Short-term mortality and morbidity of very low-birthweight infants over 9 years at Groote Schuur Hospital, Cape Town, South Africa

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Background. With the advancement of neonatal care there has been a decrease in mortality rates of very low-birthweight (VLBW) (≤1 500 g) infants worldwide. However, this has been at the cost of increased morbidity in this vulnerable group. Currently there are little up to date data on short-term morbidities for VLBW infants in low and middle-income countries.
Objectives. The primary objective was to describe the neonatal mortality rate in infants weighing 401 to 1 500 g admitted to Groote Schuur Hospital neonatal unit over a 9-year period. Secondary objectives were to evaluate the main neonatal short-term morbidities.
Methods. We conducted a secondary analysis of prospectively collected observational data. All VLBW infants admitted to GSH neonatal unit from 2012 - 2020 were included in the study. Data were benchmarked against the Vermont Oxford Network (VON) database.
Results. A total of 4 645 infants were included in the study. The overall mortality rate was 19.8%, which remained static over the study period. There was a significantly higher mortality rate associated with decreasing birthweight. The mortality rate for outborn v. inborn infants was higher: 30.3% v. 18.4% (p=0.046). There was a significant risk of higher short-term morbidity in infants <1 000 g. The survival rate without major morbidity was 68.5% which compared favourably with that of the VON.
Conclusion. The results demonstrate that mortality rates are higher compared with developed countries. However, and importantly, survival without morbidity was comparable. Strategies to improve mortality and morbidity in VLBW infants are multifaceted and require a collaborative and innovative approach.

S Afr J Child Health 2024;18(2):e1516. https://doi.org/10.7196/SAJCH.2024.v18i2.1516

Preterm birth is a global public health issue, with 15 million preterm births occurring annually worldwide – more than 81% of these occurring in sub-Saharan Africa and South Asia.[1] Preterm infants are a vulnerable subset of infants who are at an increased risk of complications and mortality with nearly half (47%) of all under-5 deaths occurring in the first 28 days of life in 2020.[2] With the advancement of neonatal care, neonatal mortality has declined globally, owing to improved access to interventions, such as continuous positive-airway pressure (CPAP), surfactant replacement therapy and ventilation. High-income countries(HICs), e.g. Switzerland and Sweden had neonatal mortality rates of 2.8 and 1.4/1 000 live births, respectively, in 2020.[3] South Africa (SA) is among the many nations who have adopted the United Nations Sustainable Development Goals (SDGs) and has made progress in achieving SDG 3, which aims to end preventable deaths of newborns and to reduce neonatal mortality to at least as low as 12 per 1 000 live births. SA's neonatal mortality rate has fallen from 28.5 deaths per 1 000 live births in 1975 to 10.5 deaths per 1 000 live births in 2020.[4] Notably, there are significant variations of the neonatal mortality rates across the provinces in SA.[4]

Survival of preterm infants <1 500 g across 10 HICs was reported to be 78 to 93%.[5] SA is considered a middle-income country (MIC) and studies at two public hospitals in SA, between 2000 and 2017, reported infant survival rates of very low-birthweight (VLBW) infants to be between 72 and 75%.[6,7] Low-income countries (LICs) have lower survival rates. In Malawi, 42% of VLBW infants survived to discharge, with only 11% of infants <1 000 g surviving to discharge.[8] Ethiopia reported a survival rate of VLBW (<1 500 g) infants of 49%.[9] Africa consists of low- and middle-income countries (LMICs) and faces significant healthcare challenges compared with HICs in caring for preterm infants. There is a wide discrepancy in survival in VLBW infants across the African continent, with limited access to resources. In 2020, a review of resources in 49 African countries reported that proven life-saving neonatal interventions, such as CPAP, surfactant replacement therapy and saturation monitoring of infants were inadequate and inequitably distributed between countries, rural and urban areas, as well as public and private sectors.[10] A study conducted at Mowbray Maternity Hospital (Cape Town, SA) and Groote Schuur Hospital (GSH; Cape Town, SA) in infants ≤1.8 kg modelled the removal of mechanical ventilation, surfactant therapy and CPAP – the model predicted that their mortality rate would triple without these interventions.[11]

VLBW and extremely low-birthweight (ELBW) (<1 000 g) infants are at increased risk of long-term neurodevelopmental disabilities, such as cerebral palsy, cognitive impairment, and visual and hearing impairments. Improved survival rates and complications of prematurity pose a significant public health challenge globally, especially in LMICs with limited abilities to provide multidisciplinary follow-up support for these families.

There are currently limited recent data on short- and long-term morbidity associated with preterm outcomes in SA. A study conducted

in Tshwane, showed survival without major morbidity in VLBW infants was 35% overall, (39% in the 1 001 g - 1 500 g subgroup and 26% in infants <1 000 g).[7]

GSH is a 75-bed state-sector neonatal unit and admits more than 2 000 neonates per year, with ~500 weighing <1 500 g. The GSH Maternity Centre is a tertiary referral centre and provides level 3 specialist care for high-risk pregnancies to the Metro West Health District in Cape Town (population 4.5 million), SA. The neonatal unit is one of two tertiary referral hospitals in the city for small and sick neonates. The neonatal nursery offers intensive care facilities, with 10 beds for invasive ventilation and 10 beds for non-invasive ventilation. Owing to resource limitations and the high level of morbidity associated with ELBW infants, only non-invasive ventilation is offered to babies weighing <800 g and who are younger than 27 weeks at GSH in line with the Western Cape provincial policy guidelines.

The Vermont Oxford Network (VON) database was established in 1988 and now comprises >1 400 neonatal units worldwide. This non-profit organisation aims to improve the quality of care of premature neonates through research, education, and quality-improvement projects.[12] Standardised neonatal data were collected for the VON network for all neonates weighing 401 g - 1 500 g who were admitted to GSH unit from 2012 to 2020.

The primary objective of the present study was to describe the neonatal mortality rate in VLBW infants weighing 401 to 1 500 g admitted to the GSH neonatal nursery over time and within weight categories. The secondary objective was to evaluate significant short-term morbidities of the infants and to compare our findings with those reported by the VON.

Methods

We conducted a secondary analysis of prospectively collected data of VLBW infants during a 9-year period between January 2012 and December 2020 at GSH neonatal unit.

Inclusion criteria

All infants <1 500 g who were admitted to GSH neonatal unit, including deaths in the delivery room.

Exclusion criteria

Outborn infants admitted after 28 days of life.

Definitions

Neonatal mortality was defined as death before discharge home. This includes data on infants who were transferred to other hospitals. Small for gestational age (SGA) was defined as a birthweight below the 10th centile, based on sex-specific Fenton growth charts. Definitions for infant mortality and morbidity were used in accordance with those provided by the VON (Supplementary file). VON considers the following to be key morbidities: severe intraventricular haemorrhage (IVH) (grade 3 or 4); periventricular leukomalacia (PVL); chronic lung disease (CLD) in infants younger than 33 weeks; necrotising enterocolitis (NEC); pneumothorax; late-onset sepsis (LOS); pneumothorax and severe retinopathy of prematurity (ROP).

Weight categories were used instead of gestational age owing to unsure dates and gestation of our population. Only 30 - 40% of the mothers had early (<20 weeks) obstetric ultrasounds. The remaining infants are assigned gestational age by postnatal assessment, which includes Ballard scoring and foot length.[13]

Statistical analysis

The data were analysed using STATA/IC (version 14.2; Stata Corp., USA). Continuous variables were expressed as medians (interquartile range (IQR)) since the continuous data were skewed. Proportions and percentages were used to describe categorical variables. The association between categorical variables was evaluated using Pearson's chi-squared test. *P*-values ≤0.05 were considered statistically significant. VON median, Q1 and Q3 were computed by calculating each member hospital's mean rate over the 9-year study period and ranking them from highest to lowest. The rate at the 50th percentile was the median, the rate at the 25th percentile was the Q1 and the rate at the 75th percentile was the Q3.

Ethics

All data captured in the VON database were automatically de-identified and assigned a study number to ensure confidentiality. Approval for the present study was obtained from the University of Cape Town Human Research Ethics Committee (ref. no. HREC 505/2021).

Results

A total of 4 645 infants with a birthweight 401 g - 1 500 g were included in the study.

Maternal characteristics

Eighty-five percent of infants had mothers who attended at least one antenatal visit. Over the study period, 69.3% (*n*=2 967/4 280) of the mothers who delivered before 34 weeks gestation received any antenatal steroids prior to delivery. The caesarean section rate was 67.1%.

Infant characteristics

Male infants comprised 47.5% of the study cohort. Overall, 27% of the infants were classified as SGA. Major life-threatening congenital anomalies (chromosomal or structural) were present in 121 (2.6%) infants, of whom 80 (66%) died.

Mortality

The mortality rate was 19.8% overall (Fig. 1), with a 100% mortality rate in infants weighing <500 g. There were 25 deaths in the delivery room and the mortality rate remained relatively static during the study period. The mortality rate for inborn infants was significantly lower compared with outborn infants, i.e. 18.4% v. 30.3%, respectively (*p*=0.046).

Morbidities

The main morbidities were more frequent in the ELBW infants (Table 1), where LOS and NEC showed the most variation - which fluctuated over the study period but with no specific pattern. These values ranged from 5.2% to 10.4% (LOS) and 3.1% to 8% (NEC), respectively, over the study period.

Survival without morbidities

The survival rate without major morbidity was 68.5% overall. There was a higher survival rate without morbidities with increasing birthweight: 763 (47.6%) of the infants weighing 501 - 1 000g and 2 419 (79.8 %) infants weighing 1 001 - 1 500 g.

Overall, 48.6% of infants were moderately hypothermic (temperature of 32 - 35.9 °C recorded within 1 hour of admission). Of those infants with available data, ELBW infants were more likely to be hypothermic (53.1%; *n*=809/1 523) compared with VLBW infants (46.1%; *n*=1 300/2 820) (*p*=0.001). More than two-thirds (72.2%) of the infants were exclusively breastfed at discharge. The median length of stay for all surviving infants admitted between 2012 and 2020 was 43 days from admission (Table 2).

Table 1. Mean percentage of morbidities within weight categories at GSH NICU: 2012 - 2020

Morbidities	VLBW	501 - 1 000 g	1 001 - 1 500 g	*p*-value
Cystic PVL	2.4	3.5	1.9	<0.00
Severe IVH	5.8	7.9	4.8	<0.00
NEC	5.9	8.6	4.5	<0.00
Severe ROP	3.4	7	1.5	<0.00
Pneumothorax	0.6	0.6	0.6	0.79
CLD <33 w	4.5	8.7	2.6	<0.00
LOS	8.3	14.9	5.2	<0.05

GSH = Groote Schur Hospital; NICU = neonatal intensive care unit; VLBW = very low-birthweight; PVL = periventricular leukomalacia; IVH = intraventricular haemorrhage; NEC = necrotising enterocolitis; ROP = retinopathy of prematurity; CLD = chronic lung disease; LOS = late-onset sepsis.

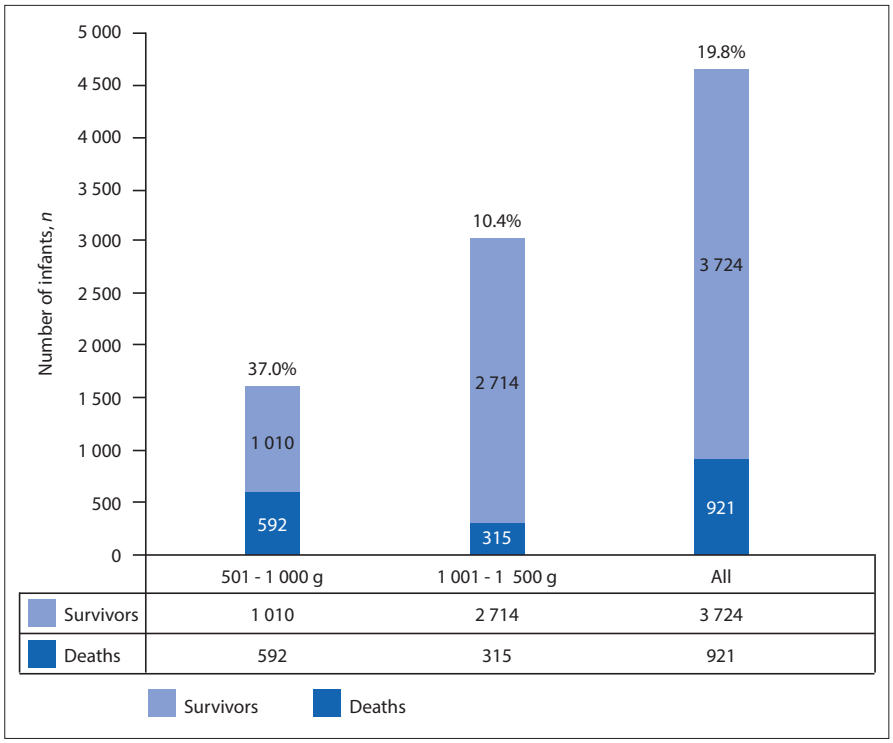

Fig. 1. Mortality rate by weight band. All 14 infants weighing <500 g died.

Comparison with the VON Network

Compared with the median rates of VON member hospitals, exposure to antenatal steroids before 34 weeks' gestation was lower in the present study (69.3% v. 86.2%), moderate hypothermia was higher (48.6% v. 10.2%), and discharge home on any human milk was higher (72.2 % v. 59.6%).

The GSH mortality rate (19.8%) was higher than the Q3 rate of the VON hospital rates (16.7%). However, the death or morbidity was below the Q1. All morbidities fell within the IQR, except for CLD in infants born before 33 w and pneumothorax, which was markedly lower than the Q1 for VON member hospital rates (Table 3).

Discussion

The present study includes one of the largest cohorts of VLBW infants from a single centre in a LMIC setting. While SA is considered an upper-middle income country, we have significant discrepancies in available resources and infrastructure to combat neonatal mortality and morbidity.

The overall mortality rate for VLBW infants at GSH was 19.8%, which is favourable compared with studies conducted elsewhere in SA but it remains higher than rates reported in HICs.[7,14,15] Possible reasons for the higher mortality rate include differences in antenatal care as well as resource limitations, which directly impact nursing staff-to-infant ratios and the availability of respiratory support for smaller infants. As expected, ELBW infants were significantly more likely to die owing to being more preterm and/or growth-restricted. These infants would also be primarily affected by policies affecting the availability of full intensive care services.

Further focus is required in tackling the socioeconomic barriers to mothers receiving antenatal care, encouraging early booking of pregnancies, and improving antenatal steroid administration to mothers in preterm labour, i.e. before 33 weeks' gestation. The World Health Organization (WHO) recommends the use of antenatal steroids in women who are at risk of preterm birth with the provision of adequate neonatal care.[16] A prospective study done at GSH found that although antenatal steroid use was relatively high (74.3%), only 17.3% of mothers who were at risk of preterm birth received the recommended optimal regimen of two doses of antenatal steroids more than 24 hours and less than 7 days prior to delivery.[11]

Hypothermia within one hour of admission is an important focus area, as normothermia has been shown to improve outcomes of preterm infants.[17] Encouragingly, the rates of breastfeeding were higher in comparison with rate reported by the VON network. The promotion of breastfeeding is an important strategy in reducing NEC in our setting, improving maternal bonding with their babies and health promotion in preterm infants.

In the present study, the mortality rate of outborn infants was higher compared with inborn infants, which agreed with findings of a previous study at GSH.[18]

Efforts have been made towards regionalisation of perinatal care to ensure that high-risk pregnancies are delivered at tertiary level hospitals in SA. This policy is aimed at allowing high-risk infants access to neonatal ICU, staff trained in neonatal care and screening facilities, e.g. ROP and cranial ultrasound screening. This is an important strategy to improve outcomes and minimise morbidity in preterm babies.

While GSH mortality rates are higher than the VON rates, our death or morbidity rates were lower owing to a markedly lower

Table 2. Median length of stay of VLBW infants at GSH NICU 2012 - 2020

	Length of stay (days), median (IQR)		
Birthweight (g)	All infants	Survivors	Death
501 - 750	7 (2 - 57)	73 (66 - 86)	3 (2 - 7)
751 - 1 000	53 (21 - 65)	60 (51 - 70)	4 (2 - 9)
1 001 - 1 250	42 (34 - 52)	44 (37 - 54)	4 (2 - 10)
1 250 - 1 500	29 (23 - 37)	29 (24 - 37)	4 (2 - 10)
All weights	38 (24 - 54)	43 (31 - 57)	4 (2 - 8)

GSH = Groote Schuur Hospital; NICU = neonatal intensive care unit; IQR = interquartile range.

Table 3. Mortality and morbidity v. VON network 2012 - 2020

	GSH	VON	
Variables	Mean % (*N*=4 645)	Hospital median (Q1, Q3)	Mean % (*N*=554 397)
Mortality*	19.8	12.3 (9.3, 16.7)	14.1
Death or morbidity†	31.5	40.0 (32.0, 48.3)	43.6
NEC	5.9	3.6 (1.7, 9.3)	5.2
Any late infection	8.3	9.5 (5.9, 15.0)	12.3
Severe IVH	5.8	6.6 (3.9, 8.9)	8.0
PVL	2.4	2.2 (1.1, 3.7)	2.9
Severe ROP	3.4	4.2 (1.5, 7.2)	6.3
CLD†	4.4	21.7 (12.7, 31.1)	26.8
Pneumothorax†	0.6	3.4 (1.9, 5.0)	4.3

VON = Vermont Oxford Network; GSH = Groote Schuur Hospital; Q1 = first quartile; Q3 = third quartile ; NEC = necrotising enterocolitis; IVH = intraventricular haemorrhage; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; CLD = chronic lung disease.
*Above the interquartile range for the VON hospitals.
†Below the interquartile range for the VON hospitals.

incidence of CLD in infants born before 33 weeks' gestation. More than two-thirds of all infants survived to discharge without major morbidity, although this dropped to 50% in the ELBW category, highlighting the vulnerability of this subgroup of infants. Determining the limits of viability in resource-limited settings is complex and remains an ongoing challenge. All categories of morbidities were significantly higher in infants weighing <1 001 g, except for pneumothorax.

Although GSH's mean percentage of NEC fell within the IQR of the VON it was on the upper limit of the VON network data. NEC rates were almost double in infants ≤1 000 g v. infants 1 001 - 1 500 g. As many of the most preterm infants die before the typical age that NEC develops in our unit (median age of 8 days), it is worth interrogating why the NEC rate is not lower. A study previously conducted in our unit described an increased risk of adverse outcomes in HIV-exposed infants, with an increased risk of NEC, especially in infants weighing <1 000 g.[19] Also, the prevalence of SGA infants is higher in our setting compared with developed countries – this has been shown to be carry an increased risk of NEC and mortality.[20] It is imperative to enforce rigorous handwashing protocols, champion infection control, limit invasive procedures and prevent overcrowding in our unit. LOS and NEC are both serious complications of prematurity associated with higher mortality and short- and long-term morbidities. In the prevention of NEC, efforts should be focused on promoting exclusive breastmilk feeds with the mother's own milk or donor milk, where possible.

As expected, severe IVH and cystic PVL were higher in weight categories below 1 001 g. A study in Johannesburg[21] had comparable rates of severe IVH (7% v. 5.8% in our centre) and lower rates of cystic PVL (0.9 % v. 2.4% in our centre). Severe IVH and cystic PVL are associated with adverse neurodevelopmental outcomes and increased risk of cerebral palsy. Identifying infants with severe IVH and PVL is important in stratifying infants for long-term neurodevelopmental follow up.

The rate of CLD in infants born before 33 weeks' gestation was lower than that of the VON owing to the application of limitations of care to infants younger than 27 weeks and weighing <800 g–with significant respiratory compromise, these infants are less likely to survive. Less ventilation as well as less chest imaging could also explain the low rates of pneumothorax.

GSH is one of the better equipped government hospitals in Africa. It is important to compare the differences in outcomes of neonates in LMICs with HICs to highlight the discrepancies of available resources, in attempts to improve available resources in the context of LMICs. This information is invaluable in motivating public healthcare efforts, political commitment and in implementing strategies aimed at preventing preterm deliveries and their care after birth. Furthermore, these data are paramount in the appropriate counselling of parents in terms of expectations of survival and morbidity in our setting. In the context of LMICs, it has been shown that relatively inexpensive measures can have a meaningful impact in improving survival of VLBW infants in poorly resourced settings. Important strategies include improved access to antenatal care, neonatal resuscitation training, prevention of mother-to-child transmission of HIV, and promotion of breastmilk and kangaroo mother care.[14] High-impact strategies recommended by the WHO in 2015 include antenatal corticosteroids, CPAP, and surfactant replacement therapy. Importantly, combined interventions are the most effective strategy in reducing neonatal mortality.[22]

The goal of caring for preterm infants should be to improve morbidity-free survival. Further efforts need to be focused on

addressing the cost of morbidities on the healthcare system and the ability to support families in the long-term care of these infants, especially in the LMIC setting.

Study strengths and limitations

The large sample size and prospective data collection are strengths of the present study. All records were audited and corrected at discharge, ensuring data quality. This is a single centre study and may not be generalisable to other resource-limited settings. A limitation of our study was that weight categories were used instead of gestational age due to unsure dates and gestation of our population. In depth folder review of morbidities may have identified additional risk factors for each individual morbidity. Our centre's membership in VON allows access to a large database with the ability to benchmark against hospitals around the world. Data obtained from the present study enable our centre to identify and implement quality improvement interventions at GSH.

Conclusion

The mortality rate of GSH VLBW infants was higher than the rate reported by VON, but with lower morbidity rates. Implementing sustainable and effective measures to shift mortality rates of our preterm infants, within the constraints of our setting and resources, remains challenging. Our goal is to optimise morbidity-free survival of our VLBW infants, especially in the context of limited resources, given the economic and psychosocial impact which morbidity has on families in caring for infants with complex health needs or neurodevelopmental impairment.

Ongoing audits and publication of our local mortality and morbidity data are important to update health protocols, create awareness, bolster political will and guide intervention and in the counselling of parents appropriately.

Declaration. This manuscript was submitted in partial fulfilment of the requirements for HC's MMed (Paed) degree at the University of Cape Town.

Note: Vermont Oxford Network played no role in the design, analysis, interpretation, or reporting of this research. The views, conclusions, and opinions expressed are solely those of the authors and do not represent Vermont Oxford Network. Unpublished data were provided courtesy of Vermont Oxford Network.

Acknowledgements. Thanks to all those who so diligently collected data over the 9-year period. AlsoThe authors also gratefully acknowledge Erika Edwards at VON for her assistance with the network data.

Author contributions. HC and LT designed the study. HC collected and analysed the data. HC drafted the manuscript, which was critically revised by LT. Both authors approved the final version.

Funding The authors gratefully acknowledge the Paediatric Management Group for financial assistance for the data collection. No funding was received for any other aspect this research.

Conflicts of interest. None.

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Accepted 11 March 2024.