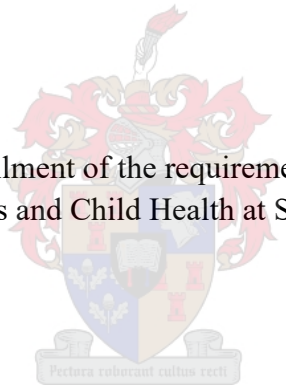
Morbidity, mortality and neurodevelopmental outcomes of extremely low birth weight neonates in the first year of life: a retrospective cohort study

Grace Musiime



Thesis presented in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics and Child Health at Stellenbosch University

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DECLARATION

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ABSTRACT

Background: Neonatal deaths are a leading cause of child mortality worldwide, with sub-Saharan Africa bearing the largest burden. Extremely low birth weight (ELBW) neonates (less than 1000 grams) have the highest mortality. There is a lack of data evaluating long- and short-term outcomes of ELBW neonates in South Africa and because of variations in outcomes over time and between different regions, existing statistics cannot be easily transposed. Given the increased focus on reducing neonatal mortality, data are needed to guide resource allocation and policy development to optimise outcomes.

Objective: The purpose of this study was to describe the morbidity, mortality and neurodevelopmental outcomes at one year corrected gestational age (CGA) of ELBW infants treated at a tertiary hospital.

Methods: This was a retrospective cohort study of live-born infants treated at Tygerberg Hospital (TBH) between 1 January and 31 December 2016. All live born ELBW infants were included. Eligible infants were identified via the Vermont Oxford Network database. Data were extrapolated from this database and additional data were obtained from patient records. Follow-up data from time of discharge until one year CGA were obtained from high-risk clinic case notes. Multiple logistic regression and survival analysis were undertaken in STATA to identify risk factors for mortality.

Results: A total of 256 ELBW infants were admitted during the study period, 240 born within TBH and 16 transferred from surrounding medical facilities. The majority were managed in the neonatal high-care wards, with only 11.3% admitted to the neonatal intensive care unit (NICU) at any time during their hospitalisation. Respiratory distress syndrome was diagnosed in 83.2% and 93% required nasal continuous positive airways pressure (NCPAP). The survival to hospital discharge rate was 63.3%. The majority of deaths occurred in the first three days of life (19.5%; 95% CI 14.7–24.3%). Cause of death was documented as extreme prematurity in 41% of the inpatient deaths. Birth weight was a significant predictor of mortality (hazard ratio 0.99; 95% CI 0.992–0.999). Of the 151 neonates who survived until discharge, 11 died following discharge and 86 were lost to follow-up (57%). Sixty-five neonates attended follow-up at one year CGA: 2.6% of these had severe neurodevelopmental impairment and 37.3% manifested no significant developmental delay, as assessed clinically according to extent of delay in neurodevelopmental milestones.

Conclusions: Mortality and morbidity rates remain high among ELBW neonates. In order to improve survival, resources need to be allocated to neonatal resuscitation, surfactant therapy, NCPAP and increasing availability of NICU beds. Further research is needed to adequately assess long-term neurodevelopmental outcomes of ELBW neonates in this setting.

OPSOMMING

Agtergrond: Neonatale sterftes is ’n hoofoorsaak van kindersterftes wêreldwyd, met Afrika suid van die Sahara wat die grootste las dra. Neonate met ’n uiters lae geboortegewig het die hoogste sterftesyfers. Daar is ’n gebrek aan data wat die lang- en korttermynuitkomste van neonate met uiters lae geboortegewig in Suid-Afrika evalueer, en as gevolg van die streeks- en tydelike variasies kan bestaande statistieke nie maklik oorgedra word nie. Gegewe die toenemende fokus op die vermindering van neonatale sterftes, is data nodig om hulpbrontoekenning en beleidsontwikkeling te rig om uitkomste te optimaliseer.

Doelstelling: Die doel van hierdie studie was beskrywing van die morbiditeit, sterftes en neuro-ontwikkelingsuitkomste op een jaar gekorrigeerde gestasie-ouderdom van neonate met uiters lae geboortegewig wat in ’n tersiêre hospitaal met beperkte toegang tot neonatale intensiewe sorg weens hulpbronbeperkings behandel is.

Metodes: Hierdie studie was ’n retrospektiewe kohortstudie van lewendgebore neonate wat in Tygerberg Hospitaal (TBH) tussen 1 Januarie en 31 Desember 2016 behandel is. Kwalifiserende neonate is via die Vermont Oxford Netwerk-databasis geïdentifiseer. Data is uit hierdie databasis geëkstrapoleer en bykomende data is uit pasiëntrekords verkry. Opvolgdata vanaf hospitaalontslag tot en met een jaar gekorrigeerde gestasie-ouderdom is vanuit hoërisiko-kliniekpasiëntnotas verkry. Veelvuldige logistiese regressie en oorlewingsanalises is in STATA gedoen om risikofaktore vir sterftes te identifiseer.

Resultate: Altesaam 256 neonate met uiters lae geboortegewig is gedurende die studietydperk opgeneem – 240 gebore in TBH en 16 vanaf omliggende mediese fasiliteite oorgeplaas. Die meerderheid neonate is in die neonatale hoësorgsale behandel, met slegs 11.3% wat te eniger tyd tydens hul hospitalisasie in die neonatale intensiewe eenheid opgeneem is. Hialienmembraansiekte is by 83.2% gediagnoseer en 93% het nasale deurlopende positiewe lugwegdruk benodig. Die oorlewingskoers tot hospitaalontslag was 63.3%. Die meerderheid sterftes het in die eerste drie dae van lewe (19.5%; 95% CI 14.7–24.3%) plaasgevind. Die oorsaak van dood is opgeteken as uitermate prematuriteit in 41% van sterftes tydens hospitalisasie. Geboortegewig was ’n beduidende voorspeller van sterftes (gevaarverhouding 0.99; 95% CI 0.992–0.999). Van die 151 neonate wat tot ontslag oorleef het, het 11 ná ontslag gesterf en 86 (57%) het nie opvolgbesoeke bygewoon nie. Vyf-en-sestig neonate het die opvolgkliniek op een jaar gekorrigeerde gestasie-ouderdom bygewoon; 2.6% hiervan het erge neuro-ontwikkelingsgebreke gehad en 37.3% het normale ontwikkeling gehad.

Gevolgtrekkings: Sterfte- en morbiditeitsyfers bly hoog onder neonate met uiters lae geboortegewig. Ten einde die oorlewing van hierdie neonate te verbeter, moet hulpbronne aan neonatale resussitasie, surfaktantterapie, nasale deurlopende positiewe lugwegdruk en verhoogde beskikbaarheid van neonatale intensiewesorg-beddens toegeken word. Verdere navorsing is nodig om die langtermyn-neuro-ontwikkelingsuitkomste van hierdie babas voldoende te assesseer.

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Most importantly, I am grateful for my family's unconditional support and to God Almighty; without his blessings, this accomplishment would not have been possible.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CGA	Corrected gestational age
CI	Confidence interval
CRP	C-reactive protein
ELBW	Extremely low birth weight
GA	Gestational age
HIV	Human immunodeficiency virus
HR	Hazard ratio
IQR	Interquartile range
IVH	Intraventricular haemorrhage
KMC	Kangaroo mother care
LMICs	Low- and middle-income countries
NCPAP	Nasal continuous positive airway pressure
NDI	Neurodevelopmental impairment
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PMTCT	Prevention of mother to child transmission (of HIV)
PPIP	Perinatal Problem Identification Program
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SGA	Small for gestational age
TBH	Tygerberg Hospital
VLBW	Very low birth weight
VON	Vermont Oxford Network

1 INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Neonatal deaths are a leading cause of mortality worldwide, accounting for an estimated 2.7 million deaths globally in 2017 (1). Preterm birth rates are highest in low- and middle-income countries (LMICs) and are estimated to have increased in a majority of countries between 2000 and 2014, with most preterm births occurring in Asia and sub-Saharan Africa (2). Prematurity is a significant risk factor for neonatal death; a majority of neonatal mortalities can be directly attributed to preterm birth and associated complications (3). Extremely low birth weight (ELBW) neonates are defined as neonates weighing less than 1000 grams at birth irrespective of gestational age (4).

1.2 Causes of prematurity, associated morbidity and factors influencing outcome

Preterm births, defined as all live births before 37 completed weeks, can be broadly classified into two groups: provider-initiated and spontaneous. Provider-initiated preterm delivery may occur as a consequence of non-medical, obstetric or foetal indications. There are multiple risk factors for spontaneous preterm birth. Maternal factors include infection, chronic medical conditions, depression, poor nutrition, smoking, use of recreational drugs and alcohol, advanced maternal age or teenage pregnancy, short intervals between pregnancies, cervical incompetence, family history of prematurity, human immunodeficiency virus (HIV) infection and anti-retroviral therapy. Congenital anomalies and intrauterine growth restriction are also associated with spontaneous preterm birth (5,6).

Complications of prematurity include intracranial haemorrhage, periventricular leukomalacia (PVL), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and necrotising enterocolitis (NEC) (7–11). NEC occurs more frequently in HIV-infected infants (12). Antenatal corticosteroid treatment is associated with a reduction in NEC, RDS, mechanical ventilation, intraventricular haemorrhage (IVH), systemic infection in the first two days of life and both perinatal and neonatal mortality (13).

A majority of preterm neonates survive without neurodevelopmental impairment (NDI), although intrauterine and neonatal insults are associated with long-term disability (14,15). Preterm birth and ELBW are independent risk factors for NDI (15,16). Other risk factors include hypoxic ischaemic encephalopathy, sepsis, tetanus, severe hyperbilirubinaemia, infection and meningitis (15). In ELBW infants, mechanical ventilation for more than 15 days increases the risk of cerebral palsy and attention deficit and hyperactivity disorder, and cardiorespiratory events negatively impact language development (17,18). Cognitive outcomes are improved by early developmental interventions such as physiotherapy and occupational therapy, infant stimulation, neurodevelopmental therapy and optimisation of the parent–infant relationship (19). In addition, antenatal exposure to magnesium sulphate is associated with a reduced risk of cerebral palsy in infants after less than 34 weeks' gestation (20–22).

Accurate determination of gestational age (GA) is important, as this influences clinical management, prognosis and research. In high-income settings, widespread access to early ultrasound dating in pregnancy minimises uncertainty regarding GA. In LMICs, limited access to early ultrasound, inconsistent recall of last menstrual period for dating and variation in clinical assessments of neonates often result in inaccurate estimation of antenatal GA (23,24). There is a need for simplified methods of appropriately identifying preterm infants in LMICs to enable timely intervention and optimal care provision. Postnatal foot length has been shown to correlate well with GA in a cohort of hospitalised South African neonates, but further research is required prior to widespread implementation (25).

1.3 Mortality

Although there has been a global reduction in neonatal mortality rates between 1990 and 2017, there is significant regional variation and sub-Saharan Africa continues to bear a large burden of neonatal mortality (1). In high-income countries there has been an increase in survival of ELBW neonates over the past two decades (26–32), with increased attention now focused on neonates born at the limits of viability (33–37). In middle-income countries there has also been a decline in the mortality of ELBW neonates, although mortality rates are still higher than in high-income countries (38). Data from low-income countries are limited; the mortality of ELBW neonates in these settings remains high, largely as a consequence of significant limitations in access to even basic neonatal care (39).

Preterm birth complications account for a majority of neonatal deaths worldwide (3). Hypothermia and HIV infection are associated with increased mortality (40–42). Preterm neonates who are small for gestational age (SGA) have a higher mortality risk than those who are appropriate for GA in LMICs (43). Skilled attendance at birth and delivery in a tertiary centre, early surfactant administration and early identification and treatment of infection are associated with reduced mortality (44–46).

Cause of neonatal death varies according to location. Complications of prematurity and congenital anomalies predominate in high-income settings, whereas infection and asphyxia are leading causes in a majority of LMICs. Most deaths occur early in the period immediately after birth (26,47,48). In South Africa, the main causes of all neonatal deaths (birth weight greater than or equal to 500 grams) in 2016 from national data were complications of prematurity (47.9%), intrauterine hypoxia and other intrapartum-related events (24.3%) and infections (11.6%) (49). Infection may account for a greater proportion of neonatal deaths than previously documented. Data from minimally invasive tissue sampling in a neonatal cohort in Johannesburg showed that bacterial infection was the immediate cause of death in a majority of neonatal deaths attributed to complications of prematurity (50).

1.4 Existing data on outcomes of extremely and very low birth weight neonates in South Africa

In South Africa, there have been significant efforts to document perinatal mortality countrywide through an audit tool: the Perinatal Problem Identification Program (PPIP) (47). Most deaths and deliveries occur at district hospitals, and regional variations exist (51). Over the past two decades, ELBW neonates have had limited access to intensive care because of

resource constraints (52–54). They have the highest mortality, require delivery room resuscitation more frequently than infants weighing more than 1 000 grams and have a significantly higher mortality following resuscitation (51,55). Neonates delivered in tertiary centres have better outcomes (56).

Data from tertiary centres in Johannesburg demonstrate an improvement in survival of ELBW infants over time, with 32% surviving between 2000 and 2002, 34.9% surviving between 2006 and 2007 and 52.4% surviving in 2013 (57–59). Only one published study conducted in Johannesburg has specifically focused on outcomes of ELBW neonates using an inclusion weight criteria of 900 grams or less; none of these neonates were offered mechanical ventilation due to resource constraints and the survival rate was 26.6% between 2006 and 2010 (54). In Cape Town, survival of ELBW neonates in Groote Schuur Hospital has improved from 42% between 1988 and 1989 to 68% between 2003 and 2005 (60,61). In Tygerberg Hospital (TBH), 74.8% of ELBW neonates survived to discharge between 2007 and 2009. This study included all ELBW infants treated at TBH during this period. All neonates received nasal continuous positive airway pressure (NCPAP); 68% were managed with NCPAP only, 26.5% received surfactant and NCPAP and 5.3% were admitted to the neonatal intensive care unit (NICU) (53).

Several studies have assessed long-term neonatal outcomes in South Africa. In 1988, 22% of a cohort of neonates weighing less than 1 250 grams at birth followed up at Groote Schuur Hospital had major NDI at two years (61). Of a subsequent cohort of ELBW infants born at the same hospital between 2003 and 2005, 17% had NDI at seven months (60). In Johannesburg, 10% of a cohort of ELBW neonates delivered at Chris Hani Baragwanath Hospital in 1990 had NDI at one year corrected gestational age (CGA) (62), 15.1% of a cohort of very low birth weight (VLBW) neonates born between 2006 and 2007 treated at Charlotte Maxeke Johannesburg Academic Hospital had impairment of a single cognitive, motor or language subscale at 15 to 18 months CGA (63), whereas 7% of a cohort of VLBW infants delivered in 2013 had NDI at 15 to 18 months (64). This decline in occurrence of NDI may, in part, be a result of changes in the management of VLBW neonates, such as increased availability of surfactant and NCPAP (64).

1.5 Problem statement and justification for study

If the sustainable development goal of reducing neonatal mortality to at least 12 per 1 000 live births by 2030 is to be realised in LMICs (65), urgent attention must be focused on reducing the mortality of ELBW neonates. There is limited data evaluating the long-term outcomes of ELBW neonates in sub-Saharan Africa and South Africa, and few studies focus specifically on short-term outcomes of these infants. In addition, because of variations in outcomes over time and between regions, and increased access to NCPAP and surfactant in recent years, morbidity and mortality data cannot be easily transposed. Consequently, there is a need for recent data focusing on both long- and short-term outcomes of ELBW neonates in South Africa and LMICs in general to guide forward planning, resource allocation and policy development with a view to optimising outcomes and decreasing mortality.

2 AIM AND OBJECTIVES

The aim of this study was to describe the morbidity, mortality and neurodevelopmental outcomes of a cohort of ELBW infants treated at TBH in 2016. The primary outcomes were neonatal morbidities, all-cause mortality and neurodevelopmental outcomes at one year CGA. The secondary outcomes were neonatal risk factors for mortality.

3 METHODS

3.1 Participants and outcomes

3.1.1 Study design

This was a retrospective cohort study.

3.1.2 Study population

All live-born inborn and outborn neonates with a birth weight less than or equal to 1 000 grams admitted to TBH between 1 January 2016 and 31 December 2016 within 28 days of birth were included in this study. Outborn neonates admitted to TBH after day 28 of life were excluded. This cohort was identified via the Vermont Oxford Network (VON) database (66). TBH submits data to the VON database annually. Data are collected by admitting doctors using a standardised form and then verified and entered onto the password-protected database by a consultant.

3.1.3 Study centre

TBH is the tertiary referral centre covering a large catchment area with 50 000 neonates delivered annually. The NICU has eight beds and a linked four-bed step-down high-care ward. There are two neonatal high-dependency wards, one for inborn infants and one for all outborn infants (referred from Level 1 and 2 hospitals or midwifery obstetric units) or NICU discharges, and two step-down pre-discharge kangaroo mother care (KMC) wards. There are a total of 124 beds, including the NICU, high-dependency and KMC wards.

3.1.4 Standard of care

All infants were managed according to hospital guidelines at the time. All inborn neonates who did not require immediate mechanical ventilation following delivery were admitted to the neonatal high-dependency ward. Nasal prong oxygen, NCPAP and surfactant were administered in the high-dependency ward when indicated. Due to resource constraints, infants with a birth weight less than 750 grams and GA less than or equal to 26 weeks received surfactant selectively. Neonates requiring neonatal intensive care would be considered for admission to the NICU once they were 28 weeks CGA and weighed 1 000 grams or more. Neonates with severe congenital anomalies, severe birth asphyxia, requiring prolonged resuscitation or deemed to have poor prognosis by the attending neonatologist, such as severe IVH or PVL, were not eligible for NICU admission, irrespective of birth weight or GA. Under exceptional circumstances and depending on bed availability, infants not meeting these criteria were considered for admission to the NICU on a case-by-case basis. NICU eligibility criteria for neonates delivered outside TBH were the same as for inborn neonates.

GA was routinely determined by early ultrasound, defined as an ultrasound undertaken at less than 24 weeks' gestation as per hospital protocol. Foot length at birth was used where early ultrasound was not available.

All neonates with risk factors for early-onset neonatal sepsis were initiated on penicillin and gentamicin following delivery after obtaining a blood culture. Septic risk factors were defined as per hospital guidelines as follows: chorioamnionitis, infant of Group B streptococcal carrier with clinical features suggestive of sepsis, spontaneous preterm labour or any neonate with clinical features suggestive of sepsis following delivery. A C-reactive protein (CRP) was done between 12 and 24 hours of life and antibiotic therapy stopped if the CRP was less than 10 and the blood culture negative, provided the infant did not have clinical features suggestive of infection. Prevention of mother to child transmission of HIV (PMTCT) entailed initiation of single or dual antiretroviral prophylaxis after delivery according to risk stratification. A blood sample was obtained for HIV polymerase chain reaction at birth and three-drug antiretroviral therapy was initiated in the event of HIV seroconversion. Exclusive breast feeding was recommended as per hospital guidelines and donor breast milk was used, with informed maternal consent, if there was insufficient expressed breast milk.

All neonates weighing less than 1 500 grams at birth are routinely followed up in a high-risk outpatient clinic at TBH after hospital discharge at three-monthly intervals. This clinic is run by a single senior medical officer. A standardised neurodevelopmental assessment tool is not routinely used in this clinic because of the high patient load. All babies are screened for hearing loss using evoked otoacoustic emissions and, if abnormal, auditory brainstem responses. Neonates with abnormalities in both tests are referred for further audiological assessment.

3.1.5 Outcomes

Variable definitions were adapted from the VON database and are summarised in Table 1 (67). The definition for BPD was not derived from the VON database, as the definitions manual did not categorise BPD. In addition, a definition for presumed sepsis was included, as at TBH neonates fulfilling these criteria are treated with antibiotics for five days or longer at the discretion of the attending neonatologist.

Maternal demographics included antenatal care attendance, syphilis, HIV status and perinatal interventions, namely administration of antenatal steroids and magnesium sulphate. Delivery details included; place of birth, indication for delivery, multiple gestation, mode of delivery, Apgar score at 1, 5 and 10 minutes, resuscitation including surfactant administration and temperature on admission to neonatal unit. Neonatal information included birth weight and gestation. Birth weight below the 10^{th} centile for the GA, as plotted on the growth curves of Fenton, was classified as SGA (68).

Neonatal morbidity data included details of congenital anomalies, respiratory support required after birth and duration of oxygen therapy, NICU admission and duration of mechanical ventilation, patent ductus arteriosus (PDA), BPD, RDS and surfactant administration, IVH and grade, PVL, NEC and management, focal intestinal perforation and management, ROP (as

diagnosed by an ophthalmologist) and management, sepsis (early-onset, late-onset and presumed sepsis), HIV prophylaxis and HIV status at birth and subsequent follow-up.

Mortality was classified according to the primary cause of death. NDI was classified as follows: no impairment, suspected NDI or severe impairment based on clinical examination at one year CGA. Suspected NDI was defined as a three-month delay in developmental milestones. Severe impairment was defined as any one of the following: delay in developmental milestones greater than three months, clinical features of cerebral palsy, hearing impairment as determined by an audiometric test or visual impairment as determined by reduced visual acuity. This is the clinical classification system used in the TBH high-risk follow-up clinic. This clinic is run by a single medical officer.

3.2 Data collection, management and analysis

3.2.1 Data collection and management

Data were abstracted from the VON database onto a secure Microsoft Excel database; no patient-identifiable information was stored in the database. Additional data were obtained from patient records using a standardised data collection form (Appendix 1).

3.2.2 Statistical methods

Descriptive analysis was undertaken using SPSS (69). Results are presented as numbers with proportion (%), 95% confidence interval (CI) and median with interquartile range (IQR). Survival analysis and simple regression and multiple cox regression were undertaken to identify risk factors for mortality in STATA (70); results are presented as a Kaplan-Meier curve, p-values and hazard ratios (HRs) with 95% CI. For this analysis it was assumed that all loss to follow-up cases did not die within the specified study period. A sub-group analysis was undertaken for risk factors for inpatient mortality.

A sample size estimation was done *a priori*, using the OpenEpi sample size calculator for cohort studies (71). A value of 25% was used for percentage of exposed with outcome, which represents the proportion of ELBW infants with RDS as the primary cause of death; this figure was derived from published South African data (54). An additional figure of 20 was added to the total sample size derived by the calculator for each additional cause of death as classified in the study. A minimum sample size of 118 was required to evaluate factors associated with mortality with 80% power, 95% CI assuming an equal number of exposed and unexposed.

3.3 Ethical considerations

Ethical approval for the study was obtained from the Human Research Ethics Committee of Stellenbosch University. A waiver of individual informed consent was granted by the committee. Permission to conduct research at TBH was obtained from the Western Cape government.

Table 1 Variable definitions

Variable	Definition
Definitions adapted from VON manual of operations (67)	
Inborn	Infant delivered at TBH
Outborn	Infant delivered outside TBH (Level 1 or 2 hospital or midwifery obstetric unit)
Antenatal care	Obstetric care administered prior to admission for delivery of infant
Antenatal steroids	Corticosteroids administered to mother intramuscularly during pregnancy (before delivery)
Antenatal magnesium sulphate	Intravenous magnesium sulphate administered to mother during pregnancy (before delivery)
Surfactant	Administration of exogenous surfactant at any time
Maternal diabetes	Type I, Type II or gestational diabetes
Bacterial sepsis or meningitis	Bacterial pathogen isolated from blood or cerebrospinal fluid
Other infection	Isolation of fungal or viral pathogen
Early infection	Infection before 72 hours of life
Late infection	Infection after 72 hours of life
Coagulase negative staphylococcal infection	Positive culture and features of generalised infection and antibiotic treatment for five days or longer
Intraventricular haemorrhage	Features of intracranial haemorrhage as diagnosed by imaging prior to 28 days of life, classified as follows: Grade 0: No bleed Grade 1: Germinal matrix haemorrhage Grade 2: IVH without ventricular dilatation Grade 3: IVH with ventricular dilatation Grade 4: Parenchymal bleed
PVL	Multiple small periventricular cysts identified on cranial ultrasound or computed tomography or magnetic resonance imaging
NEC	One of the following clinical features: bilious vomiting or gastric aspirates, haematochezia/melaena/occult blood in stool, abdominal distension accompanied by one of the following radiological signs: pneumatosis intestinalis, pneumoperitoneum or portal venous gas
Focal intestinal perforation	Bowel perforation without features of NEC
RDS	Supplemental oxygen needed to maintain oxygen saturation as measured by pulse oximeter >85% and a chest X-ray consistent with RDS within the first 24 hours of life
ROP	Features consistent with ROP as diagnosed by retinal examination by an ophthalmologist (at TBH examination done at four weeks post-delivery or between 31 and 32 weeks after conceptual age)
PDA	Echocardiogram showing bidirectional shunting or left to right shunting and murmur, wide pulse pressure, cardiomegaly or pulmonary vascular congestion, bounding pulses
Additional definitions	
BPD (9)	Treatment with supplemental oxygen >21% for more than 28 days or supplemental oxygen and/or positive pressure respiratory support required at 36 weeks CGA or discharge
Hypothermia	Core body temperature <36.5 ºC
Presumed sepsis or meningitis	Signs of generalised infection, elevated inflammatory markers (CRP greater than 10, leucocytosis) and elevated cerebrospinal protein count or pleocytosis in the absence of a positive blood or cerebrospinal fluid culture requiring antibiotic treatment for at least five days

4 RESULTS

4.1 Study population

A total of 256 ELBW neonates were admitted to TBH during the study period; only 16 (6.3%) were delivered outside TBH. There were 151 (59%) survivors; of these, 65 (43%) had complete one-year follow-up data and 86 (57%) were lost to follow-up (Figure 1).

4.2 Characteristics and perinatal interventions

The characteristics of the cohort and perinatal interventions are presented in Table 2. The majority of the infants were female (53.9%). The GA range was 23 to 34 weeks (median 27 weeks, IQR 26–28 weeks), the median birth weight was 850 grams (IQR 750–927.5 grams) and 20.7% were SGA. Antenatal care attendance was high (91.8%); 82.4% received antenatal steroids and 47.4% received antenatal magnesium sulphate. In total, 21.5% of the infants were HIV-exposed and 2.7% syphilis-exposed. Some form of delivery room resuscitation was required by 54.7% of the infants and 41% received surfactant. Most neonates were managed in a neonatal high-care ward, 11.3% were admitted to the NICU during the course of admission and 72.8% were hypothermic on admission to a neonatal unit.

4.3 Morbidity and neonatal intensive care unit or high-care treatment

Neonatal morbidity and treatment are summarised in Table 3. Of the total number of neonates, 83.2% had RDS and most infants required respiratory support; 93% of the neonates had NCPAP, 56.3% high-flow nasal cannula and 7% mechanical ventilation. Some neonates received more than one form of respiratory support. NEC was diagnosed in 10.5%, and 2.7% underwent surgery. In total, 36% developed sepsis (early-onset, late-onset or presumed sepsis), 8.2% had BPD and 34.5% had IVH, of which 7.1% had severe IVH (Grade 3 or 4). Only one infant was diagnosed with PVL, although 34.4% of the cohort did not have a cranial ultrasound. A total of 170 neonates survived to four weeks post-delivery or between 31 and 32 weeks after conceptual age for ROP screening; of these, 31.2% had ROP of any stage and three neonates (5.6% of neonates with ROP) required laser surgery. No neonates were treated with bevacizumab and 28 eligible neonates (16.5%) were not screened for ROP.

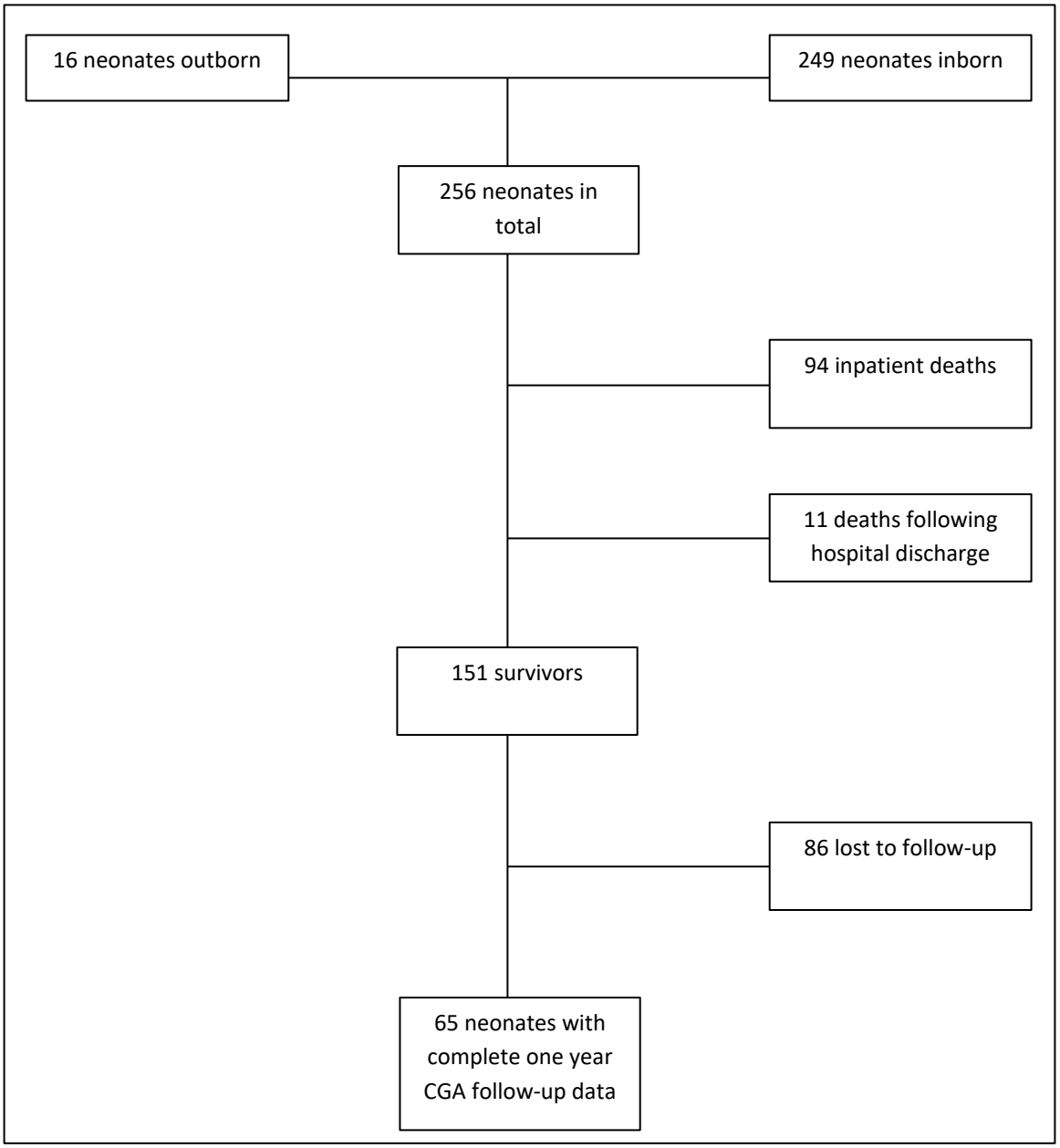

Figure 1 Flow diagram of study population

Table 2 Characteristics and perinatal interventions of live-born infants

	23–26 weeks	27–30 weeks	31–34 weeks	Unknown (missing data)	23–34 weeks (total)
Overall number of infants and NICU admissions, n (% of live births)					
Total, n (%)	84 (32.8)	154 (60.2)	18 (7)	0	256 (100)
Admitted to NICU, n (%)	7 (8.3)	20 (13)	3 (11.1)	0	29 (11.3)
Characteristics of live-born infants, n (% of live births)					
Birth weight, median (IQR)	785 (690–870)	870 (787.5–940)	920 (822–950)	0	850 (750–927.5)
Male, n (%)	43 (51.2)	65 (42.2)	10 (55.6)	0	118 (46.1)
Female, n (%)	41 (48.8)	89 (57.8)	8 (44.4)	0	138 (53.9)
Multiple births, n (%)	18 (21.4)	19 (12.3)	4 (22.2)	0	41 (16)
SGA, n (%)	2 (2.4)	36 (23.4)	15 (83.3)	0	53 (20.7)
Congenital abnormalities, n (%)	1 (1.2)	0	0	0	1 (0.4)
Born outside TCH, n (%)	8 (9.5)	7 (4.5)	1 (5.6)	0	16 (6.3)
Antenatal care and HIV and syphilis exposure, n (% of live births, unless otherwise specified)					
Antenatal care attended, n (%)	71 (91)	134 (91.2)	18 (100)	13 (5.1)	223 (91.8)
HIV-exposed, n (%) Adequate PMTCT, n (% of HIV-exposed) HIV positive at birth, n (% of HIV-exposed) HIV positive after birth, n (% of HIV-exposed)	21 (25) 18 (85.7) 1 (4.7) 1 (4.7)	31 (20.1) 30 (96.7) 0 0	3 (16.7) 3 (100) 0 0	0 1 (0.4) 9 (3.5) 12 (4.7)	55 (21.5) 51 (92.7) 1 (1.8) 1 (1.8)
Syphilis-exposed, n (%) Congenital syphilis, n (% of syphilis-exposed)	2 (2.4) 1 (50)	4 (2.6) 1 (25)	1 (5.6) 1 (100))	1 (0.4) 0	7 (2.7) 3 (42.8)
Delivery and perinatal interventions, n (% of live births)					
Antenatal magnesium sulphate, n (%)	37 (44)	78 (50.6)	7 (38.9)	0	122 (47.7)
Antenatal steroids, n (%)	62 (73.8)	131 (85.1)	18 (100)	0	211 (82.4)
Caesarean delivery, n (%)	20 (23.8)	124 (80.5)	16 (88.9)	0	160 (62.5)
Five-minute Apgar below 5, n (%)	15 (17.8)	9 (5.8)	2 (11.1)	0	26 (10.1)
Surfactant in delivery room, n (%)	1 (1.2)	5 (3.2)	0	1 (0.4)	6 (2.4)
Surfactant post-delivery room, n (%)	30 (36.1)	65 (43.6)	1 (5.9)	0	96 (38.6)
Delivery room resuscitation, n (%) Bag-mask ventilation, n (%) Intubation, n (%) CPR, n (%)	50 (59.5) 49 (58.3) 6 (7.1) 14 (16.7)	86 (55.8) 85 (55.2) 5 (3.2) 16 (10.4)	4 (22.2) 4 (22.1) 0 1 (5.6)	0 0 0 0	140 (54.7) 138 (53.9) 11 (4.3) 31 (12.1)
Hypothermia on admission to neonatal unit, n (%)	63 (77.8)	101 (68.7)	15 (83.3)	10 (3.9)	179 (72.8)

Table 3 NICU/ neonatal high-care treatment and morbidity of live-born infants

	23–26 weeks	27–30 weeks	31–34 weeks	Unknown (missing data)	23–34 weeks (total)
Treatment of infants admitted to NICU/neonatal high-care unit, n (% of live births)					
Mechanical ventilation, n (%)	4 (4.8)	12 (7.8)	2 (11.1)	0	18 (7)
High-flow nasal cannula, n (%)	24 (29.3)	108 (70.1)	11 (61.1)	2 (0.8)	143 (56.3)
Nasal CPAP, n (%)	77 (91.7)	146 (94.8)	15 (83.3)	0	238 (93)
Inhaled nitric oxide, n (%)	1 (1.2)	4 (2.6)	0	0	5 (2)
Surgery for NEC, n (%)	2 (2.4)	5 (3.2)	0	0	7 (2.7)
Intercostal drain for pneumothorax, n (%)	0	2 (1.3)	0	0	2 (0.8)
Morbidities, n (% of live births, unless otherwise specified)					
PDA, n (%)	12 (14.3)	17 (11)	1 (5.6)	0	30 (11.7)
Early-onset sepsis, n (%)	3 (3.6)	1 (0.6)	0	0	4 (1.6)
Late-onset sepsis, n (%)	14 (16.7)	28 (18.2)	2 (11.1)	0	44 (17.2)
Presumed sepsis, n (%)	12 (14.3)	26 (16.9)	6 (33.3)	0	44 (17.2)
IVH, n (%) Grade 1–2, n (%) Grade 3–4, n (%)	22 (51.2) 17 (39.5) 5 (11.6)	34 (29.8) 27 (23.7) 7 (6.1)	2 (18.2) 2 (18.2) 0	 88 (34.4)	58 (34.5) 46 (27.4) 12 (7.1)
PVL, n (%)	0	1 (0.9)	0	88 (34.4)	1 (0.6)
BPD, n (%)	9 (10.7)	12 (7.8)	0	0	21 (8.2)
RDS, n (%)	77 (91.7)	127 (82.5)	9 (50)	0	213 (83.2)
NEC, n (%)	6 (7.1)	18 (11.7)	3 (16.7)	0	27 (10.5)
Spontaneous intestinal perforation, n (%)	2 (2.4)	3 (1.9)	1 (5.6)	1 (0.4)	6 (2.4)
ROP, n (% of infants eligible for screening) Anti-Vascular endothelial growth factor treatment, n (% of ROP infants) Surgery, n (% of ROP infants)	14 (37.8) 0 1 (7.1)	36 (31) 0 2 (5.5)	3 (17.6) 0 0	28 (16.5) 0 0	53 (31.2) 0 3 (5.6)

4.4 Mortality

4.4.1 Overall mortality and cause of death

There were 94 (36.7%) inpatient deaths and 11 (4.2%) deaths following hospital discharge. In total, 162 neonates survived to discharge (63.3%). Mortality according to GA is presented in Table 4 and cause of death in Table 5. The majority of the in-hospital deaths occurred within the first three days of life (19.5%; 95% CI 14.7–24.3). Most deaths occurred among infants of less than 30 weeks GA. Extreme prematurity was listed as the most common cause of inpatient deaths (41%), followed by sepsis (10.5%), RDS (9.5%) and NEC (9.5%). In 18.1% of deaths the cause of death was classified as unknown; in these cases a final cause of death was not documented in the patient records.

4.4.2 Risk factors for mortality and survival analysis

Multiple cox regression for mortality risk factors is shown in Table 6. Variables included birth weight, GA, SGA (as compared to appropriate for GA), sepsis (early-onset, late-onset and presumed sepsis), NEC, IVH Grade 3 and 4 (as compared to no IVH and IVH Grade 1 and 2), five-minute Apgar score below 5, RDS, surfactant, NCPAP and absence of hypothermia. These variables were selected on the basis of known association with mortality or statistical significance of their association with mortality on univariate analysis ($p<0.05$). Not all potential confounding variables were included in the model in view of small sample size. Antenatal care was not included due to high attendance (91.8%). NICU admission was not included, as only 11.3% of the cohort was admitted to the NICU.

Birth weight was a significant predictor of mortality (HR 0.99; 95% CI 0.992–0.999). A sub-group analysis was undertaken for risk factors for inpatient mortality and the same variables were incorporated into the model. Birth weight was the only significant predictor of mortality (HR 0.99; 95% CI 0.992–0.995).

A Kaplan-Meier curve for overall survival from birth until one year CGA is shown in Figure 2. The incidence rate of mortality was 2 per 1 000 days, assuming all infants lost to follow-up did not die during the specified study period.

4.5 Neurodevelopmental outcomes at one year corrected gestational age

Only 65 infants (43% of survivors) had complete follow-up data at one year CGA. Of these, 37.7% manifested no significant developmental delay, 2.6% had suspected NDI and 2.6% had severe NDI. Neurodevelopmental outcomes are presented in Table 7.

Table 4 Mortality rates by gestational age

Gestational age	Inpatient mortality n (%; 95% CI)			Death following hospital discharge n (%; 95% CI)	Total number of deaths, n (%, 95 % CI)
	Death <3 days of life	Death day 3–7 of life	Death >7 days of life		
23–26 weeks	31 (36.9; 30.9–42.8)	10 (11.9; 7.9–15.9)	8 (9.5; 5.9–13.1)	1 (1.5; 0–3)	50 (58.3; 52.3–64.3)
27–30 weeks	19 (12.3; 8.3–16.3)	10 (6.5; 3.5–9.5)	14 (9.1; 5.6–12.6)	7 (7.1; 3.9–10.3)	50 (32.4; 25–39.7)
31–34 weeks	0	0	2 (11.1; 7.3–14.9)	3 (37.5; 31.6–43.4)	5 (27.8; 22.3–33.3)
23–34 weeks (total)	50 (19.5; 14.7–24.3)	20 (7.8; 4.5–11.1)	24 (9.4; 5.8–12.9)	11 (6.4; 3.4–9.4)	105 (41; 34.9–47)

Table 5 Cause of death

Cause of death	n (% of all deaths)
Extreme prematurity	43 (41)
Sepsis	11 (10.5)
Pulmonary haemorrhage	7 (6.7)
RDS	10 (9.5)
NEC	10 (9.5)
Spontaneous intestinal perforation	1 (1)
Infective endocarditis	1 (1)
Infected ventriculoperitoneal shunt	1 (1)
IVH	1 (1)
Aspiration	1 (1)
Unknown	19 (18.1)

Table 6 Risk factors and prediction of mortality

Variable	HR (95% CI)	
	Simple regression (p-value)	Multiple cox regression
Apgar <5	0.2024	HR 0.67 (0.14–3.10)
Hypothermia absent	0.8452	HR 1.35 (0.62–2.96)
Birth weight	<0.001	HR 0.99 (0.992–0.999)
GA	<0.001	HR 1.09 (0.88–1.35)
*SGA	0.6505	HR 1.11 (0.21–15.67)
Sepsis	0.0042	HR 0.56 (0.26–1.21)
NEC	0.3308	HR 2.36 (0.94–5.92)
**IVH Grade 3–4	0.0823	HR 3.02 (1.00–9.06)
RDS	0.0340	HR 1.83 (0.63–5.27)
Surfactant	0.9414	HR 0.86 (0.40–1.84)
CPAP	0.6299	HR 1.77 (0.20–15.15)

* Compared to appropriate for GA

** Compared to no IVH or IVH Grade 1–2

Table 7 Neurodevelopmental outcomes at 1 year CGA

Gestational age	Survivors, n (%)	Number of infants with complete one-year follow-up data, n (% of survivors)	No significant developmental delay, n (%)	Suspected NDI, n (%)	Severe NDI, n (%)
23–26 weeks	34 (40.5)	14 (40)	12 (35.2)	0	2 (5.8)
27–30 weeks	104 (67.5)	48 (46.1)	42 (40)	4 (3.8)	2 (1.9)
31–34 weeks	13 (72.2)	3 (23.1)	3 (23.1)	0	0
23–34 weeks (total)	151 (58.9)	65 (43)	57 (37.7)	4 (2.6)	4 (2.6)

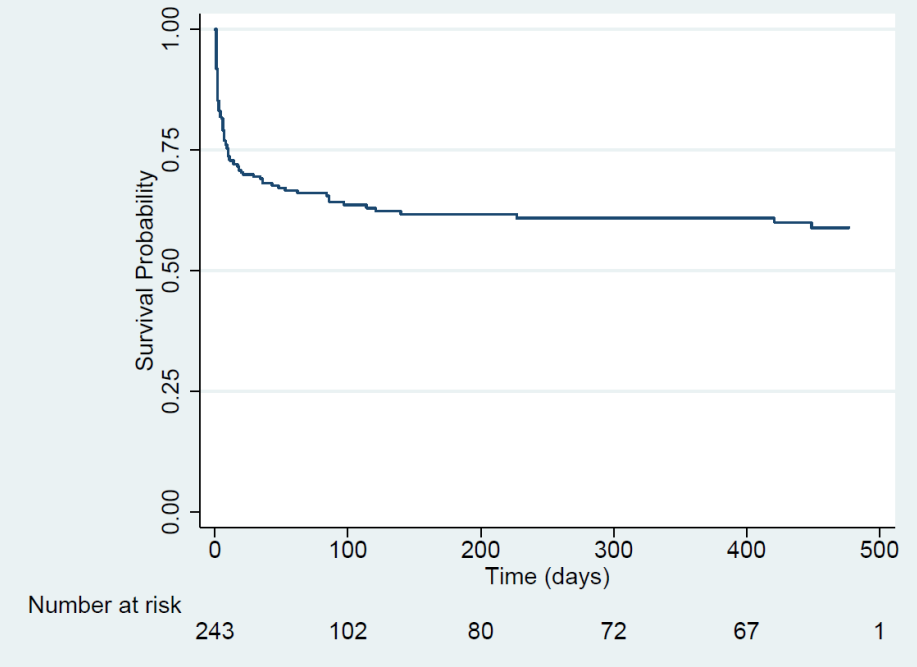

Figure 2 Kaplan-Meier curve for overall survival from birth until one year CGA

5 DISCUSSION

This retrospective cohort study provides updated data on the outcomes of ELBW neonates in TBH. The overall survival to discharge rate was 63.3% for ELBW neonates born in 2016. This is lower than the 74.8% survival to discharge rate reported at TBH between 2007 and 2009 (53). Although the mean birth weight and GA were similar during both study periods, the higher survival rate may, in part, be accounted for by differences in access to intensive care. Neonates weighing 750 grams or of 26 weeks GA were eligible for NICU admission at TBH between 2007 and 2009. The NICU admission criteria were subsequently revised because of a significant increase in the number of neonates admitted over time with a corresponding shortage of NICU bed space. In addition, the higher patient load and turnover noted in 2016, in the absence of a substantial increase in bed capacity or staffing due to resource constraints, conferred an increased risk of infection and therefore mortality (72).

In comparison with other tertiary centres in South Africa, this rate is slightly higher than the 52.4% survival rate reported for the Charlotte Maxeke Johannesburg Academic Hospital in 2013 (57), but lower than the 68% survival rate for Groote Schuur Hospital between 2003 and 2005 (61). In comparison with other upper middle-income countries, this survival rate is lower than rates reported in Jamaica and the South American Neocosur Network (five countries), similar to rates reported in Thailand, Bulgaria and Malaysia and significantly higher than the rate in Iran (73–78). These differences may partly be explained by variations in access to NICUs, with the countries with lower mortality rates using lower birth weight and GA criteria for NICU admission and mechanical ventilation. Most deaths occurred early in the first three days of life, similar to global mortality data (48). These neonates did not qualify for NICU admission.

In comparison with the 2016 VON average (66), the rates of infection and NEC were higher at TBH, the rate of RDS similar, and the rates of IVH, focal intestinal perforation, cystic PVL, severe ROP and BPD lower at TBH. As the VON encompasses data from multiple centres in high-income countries where ELBW infants are routinely managed in the NICU, the higher average rates of ROP and BPD are probably a result of the data from these centres where prolonged ventilation of ELBW infants is not uncommon. Conversely, the lower VON average infection rate could also be attributed to the data from high-income centres, as LMICs bear the greatest burden of neonatal infection worldwide (79). Outbreaks of infection occur more frequently in neonatal units in LMICs as a result of overcrowding, inadequate staffing, breaches of infection control practices and reuse of equipment (72).

Birth weight was a statistically significant risk factor for inpatient mortality in this study, with increasing birth weight associated with reduced risk of death consistent with global and South African data (59,80). Other factors known to be associated with inpatient mortality were not found to be of statistical significance in the regression analysis. This is likely a consequence of the sample size being relatively small. The most commonly listed cause of death in this study was extreme prematurity, consistent with national South African data (51).

Although the majority of the neonates who attended follow-up at one year CGA had no features of NDI, the loss to follow-up was large, and therefore this is not reflective of the entire study population. It is therefore difficult to draw conclusions about the prevalence of NDI or to assess risk factors for NDI in this setting. Furthermore, as a standardised neurodevelopmental assessment tool was not used due to the high case load in the follow-up clinic, the extent to which findings from this study can be compared to existing data is limited.

The results of this study have highlighted areas of good clinical practice. The majority of HIV-exposed infants (92.7%) received adequate PMTCT as per hospital guidelines. There was only one neonate who tested HIV positive; this baby was born before arrival and there was no PMTCT or antenatal care attendance. In addition, antenatal care attendance was 91.8%. The utilisation of antenatal care is associated with reduced neonatal mortality in sub-Saharan Africa (81).

The findings of this study also have implications for improving clinical practice. Twenty-eight eligible neonates were not screened for ROP. As there is only one ophthalmologist who conducts ROP screening at TBH, the case load is extremely high. However, efforts should be made to ensure that all ELBW neonates are screened for ROP to prevent long-term visual impairment. Eighty-eight neonates did not have a cranial ultrasound; of these, 50 died in the first three days of life. At TBH, cranial ultrasounds are done on specific days by the radiology department for neonates in high-dependency units and all NICU ultrasounds are done by neonatology fellows and neonatologists. It is therefore not always possible to obtain cranial ultrasounds for neonates in high-dependency wards within 72 hours of delivery. Ideally, all ELBW infants should have at least one cranial ultrasound. Training of junior doctors to perform cranial ultrasounds may be an option for improving coverage; however, this may be difficult to implement because of high staff turnover, as registrars and medical officers rotate through different neonatal wards on a monthly basis. There is also scope to optimise the administration of antenatal magnesium sulphate for neuroprotection and antenatal steroids, especially given the limited access to mechanical ventilation in this setting because of resource constraints.

The largest limitation of this study was that due to the retrospective design, data were incomplete. In addition, verification of final diagnosis was not possible and diagnoses were provided by different caregivers with varying levels of training and experience. The loss to follow-up was large. There was also a risk of confounding, as for the survival analysis it was assumed that all cases lost to follow-up did not die during the specified study period and the study was not sufficiently powered to incorporate all potential confounding variables into the regression analysis.

This study highlights further research questions. There is a need for a well-designed, adequately powered prospective cohort study evaluating short- and long-term outcomes of ELBW infants encompassing a standardised clinical assessment tool for NDI and including surveillance of death registry data to identify deaths among cases lost to follow-up. This would enable the assessment of prevalence of NDI and risk factors for NDI, and facilitate a comparative analysis of morbidity and mortality rates. As the weight criteria for eligibility for surfactant and NICU admission have been revised downwards since 2016, it is possible that there may be a

corresponding decline in the mortality rate. There was insufficient follow-up data to assess the association between discharge weight and GA and death following hospital discharge. Further research is needed to determine whether discharge weight or GA influences risk of mortality following discharge in this setting, as this would significantly influence clinical practice. The development of a regional electronic records database and audit tool, similar to the PPIP database for mortality data (47), may facilitate the collection of long-term outcome data for the infants who do not return to TBH for follow-up clinical review.

6 CONCLUSION

Mortality and morbidity rates remain high among extremely preterm infants. In order to improve survival, resources need to be allocated to neonatal resuscitation, surfactant therapy, NCPAP and increased availability of NICU beds. Antenatal care attendance and PMTCT coverage are high; however, ROP screening and administration of antenatal magnesium sulphate and antenatal steroids should be optimised to minimise morbidity. Further research is needed to adequately assess long-term neurodevelopmental outcomes of ELBW infants in this setting.

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APPENDIX 1: DATA COLLECTION FORM

Maternal and antenatal history								
Age				**Hypertension**	PET	Eclampsia	HELLP	
					Chronic	None		
Ethnicity				**Chorioamnionitis**	Yes		No	
Gravida				**Mode of delivery**				
Parity				**Indication for delivery**				
Antenatal care attended	Yes	No	Unknown	**Medication during pregnancy**				
				VDRL	Negative	Positive	Unknown	
Antenatal steroids	Yes	No	Unknown	**VDRL treatment**	Complete	Incomplete	Unknown	
				HIV	Negative	Positive	Unknown	
Antenatal magnesium sulphate	Yes	No	Unknown		If yes, duration of anti-retroviral therapy:			
					<4 weeks	Lifelong	Unknown	

Neonate							
Birth							
Birth weight (grams)				Singleton	Twins	Triplets	More
Gestation (weeks and days)				**Inborn**	Yes	No	
				Outborn	Yes	No	
By	Early US	Foot length	Other	**Apgar**	1	5	10
Head circumference (cm)				**Delivery room resuscitation**	None	Oxygen Fi02	NCPAP
Length (cm)					Mask CPAP	Face mask ventilation	Intubation
Small for GA	Yes	No			CPR	Adrenaline	

Hospital admission					
NICU admission	Yes	No	**Duration of admission (days)**		
Indication for NICU admission			**Discharge destination**	Home	Other hospital
Duration of NICU admission			**Still hospitalised at 1 year CGA**	Yes	No
			Re-admission to TBH after discharge	Yes	No
Date of hospital discharge					
Weight at discharge					

Respiratory system						
Respiratory support after delivery room				**BPD**	Yes	No
None	*Nasal prongs* Duration:		*NCPAP*	If yes:	Grade	
					Treatment	

	Fi02:		*High-flow nasal cannula* Duration: Fi02:	Duration : FiO2:		None	Steroids
						Diuretics	Other
Conventional ventilation Duration: Fi02:	*HFOV* Duration: Fi02:		*INO* Duration: FI02:	*Other* Duration :	**Pneumothorax**	Yes	No
RDS	Yes		No		**Other**		
	If yes, grade:						
Surfactant	Yes	No	If yes :	Indication			
				Number of doses			

Cardiovascular system					
PDA	Yes	No	If yes:		
			Diagnosis	Clinical	
				Echo	
			Treatment	None	Ibuprofen
				Paracetamol	Surgery
Resuscitation post-delivery room	Yes	No	If yes:	CPR	Adrenaline
Other cardiac abnormality					
Gastrointestinal system					
NEC	Yes	No	If yes, treatment:		
			None	Peritoneal drain only	Surgery
Focal intestinal perforation	Yes	No	If yes, treatment:		
			None	Peritoneal drain only	Surgery
Other					
Abdominal surgery					
Other systems					
ROP screening	Yes	No	If yes:		
			Stage	Treatment	
Other general surgery					
Congenital anomaly					
Hyperbilirubinaemia above exchange threshold	Yes	No	If yes, exchange transfusion:		
			Yes	No	
Infection					

Early bacterial sepsis (before day 3)	Yes					No	
Late bacterial sepsis (after day 3)	Yes					No	
Meningitis	Yes					No	
Presumed sepsis	Yes					No	
Bacterial pathogen	Organism						
	Sensitivity						
	Treatment						
Viral pathogen	Organism						
	Sensitivity						
	Treatment						
Fungal infection	Organism						
	Sensitivity						
	Treatment						
HIV	Prophylaxis	None	Nevirapine	AZT + nevirapine		Other	
	HIV PCR	Birth		10 week		Other	
		Positive	Negative	Positive	Negative	Positive	Negative

Mortality				
Date of death				
Age at death (days, hours if <72 hours)				
Final cause of death				
Death after decision to limit or withdraw care	Yes		No	
Death within first 12 hours of life	Yes		No	
Survival to discharge	Yes		No	
Death after hospital discharge	Yes	No	If yes, location:	
Outcome at 1 year CGA				
Attended follow-up clinic	Yes		No	
Neurodevelopmental impairment	Yes		No	
If yes: **Hearing impairment**	Yes		No	
Visual impairment	Yes		No	
Delayed milestones	Yes		No	
Features of cerebral palsy	Yes		No	