48	158		
Weight: <1249	106 (27.6%)	33	72	3.73 (1.96, 7.25)	<0.001
>=1249 (ref)	278 (72.4%)	37	241		

For factors associated with development of hypoglycaemia; temperature, gender and weight were statistically associated with the development of hypoglycaemia, p-values <0.01 at 5% significance level. Babies who were admitted with moderate hypothermia were 22.51 times more likely to develop hypoglycaemia compared to those admitted with normal temperatures. Female babies were 69% less likely to develop hypoglycaemia compared to male babies while babies with weights of <1249 grams were 3.73 times more likely to develop hypoglycaemia compared to those with weights of above 1249 grams (table 15).

Table 16: Factors associated with necrotizing enterocolitis

Factor	Frequency (%)/ Median (IQR)	**Necrotizing enterocolitis**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 19	No (ref) N = 333		
Temperature: Normal (ref)	142 (37.0%)	5	131		
Mild	70 (18.2%)	2	63	0.41 (0.05, 2.12)	0.31
Moderate	172 (44.8%)	12	139	1.56 (0.54, 5.21)	0.45
Weight: <1249	106 (27.6%)	9	80	2.00 (0.67, 5.72)	0.20
>=1249 (ref)	278 (72.4%)	10	253		
Gestation:<28 (ref)	10 (2.6%)	2	8		
28-32	261 (68.0%)	16	216	0.44 (0.08, 3.40)	0.37
>32	113 (29.4%)	1	109	0.07 (0.003, 0.96)	0.05

Babies with moderate hypothermia were 56% more likely to develop necrotizing enterocolitis compared to those with normal temperature. Weights of less than 1249 grams increased the odds of developing necrotizing enterocolitis by 2.00 times while gestation age of >32 weeks reduced the odds of developing necrotizing enterocolitis by 93% OR 0.07 (0.003, 0.45) (table 16).

Table 17: Factors associated with persistent RDS

Factor	Frequency (%)/ Median (IQR)	**Persistent RDS**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 127	No (ref) N =232		
Temperature: Normal (ref)	142 (37.0%)	15	122		
Mild	70 (18.2%)	28	38	3.41 (1.51, 7.96)	0.004
Moderate	172 (44.8%)	84	72	10.28 (5.27, 21.43)	<0.001
Weight: <1249	106 (27.6%)	60	33	4.97 (2.62, 9.72)	<0.001
>=1249 (ref)	278 (72.4%)	67	199		
Gestation:<28 (ref)	10 (2.6%)	8	2		
28-32	261 (68.0%)	100	138	0.25 (0.03, 1.29)	0.12
>32	113 (29.4%)	19	92	0.81 (0.02, 1.02)	0.07

Temperature and weight were found to be significantly associated with persistent RDS at 5% significance level, p-values <0.05. Babies admitted with mild temperature were 3.41 times more likely to have persistent RDS compared to those with normal temperature after adjusting for weight and gestational age. The odds of persistent RDS for weights below 1249 grams were 4.98 the odds of weights of 1249 grams and above after adjusting for temperature and gestational age (table 17).

Table 18: Factors associated with intraventricular hemorrhage

Factor	Frequency (%)/ Median (IQR)	**Intraventricular haemorrhage**		Crude OR (95% CI)	p-value
	N = 384	Yes N = 16	No (ref) N = 336		
Temperature: Normal (ref)	142 (37.0%)	0	136		
Mild	70 (18.2%)	3	62	NA	1.00
Moderate	172 (44.8%)	13	138	NA	1.00
Weight: <1249	106 (27.6%)	8	81	3.77 (1.20, 12.06)	0.02
>=1249 (ref)	278 (72.4%)	8	256		
Referral: No	251 (65.4%)	16	215	NA	1.00
Yes (ref)	133 (34.6%)	0	121		

After adjusting for temperature and referral status, only weight was found to be significantly associated with development of intraventricular haemorrhage, p-value 0.02 at 5% significance level. Babies admitted with weights <1249 grams were 3.77 times more likely to develop intraventricular haemorrhage compared to those with weights 1249 grams and above (table 18).

Objective 2: To determine the relationship between neonatal mortality and admission hypothermia within 7 days of admission among VLBW neonates admitted in KNH NBU.

Mortality levels among the study participants

Figure 5 shows that there was a survival rate of 83% within the first week of admission among the very low birth weight participants. The prevalence of mortality in this study was 17% (95% CI 14%, 21%).

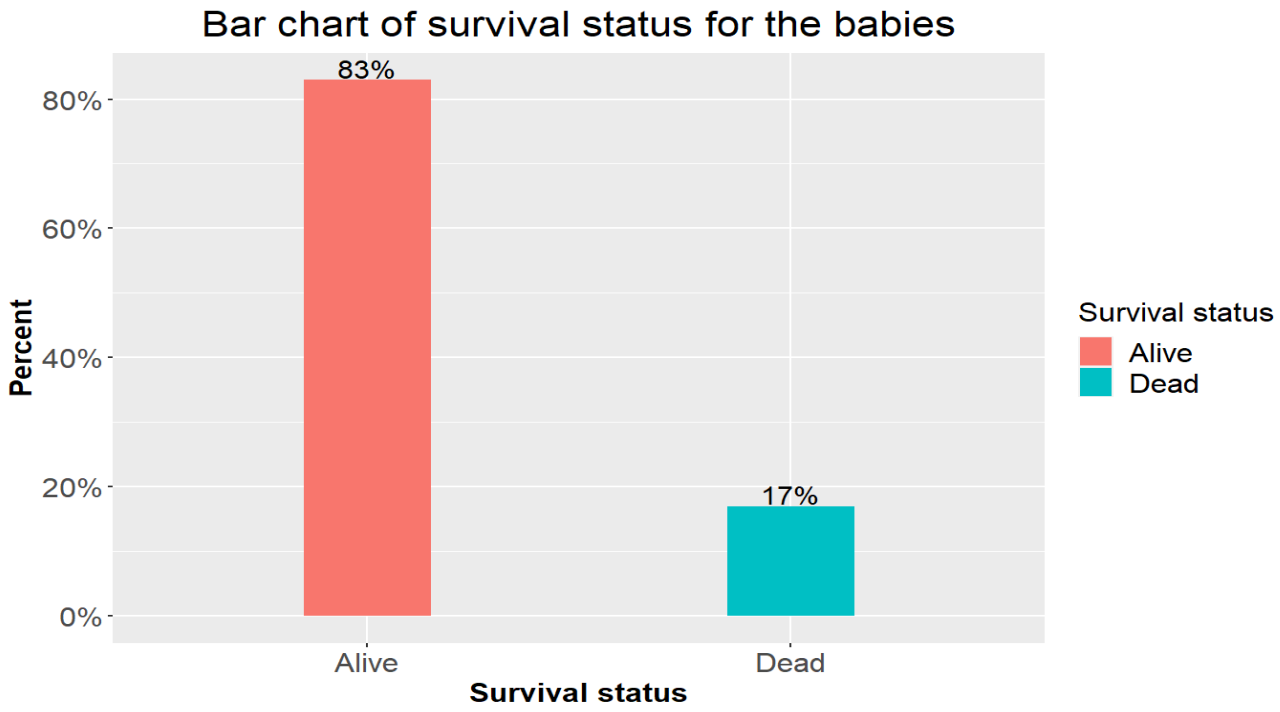


Figure 5: Survival status within the first 7 days of admission

Bivariate analysis

Association between temperature and survival within 7 days of admission

The density plot in figure 6 gives a comparison of survival status at different temperatures. It is clear that below 35.5 degrees Celsius, those who died were more than those who survived while above 35.5 degrees Celsius, those who survived were more than those who died. To test whether there was a significant association between temperature and mortality, a Wilcoxon test for independent samples was carried out to compare median temperature between those who died and those who survived. This test yielded a p-value < 0.01 at 0.05 significance level (figure 7). This result leads us to the conclusion that there was a statistically significant difference in admission temperature between those who died and those who survived within the first 7 days of admission among VLBW babies.

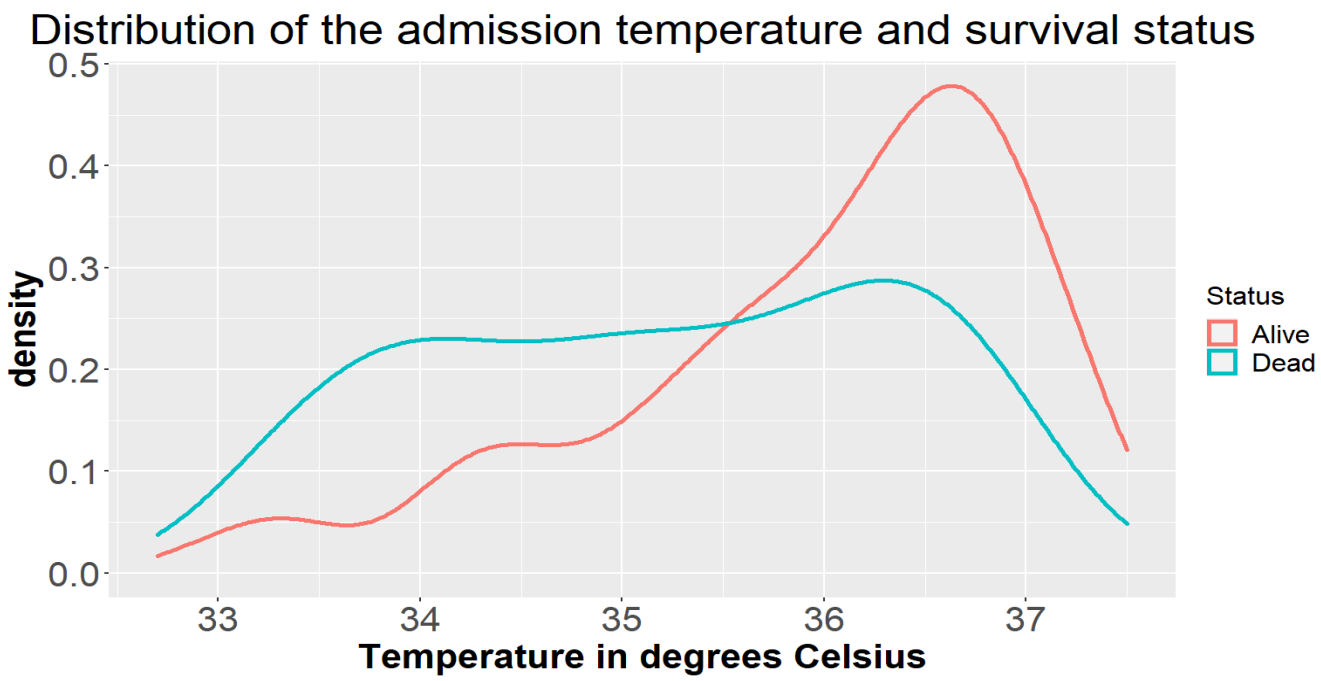


Figure 6: Density plot of temperature and survival within the first 7 days

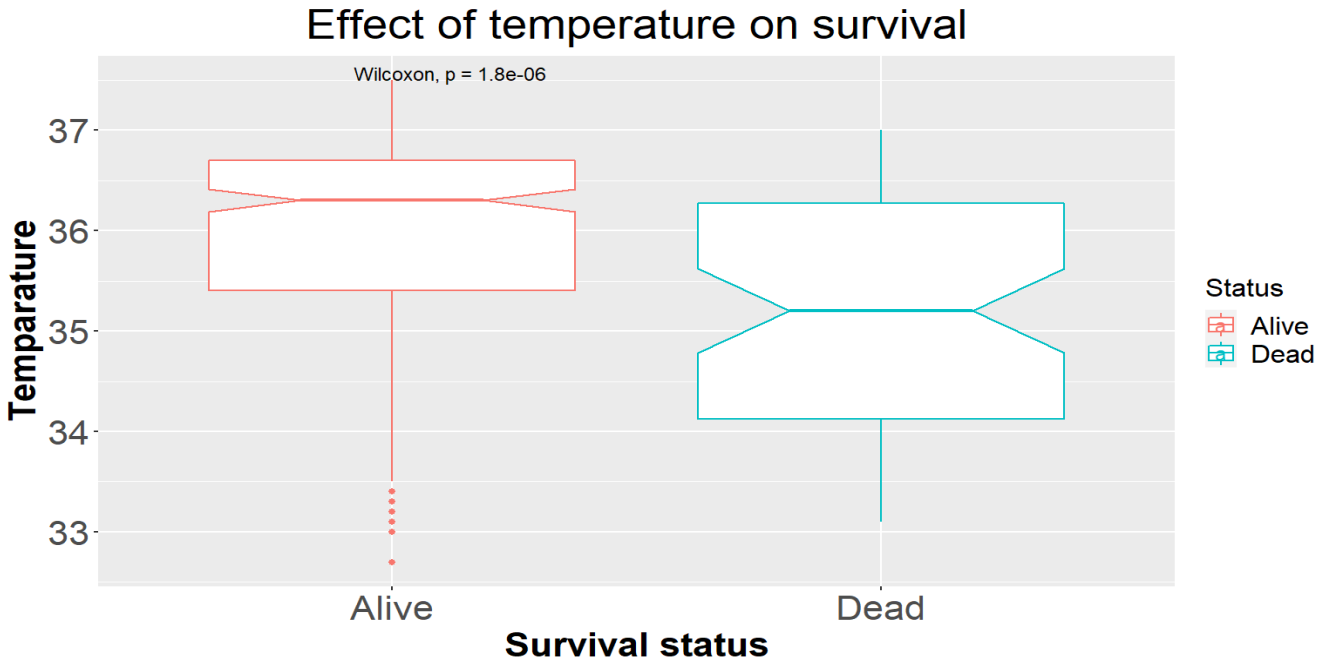


Figure 7: Boxplots showing effect of temperature on survival

Association between patient characteristics and mortality

This section examines the association between patient characteristics and survival status within the first seven days of admission. These patient factors are; age, weight, gestational age at birth, gender and whether patient was resuscitated or not.

Table 19: Patient factors associated with survival status within the first 7 days of admission

Factor	Survival N = 384			
	+Dead N = 66	Alive- (ref) N = 318	Crude odds ratios (95% CI)	p-value
Gender: Female	31	147	1.03 (0.61, 1.75)	0.91
Male (ref)	35	171		
Age: <=1 hour (ref)	33	159		
Above 1 hour	33	159	1.0 (0.59,1.71)	1.00
Weight (grams): >1249	35	243	0.35 (0.20, 0.60)	<0.01
>=1249 (ref)	31	75		
Resuscitated: Yes	14	23	3.45 (1.67, 7.14)	<0.01
No (ref)	52	295		
Gestation: <28 weeks (ref)	3	7		
28-32 weeks	55	206	0.62 (0.16, 2.48)	0.50
Above 32 weeks	8	105	0.18 (0.04,0.82)	0.01

From table 18 above, it is clear that weight and whether the patient was resuscitated were significantly associated with survival status within the first 7 days of admission p-values < 0.01 at 0.05 significance level. As for the gestational age, only the third level provided information on survival status.

Interpretation of odds ratios

Those babies who were born above 1249 grams were 65% less likely to die compared to those born with weights of between 1000-1249 grams OR 0.35 (95% CI 0.20, 0.60). The babies who underwent resuscitation were 3.45 times more likely to die compared to those who had not underwent resuscitation OR 3.45 (1.67, 7.14).

Babies who were born between 28- and 32-weeks' gestation were 38% less likely to die compared to those born below 28 weeks gestation. Those babies born above 32 weeks gestation were 82% less likely to die compared to those born below 28 weeks gestation.

Multivariable analysis

Under multivariable analysis, we focused on the variables that were significant under bivariate analysis. We fitted a binary logistic regression model to predict mortality using the significant independent variables from the bivariate analysis.

Table 20: Factors associated with survival within the first 7 days of NBU admission for VLBW infants

Factor	Survival			
	+Dead N = 66	Alive- (ref) N = 318	Adjusted odds ratios (95% CI)	p-value
Temperature: Normal (ref)	43	129		
Mild hypothermia	14	128	0.62 (0.23, 1.61)	0.33
Moderate hypothermia	9	61	2.01 (1.02, 4.15)	0.05
Weight (grams): >1249	35	243	0.37 (0.19, 0.70)	0.002
1000-1249 (ref)	31	75		
Resuscitated: Yes	14	23	3.17 (1.40, 7.01)	<0.01
No (ref)	52	295		
Gestational age: <28 weeks (ref)	3	7		
28-32 weeks	55	206	0.62 (0.12, 2.83)	0.50
Above 32 weeks	8	105	0.68 (0.12,4.52)	0.67

After adjusting for other factors, weight and resuscitation were found to be significantly associated with survival status within the first seven days of admission, p-values 0.002 and < 0.01 respectively at significance level 0.05.

Interpretation of odds ratio

Holding the other factors constant;

Babies who were admitted with moderate hypothermia were 2.01 times more likely to die compared to those who were admitted with normal temperatures. However, babies admitted with mild hypothermia showed lower odds for death compared to those with normal temperature; babies with mild hypothermia were 38% less likely to die compared to those admitted with normal temperatures.

The babies who were admitted with weights above 1249 grams were 63% less likely to die compared to those who weighed between 1000 and 1249 grams after adjusting for other factors. The odds of dying for the resuscitated babies were 3.17 times those who were not resuscitated.

The babies born between 28-32 weeks were 38% less likely to die compared to those born below 28 weeks gestation OR 0.62 (0.12, 2.83). Those born above 32 weeks gestation were 32% less likely to die compared to those born below 28 weeks gestation OR 0.68 (0.12,4.52) after adjusting for the other factors (table 20).

CHAPTER 5: DISCUSSION

5.1 Admission Hypothermia and associated comorbidities within 7 days of admission

This study revealed that admission hypothermia increased the risk of developing late onset neonatal sepsis (LONNS) by 11 times OR-11.35 (95% CI, 6.14, 20.96 p<0.01) among the very low birth weight neonates with in the first 7 days of admission. Consequently, moderate hypothermia increased the risk of LONNS by 19 times OR -19.3 (95% CI, 10, 36.8) while mild hypothermia at admission increased the risk four fold. This is consistent with the results in previous studies by Laptook et al (10), where there was reported increase in sepsis by 11% for each degree reduction in body temperature. Birth weight and referral status were among the other factors shown to increase LONNS. Neonates weighing <1249 g at birth, were more susceptible (p-0.02)to developing LONNS as compared to those weighing more than 1249g. Whereas, neonates referred shown an increased risk for developing LONNS (p-0.04) in comparison to those born in KNH. This could possibly be explained by exposure to pathogens during transportation. According to multivariate analysis, only hypothermia at admission was found significantly associated with LONNS (p<0.01).

Moreover, neonates with very low birth weight admitted with hypothermia were 13 times more likely to develop at least one episode of hypoglycemia within the first 7 days of admission (OR-13 p<0.01) as compared to those admitted with normal temperatures. Both mild and moderate hypothermia showed significant association with the development of hypoglycemia (p-0.04 and P<0.001 respectively). However, under multivariate analysis, only moderate hypothermia increased risk of hypoglycemia (p<0.001). Neonates with weight of <1249g and male, were more likely to develop hypoglycaemia (p< 0.01). Neonates with hypothermia have increased basal metabolic rates to generate heat. This exhausts glucose and glycogen stores leading to

hypoglycemia. In addition, neonates admitted with hypothermia are usually sicker than those with normal temperature leading to a delayed initiation of feeds which could result to hypoglycemia. This means that the hypothermia is more of an association than causal factor of hypoglycemia. The results align with findings of a study by Chia Saw et al (3)in Western Australia on risk factors of hypoglycemia and hypothermia in neonates that established that 49.5% of neonates with hypoglycemia had hypothermia.

Low temperatures at admission were not associated with development of NEC among very low birth weight neonates within first 7 days of admission (p-0.26). the results are consistent with the study by Laptook et al (10) and a study by Chang et al(26). However, gestation age was found to be associated with risk of development NEC with those born above 32 weeks gestation being 94% less likely to develop NEC as compared to those born >28 weeks gestation. This could be as a result of gut immaturity in those born in less than 28 weeks gestation.

Very low birth weight neonates admitted with hypothermia were 7 times more likely to have RDS persist to seven days post admission as compared to those who have normal temperatures at admission ($p< 0.01$). The results are higher in comparison to a study done by Chang et al (26) that revealed the risk of RDS requiring surfactant were 3 times in hypothermic neonates compared to normal thermic neonates. Hypothermia leads to reduced surfactant release which could worsen respiratory distress in VLBW neonates who already have low surfactant levels due to immaturity. VLBW neonates with weigh of <1249g were 4 times more likely to have persistent RDS as compared to those above 1249g weight OR- 3.62 (95% CI, 2.01, 6.64 $p<0.01$). The possible explanation is that those neonates who are less than 1249g are more premature and therefore have reduced surfactant levels.

Admission hypothermia was not found to be associated with the development of IVH within the first 7 days of admission. However babies with a weight of <1249g were 4 times more likely to develop IVH as compared to those weighing above 1249g (p-0.02).This is consistent with a study by Chang et al (11)that showed no significant increased risk of IVH in those with admission hypothermia. However, our findings are in contrast with a study by Miller et al(16) that showed increased risk of development of IVH in VLBW neonates with moderate admission hypothermia.

5.2 Admission Hypothermia and mortality within 7 days of admission

In this study 17% of the participants died within the first 7 days of admission. The neonates who had moderate hypothermia at admission were two times more likely to die more than those with normal temperatures (AOR 2.01). this is comparable to the study by Laptook et al(10) that showed an increased risk of death by 1.64fold for neonates with temperatures less than 36 ₀c. Also, a study done in KNH by Sharon (unpublished) showed a 2.34 fold increase in mortality among neonates admitted with hypothermia. The increased risk in neonates with hypothermia could be due to the fact that the neonates with hypothermia at admission tend to be sicker than those with normal temperatures.

Other factors associated with mortality were birth weight, gestation and resuscitation after birth. The neonates weighing >1249g at birth were 63% more likely to survive compared to those with birth weight of less than 1249g. Those resuscitated at birth were 3 times more likely to die than those not resuscitated (AOR-3.17). Neonates born at gestation more than 32 weeks were 82% likely to survive compared to those born at gestation less than 28 weeks.

5.3 Strength and Limitations of the study

Strength: There was easy availability of the data and files were easily retrieved from the records department.

Limitation: There was heavy reliance on the accuracy of the data that was already filled in the neonates' files. This poses a risk to measurement error especially on the temperatures abstracted from the medical records.

5.4 Conclusion

There is an association between hypothermia at admission with comorbidities: late onset neonatal sepsis, hypoglycemia and persistent RDS within the first 7 days after admission. There is no association between the admission hypothermia with NEC and IVH within the first 7 days after admission.

Moderate hypothermia is associated with increased risk of death among very low birth neonates within the first 7 days after admission.

5.5 Recommendations

Neonatal hypothermia is a major problem and should be considered as an admission diagnosis because of the increased risk of mortality among neonates with hypothermia at admission.

Neonates noted to have hypothermia at admission should be keenly monitored for comorbidities including late onset neonatal sepsis, hypoglycaemia and RDS.

Prevention of neonatal hypothermia should be emphasised to the members of staff in the new born unit, maternity theatre, labour ward and referring facilities. This can be done through regular training on warm chain management.

References

1. WHO | Pocket book of hospital care for children: Second edition [Internet]. [cited 2021 May 8]. Available from: https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/

2. Hypothermia in Neonates - Pediatrics - MSD Manual Professional Edition [Internet]. [cited 2021 Jun 14]. Available from: https://www.msdmanuals.com/professional/pediatrics/perinatal-problems/hypothermia-in-neonates

3. Saw C, Tan J, Srinivasjois R. Pediatrics & Therapeutics Risk Factors for Hypoglycaemia with Hypothermia in Neonates: An Audit in a Level II Special Care Nursery. Pediatr Ther. 2021;10(6):379.

4. Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants - UpToDate [Internet]. [cited 2021 Jun 14]. Available from: https://www.uptodate.com/contents/clinical-features-evaluation-and-diagnosis-of-sepsis-in-term-and-late-preterm-infants

5. Gregory KE, DeForge CE, Natale KM, Phillips M, Van Marter LJ. Necrotizing enterocolitis in the premature infant: Neonatal nursing assessment, disease pathogenesis, and clinical presentation. Adv Neonatal Care [Internet]. 2011 Jun [cited 2021 Jul 5];11(3):155–64. Available from: /pmc/articles/PMC3759524/

6. MINISTRY OF HEALTH REPUBLIC OF KENYA MINISTRY OF HEALTH 4th Edition. 2016

8. Nyandiko WM, Kiptoon P, Lubuya FA. Neonatal hypothermia and adherence to World

Health Organisation thermal care guidelines among newborns at Moi Teaching and Referral Hospital, Kenya. medRxiv. medRxiv; 2020.

9. Hypothermia in Neonates - Pediatrics - MSD Manual Professional Edition [Internet]. [cited 2021 May 8]. Available from: https://www.msdmanuals.com/professional/pediatrics/perinatal-problems/hypothermia-in-neonates

10. Laptook AR, Salhab W, Bhaskar B. Admission temperature of low birth weight infants: Predictors and associated morbidities. Pediatrics [Internet]. 2007 Mar [cited 2021 Jun 16];119(3). Available from: https://pubmed.ncbi.nlm.nih.gov/17296783/

11. Chang HY, Sung YH, Wang SM, Lung HL, Chang JH, Hsu CH, et al. Short- And long-term outcomes in very low birth weight infants with admission hypothermia. PLoS One [Internet]. 2015 Jul 20 [cited 2021 Jun 16];10(7). Available from: https://pubmed.ncbi.nlm.nih.gov/26193370/

12. Onalo R. Neonatal hypothermia in sub-Saharan Africa: A review. Niger J Clin Pract. 2013 Apr;16(2):129–38.

13. Urubuto F, Agaba F, Choi J, Dusabimana R, Teteli R, Kumwami M, et al. Prevalence, risk factors and outcomes of neonatal hypothermia at admission at a tertiary neonatal unit, Kigali, Rwanda–a cross-sectional study. J Matern Neonatal Med. 2019;

14. Forman KR, Diab Y, Wong ECC, Baumgart S, Luban NLC, Massaro AN. Coagulopathy in newborns with hypoxic ischemic encephalopathy (HIE) treated with therapeutic hypothermia: A retrospective case-control study. BMC Pediatr [Internet]. 2014 Nov 3 [cited 2021 Jun 16];14(1):1–6. Available from: http://www.biomedcentral.com/1471-

2431/14/277

15. Wolberg AS, Meng ZH, Monroe DM, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma - Inj Infect Crit Care [Internet]. 2004 [cited 2021 Jun 16];56(6):1221–8. Available from: https://pubmed.ncbi.nlm.nih.gov/15211129/

16. Miller SS, Lee HC, Gould JB. Hypothermia in very low birth weight infants: distribution, risk factors and outcomes. J Perinatol [Internet]. 2011 [cited 2021 Jul 5];31:49–56. Available from: www.nature.com/jp

17. Nonshivering Thermogenesis - an overview | ScienceDirect Topics [Internet]. [cited 2021 Jul 2]. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/nonshivering-thermogenesis

18. Soll RF. Heat loss prevention in neonates. J Perinatol. 2008;28:S57–9.

19. Oatley HK, Blencowe H, Lawn JE. The effect of coverings, including plastic bags and wraps, on mortality and morbidity in preterm and full-term neonates. Vol. 36, Journal of Perinatology. Nature Publishing Group; 2016. p. S82–8.

20. (7) Hypothermia at birth and its associated complications in newborns: A follow up study | Request PDF [Internet]. [cited 2021 Jun 16]. Available from: https://www.researchgate.net/publication/291842835_Hypothermia_at_birth_and_its_associated_complications_in_newborns_A_follow_up_study

21. Pal S, Curley A, Stanworth SJ. Interpretation of clotting tests in the neonate. [cited 2021 Jul 5]; Available from: http://fn.bmj.com/

22. Carns J, Kawaza K, Quinn MK, Miao Y, Guerra R, Molyneux E, et al. Impact of

hypothermia on implementation of CPAP for neonatal respiratory distress syndrome in a low-resource setting. PLoS One [Internet]. 2018 Mar 1 [cited 2021 Jun 16];13(3). Available from: /pmc/articles/PMC5854332/

23. Jensen C, Ebbesen F, Petersen J, Sørensen A, Henriksen T. PO-0742 Hypothermia A Risk Factor For Respiratory Distress Syndrome In Premature Infants? Arch Dis Child [Internet]. 2014 Oct 1 [cited 2021 Jun 16];99(Suppl 2):A498.1-A498. Available from: http://adc.bmj.com/

24. Mullany LC, Katz J, Khatry SK, LeClerq SC, Darmstadt GL, Tielsch JM. Risk of mortality associated with neonatal hypothermia in southern Nepal [Internet]. Vol. 164, Archives of Pediatrics and Adolescent Medicine. Arch Pediatr Adolesc Med; 2010 [cited 2021 Jun 16]. p. 650–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20603466/

25. Mullany LC. Neonatal hypothermia in low-resource settings. 2010;

26. Chang HY, Sung YH, Wang SM, Lung HL, Chang JH, Hsu CH, et al. Short- And long-term outcomes in very low birth weight infants with admission hypothermia. PLoS One [Internet]. 2015 Jul 20 [cited 2021 Jun 12];10(7):e0131976. Available from: https://doaj.org/article/51b76980295a4b769fededd7d246ab54

Appendix 1: Data abstraction tool

Neonatal hypothermia: Day seven outcome of VLBW neonates with hypothermia at admission in Kenyatta National Hospital New Born Unit.

Serial no: _____

A. <u>Clinical profile of study subjects.</u>

A. What was the admission temperature :

B. What was the age at admission in hours :

C. What was the gestational age at birth in weeks:

D. What was the birth weight in grams

E. What is gender of neonate : Male Female

F. What was the mode of delivery : SVD C/S

G. Where was the baby born : Inborn Outborn

H. What was the APGAR score : 1 minute 5 Minutes 10 Minutes

I. Was the baby resuscitated after delivery: YES NO

B. <u>What was the Diagnosis at admission.</u>

1. Respiratory Distress Syndrome(RDS)

2. Neonatal Sepsis(NNS)

3. Birth asphyxia

4. Other :

i) _____

ii) _____

C. Status at day 7 post admission:

Admitted Discharged Dead

D. What are the additional morbidities from admission to day seven of admission*

***include those neonates discharged or died before seven day of admission.

1. Hypoglycemia yes no

   If yes, lowest RBS (Mmol/l)

2. Late onset Neonatal sepsis YES NO
3. Necrotizing enterocolitis YES NO

4. RDS YES NO

5. Intraventricular Haemorrhage YES Grade_____ NO

6. Coagulopathy : PT APTT

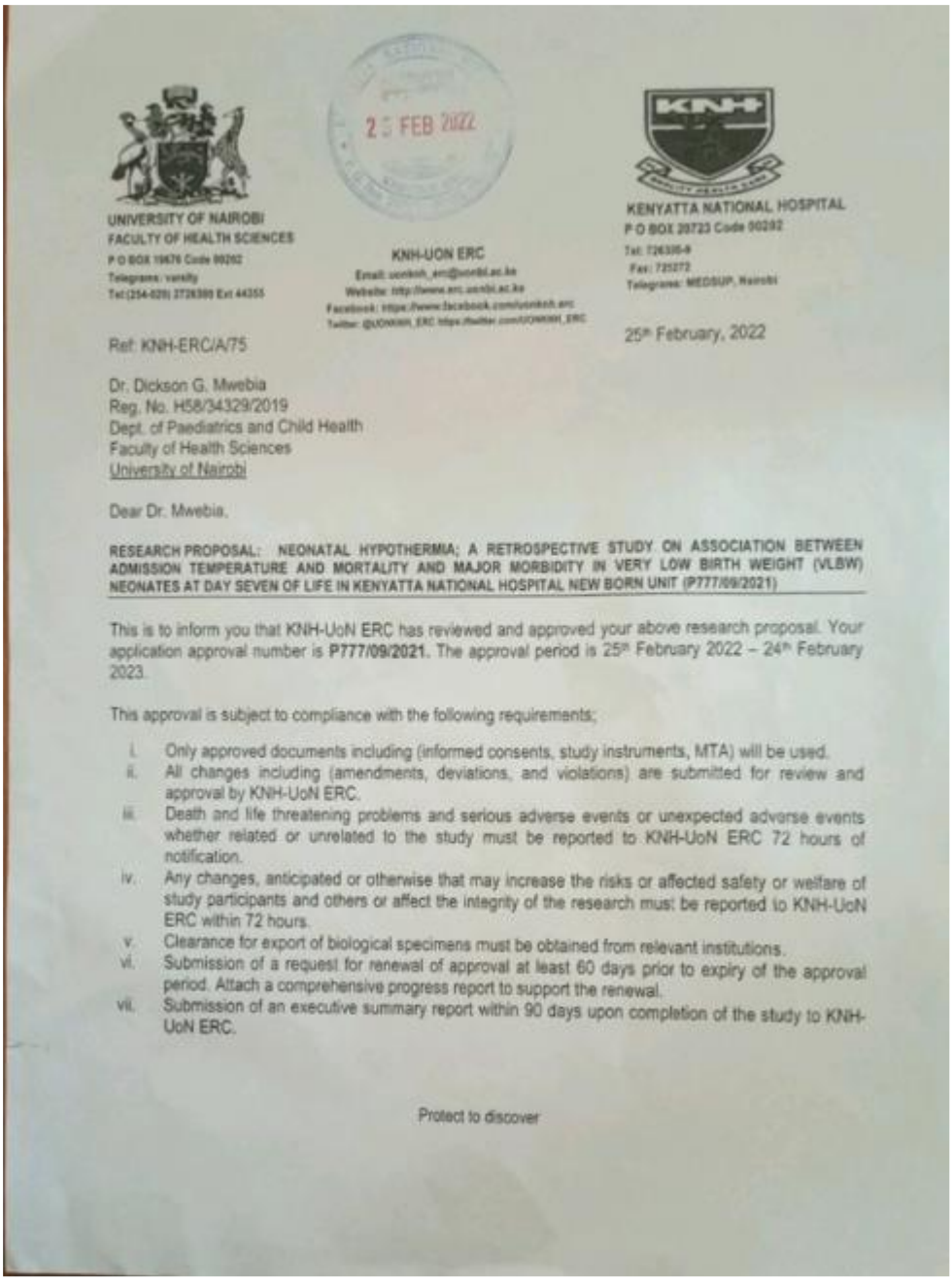
VLBW: birth weight:1000 - 1499grams

Appendix 2: Study Budget

ITEM	COST (Kshs)	NUMBER	TOTAL (kshs)
Pens	10	5	50
Printing of data abstraction tools.	10 per page	2×400×10	8,000
Statistical analyst			30,000
KNH ethics charges			2,000
KNH records charges			1,500
Printing of books		5	5,000
TOTAL			46,550

Source of funds: Personal savings.

Appendix 3: Approval letter



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Ref: KNH-ERC/A/75

25th February, 2022

Dr. Dickson G. Mwebia
Reg. No. H58/34329/2019
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

Dear Dr. Mwebia,

RESEARCH PROPOSAL: NEONATAL HYPOTHERMIA; A RETROSPECTIVE STUDY ON ASSOCIATION BETWEEN ADMISSION TEMPERATURE AND MORTALITY AND MAJOR MORBIDITY IN VERY LOW BIRTH WEIGHT (VLBW) NEONATES AT DAY SEVEN OF LIFE IN KENYATTA NATIONAL HOSPITAL NEW BORN UNIT (P777/09/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P777/09/2021**. The approval period is 25th February 2022 – 24th February 2023.

This approval is subject to compliance with the following requirements;

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

Protect to discover

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Paediatrics and Child Health, UoN
Supervisors: Dr. Bhupinder Reel, Dept. of Paediatrics and Child Health, UoN
Dr. Maugo Brian, Dept. of Paediatrics and Child Health, UoN

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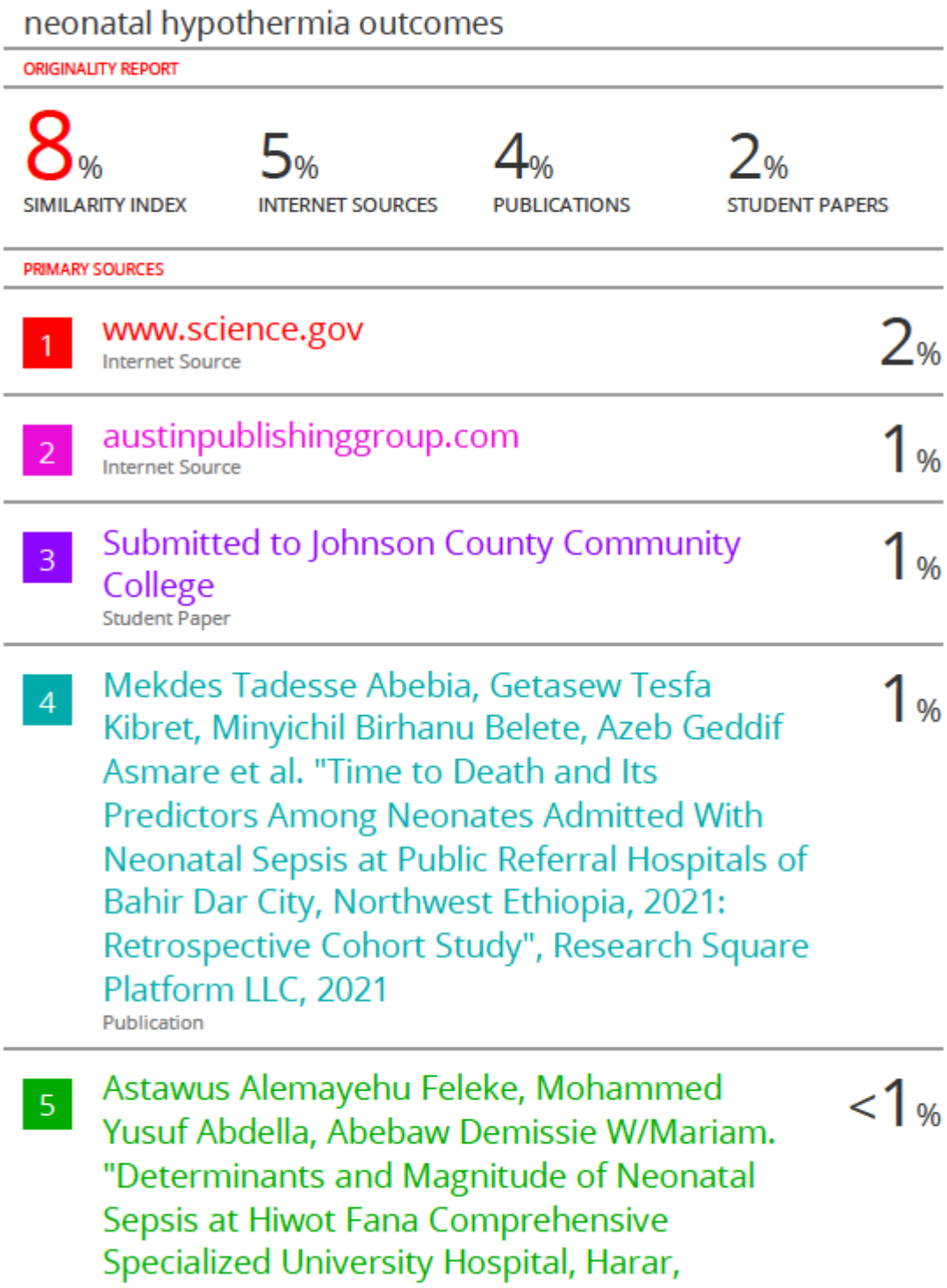
Appendix 4: Plagiarism Report



neonatal hypothermia outcomes

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