COLLEGE OF HEALTH SCIENCES
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DEPARTMENT OF PREVENTIVE MEDICINE
EPIDEMIOLOGY AND BIOSTATISTICS TRACK

ASSESSMENT OF ADMISSION HYPOTHERMIA AS A MARKER OF NEONATAL DEATH IN NEONATES ADMITTED TO NEONATAL INTENSIVE CARE UNIT OF HAWASSA REFERRAL HOSPITAL, ETHIOPIA

BY: TESFAHUN MULATU (BSc IN PUBLIC HEALTH)

ADVISORS: PROF. ALEMAYEHU WORKU (PROFESSOR, PhD IN BIOSTATISTICS)

MR. YIMER SEID (LECTURER, MPH IN EPIDEMIOLOGY AND BIOSTATISTICS)

A THESIS SUBMITTED TO GRADUATE STUDIES, ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF PUBLIC HEALTH, DEPARTMENT OF PREVENTIVE MEDICINE, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF PUBLIC HEALTH IN EPIDEMIOLOGY AND BIOSTATISTICS

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Acronyms

AAU: Addis Ababa University

AHR: Adjusted Hazard Ratio

CHR: Crude Hazard Ratio

CI: Confidence Interval

CPAP: Continuous Positive Airway Pressure

EDHS: Ethiopian Demographic and Health Survey

HMIS: Health Management Information System

HR: Hazard Ratio

HSTP: Health Sector Transformation Plan

KMC: Kangaroo Mother Care

NICU: Neonatal Intensive Care Unit

OR: Odds Ratio

PI: Principal Investigator

RR: Relative Risk

SDGs: Sustainable Development Goals

SNNPR: Southern Nations Nationalities and Peoples Region

SPH: School of Public Health

TTI: Tetanus Toxoid Injections

UN: United Nations

WHO: World Health Organization

Abstract

Background: It has been more than a century since the world recognized the necessity of warm environment for the care of the newborn unless which may lead to morbidity and mortality of the neonate. Even though there is change in the trend of neonatal mortality both globally and nationally, the change is not as such significant as child mortality that may tackle the achievement of global and national goal of reducing neonatal mortality. Studying the effect of hypothermia on neonatal death will help to provide an evidence for further clinical trials and programs that focus on revising management guideline in Neonatal Intensive Care Unit.

Methods Retrospective cohort study was conducted in Hawassa Referral Hospital. The study population was neonates who were admitted to Neonatal Intensive Care Unit and the study participants were selected by using simple random sampling technique from the record of neonates. Total sample size was determined to be 1062 and their records were reviewed. Proportional hazard assumption was checked, death rate was estimated, life table, Kaplan Meir survival curve and cox regression was used to estimate Hazard ratio. Statistical significance was declared by p value < 0.05.

Result: Out of 1010 (505 Hypothermic and 505 Normothermic) neonates 244 (24.16%) of them died and 766 (75.84%) were censored. Total follow up time was 4922 days for hypothermic and 4666 days for normothermic neonates. Death rate was 31 and 20 per 1000 neonates per day for hypothermic and normothermic neonates respectively. There was a significant difference in survival function between the two groups. Hypothermic neonates were 37% (AHR 1.37; CI 1.03, 1.82) more likely to die as compared to normothermic neonates. Clinical problems; respiratory distress (AHR 1.68; CI 1.22, 2.32), perinatal asphyxia (AHR 1.72; CI 1.12, 2.64) and congenital malformation (AHR 1.75; CI 1.22, 2.52) were statistically significant covariates for neonatal death.

Conclusion and Recommendation: Death rate in hypothermic neonates was significantly higher than normothermic neonates. Neonatal temperature should be monitored regularly and management for hypothermia needs evaluation, which should be supported by studies at community setting.

Keywords: Admission hypothermia, Neonatal death, Survival, Neonatal Intensive Care Unit

1. Introduction

1.1 Background

The world first recognized the necessity of warm environment for the care of low birth weight newborn in early 1900s and World Health Organization (WHO) in late 1900s developed the guideline for the prevention and management of hypothermia. It defined hypothermia as the drop of body temperature of the newborn below 36.5 ºC (97.7 ºF) and classified as mild (cold stress) between 36.0 and 36.4 ºC (96.8 – 97.5 ºF), moderate between 32.0 – 35.9 ºC (89.6 – 96.6 ºF) and below 32 ºC is severe hypothermia. Normal body temperature ranges from 36.5 to 37.5 ºC (1).

Neonatal mortality is the probability of dying within the first month of life and neonatal mortality rate is number of deaths during the first 28 completed days of life per 1000 live births in a given year or other period (2).

Neonatal mortality have a great impact on socioeconomic development and quality of life, which also takes a major part from mortalities in under five children. Global projection on child mortality revealed that 4·4 million under 5 children will die in 2030 and 60% of deaths will be in sub-Saharan Africa as compared to 50% in 2013 (3).

Hypothermia occurs when the body can no longer sustain normal core temperature by physiologic mechanisms such as vasoconstriction, shivering, muscle contraction, and non-shivering thermogenesis. When shivering ceases, the body is unable to maintain its core temperature; when the body core temperature falls below 35°C, the syndrome of hypothermia occurs (4).

Newborns are prone to develop hypothermia because of their larger surface area per unit body weight, decreased thermal insulation due to lack of subcutaneous fat (low birth weight infant) and reduced amount of brown fat (low birth weight infant) (5).

A newborn who developed neonatal hypothermia will become acidotic and hypoglycemic, have abnormal clotting and will be at increased risk of respiratory distress. Prolonged cold injury leads to edema, sclerema, general hemorrhage (especially pulmonary hemorrhage), jaundice, impaired cardiac function and impaired growth and death (6, 7).

1.2 Statement of the problem

Neonatal mortality took 34% of Under five deaths and more than half of infant mortality was in African region and from 1990 to 2015 under-five mortality rate declined by 56% whereas neonatal mortality rate decreased only by 38% in the region (2, 8). As the registration of vital events in Ethiopia is not well established throughout the country, studies conducted by survey shows that Neonatal mortality rate ranges from 27.5 to 62.5 per 1000 live births in different parts of the country (8-11).According to a study conducted in Gondar University teaching hospital in Ethiopia death of neonates in neonatal intensive care unit was 23.1% (12).

Predictors of neonatal mortality include low birth weight, preterm birth, infection, hypothermia, Shock, lethargy, maternal age below 18, unimmunized or uneducated mother (2, 13-16).

United Nations (UN) set a goal of achieving 12 deaths/1000 live births in 2030(8),WHO developed a guideline for management of hypothermia in NICU (1) and Ethiopia have been developing community-based newborn care, implementing integrated community case management of common childhood illnesses, and establishing newborn corners in Health centers, neonatal units in regional hospitals, and neonatal intensive care units in tertiary hospitals but they are not well established and equipped (17).

Despite of the efforts, awareness on the burden of hypothermia in sub-Saharan is still low (18) and the change in neonatal mortality is not as significant as child mortality (11). In the author's best knowledge, only few studies assessed the relation between admission hypothermia and neonatal morbidity and mortality (7, 15, 19-22) and none of them have assessed survival of neonates after admission to NICUs. Moreover, there was no study in the horn of Africa assessing the effect of hypothermia on death of neonates. In addition, there is controversies on the use of hypothermia for therapeutic purposes and on the range of temperature classification for hypothermia (7).

Therefore, despite of the routine care in Neonatal Intensive Care Unit (NICU) in the hospital this study will show the effect of hypothermia on death difference between hypothermic and normothermic neonates.

1.3 Significance of the study

Neonatal mortality contributes to more than half of the infant mortalities and one third of under-five mortality. Breaking this will lead to better child survival, but the trend globally (2) and nationally (11) showed that the change in neonatal mortality is slowest as compared to infant and child mortality. In addition, evidence based analysis revealed that prevention and management of hypothermia could reduce 18% - 42% of all cause neonatal mortality or morbidity globally (23).

According to the UN sustainable development goal (SDG) 3 target 3.2.1 the world setsto achieve the neonatal mortality rate of 12 per 1000 live births by 2030 (8). In line with this Ethiopia developed Health Sector Transformation Plan (HSTP) which aims to reduce neonatal mortality to 10/1000 live births by 2020 (24).

Realizing this global and national plan requires being aware of the burden, having an evidence and making the great effort to halt the effect.

Therefore, this study will help to evaluate the care in NICU and it will provide an evidence to governmental and non-governmental program developers and clinical researchers that may work on revising management guideline of hypothermia so that neonatal mortality will significantly decrease.

2. Literature review

2.1 Burden of Hypothermia

A systematic review on global burden of neonatal hypothermia showed that the prevalence of hypothermia in neonates born in hospitals and homes ranged from 32% to 85% and 11% to 92% respectively. This review also suggested that practices contributing to heat loss in the newborn were deeply rooted in many tropical countries and technologies adopted to resource-poor environments were not adequate. Even simple thermo-protective interventions and behaviors were not well practiced, providers and caretakers lack an understanding of the problem, and adverse health outcomes continued to take their role in morbidity and mortality in newborns (25).

Another review in sub-Saharan Africa stated that neonatal hypothermia has the major public health importance and poverty, home delivery, low birth weight, early bathing of babies, delayed initiation of breastfeeding and inadequate knowledge among health workers were the risk factors It also revealed that awareness of the burden of the condition in the region was low (18).

A community based prospective cohort study in Southern Nepal (7) indicated that 55.2% and 44.75% of babies had moderate or severe hypothermia respectively and the risk was higher in the first 1 to 3 days of life. Besides, for every 5ºC decrease in average ambient temperature the risk of moderate or severe hypothermia increased by 41.3% (95% CI, 40.0% - 42.7%) (26).

A hospital-based study in Pakistan showed that 58% of admitted cases of sepsis had normal temperature, 13.1% had hyperthermia, 13.4% had mild hypothermia and 15.5% had moderate hypothermia (16). In a study in Neonatal Care Unit of tertiary referral center and teaching hospital in Tanzania the prevalence of hypothermia was 22.4% and 13% of hypothermic neonates had severe hypothermia (27).The prevalence of hypothermia among newborns at Gondar University Teaching and Referral Hospital, was 69.8% (28).

2.2 Effects of hypothermia on neonatal morbidity and mortality

Dr. Richard Onalo in his review explained the pathophysiologic effects of neonatal hypothermia on changes in metabolism, serum electrolytes, respiratory system, cardiovascular system, gastrointestinal system, nervous system, blood, blood gases and kidneys (18).

A study on very low birth weight neonates showed that admission hypothermia was associated with severe intraventricular hemorrhage (22). In another study in Pakistan proportion of neonatal mortality was 6.1%, 32.6%, 33%, 11.6% in normothermic, mild hypothermic, moderate hypothermic and hyperthermic neonates respectively (16). Similarly a cohort study in Europe showed that admission temperature <35.5 ºC was associated with increased mortality at postnatal ages 1 to 6 days, (risk ratio 2.41; 95% CI 1.45-4.00), and 7 to 28 days (risk ratio 1.79; 1.15-2.78) but not after 28 days of age (29).

A study of neonates born before 33 weeks of gestation in Canadian NICUs revealed U-shaped relationships between admission temperature and a composite mortality/morbidity outcome. The range of temperature from 36.5°C to37.2°Cwas related with lowest rate of the outcome (30). Arenda Mank et al. studied neonates of 32 weeks of gestation and found neonates with hypothermia at admission had significantly lower temperature until 80 minutes after birth when compared to neonates without hypothermia at admission (31).

Another prospective cohort study on preterm infants in Brazil indicated that the incidence of hypothermia is higher in admission at NICU (51%) than 5 minutes after birth (44%) and they are strongly associated to each other, besides hypothermia at NICU admission increased the probability of early neonatal death by 64% (Relative Risk (RR) =1.64; CI: 1.03, 2.61) (32). A study in NICUs of Neonatal Research Networks indicated that for every 1°C decrease in admission temperature, the odds of late-onset sepsis were increased by 11% (OR: 1.11; CI: 1.02–1.20), and the odds of dying were increased by 28% (OR: 1.28; CI: 1.16–1.41) (33).

A community based cohort study in Southern Nepal that estimated the risk of mortality associated with Neonatal Hypothermia adjusted the estimates for the effect of age, ambient temperature and other potential confounders revealed RR of mortality among mild, moderate and severe hypothermia is 1.70, 4.66, and 23.36 respectively as compared to normothermic neonates. It also indicated that mortality increased by approximately 80% for every degree Celsius decrease in first observed axillary temperature and that relative risk of death ranged from 2 to 30 times within the current WHO classification for moderate hypothermia, increasing with greater severity of hypothermia (7).

A systematic review showed that case fatality rate for newborn hypothermia globally ranges from 8.5% to 52% (25). Retrospective cohort study in Guinea-Bissau, West Africa, by controlling low birth weight found hypothermia to be associated with a 4.81 times higher mortality from 0 to 7 days and 2.55 times increased mortality risk from 8 to 56 days after birth (34).

2.3 Management of Hypothermia

Retrospective analytic study comparing the effect of thermal control by exothermic mattresses, polythene bags or a traditional approach indicated that incidence of hypothermia was significantly lower in the mattress and bag group compared with the bag only group (difference = 43%, 95% CI 26, 69%), and the traditional care group (difference = 58%, 95% CI 26, 84%). However, a significantly greater proportion of babies in the bag and mattress group were hyperthermic, 27% (18, 36%) more compared with the traditional care and 24% (13, 34%) more compared with the bag only group and the median time to admission was longest in the 'bag and mattress' group (23 min). Exothermic mattresses can be used to reduce hypothermia during resuscitation and transfer of preterm babies, but with an increased risk of hyperthermia (35).

WHO recommends that baby must kept warm at the place of birth (home or hospital) and during transportation for special care. Adequate control demands both prevention of heat loss and promotion of heat gain by "warm chain" which is a set of ten interlinked procedures carried out at birth and later, which will minimize the likelihood of hypothermia in all newborns. It includes warm delivery room, warm resuscitation, immediate drying skin to skin contact between baby and mother, breastfeeding, bathing and weighing postponed, appropriate clothing and bedding, mother and baby together and warm transportation.

In addition to the above procedures WHO recommends the following methods for management of hypothermia. Generally, it is recommended to take axillary temperature than rectal temperature because of safety, hygiene and ease and besides if properly measured can be a good approximation of body core temperature. Monitor axillary temperature every ½ hour till it reaches 36.5 °C, then hourly for next 4 hours, 2 hourly for 12 hours thereafter and 3 hourly as a routine (5).

A systematic review and meta-analysis revealed that hypothermia can be used as a treatment for hypoxic-ischemic encephalopathy (36). International consensus statements based on randomized controlled trials recommended that hypothermia treatment for hypoxic ischemic encephalopathy

should be restricted to newborn infants who have evidence of moderate to severe encephalopathy 1-6 hour after birth and newborn infants who have evidence of peripartum asphyxia. It also revealed the contraindications for hypothermia treatment and which are birth weight < 1.8 kg, major (or suspected major) congenital abnormalities, overt bleeding (including sublingual hemorrhage) or if death is considered imminent (37).

2.4 Magnitude of Neonatal mortality

Globally 5.9 million children under 5 years of age died in 2015, with under-five mortality rate of 42.5 per 1000 live births. From which 45% were newborns, with a neonatal mortality rate of 19 per 1000 live births. Levels of child mortality are highest in sub-Saharan Africa, where 1 child in 12 dies before their 5thbirthday, followed by South Asia where 1 in 19 dies before age five. The rate of reduction annually in under-five mortality was 3.9% between 2000 and 2015, by this progress the global under-five mortality rate could be less than 25 under five deaths per 1000 live births by 2030 (8).

In Ethiopia a study, which reviewed Ethiopian Demographic and Health Survey (EDHS), showed that the neonatal mortality rate declined by 1.9% per annum from 1995 to 2010, logarithmically. The early neonatal mortality rate declined by 0.9% per annum and was where 74% of the neonatal deaths occurred (15). A study in Referral hospital neonatal unit showed that neonatal mortality was 10% (38).

According to EDHS 2016 under five mortality, infant mortality and neonatal mortality rate is 67, 48 and 29 deaths per 1000 live births respectively. This means 1 in 15 children dies before the age of 5 year, 1 in 21 children dies before the age of 1 year and 1 in 15 children dies with in the first month of life. The trend from 2000 to 2016 shows that there is 60%, 50%, 41% reduction in under five, infant and neonatal mortality respectively. Amhara region has the highest neonatal mortality (47 deaths/1000 live births) and Addis Ababa (18 deaths/1000 live births) has the lowest neonatal mortality rate whereas Southern Nations Nationalities and Peoples Region (SNNPR) has 35 deaths/1000 live births that is higher than the national average (11).

Target 3.2.1 and 3.2.2 of UN SDG 3 states to reduce neonatal mortality to at least as low as 12 per 1000 livebirths and under-5 mortality to at least as low as 25 per 1000 livebirths by 2030 (39). In

line with this Ethiopia aspires to achieve under five-year, infant and neonatal mortality rates 30, 20 and 10 per 1,000 live births respectively (24).

2.5 Predictors of neonatal mortality

WHO reported that major causes of neonatal mortality globally in 2015 were prematurity, birth-related complications (birth asphyxia) and neonatal sepsis, while leading causes of child death in the post-neonatal period were pneumonia, diarrhea, injuries and malaria (8).

A prospective study in teaching hospital of South India indicated that birth weight ≤ 1.5 kg, shock and lethargy were independent predictors of mortality in neonates admitted with culture proven neonatal sepsis (40). A retrospective study in Kenyatta National Hospital of Kenya point out that low birth weight, pneumonia, hypothermia are dehydration independent predictors of neonatal mortality (41).

In Ethiopia the major causes of under 5 mortality according to 2014 estimate of WHO were acute respiratory infection (18%), birth asphyxia (14%),premature births (11%), diarrhea (9%), sepsis (9%), meningitis (6%), injury (6%), measles (3%), and others (21%). The most common causes of neonatal deaths were prematurity (37%), infection (28%) and asphyxia (24%) (24). Assefa et al. conducted surveillance in a cohort of population that showed us more than 80% of deaths are a result of perinatal causes and bacterial sepsis is the leading specific cause of neonatal death followed by birth asphyxia, perinatal respiratory disorder and prematurity (9).

National survey shows that under-5 mortality is higher in rural areas than urban areas (83 versus 66 deaths/1000 live births) but neonatal mortality is higher in urban areas than rural areas (41 versus 38/1000 live births). Bio-demographic risk factors includes being a boy, shorter intervals between births, small or very small birth weight (11).

A review of EDHS from 1995 to 2010 showed that increased neonatal mortality risk was associated with male sex (hazard ratio (HR) = 1.38; 95% confidence interval (CI), 1.23 − 1.55); neonates born to mothers aged < 18 years (HR = 1.41; 95% CI, 1.15 − 1.72); and those born within 2 years of the preceding birth (HR = 2.19; 95% CI, 1.89 − 2.51). Winter birth increased the risk of dying compared with spring births (HR = 1.28; 95% CI, 1.08 − 1.51). Giving two Tetanus Toxoid Injections (TTI) to the mothers before childbirth decreased neonatal mortality risk (HR = 0.44;

95% CI, 0.36 − 0.54). Neonates born to women with secondary or higher schooling vs. no education had a lower risk of dying (HR = 0.68; 95% CI, 0.49 − 0.95) (15). Another systematic review reveled that delayed initiation of breast feeding decreases infant survival (42).

A study conducted in a teaching hospital of North West Ethiopia indicated highest case fatality rate in neonates with hyaline membrane disease and in very low birth weight neonates (43). Similar study in the area in 2016 revealed that prematurity, meningitis, hemorrhagic diseases, hyaline membrane disease, neonatal sepsis, meningitis, perinatal asphyxia, neonatal seizure, home delivery and meconium aspiration were factors that independently affects neonatal mortality (12).

Yaya Y. et al in 2014 showed that, neonatal mortality was 2.62 times higher in households with the poorest quartile compared to the richest, 3.54 times higher in households headed by illiterates compared to better educated, 2.45 times higher in mothers that had three or more births in five years compared to two or less in South west Ethiopia (44). Similarly, a population based nested case control study in 2017 point out that neonatal mortality declined with an increase in family size, neonates who were born among a family of more than two had lesser odds of death in the neonatal period than those who were born in a family of two in rural northern Ethiopia (45).

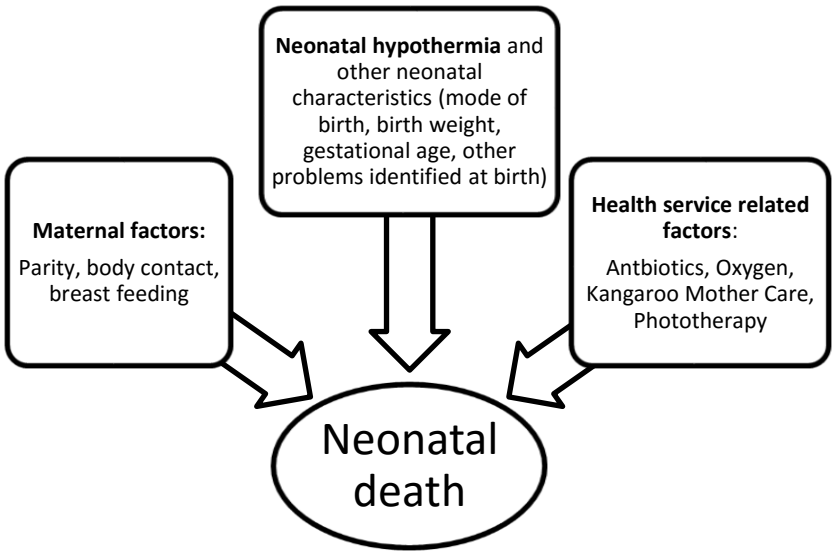

Figure 1: Modified framework from an Analytical Framework for the Study of Child Survival in Developing Countries by W. Henry Mosley and Lincoln C. Chen (*46*).

3. Research question

What is the effect of admission hypothermia on neonatal death in neonates admitted to neonatal intensive care unit?

4. Hypothesis

Death rate in neonates with admission hypothermia is higher than normothermic neonates.

5. Objective

5.1 General objective

To assess the effect of admission hypothermia on death of neonates who were admitted to NICU in Hawassa Referral Hospital

5.2 Specific objectives

To determine the incidence of death in neonates admitted with hypothermia

To determine the effect of hypothermia on survival of neonates

6. Methods

6.1 Study area and period

The study was conducted from Jan 20 to February 20, 2018 in Hawassa Referral Hospital, which is a teaching hospital of Hawassa University. It started providing services in 2006 and serving for about 15 million populations from all over SNNPR and neighboring region. Currently, it has over 400 beds in a broad range of services to over 90, 200 outpatient, 18, 116 hospitalized patients and 1,092 emergency cases annually. It offers services at general and specialty levels including Internal Medicine, Pediatrics and Child Health, neonatal intensive care unit (NICU), Surgery, Gynecology & Obstetrics, ENT (Ear, Nose and Throat), Neurology, Urology, Psychiatry, Ophthalmology, Dermatology, Dentistry, Radiology, Pathology, Laboratory and Pharmacy services. It is the first Hospital in South Ethiopia in starting special services like screening for diabetic retinopathy with Retinal Photo camera. The hospital has also launched other special services including Oncology Unit (initially for Breast Cancer), Intensive Care Unit (ICU) (47).

Ambient temperature of the study area was classified in to hot and cold months of the year by taking 23º C as a cut off environmental temperature depending on average annual temperature of Hawassa city (48) and neonates were classified accordingly based on the month of admission to the hospital.

6.1 Study design

Retrospective cohort study: exposure variable and outcome variable is admission hypothermia and time to death (the difference between day of admission and death) respectively which was reviewed from the record of the NICU. Both hypothermic and normothermic neonates was followed retrospectively, until their age of 28 days, for the time to death.

6.2 Source and study population

Neonates who were admitted to NICU in SNNP region were the source population and neonates admitted to NICU of Hawassa Referral Hospital in the last three years were study population.

6.3 Inclusion criteria

Neonates who were admitted in the last three years and had temperature measurement of < 37.5 ºC at admission were included in sampling.

6.4 Sample size determination and sampling technique

I. Sample size determination

There was no previous study conducted so far that assessed the incidence density in neonates admitted to NICU therefore sample size was calculated by using the proportion of death as the death is rare, proportion can be approximated to incidence density.

For objective one by assuming:

- Proportion of death in hypothermia: 11.6 % (16), margin of error: 3%, level of significance: 5%, power: 80%, 10% for incomplete records and calculated by using open epi v2 the final sample size is 421.

For objective two by assuming:

- Proportion of neonatal mortality in normothermic- 6.1% (16),
- RR of neonatal mortality in hypothermia as compared to normothermia-1.87 (7),
- 1 to 1 ratio of hypothermic to normothermic,
- 80% power and 5% level of significance.

By using Open epi v2 total adjusted sample size was 483 hypothermic and 483normothermic neonates and by considering 10% for incomplete records the final sample size was1062 (531 hypothermic and 531normothermic neonates).

Therefore, the sample size calculated for the second objective was larger and inclusive of the first one so that we have used sample size of the second objective (1062 neonates)

II. Sampling technique

Records of 2390 neonates whose recoding system was similar and who were admitted from January 1, 2015 to December 31, 2017 was reviewed and 789 (33%) of them were normothermic, 1004 (42%) of them were hypothermic and 597 (23%) of them were hyperthermic or had no temperature record. Depending on the sample size we needed (1062 neonates) from hypothermic (531 neonates) and normothermic (531 neonates) we have used simple random sampling technique by using list of admissions for each group and they were followed retrospectively until the time of death or censoring.

6.5 Variables

I. Dependent variable

- Neonatal Death

II. Independent variable

- Neonatal temperature at admission

Covariates:

- Neonatal conditions-age at admission, birth weight, gestational age, crying at birth and clinical problems at admission
- Maternal condition- parity, ANC follow up, mode of delivery and body contact
- Health related factors - treatment provided like KMC, antibiotics, phototherapy, oxygen

6.6 Operational definitions

Depending on WHO classification (1) the following operational definition was given for hypothermia

- Admission hypothermia-if recorded temperature is < 36.5 degree centigrade
- Mild hypothermia- if recorded temperature is from 36 to < 36.5 degree centigrade
- Moderate hypothermia- if admission temperature is from 32 to < 36 degree centigrade
- Severe hypothermia- if admission temperature is < 32 degree centigrade
- Admission normotheria- if admission temperature is ≥ 36.5 and < 37.5 degree centigrade

6.7 Data collection instrument and measurement

Data compilation form was used for collecting maternal information, neonatal characteristics & hospital care related factors that were extracted from HMIS (Health Management Information System) case registry of NICU.

- Event: death of neonates per days of admission
- Survival- lack of experience of death with in admission period
- Censored- neonates who were discharged with improvement or complications, self-discharged (loss to follow up), or transferred to other health institution (referred), age > 28 days while being followed.
- Entry time- the day of admission which was taken from the record
- Exit time - the day of death or censoring which was taken from the record
- Time to event (Period of follow up)- the difference between exit time and entry time

6.8 Data collection and quality control

The data compilation form was prepared based on NICU HMIS case registry of the hospital. As the record was written in English and data collectors can read and write English the tool was not translated to local language. The cutoff for classification of temperature was based on WHO recommendation which was proven to be used for evaluation of death (21).

Data collectors were two clinical midwifery students at Hawassa University. Two days training was provided on the contents and flow of data compilation form in order to avoid bias (misclassification) while extracting data from records. One supervisor (General practitioner) was assigned and crosschecked the record for omission and error daily and adjustment (editing or cleaning) was done before storage and analysis.

6.9 Data entry, analysis and processing

After data was entered and cleaned by Epi data v.4.2.0.0 software, it was exported to STATA v.14. Open epi v. 2.3 was used to calculate power of the study by considering the proportion of death in hypothermic and normothermic neonates.

Assumption for normality was checked for continuous covariates (temperature and age at admission) by using Shapiro-Wilk normality test and it was significant which means assumption of normality was violated for temperature and age so that we have reported the median and IQR (interquartile range) for those variables. Other descriptive including incidence density (for all variables), life table (for admission temperature), Kaplan Meir (for admission temperature and severity of hypothermia). X^2 test (for ambient environmental temperature), log-rank test (for admission temperature, severity of hypothermia, KMC and phototherapy) was used to test the difference between groups.

Crude HR was computed for all variables and interaction was assessed for preterm birth as it was significant in previous study (4, 7). Depending on p value (< 0.25) (49) in crude cox regression, clinical significance (age at admission, meconium aspiration, mode of delivery and number of ANC visits), consideration of collinearity (all treatments were removed because of collinearity with the clinical problems) and maximum number of covariates it is reasonable to enter (50); we adjusted for potential confounders by multivariable cox regression. Then proportional hazard assumption was checked by using global test (Schoenfield residuals) for the adjusted model.

6.10 Ethical consideration

The proposal was submitted to Research and Ethics committee of School of Public Health, College of Health Sciences, Addis Ababa University and following the approval by the committee it was submitted to Institutional Review Board (IRB) for obtaining approval and waiver of consent, as it is retrospective study. After which letter of cooperation was written by the School of Public Health to the concerned bodies. The raw data obtained have been secured and will not be accessed by anyone except the Principal investigator and personal identifiers was not been revealed to keep the confidentiality.

6.11 Dissemination of the results

The findings of the study will be submitted to the School of Public Health, AAU and it will be communicated to Hawassa Referral Hospital. For broader dissemination, the manuscript will be submitted to one of peer-reviewed journals for publication.

7 Results

7.1 Description of neonates in the cohort

Total number of neonates in the cohort were 1010 giving a response rate of 95.10% (4.90% incomplete records) and had total follow up (at risk) time of 9588 days. The power of the study was 98.77%. Half (505 neonates) of neonates in the cohort were hypothermic and the other half (505 neonates) were normothermic. From hypothermic neonates 188 (37.23%) had mild hypothermia out of which 34 (18.09%) were died, 314 (62.18%) had moderate hypothermia out of which 114 (36.31%) were died and 3 (0.59%) had severe hypothermia and all of them were died (Figure 1).

Hypothermic and normothermic neonates had 4922 and 4666 follow up time respectively. Median survival time for hypothermic and normothermic neonates was 24 and 28 days respectively and overall median survival time was 26 days. Quarter of neonates, 244 (24.16%), in the cohort were died and 3/4th of neonates, 766 (75.84%), were censored in the follow up period (Figure 1).

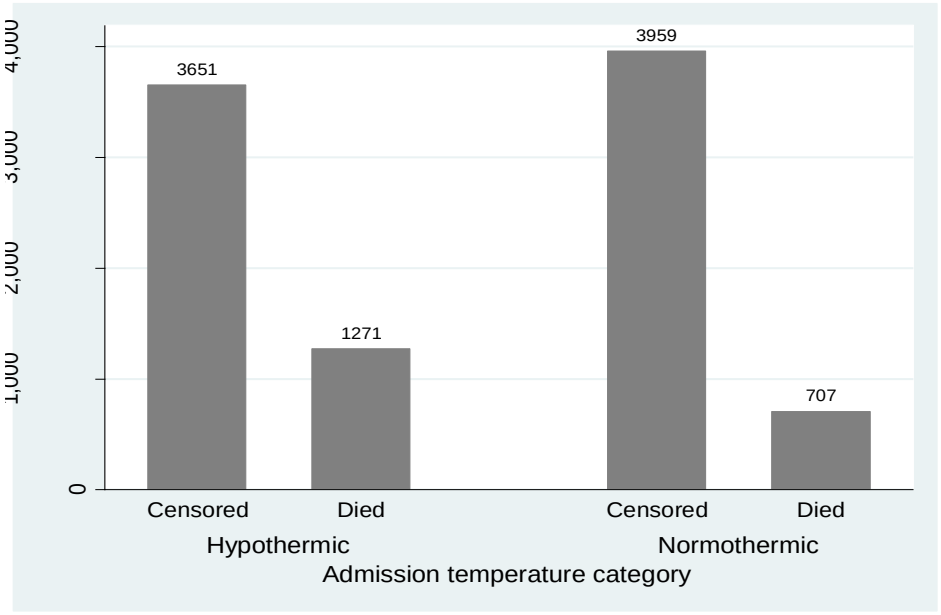

Figure 2: Total days of follow-up over temperature category and corresponding outcome status for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Median (IQR) admission temperature for all neonates was 36.45 ºC (1.40), for hypothermic 35.60 ºC (1.10) and for normothermic 37.00 ºC (0.90). Median admission temperature in February (36.35 ºC, IQR = 1.1) and March (36.50 ºC, IQR = 1.2). There was no statistically significant difference (P value 0.833) between neonates admitted in cold and hot months for being hypothermic or normothermic (Figure 2 and Table 1).

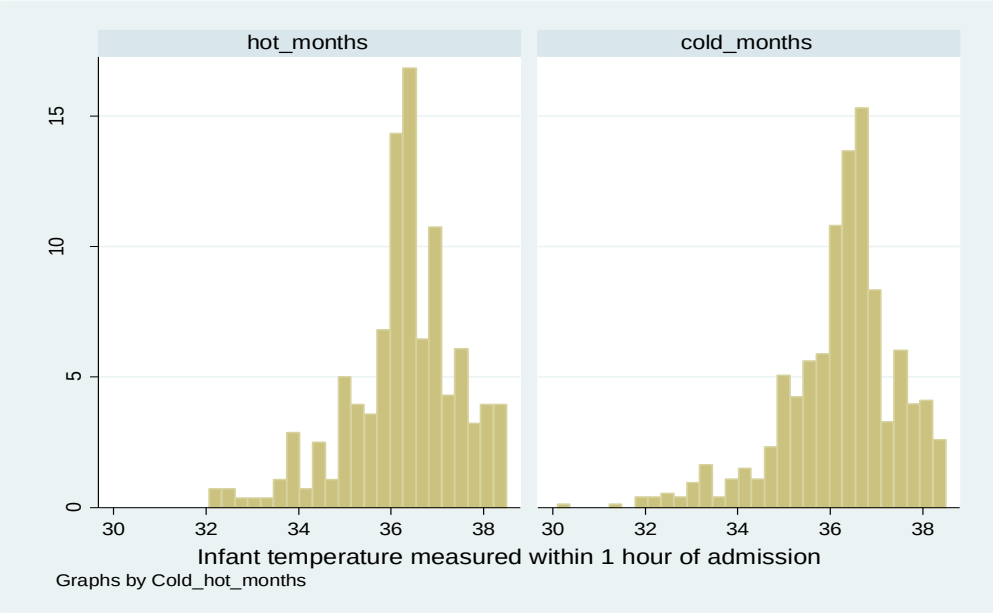

Figure 3 Ambient environmental temperature for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Table 1 : Admission temperature classification and ambient environmental temperature for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Season	Hypothermia N (%)	Normothermia N (%)	Total	P value [c]
Hot months [a]	141 (50.54)	138 (49.46)	279 (27.62)	0.833
Cold months [b]	364 (49.79)	367 0.21)	731 (72.38)	

a. Indicates neonates admitted in months (February, March, April and May) with average monthly environmental temperature of ≥ 23 ºC
b. Indicates neonates admitted in months (June, July, August, September, October, November, December and January) with average monthly environmental temperature of < 23 ºC
c. Chi^2 test at 1 df and 5% significance level

From the hypothermic neonates half of them, 254 (50.30%), were admitted at early neonatal period and had moderate/severe hypothermia whereas 50 (9.90%) were admitted at late neonatal period and had mild hypothermia (Figure 4).

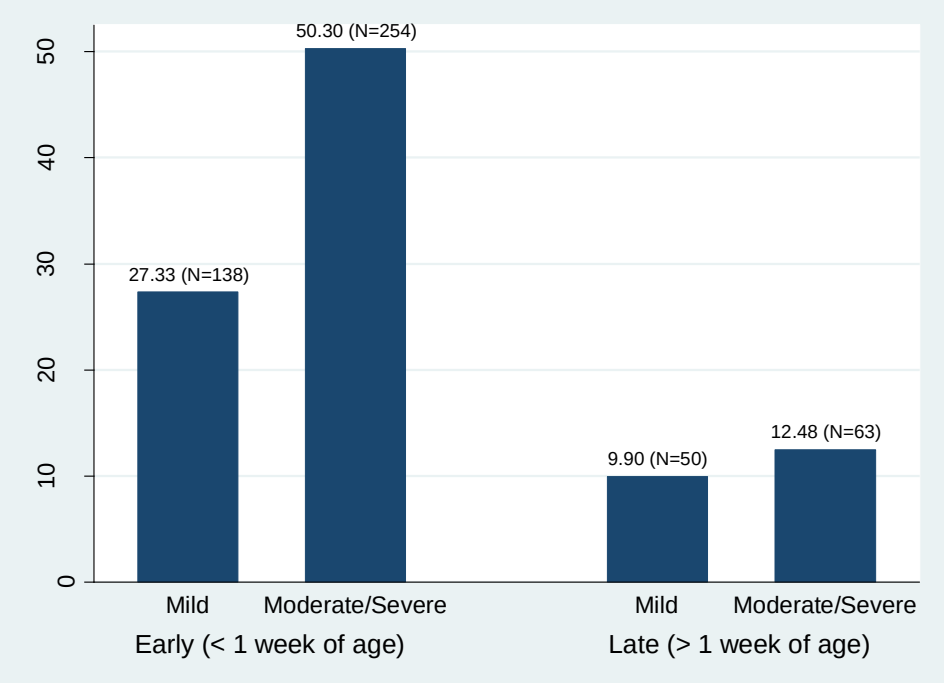

Figure 4: Severity of hypothermia by age of admission for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

In decreasing order the treatments provided for hypothermic neonates were antibiotics (36.12%), glucose (28.3%), oxygen (21.97%), KMC (7.91%), CPAP (2.37%), other treatment (2.37%) and blood transfusion (0.97%) and for normothermic neonates; antibiotics (44.58%), glucose (25.99%), oxygen (17.19%), KMC (4.73), other treatment (4.62%) and blood transfusion (1.72%) (Figure 5).

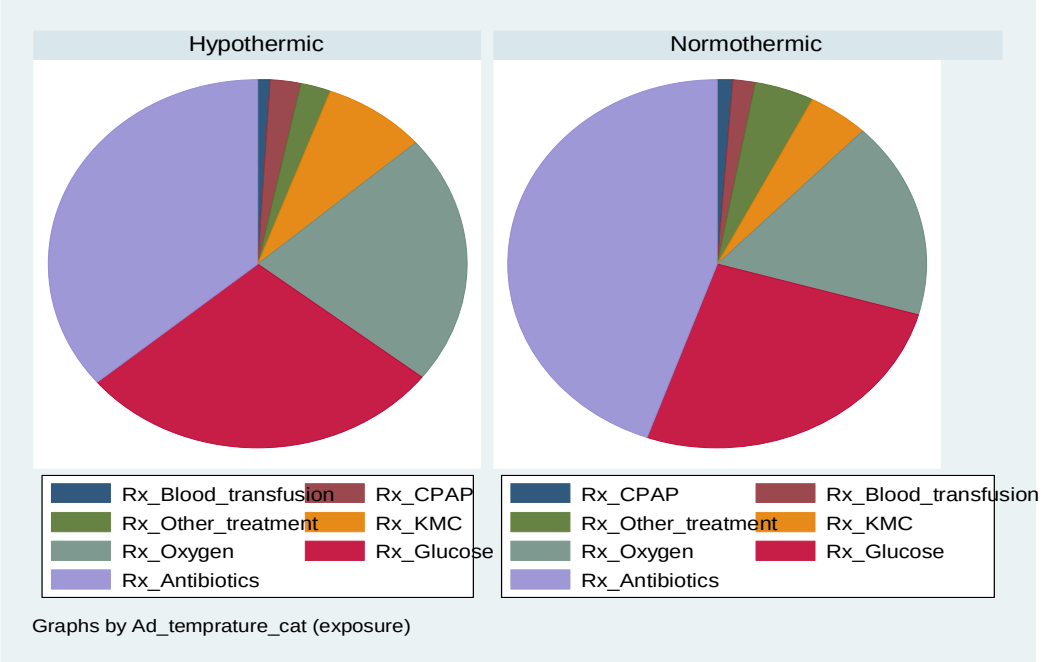

Figure 5: Proportion of each treatment provided for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

7.2 Incidence density for neonates in the cohort

Death rate for hypothermic neonates and normothermic neonates was 31 and 20 per 1000 neonates per day respectively. From the neonates in the cohort 649 (64.26%) were males and death rate for them were 25 per 1000 neonates per day whereas 27 deaths per 1000 neonates per day for females. Neonates admitted in the first seven days of life had death rate of 26 per 1000 neonates per day. Those neonates who did not breastfed had death rate of 102 per 1000 neonates per day but 26 deaths per 1000 neonates per day for neonates who started breast feeding with one hour of birth (Table 2).

Neonates who had birth weight of 1500 kg or less had death rate of 40 per 1000 neonates per day whereas those with more than 2500 kg had 20 deaths per 1000 neonates per day. Preterm (37 weeks of gestation) and term (≥ 37 weeks of gestation) neonates have death rates of 32 and 22 per 1000 neonates per day (Table 2).

From the maternal factors, grand multi parity (≥ 5 deliveries including the current one) and having less than four ANC visits had death rate of 38 and 26 deaths per 1000 neonates per day respectively (Table 2).

Table 2 : Incidence density by admission characteristics for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Admission Characteristics	Person time (in days)	Death	Rate (95% CI) per 1000
Admission temperature			
Hypothermic	4922	151	31 (26, 36)
Normothermic	4666	93	20 (16, 24)
Sex			
Male	6025	149	25 (21, 29)
Female	3563	95	27 (22, 33)
Age at admission			
< 1 week (Early)	7264	187	26 (22, 30)
> 1 week (Late)	2324	57	24 (19, 32)
Crying at birth			
Yes	8210	188	23 (20, 26)
No	1378	56	41 (31,53)
Multiple birth			
Yes	1867	48	26 (20, 34)
No	7721	196	25 (22, 30)
Breast feeding initiated			
< 1 hour	893	23	26 (17, 39)
1-2 hour	3499	56	16 (12, 21)
> 2 hours	4220	65	15 (12, 19)
Not at all	976	100	102 (84, 125)
Body contact with mother (for 1 hour)			
Yes	2896	57	20 (15, 25)
No	6692	187	28 (24, 32)
Mode of delivery			
Vaginal	7052	186	26 (23, 30)
C/S	2536	58	23 (18, 29)
Number of ANC visits			
≥ 4	2168	53	24 (19, 32)
< 4	7420	191	26 (22, 30)

Birth weight			
> 2500	5020	100	20 (16, 24)
2001 – 2500	1373	32	23 (16, 33)
1501 – 2000	1871	59	31 (24, 41)
< 1500	1324	53	40 (30, 52)
Gestational age			
< 37 weeks	3168	102	32 (26, 39)
≥ 37 weeks	6420	142	22 (19, 26)
Parity			
1	3911	98	25 (20, 30)
2 – 4	4481	101	22 (18, 27)
≥ 5	1196	45	38 (28, 50)
KMC for Hypothermia			
Yes	1481	23	15 (10, 23)
No	3441	128	37 (31, 44)
Phototherapy for jaundice			
Yes	1246	18	14 (9, 23)
No	155	5	32 (13, 77)

Death rate from jaundice, sepsis, anemia, meconium aspiration, congenital malformation, perinatal asphyxia and respiratory distress was 16, 21, 26, 35, 38, 40 and 41 per 1000 neonates per day respectively (Table 3).

Table 3: Incidence density by their clinical problems for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Clinical problems	Person time (in days)	Death	Rate (95% CI) per 1000
Jaundice	1401	23	16 (11, 24)
Suspected sepsis	4394	93	21 (17, 26)
Anemia	191	5	26 (11, 62)
Meconium aspiration	314	11	35 (19, 63)
Congenital malformation	1492	57	38 (29, 49)
Perinatal asphyxia	824	32	40 (27, 55)
Respiratory distress	1300	53	41 (31, 53)

7.3 Life table and Kaplan Meier survival estimate for neonates in the cohort

Median survival time for hypothermic and normothermic neonates was 24 and 28 days respectively and overall median survival time was 26 days. As the admission period increases survival in both groups decreases proportionally over time. Five hundred five neonates who were at risk for death in each group at the start of follow up decreases to 200 (hypothermic neonates) and 180 (normothermic neonates) at the 10^{th} day of follow up and only 70 (hypothermic neonates) and 51 (normothermic neonates) remained at the 20^{th} day of follow up. The probability of surviving up to one week of admission for hypothermic neonates was 83.16% whereas it was 87.79% for normothermic neonates (Table 4 and Figure 6).

Table 4: Life table showing survival of hypothermic and normothermic neonates by admission interval for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Days Interval		Neonates at risk	Deaths	Censored	Survival	SE	95% Conf. Int.	
							Lower	Upper
Hypothermic								
0	7	505	74	131	0.8316	0.0178	0.7932	0.8635
7	14	300	46	135	0.6671	0.0260	0.6133	0.7152
14	21	119	17	38	0.5537	0.0331	0.4864	0.6157
21	28	64	13	37	0.3955	0.0440	0.3094	0.4803
28	35	14	1	13	0.3428	0.0621	0.2249	0.4638
Normothermic								
0	7	505	52	158	0.8779	0.0159	0.8429	0.9056
7	14	295	26	161	0.7715	0.0240	0.7202	0.8146
14	21	108	7	54	0.7048	0.0326	0.6356	0.7634
21	28	47	5	33	0.5893	0.0545	0.4746	0.6871
28	35	9	3	6	0.2946	0.1233	0.0915	0.5356

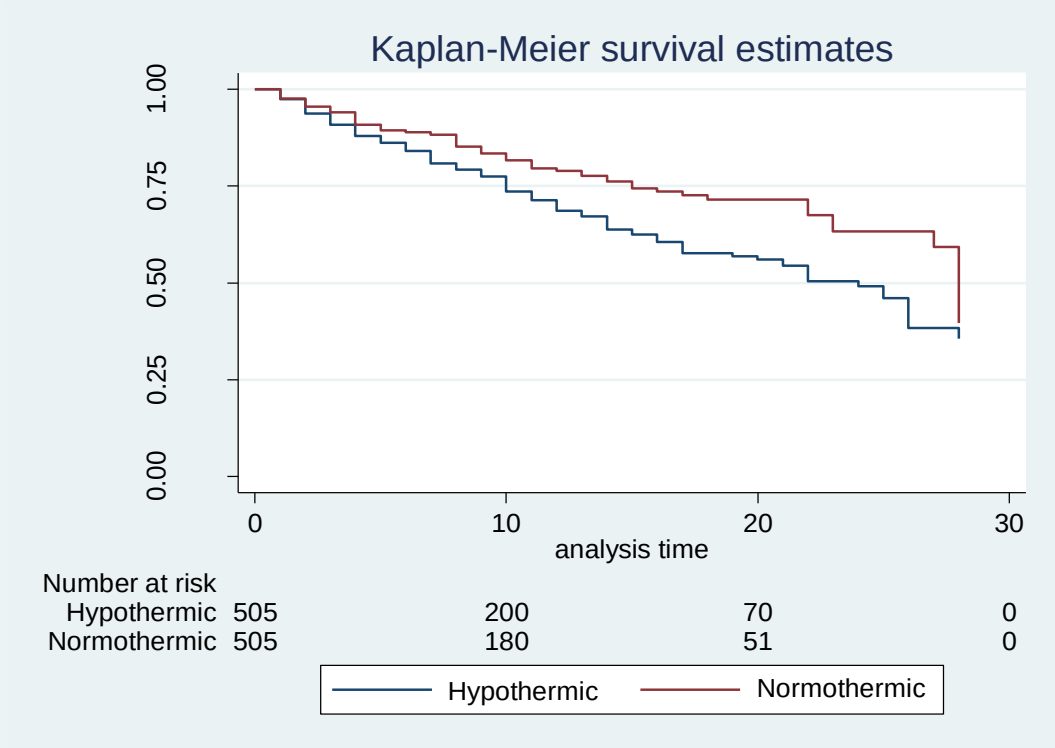

Figure 6: Survival function of hypothermic and normothermic neonates by their days of admission for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

The probability of surviving up to two weeks for hypothermic and normothermic neonates was 63.72% and 76.19% respectively. Among hypothermic neonates, the probability of surviving past one week of admission was 87.22% for mild hypothermic and 77.06% for moderate/severe hypothermic neonates (Figure 7).

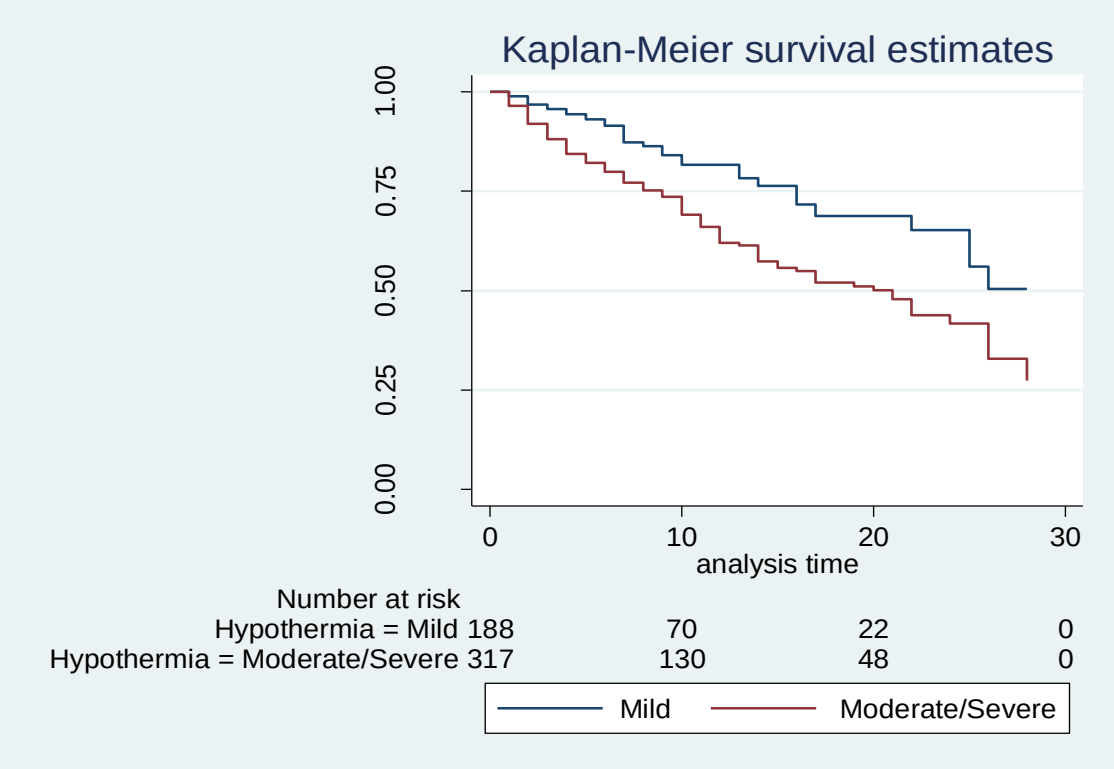

Figure 7: Survival function of mild and moderate/severe hypothermic neonates by their admission days in neonates admitted to NICU of Hawassa Referral Hospital, April 2018

7.4 Log rank test for neonates in the cohort

Log rank test for equality of survival function between hypothermic and normothermic neonates indicated significant difference (P value < 0.001); therefore, hypothermic neonates had significantly better survival than normothermic neonates did. Also mild and moderate/severe hypothermic neonates showed significant test (P value < 0.0001) for survival difference between two groups. Similarly, there is statistically significant survival difference (P value < 0.0001) between hypothermic neonates who received KMC and did not receive KMC. Whereas treatment with phototherapy did not bring statistically significant difference (P value < 0.092) in survival function of neonates (Table 5).

Table 5: Log-rank test for equality of survival function of neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Admission characteristics	Observed death	Expected death	X^2, 1 df	Log-rank test (Pr > X^2)
Hypothermic	151	125.79	10.86	0.001
Normothermic	93	118.21		
Mild hypothermia	34	54.98	13.05	0.000
Moderate/Severe	117	96.02		
KMC for hypothermia	23	46.18	18.46	0.000
No KMC for hypothermia	128	104.82		
Phototherapy for jaundice	18	20.50	2.83	0.092
No phototherapy for jaundice	15	2.50		

7.5 Cross tab and Bivariate cox regression output for neonates in the cohort

The median age at admission in days and IQR was 2 and 7 respectively. Majority, 756 (74.85%), of neonates were admitted on their early neonatal period and hypothermic neonates had 1.52 (1.18, 1.97) CHR as relative to normothermic neonates. More than half, 587 (58.12%), of neonates had normal birth weight and neonates who were less than 1500 kg had 2.06 (1.47, 2.89) CHR when compared to normal birth weight neonates. Preterm neonates were 274 (27.13%) and had 1.47 (1.14, 1.90) CHR than term neonates. Singletons were 818 (80.99%) and body contact with mother before one hour is protective with CHR of 0.70 (0.52, 0.95) (Table 6).

Majority, 888 (87.9%), of mothers had four or less parity and neonates whose mothers had five or more births had CHR of 1.51 (1.06, 2.16) as compared to neonates whose mothers had one birth. 142 (14.06%) neonates didn't breastfed and had 4.27 (2.71, 6.75) CHR than those who breast fed for less than one hour. Mothers with four or more ANC visits and Cesarean delivery was 248 (24.55%) and 291 (28.81%) respectively (Table 6).

Table 6 : Description of Admission characteristics by treatment outcome and their bivariate cox regression output for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Neonatal admission characteristics	Treatment outcome		Total (N=1010) N (%)	CHR(95% CI)	P Value
	Death (N=244) N (%)	Censored (N=766) N (%)			
Admission temperature					
Hypothermic	151 (29.90)	354 (70.10)	505 (50.00)	1.524 (1.177, 1.975)	0.001
Normothermic	93 (18.42)	412 (81.58)	505 (50.00)	1	
Age at admission					
< 1 week (Early)	187 (24.74)	569 (75.26)	756 (74.85)	1.054 (0.783, 1.418)	0.729
> 1 week (Late)	57 (22.44)	197 (77.56)	254 (25.15)	1	
Sex					
Male	149 (22.96)	500 (77.04)	649 (64.26)	1.067 (0.825, 1.381)	0.621
Female	95 (26.32)	266 (73.68)	361 (37.74)	1	
Birth weight					
> 2500	100 (17.04)	487 (82.96)	587 (58.12)	1	
2001 – 2500	32 (21.62)	116 (78.38)	148 (14.65)	1.191 (0.799, 1.773)	0.390
1501 – 2000	59 (34.10)	114 (65.90)	173 (17.13)	1.596 (1.155, 2.204)	0.005
< 1500	53 (51.96)	49 (48.04)	102 (10.10)	2.062 (1.473, 2.888)	0.000
Gestational age					
< 37 weeks	102 (37.23)	172 (62.77)	274 (27.13)	1.472 (1.139, 1.902)	0.003
≥ 37 weeks	142 (19.29)	594 (80.71)	736 (72.87)	1	
Multiple birth					
Yes	48 (25.00)	144 (75.00)	192 (19.01)	1.031 (0.751, 1.415)	0.848
No	196 (23.96)	622 (76.04)	818 (80.99)	1	
Maternal factors					
Parity					
1	98 (22.63)	335 (77.37)	433 (42.87)	1	
2 – 4	101 (22.20)	354 (77.80)	455 (45.05)	0.907 (0.687, 1.198)	0.492
≥ 5	45 (36.89)	77 (63.11)	122 (12.08)	1.515 (1.064, 2.158)	0.021
Breast feeding initiated					
< 1 hour	23 (25.00)	69 (75.00)	92 (9.11)	1	
1-2 hour	56 (15.47)	306 (84.53)	362 (35.84)	0.640 (0.393, 1.041)	0.072
> 2 hours	65 (15.70)	349 (84.30)	414 (40.99)	0.620 (0.385, 0.998)	0.049
Not at all	100 (70.42)	42 (29.58)	142 (14.06)	4.275 (2.706, 6.754)	0.000
Number of ANC visits					
≥ 4	53 (21.37)	196 (78.63)	248 (24.55)	1	
< 4	191 (25.07)	571 (74.93)	762 (75.45)	1.040 (0.766, 1.412)	0.802

Mode of delivery					
Vaginal	186 (25.87)	533 (74.13)	719 (71.19)	1	
C/S	58 (19.93)	233 (80.07)	291 (28.81)	0.881 (0.656, 1.184)	0.401
Body contact with mother					
Yes	57 (19.00)	243 (81.00)	300 (29.70)	0.704 (0.523, 0.948)	0.021
No	187 (26.34)	523 (73.66)	710 (70.30)	1	

Neonates with common clinical problems include sepsis 473 (46.83%), respiratory distress 145 (14.36), perinatal asphyxia 102 (10.10%), anemia 22 (2.18%), congenital malformation 127 (12.57%), meconium aspiration 39 (3.86%) and jaundice 162 (16.04%). In the bivariate cox regression neonates with respiratory distress and perinatal asphyxia had 1.75 and 1.64 CHR respectively as compared to those who didn't have the condition (Table 7).

Table 7 Clinical problems identified and their bivariate cox regression for neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Clinical problems at admission	Treatment outcome		Total N (%)	CHR(95% CI)	P Value
	Death N (%)	Censored N (%)			
Suspected sepsis					
Yes	93 (19.66)	380 (80.34)	473 (46.83)	0.725 (0.559, 0.934)	0.015
No	151 (28.12)	386 (71.88)	537 (53.17)	1	
Respiratory distress					
Yes	53 (36.55)	92 (63.45)	145 (14.36)	1.748 (1.289, 2.371)	0.000
No	191 (22.08)	674 (77.92)	865 (85.64)	1	
Perinatal asphyxia					
Yes	32 (31.37)	70 (68.63)	102 (10.10)	1.644 (1.132, 2.388)	0.009
No	212 (23.35)	696 (76.65)	908 (89.90)	1	
Anemia					
Yes	5 (22.73)	17 (77.27)	22 (2.18)	1.005 (0.414, 2.440)	0.991
No	239 (24.19)	749 (75.81)	988 (97.82)	1	
Congenital malformation					
Yes	57 (44.88)	70 (55.12)	127 (12.57)	1.627 (1.207, 2.195)	0.001
No	187 (21.18)	696 (78.82)	883 (87.43)	1	
Meconium aspiration					
Yes	11 (28.21)	28 (71.79)	39 (3.86)	1.430 (0.780, 2.622)	0.248
No	233 (24.00)	738 (76.00)	971 (96.14)	1	

7.6 Multivariable cox regression output for neonates in the cohort

Based on their significance level (p-value < 0.25) at bivariate cox regression analysis possible confounders for admission temperature which needs adjustment were age, not crying at birth, body contact with mother, all common clinical problems at admission, mode of delivery, ANC visit, birth weight, gestational age, breast feeding and parity. Variables related with the treatment received were not included in adjusted model because of higher correlation with the clinical problems identified. Effect modification was assessed for potential effect modifier (preterm birth) and was not statistically significant modifier (for interaction term HR 0.637; CI: 0.368, 1.107) so that it was not included in final adjusted model. In addition, global test was done for adjusted model and except breast-feeding all other variables satisfies proportional hazard assumption. After adjustment admission temperature, body contact with mother, respiratory distress, perinatal asphyxia, congenital malformation, breast-feeding and parity were significantly associated with neonatal death. The remaining variables like sepsis, jaundice, low birth weight and preterm birth have lost significance in adjusted cox regression.

Neonates with admission hypothermia were by 37% (AHR 1.37 CI: 1.03, 1.82) more likely to die as compared to normothermic neonates. Initiating body contact with mother within one hour of birth was protective of neonatal death by 31.6% (AHR 0.68 CI: 0.50, 0.93). From the clinical problems identified; respiratory distress had 1.68 AHR (1.22, 2.32), perinatal asphyxia had 1.72 AHR (1.12, 2.64) and congenital malformation had 1.75 AHR (1.27, 2.52). Neonates who did not breast fed at all were 3.29 times more likely to die than neonates who did start breast-feeding within one hour of birth (AHR 3.29 ; CI: 2.01, 5.40). Neonates for whom breast feeding was initiated with in one to two hours and after two hours were 46.3% (AHR 0.537; CI: 0.326, 0.883) and 46.1% (AHR 0.539; CI: 0.330, 0.883) less likely to die as compared to whom breast feeding was initiated within one hour of birth. Neonates of mothers who gave five or more births were 55.1% (AHR 1.55; CI: 1.07, 2.25) more likely to die than neonates of mothers who gave one birth only (Table 8).

Table 8: Multivariable Cox regression output and test of proportional hazard assumption for adjusted model in neonates admitted to NICU of Hawassa Referral Hospital, April 2018

Admission Characteristics	CHR (95% CI)	P Value	AHR (95%CI)	P value	P(PH)
Admission temperature					
Hypothermic	1.524 (1.177, 1.975)	0.001	**1.370 (1.032, 1.817)**	**0.029***	0.113
Normothermic	1 (base)		1 (base)		
Age at admission					
< 1 week (Early)	1.053 (0.783, 1.418)	0.729	0.760 (0.555, 1.041)	0.088	0.643
> 1 week (Late)	1 (base)		1 (base)		
Crying at birth					
Yes	1 (base)		1 (base)		
No	1.774 (1.316, 2.391)	0.000	1.230 (0.880, 1.720)	0.226	0.347
Body contact with mother (with in 1 hour)					
Yes	0.704 (0.523, 0.948)	0.021	**0.684 (0.500, 0.934)**	**0.017***	0.067
No	1 (base)		1 (base)		
Suspected sepsis					
Yes	0.725 (0.559, 0.934)	0.015	0.882 (0.668, 1.165)	0.377	0.662
No	1 (base)		1 (base)		
Respiratory distress					
Yes	1.748 (1.289, 2.371)	0.000	**1.683 (1.220, 2.325)**	**0.002***	0.323
No	1 (base)		1 (base)		
Perinatal asphyxia					
Yes	1.644 (1.132, 2.388)	0.009	**1.720 (1.119, 2.643)**	**0.013***	0.157
No	1 (base)		1 (base)		
Congenital malformation					
Yes	1.627 (1.207, 2.195)	0.001	**1.751 (1.216, 2.521)**	**0.003***	0.333
No	1 (base)		1 (base)		
Meconium aspiration					
Yes	1.430 (0.780, 2.622)	0.248	1.062 (0.560, 2.013)	0.854	0.510
No	1 (base)		1 (base)		
Jaundice					
Yes	0.607 (0.395, 0.933)	0.023	0.705 (0.452, 1.101)	0.125	0.197
No	1 (base)		1 (base)		
Mode of delivery					
Vaginal	1 (base)		1 (base)		
C/S	0.881 (0.656, 1.184)	0.401	0.876 (0.644, 1.193)	0.403	0.427
Number of ANC visits					
≥ 4	1 (base)		1 (base)		
< 4	1.040 (0.766, 1.412)	0.802	1.347 (0.980, 1.852)	0.066	0.443

Birth weight					
> 2500	1 (base)		1 (base)		
2001 – 2500	1.191 (0.799, 1.773)	0.390	1.005 (0.664, 1.522)	0.979	0.948
1501 – 2000	1.596 (1.155, 2.204)	0.005	1.460 (0.923, 2.310)	0.106	0.279
< 1500	2.062 (1.473, 2.888)	0.000	1.329 (0.763, 2.315)	0.316	0.794
Gestational age					
< 37 weeks	1.472 (1.139, 1.902)	0.003	1.090 (0.705, 1.686)	0.699	0.771
≥ 37 weeks	1 (base)		1 (base)		
Breast feeding initiated					
< 1 hour	1 (base)		**1 (base)**		
1-2 hour	0.640 (0.393, 1.041)	0.072	**0.537 (0.326, 0.883)**	**0.014***	0.093
> 2 hours	0.620 (0.385, 0.998)	0.049	**0.539 (0.330, 0.883)**	**0.014***	0.029
Not at all	4.275 (2.706, 6.754)	0.000	**3.297 (2.010, 5.407)**	**0.000***	0.432
Parity					
1	1 (base)		1 (base)		
2 – 4	0.907 (0.687, 1.198)	0.492	1.037 (0.775, 1.388)	0.805	0.758
≥ 5	1.515 (1.064, 2.158)	0.021	**1.551 (1.067, 2.254)**	**0.021**	0.777
Global test					**0.411**

P(PH) – Prob>X^2 global test for proportional-hazards assumption

8 Discussion

The assumption of linking hypothermia to neonatal death in our study is supported by a study (34) which have showed that excess mortality from hypothermia can extend beyond perinatal period up to 2 months of life. Even though there was a difference in environmental temperature at admission between months of a year, which affects body temperature of neonates (25, 26), there was no significant difference between cold and hot months in our study so that being hypothermic was not significantly affected by ambient environmental temperature.

In our study the median age at admission was 2 days and most of the admissions and deaths were at the early neonatal period of life as early neonatal period is associated with birth problems including hypothermia (9, 26, 29, 34). This might be related to their body structure and function which is not well developed, besides there might be birth traumas at the time of delivery.

The commonest treatment provided for the neonates during the admission period was antibiotics as majority of the admission problem was sepsis (46.83%) and KMC was provided more for hypothermic neonates than normothermic neonates, which is because low birth weight neonates had higher probability to be hypothermic (18) and an indication for KMC considers birth weight of $\leq$ 2000g (51).

We indicated that survival of neonates decreases proportionally as the admission period increases in both hypothermic and normothermic groups but not in the same rate. The median survival time is lower in hypothermic neonates (26 days) than normothermic (28 days) neonates which means normothermic neonates survive longer than hypothermic neonates so that death rate is higher in hypothermic neonates. At the starting point of follow up equal number of neonates (505 neonates) in each group were followed and the probability of surviving up to one week of admission was 0.83 in hypothermic and 0.88 in normothermic neonates.

Our study revealed death rate in hypothermic neonates is higher than normothemic neonates (31 versus 20 per 1000 neonates per day), the former is higher than national review (9). Neonatal hypothermia is associated with pathophysiologic changes in body system (18) which leads to intraventricular hemorrhage and death (22). Death rate in our study is higher than a study in Nepal (7) which is because of the difference in study setting, as our study was in hospitalized neonates the death could be higher than the community setting.

Our finding showed that more than one-third (37.23%) of hypothermic neonates were admitted with mild hypothermia and majority (62.18%) were admitted with moderate hypothermia and which is similar to a community-based study in southern Nepal (7). Unlike higher prevalence of severe hypothermia (13%) in a study in Dar-es-Salaam (27) there were only 3 neonates (0.59%) with severe hypothermia in the current study. The variation could be because of the difference in age at admission, as neonates in our study were elder and as age increases so does body temperature (26).

We found that neonates with vaginal and cesarean delivery had death rate of 26 and 23 respectively. The difference is very minimum and it might be ascribed to the inclusion of instrumental deliveries in vaginal deliveries so that it may overestimate the death rate. In addition, another study have showed that there was no significant difference in perinatal mortality between cesarean and vaginal delivery (52). All of neonates included in our study were admitted for one or more of the clinical problems from which respiratory problems (respiratory distress and perinatal asphyxia) led to death of 81 neonates per 1000 neonates per day which is one of the leading causes of death globally (8) and nationally (12, 24).

Our finding showed that there was significant difference in survival function of hypothermic and normothermic neonates (p value < 0.001 for log rank test) which was also supported by the regression after adjusting for confounders. Survival of moderate/severe hypothermic neonates was lower than those with mild hypothermia (0.77 versus 0.87) as death rate is higher in moderate/severe hypothermia which is expected as the severity of hypothermia increases the death rate would be higher (7, 30, 32).

Moreover, there was significant difference in survival of mild and moderate/severe hypothermic neonates (p value < 0.0001) for log-rank test. Even though our study did not show severity related effect by controlling for confounders there was significant difference in death for log rank test between mild and moderate/severe hypothermic neonates. This is due to the fact that physiology of hypothermic neonates would be altered and led to disturbance in metabolism, blood flow, renal function and nervous system which led to cascade of events that brought loss of cerebral functions as the body temperature decreases the progress to death would be higher (18, 22).

The test also revealed that providing KMC led to significant difference (p value < 0.0001) in survival function which is supported by the evidence that continuous KMC was associated with 40% reduction in mortality compared with conventional care (51) even though our study hadn't considered the type of KMC provided and an indication for it.

Admission temperature had significant effect on neonatal mortality; neonates with admission hypothermia were more likely to die by 37% than normothermic neonates after controlling for potential neonatal and maternal confounders. A systematic review showed that case fatality rate for newborn hypothermia globally ranges from 8.5% to 52% for which our study is within the range but our study was in neonates who were admitted for one or more clinical problems. A study in Brazil (32) have showed 64% increased mortality in hypothermic neonates admitted to NICU; the variation form our study could be ascribed to the difference in gestational age as they conducted only in preterm neonates which may overestimate the death rate. Another community-based study in Nepal (7) had showed that as the severity of hypothermia increased from mild to moderate the RR of mortality increased from 1.70 to 4.66.

From the clinical problems at admission; respiratory distress (AHR 1.68), perinatal asphyxia (AHR 1.72) and congenital malformation (AHR 1.75) were other significant predictors of neonatal mortality but the adjusted model did not consider their confounders, so that the interpretation for the significance of them did not necessarily to mean they were independent predictors of neonatal mortality. Similarly, maternal body contact (AHR 0.68), neonates for whom their mothers had five or more children (AHR 1.55) and neonates for whom breast feeding was not initiated (AHR 3.30) should be interpreted in similar fashion as the objective of the study was to identify the independent effect of hypothermia by controlling their effect but not vice versa.

A study on evidence based cost effective intervention (23) have showed that we can reduce 18% - 42% of all cause neonatal mortality or morbidity globally if we control hypothermia. Our study showed, still hypothermia have significant effect on neonatal death even though neonates on admission were supposed to be on treatment and we did not expect the difference in death to be significant. Moreover, admitted neonates may had additional medical problems which might be the primary diagnosis and reason for admission so that management might primarily focus for it and attention might not be given for managing hypothermia.

8.2 Limitation of the study

- We were unable to control the effect of radiant warmer, as the record was not available and adjustment was merely considers variables found on the record.
- Measurement of temperature was only based on single measurement record and also the instrument used, the person who took the measurement, the site and time of measurement taken might not be similar for all neonates, which may undifferentially bias the result.
- Even though the proportional hazard assumption was violated by variable related to breast-feeding we have incorporated in adjusted model, as including it outweigh removing the variable so that its interpretation should consider it.
- Neonates (normothermic neonates) who were used as comparison were admitted for some form of medical problems whom might not be the best comparison group.

9 Conclusion and Recommendation

9.2 Conclusion

Death rate in hypothermic neonates was higher than normothermic neonates and hypothermia was independent predictor of neonatal death that is unforeseen as neonates on admission were expected to be on management and there should not be significant difference between the two groups. Moreover, neonates with mild hypothermia had significantly better survival than neonates who had moderate /sever hypothermia.

9.3 Recommendation

The hospitals should undertake studies on evaluation of effectiveness of management applied for hypothermia in NICUs.

Health workers at NICUs should monitor temperature based on WHO recommendation and should manage accordingly.

Future researches should focus on studying the effect of hypothermia at the community setting.

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Annex I: Data compilation form

101	Date of birth (DD/MM/YY) in EC	____/____/_____
102	Date of admission (DD/MM/YY) in EC	____/____/_____
103	Date of discharge (DD/MM/YY) in EC	____/____/_____
104	Period of follow up in days	_____
105	Sex of the new born	1. Male 2. Female
106	Mode of birth	1. SVD 2. Assisted vaginal 3. C/S
107	Antenatal care visit	1. ≥ 4 2. 1 – 3 3. None
108	Did the new born cry/ breath at birth	1. Yes 2. No 3. Unknown
109	If not crying or breathing, did the new born receive bag and mask ventilation at birth	1. Yes 2. No 3. Unknown
110	Birth weight in grams	_____
111	Gestational age	_____
112	Multiple birth	1. Yes 2. No
113	If the baby was less than 2000 grams, did the baby receive KMC?	1. Yes 2. No 3. Unknown
114	Infant temperature measured within 1 hour of admission	_____º C
115	Was the baby treated with radiant warmer	1. Yes 2. No 3. Unknown
116	Breast feeding initiated	1. < 1 hour 2. 1-2 hours 3. > 2 hours 4. Not at all

117	Baby was put on abdomen after delivery for at least for one hour	1. Yes 2. No 3. Unknown
118	Treatment	1. Oxygen 2. KMC 3. Antibiotics 4. Glucose 5. Blood transfusion 6. Other _____
119	Was the baby treated with phototherapy machine for jaundice	1. Yes 2. No 3. Unknown
120	Problems identified at birth	1. Pre maturity 2. Suspected sepsis 3. Respiratory distress 4. Perinatal asphyxia 5. Anemia 6. Congenital malformation 7. Meconium aspiration 8. Jaundice 9. Other_____
121	Outcome	1. Improved 2. No change 3. Died 4. Referred 5. Other _____
122	If died cause of death	1. Prematurity 2. Infection 3. Asphyxia 4. Congenital malformation 5. Other _____

Annex II: Information Sheet for the head of the hospital

Description of the study

Title of the study: Assessment of admission hypothermia as a marker of neonatal mortality among neonates admitted to Neonatal Intensive Care Unit, Hawassa Referral Hospital, Ethiopia.

Objective of the study: To assess the effect of admission hypothermia on mortality of neonates who are admitted to NICU in Hawassa Referral Hospital

Introduction:

Hypothermia is common in newborns and associated with morbidities and mortalities of the new born. The problem is more common in developing countries but the care to the newborns are ill equipped. Neonatal mortality takes one third of under-five mortality and half of infant mortality. Although there is management guideline developed by WHO and different neonatal care related activities have been implemented nationally, neonatal mortality is not decreasing as planned.

Rationale of the Study and its benefits:

Realizing global and national plan of decreasing neonatal death requires being aware of the burden, having an evidence and making the great effort to halt the effect.

Therefore, this study will help to evaluate the care in NICU and it will provide an evidence to governmental and non-governmental program developers and clinical researchers that may work on revising management guideline of hypothermia so that neonatal mortality will significantly decrease.

Information which is necessary for the study will be taken from neonatal and maternal information sheet and case registry of the hospital. Therefore neonates and mothers will not be subjected to any harm as far as the confidentiality is kept. To keep the confidentiality of the patients, personal identifiers will not be included in the data collection format. For any questions about this study contact principal investigator Tesfahun Mulatu (Cell phone: +251945134863 or E-mail: tesfahunlucky@yahoo.com)

Annex III: Consent Form for the head of the hospital

My name is Tesfahun Mulatu, I am working a thesis in partial fulfilment of the requirements for the Degree of Masters of Public Health in Epidemiology and Biostatistics and for that I am here to collect a data from neonates who were admitted to NICU of your Hospital.

We believe that the findings of this study will be used as an evidence for decision making and reviewing management protocol in the NICU.

Information which is necessary for the study will be taken from information sheet and case registry of the hospital. As the study will be conducted through review of medical records alone, it will not harm participants as far as the confidentiality is kept. Name and other personal identifiers will not be recorded on data collection format and the information that is obtained will be kept confidential and will only be used for this study. You have full right not to let the information to be used for this study. But the information that would be taken will be quite useful for the study. If you have any questions about this study you may ask principal investigator:

Tesfahun Mulatu (Tel: +251945134863 or E-mail: tesfahunlucky@yahoo.com)

Are you willing to let the information to be used for this study?

1. Yes 2. No

Signature of the head of the hospital _____ Date _____

Approval

I, the undersigned, MPH student declare that this thesis is my original work in partial fulfillment of the requirement for the Master of Public Health in Epidemiology and Biostatistics.

Name of the student: Tesfahun Mulatu

Date._____ Signature _____

Approval of the primary advisor and examining board

This thesis work has been submitted with our approval as university advisor and examining board.

Name of the primary advisor: Prof. Alemayehu Worku

Date._____ Signature _____

Name of external examiner: Dr. Gizachew Jembere

Date._____ Signature _____

Name of internal examiner: Dr. Mulugeta Betre

Date._____ Signature _____