MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG PREMATURE NEONATES ADMITTED AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM- A PROSPECTIVE COHORT STUDY

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By

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A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **''*Mortality rate and associated risk factors among premature neonates at Muhimbili Hospital, Dar es Salaam., A prospective cohort study*'',** in (partial) fulfilment of the requirements for the degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

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Date

DECLARATION AND COPYRIGHT

I, **Anna Francis Magembe,** I declare that this **dissertation** is my original work and it has not been presented and shall not be presented to any other University for a similar or any other degree award.

Signature..... **Date**…….....

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Finally, I would like to say thanks to my family and my beloved children Hellen and Henry for their support and love during the entire time of my studies.

DEDICATION

This work is dedicated to my children Hellen and Henry

ABSTRACT

Background

Globally, it is estimated that 15 million (11.5%) babies are born before term each year, and of these, 1.1 million die within the first 28 days of life. Prematurity and its complications is an important cause of death during the first month of life, contributing to 35% of all neonatal death worldwide. In Tanzania, 27% of such deaths are secondary to complications of prematurity. According to World Health Organization (WHO) report of 2015, those who survive face a lifetime of disability, including learning disabilities, chronic lung disease (40%) visual problems (25%) and may have hearing problems (5-10%). There is little understanding of the rate and predictors of deaths among neonates who are born prematurely at Muhimbili National Hospital in Dar es Salaam.

Aim: To determine the mortality rate and associated factors among preterm neonates admitted at Muhimbili National Hospital.

Methods: A hospital based prospective cohort study was conducted from October 2018 and January 2019 where preterm neonates were recruited and followed up until 28 days of life. Information collected from mothers, patient records and physical examination of the preterm neonates was recorded in a data collection form. Univariate and multivariate analyses were used to determine and quantify the relationship between predictors associated with preterm mortality.

Results: A total of three hundred premature neonates of mean birth weight 1850gram ±670gram and gestational age 32 weeks ± 9.4 were recruited; 114 (27.7%) died giving an overall mortality rate of 10 deaths per1000 live preterm births. The leading causes of death were respiratory distress syndrome 59 (52%), septicaemia 25(47.2%), hemorrhagic disease of the new born and intraventricular haemorrhages 15(28.3%), aspiration pneumonia 14(12.3%), and metabolic disturbances6 (11.3%). Predictors for mortality were found to be presence of intracranial hemorrhage Hazard ratio (HR); 1.9, 95% CI (1.12, 3.25), respiratory distress syndrome, HR; 4.4, 95% CI (1.59, 12.6).

Neonates who needed suction HR; 4.2, 95% CI (2.29, 7.45) and presence of necrotising enterocolitis (NEC) HR; 4.7, 95% CI (1.75, 12.6) a raised CRP, HR; 2.5, 95% CI (1.3, 6.6) and an elevated serum creatinine HR; 4.3, 95% CI (1.3, 11.4),. On the other hand undergoing caesarean section delivery and receiving antenatal corticosteroid prior to delivery were associated with a 46% and a 43% reduced risk of mortality, HR; 0.54, 95% CI (0.32, 0.92), *p*=0.024 and HR; 0.57, 95% CI (0.36, 0.91), *p*=0.017, respectively

Conclusion: Preterm neonatal mortality rate is 10/1000 live preterm birth. Risk factors for preterm neonatal mortality include: presence of RDS and IVH; whilst caesarean section and ACS were found to be protective.

Recommendations: Stakeholders should ensure all mothers with impeding preterm delivery to receive antenatal corticosteroids and to undergo timely caesarean when indicated. Similarly, early screening and appropriate management of IVH and RDS in neonates should be done to reduce the risk of neonatal mortality

MUHTASARI

Utangulizi: Takwimu ulimwenguni zinaonesha kila mwaka watoto milioni 15 huzaliwa njiti na milioni moja hufariki ndani ya siku 28 zamaisha yao.Vifo vya watoto chini ya miaka mitano, asilimia 45% husababishwa na watoto chini ya mwezi mmoja, wakati kati yao 25% ni kutokana na matatizo ya mtoto kuzaliwa njiti. Tanzania 27% ya vifo vya watoto wachanga husababishwa na matatizo ya kuzaliwa njiti,na wanaosalia hupata matatizo kama ya mapafu (40%),kuona (25%),kusikia (5-10%).Kuna uhaba wa kutambua ukubwa wa tatizo, sababu hatarishi ziletazo vifo vya watoto niti katika eneo letu

Lengo la utafiti: Kutambua sababu za vifo vya watoto njiti waliolazwa katika hospitali ya taifa ya muhimbili kuanzia mwezi Octoba 2018 mpaka Januari 2019.

Mbinu: Uchunguzi ulifuatilia watoto wachanga waliozaliwa njiti waliolazwa hospitali ya taifa Muhimbili kati ya mwezi Oktoba 2018 hadi Januari 2019. Watoto wote waliokidhi vigezo vya kushiriki walikaribishwa kushiriki kwenye utafiti. Jumla ya watoto 300 walishiriki kwenye utafiti na kufuatiliwa toka siku walipolazwa hadi siku 28 za maisha yao au kifo. Vifo vilihesabiwa. Visababishi vya vifo vilibainishwa na mchango wake kwa kifo kutathiminiwa.

Ukokotoaji wa takwimu: Tulitumia mchanganuo mbali mbali kukokotoa takwimu. ikiwa namba za kujirudia, na asilimia katika kutoa taarifa za idadi za vifo na sababu za vifo. Tulitumia kiwango cha uwiano kutambua viashiria vya vifo vya watoto wachanga waliozaliwa njiti kwa kutumia SPSS 25

Matokeo: Vifo vya watoto wachanga njiti vilikuwa 10 kati ya watoto 1000 waliozaliwa njiti sawa na asilimia 27.7% ya watoto walioshiriki katika utafiti. Sababu kuu za vifo zilikuwa ni kushindwa kupumua kutokana na mapafu kutokomaa 59(53.1), maambukizi katika damu 25(47.2%),damu kuvuja na kuvilia katika ubongo 15(28.3%),kupaliwa kuletako homa ya mapafu 14(12.4%).Viashiria vya vifo vilivyobainishwa ni pamoja na ,mtoto kuwa na umri, uzito mdogo chini ya gramu 1000,kupata maksi chache wakati wa kuzaliwa hasa dakika ya 5,kupata shida kupumua, damu

kuvijia katika ubongo,wingi wa damu na chembe hai sahani kushuka,wakati kujifungua kwa upasuaji na mama kupata sindano ya kukomaza mapafu vilionekana kupunguza vifo hivi.

Hitimisho: Vifo vya watoto wachanga njiti ni 10/1000 watoto waliozaliwa njiti sawa na asilimia 27.7%.Kushindwa kupumua kwa mapafu kutokukomaa, damu kuvuja na kuvilia kwenye ubongo na maambukizi ya damu vinaongoza kwa kuuwa watoto njiti hasa katika siku 7 za mwanzo za maisha yao.Mama kutokupata sindano ya kukomaza mapafu ya mtoto, mtoto kuzaliwa umri na uzito mdogo, kupata maksi chache hasa dakika ya 5,ni miongoni wa viashiria vya vifo kwa watoto wachanga walio njiti

Mapendekezo: Kwa kutumia viashiria tajwa hapo juu yatubidi tuweze kutambua watoto njiti walio katika hatari ya kufa hasa siku za mwanzo na tuweze kuwaangalia kwa ukaribu na umakini wa huduma stahik.Ugunduzi wa mimba hatarishi ufanyike mapema na mama apewe rufaa kwa wakati, pia sindano ya kukomaza mapafu ya mtoto alieko tumboni

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LIST OF ABBREVIATIONS

ANC:	Antenatal clinic
APH:	Ante partum haemorrhage
CMR:	Cause specific mortality rate
CPAP:	Continuous positive airway pressure
ELBWT:	Extreme low birth weight
GA:	Gestational age
HIV:	Human immunodeficiency virus
IOR:	Inter quartile range
IVH:	Interventicular hemorrhage
LBW:	Low birth weight
MNH:	Muhimbili national hospital
MUHAS:	Muhimbili University of health and allied science
NEC:	Necrotizing enterocolitis
PPROM:	Preterm premature rupture of membrane
RDS:	Respiratory distress syndrome
ROM:	Rupture of membrane
SGA:	Small for gestational age
UTI:	Urinary tract infection
CRP:	C reactive protein

DEFINITION OF TERMS

Preterm neonate is a neonate being born alive but before completed 37 weeks of gestation.

Maternal hypertension: Maternal diagnosis of pregnancy induced hypertension or chronic hypertension.

Delivery room (DR) resuscitation was defined as when respiratory support was given, cardiac compression, or medication was administered during delivery.

Respiratory distress syndrome is a pulmonary disorder occurring in preterm neonates commonly <32 weeks gestation due to decrease in quantity and quality of pulmonary surfactant.

Very low birth weight when newborn birth weight >1000gm but <1500gm.

Extremely low birth weight when birth weight less than 1000gm.

WHO defines underlying cause as disease or injury that initiated the train of events leading directly to death or circumstance of the accident or violence, which produce the fatal injury (48)

The immediate cause of death was defined as a final disease or injury causing the death (49).

Preterm neonatal mortality rate was the probability of dying preterm neonate during the first 28 days of life, expressed per 1000 live preterm births (Number of preterm neonates died/Total live birth preterm in specific period time (1 month) times 1000.)

Preterm neonatal sepsis was defined when a neonate has at least three out of the following. Temperature instability (<36.5 and >37.5) Fast breathing (RR>60breath/min), unconscious or lethargic (no spontaneous movement),no feeding or feeding poorly after having fed well or intolerance to gastric feeds, seizures, with elevated C reactive protein, thrombocytosis or thrombocytopenia, leucopenia or leucocytosis ,Positive blood culture and presence of positive focus for infection(50)

Neonatal enterocolitis (NEC) was defined as (xii) plus abdominal distention, vomiting with or without bloody diarrhea.

Any episode of hypoglycemia, hypothermia was defined as presence of hypoglycemia, hypothermia respectively during the course of admission.

Any corticosteroid use to mother during pregnancy was defined as received corticosteroid

1.0 INTRODUCTION

1.1 Background

A preterm birth is when a baby is born alive before 37 completed weeks of gestation. Globally, preterm birth is a major clinical problem associated with significant mortality and morbidity in the neonatal period, the global concern about the burden of preterm birth has resulted in November 17th being earmarked as World Prematurity Day. In response to this threat, a goal to reduce preterm-specific mortality by 50% by 2025 globally has been set by the World Health Organization (WHO) (1-4)

1.2 Magnitude of the problem

Globally, among 135 million live births worldwide in 2013, about 15 million babies were born preterm, representing 11.1% of all live births. There is a dramatic survival gap for premature neonates depending on where they are born. Over 90% of extremely preterm babies (<28weeks) born in low-income countries die due to a lack of feasible, cost-effective care within the first few days of life; yet less than 10% of babies of this gestation die in high-income settings, a 10:90 survival gap. (5) Complications of preterm birth were the leading cause of death in children younger than 5 years of age globally in 2016, accounting for approximately 16% of all deaths, and 35% of deaths among newborn babies. (6)

South Asia and sub-Saharan Africa account for half of the world's births, more than 60% of the world's preterm babies and over 80% of the world's 1million deaths due to preterm birth complications. Around half of these babies are born at home. Even for those born in a health clinic or hospital, essential newborn care is often inadequate. (1-8)

Tanzania is making great strides in reducing child mortality, most of the decline has come after the first month of life and neonatal mortality has remained high. Each year, 51,000 newborns die in Tanzania, which places it to be among the top five countries with the most newborn deaths in sub-Saharan Africa with 27% deaths from complications of preterm birth. (9) According to WHO report of 2016, Tanzania has a neonatal mortality rate (NMR) of

21.7/1000 live birth while fighting to reduce the neonatal mortality rate to < 12per 1000 live births by 2030- 2035,

This could be achieved through identification of risk factors for preterm neonatal death as the neonatal mortality is largely contributed by preterm deaths.

1.3 Problem of statement

Muhimbili National Hospital (MNH) has approximately 570 births per month; 124 of these neonates are born preterm of whom 15% die. According to annual report of 2017 from Muhimbili National hospital (unpublished data), a total of 106 neonatal deaths occurred per month including both inborn and out born neonates, with 78.1% of deaths occurring within the first week of life. Prematurity is the leading cause of neonatal mortality (43%) followed by neonatal sepsis, birth asphyxia, hemorrhagic disease of the new born, and congenital anomalies.

Although there may be individual documentation on the cause of death among neonates in our setting, there is still inadequate analytical data on the cause and pattern of deaths in preterm neonates and associated risk factors for preterm neonatal death, hence making it difficult to tailor locally relevant interventions.

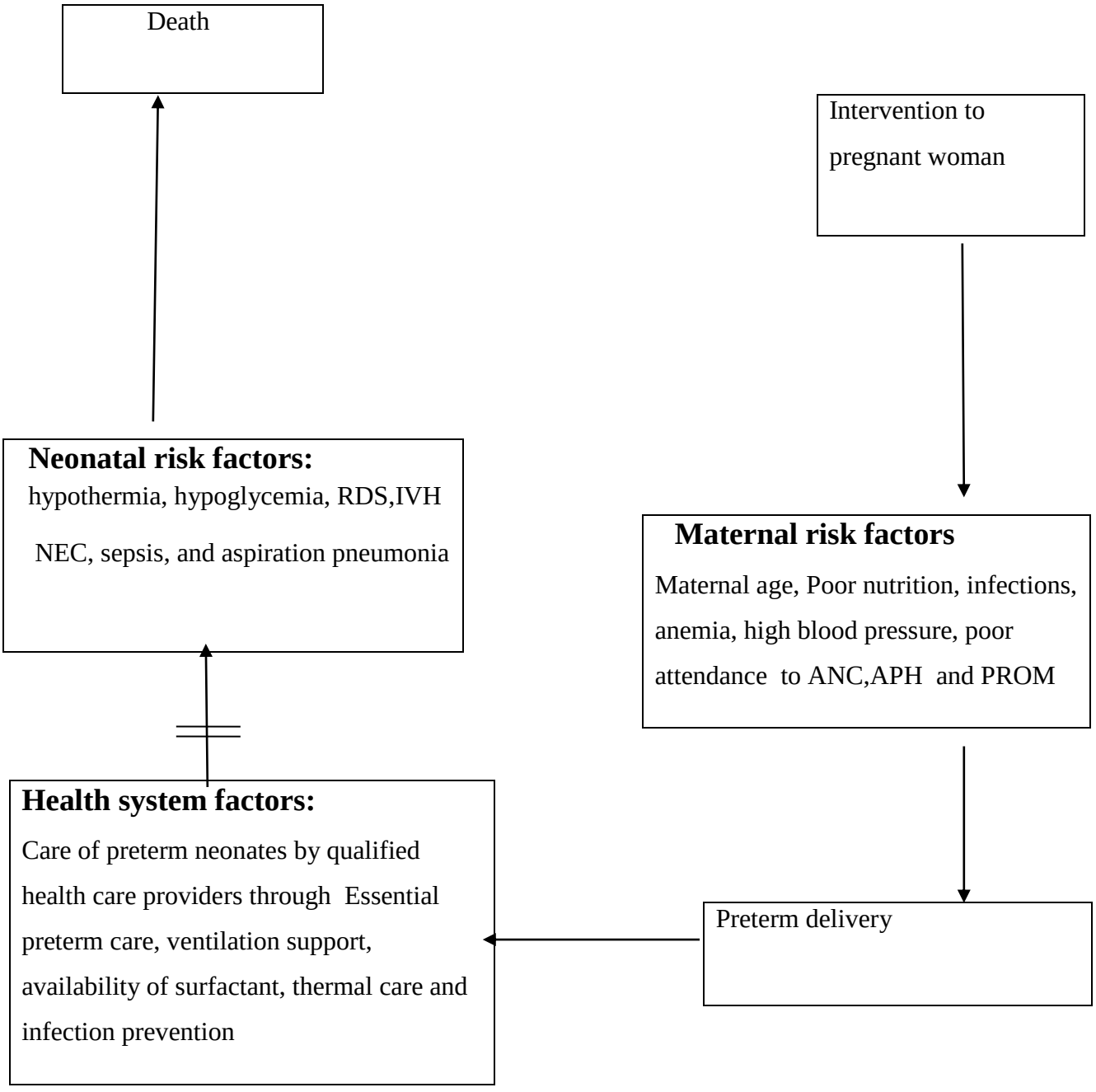
There are few studies conducted to assess the risk factors of neonatal mortality among preterm's in Tanzania. These studies focused in the first week of life and had small sample sizes. Hence in a tertiary setting like MNH it is crucial to conduct a study that will analyse the pattern and cause of death in preterm neonates during the entire neonatal period.

1.4 Rationale of the study

The findings of this study will help to create awareness on the causes and pattern of death among preterm neonates and will enable early identification of the risk factors (maternal, neonatal and health system factors) which may contribute to mortality during the neonatal period. This will help physicians in making locally appropriate interventions to reduce the mortality in preterm neonates.

1.5 Conceptual framework of risk factors for preterm delivery and mortality (Figure 1)

Poor maternal nutrition, poor attendance to antenatal clinic (ANC), antepartum hemorrhage (APH), and premature rupture of membrane (PROM**)** increases the risk of preterm delivery as well contribute to preterm mortality. Availability of adequate number of qualified health care providers will ensure a good and early preterm neonatal care to prevent preterm complications and preterm neonatal mortality is essential.



1.6 Research questions

1. What is the mortality rate among preterm neonates admitted at MNH?
2. What are the maternal risk factors associated with mortality among preterm neonates admitted at MNH?
3. What are the neonatal risk factors associated with mortality among preterm neonates admitted at MNH?
4. What are the health system factors associated with mortality among preterm neonates admitted at MNH**?**

1.7 Objectives

1.7.1 Broad objectives

To determine the mortality rate and associated risk factors among preterm neonates admitted at Muhimbili National Hospital.

1.7.2 Specific objectives

1. To determine mortality rate among preterm neonates admitted at Muhimbili National Hospital

2. To identify maternal risk factors associated with mortality among preterm neonates admitted at Muhimbili National Hospital

3. To identify neonatal risk factors associated with mortality among preterm neonates admitted at Muhimbili National Hospital

4. To identify health system factors associated with mortality among preterm neonates admitted at Muhimbili National Hospital

2.0 LITERATURE REVIEW

2.1 Preterm neonates mortality burden

Globally, preterm neonatal mortality rate is still high according to the WHO report of 2017 on the contribution of under 5 mortality the deaths due to prematurity were 878 per 100,000 live preterm neonates (11). A retrospective study done by Park *et al* in 2001-2005(period 1) and 2005 -2011(period ll) in Korea on Trends in Overall Mortality, and Timing and Cause of Death among Extremely Preterm with 382 preterm aged 23-26 weeks gestation found preterm neonatal mortality rate of 30.0% and 16.7% in period 1 and ll respectively(12). Majority of these deaths occur within the first 24 hours of life where by factors contributing to the increase in preterm mortality differs between the high and low income countries. In the former, advancement of medical facilities for the survival of the extreme premature below 28 weeks means that the risk of mortality is increased when managing extreme preterm babies, while in low income countries, this might be explained by the increase in hospital deliveries whereby more women are delivering in hospital with limited to services available (4-5, 12).

In sub-Saharan Africa preterm neonatal mortality is persistently high with an estimation of 300,000 among 9 million live preterm births each year with preterm complications contributing up to 25% of all neonatal deaths (13). A meta-analysis study done in East Africa by Marchant *et al* in 2012 to review contribution of low birth weight and prematurity in neonatal mortality, noted that 28% of neonatal mortality was associated with prematurity while 52% of neonatal mortality was associated with either being premature or low birth weight (14). While in Tanzania, 2009 situational analysis done by Manji *et al* showed 27% contribution of prematurity in neonatal mortality, hence the sustainable development goals (SDG 3) cannot be achieved without a substantial reduction in preterm mortality rate (PNMR) which has direct contribution to neonatal mortality rate (NMR)

2.2 Risk factors for mortality in preterm neonates:

Preterm neonates have immature organ systems that are not yet prepared to support life in the extra uterine environment. They are faced with complications which worsen with decrease in gestational age, reflecting the fragility and immaturity of the brain, lungs, immune system, kidneys, skin, eyes, and gastrointestinal system. The response of the infant's organ systems to the demands of the extra uterine environment and the life support provided also have an important impact on the infant's short and long-term health and neurodevelopment outcome. These outcomes are also influenced by the etiology of the preterm birth including: maternal and family risk factors; and the extra uterine environment including: hospital, home, and community care (15, 16).

2.2.1 Maternal factors for preterm mortality

2.2.1.1 Maternal age and level of education:

Maternal young age (<24 years) or advanced age (>35 years), poor maternal nutrition and illiteracy has been associated with high rate of preterm neonatal death. A nested cohort study of 10,745 participants done in rural Nepal by Sharma *et al* on young maternal age and risk of preterm mortality showed the lower the maternal age the higher the odds ratio of preterm mortality as from 12-15 years their preterm had 2 times risk of dying compared to preterm born to mothers aged20-24 years(17). Another prospective descriptive study of 100 participants done in Bugando Hospital in Western Tanzania by Mbawala *et al* in 2014 on factors associated with mortality in preterm neonates showed higher proportional of mortality to preterm neonates born to mothers with primary level of education compare to those with secondary level of education by 45.7% to 24.1% respectively(18).

2.2.1.2 Mode and place of delivery*:*

Mode and place of delivery has great impact on preterm neonates' outcomes, as home delivery increases risk of infection, and also lack of resuscitation equipments. Study done by Mbawala *et al* in 2014 on factors associated with mortality in preterm neonates showed that 53.5% of

premature babies who died were delivered through spontaneous vagina delivery while 19.5% for those delivered by caesarean section died (18).

2.2.1.3 Maternal anemia and hemorrhage:

Anemia or anterpaturm hemorrhage, are associated with preterm delivery with small for Gestation age (SGA) newborn, but also contributes to high mortality rate in these preterm neonates as most die due to early anemia of prematurity caused by inadequate iron storage due to low maternal serum iron, but also short intrauterine life for iron storage. A prospective study of 412 participants done by Nair *et al* in 2016 India, on evaluation of maternal anemia in a tertiary care centre and its neonatal outcomes showed that 27.9% of anemic pregnant women give birth to preterm newborns of whom 2% died during neonatal period (19). Another cross-sectional population study of 21,075 participants done by Nadin *et al* in 2017 in Jordan, on the incidence, risk factors and mortality of preterm neonates showed a preterm mortality rate of 123/1000 live birth with an abruption placenta contributing to 2.7% of preterm neonatal death(20).

2.2.1.4 Maternal hypertensive disease:

Hypertensive disease during pregnancy which can include: pregnancy induced hypertension, pre-eclampsia or eclampsia is a major factor associated with preterm birth with SGA newborn with increased risk of death due to preterm complications. A retrospective study of 129 participants done in 2017 in tertiary Hospital Tobago by Cupen *et al* on risk factors associated with preterm neonatal mortality showed maternal hypertension and eclampsia contribute to 22.2% and 23.1% respectively (21).

2.2.1.5 Maternal infection:

Maternal infection, or colonization during labor, which can be through Laboratory-confirmed bacterial infections or clinical signs of infection like intrapartum maternal fever, uterine tenderness, malodorous vaginal discharge and preterm premature rupture of membrane (PPROM) or rupture of membrane (ROM) prior to onset of labor <37 wk gestation and

prolonged ROM (duration of ROM≥18–24 h or undefined). These can be a risk for preterm delivery but also through hematogenous or ascending infection can affect a preterm unborn neonate who has an immature immune system causing severe sepsis after birth which could increase chances of dying. A global systematic review and meta-analysis of 83 studies done in 2013 by Chan *et al* on risks of early neonatal infection with maternal infection or colonization found those preterm neonates of mother with PPROM or other risk factors had a 2.3-fold higher risk of infection which contributed to preterm mortality compared with those whose mothers had no infection (22).

2.2.1.6 Antenatal Maternal use of corticosteroids

Pregnant women at higher risk of preterm delivery are advised to receive at least two doses of injectable corticosteroids (dexamethasone or betamethasone) prior to delivery this will help in improving preterm unborn baby lung maturation helping improving quality and quantity of surfactant preventing respiratory distress syndrome(RDS),Intraventricular hemorrhage(IVH) necrotizing enterocolitis(NEC) and newborn severe sepsis. Cochrane review done in 2017 by Vogel *et al* on antenatal corticosteroid for women at risk of imminent preterm birth in low resource countries, showed antenatal corticosteroids can reduce preterm neonatal mortality through preventing RDS, IVH, NEC and sepsis especially in 1st 48 hours of birth (23), similar to WHO recommendation in improving preterm neonates' outcome (24).

2.2.2 Neonatal factors for preterm mortality

Preterm infants are at risk for developing short-term complications that result from anatomic or physiological immaturity at birth. These include:

2.2.2.1 Gestation age at birth and birth weight:

The lower the gestation age at birth and birth weight, the more the preterm complications and the higher the risk of mortality. A retrospective study done by Cupen *et al* in 2017 in tertiary hospital Tobago on risks associated with preterm neonatal mortality showed that 75% of extreme low birth weight died due to immature organ systems, amongst those born at GA<28

weeks 37.5% died while between 33-36 weeks only 12.5% died. Those with BW <1000gm 56% died while between 1000-1500gm 31.2% died (21).

2.2.2.2 Meconium aspiration and aspiration pneumonia:

Preterm neonates have difficulties in feeding since the coordinated suck and swallow process only starts at 34 weeks' gestation. Hence, are more likely to aspirate. Feeding large amount of milk may increase risk of aspiration of gastric contents. A retrospective study done by Cupen *et al* in 2017 in tertiary hospital on risk associated with preterm neonatal mortality showed that up to 31.3% of preterm neonates died due to aspiration pneumonia (21).

2.2.2.3 Respiratory Distress syndrome (RDS)

Majority of children born below 32 weeks' gestation develop Respiratory distress syndrome (RDS) due to lung immaturity and lack of surfactant in the alveoli, resulting in collapsing lungs that take extra pressure to inflate(15, 16). According to Velaphi *et al* in a retrospective cohort study in South Africa on survival of very low birth weight (VLBW) infants according to birth weight and gestational age in public hospitals; a high mortality rate was associated with gestation age below 28 weeks, and birth weight below 1000gm together with lack of respiratory support (25). Another prospective study done in 2015 by Patel *et al* on causes and timing of death in extremely premature neonates aged 22 to 28 weeks showed 40.4% extremely premature neonates died within 12 hours of delivery due to RDS. However, the use of antenatal corticosteroids to mothers with preterm labor, CPAP and surfactants reduced significantly the mortality rate in preterm neonate (26).

2.2.2.4 Hypothermia:

Hypothermia which is defined as an axillary body temperature below 36.50C can be caused by rapid heat loss that occurs in preterm neonates because of their relatively large body surface area and inability to produce enough heat. Hypothermia may contribute to hypoglycemia and metabolic acidosis. In preterm infants, hypothermia is associated with an increased mortality and those who survive may develop intraventricular hemorrhage (IVH), and pulmonary insufficiency and/or hemorrhage.

In study done by Mathur *et al* in India which included only hypothermic preterm babies specifically investigated morbidities and mortalities, found case fatality rate (CFRs) that ranged from 39.3% for mild hypothermia to 80% for severe hypothermia. This study demonstrated a dramatic effect of co- morbidity and confirmed that hypothermia has a much worse outcome when associated with other newborn problems. Fatality rates increased to 71.4% with hypoglycemia, 83.3% with hypoxia, and 90.9% with shock (27).

Another study done by Mullany LC, on neonatal hypothermia in low-resource setting 21,459 newborn of whom 23,240 babies (92.3%) had one or more axillary temperature measured <36.5°C, mortality was increased by approximately 80% for every degree decrease in first observed axillary temperature, while association with hypothermia was substantially higher among preterm babies, and relative risk of death ranged from 2 to 30 times within the current WHO classification for moderate hypothermia, increasing with greater severity of hypothermia(28).

2.2.2.5 Hypoglycemia and electrolyte imbalance

Hypoglycemia (according to pediatrics endocrinology society) is defined as plasma glucose values drop down to 30 mg/dL (1.67 mmol/L) in the first 2 hours of life and subsequently rise to a value of at least 45 mg/dL (2.5 mmol/L) before stabilizing around 12–24 hours. Preterm neonates are at higher risk of hypoglycemia due to several factors including hypothermia, inadequate glycogen and fat storage, poor feeding in respect to increase their basal metabolic rate, this predisposes them to short term as well as long term complications like seizure disorders, poor sensory neural development with worse outcome of death. Study done by Sharma *et al* on hypoglycemia in preterm neonates showed that 30-60% of preterm neonatal mortality was due to hypoglycemia (29).

2.2.2.6 Necrotizing enterocolitis (NEC)

Is a common condition affecting the intestinal wall of very preterm neonates this is due to inadequate mesenteric blood flow in the intestine, inadequate digestive enzymes production with a typical x-ray image of gas in the wall of intestines. Formula feeding increases the risk

tenfold compared to babies who are fed breast milk, also feeding larger amount to preterm neonates increases the risk of NEC (15, 16, and 30). In 2015, a prospective study on extreme premature neonates done by Ravin *et al* on causes and timing of death in extremely premature neonates, 6075 participants died of whom 30% were due to neonatal sepsis and NEC (20). Another retrospective study done by Cupen *et al* in 2017 in tertiary hospital Tobago with sample size of 129 on risk associated with preterm neonatal mortality showed that NEC contributed to 25% of preterm neonatal death (21).

2.2.2.7 Intraventricular hemorrhage (IVH)

IVH in preterm neonates occurs in the first few days after birth in about 1 in 5 babies under 2,000g. This is due to rupture of small fragile blood vessels in the germinal matrix and often linked to the severity of RDS and hypotension. A population based retrospective cohort study done in 10 regions Hospital Australia by Schindler *et al* in 2017 on causes of death in very preterm infants born below 32 weeks GA showed the most common cause of death across all gestational groups was IVH with a cause-specific mortality rate (CMR) of 22 per 1000 infants, followed by acute respiratory illnesses (ARI) CMR 21 per 1000 infants and sepsis CMR 12 per 1000 infants (31).

Similarly, according to Swai *et al* in 2005 at MNH in a prospective study on VLBW preterm neonates 32.5% had periventricular leucomalacia and 61.8% had IVH in which the high mortality was found in babies with grade 3, and 4 IVH. Occurrences of IVH and PVL were within the first 3 days of life and were associated with neonatal low hemoglobin and maternal low hemoglobin respectively (32).

2.2.2.8 Anaemia of prematurity:

This often becomes apparent at a few weeks of age due to delay in producing red blood cells as the bone marrow is immature together with low iron storage in preterm neonates. Also due to immature liver causing inadequate vitamin K coagulating factors predispose them to hemorrhagic disease of the new born together with IVH precipitate severity of anemia in this risk group. A retrospective study of 100 preterm neonates done by Edo *et al* in 2016 in Teaching hospital in Sarajevo Bosnia on evaluation and treatment of anemia in preterm

neonates showed those with GA (<32weeks) had higher mortality of 27.42% due to anaemia of prematurity in contrast with 10.53% mortality for GA between 33-37(33).

2.2.2.9 Severe infections:

Premature babies are at higher risk of dying once they get an infection. They acquire infection intrauterine, during delivery or post delivery in the hospital, as they have long hospital stay and are dependent on central catheters to deliver nutrition and medications or ventilators for respiratory support. A retrospective observational study of 1040 preterm neonates, conducted in tertiary hospital India in 2015 by Ananya *et al* on preterm birth, analysis of risk factors and their outcomes showed that mortality due to septicaemia was 31%. Neonates with a GA between 28-32 had higher numbers of sepsis than those with 34-36 weeks (34).

2.2.2.10 Congenital anomalies:

Congenital anomalies in preterm babies contribute to higher mortality in preterm neonates especially when delays in management occur, they can be single or multiple, isolated or associated with certain syndrome. A cross-sectional population based study of 21075 preterm neonates done in 2017 by Razeq *et al* in Jordan on incidence, risk factors and mortality of preterm neonates showed that 24.8% of the death was due to congenital abnormalities (35).

2.2.3 Health system factors for preterm mortality

2.2.3.1 Equipments

Lack and inadequate supporting equipments like resuscitation equipments, warmers, incubators, and continuous positive airway pressure (CPAP) machines, suction machines, glucometers and the lack of Neonatal Intensive Care Units (NICU) has great impact on preterm outcome. A prospective cohort study of 7164 preterm neonates done in rural Bangladesh in 2014 by Shah *et al* on neonatal mortality risks among preterm births showed that nearly half (46.4%) of preterm neonates died within 1st 28 days of life with identified risk factors being first born child, poorest households, neonates with symptoms of infection whom had risk of dying by 1.4, 1.7 and 5.6 respectively while delayed visit to trained community

health workers (CHW) before and after delivery increased the mortality rate in the study population (36)**.** Almost the entire population studied came from rural areas where health facilities are sparse and lacked emergency care especially for preterm babies Another prospective cohort study done in Bugando hospital by Mbawala *et al* in 2014 on factors associated with mortality in preterm neonates showed 81.1% of preterm neonates who had Respiratory distress syndrome (RDS) died due to lack of respiratory support like CPAP machine and ventilators in NICU (18).

2.2.3.2 Human resource and timing of death in preterm neonates

When looking at availability of healthcare providers this has great impact on the preterm neonatal outcome whereby limited number of Doctors and nurses (registered and enrolled) especially evening/night shift and during weekends, this contribute to higher mortality to this risk group because of lower levels and expertise of staffing, including support personnel, and reduced access to diagnostic and therapeutic services after working hours.. Other reasons may include errors of judgment related to physical and mental fatigue from night shifts (37-42). An observational retrospective study done in Sweden by Luo *et al* looking at 2,102,324 spontaneous live births of infants without congenital malformation showed preterm neonates born at night had higher mortality rate by 30% with 2 times risk of dying compare to those delivered during day shift. Early neonatal mortality (with in first 7 days of life) was higher from 5 pm to 1 am and around 9 am for both weekdays and weekend day (43). Prospective study done in Kenya in 2017 on Expectations for nursing care in newborn units showed neonatal patient to nurse ratios of 15:1which was an extreme contrast to the international recommended ratios of newborns to nurses of: 4:1 for basic or continuing care; 2-3:1 for stable babies requiring intervention; and 1:1 for high-dependency care.(44, 45) A cross-sectional study conducted at Muhimbili National Hospital Tanzania in 2012 by Mgaya et al which compared perinatal outcomes across three working shifts over 24 hours showed Neonatal distress and early neonatal deaths were more significantly associated with deliveries occurring during night shifts compared to evening and morning shifts with odd ratio of 1.48 and 1.70 respectively(46).

3.0 METHODOLOGY

3.1 Study design

A prospective cohort study was designed to analyse mortality rate and the associated risk factors occurring to preterm neonates admitted in the neonatal wards at MNH.

3.2 Study setting

A study was conducted at Muhimbili National Hospital (MNH) at the Department of Paediatrics and Child Health in the neonatal ward, a teaching hospital for Muhimbili University of Health and Allied Sciences (MUHAS). It is the largest hospital in the country situated in Dar es Salaam region. It receives referrals from different hospitals around Dar es Salaam mainly from regional referral hospitals namely Amana, Temeke and Mwananyamala hospitals as well as other private health facilities in the city. It also receives the referral cases from different regions needing advanced diagnostics tools and expertise. The Muhimbili Neonatal Unit has been divided into two parts ward 36 (term neonates) and 37 (for preterm neonates) with a total of 148 beds and receives neonates born at MNH and from referral hospitals, with an average of five hundred sixty five total admissions per month, and among those admission 170 are premature babies (10). Each ward has interns, residents, registrar and specialists; both have responsibility to take care of the neonates

In ward 37 we have a total of 4 ventilator machine out of which 3 are working, 13 CPAP machines, 4 radiant warmers, 2 suction machines, 24 infusion pumps, one blood gases analyzer machine, 3 glucometer,4 pulse oxymeter and one portable ultrasound machine however the unit lack incubators.

3.3 Study population

All in born and out born preterm neonates admitted at MNH neonatal unit during study period.

3.4 Inclusion criteria

Preterm neonates born ≤ 24 hours with gestation age (GA) between 24 to 36 weeks using Ballard score.

3.5 Exclusion criteria

I. Preterm neonates who died before GA assessment.
II. Preterm neonates whose mothers declined to sign an informed consent

3.6 Sample size

Sample size was calculated from Open Epi using Fleiss Methods for Rates and proportions (47). The preterm mortality due to RDS from the study done by Ravin *et al* in 2015 (26) was used for estimating sample size.

Whereby:

Two-sided confidence level (1-alpha): 95
Power (% chance of detecting): 80
The ratio of sample size, unexposed/exposed: 3
Percentage of exposed with an outcome (patient who died due to RDS) 40.4%
Percentage of unexposed with an outcome (preterm neonates who died without RDS) 59.6%
Odds ratio: 0.46

- Sample size - exposed: 71
- Sample size - unexposed: 212
- Total sample size: 283

❖ The minimum sample size is 283

After adjusting for a 10% loss to follow up a final sample size of 311 was reached.

3.7 Sampling procedure

Participants who met the inclusion criteria were consecutively enrolled until sample size was attained.

3.8 Data collection

3.8.1 Data collection tools

A standard questionnaire was used to collect information (Appendix 1). The tool was developed after reviewing the different literature on causes of mortality in different countries. Participants were assigned a study identification number and were given an identification card. Questionnaires developed in English and translated into Swahili language were administered by the investigator so that mothers could understand and respond appropriately to questions Questionnaire was pre-tested and refined it before actual data collection started. The questionnaire had four sections: social demographic characteristics, clinical presentation, laboratory investigation and causes of deaths. Other tools included:

3.8.2 Reproductive, child health card No 4 and partogram

These were used to retrieve information such as gestation age, maternal weight, blood pressure measured during visits, time of rupture of membranes, color of the liquor, hemoglobin level during the third trimester and neonatal factors e.g. APGAR score at birth

3.8.3 Ballard's score

This was used to assess the GA for physical and neurodevelopment maturation of preterm neonates within 24 hours of delivery.

3.8.4 Weighing scale

In a warm and clean room, a SECA beam was set to 0.00g. On admission, preterm neonates were undressed and placed on the beam balance so as to measure their body weight in nearest 10g

3.8.5 Tape measure

The occipital-frontal circumference (OFC) was measured by non-stretchable nylon measuring tape from the occiput passing just above the eyebrows to the nearest 0.1cm.

3.8.6 Cranial ultrasound

Cranial ultrasound was done on all study participants within 72 hours of life to determine the presence or absence of IVH. The ultrasound scan was performed by using Toshiba 5MHz probe through the anterior fontanel for both coronal and sagittal sections.

3.8.7 Thermometer.

On arrival and every 8 hours in the first 72 hours of life body temperature of study participants were measured by using digital thermometer (Anderson's type) in degree centigrade to the nearest one decimal place.

3.8.8 Pulse oximeter

A fingertip pulse oximeter (Choice mmed) was used to measure oxygen saturation in percentages and pulse rate of study participants on arrival and whenever necessary.

3.8.9 Glucometer

Blood glucose of preterm neonate was measured using a commercial glucometer (gluco- plus) to nearest 0.1mmol/L through aseptic technique of obtaining one drop of participant's blood from a heel prick.

Study variables

Dependent variables (outcome): Death or survival was the primary outcome measured as a binary variable where death = 2, survival = 1

Cause of death was defined as the primary underlying illness; for a patient with multiple diagnoses both underlying cause of death, the immediate cause of death and co-morbid conditions were recorded.

The immediate cause of death was reported as the immediate cause of death as recorded in the patient file after a mortality audit, which is done by more than one clinician in the unit. Causes of death were discussed in a review clinical presentation, and any supportive laboratory findings if any as well as circumstance around that death is taken into consideration when reporting the cause of death. Finally, causes of death were documented in the file after a consensus is reached. Mortality audits were done weekly. Comorbid conditions are those related to the cause of death or complication of underlying disease for example congenital malformations, congenital heart disease in preterm neonate.

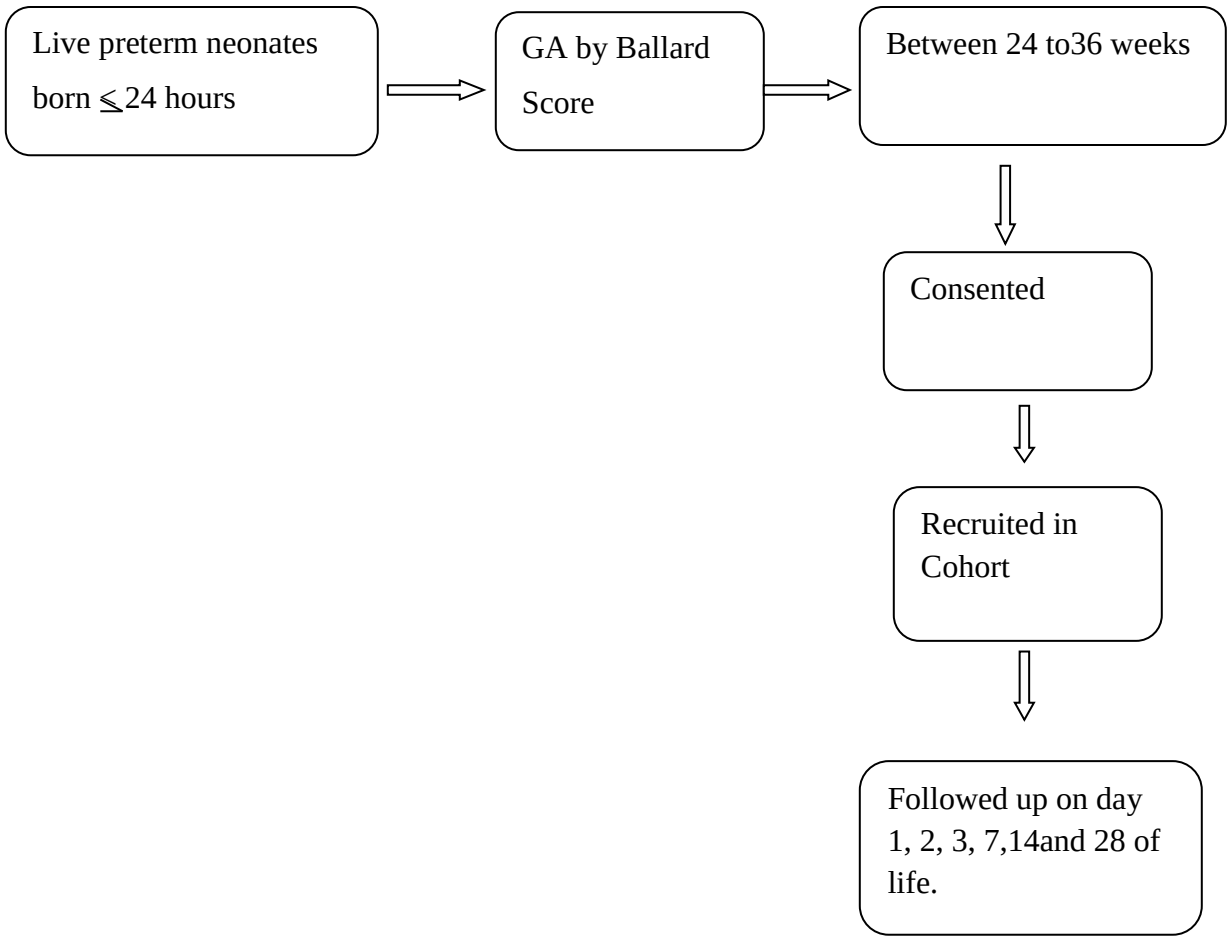
Independent variables:

- ✓ Maternal factors includes: Age measured as ordinal while pregnancy induced hypertension, ante-partum hemorrhage(APH) Anaemia, infections like urinary tract infection (UTI) malaria, lack of corticosteroids given in premature rupture of membrane (PROM) measured in dichotomous categorical data ,
- ✓ Place of delivery measured by nominal level of education, occupation and under nutrition. Parity, gravidity, measured as ordinal variables while and mode of delivery, ante natal clinic (ANC) attendance as dichotomous variables
- ✓ Preterm neonates' factors: gestation age (GA) at birth, birth weight in grams were measured as ordinal variable while gender as nominal and , intraventricular hemorrhage(IVH), respiratory distress syndrome (RDS) hypothermia, hypoglycemia, necrotizing enterocolitis(NEC), aspiration pneumonia ,anemia, hemorrhagic disease of new born, diagnosis in ward, and the need for neonatal cardiopulmonary resuscitation at birth as dichotomous categorical variables.

Determination of cause of death.

Causes of death being immediate and the underlying one, we used findings from mortality audit reviews and Perinatal Problem Identification Program Version 3. (PPIPv3) .This is the tool used to simplify audit for perinatal and maternal death which was adopted in South Africa it has three distinct data elements which are, number of deliveries, early and late neonatal death, causes of deaths (primary obstetric cause and final cause of death, also it has avoidable factors for these mortality.

3.9 Data Collection Procedure (figure 2)



At the time of admission, all participants gestational age were assessed using Ballard's score, examination for the signs of complications due to prematurity including: hypothermia using axillary body temperature in degree centigrade was taken 8 hourly in the first 72 hours of life, Hypoglycemia by measuring a Random Blood Glucose at the time of admission then anytime depending on the child's condition using heel prick blood and measured using a gluco plus glucometer machine in mmol/l (units).The preterm was examined for signs of RDS by counting the respiratory rate per minute and measuring the oxygen saturation and pulse rate using a finger/toes pulse oximeter.

A serum C - reactive protein was done by taking 1 ml of blood, using aseptic technique in a green topped vacutainer bottle and for preterm's suspected to have sepsis, blood for culture and sensitivity was taken whereby 1-3mils of blood aseptically drawn from the anterior cubital fossa vein. A diagnosis of congenital malformation was based on the child's clinical presentation and aided by radiological imaging including: x-rays, ultrasound scan, echocardiography and CT scan when applicable. All participants were managed according to the standard National guideline. Patients were followed day 1-3(early preterm complications) day 7 and 14(intermediate) and day 28 for identification of late preterm neonatal complication. Verbal autopsy was conducted amongst mothers of neonates who were discharged home alive but sadly passed away at home or at other hospitals during the follow up period. (Appendix II)

3.10 Data Management and analysis

Data was cleaned; variables were coded, labeled and categorized as necessary. Data analysis was performed using SPSS version 25. Mortality rate was calculated as the cumulative proportional of total numbers of deaths divided by the total number of study participants multiplied by personal year which is time for follow up (1 month) time's 1000 live preterm births. Kaplan-Meier curves were presented showing the overall mortality rate and by select characteristics. Mean ± SD and median (IQR) were calculated for continuous normally distributed and skewed variables, respectively. The relationships of maternal and neonatal independent characteristics with the risk of preterm mortality were estimated using Cox

hazards regression models. A variable was considered statistically significant if the p-value was < 0.05.

Factors associated with mortality in bivariate analysis with a p value <0.05 were entered in the multivariable logistic regression model to identify and quantify risk factors associated with preterm mortality while controlling for potential confounders. Crude and adjusted hazard ratio with 95% confidence intervals were calculated and risk factors with P-value <0.05 were considered significant after analysis.

3.11 Ethical consideration

Ethical clearance was obtained from MUHAS Institution Review Board and permission to conduct the study at the paediatric department was obtained from Muhimbili National Hospital administration. Informed consent was obtained from mothers of preterm neonates and participants had study identification number during the study in order to make the follow-up but during analysis participants were de-identified. Mothers of neonates who passed away at our hospital or who were discharged home alive but sadly passed away at home or at other hospitals during the follow up period were counseled by the counselor, as mothers should not blaming themselves for the deaths of their neonates, but also on importance of early visit to clinic when she discovers she is pregnant so as early investigations, proper management and follow-up on risk factors (problems) that could lead to prematurity. They were informed on ways to know danger sign/symptoms in preterm neonates so as can seek for early medical help in the near health centre.

4.0 RESULTS

A total of 412 preterm neonates were admitted from October 2018 to January 2019 of whom 300 premature neonates were enrolled in this study as shown in the flow diagram (**Figure 3**)

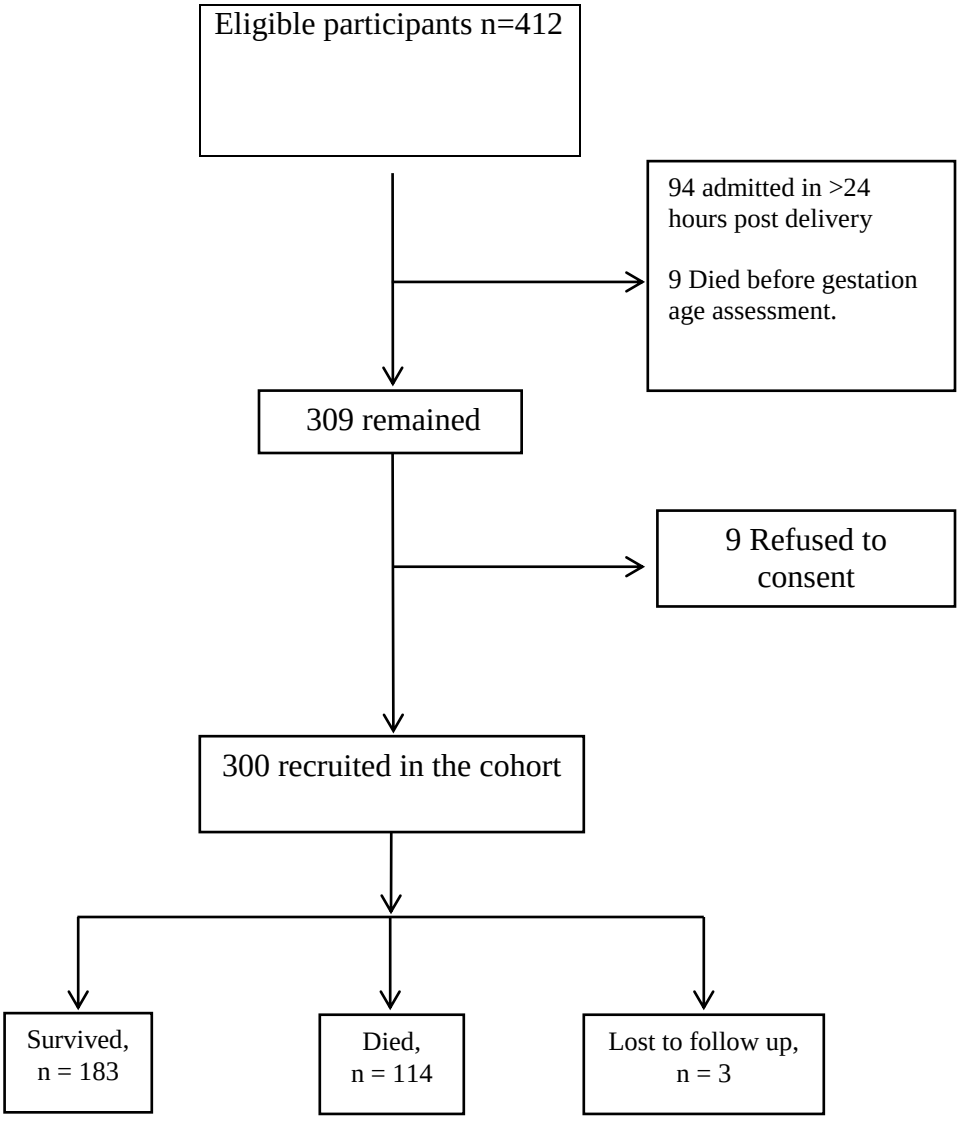


Figure 3: Flow chart showing enrollment of study participants

4.1: Survival experiences of preterm neonates during a 28 day follow up period.

Among the 300 of study participants, 114 died equivalent to 114/412 live preterm neonates (27.7%), where by 34/114(30%) of deaths occurred within first 24 hours and 77/114(68%) of total deaths occurred within 72 hours, as shown in **figure 4** below

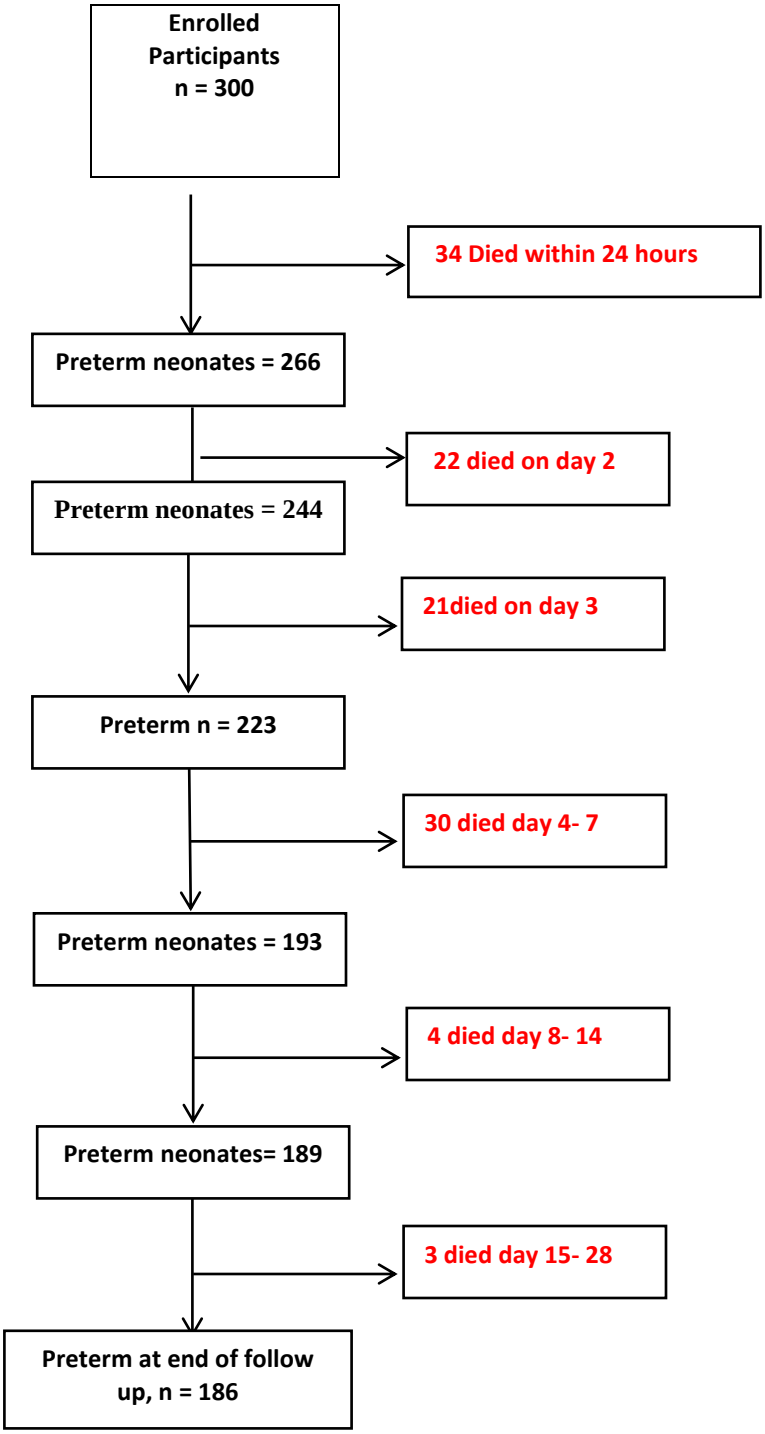


Figure 4: Survival experiences of preterm neonates during follow up period.

4.2: Baseline social-demographic characteristics of mothers of the participants (antenatal)

As shown in **Table 1,** nearly half 145 (48%) of enrolled mothers were aged between 25 to 34 years with the median age of 27.8 years (IQR 22.6-34.7years), half of all mothers reported to have a secondary school education. More than half of interviewed mothers had a history of <4 ANC visit and 214 (71.3%) had history of PROM but were not treated. Dexamethasone injection was given to more than half 157 (52.3%) of delivered mothers. More than half 172 (57.3%) of all deliveries occurred at MNH whereas SVD being the commonest 200(66.7%) mode of delivery. Most women had delivered a single preterm baby 198(66%) followed by those who had two live births 93 (31%).

Table 1: Baseline characteristics of mothers of the participants

Variable	n	%
Age category (years)		
15-24	107	35.0
25-34	145	48.0
35-44	48	17.0
Education		
No formal education	13	4.3
Primary education	137	45.7
Secondary education and above	150	50.0
Number of ANC visits		
<4	163	54.3
>4	129	43.0
None	8	2.7
HIV Status		
PMTCT 1	42	14.0
PMCTC 2	253	84.3
Unknown	5	1.7
History of Urinary tract Infection		
Yes	188	62.7
No	112	37.3
History of PV bleeding		
Yes	81	27.0
Anemia in pregnancy		
Yes	89	29.7
PROM treatment		
No	214	71.3
Yes	55	18.3
Did not have PROM		
Received ante-natal corticosteroid		
Yes	157	52.3
Place of delivery		
MNH	172	57.3
AMANA	20	6.7
TEMEKE	30	10.0
MWANANYAMALA	7	2.3
SINZA	21	7.0
HOME/BBA	10	3.3
OTHER HOSPITAL	40	13.4
Mode of delivery		
CS	100	66.7
SVD	200	33.3

ANC=Antenatal clinic, PMTCT =Prevent mother to child transmission, PV=per-vaginal, PROM =Premature rupture of membrane, CS=Caesarian section, SVD= Spontaneous vagina delivery

4.3 Baseline characteristics of preterm neonates admitted at MNH

Characteristics of preterm neonates are being summarized in **table 2.** A little over a third 112(37.3%) of all newborn were born at a gestation of 28 to 31 weeks. Almost all 281 (93.6%) newborn pre-term had an Apgar score of <7 in a first minute. The Apgar score of more than 7 was found on 214(71.3%) of pre-term at the fifth minute. Female preterm accounted for half of all deliveries. Respiratory distress presented in 209(69.7%) of neonates while on laboratory results showed Anemia in 53 (17.7%), Fifty four (18%) neonates presented with thrombocytopenia. Positive blood culture was found in 10(3.3%) of all neonates

Table 2(a): Baseline clinical characteristics of pre-term neonates admitted at MNH

Variable	Individual (n)	%
Gestation age by Ballard score		
<28 weeks	82	27.4
28 to 31 weeks	112	37.3
32 to< 37 weeks	106	35.3
Apgar score in 1 minute		
<7	281	93.6
>7	11	3.7
Not done	8	2.7
Apgar score in 5 minute		
<7	78	26.0
>7	214	71.3
Not done	8	2.7
Resuscitation in delivery room		
Yes	153	51.0
No	139	46.3
Not done but indicated	8	2.7
Gender		
Male	139	46.3
Female	151	50.4
Ambiguous	10	3.3
Weight (gm)		
<1000	68	22.7
1000-1499	95	31.7
1500-2499	121	40.3
2500 and above	16	5.3
Intracranial bleeding		
Yes	63	21
Sign of Respiratory Distress		
Yes	209	69.7
NEC		
Yes	13	4.3
Kept on CPAP		
Yes	153	51.0
Not need	4	1.3
Hypothermia		
Yes	172	57.3
Aspiration		
Yes	26	8.7

(b)Baseline Laboratory characteristics

Variables	individual (n)	
WBC ($\times 10^3$ /L)		
<5	14	4.7
5 – 20	153	51
>20	108	36
Not done	25	8.3
HB (g/dl)		
<10	53	17.7
10 – 12	147	49
>12	75	25
Not done	25	8.3
Platelets ($\times 10^3$ /L)		
<150	54	18
150 – 450	156	52
>450	65	21.7
Not done	25	8.3
CRP (ng/L)		
<10	100	33.3
>10	175	58.4
Not done	25	8.3
Total serum Bilirubin (mg/dl)		
<17	105	35
>17	170	56.7
Not done	25	8.3
Serum potassium (mmol/L)		
<2.5	13	4.3
2.5 – 3.5	105	35
3.5 – 5	153	51
Not done	25	8.4
Serum creatinine (micromol/L)		
<88.4	259	86.3
>88.4	13	4.3
Not done	28	9.4
Blood culture		
Positive growth	10	3.3
No growth	64	21.3
Not done	226	75.4
Received Surfactant		
Yes	34	11.3
No	266	88.7

NEC= Necrotizing enterocolitis, CPAP=Positive airway pressure, WBC=White blood cell HB=Hemoglobin level

4.4: Maternal complications of study participants

Maternal complications of the study participants are displayed in **Figure 5.** The most frequent conditions observed amongst mothers of study participant were premature rupture of membrane (PROM) 269 (89.7%) followed by Urinary tract infection 188(62.7%) and Hypertension 132(44%) with previous history of premature deliveries as shown below:

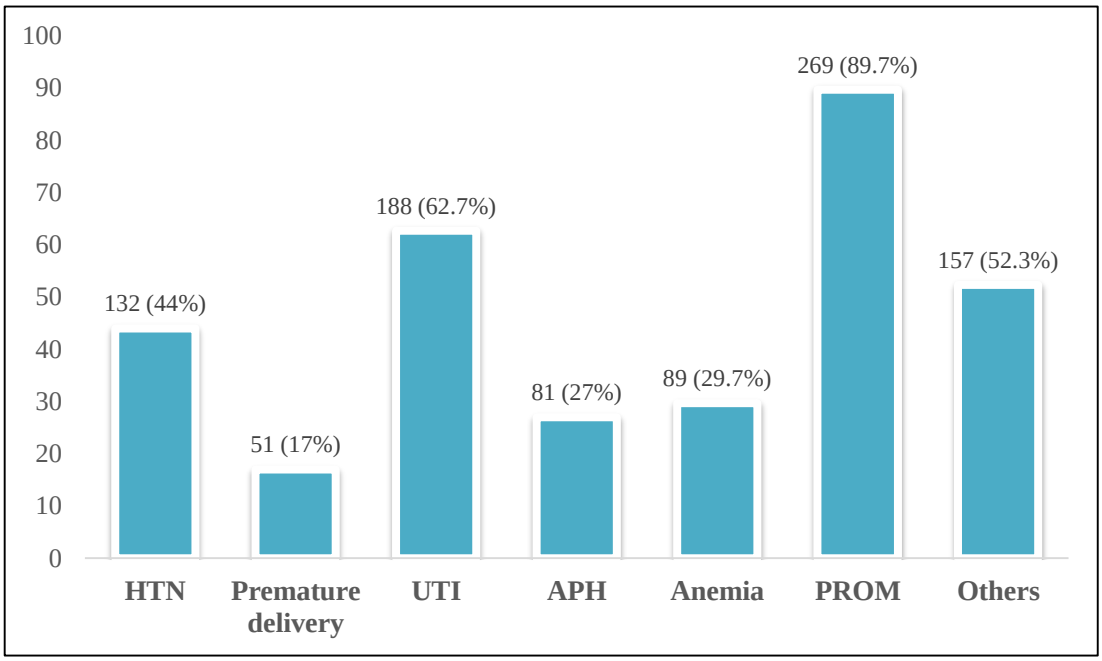


Figure 5: Frequency of Maternal complications for 300 preterm mothers who were admitted at MNH from October 2018 to January 2019

(*** 102 mothers had multiple complications)

4.5: Preterm mortality rate and overall survival time estimate

Overall mortality rate was 10 deaths/1000 live preterm births. The overall survival probability in preterm neonates for the period of 28 days is displayed on **Figure 6.** The probability of survival rapidly decreased from day 0 to day 2 of life and progressively to day 7. However, survivial probability remained constant thereafter upto day 28,with the last event occuring at day 28 of life.

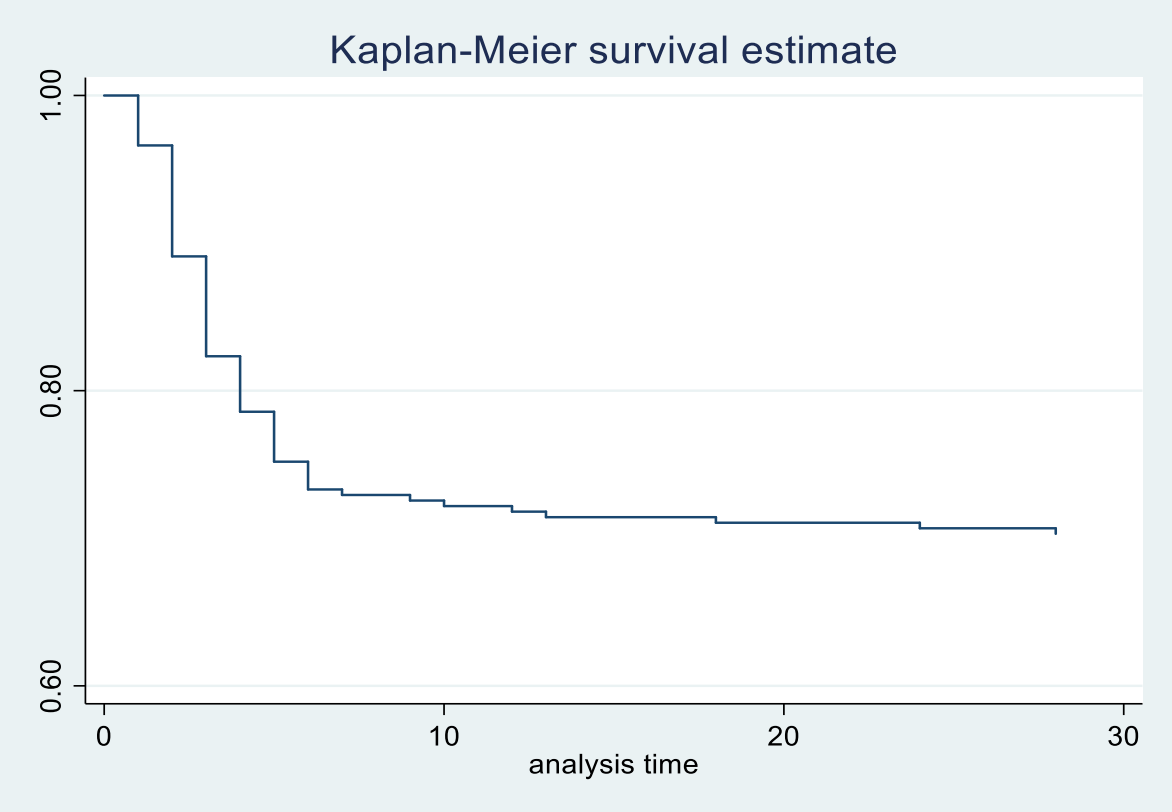
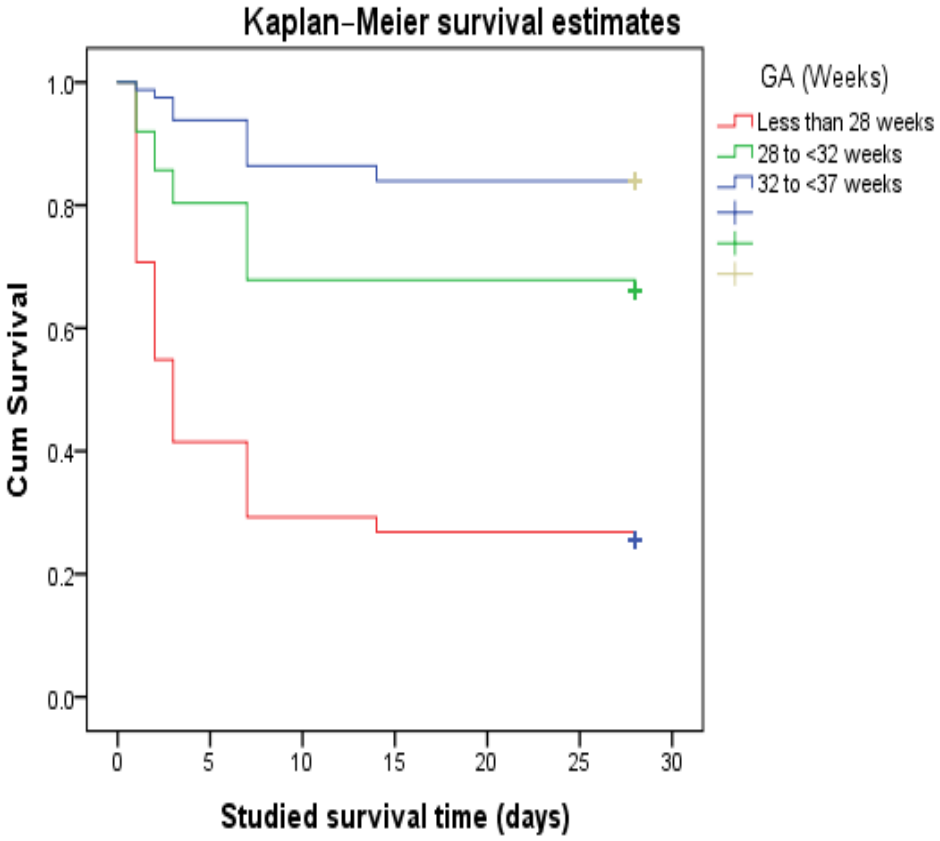


Figure 6: Kaplan-Meier overall survival estimate for pre-term neonates admitted at MNH from October 2018 to January 2019

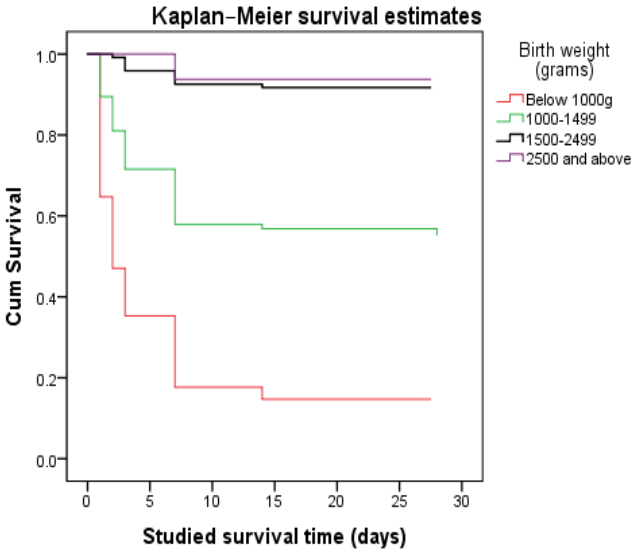
More deaths were observed in extremely preterm neonates <28 weeks (p value <0.001), those with extreme low birth weight (<1000gram) (p=0.002) as well as those with Apgar score below 7 in 1st minute (p<0.001) and below7 in 5th minute (p=0.004) with majority of these deaths occurring during the first 72 hours of birth as shown in **Figure 7** below

(a) **Kaplan-Meier survival estimate based on gestation age (GA)of study participants**



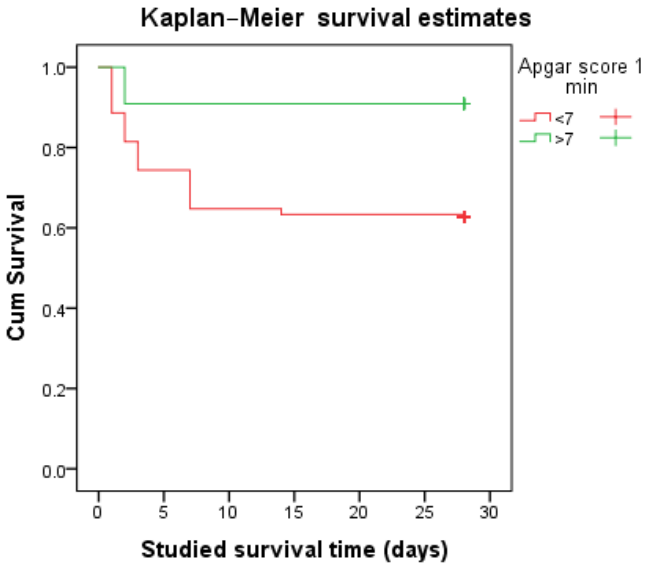
(**Log rank test**,P value <0.001)

(b) **Kaplan-Meier survival estimate based on birth weight of study participants**



(**Log rank test**,P value <0.002)

(c) **Kaplan-Meier survival estimate based on birth weight of study participants**



(**Log rank test**,P value <0.002)

(d) Kaplan-Meier survival estimate based on apgar score in 5th minutes of study participants with p value of 0.004 through log rank test

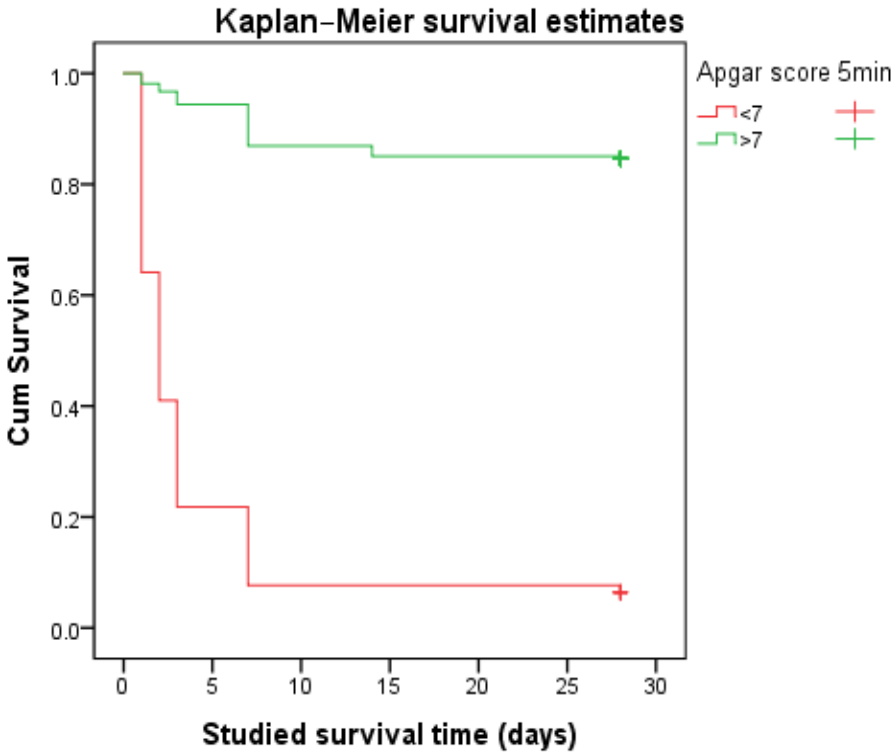


Figure 7: Kaplan-Meier survival curves of study participants for different variables

4.6: Immediate Causes of death among study participants

The leading immediate causes of death amongst the participants included: respiratory distress syndrome 59 (52%), hemorrhagic disease of the newborn and IVH 20 (17.5%), aspiration pneumonia 14 (12.3%), NEC 7 (6%), and septicemia 3 (2.6%) shown in **Figure 8.**

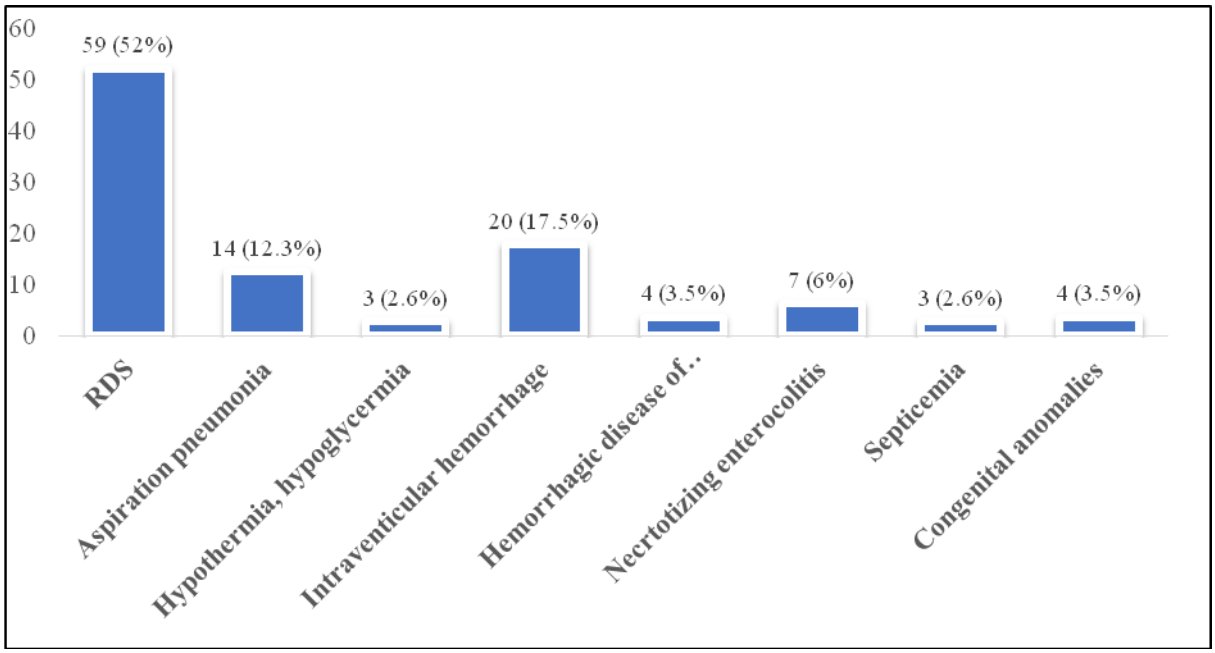


Figure 8: Immediate Cause of death among of Preterm neonates admitted at MNH from October 2018 to January 2019

RDS: Respiratory distress syndrome

4.7 Underlying causes of death

The top three underlying causes of deaths were septicemia 25 (47.2%), IVH 15 (28.3%) and ,metabolic disturbances 6 (11.3%) as shown in **Figure 9.**

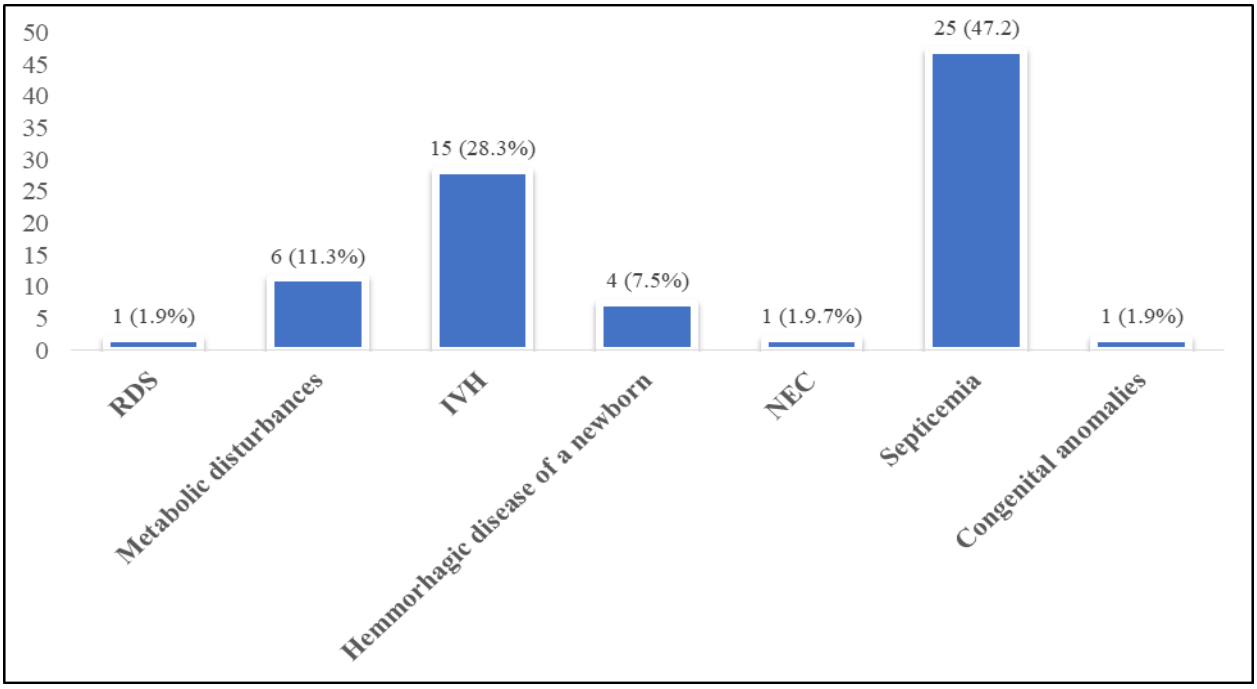


Figure 9: Underlying causes of death among study participants

RDS: Respiratory distress syndrome, IVH: Intraventicular hemorrhage, NEC: Necrotizing enterocolitis

4.8: Factors associated with preterm neonatal mortality

4.8.1. Maternal characteristics associated with preterm neonatal mortality (PNMR)

Maternal characteristics associated with PNMR are shown in Table **3.** Mode of delivery and Dexamethasone injection were significantly associated with PNMR. Neonates delivered by CS had less hazard of dying HR; 0.48, 95% CI (0.28, 0.80) *p*=0.005 as compared to those who delivered by SVD. Similarly, low hazard of dying was found among preterm neonates whose mothers had received dexamethasone injection as compared to those who didn't receive it HR; 0.49, 95% CI (0.32, 0.76), *p*=0.002. Higher hazard of Neonatal mortality was found to mothers who had not attended ANC HR; 1.44, 95% CI (0.45, 4.62)

Table 3: Maternal, Health system factors associated with preterm neonatal mortality

Variable	Rate/1000PYAR	Crude HR 95% CI)	P-Value
Age category (years)			
15-24	15.6	1.00 (Ref)	
25-34	13.0	0.85 (0.53, 1.36)	0.501
35-44	14.8	0.97 (0.51, 1.83)	0.926
Education			
No education	18.7	1.00 (Ref)	
Primary education	18.3	0.98 (0.37, 2.60)	0.962
Secondary education and above	10.6	0.62 (0.23, 1.68)	0.350
Drinking alcohol in pregnancy			
No	13.3	1.00 (Ref)	
Yes	22.5	1.57 (0.87, 2.82)	0.131
Smoking Cigarette in Pregnancy			
No	14.2	1.00 (Ref)	
Yes	13.3	0.99 (0.33, 2.96)	0.981
Diet			
Less than 3 meal/day	14.5	1.00 (Ref)	
3 or more meals/day	13.6	0.92 (0.59, 1.43)	0.724

Number of ANC visits			
<4	16.3	1.00 (Ref)	
>4	11.5	0.74 (0.47, 1.17)	0.198
None	21.0	1.44 (0.45, 4.62)	0.539
Number of pregnancy delivered			
1	12.6	1.00 (Ref)	
2-4	16.8	1.29 (0.82, 2.04)	0.270
5 and above	32.3	2.18 (0.71, 6.73)	0.174
History of HTN during Pregnancy			
No	17.0	1.00 (Ref)	
Yes	11.0	0.68 (0.44, 1.06)	0.091
History of Diabetes			
No	15.6	1.00 (Ref)	
Yes	11.4	0.46 (0.31, 1.8)	0.311
History of Eclampsia			
No	18.0	1.00 (Ref)	
Yes	16.6	0.84 (0.69, 1.15)	0.182
History of Premature delivery			
No	14.4	1.00 (Ref)	
Yes	13.0	0.92 (0.51, 1.65)	0.783
History of Urinary Tract Infection			
No	17.0	1.00 (Ref)	
Yes	12.5	0.75 (0.49, 1.15)	0.193
History of anemia during pregnancy			
No	12.1	1.00 (Ref)	
Yes	19.8	1.55 (0.99, 2.41)	0.051
PROM Treatment			
No	15.0	1.00 (Ref)	
Yes	12.3	0.84 (0.46, 1.50)	0.551
Did not have PROM	12.5	0.84 (0.41, 1.74)	0.648
Mode of Delivery			
SVD	18.0	1.00 (Ref)	
CS	7.9	0.48 (0.28, 0.80)	**0.005**
History of PV bleeding			
No	13.2	1.00 (Ref)	
Yes	17.2	1.27 (0.80, 2.04)	0.314

Dexamethasone injection			
No	21.0	1.00 (Ref)	
Yes	9.4	0.49 (0.32, 0.76)	**0.002**
Number of preterm in the ward			
20 - 30	5.2	1.00 (Ref)	
31- 40	31.6	1.3 (0.66, 2.8)	**0.144**
41 - 50	10.4	1.1 (0.37, 2.14)	**0.552**
Number of Drs day shift			
1 -2	8.1	1.00 (Ref)	
3 - 4	33.8	2.8 (0.68, 11.6)	**0.088**
Number of Drs night shift			
1 -2	56.5	1.00 (Ref)	
3 - 4	1.3	0.07 (0.02, 1.21)	**0.053**
Number of Nurses night shift			
1 -2	19.6	1.00 (Ref)	
3 - 4	5.6	0.37 (0.2, 0.69)	**0.002**

ANC=Antenatal clinic, PMTCT =Prevent mother to child transmission, HTN=Hypertension, PV=per-vaginal, PROM =Premature rupture of membrane, CS=Caesarian section,

4.8.2 Neonatal characteristics associated with preterm neonatal mortality

The association between neonatal factors with preterm neonatal mortality is shown on **Table 4**. Crude analysis was done using proportional hazard Cox regression model. Neonates born at a higher GA (32 to 37 weeks) has less hazard of dying as compared to those who were born at a lowest Gestation age HR; 0.18, 95% CI (0.09, 0.34), p<0.001. Significantly, a higher risk of dying was seen among neonates whom no investigation was taken as they were very sick and died few hours post admission. Similarly preterm neonate with an elevated CRP (>10ng/L) and an elevated serum creatinine (>88.4 umols/L) also has an increased risk of dying; HR; 3.8, 95% CI (2, 7.1), p<0.001and HR; 5, 95% CI (1.5, 16.8), p=0.009, respectively.

Table 4: Neonatal characteristics associated with pre-term mortality

Variable	Rate/1000PPYAR	Crude HR (95% CI)	P-value
Intracranial bleeding			
No	8.8	1.00 (Ref)	
Yes	50.3	4.19 (2.73, 6.43)	<0.001
Sign of Respiratory Distress			
No	2.0	1.00 (Ref)	
Yes	23.6	9.47 (3.87, 23.16)	<0.001
Received suction			
No	7.3	1.00 (Ref)	
Yes	64.7	5.87 (3.83, 9.00)	<0.001
NEC			
No	13.4	1.00 (Ref)	
Yes	33.5	1.94 (1.02, 3.72)	0.045
Apgar score in 1 min			
<7	13.13	1.00 (Ref)	
>7	1.3	0.22 (0.04, 0.65)	0.040
Apgar score in 5 min			
<7	9.1	1.00 (Ref)	
>7	4.1	0.3 (0.52, 0.78)	<0.001
Hypothermia			
No	7.1	1.00 (Ref)	
Yes	22.2	2.74 (1.69, 4.47)	<0.001
Hypoglycemia			
No	10.0	1.00 (Ref)	
Yes	24.6	2.15 (1.41, 3.30)	<0.001

Aspiration pneumonia			
No	12.9	1.00 (Ref)	
Yes	29.1	1.75 (1.06, 2.88)	0.027
Received surfactants			
No	32.5	1.00 (Ref)	
Yes	9.6	0.45 (0.09, 0.61)	<0.001
Kept of CPAP			
No	24.4	1.00 (Ref)	
Yes	11.3	0.7 (0.26, 0.81)	0.023
WBC ($\times 10^3$ /L)			
<5	2.8	1.00 (Ref)	
5 – 20	30.9	0.3 (0.11, 1.08)	0.070
>20	21.8	1.2 (0.40, 3.80)	0.710
Not done	5.1	3.2 (1.1, 30.7)	0.003
HB (g/dl)			
<10	10.7	1.00 (Ref)	
10 – 12	29.7	0.19 (0.09, 0.37)	<0.001
>12	15.2	0.13 (0.058, 0.28)	<0.001
Not done	5.1	1.2 (1.15, 9.8)	0.018
Platelets ($\times 10^3$ /L)			
<150	10.9	1.00 (Ref)	
150 – 450	31.6	0.18 (0.09, 0.35)	<0.001
>450	13.1	0.72 (0.35, 1.5)	0.392
Not done	5.1	1.9 (2.4, 15.2)	0.005
CRP (ng/L)			
<10	20.2	1.00 (Ref)	
>10	35.4	3.8 (2, 7.1)	<0.001
Not done	5.1	12 (1.5, 19.9)	<0.001
Total serum Bilirubin (mg/dl)			
<17	21.2	1.00 (Ref)	
>17	34.4	1.4 (0.8, 2.5)	0.157
Not done	5.1	6.2 (1.8, 18.6)	<0.001
Serum creatinine (micromol/L)			
<88.4	52.4	1.00 (Ref)	
>88.4	2.6	5 (1.5, 16.8)	0.009
Not done	5.7	18 (5.7, 63)	<0.001
Blood culture			
Positive growth	2.0	1.00 (Ref)	
No growth	12.9	4.8 (0.95, 24.5)	0.058
Not done	45.7	0.81 (0.06, 9.9)	0.366

NEC= Necrotizing enterocolitis, CPAP=Positive airway pressure, WBC=White blood cell HB=Hemoglobin level, CRP: C reactive protein

4.8.3: Multivariable logistic regression of preterm mortality in relation to maternal, neonatal characteristics and their laboratory parameters among study participants

Maternal factors, neonatal factors which were found to be statically significant (p value < 0.005) were added on adjusted model for multivariate analysis. Modes of delivery and Dexamethasone injection were maternal factors that remained to be independent predictors for preterm neonatal mortality. Cesarean section delivery was associated with lower risk of dying HR; 0.54, 95% CI (0.32, 0.92), *p*=0.024 whereas dexamethasone injection was associated with lower risk of dying HR; 0.57, 95% CI (0.36, 0.91), *p*=0.017.

Neonatal factors, intracranial hemorrhage HR; 1.9, 95% CI (1.12, 3.25), sign of respiratory distress syndrome, HR; 4.4, 95% CI (1.59, 12.6) increased risk of dying. Raised CRP, HR; 2.5, 95% CI (1.3, 6.6) and Serum creatinine HR; 4.3, 95% CI (1.3, 11.4) were found to be associated with increased neonatal mortality Most of death occurred during the night time 84 (73.7%) whereas Wednesday accounted for the most of mortality days 26 (22.8%) (**Table 5**).

Table 5: Multivariate analysis on maternal, neonatal and health system factors associated with preterm neonatal mortality

Variable	Adjusted HR (95% CI)	P-value
Mode of Delivery		
SVD	1.00 (Ref)	
CS	0.54 (0.32, 0.92)	**0.024**
Dexamethasone injection		
No	1.00 (Ref)	
Yes	0.57 (0.36, 0.91)	**0.017**
Weight (gm)		
<1000	1.00 (Ref)	
1000-1499	0.43 (0.21, 0.88)	**0.020**
1500-2499	0.12 (0.04, 0.39)	**<0.001**
2500 and above	0.0 (0.03, 1.38)	0.104
Intracranial bleeding		
No	1.00 (Ref)	
Yes	1.90 (1.12, 3.23)	**0.017**
Sign of Respiratory Distress		
No	1.00 (Ref)	
Yes	4.48 (1.59, 12.62)	**0.005**
Need suction		
No	1.00 (Ref)	
Yes	4.2 (2.29, 7.41)	**<0.001**
NEC		
No	1.00 (Ref)	
Yes	4.72 (1.75, 12.62)	**0.005**
Apgar score in 5 min		
<7	1.00 (Ref)	
>7	0.4 (0.6, 0.82)	**<0.001**
Received surfactants		
No	1.00 (Ref)	
Yes	0.45 (0.09, 0.61)	**<0.001**
Kept of CPAP		
No	1.00 (Ref)	
Yes	0.7 (0.26, 0.81)	**0.023**
WBC ($\times 10^3$ /L)		
<5	1.00 (Ref)	
5 – 20	0.28 (0.14, 1.05)	0.065

>20	1.8 (0.60, 4.40)	0.511
Not done	3.1 (1.2,25.4)	**0.002**
HB (g/dl)		
<10	1.00 (Ref)	
10 – 12	0.12 (0.65, 0.21)	**<0.001**
>12	0.3 (0.06, 0.41)	**<0.001**
Not done	1.3 (1.1, 6.6)	**0.022**
Platelets ($\times 10^3$ /L)		
<150	1.00 (Ref)	
150 – 450	0.17 (0.05, 0.21)	**<0.001**
>450	0.65 (0.22, 1.4)	0.441
Not done	1.7 (1.61, 11.3)	**0.002**
CRP (ng/L)		
<10	1.00 (Ref)	
>10	2.5 (1.3, 6.6)	**<0.001**
Not done	8 (1.2, 13.3)	**<0.001**
Total serum Bilirubin (mg/dl)		
<17	1.00 (Ref)	
>17	1.5 (0.9, 2.3)	0.112
Not done	5.0 (1.1, 11.1)	**<0.001**
Serum creatinine (micromol/L)		
<88.4	1.00 (Ref)	
>88.4	4.3 (1.3, 11.4)	**0.003**
Not done	10 (3.5, 40)	**<0.001**
Number of Nurses night shift		
1 -2	1.00 (Ref)	
3 - 4	0.33 (0.18, 0.82)	**0.001**

ANC=Antenatal clinic, CS=Caesarian section, HB=Hemoglobin, CRP=c reactive protein, NEC= Necrotizing enterocolitis, WBC=White blood cell

5.0 DISCUSSION

The aim of this study was to estimate the mortality rate and determine the risk factors associated with preterm neonatal deaths at MNH. We observed an overall mortality rate of 10 per 1000 live preterm neonates equivalent to 114 (27.7%) mortality. Identified risk factors included: spontaneous vaginal delivery, absence of maternal antenatal corticosteroids a smaller gestation age below 28 weeks with extremely low birth weight below 1000grams. Preterm neonates having an Apgar score below 7 in 5th minute, respiratory distress syndrome, hemorrhagic disease of the newborn and intraventricular hemorrhage were also more likely to die.

5.1 Preterm Neonatal Mortality

The preterm neonatal mortality rate observed in this study was 27.7% which is comparable to East Africa study done by Marchant *et al* in 2012 with PNMR of 28% while Manji *et al* in situation analysis of the newborn health in Tanzania had mortality rate of 27% (9, 14), but was lower than global estimation of 35% in 2016 (6), and that reported in another referral hospital in Mwanza, Tanzania where a case fatality rate of 39 % was reported in 2014(18). On the contrary, the observed mortality in our study was slightly higher than reported in Trinidad and Tobago by Cupen *et al* 12% and in Korea by Park *et al* which were 16% (21, 12).

These differences could be explained by retrospective study designs used in which rely on routinely collected data that may have resulted in underreporting due to missing or incomplete data (12, 14), small sample size, and majority of participants were moderate to late preterm whom were managed in NICU.

5.1.1 Patten of preterm neonatal death

Majority of study participants 290 (96.7%) were born in hospitals/health centre but 27.7% died before completing 28 days of life, with 111(97.4%) of mortality occurred in hospital setting. The risk of death in this study was observed to be high during the first 7 days. The initial 24 hours were the most critical for survival as 30% of all deaths occurred during this period. By the end of third day, two thirds of all deaths had occurred, and by the end of 7 days, 90% of all deaths had occurred. The pattern observed is almost similar to that reported by

WHO were half of newborn deaths occurs within first 24 hours and two-thirds within 72 hours (1-3).Similar to findings in a study done by Patel *et al* in Atlanta 2000-2011 in extremely preterm neonates whereby 40.4% of deaths occurred within 12 hours after birth (26).This observed results can be explained by the adaptation response of the preterm infants' organ systems to the demands of the extra uterine environment with the immature organ system they have (11). The results observed by Patel *et al* were slightly higher which can be explained by increase risk of mortality when these extreme preterm of 22 weeks of gestation being managed in facilities with advancement of medical facilities which is contrary to our study whereby being born to hospitals where there is in adequate qualified health care personnel for proper caring of premature neonates, lack of supporting equipment's, medications and delay referrals to Hospital where these neonates can be managed properly contribute to higher mortality rate. Also MNH is a national, tertiary hospital receiving large number of preterm neonates with early complications of prematurity whom require attention with well functioning medical equipment's to support them but due to large number of preterm admitted with limited equipment's become difficult to manage them as required and expected (4,5, 12). This confirms that the initial 24 hours of life are critical for preterm neonate survival hence guidelines should thus ensure clinical preparedness and availability of responsive emergency services through simple affordable, cost effectively methods to support and manage preterm neonates that may contribute to mortality reduction in this vulnerable group.

The leading immediate causes of death in this study were respiratory distress syndrome hemmorragic disease of the newborn and intraventricular hemorrage, aspiration pneumonia and necrotising enterocolitis. On the other hand, septicemia, IVH and metabolic disturbances were observed to be the leading underlying causes of death. .This was similar to findings in the study by Patel *et al* in 2011 done in Atlanta which reported 49.5% of deaths occurred within 14 days were due to RDS followed by NEC which was the most common cause of death; after 60 days, The study was a prospective cohort, in large sample size of 22,248 extremely preterm neonates(22-28 weeks GA) conducted in duration of 11 years.(26) Velaphi *et al* also showed RDS contributed to 16% mortality in very low birth weight preterm neonates weighted 500 -1499 whom were not offered

mechanical ventilation (25), this is similar to our setting also to Mbawala et al in Bugando Mwanza in 2014 whereby 81.1% of those had RDS died neither CPAP nor ventilator were offered to these preterm (18)

5.2 Maternal factors

Spontaneous vaginal delivery (SVD) was associated with an increased risk of preterm death while those born through caesarean section had lower risk of dying. This is similar to study done by Mbawala et al in Bugando neonates delivered by caesarean section had lower mortality (19.5%) as compared to those delivered by spontaneous vaginal delivery (53.5%).The observed similarities can be explained by the study settings as both conducted in tertiary hospitals same country, where specialists (obstetricians and neonatologist) are available for early and proper intervention to pregnant women at risk but also care of these preterm neonates once are born (18).Studies have shown the benefit of using antenatal corticosteroids for pregnant women at risk of preterm delivery to prevent RDS, IVH and NEC, which are commonest causes of death in premature neonatal <32 weeks' gestation. In this study preterm born to mothers who received antenatal corticosteroids had a 43% lower risk of dying [HR; 0.57, 95% CI (0.36, 0.91), *p*=0.017]. These findings were similar to those in a study by Vogel *et al* (23).Similarly, in the study by Patel *et al* done in 2011 a lower mortality was reported amongst preterm's whose mothers received prenatal corticosteroids compared to those preterm whom their mothers did not receive 62.0% vs. 87.6%, respectively. Despite the similarity in study design, the study done by Patel *et al* reported a higher overall mortality compared to this study because it included extreme preterm neonates up to 22 weeks of gestation who by default are less likely to survive even with the best interventions(26). Contrary to Mbawala *et al*, this study other maternal factors such as low maternal age, low level of education, diet, maternal anemia, APH, and history of PROM were not associated with preterm neonatal mortality as our study participants mothers aged 25-34(48%) while 150(50%) had secondary and/or university level of education (18).

Maternal anemia was not associated to preterm neonatal mortality as only 89(29.7%) of participant's mothers had anemia, which is contrary to Nair *et al* study whereby almost half of

the pregnant women had anemia, giving birth to preterm newborn with Intrauterine growth restriction(IUGR 12.3%) and 2% their preterm neonates died. These differences could be due to delay in diagnosis and management, as in Nair study anemia was detected during hospital admission for delivery in which little could be done to correct anemia, and its impact to unborn preterm neonate. While in this study some of the anemic mother's were given iron supplements and nutritional counseling on eating iron rich foods and control hemoglobin was taken before delivery (19). Premature rupture of membrane (PROM) was not associated with preterm neonatal mortality in this study, whereby 214(71.3%) of mothers who reported to have PROM were not treated; only 55(18.3%) with PROM were given antibiotic prophylaxis. These findings are contrary to Chan *et al* whereby a Meta-analysis of 7 studies from high neonatal mortality settings reported a 2.3 fold increased risk dying amongst preterm neonates whose mother had PROM. The differences in these study findings could be explained by different in study design where by Chan *et al* reviewed studies with confirmed clinical and laboratory evidence of bacterial infection in pregnant women and she excluded studies where pregnant women with PROM were given antibiotics while in this study women treated for PROM were included which might have reduced the risk of preterm neonatal mortality (22).

5.3 Neonatal factors:

The identifiable neonatal risk factors for mortality were gestational age and birth weight. The lower the GA and birth weight, the higher the mortality. Preterm neonates with GA <28 weeks has a 16 times higher risk of dying compared to those between 28-31 weeks. Likewise, the risk of death increased 8 fold if the preterm neonate had a birth weight <1500. These findings concur with other previous reports that have showed the protective effect of increasing GA and birth weight Cupen *et al* in Tobago tertiary hospital in 2017 and Mbawala *et al* in Bugando Medical Centre in 2014 (21 , 18). The smaller the preterm, the higher the chance of having other complications such as low Apgar score in 5^{th} minute. Hence proper gestation age assessment during pregnancy with provision of all essential care including antenatal corticosteroids GA between 24 to 34, magnesium sulphate in pregnant women with impending labour at GA <32 week. Other simple measures to support these preterm once born include:

providing respiratory support, suction and oxygen provision, thermal support by wrapping in plastic bags during stabilization (24).Preterm neonates with respiratory distress syndrome or intraventricular hemorrhage had four fold increased risk of dying compared to their counterparts. These finding were similar to study done by Velaphi *et al* in 2005 South Africa, Petel *et al* in 2015 in Atlanta and Mbawala *et al* in Bugando Mwanza Tanzania. (18, 25, 26,) Another study done showing IVH to be the risk for preterm mortality are Schindler *et al* in 2017 and Swai *et al* in 2005 at MNH Tanzania in these studies higher mortality rate observed to preterm born below 32 weeks gestation with grade 3 and4 (31-32). Similarity of results could be due to immature organ functions including lack of surfactant especially those <32 weeks GA which face majority of preterm neonates worldwide. Lack of respiratory support to this risk group predisposes them to the severe form of RDS which may complicate to IVH. The WHO recommends early initiation of CPAP to all preterm neonates with RDS (24). However, in this study, 143(47.7%) of our patients did not receive CPAP due to inadequate machines. Daily screening for IVH through trans-cranial ultrasound should be done especially in the first 72 hours of life for early diagnosis and proper intervention before advancing to grade 3 and 4 which has poor outcome.

Septicemia and NEC are among the predictors of preterm mortality, whereby those with clinical and laboratory features of sepsis had a 2.5 higher risk of dying while those with NEC had a 4.7 risk of dying compared to their counterparts. Laboratory parameters associated with and increased risk of mortality included: a low hemoglobin level <10g/dl, low platelet count of <150 **(**$\times 10^3$ /l) high C reactive protein of >10 (ng/l)a high serum creatinine level of >88.4 **(**micromol/l**)**, and those to whom no investigation was done as they were very sick and majority died before base line investigation to be taken < 24 hours.

These findings were comparable to study done by Hasanbegovic *et al* in 2016 in a Teaching hospital in Sarajevo, Bosnia and Das *et al* in 2015 at a tertiary hospital India (33, 34). Observed similarity in results can be explained by the immature immune system and gastrointestinal tract of preterm neonates which increases the risk of infections acquired during delivery, in the neonatal wards (hospital acquired infection) with long hospital stay and central

line. Septicemia complications can cause thrombocytopenia, anemia, DIC, which worsens the preterm's' outcome.

Hence effort to prevent sepsis in preterm neonates should include early recognition and proper management (50).Other factors like hypothermia, hypoglycemia and aspiration pneumonia were found to significantly contribute to preterm mortality on bivarient analysis but did not hold on multivariate analysis after accounting for confounders.

This was contrary to what was observed in a study done by Mathur *et al* in India and Mullany LC, in 2010 on neonatal hypothermia (27, 28), and also contrary to a study done by Sharma *et al* on hypoglycemia in preterm neonates and retrospective study done by Cupen *et al* in 2017 in tertiary hospital on aspiration pneumonia in preterm neonates (29, 21). The observed differences could be due to the different study design as Mathur included only hypothermic preterm, while Cupen used retrospective data, in private hospital with small sample size of 129 in which the results cannot be generalized.

5.4 Health system factors

Shortage of human resource in neonatal unit can directly or indirectly contribute to preterm neonatal death, as shown in this study whereby most deaths occurred during night shift 84 (73.7%) with lower number of nursing (patient to nurse ratio of 23:1)compared to morning shift which had patient to nurse ratio of 12:1. These findings are similar to study done by Murphy in Kenya whereby high mortality was observed with patient (preterm, SGA): nurse ratio of 15:1which is very high compared to WHO recommendation (44, 45). Similarly a retrospective study done in Sweden by Luo *et al* (43) and Mgaya *et al* at MNH Tanzania whereby in both studies a higher mortality was observed during night shift (46). This could be due to shortage of staffing including support personnel, and reduced access to diagnostic and therapeutic services after working hours. Other reasons may include errors of judgment related to physical and mental fatigue which might occur during night shifts (37-42).

Inadequate CPAP machines are among the health system factors which hinder the care of preterm neonates as at MNH. There are 8 CPAP machines which are working. which limits the level of care and the provision of surfactant These findings are similar to study done by

Mbawala *et al* in Bugando Medical Centre where by majority of preterm neonates died due to RDS due to lack of CPAP, and ventilators (18).

5.5: Strength of the study

1. This study used prospective cohort study design and thus was able to infer causality to identified risk factors associated with preterm neonatal mortality

2. Recruitment of participants was based on gestation age assessment which prevented the bias of using birth weight criterion as a proxy of prematurity

3. The immediate and the underlying causes of death were obtained from the mortality audit reviews and Perinatal Problem Identification Program Version 3(PPIPv3), rather than extracting from the death certificates, which is filled by different clinicians and might result in inter-observer bias and lack of consistency

5.6: Limitation of the study

1. This was a hospital based study conducted in a tertiary level of care; findings of this may not be generalized to the lower levels of health facilities and to the community

2. Even though the causes of deaths were obtained from the mortality audit and from adopted Perinatal Problem Identification Program Version 3 (PPIPv3), it is still a challenge to accurately identify the primary cause of death for preterm neonates with multiple diagnoses

3. Preterm neonates delivered more than 24 hours before admission were excluded; hence, this may have resulted in an underestimation of the mortality rate.

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Preterm neonatal mortality rate in our setting is very high. Risk factors for preterm neonatal mortality include: small gestation age especially below 28 weeks with extremely low birth weight below 1000grams, Apgar score below 7 in 5^{th} minute, respiratory distress syndrome, hemorrhagic disease of the newborn and intraventricular hemorrhages. On the other hand, timely caesarian section and use of antenatal corticosteroids where indicated, were shown to reduce the preterm mortality.

6.2 Recommendations

1. Stakeholders should ensure all mothers with impeding preterm delivery to receive antenatal corticosteroids and to undergo timely caesarean section when indicated

2. Respiratory support equipments like ambu bag and appropriately sized face mask for preterm neonates , should be available in all health centers where delivery is taking place whilst advanced equipments like CPAP machines and ventilators should be made available in all regional and tertiary hospitals

3. Early screening and appropriate management of IVH and RDS in neonates should be done to reduce the risk of preterm neonatal mortality.

4. Health care services provided during the night need to be improved. Hospital administrators should discuss with health care workers to point out the problems contributing to more deaths during night shift and outline possible solutions

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Appendices

Appendix I: Data Collection Tool

TITLE: MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG PREMATURE NEONATES ADMITTED AT MUHIMBILI NATIONAL HOSPITAL FROM OCTOBER 2018 TO JANUARY 2019

S/N	QUESTION	RESPONSE
1.	ID PHONE NUMBER:	_____ .....
2	Age of mother *(Complete years)*	_____(Years)
3	Maternal age in group	1. 15-24 2. 25-34 3.35-44
4	Education	1. No formal education 2.Primary 3. Secondary and above
5	History of alcohol use during pregnant	1. No 2. Yes
6	Cigarette use during pregnant	1. No 2.Yes
7	Number of diet taken per day	1. <3 2. 3 and more
8	Booking status to Antenatal clinic	1. Not booked 2. Booked
9	Number of visits to clinic	1.<4 2.>4 3.None
10	HIV status	1. PMTCT 1 2.PMTCT 2 3. Unknown
11	Gravidity	1. Prime gravid 2.multigravida (2-4) 3.Grand multigravida 5 and more
12	Parity	1. 1 2. 2-4 3.5 and above

13	History of Pregnant induced Hypertension	1. No 2 Yes
14	History of eclampsia	1. No. 2.Yes
15	History of diabetic mellitus during pregnant	1. No 2. Yes
16	History of previous preterm delivery	1. No 2. Yes
17	History of Urinary tract infection from 6 months of pregnant	1. No 2. Yes
18	History of per-vaginal bleeding before labour	1. No 2. Yes
19	History of anemia during pregnancy	1. No (Hb >11gm/dl) 2. Yes (Hb <11gm/dl)
20	History of preterm premature rupture of membrane(pprom) >18 hours	1. Has prom not treated 2. Has prom treated 3. No pro
21	Received antenatal corticosteroids	1. No 2. Yes
22	Place of delivery	1. Muhimbili national hospital 2. Amana 3. Temeke 4. Mwananyamala 5.Sinza 6.Home/ BBA 7. Other hospitals
23	Mode of delivery	1. SVD 2. Caesarean section 3. Assisted vacuum delivery
24	Apgar score in the 1st 1 minutes	1. <7 2. >7 3. Not done
25	Apgar score in the 5th minutes	1. < 7 2. >7 3. Not done
26	Delivery room resuscitation	1. No 2. Yes 3. Not done
27	Number of recent live birth	1. 1 2. 2 3. Triplet and more

28	Child ID		
29	Date of birth	____/_____/_____ (Day/Month/year	
30	Date of admission	____/_____/_____ (Day/Month/year	
31	Gastation age by Ballard score (weeks)	_____	
32	Gastation age by Ballard score in groups	1. <28 weeks 2.28-<32 weeks 3. 32<37 weeks	
33	Gender of the child	1. Male 2. Female 3. Ambiguous genitalia	
34	Weight of the child (grams)	_____	
35	Weight of the child in groups (grams)	1. <1000 2. 1000-1499 3. 1500-2499 4. 2500 and above	
36	Sign of respiratory distress	1. No 2.Yes	
37	Presence of intracranial bleeding	1. No 2. Yes	
38	Presence of hypoglycaemia (RBG <2.5 mmo/l)	1. No 2. Yes	
39	Presence of hypothermia(Temp <36.5 ^{0}C)	1. No 2. Yes	
40	Evidence of necrotizing entero colitis	1. No 2. Yes	
41	Did he child aspirated during or after feeding	1. No 2. Yes	
42	Did the child receive suction	1. No 2. Yes 3. Not available	

43	Surfactant given to the preterm neonate?	1. No 2. Yes 3. Not available
44	Baby kept on CPAP	1. No 2. Yes 3. Not available
45	Baby received required medication (antibiotic, vitamin k, aminophyline, D10%)	1. No 2. Yes 3. Not available
46	WBC **(x 10^3 /L)**	1. < 5 2. 5-20 3. >20 4. Not Done
47	HAEMOGLOBIN**(g/dl)**	1. < 10 2. 10-12 3. >12 4. Not Done
48	PLATELET**(x10^3 /L)**	1. < 150 2. 150-450 3.>450 4.Not done
49	CRP**(ng/L)**	1.< 10 2.>10 3.Not done
50	SERUM BILIRUBIN TOTAL (**(mg/dl)**	1< 17 2.>1 3.Not done
51	SERUM SODIUM **(mmo/L)**	1. < 125 2. 125-135 3. 136- 145 4.>145 5. Not done
52	SERUM POTASSIUM**(mmo/L)**	1. < 2.5 2. 2.5-3.5 3. 3.5-5 4. >5 5.Not done
53	SERUM CALCIUM **(mmo/L)**	1. < 1.7 2. 1.7- 2 3. 2.1- 2.6 4. >2.6 5. Not done
54	SERUM CREATININE**(micro** mmo/L)	1.< 88 2.>88 3.Not done

55	BLOOD CULTURE	1. Positive growth 2. No growth 3. Not taken
56	Death occurred day 1	1. No 2. Yes
57	Death occurred day 2	1. No 2. Yes
58	Death occurred day 3	1. No 2. Yes
59	Death occurred day 7	1. No 2. Yes
60	Death occurred day 14	1. No 2. Yes
61	Death occurred day 28	1. No 2. Yes
62	Day of death	
63	Day of death in groups	1. Within 24 hours 2.2 -7 days 3. 8-14 4. 15-28
64	Date of death	____/_____/_____ (Day/Month/year
65	What shift is the death occurred	1. Day 2. Night
66	On what day of the week did the preterm neonate died?	1. Monday 2. Tuesday 3. Wednesday 4. Thursday 5. Friday 6. Saturday 7. Sunday
67	Cause of death according to PPIPV3 and in the order written on death certification: **Immediate cause of death**	1. Reapiratory distress syndrome 2. Aspiration pneumonia 3. Hypoglycaemia 4. Intravenricular haemorrhage 5.Hemorragic disease of the newborn 6.Necrotizinig enterocolitis 7.Septicemia 8. Congenital anomalities of alimentary tract 9 Cardiovascular system abnormalities 10.Hypotermia 11.Metabolic hypernatrermia

		12. Metabolic Hyperkalemia
68	**Underlying cause of death**	1) Respiratory distress syndrome 2. Aspiration pneumonia 3. Trauma 4. Hemorrhagic disease of the newborn 5. Haemolytic disease of the newborn 6. NEC 7. Septicaemia 8. Congenital anomalities of GIT
69	Avoidable factors to prevent preterm neonatal mortality (Ref PPIP V3)	1) Patient (mother) associated 2) Administrative problems 3) Medical personnel associated
70	Total number of preterm in the ward	1. 20-30 2.30-40 3. 40-50
71	Number of qualified doctors(resident and specialists) in day shift	1. 1-2 2. 3-4
72	Number of qualified doctors(resident and specialists) in night shift	1. 1-2 2. 3-4
73	Number of qualified nurses (RN, EN) day shift	1. 1-2 2. 3-4
74	Number of qualified nurses (RN, EN) night shift	1. 1-2 2. 3-4
75	Loss to follow-up	1. Yes 2. No

Appendix II: Verbal autopsy questionnaires:

Starting with greeting and introduce myself to the mothers of the study participant, then will ask how is the neonate doing,(waiting for the mothers response)If the baby is alive and well I will encourage for exclusive and frequent day and night breast feeding, keeping warm through kangaroo mother care and proper clinic attendance.

If the baby passed away, I will sympathize with the mother and ask what were the symptoms (presenting features) before she/he passed away.

Symptoms	**Response**
Un able to suck duration	
Fever with duration	
Convulsion	
Child become cold to touch (duration)	
Unresponsive (duration)	
Cough (duration, associated with/after feeding	
Bluish discoloration of the lips, tongue	
Vomiting (after feeding, or blood vomits)	
Abdominal distention and or blood diarrhea	
Redness or discharge from umbilical cord	
Baby had yellow palm or soles	

Appendix III: Consent forms (English Version)

ID NO……..

PERMISSION FOR A BABY TO TAKE PART IN RESEARCH

Study title **MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG PREMATURE NEONATES AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM:**

Introduction:

My name is Dr Anna Magembe; I am a 2nd year master's student working on my thesis. Your baby is being asked to take part in this study because I am trying to determine the preterm neonatal mortality rate and their associated risk factors among preterm. Your decision whether or not to allow your neonate to take part will have no effect on the quality of your neonate's medical care. Please ask any questions if there is anything about this study you do not understand.

Will you benefit from taking part in this study?

Your preterm neonate will be a volunteer and will benefit from being in this research study. Also the study may help other preterm neonates in the future. If you choose not to take part in the study, your neonate will continue to receive regular care at the hospital as required

What does this study involve?

Your neonates' evaluation as part of this study will be done in the ward and the investigations that could be done on your neonate are the part of standard of care for preterm neonates

What are the risks involved with taking part in this study?

There are no risks involved as everything that could be done to your preterm neonate will be part of the standard care

Leaving the study: You may choose to stop taking part in this study at any time and for any reason. If you decide to stop taking part, it will have no effect on your neonate's medical care.

New Information: New information related to this study and specifically new information about your neonates will be made known to you immediately if becomes available.

How will your privacy be protected?

The information obtained from you and your neonate will be kept strictly confidential. The study information will be stored in protected computer files and in paper records stored in locked filing cabinets. Only study staff will have access to the information.

Who may use or see your health information?

By signing this form, you allow only the research team to use your neonate's health information.. The research team includes the study director the supervisors working on this study at MUHAS.

Your permission to use your neonate's health information for this study will not end until the study is completed. You may ask for your neonate's study data at any time.

What if you decide not to give permission to use and share your personal health information?

If you do not allow the use of your neonate's health information for this study, you may not take part in this study.

If you choose to stop taking part in this study, you may cancel permission for the use of your neonate's health information. You should let the researcher know if you want to cancel your permission. The study team will assist you in putting your wishes in writing. Information collected for the study before your permission is cancelled will continue to be used in the research.

Whom should you call about this study?

If you have questions about this study, you can call your doctor or the research director for this study: Dr. Anna Magembe (0713 048397) any time during study duration. If you have questions about your rights as a participant, you may contact **Director of Publications and Research, Muhimbili University of Health and Allied Sciences, Research and Publication Committee, P. O. Box 65001, Dar es Salaam, Telephone number 2150302-6 during working hours.**

What about the costs of this study?

There will be no additional costs for you besides normal hospital fees if you agree to have your neonate participate in the study. All study costs will be supported by the research team.

Will you be paid to take part in this study?

There will be no payment to you for participating in the study.

If you agree that your neonate take part in this study and you sign this consent form, you are not giving up any of your legal rights.

CONSENT

I have read the above information concerning **MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG PREMATURE NEONATES AT MUHIMBILI NATIONAL HOSPITAL** and have been given time to ask questions. I agree to take part in this study and I have been given a copy of this signed consent form.

SIGNATURE

_____

Researcher or Designee Signature and Date Printed Name

_____

Legally Authorized Representative (mother) and Date Printed name

Appendix IV RIDHAA YA KUSHIRIKI KWENYE UTAFITI HUU

Namba ya Utambulisho……

Utafiti: **VIDOKEZO HATARISHI NA SABABU ZILETAZO VIFO KWA WATOTO NJITI WALIOLAZWA KATIKA HOSPITALI YA TAIFA YA MUHIMBILI, DAR ES SALAAM.**

Utangulizi:

Habari! Mimi Naitwa Dk. Anna Magembe. Daktari Mwanafunzi katika chuo kikuu cha Muhimbili, kitengo cha watoto

Je dhumuni la utafiti huu ni nini?

Dhumuni la utafiti huu ni kuchunguza vidokezo hatarishi na sababu ziletazo vifo kwa watoto njiti waliolazwa katika Hospitali ya Taifa Muhimbili.

Je utafaidika kwa mwanao kushiriki kwenye utafiti huu?

Mtoto wako atapimwa kwa ridhaaa yako, na atafaidika kwa kuwepo kwenye utafiti huu. Pia, utafiti unaweza kusaidia watoto wengine njiti katika siku zijazo. Kama ukichagua kutoshiriki katika utafiti mtoto wako ataendelea kupokea huduma stahiki katika hospitali hii .

Je Utafiti huu unahusisha nini?

Uchunguzi wa mtoto wako kama sehemu ya utafiti huu utafanyika wodini na vipimo atakavyofanyiwa ni vile vifanyikavyo kwa watoto njiti wote hapa hospitalini kama sehemu ya matibabu

Je itakuwaje kama hutataka kushiriki kwenye utafiti huu?

Kushiriki kwa mtoto wako kwenye utafiti huu ni hiari kabisa. Mtoto wako ataendelea kupata huduma bila kujali kama ameshiriki kwenye utafiti ama la.

Je kuna athari gani za kushiriki katika utafiti huu

Hakuna athari zozote zitokanazo na kushiriki katika utafiti huu

Kuondoka kwenye utafiti: Unaweza kuamua kusitisha kuendelea kushiriki kwenye utafiti huu muda wowote na kwa sababu yoyote. Kama utaamua kuacha kushiriki hautaathiri huduma za afya kwa mtoto wako.

Maelezo mapya: Maelezo mapya kuhusiana na utafiti huu na hasa maelezo mapya kuhusu mtoto wako utajulishwa mara tu yatakapokuwa yamepatikana.

Utunzaji wa siri?

Habari utakazotoa wewe na za mtoto wako pamoja na majibu ya vipimo yatatunzwa kwa usiri mkubwa. Habari zihusuzo utafiti zitatunzwa kwenye kompyuta zenye ulinzi na rekodi, zilizopo kwenye makaratasi zitatunzwa kwenye makabati yanayofungwa. Ni wafanyakazi wanaohusika na utafiti tu ndio watakaoweza kuona taarifa, na taarifa hizi zitatunzwa siku zote.

Ni nani anaweza kutumia au kuona taarifa zako za afya?

Kwa kuweka sahihi kwenye fomu hii umeruhusu watafiti kutumia taarifa za afya za mtoto wako na kuwapatia wengine wanaohusika na utafiti huu. Watafiti ni pamoja na mwendesha utafiti pamoja na wengine wanaohusika na utafiti huu ambao wapo Chuo Kikuu cha Muhimbili.

Ruhusa ya kutumia taarifa za afya za mtoto wako itaisha wakati utafiti utakapokamilika. Unaweza kuomba taarifa za mtoto wako wakati wowote.

Kama hautaruhusu taarifa ya afya ya mtoto wako zitumike, hautaweza kushiriki kwenye utafiti huu..Kama utachagua kuacha kushiriki katika utafiti huu, unaweza kufuta ruhusa ya matumizi ya taarifa za afya za mtoto wako. Watafiti watakusaidia kuweka matakwa yako kwenye maandishi. Taarifa zitakazokuwa zimekusanywa kabla ya kufuta ruhusa zitaendelea kutumika kwenye utafiti.

Je utampigia nani kuhusu utafiti huu?

Kama una maswali kuhusu utafiti unaweza kumpigia daktari wako au mwendesha utafiti huu: Dr Anna Magembe(0713 048397) muda wowote . Kama una swali kuhusu haki zako kama

mshiriki unaweza kuwasiliana na **Mkurugenzi wa Kamati ya Kitengo cha Utafiti, Chuo Kikuu Cha Sayansi na Tiba Cha Muhimbili, S.L.P 65001, Dar es Salaam, Namba ya Simu 2150302-6 muda wa masaa ya kazi**

Je kuna gharama juu ya tafiti huu?

Hakuna gharama kama utakubali mtoto wako ashiriki kwenye utafiti huu. Watafiti na Chuo kikuu cha Muhimbili watasaidia gharama zote za utafiti .

Je utalipwa kwa kushiriki kwenye utafit:

Hapatakuwa na malipo kwako au mtoto wako kwa kushiriki kwenye utafiti

Kama utakubali mtoto wako ashiriki kwenye utafiti huu na ukasaini fomu hii ya ridhaa, haujiondolei haki yoyote ya kisheria.

Ridhaa

Nimesoma/nimesomewa maelezo hapo juu kuhusu uchunguzi wa vidokezo hatarishi na visababishi vya vifo kwa watoto njiti waliolazwa katika Hospitali ya Taifa Muhimbili na nimepewa muda wa kuuliza maswali. Nakubali kushiriki katika utafiti huu kwa kutia sahihi katika fomu hii ya ridhaa.

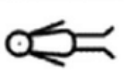
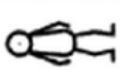
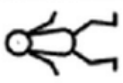
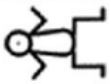
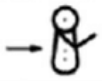
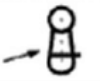
Sahihi

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Sahihi na jina la mtafiti au kaimu tarehe

Appendix V: BALLARDS SCORE

Neuromuscular Maturity

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	90°	 60°	 45°	 30°	 0°	
Arm recoil		 180°	 140°–180°	 110°–140°	 90°–110°	 <90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf sign							
Heel to ear							

Physical Maturity

Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale areas; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior ⅔	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity Rating

Score	Weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Appendix VI. ETHICAL CLEARANCE

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

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Ref. No. DA.287/298/01A/ 6th July, 2018

Dr. Anna G. Magembe
MMed. Paediatrics and Child Health
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: "MORTALITY RATE AND ASSOCIATED RISK FACTORS AMONG PREMATURE NEONATES AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 2nd July, 2018 to 1st July, 2019. In case you do not complete data analysis and dissertation report writing by 1st July, 2019, you will have to apply for renewal of ethical clearance prior to the expiry date.

Prof. P. Muganyizi
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Medicine