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Trends in the survival of low birth weight neonates to hospital discharge at Charlotte Maxeke Johannesburg Academic Hospital from 1st January 2013 – 30th June 2019

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2020
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SCHOOL OF PUBLIC HEALTH

TRENDS IN THE SURVIVAL OF LOW BIRTH WEIGHT NEONATES TO HOSPITAL DISCHARGE AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL FROM 1ST JANUARY 2013 – 30TH JUNE 2019.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology (Epidemiology and Biostatistics)

October, 2020.

DECLARATION

I, Wuraola Aduke Aderounmu declares that this research report was conducted and written by me. It is being submitted for the award of a Master of Science degree in epidemiology in the field of epidemiology and biostatistics to the University of the Witwatersrand, Johannesburg. The research report has not been submitted before for any examination of degree at the University of the Witwatersrand or any other university.



6th day of October 2020

DEDICATION

I am dedicating this research report to God, my fiancé (Dr. Opeyemi Bamigbetan), and my parents.

ABSTRACT

Introduction: According to the South Africa District Health Information System (SADHIS), 12 neonates per 1000 live births die annually. In order to reduce mortality, especially among the low birth weight (LBW) neonates, hospitals in SA must carry out regular mortality audit among neonates. The audit will track and count mortality among every new-born and LBW babies.

Aim and objectives: The present study aims to explore changes in the survival of LBW neonates to hospital discharge at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1st January 2013 – 30th June 2019. Furthermore, the study will identify the prevalence of mortality over time, and the factors influencing the survival of neonates to hospital discharge. Lastly, the study sought to estimate the survival time of LBW neonates according to the length of hospital stay.

Methods: We retrospectively reviewed the database of neonates who weighed between 400 g and 2500 g and were either inborn or admitted to the neonatal unit at CMJAH between 1st January 2013 – 30th June 2019. The Pearson's chi-square test and join point regression were used to determine the prevalence of mortality over time and to identify changes in the survival of LBW babies over time. Additionally, logistic regression and Cox proportional hazard regression was used to explore factors influencing the survival of LBW babies.

Results: We classified the birth weight of neonates into extremely low birth weight (ELBW) (≤ 1000 g), very low birth weight (VLBW) (1001-1500 g), and LBW (1501-2500 g). There was a 1.1 % downward trend in the survival of LBW neonates to hospital discharge over time. A 9.8 % downward survival trend was observed among neonates who weighed ≤ 1000 g over time. Overall, the survival rate among LBW neonates in the study was 82.7 %. The main significant factors that were found to be associated with neonatal mortality were birth weight, early-onset sepsis (EOS), and major birth defects. The odds of dying among neonates who weighed 1001-1500 g was 90 % less likely than the odds of dying among neonates who weighed ≤ 1000 g (OR: 0.10; 95 % CI = 0.08; 0.12; p=0.001). The odds of dying among neonates who weighed 1501-2500 g was 97 % less likely than the odds of dying among neonates who weighed ≤ 1000 g (OR: 0.03; 95 % CI = 0.02; 0.04; p=0.001). Additionally, the odds of dying among neonates who presented with EOS was 55 % times higher than those who did not have EOS (OR: 1.55; 95 % CI = 1.06; 2.27; p=0.02). The presence of a birth defect

places neonates at higher odds of dying than those who did not have a birth defect (OR: 16.37; 95 % CI = 12.22; 21.93; p=0.001). The majority of neonates died within the first seven days of hospital admission.

Conclusion and recommendations: The present study shows that there is a decrease in the survival of LBW babies over time, mostly among neonates who weighed ≤ 1000 g. The study found birth weight, sepsis infection, and birth defects to be the major contributing factors to the survival of a baby to hospital discharge. Also, the majority of the neonates died within the first seven days of hospital admission. Regular mortality audit should be done in health care places to identify areas for direct interventions to reduce mortality among LBW neonates. More trend studies should be done with hospital data to identify the patterns of variation in neonatal mortality over time.

ACKNOWLEDGMENTS

I want to express gratitude to my supervisors, Professor Daynia Ballot, and Professor Tobias Chirwa, for the guidance during the period of writing my thesis. Thank you for always having an open door to address the challenges faced during my research despite their busy schedule. Also, thank you both for sharing your knowledge, expertise, critical reviews, and providing suggestions that helped to improve the standard of the research. I always looked forward to your feedback.

I am grateful to the CEO and Head of Paediatrics of CMJAH for granting access to use the data.

I am also grateful to my fiancé, Dr. Opeyemi Bamigbetan for his support towards the completion of my degree. I am grateful to my parents (Mr. and Mrs. Aderounmu) for their endless prayers and words of support that kept me going during the period of writing my thesis.

To my siblings, friends, and all who directly or indirectly made this journey a memorable one. I say a big thank you.

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LIST OF ABBREVIATIONS

ANC	Antenatal Care
ELBW	Extremely Low Birth Weight
EOS	Early Onset Sepsis
HMD/RDS	Hyaline Membrane Disease/ Respiratory Distress Syndrome
IVH	Intraventricular Hemorrhage
KMC	Kangaroo Mother Care
LBW	Low Birth Weight
LOS	Late Onset Sepsis
MDG	Millennium Development Goals
MOU	Midwife Obstetrics Units
NaPeMMCo	National Perinatal Morbidity and Mortality Committee
NCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotizing Enterocolitis
PDA	Patent Ductus Arteriosus
PPIP	Perinatal Problem Identification Programme
SDG	Sustainable Development Goal
UNIGME	United Nations Interagency Group for Child Mortality Estimation
VLBW	Very Low Birth Weight
WHA	World Health Assembly
WHO	World Health Organization

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DEFINITION OF TERMS

Neonatal mortality in the current study was defined as death that occurred before hospital discharge from the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

The term “survival of neonates to hospital discharge” in the present study refers to a state whereby the neonate is released alive from the hospital after birth based on physiological stability, family readiness, and capability to deliver satisfactory care for the new-born at home, and sure access to the hospital and resources (1,2).

CHAPTER 1 INTRODUCTION

This chapter provides a brief background of the study. It summarises findings from similar studies, highlights gaps in the literature, and establishes the significance of the study in addressing the gaps. The chapter concludes with the overall aim and objectives of the study.

1.1 Background of the study

Globally, 2.5 million neonates die according to the 2019 key facts of new-borns and about one million neonates die within the first twenty-four hours (3). Neonatal mortality accounted for 47 % of all under 5 mortality deaths in 2018 (4). In the year 1990, neonatal mortality was reported to be 37 deaths per 1000 live births, decreased slowly to 31 deaths per 1000 live births in 2000, and decreased rapidly to 18 deaths per 1000 live births in 2018 (4). The 2019 mortality report shows a decline in the rate of neonatal mortality from 5 million in 1990 to 2.5 million in 2018 (3). However, the neonatal mortality rate from 1990 to 2018 was reported to have had a slower reduction rate compared to the reduction in mortality for children aged between 1 – 59 months (5).

The World Health Organization (WHO) reported that close to 15 % of neonates globally are born with low birth weight (LBW) (6). The WHO termed neonates with a birth weight less than 2500 g regardless of their gestational age as LBW baby (7). Globally, there has been a slow decrease in the prevalence of LBW neonates, from 17.5 % in 2000 to 14.6 % in 2012 (6).

According to the United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) report in 2019, Sub-Saharan Africa (SSA) has the highest rate of neonatal mortality (28 deaths per 1000 live births), followed by Southern Asia (25 deaths per 1000 live births (4). The United Nations International Children's Emergency Fund (UNICEF) global estimate shows that 14.3 % of neonates in Africa are born with LBW (8). There has been a slow decline in mortality rate among LBW babies in SSA from 46 deaths per 1000 live births in 1990 to 44 deaths in 1995, 41 deaths in 2000, 36 deaths in 2005, 32 deaths in 2010, 29 deaths in 2015 and decreased to 28 deaths in 2018 (4). Furthermore, the WHO report shows a slow decline in the prevalence of LBW neonates in Africa from 18.7 % in 2000 to 15.4 in 2015 (6).

In South Africa (SA), 12 neonates per 1000 live births die annually according to the District Health Information System (DHIS) data (9). In contrast, 21 neonates per 1000 live births die according to the SA demographic health survey (SADHS), with 81 % of the neonatal deaths happening in the first week of life (9). The contrast in neonatal death rates between DHIS and

SADHS sources is because some deaths occur outside of healthcare facilities and are not captured in the DHIS data (10). The UNIGME report shows that neonatal mortality in SA has declined from 20 deaths per 1000 live births in 1990 to 11 deaths per 1000 live births in 2018 (4). However, there has been no significant change in the prevalence of mortality among LBW neonates in SA from 15.0 % in 2000 to 14.3 % in 2015 to 14.2 % in 2018 (6). The insignificant change in mortality is attributed to a lack of accurate statistics on neonatal mortality in SA, high prevalence of HIV/AIDS, tuberculosis, and lack of adequate interventions (11). Furthermore, neonatal mortality in SA is attributed to preterm birth complications, intrauterine hypoxia infections, birth asphyxia, and other miscellaneous factors (10).

The third Sustainable Development Goal (SDG) aims to ensure good health and well-being for all including the prevention of avoidable deaths of new-born babies. In agreement with the third SDG target, countries must aim to reduce mortality among neonates to 12 per 1000 live births and under 5 mortality to as low as 25 per 1000 live births by 2030 (12). Furthermore, the World Health Assembly (WHA) has set up a target to assist with achieving the SDG target, which is to reduce the prevalence of LBW to 30 % between 2012 and 2025 (8). Mortality among neonates, especially the LBW, is a significant public health concern in SA that requires urgent and effective interventions (13). If all countries should reach the SDG neonatal mortality targets, more than half the lives of babies in SSA would be saved, thereby preventing the possibility of the recent trends predicting that about 52 million children will die between 2019 and 2020 (4).

To reduce neonatal mortality, especially among the LBW neonates, SA has developed different strategies and audit programs in hospitals to track and count every new-born, LBW, and mortality for better improvement of the health outcome of neonates. SA is one of the few countries in SSA with functional mortality audit tools such as the Perinatal Problem Identification Programme (PPIP), which allows for easy data entry and analysis. The PPIP has allowed the establishment of policies due to the facility data and gives feedback to the facility (14). Audit for neonatal mortality patterns is a very important process because it provides the required information for health planning and budget allocation.

1.2 Literature review

1.2.1 Prevalence and trends of neonatal mortality

Globally, 18 neonates die per 1000 live births annually, which is close to 2.5 million deaths (4,15). Further, 39 children under the age of five die per 1000 live births annually (4,15). The 2019 UNIGME report shows that South Asia and SSA accounts for about 79 % of the neonatal deaths, west, and central Africa accounts for 23 %, and east and southern Africa accounts for 18 % of the neonatal death (15). The UNIGME reported a high annual mortality rate reduction in central Asia, where the neonatal mortality decreased from 5.6 % (1990 – 2000) to 2.1 % (2000 – 2018) compared to low and middle-income countries (LMIC) in SSA, with an increased neonatal mortality rate (15).

The statistical release of neonatal deaths in SA shows that neonatal mortality rates declined from 7.9 deaths in 1998 to 5.7 deaths per 1000 live births in 2001, thereafter rising and peaking at 11.1 deaths in 2009. Between 2009 and 2013 a general decline in the number of early neonatal deaths was observed (from 11.1 deaths to 7.8 deaths). The recorded deaths in 2014 were 7.9 neonates, 8.0 deaths in 2015, and 6.7 deaths per 1000 live births in 2016 (9). Similarly, a study was done on child mortality trends and causes of death in SA from 1997 – 2012. The study shows that neonatal mortality in SA peaked in 1997 with 19 deaths per 1000 live births and declined to 12 deaths per 1000 live births in 2002 and since became steady till 2012 (5). The 2019 UNIGME report shows that neonatal mortality in SA reduced between 1975 and 2018 (4). A decrease in neonatal mortality was observed from 2013 (12 deaths per 1000 live births), 2014 (11.9 deaths per 1000 live births), 2015 (11.6 deaths per 1000 live births), 2016 (11.3 deaths per 1000 live births), 2017 (11.1 deaths per 1000 live births) to 2018 (10.7 deaths per 1000 live births) (4). Despite the observed decrease in neonatal mortality, the UNIGME report indicated that SA did not achieve the fourth target of the Millennium Development Goals (MDG) by 2015, which was to reduce neonatal mortality by two thirds (15,16). However, SA is among the 12 countries in SSA where neonatal mortality has decreased since the reference line for the MDG in 1990 (4,11). There have been challenges with getting good data estimates of neonatal mortality in LMIC. This explains the big differences in the estimates or findings from different reports on neonatal mortality. Therefore, WHO encourages countries, hospitals to audit neonatal mortality regularly for urgent health interventions to reduce neonatal mortality (17).

The WHO report on LBW shows that the progress in reducing LBW globally has been stagnant since 2000 (18). Other African countries do not have available data on the prevalence of LBW, however, the data available for SA showed an insignificant decrease in the percentage of LBW from 2000 (15.0 %) to 2015 (14.2 %) (18). The WHO recommended that governments, especially in African countries, should improve the data systems, target tracking tools, or audit programs to enable policy-makers to track the annual average reduction rates of LBW and monitor the progress at national levels. Therefore, the proposed recommendation would help to develop effective programs to prevent LBW, and potentially improve the pregnancy experience of several women, protect the survival, growth, and long-term development of the children.

Moreover, monitoring the trend of neonatal mortality over time gives a good idea of the progress of the country and it assists the health authorities to identify where to focus their attention. A study has shown that a neonate born in SSA is nine times more susceptible to die compared to a neonate born in a high-income country (15). A meta-analysis was done on the income and child survival in a LMIC country, it was found that the high rate of neonatal mortality shows the condition of the health care services provided to pregnant women and their babies in the country (19). It is a good indicator of the socio-economic status of the country. If the standard of living of a country is improving, the neonatal mortality is expected to reduce (19). Many of the neonatal deaths have been attributed to preventable infectious diseases and could be prevented with simple and inexpensive interventions (1).

1.2.2 Determinants of the survival of neonates

Several factors have been shown to determine the survival of neonates. The factors include the demographic characteristics of the mother and neonate, the biological or clinical factors, and the environmental factors (20).

1.2.2.1 Demographic characteristics of the mother associated with neonatal mortality

The wellbeing of pregnant mothers is an important tool that has a big impact on the survival of neonates. According to Mosley and Chen's analytical framework on the determinants of child survival, maternal factors have been shown to directly affect the outcome of the pregnancy and the survival of the neonates (20). The maternal factors include the age of the mother, race, and access to antenatal care (ANC) (20). The UN report on adolescent pregnancy reveals that close to 16 million teenagers give birth every year, of which close to 90 % of the teenage pregnancy occur in developing countries (21). A report from the demographic profile of adolescents in

SA shows that 30 % of adolescents in the age group of 15 – 19 years deliver babies every year (22). Additionally, the statistics of birth to teenage mothers revealed that 12.5 % are black, 11.1 % are colored, 2.4 % are Indian/Asian and 1.8 % are white (22). The UNIGME report shows that the biological immaturity of the teenage mother, the effect of social and environmental factors, lack of education, and lack of income to sustain themselves and the baby, decreases the chances of survival of the neonates (15). The UN report on adolescent pregnancy reveals that, neonates who are born to teenage mothers are 1.5 times more likely to die compared to neonates born to older women (23).

The UNICEF report indicated that SA is a middle-income country with quite a high percentage of poverty, which could limit pregnant women from getting access to good health care (24). However, the SA government has provided free access to health care for pregnant women and children under the age of six to reduce infant and child mortality (11). A systematic review and meta-analysis study was done on the income and child mortality in LMIC countries. It was found that income plays a huge role in the survival of a child (19). Furthermore, countries with high infant and neonatal mortality tend to have a very low GDP per capita and SA is not an exception (19). A study done on the challenges and progresses in SA since 2009 found that, the poor economic status of the country is related to a high rate of infectious diseases such as sepsis and HIV/AIDS among pregnant women. This is partly because of the inability to maintain a healthy lifestyle thereby posing a risk to the new-born and unborn child (25,26).

Furthermore, a study was conducted on the health system in SA and found that the high rate of poverty can also lead to lack of access to nutritional diet, which can place the mother and child in a malnourished condition. The malnourished condition can increase their susceptibility to complications during pregnancy or delivery, faltered growth of the baby, LBW, sepsis infection, and death (11). A study that was conducted on the adverse effect of maternal Sexually Transmitted Infections (STIs) on pregnancy and neonates found that the demographic factor of the pregnant women can affect the treatment-seeking behavior of those who present with the symptoms of STIs. The study proposed that the presence of STIs can lead to an increased risk of HIV, which can get transmitted to the neonates, thereby leading to preterm birth, LBW, birth defects, and mortality (27).

1.2.2.2 Biological and clinical factors associated with neonatal mortality

The biological factors include the sex and weight of the neonates. The 2019 UNIGME report has shown that on average, male babies have a higher probability of dying before attaining the

age of five than female babies (4). Similarly, a study found that male babies are more likely to die compared to females (28). In contrast, a study found that female babies are three times more likely not to survive compared to male babies (29). The contradiction might be attributed to the differences in the number of male and female observations in each study.

The birth weight of the neonate is another significant factor that has been found to influence the survival of neonates. Results from previous studies have shown that the lower the birth weight, the higher the probability of not surviving (28–31). A study was done on the survival of VLBW neonates inborn or admitted to Chris Hani Baragwanath Johannesburg Hospital from 2000 to 2002. The study found an overall survival rate of 72 % and survival was higher among neonates who weighed between 1000 g and 1499 g compared to 32 % survival rate among neonates who weighed less than 1000 g (28). Similarly, a study was done among VLBW neonates born between 2006 and 2007 in a public hospital in Johannesburg. The study found an overall survival rate of 70.5 % and survival rate was lower among neonates who weighed less than 1001 g (34.9 %) compared to 85.8 % survival among neonates who weighed between 1001 g and 1500 g (29). Another study was done in the same facility to compare the survival rate among VLBW neonates born between 2006/2007 and 2013. The study found an overall survival rate of 73.4 %. However, there was a significant improvement in the survival rate of neonates who weighed 750 g to 900 g from 20.4 % in 2006/2007 to 52.4 % in 2013 (30). The improvement in survival was attributed to the provision of surfactant and nasal continuous airway pressure (NCPAP) for the group of neonates weighing 750 – 900 g (30).

Additionally, a study was done on the survival of ELBW neonates who weighed ≤ 900 g and found a low overall survival rate of 26.5 % (31). The low survival rate was attributed to the limited NCPAP machines for the ELBW neonates, thereby leading to the provision of NCPAP to the sickest babies in the unit. The survival rate was lower compared to the survival rate of 83 % to 90 % among VLBW and ELBW neonates in developed countries (32). The finding shows the benefit of regular clinical audits in hospitals with limited resources, brings awareness to health care workers about the survival rates and areas that require improvement. Furthermore, the information obtained from clinical audits in various hospitals will positively contribute to change in policy to improve the survival of the vulnerable neonates.

Several clinical factors have been reported to contribute to the survival of LBW neonates. The factors are birth asphyxia, antenatal steroids, mode of delivery, patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), congenital pneumonia, major birth defects, mechanical

ventilation and oxygen (10,28–30,32–35). Also, the length of hospital stay, bronchopulmonary dysplasia (BPD), early-onset sepsis (EOS), late-onset sepsis (LOS), Necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) are factors reported to contribute to the survival of neonates to hospital discharge (10,28–30,32–35).

A study done on the major causes of neonatal mortality globally, reported that approximately 30 % of the neonatal mortality is caused by birth asphyxia, which occurs as a result of failure to start and sustain normal breathing at birth (34). The study proposed that if there is no proper intervention, asphyxia can lead to brain damage and multiple organ dysfunction. A case-control study was done on the risk factors of birth asphyxia among neonates in public hospitals, it was found that vaginal breech deliveries, birth defects, pregnancy-induced hypertension, and prolonged labor or rupture of the membranes were all risk factors of birth asphyxia (35). The findings from these studies signify the importance of mortality audit to identify the care practices needed to improve the survival of neonates.

The main causes of death in SA according to the PPIP mortality audit are extreme multi-organ immaturity (40 %), hyaline membrane disease (25.9 %), nosocomial infection (10 %), NEC (10 %), asphyxia (12.1%), sepsis (2.1 %), IVH (2.1 %) and congenital infection (1.4 %), birth defect (2.8 %), pulmonary haemorrhage (1.4 %) and unspecified causes (2.1 %) (10,33).

A study was done on the survival of ELBW neonates born between 2006 and 2010 in Johannesburg hospital. The study found an increase in the causes of neonatal mortality compared to the findings from the study done between 2006 and 2007. The causes of neonatal mortality were found to be extreme multi-organ immaturity (63.9 %), RDS (25.9 %), sepsis (4.29 %), (NEC) (1.79 %), asphyxia (1.43 %), IVH (0.71 %) and HIV infection (31). The statistics provided above indicate that tackling the avoidable factors of neonatal mortality is still a huge challenge in LMIC like SA (36). Furthermore, the study investigated the relationship between the length of hospital stay and neonatal mortality. They found that most neonates died within the first few days of life, 60 % within three days, and 79 % by the end of the seventh day (31).

According to the study done on the chronic lung disease (CLD) in neonates at CMJAH from 1st January 2013 to 31st December 2014, it was found that neonates born with VLBW are at high risk (15.8 %) of developing CLD compared to the normal birth weight neonates (37). Therefore, a report on the perinatal care in SA proposed that antenatal steroids should be given

to pregnant mothers who are at risk of preterm birth before delivering the baby to help develop the lungs of the baby (33).

The mode of delivery of the babies is a significant factor associated with the survival of the LBW neonates to hospital discharge (28,30). The studies found that vaginal delivery was associated with a lower survival rate compared to delivery by cesarean section (28–31).

Neonatal sepsis is the invasion of bacteria into the bloodstream of the neonates. A study was done to determine the epidemiology of neonatal sepsis in Johannesburg Hospital between 2002 and 2003. It was found that neonates can acquire either early-onset sepsis (EOS) (which occurs within the first 3 days of birth) via the maternal genital tract or late-onset sepsis (LOS) (which occurs after day 3 through 28 days) via the hospital environment also known as Nosocomial infection (38). The study reported that if the bacteria in the blood are left untreated, it can spread to the different parts of the brain thereby leading to neonatal meningitis and long term complications (38). The study reported that 40 % of the neonates died due to EOS and 19.7 % died due to LOS. Additionally, the study found that antibiotic resistance in the treatment of sepsis in neonates is a huge challenge and a public health concern (38).

Mortality audit in health care facilities should be done routinely to allow awareness of the survival rate of neonates according to the maternal, biological, and clinical characteristics. Knowledge of the factors associated with mortality over time would help the health care workers to know the areas to improve on. Few studies have investigated the trends in the survival of neonates to hospital discharge to identify if there is a variation in the survival of neonates over time which is a gap the present study is going to fill.

1.2.2.3 Policies put in place to reduce neonatal mortality over the years

Policies have been put in place by the South African government to reduce neonatal mortality nationally (23,39). A review was done to determine the right steps to follow for better improvement of birth outcomes in low and middle-income countries (23). It was projected that importance should be directed towards the delivery care, providing patients access to the right health care, and providing the need promptly for an efficient way to reduce neonatal mortality. To reduce childbirth complications, there is a need for pregnant mothers to carry out certain steps on time. These include identifying what the problem is, making a decision to seek medical care, getting to the right medical care center on time, and get the needed care (23). Another study was done on what needs to be done to save the lives of SA mothers and babies. They

proposed that the first step is to educate and train pregnant women to enable a positive attitude toward their behavior to neonatal mortality (11).

A study was done to review the policies put in place in SA to reduce the rate of neonatal mortality (10). They went further to propose approaches to reduce avoidable factors causing neonatal mortality to ensure SA meets the SDG target by 2030. The study reported that the top ten avoidable causes of death due to the health care system in SA are the shortage of facilities in the neonatal unit, hospital-acquired infections, not detecting fetal distress intrapartum, and not referring patients for tertiary treatments at the right time. Additionally, shortage of neonatal intensive care units (NICU) bed with ventilator, inadequate monitoring and plan for neonatal care, shortage of nurses on duty to attend to the pregnant women and their neonates, and lack of transportation from home to the institution and within the institution. The study reported that these avoidable factors contributed to not meeting the MDG 4, which is to reduce child mortality (10).

The National Department of Health (NDoH) has developed different schemes to reduce the avoidable factors causing neonatal mortality SA (10). The schemes include an appointment of neonatal care improvement advisor and the establishment of the national neonatal coordinating committee in 2013 to coordinate and give insight to the improvement of neonatal care in SA (10). The National Perinatal Morbidity and Mortality Committee (NaPeMMCo) was also established and made its recommendations towards saving the lives of babies in SA (14). These recommendations include the improvement of the health care system for mothers and their neonates, the improvement of health care workers with the necessary skills in maternal and neonatal care, and the reduction of neonatal deaths that are caused by asphyxia, LBW, and infections (10). The study reported that the training programs have been implemented in SA and they include assisting neonates in breathing, management of sick and VLBW neonates, and vital steps in managing obstetrics emergencies (10). The NDoH has provided all provinces with highly trained personnel to conduct these programs.

The NDoH reported that anti-retroviral prophylaxis has been made available in clinics for the prevention of mother to child transmission (PMTCT) before and during pregnancy, through labor, delivery, and after birth up to 18 months (40). Additionally, HIV testing, counseling on infant feeding, and regular monitoring of baseline CD4 are readily available for pregnant women who are at high risk of HIV infection (40). SA is reported to be among the countries that have a low rate of exclusive breastfeeding in the world (10). Therefore, the SA government

has put in place awareness to increase exclusive breastfeeding practice in SA (10). One study has reported that the low rate of exclusive breastfeeding practice could contribute to the high rate of neonatal mortality in SA because breastfeeding passes on the vital antibodies to the neonate, which is needed by the body to fight against infections (26).

A review of the progress and challenges in reducing neonatal deaths in SA found that the neonatal care practices causing neonatal mortality are slowly improving in hospitals in efforts to increase the survival rate of neonates to hospital discharge (10). The care practices include the use of steroids, antibiotics, cesarean delivery, resuscitation at birth, and respiratory support (10). The improvement of neonatal care practice is possible because of regular hospital mortality audits and the monitoring of the survival rate of neonates over time. Also, the study proposed that more NICU facilities need to be built and they should be equipped with skilled staff, provision of kangaroo mother care (KMC), and NCPAP machines to reduce mortality among LBW neonates (10). The KMC is a process of having skin to skin connection between mother and new-born. It has been an efficient way to provide warmth and reduce mortality among the ELBW neonates (41). If efforts to reduce neonatal mortality in SA are not intensified, it will be very difficult to meet the SDG target, which is to reduce neonatal mortality by 2030.

1.3 Problem statement

Despite the efforts that are made to improve the care practices in hospitals to ensure high survival of LBW neonates to hospital discharge, mortality remains significantly high and big public health concern (10,28–30). Moreover, studies have been done to determine the factors associated with LBW mortality over the years (5,42). However, such studies are limited and do not show variations in the prevalence and factors influencing the survival of neonates to hospital discharge over time. Most studies on neonatal mortality often analyze the prevalence at a single time point and make use of logistic regression to determine the factors associated with mortality (10,28–30). Although, the importance of using the conventional approach of analysis to estimate the prevalence and factors associated with neonatal mortality cannot be disputed. However, it does not allow efficient analysis of data collected at different time points and observation of variations in the prevalence of neonatal mortality at different time points.

In response to the problem stated above, this study identifies the trends in the survival of neonates to hospital discharge over time. This will provide valuable insight regarding variations in mortality and factors influencing the variation over time.

1.4 Justification

Several studies have investigated the prevalence and factors associated with neonatal mortality over time (10,30). However, there is still limited recent information on the factors affecting the variations in the survival of neonates to hospital discharge over time. This study is important because all countries must meet the SDG 3 requirement by 2030. Therefore, mortality audit in health care facilities is a very important process to track the survival rates of neonates to hospital discharge and for health planning and resource allocation. Furthermore, the current study would assist policymakers to identify the highly susceptible neonates and put in place the appropriate interventions to reduce neonatal mortality in SA. It is important that we investigate factors that may impede the progress so that interventions can be put in place, which is why there is a need to determine the trends in survival of neonates to hospital discharge in CMJAH, South Africa from 1st January 2013 – 30th June 2019.

1.5 Research questions

1. What is the pattern of variation in the survival of neonates to hospital discharge at CMJAH from 1st January 2013 – 30th June 2019?
2. What are the factors associated with neonatal mortality from 1st January 2013 – 30th June 2019?
3. What is the survival estimate of neonates according to the length of the hospital stay?

1.6 Aim

To determine the trends in the survival of LBW neonates to hospital discharge in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), SA from 1st January 2013 – 30th June 2019**.**

1.7 Objectives

1. To describe the demographic and clinical characteristics of mothers and babies in the study.
2. To determine the prevalence of neonatal mortality.
3. To determine the trends in the survival of LBW neonates to hospital discharge over time.
4. To determine the demographic and clinical factors associated with neonatal mortality over time using bivariate analysis and multivariable analysis.
5. To estimate the survival of LBW neonates at CMJAH using the Kaplan-Meier survival plot.

CHAPTER 2 METHODOLOGY

This chapter provides information about the type of study design, where the primary data was collected, the study population, how the data was managed, and the statistical analysis conducted to address the objectives of the study. The chapter concludes with the study limitations and how ethical clearance was obtained.

2.1 Study Design

This study uses secondary data of multiple cross-sectional data from a referral health facility. For the purpose of this study, we carried out a secondary analysis by retrospectively reviewing the computer database for the medical information of neonates who were born or admitted to the neonatal unit at CMJAH between 1 January 2013 – 30 June 2019.

2.2 Description of the primary study

The data was collected cross-sectionally about the neonates inborn or admitted into the neonatal unit at CMJAH, Johannesburg. The data was collected weekly on discharge or death of the neonate by in house doctors for the purpose of clinical audit. The Head of the Department then verified the data before it was certified and uploaded onto the database. The database is managed using the Research Electronic Data Capture (REDCap) hosted by the University of the Witwatersrand (43). After verification, trained staff members at the neonatal unit capture the information about the mother and neonate from the paper forms into the electronic database for clinical audit purposes.

2.3 Study setting

The current study was conducted in the neonatal unit at CMJAH, Johannesburg, SA. It is a central hospital in Johannesburg with a total of 1,088 beds. The hospital provides tertiary services and highly specialized services, functions as a referral hospital for neighboring clinics and hospitals in its referral chain. It is the main teaching hospital for the University of the Witwatersrand, Faculty of Health Sciences and provides the service foundation for undergraduate and post-graduate training in the field of health.

2.4 Study Population

The study population included all neonates with a birth weight between 400 g and 2500 g, who were either inborn or admitted to the neonatal unit at CMJAH between 1st January 2013 – 30th June 2019. The study excluded neonates who had missing information.

2.5 Sampling

No sampling was done for this study. There were 6823 neonates in the study.

2.6 Data Collection

Secondary data was used hence, there was no need for data collection. However, the secondary data was available for collection from the neonatal unit, CMJAH after an ethical clearance certificate was issued.

2.7 Measurements

2.7.1 Outcome variable

The main outcome variable was binary, it was either the neonates died or survived to hospital discharge. It was recoded as "0" if neonates survived and "1" if neonates died.

2.7.2 Exposure variables

The primary exposure variable was the year of birth. It was treated as a categorical variable. The secondary exposure variables below were selected based on variables used in previous literature and the available data collected. The demographic characteristics of the mother included the following variables: maternal age, maternal race, mode of delivery, maternal HIV, and maternal syphilis (Table 2.7.2.1). The biological and clinical characteristics such as gender, gestational age, birth weight, antenatal care (ANC), major birth defects, initial resuscitation in the delivery room, congenital pneumonia, bronchopulmonary dysplasia (BPD). Additionally, Necrotizing enterocolitis (NEC)**,** mechanical ventilation, early-onset Sepsis (EOS), late-onset sepsis (LOS), Hyaline membrane disease (HMD), birth asphyxia, Nasal continuous positive airway pressure (NCPAP) patent ductus arteriosus (PDA), and intraventricular hemorrhage (IVH) (See Table 2.7.2.2).

Table 2.7.2.1: The exposure variables (Maternal factors)

Characteristics	Types	Value labels
Demographic Factors		
Maternal age	Categorical	0 = ≤ 19; 1 = ≥ 20
Maternal race	Categorical	0 = Black; 1=White; 2 =Coloured; 3 = Asian; 4 = Indian
Non-Demographic factors		
Maternal HIV	Categorical	0 = No; 1 =Yes
Maternal syphilis	Categorical	0 = No; 1 =Yes
Mode of delivery	Categorical	0 = Assisted vaginal delivery; 1=Caesarean section; 2 = Normal vaginal delivery; 3 = Vaginal breech

Place of birth	Categorical	0 = Born at Mid wives Obstetric Unit (MOU); 1=Born at another hospital; 2 = Born before arrival; 3 = Inborn

Table 2.7.2.2: The exposure variables (Neonatal factors)

Characteristics	Definition	Types	Value labels
Neonatal factors			
Gender		Categorical	0 = Female; 1 =Male
Birthweight	The weight of the newborn at birth	Categorical	0 = ELBW (≤ 1000 g); 1 = VLBW (1001-1500 g); 3 =LBW (1501-2500 g)
Year of birth		Categorical	0 = 2013; 1 =2014; 2 = 2015; 3 = 2016; 4 = 2017; 5 = 2018; 6 = 2019
Antenatal care	If mothers attended ANC or not	Categorical	0 = No; 1 =Yes
EOS	Blood infection after day three	Categorical	0 = No; 1 =Yes
LOS	Blood infection on or before day three	Categorical	0 = No; 1 =Yes
Oxygen on day 28	Provision of oxygen to the neonate on day 28	Categorical	0 = No; 1 =Yes
NEC	The invasion of bacteria into the wall intestine, thereby destroying the intestine.	Categorical	0 = No; 1 =Yes
Nasal CPAP	The provision of a steady flow of air to the lungs through the nose	Categorical	0 = No; 1 =Yes
Initial resuscitation in the delivery room	Provision of warmth, drying the baby, clearing the airways, positioning the baby's head, and giving positive pressure ventilation through bag and mask.	Categorical	0 = No; 1 =Yes
IVH	it is the bleeding in the fluid-filled areas inside the brain.	Categorical	0 = No; 1 =Yes
Congenital Pneumonia	It is an inflammatory disease of the lungs of neonates	Categorical	0 = No; 1 =Yes
Oxygen	Provision of oxygen to sustain the life of neonates	Categorical	0 = No; 1 =Yes
BPD	A chronic lung disease	Categorical	0 = No; 1 =Yes
Birth asphyxia	A condition caused by the deprivation of oxygen to a new-born baby	Categorical	0 = No; 1 =Yes
HMD/RDS	A respiratory disease of a new-born baby	Categorical	0 = No; 1 =Yes
Gestational age	It is used to calculate the length of pregnancy	Continuous	
Major birth defect	A baby born with anomalies	Categorical	0 = No; 1 =Yes
PDA	It is an opening between the two blood vessels from the heart.	Categorical	0 = No; 1 =Yes
Antenatal steroids	It is given to mothers to speed up the development of the neonate`s lungs.	Categorical	0 = No; 1 =Yes

2.8 Data management

2.8.1 Data cleaning process

The dataset was received in an excel format from a REDCap database at the CMJAH, neonatal unit. The dataset was imported into the STATA version 15.1 for checking of range, duplicates, recoding, renaming of variables, generation of new variables, restriction of data, and merging of datasets to suit the study objectives and statistical analysis of the study. The unknown information were treated as missing and were excluded from the analysis. The outcome variable was recoded into a binary variable, with newborns who died during hospital admission as "1" and those who survived to hospital discharge as "0".

2.9 Data Analysis Plan

2.9.1 Descriptive analysis

The demographic characteristics of the mother and neonates were analyzed. The categorical variables such as EOS, LOS, gender, etc. were summarized using frequency tables. The continuous variable such as gestational age was summarized as mean and standard deviation for normally distributed data.

2.9.2 Prevalence and trends in the survival of neonates over time

The demographic, biological, and clinical characteristics of the mother and neonates were analyzed. The prevalence of mortality among the babies observed was analyzed for each year of birth by conditioning during analysis. The categorical variables were summarized using frequency tables. The join point regression modeling was used to identify any variation in the pattern of survival of LBW neonates over time. (44,45). The join point regression modeling allows us to detect when statistically significant changes occur in the trend of survival of neonates over time. The model assumes a linear trend over the years. The analysis were done on STATA version 15.1 and join point regression program version 4.7.0.0.

2.9.3 Bivariate analysis

The demographic and clinical characteristics of the neonates were analyzed using bivariate analysis. Cross-tabulations were carried out for categorical variables using the Pearson's Chi-square test to compare the demographic and clinical characteristics between the two groups (died and survived). Statistical significance was considered at a 5 % level.

2.9.4 Multivariable analysis

All the statistically significant factors in the bivariate analysis at a 20 % level were included in the multivariable analysis. Additionally, variables from previous literature that were found to

be associated with mortality were included in the multivariable logistic regression to determine their effects on mortality. The Stepwise forward and backward selection method was used to select the variables and statistical significance for inclusion and exclusion of variables was taken at a 10 % level. Furthermore, we investigated possible confounder and interaction terms at this stage of the analysis. To determine the suitable model for the data, the likelihood ratio test was used to compare the different models and Pearson`s goodness of fit test to determine if the model was a good fit.

2.9.5 Survival Analysis

The overall mortality rate and mortality rate by gender, birth weight, and year of birth were investigated. The survival pattern of neonates according to the length of hospital stay was determined with the descriptive Kaplan-Meier survival function. The log-rank test was used to determine if there is a difference in the survival distribution between gender and birth weights (46).

Like the multivariable logistic regression, we fitted the semi-parametric Cox regression model to determine the factors associated with neonatal mortality. The Cox proportional hazard assumption test was done to ensure that the assumption of proportionality was not violated.

All analysis was done on STATA version 15.1.

2.10 Ethical considerations

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) before the commencement of the study (Clearance certificate number: M191073). The authorization to conduct the study was obtained from the management of CMJAH. Prior to securing the data from the Head of the neonatal unit, the data was de-identified to ensure anonymity. Accessibility to the data was limited to only the principal investigator and the supervisors. The data was Personal Identification Number (PIN) protected and stored on a secured external drive.

CHAPTER 3 RESULTS

This chapter presents the findings of the statistical analysis done in the study. The findings include a descriptive analysis of the demographic and clinical characteristics of mothers and neonates in the study, the prevalence of neonatal mortality in each year of birth, and the trends in the survival of LBW neonates are presented graphically. This chapter also includes the results of the bivariate analysis and multivariable logistic regression. The mortality rates, survival estimate of the neonates, and findings from the log-rank test are presented.

3.1 Demographic and clinical characteristics of mothers and neonates in the study

There were 6823 mothers and the average age was 29 years. There were more black women (95.9 %) in the study compared to the white, colored, Asian, and Indian women (**Table 2.9.5.1**). The majority of mothers were 20 years and older (93.4 %). About 61.0 % of the mothers did not receive antenatal steroids. The largest percentage (56.5 %) of the mothers delivered via cesarean section followed by a normal vaginal delivery (40.5 %). More women visited for ANC (82.4 %). (See **Table 2.9.5.1**).

We excluded 4324 neonates with normal birth weights (> 2500 g) from the total births (11, 147) from January 2013 to June 2019 because the study focused on neonates below 2500 g. A total of 6823 neonates from 2013-2019 were included in the study. However, there were 6737 LBW neonates due to missing information in the database. We classified the birth weight of babies into ELBW (≤ 1000 g), VLBW (1001-1500 g), and LBW (1501-2500 g). More babies weighed between 1501 g and 2500 g (50.5 %) compared to 32.6 % of babies who weighed between 1001 g and 1500 g and 16.9 % of babies who weighed ≤ 1000 g. There were slightly more male babies (51.07 %) than female babies (48.9 %). (See **Table 2.9.5.1**).

Table 2.9.5.1: The demographic and clinical characteristics of mothers and neonates in the study

Variables	Frequency (-)	Percentage (%)
Maternal race		
Black	6467	95.9
White	101	1.5
Coloured	101	1.5
Asian	6	0.1
Indian	48	0.7
Other	19	0.3
Maternal age (years)		
≤ 19	380	6.5
≥ 20	5437	93.4
Maternal HIV		
Yes	2084	32.3
No	4373	67.7
Maternal Syphilis		
Yes	148	2.4
No	5984	97.6
Antenatal care		
Yes	5085	82.4
No	1088	17.6
Antenatal steroids		
Yes	2010	39.1
No	3125	60.9
Mode of delivery		
Assisted vaginal delivery	28	0.4
Caesarean section	3634	56.5
Normal vaginal delivery	2609	40.5
Vaginal breech	164	2.6
Gestational age (in weeks): Mean ± SD	31.5 ± 3.7	
Place of birth		
Born at MOU	321	4.8
Born at another hospital	769	11.5
Born before arrival	344	5.1
Inborn	5244	78.1
Gender of the neonates		
Female	3058	48.9
Male	3200	51.1
Birthweight (Grams)		
≤ 1000 g	1138	16.9
1001 - 1500 g	2198	32.6
1501 – 2500 g	3401	50.5

3.2 The prevalence of neonatal mortality and the trends in the survival of neonates to hospital discharge from 2013-2019.

3.2.1 The proportion of neonates at CMJAH surviving over time.

The study included 6823 neonates, of which 5631 neonates survived to hospital discharge (82.7 %) and 1177 (17.3 %) died during the period of hospital stay. The proportion of neonates that survived to hospital discharge decreased over time. (See **Figure 3.2.1.1** below).

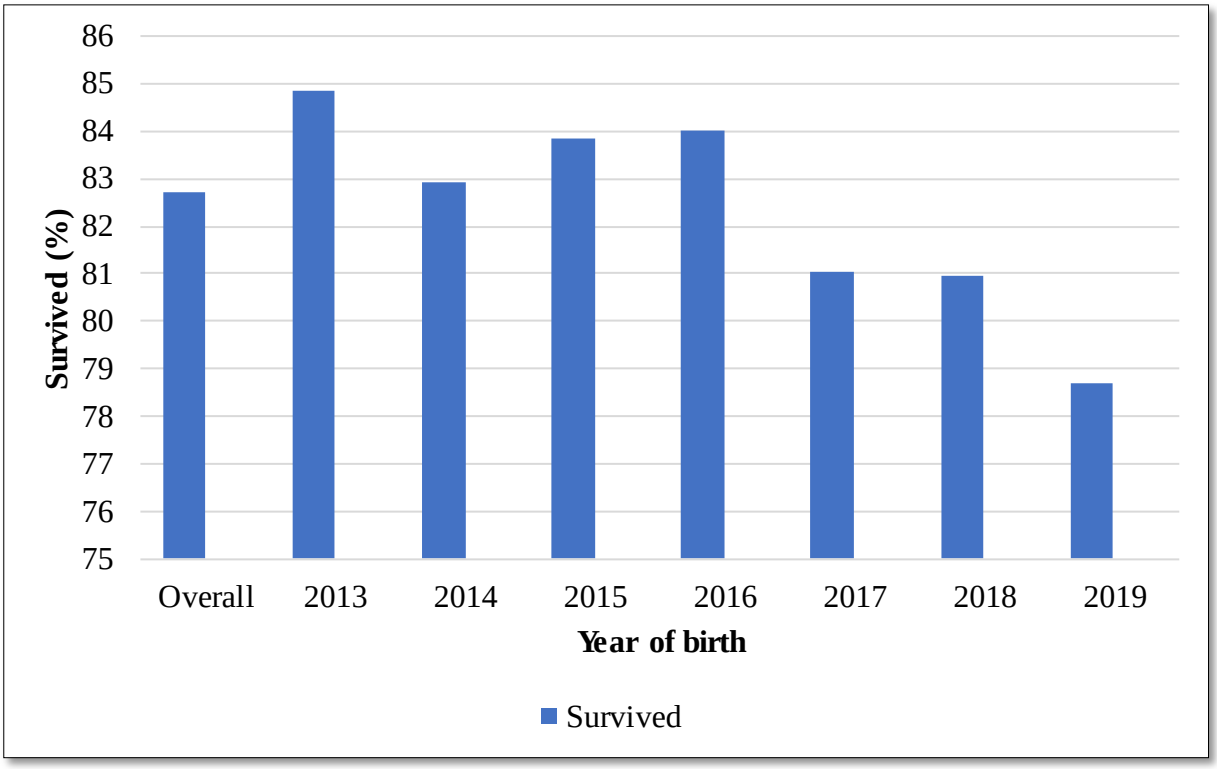


Figure 3.2.1.1: The proportion of neonates at CMJAH surviving over time.

3.2.2 The proportion of neonates at CMJAH surviving over time, by birthweight

The babies that weighed between 1501 g and 2500 g had the highest proportion of survival (93.9 %), followed by babies who weighed between 1001 g and 1500 g (85.8 %) and babies who weighed ≤ 1000 g (43.2 %). (See **Figure 3.2.2.1** below). A similar trend was observed in each year of study.

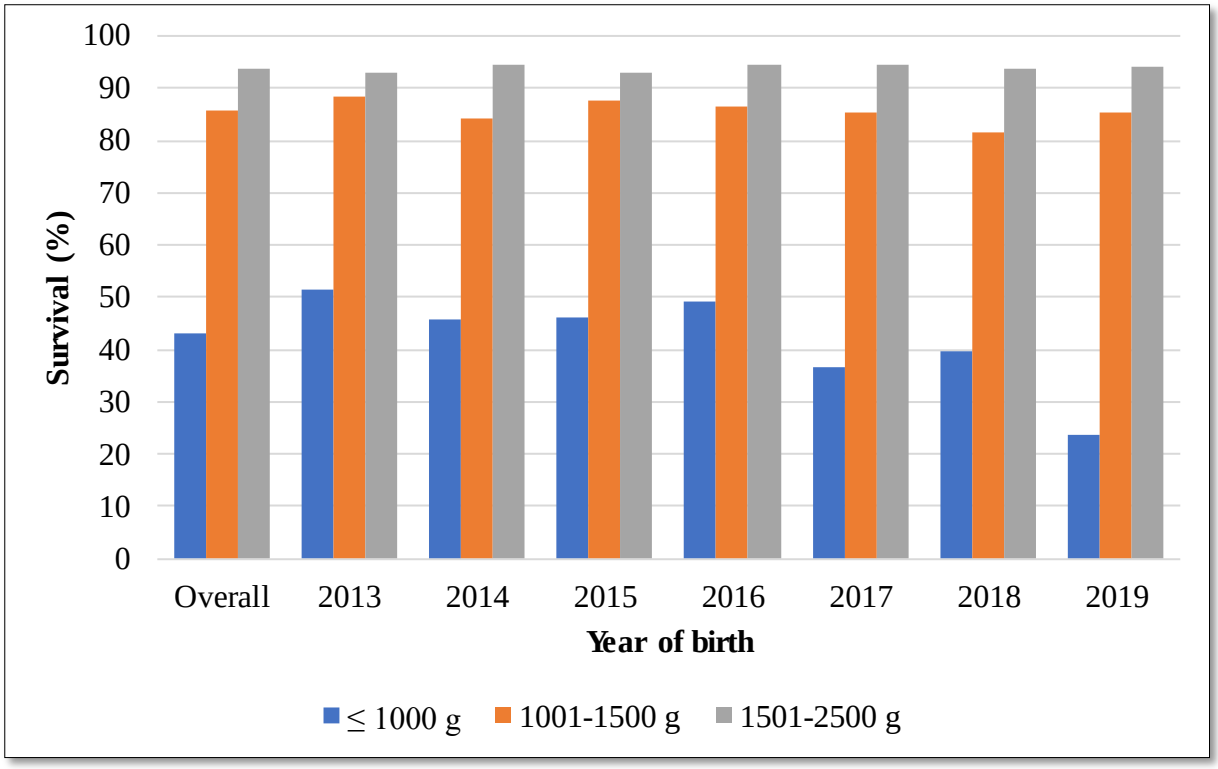


Figure 3.2.2.1: The proportion of neonates at CMJAH surviving over time, by birthweight

3.2.3 The prevalence of neonatal mortality by neonatal characteristics

Gender: Overall, not much difference in deaths was observed between male (17.1 %) and female (16.9 %) babies. The highest prevalence of mortality was observed among male babies in 2018 (20.5 %) followed by 2019 (20.4 %) and the lowest mortality was observed in 2013 (11.7 %) (See **Table 3.2.3.1** and **Table 3.2.3.2**).

Birth weight: The highest mortality was observed among neonates with birth weight ≤ 1000 g (56.9 %), followed by neonates with birth weight between 1001 g and 1500 g (14.3 %). The least mortality was observed among neonates with birth between 1501 g and 2500 g (6.1 %).

Sepsis: The overall mortality among neonates who had EOS was 24.5 % (64 out of 261). The highest prevalence of mortality among neonates with EOS was observed in 2019 (38.1 %) followed by 2016 (30.0 %) and the least mortality was observed in 2018 (15.2 %). Overall, mortality among neonates who presented with LOS was 27.7 % (366 out of 1322). It was found that mortality among babies with LOS increased over time and was highest in 2019 (38.1 %). (See **Table 3.2.3.2** and **Table 3.2.3.3**).

RDS/HMD: The mortality rate among neonates who had respiratory disease syndrome was 77.4 % (909 out of 1174). The prevalence of mortality was highest among neonates who had

respiratory diseases in 2019 (30.9 %) followed by 2017 (23.9 %) and the least mortality in 2013 (18.5 %).

Birth asphyxia: Overall, the prevalence of mortality among neonates who had asphyxia at birth was 26.9 % (25 out of 93). The prevalence of mortality was highest among neonates who had had asphyxia at birth in 2018 (44.4 %) followed by 2014 (40.0 %) and the least mortality in 2016 (14.3 %).

PDA: Overall, the mortality rate among neonates who had PDA was 22.1 % (95 out of 429). The prevalence of mortality was highest among neonates who had PDA in 2018 (27.8 %) followed by 2016 (26.7 %) and the least mortality in 2013 (13.9 %).

IVH: Overall, the mortality rate among neonates who had the respiratory disease was 17.9 % (14 out of 78). The prevalence of mortality was highest among neonates who had an intraventricular hemorrhage in 2015 (33.3 %) followed by 2018 (28.6 %) and the least mortality in 2016 (5.9 %).

Major birth defects: Overall, the prevalence of mortality among neonates who had birth defects was 41.4 % (152 out of 367). The prevalence of mortality was highest among neonates who had birth defects in 2018 (64.3 %) followed by 2017 (43.5 %) and the least mortality in 2016 (32.9 %). (Refer to **Table 3.2.3.3** and **Table 3.2.3.4**).

Table 3.2.3.1: The prevalence of neonatal mortality from 2013-2015

Characteristics	**2013-2019**		**2013**		**2014**		**2015**	
	Total	Died (%)	Total	Died (%)	Total	Died (%)	Total	Died (%)
Gender of the neonates	**6247**	**1065**	**664**	**80**	**1103**	**187**	**998**	**159**
Female	3053	517 (16.9)	313	39 (12.5)	515	81 (15.8)	494	85 (17.2)
Male	3194	548 (17.2)	350	41 (11.7)	588	106 (18.0)	503	74 (14.7)
Sepsis on or before day 3	**6559**	**1108**	**1108**	**175**	**1059**	**167**	**992**	**156**
Yes	261	64 (24.5)	31	9 (29.0)	35	8 (22.9)	44	8 (18.2)
No	6298	1044 (16.6)	1077	166 (15.4)	1024	159 (15.5)	948	148 (15.6)
Sepsis after day 3	**6670**	**1149**	**1119**	**173**	**1090**	**179**	**994**	**161**
Yes	1322	366 (27.7)	169	39 (23.1)	211	57 (27.0)	241	60 (24.9)
No	5348	783 (14.6)	950	134 (14.1)	880	122 (13.9)	754	101 (13.4)
Oxygen on day 28	**6271**	**892**	**1079**	**162**	**991**	**122**	**950**	**129**
Yes	953	125 (13.1)	108	11 (10.2)	160	21 (13.1)	165	20 (12.1)
No	5318	767 (14.2)	971	151 (15.6)	831	101 (12.2)	785	109 (13.9)
Necrotizing enterocolitis	**6590**	**1144**	**1119**	**177**	**1065**	**177**	**976**	**158**
Yes	427	170 (39.8)	81	28 (34.6)	60	31 (51.7)	58	19 (32.8)
No	6163	974 (15.8)	1038	149 (14.4)	1005	146 (14.5)	918	139 (15.1)
Birthweight (Grams)	**6734**	**1167**	**1159**	**179**	**1094**	**185**	**996**	**160**
≤ 1000g	1138	647 (56.9)	190	92 (48.4)	180	98 (54.4)	152	82 (53.9)
1001 – 1500 g	2197	313 (14.3)	400	47 (11.8)	362	57 (15.8)	343	43 (12.5)
1501 – 2500 g	3399	207 (6.09)	570	40 (7.03)	552	30 (5.43)	501	35 (7.0)
Antenatal Steroids	**5134**	**935**	**500**	**121**	**737**	**137**	**890**	**138**
Yes	2010	353 (17.6)	220	41 (18.6)	282	55 (19.5)	376	52 (13.8)
No	3124	582 (18.6)	280	80 (28.6)	455	82 (18.0)	514	86 (16.7)
Initial Resuscitation in the delivery room	**6500**	**1083**	**1166**	**173**	**1054**	**172**	**959**	**153**
Yes	3139	747 (23.8)	566	129 (22.8)	493	120 (24.3)	472	97 (20.6)
No	3361	336 (10.0)	600	44 (7.3)	561	52 (9.3)	487	56 (11.5)

Table 3.2.3.2: The prevalence of neonatal mortality from 2016-2019

Characteristics	**2016**		**2017**		**2018**		**2019**	
	Total	Died (%)	Total	Died (%)	Total	Died (%)	Total	Died (%)
Gender of the neonates	**1019**	**164**	**1048**	**197**	**958**	**182**	**465**	**99**
Female	476	82 (17.2)	538	95 (17.7)	477	82 (17.2)	240	53 (22.1)
Male	542	82 (15.1)	508	101 (19.9)	478	98 (20.5)	225)	46 (20.4)
Sepsis on or before day 3	**998**	**158**	**1014**	**188**	**936**	**171**	**452**	**93**
Yes	40	12 (30.0)	44	12 (27.3)	46	7 (15.2)	21	8 (38.1)
No	958	146 (15.2)	970	176 (18.1)	890	164 (18.4)	431	85 (19.7)
Sepsis after day 3	**1017**	**163**	**1042**	**197**	**949**	**180**	**459**	**96**
Yes	224	56 (25.0)	201	67 (33.3)	192	55 (28.7)	84	32 (38.1)
No	793	107 (13.5)	841	130 (15.5)	757	125 (16.5)	375	64 (17.1)
Oxygen on day 28	**952**	**116**	**963**	**142**	**911**	**150**	**425**	**71**
Yes	167	13 (7.8)	163	26 (16.0)	131	22 (16.8)	59	12 (20.3)
No	785	103 (13.1)	800	116 (14.5)	780	128 (16.4)	366	59 (16.1)
Necrotizing enterocolitis	**1004**	**160**	**1034**	**197**	**944**	**178**	**448**	**97**
Yes	62	24 (38.7)	74	29 (39.2)	68	26 (38.2)	24	13 (54.2)
No	942	136 (14.4)	960	168 (17.5)	876	152 (17.4)	424	84 (19.8)
Birthweight (Grams)	**1018**	**162**	**1049**	**199**	**954**	**183**	**464**	**99**
≤ 1000g	175	89 (50.9)	189	120 (63.5)	167	101 (60.5)	85	65 (76.5)
1001 – 1500 g	333	45 (13.5)	352	51 (14.5)	279	51 (18.3)	128	19 (14.8)
1501 – 2500 g	510	28 (5.5)	508	28 (5.5)	508	31 (6.1)	251	15 (6.0)
Antenatal Steroids	**879**	**136**	**925**	**171**	**813**	**149**	**390**	**83**
Yes	340	49 (14.4)	336	60 (17.9)	315	63 (20.0)	141	33 (23.4)
No	539	87 (16.1)	589	111 (18.9)	498	86 (17.3)	249	50 (20.1)
Initial Resuscitation in the delivery room	**975**	**145**	**993**	**181**	**912**	**169**	**441**	**90**
Yes	474	94 (19.8)	496	129 (26.0)	417	110 (26.4)	221	68 (30.8)
No	501	51 (10.2)	497	52 (10.5)	495	59 (11.9)	220	22 (10.0)

Table 3.2.3.3: The prevalence of neonatal mortality from 2013-2015

Characteristics	**2013-2019**		**2013**		**2014**		**2015**	
	Total	Died (%)	Total	Died (%)	Total	Died (%)	Total	Died (%)
Oxygen	**6543**	**1094**	**1169**	**174**	**1062**	**174**	**967**	**154**
Yes	4503	886 (19.7)	783	129 (16.5)	722	133 (18.4)	677	129 (19.1)
No	2040	208 (10.2)	386	45 (11.7)	340	41 (12.1)	290	25 (8.6)
Nasal CPAP	**6465**	**1070**	**1140**	**167**	**1050**	**170**	**961**	**153**
Yes	60	20 (33.3)	5	0	12	4 (33.3)	1	1 (100.0)
No	6405	1050 (16.4)	1135	167 (14.7)	1038	166 (16.0)	960	152 (15.8)
HMD/RDS	**6799**	**1174**	**1190**	**180**	**1107**	**188**	**1003**	**162**
Yes	4140	909 (77.4)	718	133 (18.5)	641	144 (22.5)	657	133 (20.2)
No	2659	265 (22.6)	472	47 (10.0)	466	44 (9.4)	346	29 (8.4)
Bronchopulmonary dysplasia	**3208**	**948**	**575**	**139**	**525**	**153**	**475**	**123**
Yes	7	2 (28.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
No	3202	946 (29.6)	575	139 (24.2)	525	153 (29.1)	475	123 (25.9)
Congenital Pneumonia	**6799**	**1174**	**1190**	**180**	**1107**	**188**	**1003**	**162**
Yes	157	13 (8.3)	19	4 (21.1)	33	0 (0.0)	24	2 (8.3)
No	6642	1161 (17.5)	1171	176 (15.0)	1074	188 (17.5)	979	160 (16.3)
Birth asphyxia	**6799**	**1174**	**1190**	**180**	**1107**	**188**	**1003**	**162**
Yes	93	25 (26.9)	12	3 (25.0)	15	6 (40.0)	18	5 (27.8)
No	6706	1149 (17.1)	1178	177 (15.0)	1092	182 (16.7)	985	157 (15.9)
Patent ductus arteriosus	**6755**	**1147**	**1181**	**177**	**1091**	**176**	**1000**	**160**
Yes	429	95 (22.1)	72	10 (13.9)	76	16 (21.1)	69	14 (20.3)
No	6326	1052 (16.6)	1109	167 (15.1)	1015	160 (15.8)	931	146 (15.7)
Intraventricular Haemorrhage	**3181**	**195**	**270**	**17**	**552**	**30**	**523**	**39**
Yes	78	14 (17.9)	11	3 (27.3)	12	2 (16.7)	9	3 (33.3)
No	3103	181 (5.8)	259	14 (5.4)	540	28 (5.2)	514	36 (7.0)
Major birth defect	**6622**	**1135**	**1,107**	**176**	**1072**	**170**	**993**	**159**
Yes	367	152 (41.4)	58	25 (43.1)	67	26 (38.8)	58	22 (37.9)
No	6255	983 (15.7)	1049	151 (14.4)	1005	144 (14.3)	935	137 (14.7)

Table 3.2.3.4: The prevalence of neonatal mortality from 2016-2019

Characteristics	**2016**		**2017**		**2018**		**2019**	
	Total	Died (%)	Total	Died (%)	Total	Died (%)	Total	Died (%)
Oxygen	**988**	**151**	**998**	**184**	**912**	**165**	**447**	**92**
Yes	648	121 (18.7)	697	160 (23.0)	649	136 (21.0)	327	78 (23.9)
No	340	30 (8.8)	301	24 (8.0)	263	29 (11.0)	120	14 (11.7)
Nasal CPAP	**981**	**148**	**984**	**176**	**906**	**164**	**443**	**92**
Yes	9	3 (33.3)	7	1 (14.3)	20	8 (40.0)	6	3 (50.0)
No	972	145 (14.9)	977	175 (17.9)	886	156 (17.6)	437	89 (20.4)
HMD/RDS	**1025**	**163**	**1052**	**199**	**957**	**183**	**465**	**99**
Yes	606	119 (19.6)	653	156 (23.9)	587	138 (23.5)	278	86 (30.9)
No	419	44 (10.5)	399	43 (10.8)	370	45 (12.2)	187	13 (7.0)
Bronchopulmonary dysplasia	**485**	**131**	**517**	**169**	**427**	**150**	**204**	**83**
Yes	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	7	2 (28.6)
No	485	131 (27.0)	517	169 (32.7)	427	150 (35.1)	197	81 (41.1)
Congenital Pneumonia	**1025**	**163**	**1052**	**199**	**957**	**183**	**465**	**99**
Yes	22	2 (9.1)	23	3 (13.0)	21	2 (9.5)	15	0 (0.0)
No	1003	161 (16.1)	1029	196 (19.1)	936	181 (19.3)	450	99 (22.0)
Birth asphyxia	**1025**	**163**	**1052**	**199**	**957**	**183**	**465**	**99**
Yes	14	2 (14.3)	18	3 (16.7)	9	4 (44.4)	7	2 (28.6)
No	1011	161 (15.9)	1034	196 (19.0)	948	179 (18.9)	458	97 (21.2)
Patent ductus arteriosus	**1024**	**162**	**1047**	**197**	**951**	**179**	**461**	**96**
Yes	75	20 (26.7)	57	14 (24.6)	54	15 (27.8)	26	6 (23.1)
No	949	142 (15.0)	990	183 (18.5)	897	164 (18.3)	435	90 (20.7)
Intraventricular Haemorrhage	**531**	**32**	**521**	**30**	**526**	**31**	**258**	**16**
Yes	17	1 (5.9)	18	2 (11.1)	7	2 (28.6)	4	1 (25.0)
No	514	31 (6.0)	503	28 (5.6)	519	29 (5.6)	254	15 (5.9)
Major birth defect	**1009**	**160**	**1038**	**196**	**946**	**180**	**457**	**94**
Yes	76	25 (32.9)	46	20 (43.5)	42	27 (64.3)	20	7 (35.0)
No	933	135 (14.5)	992	176 (17.7)	904	153 (16.9)	437	87 (19.9)

3.2.4 The trends in the survival of LBW neonates to hospital discharge at CMJAH from 2013 – 2019.

3.2.4.1 Overall trends in the survival of LBW neonates to hospital discharge at CMJAH from 2013 – 2019.

Figure 3.2.4.1: The trends in the survival of LBW neonates to hospital discharge at CMJAH from 2013 – 2019.**Figure 3.2.4.1** below was done with join point regression software to determine the pattern of variation in the survival of neonates to hospital discharge over time. (P=0.01). Overall, there was a significant 1.1 % downward trend in the survival of neonates to hospital discharge over time.

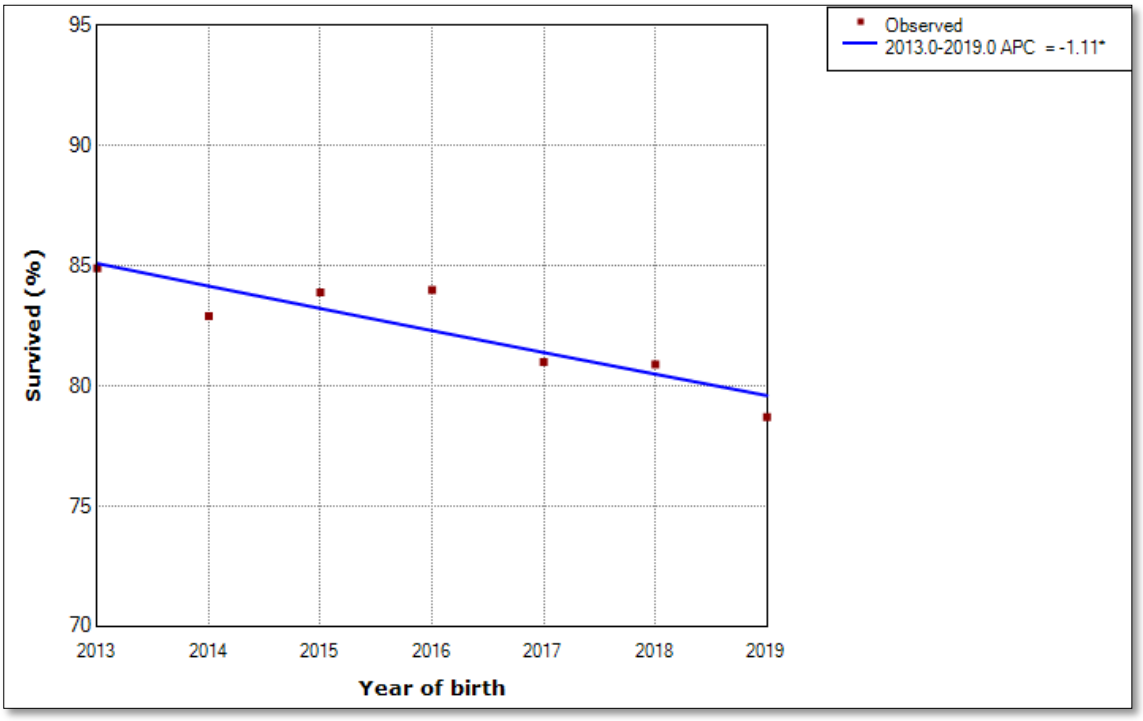


Figure 3.2.4.1: The trends in the survival of LBW neonates to hospital discharge at CMJAH from 2013 – 2019.

3.2.4.2 The trends in the survival of neonates (≤ 1000 g) to hospital discharge at CMJAH from 2013 – 2019

Figure 3.2.4.2 below shows that the mortality trend for neonates who weighed ≤ 1000 g is not stable within each year of birth. The figure shows that there was a significant 9.8 % downward trend in the survival of neonates (≤ 1000 g) to hospital discharge over time (P = 0.01).

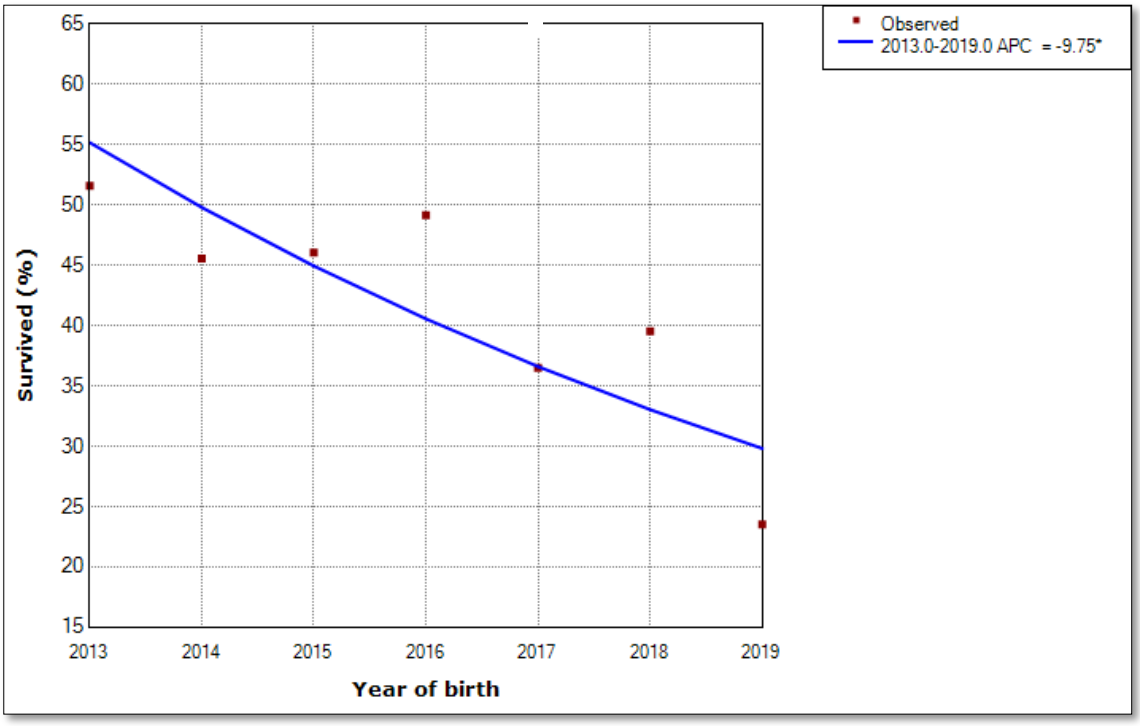


Figure 3.2.4.2: The trends in the survival of neonates (≤ 1000 g) to hospital discharge at CMJAH from 2013 – 2019

3.3 The demographic and clinical factors associated with neonatal mortality over time using bivariate and multivariable analysis.

3.3.1 Bivariate analysis of independent variables with neonatal mortality

The findings from the Pearson's chi-square test used to determine the factors that are associated with neonatal mortality are presented in **Table 3.3.1.1** below. The present study found no statistically significant association at a 5 % level between mortality and the following variables: gender, antenatal steroids, and bronchopulmonary dysplasia. However, we found a significant association between neonatal mortality and the following variables: EOS, LOS, requiring oxygen on day 28, NEC, and birth weight. Additionally, there was a significant association between neonatal mortality and those who required initial resuscitation in the delivery room,

nasal CPAP, had RDS, congenital pneumonia, birth asphyxia, cardiovascular disease, IVH, and a major birth defect. See **Table 3.3.1.1** below.

Table 3.3.1.1: The demographic and clinical factors associated with neonatal mortality over time using bivariate analysis.

Characteristics	Total	Died (%)	P-value
Gender of the neonates			
Female	3053	517 (16.9)	0.82
Male	3194	548 (17.2)	
Sepsis on or before day 3			
Yes	261	64 (24.5)	0.001 *
No	6298	1044 (16.6)	
Sepsis after day 3			
Yes	1322	366 (27.7)	0.001 *
No	5348	783 (14.6)	
Oxygen on day 28			
Yes	953	125 (13.1)	0.29 *
No	5318	767 (14.4)	
Necrotizing enterocolitis			
Yes	427	170 (39.8)	0.001 *
No	6163	974 (15.8)	
Birthweight (Grams)			
≤ 1000 g	1138	647 (56.9)	0.001 *
1001 – 1500 g	2197	313 (14.3)	
1501 – 2500 g	3399	207 (6.1)	
Antenatal Steroids			
Yes	2010	353 (17.6)	0.33
No	3124	582 (18.6)	
Initial Resuscitation in the delivery room			
Yes	3139	747 (23.8)	0.001 *
No	3361	336 (10.0)	
Oxygen			
Yes	4503	886 (19.7)	0.001*
No	2040	208 (10.2)	
Nasal CPAP			
Yes	60	20 (33.3)	0.001 *
No	6405	1050 (16.4)	
HMD/RDS			
Yes	4140	909 (22.0)	0.001 *
No	2659	265 (10.0)	
Bronchopulmonary dysplasia			
Yes	7	2 (28.6)	0.96
No	3201	946 (29.6)	
Congenital Pneumonia			
Yes	157	13 (8.3)	0.003 *

No	6642	1161 (17.5)	
Birth asphyxia			
Yes	93	25 (26.9)	0.01 *
No	6706	1149 (17.1)	
Patent ductus arteriosus			
Yes	429	95 (22.1)	0.003 *
No	6326	1052 (16.6)	
Intraventricular Haemorrhage			
Yes	78	14 (18.0)	0.001 *
No	3103	181 (5.8)	
Major birth defect			
Yes	367	152 (41.4)	0.001 *
No	6255	983 (15.7)	

3.3.2 Multivariable analysis.

The bivariate analysis was used to test the association between a single independent variable and the outcome variable. The multivariable analysis allows us to further test for the association between one or several independent variables and the outcome variable while adjusting for other possible confounding variables.

The variables in the bivariate analysis that were found to be significant at a 20 % level were included in the multivariable analysis. The variables were also included in the multivariable analysis based on stepwise forward selection and recommendation from previous literature.

3.3.2.1 Logistic regression

The logistic regression method was used because the outcome variable is binary. The stepwise method was used to select the best-fitting model. The Pearson's goodness of fit test showed that our final model was a good fit (P = 0.64). The best fit and parsimonious model included five variables such as birth weight, EOS, oxygen, NCPAP, and major birth defect. The results from the logistic regression model are presented in **Table 3.3.2.1**.

The results from the final model show that the odds of dying are significantly associated with birth weight, EOS, and major birth defect. The odds of dying among neonates that weighed 1001 – 1500 g was 90 % less likely than the odds of dying among neonates that weighed ≤ 1000 g (OR: 0.10, 95 % CI = 0.08; 0.12). The odds of dying among neonates that weighed 1501 – 2500 g was 97 % less likely than the odds of dying among neonates that weighed ≤ 1000 g (OR: 0.03, 95 % CI = 0.02; 0.04). Additionally, we found that the odds dying among neonates who presented with EOS was 55 % times higher than those who did not have EOS (OR: 1.55, 95 % CI = 1.06; 2.27). Neonates who had major birth defects have a significantly

higher odds of dying than those who did not have a major birth defect (OR: 16.37, 95 % CI = 12.22; 21.93).

The overall model was statistically significant with a likelihood ratio chi-square value of 1520.98 and a p-value < 0.001. According to Pearson's chi-square goodness of fit test, there is no evidence of a lack of fit (P= 0.06).

Table 3.3.2.1: The demographic and clinical factors associated with neonatal mortality over time using multivariable analysis.

Characteristics	**Odds ratio**	**95 % CI**	**P-values**
Constant	1.10	0.87- 1.40	0.412
Sepsis on or before day 3			
Yes	1.55	1.06 - 2.27	0.02
No	Reference		
Birthweight			
≤ 1000 g	Reference		
1001-1500 g	0.10	0.08 - 0.12	0.001
1501-2500 g	0.03	0.02 - 0.04	0.001
Major birth defect			
Yes	16.37	12.22 – 21.93	0.001
No	Reference		
Oxygen			
Yes	1.16	0.94 - 1.94	0.10
No	Reference		
NCPAP			
Yes	1.18	0.58 - 2.39	0.65
No	Reference		
Test	**Chi (2)**	**Df**	**P-value**
Overall model evaluation			
Likelihood ratio test	1520.98	6	0.0001
The goodness of fit test			
Pearson Chi2	36.55	25	0.06

3.4 The survival estimates of LBW neonates at CMJAH

3.4.1 Survival analysis

Survival analysis was used to estimate the survival of neonates according to the length of hospital stay. The outcome was either the neonate survived to hospital discharge or died during the period of hospitalization. The failure event in the present study is "death" i.e. neonates who did not survive to hospital discharge.

There were 4,425 observations after the analysis was restricted to the neonates whose length of hospital stay was within 28 days. Neonates whose length of hospital stay was beyond 28 days were right-censored because they did not experience the event of interest before 28 days. The total analysis time at risk and under observation was 45,349 days.

3.4.2 Mortality rates

We checked for the rate at which mortality occurred by birth weights, gender, and year of birth. The results from **Table 3.4.2.1** below shows that there is no much difference in the mortality rate for male babies (17.80 deaths per 1000 live births) and female babies (18.42 deaths per 1000 live births).

The highest mortality rate was observed among neonates who weighed ≤ 1000 g (140 deaths per 1000 live births) followed by those between 1501-2500 g (12.38 deaths per 1000 live births) and those who weighed between 1001-1500 g (5.56 deaths per 1000 live births). The highest mortality rate was observed in 2019 (24 deaths per 1000 live births), followed by 2018 (20.17 deaths per 1000 live births) and the least mortality in 2013 (15.42 deaths per 1000 live births).

Table 3.4.2.1: The mortality rates of LBW neonates admitted to the neonatal unit of CMJAH, by gender, birth weight, and year of birth

Characteristics	No of deaths	Person days	Rate (per 1000 live births)
Gender			
Female	395	21444	18.42
Male	406	22805	17.80
Birthweight			
≤ 1000 g	463	3308	140.00
1001-1500 g	219	17696	12.38
1501-2500 g	134	24118	5.56
Year of birth			
2013	74	4800	15.42
2014	148	8115	18.24

2015	123	7288	16.88
2016	130	7473	17.40
2017	136	7739	17.57
2018	134	6642	20.17
2019	79	3292	24.00
Overall	824	45349	18.17

3.4.3 Kaplan-Meier survival function

The Kaplan Meier survival function is a non-parametric test that was used to plot the survival experience of neonates according to their length of hospital stay.

Accordingly, as can be seen from **Figure 3.4.3.1Figure 3.4.3.1**, the graph declined gradually during the first seven days of hospitalization. This shows that a higher proportion of neonates were dying and there was a lower probability of survival. However, over the next seven days, the proportion of neonates dying has decreased and the graph decreased slowly up to the fourth week (28 days).

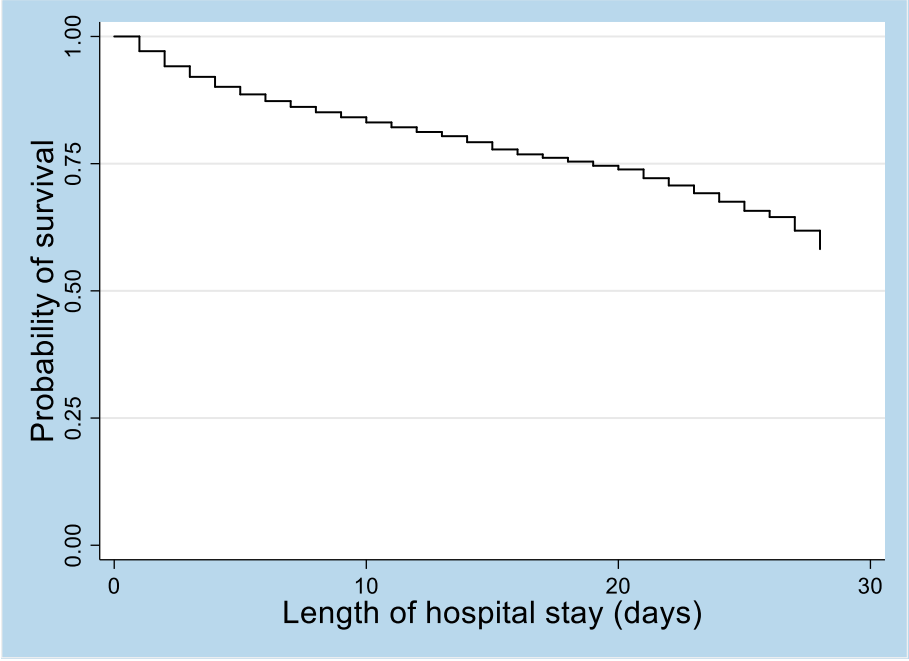


Figure 3.4.3.1: Kaplan – Meier survival estimate of LBW neonates at CMJAH.

Figure 3.4.3.2 below shows that there is no difference in survival for female and male babies.

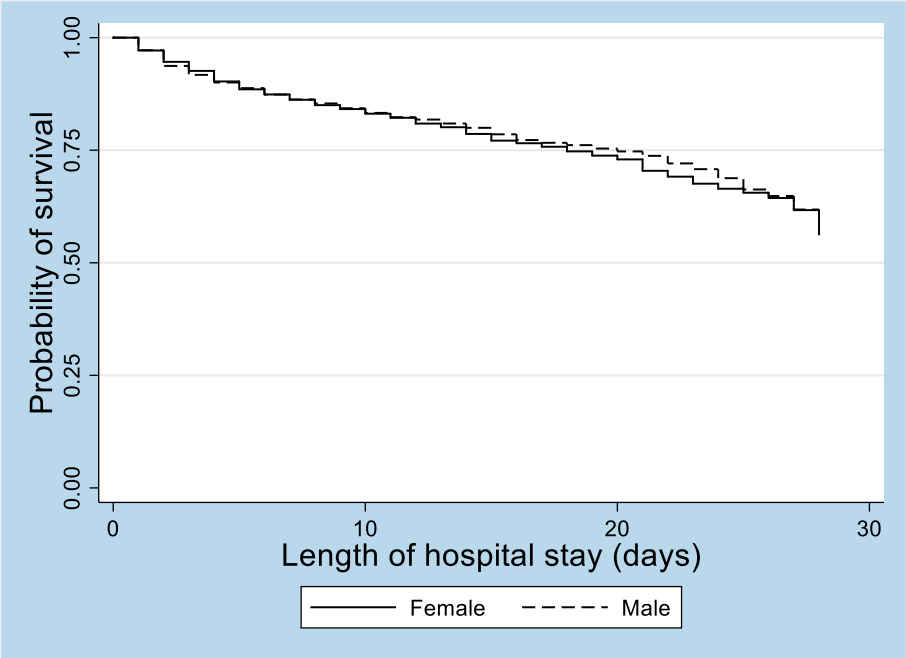


Figure 3.4.3.2: Kaplan – Meier survival estimate of LBW neonates at CMJAH, by gender.

Accordingly, as can be seen from **Figure 3.4.3.3**, during the first seven days of hospitalizations, neonates who weighed ≤ 1000 g have a lower probability of surviving to hospital discharge than those who weighed between 1001 – 1500 g and 1501 – 2500 g.

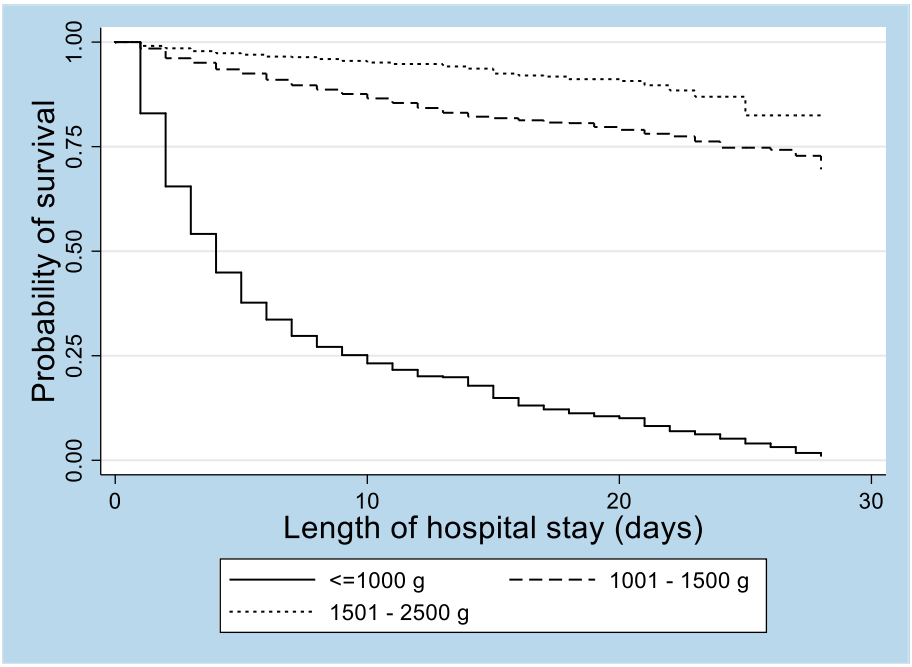


Figure 3.4.3.3: Kaplan – Meier survival estimates of neonates at CMJAH, by birth weight.

3.4.4 Log-rank test for the equality of survivor functions

The log-rank test was used to compare the survival distribution of two groups. **Table 3.4.4.1** shows the results of the log-rank test for the equality of survivor functions. We found that there is no statistical evidence to conclude that the survival distributions between males and females are different (P = 0.61). In contrast, there is statistically significant evidence that the survival distributions between the ELBW, VLBW, and LBW are different (P = 0.0001).

Table 3.4.4.1: Results of the log-rank test for the equality of survival functions

Characteristics	Events observed	Events expected	Chi2 (2)	P-value
Gender				
Female	395	387.81	0.26	0.61
Male	406	413.19		
Birthweight				
<=1000 g	463	64.92	2756.62	0.0001 *
1001-1500 g	219	295.47		
1501-2500 g	134	455.61		

3.4.5 Cox proportional hazard model

A semi-parametric method was used to determine the hazard function of how several factors affect neonatal mortality. The stepwise approach was used to select the best-fitted model. **Table 3.4.5.1** shows the results of the Cox proportional hazard model. Similar to the findings from the logistic regression, the birth weight of the neonates had a significant impact on their survival to hospital discharge (P < 0.05). The risk of the neonates not surviving to hospital discharge decreases with an increase in birth weight. Neonates who weighed between 1001-1500 g are 0.08 times at risk of dying than those less than 1000 g (P= 0.001; 95 % CI 0.07; 0.11). Neonates who weighed between 1501-2500 g had a better survival chance than those less than 1000 g (HR=0.03; P= 0.001; 95 % CI 0.02; 0.04). There is strong evidence that neonates with a major birth defect are 5.89 times at risk of not surviving to hospital discharge compared to neonates with no major birth defect (HR=6.03; P= 0.01; 95 % CI 4.54 – 8.03).

Table 3.4.5.1: Results of the Cox proportional hazard model of neonates at CMJAH, SA

Characteristics	Hazard ratio	95 % CI	P-value
Sepsis on or before day 3			
Yes	1.13	0.83 – 1.55	0.44
No	Reference		
Birthweight			

≤ 1000 g	Reference		
1001-1500 g	0.08	0.07 - 0.10	0.001
1501-2500 g	0.03	0.03 - 0.04	0.001
Major birth defect			
Yes	6.59	5.25 – 8.26	0.001
No	Reference		
Oxygen			
Yes	1.24	0.99 - 1.94	0.06
No	Reference		
NCPAP			
Yes	1.26	0.73 - 2.20	0.41
No	Reference		
Test	**Chi (2)**	**Df**	**P-value**
Overall model evaluation			
Likelihood ratio test	1465.21	6	0.0001
Proportional hazard assumption			
Global test	6.88	6	0.33

3.4.6 Proportional hazard assumption test

The proportional hazard assumption test was done to ensure our model does not violate the assumption. The Cox proportional hazard model assumes that the hazard ratios are constant over time. The null hypothesis states that the hazard ratio function is constant over time while the alternate hypothesis states that the hazard ratio function is not constant over time. There is a violation of the proportional hazard assumption if the null hypothesis is rejected.

The overall global test gives a p-value of 0.15 ($P > 0.05$), which suggests that there is no statistical evidence that our model violates the proportional hazard assumption.

CHAPTER 4 DISCUSSION

This chapter discusses the main findings of the study in terms of the prevalence of neonatal mortality and the trends in the survival to hospital discharge over time. It also discusses the findings from the factors associated with neonatal mortality and the survival estimate of neonates at CMJAH. The similarities between the findings of the present study and other literature would be explored. Lastly, this chapter will discuss the strengths and limitations of the present study.

4.1 The trends in the survival of LBW neonates to hospital discharge at CMJAH from 2013-2019

The key message from the present study is that the survival trend of LBW neonates to hospital discharge decreased by 1.1 % over the years. The present study is unique because it is the first study on the survival trend to be done with the datasets from the hospital. In contrast to the current study, the statistical release on neonatal deaths in SA showed that neonatal mortality decreased from 1998 to 2014 (9). Similarly, the UNIGME reported a mortality reduction in SA from 1990 to 2017 (15). However, the discrepancy between the previous reports and the present study can be explained in terms of the difference in the data uses, study setting, and year of studies. This study used a public hospital in Johannesburg while the previous studies used national data. We speculate that the decrease in the survival of babies to hospital discharge could be attributed to the high sepsis infection in the hospital. Our study observed an increasing trend in sepsis infection over the years. Similarly, a study done in a similar setting in Johannesburg revealed that the rate of sepsis infection has significantly increased and attributed it to overcrowding and antibiotic resistance from the overuse of broad-spectrum antibiotics (30).

This study found that survival to hospital discharge decreased over the years by 9.8 % for neonates who weighed ≤ 1000 g. In contrast, the survival trend remained stable for neonates who weighed between 1001 and 2500 g. We speculate that the decrease in survival for babies who weighed ≤ 1000 g could be attributed to the present policy in the neonatal unit that allows the provision of NCPAP to babies >750 g or the sickest babies due to the limited NCPAP machines in the facility (30). A policy that favors all birth weight should be adopted to increase survival among ELBW babies.

Overall, 82.7 % of neonates in the present study survived to hospital discharge from 2013 – 2019. A similar pattern of results was obtained from studies done in the same setting in 2005,

2010, 2013, 2015 (29–32). The studies found the overall survival rate to also be relatively high: 72 %, 70.5 %, 70.2 % respectively. We speculate that the increase in survival rate might be due to the inclusion of neonates who weighed between 1501 and 2500 g, which was excluded in the previous studies. Alternatively, it could surmise that there was an introduction of a new health care policy in the hospital that might have led to an increase in the survival of neonates to hospital discharge.

4.1.1 The prevalence of neonatal mortality at CMJAH from 2013 – 2019

Overall, the male babies had slightly higher mortality than the female babies. However, the pattern of mortality was different for male and female babies over the years. This finding is in line with previous studies (48,49). The higher mortality among male babies can be attributed to the sex difference in the biological and genetic makeup (15). Additionally, studies have shown that male babies are biologically weaker and more at risk of diseases and premature death (15,23).

The prevalence of mortality was inversely related to birth weight. The highest mortality was observed among neonates who weighed ≤ 1000 g (56.9 %), followed by those who weighed 1001 – 1500 g (14.3 %) and 1501 – 2500 g (6.1 %). There is a biological plausibility that the smaller the baby, the more vulnerable they were to the risk factors that can cause mortality (23). This study found that mortality increased over time for babies who weighed ≤ 1000 g. In contrast, mortality remained stable over the years for babies who weighed between 1501 and 2500 g. The finding is in line with the previous study done in a neonatal unit, Zimbabwe (49). A study was done in a similar facility among LBW babies between 2013 and 2015 (50). The study found the highest proportion of death among neonates who weighed < 1000 g (60.1 %) followed by those who weighed between 1000 and 1499 g (15.4 %) and those who weighed between 1500 and 2499 g (6.4 %). This finding reveals that mortality has increased over time among the ELBW unlike the stable mortality observed the VLBW and LBW babies.

The prevalence of mortality among neonates with sepsis (EOS and LOS) increased over the years. Previous studies have shown that birth weight is associated with sepsis infection (10,38). The PPIP data shows that one of the main causes of neonatal death at the tertiary hospital level is sepsis infection (33). A study was done on the epidemiology of sepsis in a similar study setting as the present study. They found that sepsis infection was a significant cause of mortality among neonates in a hospital setting. Most of the deaths were due to LOS infection, however, EOS was found to be uncommon (38).

The present study found that the use of antenatal steroids over the years was low. Mortality increased over the years among babies whose mothers were not administered antenatal steroids. Our finding is in line with the study done in a similar setting (30). Increase usage of antenatal steroids among preterm labor is one of the important avoidable factors to save newborn babies (30). Pregnant women are monitored during antenatal care visits and once an emergency delivery is to occur, they are given steroids to help develop the lungs of the preterm baby (23). We speculate that the low usage of antenatal steroids could be caused by the late presentation of pregnant women in labor and not attending antenatal care.

Overall, the prevalence of mortality among neonates who had birth defects was high and across the years. The study on the causes of neonatal deaths per level of care showed that birth defects are one of the major causes of death in tertiary hospitals in SA and have remained stable over the years (10).

There were relatively high cases of mortality among neonates with NEC. The mortality was found to increase over the years. In contrast, a study was done in a high-income country i.e. the United States of America, and found a decline in the rate of NEC cases (32). The differences in findings could be attributed to the economy and study settings in both countries. Necrotizing enterocolitis is caused as a result of bacteria invasion of the intestine leading to infection and inflammation. It is a very big challenge for LBW babies and a known factor to influence survival. A study done in the same facility revealed that NEC was the second primary cause of deaths in ELBW neonates (29). Efforts should be taken to reduce the high rate of NEC infection among vulnerable babies.

There was a relatively high mortality among babies that did not receive resuscitation in the delivery room. The finding signifies the low use of equipment such as the NCPAP machine and oxygen as seen in this study. These are factors that can be avoided to save the life of a new-born from respiratory and lung diseases. However, SA is a middle-income country with limited resources, inadequate nurses, and low skilled health care workers, which is a very big challenge towards reducing neonatal mortality in the country (10). Resuscitation at birth is an important intervention to help a new-born baby breath and control the heartbeat (10,33).

Here in our study, we presented findings of the neonates with IVH and did not classify it into the different grades of the condition due to available data. Several studies have reported IVH to be one of the major causes of neonatal mortality among LBW babies (28,29). There was a

high increase in mortality due to IVH over the years of study. However, neonates with IVH had a higher mortality rate (18.0 %) than neonates without IVH (5.8 %). IVH is a devastating condition that occurs in newborns mostly among the LBW neonates and poses a significant long-term complication. It is caused as a result of bleeding in the fluid-filled areas inside the brain.

4.2 The demographic and clinical factors associated with neonatal mortality over time using multivariable analysis.

This study aimed to determine the predictors of mortality among the LBW babies admitted to the neonatal unit at CMJAH from 2013 to 2019. Accordingly, the major significant factors associated with neonatal mortality in this study are birthweight, EOS, and major birth defects.

Birthweight is another important factor that determines the survival of a baby to hospital discharge. The present study found that neonates who weighed 1501 – 2500 g have 97 % lesser odds of dying compared to neonates who weighed less than 1000 g. In line with our findings, several hospital-based studies in Iran, SA, Ethiopia, Ghana, Uganda, Brazil, Eritrea, and Greece found a significant association between the weight of the baby and odds of survival (30,51–53). A hospital-based study was done among LBW neonates in Harare, Zimbabwe to determine the factors influencing mortality. This study found that the odds of dying was ten percent greater among neonates who weighed between 1000 – 1500 g, however, neonates who weighed between 1501 – 2000 g have a fifty-nine percent lesser odds of dying. We speculate that the lower mortality rate among babies who weighed less than 1000 g could be due to the difference in study settings and the level of resources in both hospitals.

SA is a middle-income country with limited health resources to contain the high number of neonates that require full health support in the hospital. A report has shown that the tertiary hospitals in SA came up with a policy to maximize the use of limited resources towards saving the lives of new-born (54). The policy includes the administration of surfactant and NCPAP to neonates who weigh above 1000 g and this policy places the ELBW neonates at a big disadvantage of not surviving to hospital discharge. However, the cut off for administration of surfactants and NCPAP was reviewed in 2013 and reduced to 750 g. This is a very important policy that needs to be reviewed again to contain all neonates, thereby increasing the survival rate of neonates to hospital discharge.

Low birth weight and prematurity are one of the drivers of neonatal deaths globally, with those born weighing <1000 g contributing significantly to the mortality figures. A study has shown that LBW neonates have underdeveloped immune systems and lungs, making them susceptible to infections and clinical complications (55). According to the WHO report on LBW babies, almost half of the deaths in low and middle-income settings are attributed to lack of feasible and cost-effective care such as warmth, breastfeeding support, and basic care for infections (6). At the facility level, the knowledge of the cause-specific mortality at different birth weight groups has enabled tertiary hospitals to decide on where to focus their interventions and provided the ability to target within a level of care. The reduction in ELBW deaths lies primarily in the preventable factors such as provision of antenatal steroids, consistent visit for antenatal care, and not necessarily in the building of more NICUs, which require more skilled staff.

The present study shows that neonates who developed early-onset sepsis infection are 55 % more likely to die than those who did not have sepsis infection. This finding is quite high and alarming because several reports have confirmed that sepsis infection is one of the contributing factors to neonatal mortality (10,30). The high rate of sepsis infection in the unit could be as a result of overcrowding because the facility is a central tertiary hospital in Johannesburg and provides highly specialized services, functions as a referral hospital for neighboring clinics in its referral chain. Additionally, our study includes the vulnerable neonates with underdeveloped lungs and immune systems which predisposes them to a higher risk of sepsis infection compared to the normal birth weight babies.

Here in this study, a highly significant association was observed between neonates who had a major birth defect and mortality. The odds of neonates dying from having birth defect was 16.37 times higher than those with no birth defect. To my knowledge, this is the second study in the same facility to reveal that major birth defect is a risk factor for mortality among the LBW babies. However, our result was higher than the finding from a study done in the same facility and a neonatal care unit in Eritrea (48,50). A report has shown that LBW babies are unable to survive the mechanical pressure of labor, thereby predisposing them to defects during birth delivery (23). Therefore, there is a need for advanced health facilities, high skilled birth attendants, and care to tackle complications such as birth defects that can occur during delivery.

4.3 The survival estimates of LBW neonates at CMJAH

The present study found a high mortality rate (18.17 deaths per 1000 live births). According to the 2016 SA DHIS report, the neonatal mortality rate was 12.6 deaths per 1000 live births (10). The finding from the present study shows an increase in neonatal mortality rate. However, the findings cannot be generalizable to every hospital in SA, which is one of the limitations of our study. We suggest that the increase in the mortality rate in this study could be that there is a better reporting of deaths from the neonatal unit since hospitals are now introducing mortality audits at every facility level. Additionally, being a tertiary referral level hospital means more complicated cases managed which may lead to a higher death rate.

A study was done to determine the incidence rate of mortality among neonates in a referral hospital in Ethiopia (52). They found a higher death rate (27 deaths per 1000 live births) than what was found in the current study. Another study was done among LBW babies in the neonatal care unit, Eritrea (48). The study found a higher mortality rate of 65.6 per 1000 live births. The variation in findings from different countries could be related to the various governments, policies, and interventions put in place in each facility to reduce neonatal mortality.

The present study found there was a higher proportion of neonates dying during the first seven days of hospitalization. Several studies are in line with the fact that the majority of neonates died within the first seven days of life (31,46,56). The finding suggests that interventions should be targeted at the early stage of hospital admission to reduce the number of deaths in early neonatal life. Furthermore, interventions should start during the antenatal period to prevent or reduce any complications that can occur in the early days of the baby's life.

The Cox regression method was used to further investigate the effect of several variables on time to neonatal death. The method yielded a similar result to the logistic regression method. The main significant factors that were associated with neonatal mortality after ensuring the model does not violate the proportional hazard assumption were birthweight and major birth defects.

4.4 Strengths and Limitations of the study

The primary study was done in a central hospital in Johannesburg, where complicated cases are dealt with. The findings from this study may not be generalizable to other private facilities and the entire population, especially those who do not have the means to access the facility in

Johannesburg. There were limitations on what to analyze using secondary data because of too many missing and incomplete data. Thereby, limiting the analysis by the information of data collected by the hospital. Furthermore, there was a possibility for inadequate and inaccurate information on the health problems of a sick baby because diagnoses were provided by different doctors in the unit. This can lead to the under-reporting or over-reporting of a condition in the present study. However, the hospital uses definitions according to the Vermont Oxford Network ("a nonprofit voluntary collaboration of health care professionals working together as an interdisciplinary community to change the landscape of neonatal care") for accuracy of definitions. The hospital uses the PPIP to classify the cause of death to increase the accuracy of the diagnoses of the baby's health conditions. Lastly, hospital data captures the neonatal death that occurs within the hospital, thereby excluding vital statistics of neonatal deaths that occur after hospital discharge, which could lead to under-reporting of neonatal mortality.

CHAPTER 5 CONCLUSION AND RECOMMENDATIONS

This chapter concludes the findings from the studies and recommends possible areas for future research.

5.1 Conclusion and recommendation

Overall, there was a decline in trend in the survival of LBW neonates to hospital discharge at CMJAH from 1st January 2013 to 30th June 2019. The main significant factors that were found to be associated with neonatal mortality were birth weight, early-onset sepsis, and major birth defect. Most of the babies died within the first seven days of hospital admission. Over the years, the proportion of neonates surviving to hospital discharge declined among neonates who weighed ≤ 1000 g than those who weighed between 1501 g and 2500 g. There was an increase in mortality among neonates who had sepsis infection over time.

The present study shows that mortality is still very high among the ELBW in a limited resource tertiary hospital, SA. The right measures should be followed by the government and health care workers for better improvement of the birth outcomes of the ELBW neonates in LMIC like SA. The measures include building more hospitals with basic and essential facilities to reduce overcrowding that can lead to a sepsis infection. Additionally, providing patients easy access to the right health care and providing the need promptly as an efficient way to reduce neonatal mortality. Apart from health care workers, pregnant mothers also play an important role in the survival of neonates to hospital discharge. To reduce childbirth complications such as birth defects, there is a need for the pregnant mothers to be able to identify what the problem is, decide to seek medical care, get to the right medical care center on time and get the needed care. All of these can only be achieved if pregnant mothers seek ANC. Attending ANC would serve as a platform to educate and train pregnant women to enable a positive attitude towards their behavior to neonatal mortality.

Policies have been made to reduce deaths due to LBW by ensuring that hospitals have the resources to improve the survival of LBW neonates. Additionally, ensuring that health care workers are skilled in the use of NCPAP machines to prevent birth complications in the delivery room. Lastly, there is a need to ensure that pregnant women receive antenatal steroids during preterm labor to avoid lungs related diseases. However, due to the limited resources in public hospitals, the available resources are directed towards the sickest babies or those who

weigh > 1000 g because of their high chances of survival. This then leads to a higher mortality rate among neonates with birth weight less than 1000 g. Therefore, there is a need for a policy that focuses on all babies irrespective of their birth weight without ignoring the ELBW babies, so that the high mortality rate can be reduced in all neonates. Furthermore, there should be more mortality audit in hospitals and trend studies to allow easy identification of the factors associated with mortality, to track the changes in neonatal mortality over the years to provide insights on the area to focus on for intervention. The present study only captured mortality that occurred in the hospital. Future studies should investigate neonatal deaths that occurred both during hospitalization and after hospital discharge and identify the factors associated with the mortality that occurred among neonates who were discharged from the hospital.

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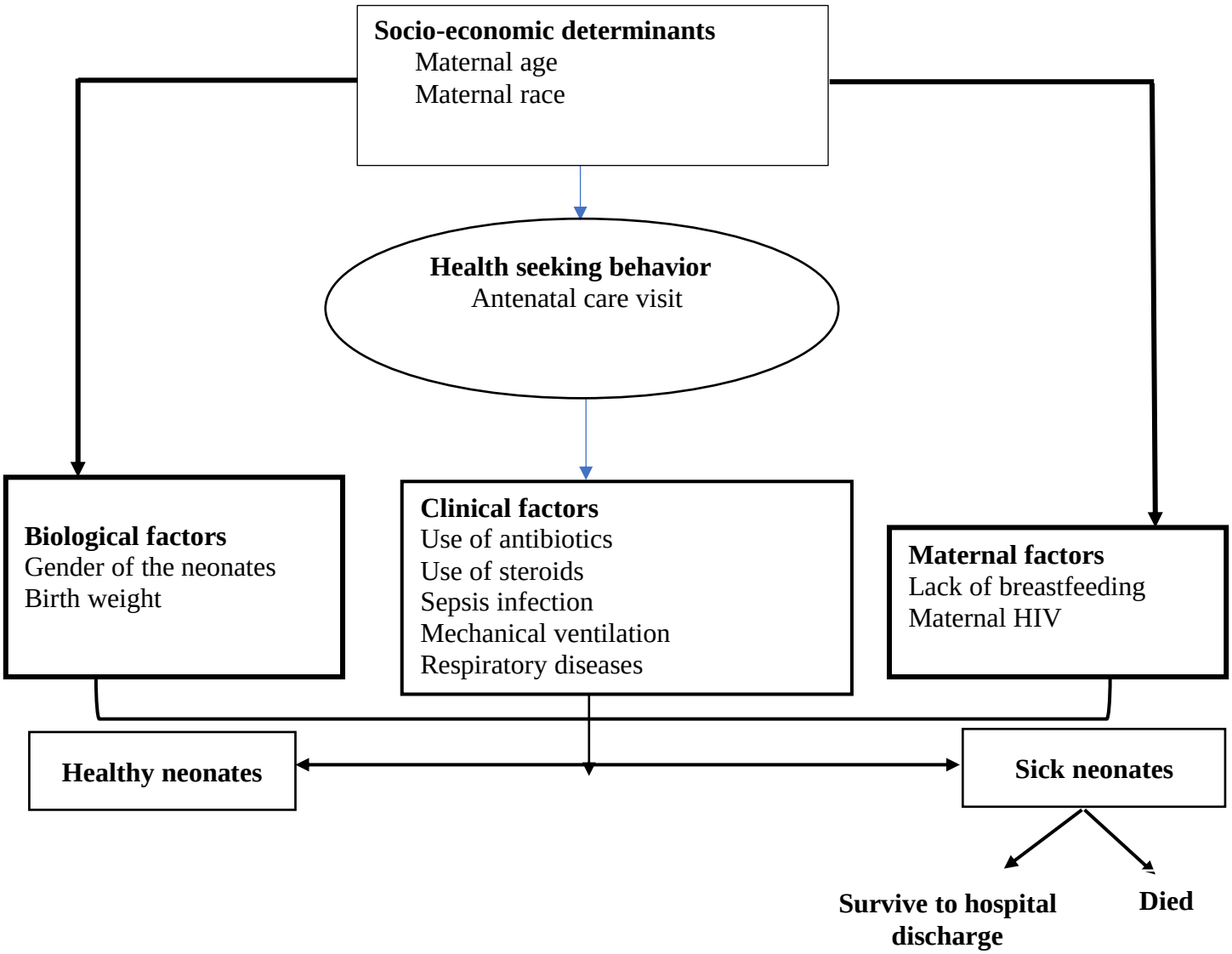
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Appendices

Appendix A: Conceptual Framework to determine the survival of neonates



Adapted from Mosley and Chen Conceptual Framework for child survival in developing countries (1984).

Appendix B: Plagiarism declaration report



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Wuraola Aderounmu (Student number: 1887347) am a student registered for the degree of Master of Science in Epidemiology and Biostatistics in the academic year 2019

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 23rd of June 2020

Appendix C: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr W Aderounmu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M191073

NAME: (Principal Investigator)	Dr W Aderounmu
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	Trend in the survival of low birth weight neonates to hospital discharge, at Charlotte Maxeke Johannesburg Academic Hospital, from 1 January 2013 to 2019/06/30
DATE CONSIDERED:	2019/10/25
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professors D Ballot and T Chirwa
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/01/03

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

28-02-2020
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES