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Risk factors for mortality in a hospitalised neonatal cohort in Botswana

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ABSTRACT

Objectives A disproportionate number of neonatal deaths occur in low/middle-income countries, with sepsis a leading contributor of mortality. In this study, we investigate risk factors for mortality in a cohort of high-risk hospitalised neonates in Botswana. Independent predictors for mortality for infants experiencing either a sepsis or a non-sepsis-related death are described.

Methods This is a prospective observational cohort study with infants enrolled from July to October 2018 at the neonatal unit (NNU) of Princess Marina Hospital (PMH) in Gaborone, Botswana. Data on demographic, clinical and unit-specific variables were obtained. Neonates were followed to death or discharge, including transfer to another hospital. Death was determined to be infectious versus non-infectious based on primary diagnosis listed on day of death by lead clinician on duty.

Results Our full cohort consisted of 229 patients. The overall death rate was 227 per 1000 live births, with cumulative proportion of deaths of 22.7% (n=47). Univariate analysis revealed that sepsis, extremely low birth weight (ELBW) status, hypoxic ischaemic encephalopathy, critical illness and infants born at home were associated with an increased risk of all-cause mortality. Our multivariate model revealed that critical illness (HR 3.07, 95% CI 1.56 to 6.03) and being born at home (HR 4.82, 95% CI 1.76 to 13.19) were independently associated with all-cause mortality. Low birth weight status was independently associated with a decreased risk of mortality (HR 0.24, 95% CI 0.11 to 0.53). There was a high burden of infection in the cohort with more than half of infants (140, 61.14%) diagnosed with sepsis at least once during their NNU admission. Approximately 20% (n=25) of infants with sepsis died before discharge. Our univariate subanalysis of the sepsis cohort revealed that ELBW and critical illness were associated with an increased risk of death. These findings persisted in the multivariate model with HR 3.60 (95% CI 1.11 to 11.71) and HR 2.39 (95% CI 1 to 5.77), respectively.

Conclusions High rates of neonatal mortality were noted. Urgent interventions are needed to improve survival rates at PMH NNU and to prioritise care for critically ill infants at time of NNU admission, particularly those born at home and/or of ELBW.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was performed at a national referral hospital which receives the highest risk deliveries and sickest newborn babies in Southern Botswana.
⇒ Our prospective daily data collection led to a high degree of data capture accuracy in terms of patient outcomes.
⇒ All causes of death, including sepsis related and non-sepsis related, were reviewed and confirmed by two study members.
⇒ As we enrolled all neonates admitted over a 4-month period, one limitation is that we were unable to account for seasonal variation.
⇒ Additionally, we did not have access to all maternal records apart from what was documented at time of delivery.

INTRODUCTION

Worldwide, 2.4 million neonates die each year, with approximately 99% of these deaths occurring in low/middle-income countries (LMICs).[1–3] The neonatal period is a particularly vulnerable period in a child's life that carries the highest mortality risk, with over half of deaths occurring in the first 3 days of life.[4 5] Worrisome rates of neonatal mortality continue to be observed in the Eastern and Southern African regions with estimated 21–30 deaths per 1000 live births. Botswana is no exception, where the current national rate is 22 deaths per 1000 live births,[4] and with cumulative in-hospital neonatal deaths most recently reported to be as high as 24.5%.[6]

Globally, sepsis is the third most common cause of neonatal mortality, with an estimated 500 000–900 000 attributable deaths per year.[7] In LMICs, the burden of sepsis is disproportionately higher than in high-income countries. Reasons for this disparity include barriers in maternal access to prenatal and peripartum care,[8] high rates of maternal comorbidities and intrapartum complications,[9] substandard infection control

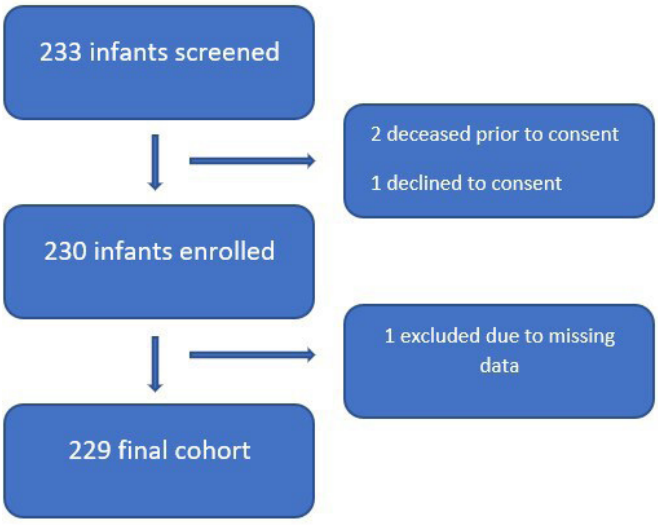

Figure 1 Flow diagram of enrolled patients.

practices at the time of delivery,[10 11] inappropriate use of broad-spectrum perinatal antibiotics[12–15] and delayed access to care for sick neonates.[16] These potentially modifiable risk factors require further exploration to decipher where resources and efforts should be focused in LMICs.

In this study, we describe risk factors for mortality in a cohort of high-risk hospitalised neonates in Botswana. We compare independent predictors for mortality for infants who experienced either a sepsis or a non-sepsis-related death with the goal of identifying interventions that might reduce neonatal mortality during this crucial time period.

METHODS

Study design, location and population

From July to October 2018, we conducted a prospective cohort study at the neonatal unit (NNU) of Princess Marina Hospital (PMH) in Gaborone, Botswana. The NNU contains 39 beds including a six-bed neonatal intensive care unit (NICU) for critically ill infants, a premature unit for infants less than 32 weeks admitted for reasons related to preterm status, a unit for late preterm infants between 32 and 37 weeks requiring nutritional support, a full-term unit for infants admitted above 37 weeks, an overflow unit to manage additional neonates when census is high, and an isolation unit for infants with known colonisation or infection with multidrug-resistant organisms. The NNU also cares for infants on the maternity floor who required intervention at birth and ongoing management in the newborn nursery setting. The unit admits infants born in hospital and at home, and receives transfers from surrounding district hospitals in Southern Botswana.[17] All neonates admitted to the NNU during the study period were eligible for inclusion. Infants admitted prior to July 2018 were excluded. Consent was obtained by a Motswana study coordinator who reviewed the study with each caregiver in their preferred language (either Setswana or English) and obtained written informed consent. Note that the study was supported by the Melissa Ketunuti Memorial Global Health Fund; however, this foundation had no role in the study design, collection, analysis, interpretation of the data, in the writing of the manuscript and in the decision to submit the paper for publication.

Patient and public involvement

Due to the nature of the study, patients and public were not involved in the design, conduct, reporting or dissemination of this research.

Data collection

After consent was obtained, the following data were collected daily from the neonatal medical record: demographics, clinical details including listed and leading diagnoses, laboratory results and antibiotic use including drug choice, dose, frequency and duration. We also collected information on the use of unit-specific clinical pathways for key conditions including sepsis and on hospital-wide resource limitations, including drug shortages. Neonates were followed to death or discharge, including transfer to another hospital. Death was determined to be infectious versus non-infectious based on clinical course and primary diagnosis listed on day of death by lead clinician on duty. Chart review was performed independently by two study members. If more than one discharge diagnosis was listed, cases were discussed between study members until consensus was achieved on both the primary diagnosis and whether that diagnosis was infectious or not.

Data definitions

A diagnosis of sepsis was defined as documentation of an episode of clinical sepsis by the lead clinician at least once in the medical record throughout the hospitalisation. Sepsis was classified as early-onset sepsis (EOS) if sepsis was documented within the first 3 days of birth, and late-onset sepsis (LOS) if sepsis was diagnosed after 3 days of birth. We defined critical illness as patients who were admitted to the NICU section of the NNU, or if they required an intubation and/or had a code event requiring neonatal resuscitation in the first 24 hours after admission to the NNU. Hypoxic ischaemic encephalopathy (HIE) was defined as a 5-minute or 10-minute Apgar score below 7, or chart documentation of HIE as a diagnosis during hospitalisation. Birth weight was classified as normal birth weight (NBW) if >2500 g, low birth weight (LBW) if 1500–2500 g, very low birth weight (VLBW) if 1000–1500 g and extremely low birth weight (ELBW) if less than 1000 g at time of birth. We reported antibiotic drug shortages based on information provided to the study's research staff who inquired daily to the nursing lead on the unit.

Data analysis

Our primary outcome was all-cause mortality among all subjects; secondary outcome was presumed infectious death among subjects who had sepsis diagnosed at least

Table 1 Patient demographics*

Total cohort n=229		Sepsis cohort n=140†	
Characteristic	**Median (IQR), or N (%)**	**Median (IQR), or N (%)**	**P value**
Sex			
Male	112 (50.22)	66 (47.48)	0.369
Female	111 (49.78)	73 (52.52)	
Location on admission			
NICU	46 (23.12)	35 (28.46)	0.023
Premature unit	45 (22.61)	32 (26.02)	
Nutritional unit	22 (11.06)	10 (8.13)	
Full-term unit	71 (35.68)	36 (29.27)	
Isolation	2 (1.01)	2 (1.63)	
Overflow	1 (0.50)	1 (0.81)	
4G maternity floor	12 (6.03)	7 (5.69)	
Birth weight			
Extremely low birth weight (<1000 g)	20 (8.77)	15 (10.71)	0.007
Very low birth weight (1000–<1500 g)	54 (23.68)	42 (30.00)	
Low birth weight (1500–<2500 g)	60 (26.32)	35 (25.00)	
Normal birth weight (≥2500 g)	94 (41.23)	48 (34.29)	
Gestational age			
<28 weeks	24 (10.67)	17 (12.32)	0.002
28–<32 weeks	50 (22.22)	40 (28.99)	
32–≤37 weeks	62 (27.56)	34 (24.64)	
≥38 weeks	89 (39.56)	47 (34.06)	
Born at home			
Yes	10 (4.93)	6 (4.88)	1
No	193 (95.07)	117 (95.12)	
Delivery type			
Vaginal	146 (66.67)	87 (65.41)	0.662
C-section	73 (33.33)	46 (34.59)	
HIV exposure			
Yes	46 (21.4)	30 (22.56)	0.732
No	169 (78.6)	103 (77.44)	
HIE			
No	174 (75.98)	102 (72.86)	0.205
Yes	55 (24.02)	38 (27.14)	
Congenital abnormality			
No	217 (94.76)	133 (95)	1
Yes	12 (5.24)	7 (5)	
Blood culture sent			
No	66 (32.84)	26 (20.63)	0.001
Yes	135 (67.16)	100 (79.37)	
Blood culture positive			
No	110 (84.62)	82 (85.42)	0.783
Yes	20 (15.38)	14 (14.58)	
Maternal illness at time of delivery			
No	197 (92.49)	118 (90.77)	0.293

Continued

Table 1 Continued

Total cohort n=229		Sepsis cohort n=140†	
Characteristic	Median (IQR), or N (%)	Median (IQR), or N (%)	P value
Yes	16 (7.51)	12 (9.23)	
Critical illness‡			
No	157 (68.56)	91 (65)	0.189
Yes	72 (31.44)	49 (35)	
Outcome			
Survived	139 (67.15)	75 (61.98)	<0.001
Infectious death	25 (12.08)	24 (19.83)	
Non-infectious death	13 (6.28)	6 (4.96)	
Unclear cause of death	9 (4.35)	6 (4.96)	
Transfer	21 (10.14)	10 (8.26)	
Clinical pathway available			
No	44 (22)	3 (2.27)	<0.001
Yes	156 (78)	129 (97.73)	
Sepsis pathway followed			
No	12 (17.39)	12 (17.39)	
Yes	57 (82.61)	57 (82.61)	
Drug shortage			
No	178 (94.18)	104 (92.04)	0.204
Yes	11 (5.82)	9 (7.96)	

*Missing data excluded. Fisher's exact test used for p value.
†Early-onset sepsis n=21 (15%); late-onset sepsis n=119 (85%).
‡Defined as being admitted to the ICU section of the NNU and/or having a code event in the first 24 hours of admission.
C-section, caesarean section; HIE, hypoxic ischaemic encephalopathy; ICU, intensive care unit; NICU, neonatal intensive care unit; NNU, neonatal unit.

once during their hospitalisation. For both analyses, we compared clinical and demographic characteristics across the two populations by using frequencies and percentages. These differences were statistically tested using Fisher's exact test. Kaplan-Meier curves and Cox proportional hazards models were used to explore the time until all-cause mortality. Variables included in the multivariable model included all factors significant with a p value of <0.15 on univariate analyses. Missing data were excluded from analyses. SAS V.9.4 and STATA V.16.1 were used for all analyses.

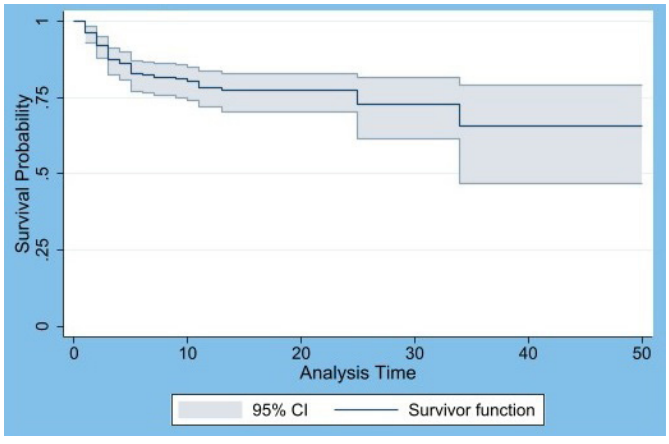

Figure 2 Kaplan-Meier survival curve for full cohort. Analysis time is in days.

RESULTS

Cohort characteristics: entire cohort

Our final cohort consisted of 229 neonates (figure 1). Approximately half were female (49.8%), and 94 (41.2%) were NBW. Most infants were born via vaginal delivery (146, 66.7%) and 10 (4.9%) were born at home. The most common comorbidities were HIV exposure (46, 21.4%), HIE (55, 24.0%) and presence of a congenital anomaly (12, 5.2%). Approximately one-third of patients (72, 31.4%) were classified as being critically ill at time of admission (table 1). Antibiotic drug shortages affected 11 (5.8%) of infants at some point during their hospitalisation.

Risk factors for all-cause mortality

Approximately one out of five enrolled babies died prior to discharge (47, 22.7%) for a rate of 227 per 1000 live births (figure 2). Our univariate analysis

Table 2 Risk factors for mortality in the entire cohort

Variable	Reference	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Birth weight*					
Extremely low birth weight (<1000 g)	Normal birth weight (>2500 g)	2.138 (1.02 to 4.50)	0.0453	1.10 (0.49 to 2.46)	0.826
Low/very low birth weight (1000–<2500 g)		0.408 (0.21 to 0.81)	0.0104	0.24 (0.11 to 0.53)	<0.001
Sepsis					
Yes	No	1.95 (1.00 to 3.82)	0.05	1.73 (0.83 to 3.63)	0.140
Blood culture sent					
Yes	No	0.69 (0.21 to 2.30)	0.55		
Bug–drug mismatch					
Yes	No	0.857 (0.05 to 13.70)	0.9132		
HIE					
Yes	No	2.20 (1.22 to 3.97)	0.0086	1.59 (0.81 to 3.11)	0.177
Maternal illness at time of delivery					
Yes	No	0.506 (0.12 to 2.09)	0.3468		
Congenital deformity					
Yes	No	1.824 (0.65 to 5.10)	0.2509		
Sex					
Male	Female	1.106 (0.62 to 1.97)	0.7342		
HIV exposure					
Yes	No	0.524 (0.22 to 1.24)	0.141		
Born at home					
Yes	No	3.025 (1.18 to 7.73)	0.0207	4.82 (1.76 to 13.19)	0.002
Mode of delivery					
C-section	Vaginal	0.726 (0.37 to 1.44)	0.3598		
Critical illness					
Yes	No	3.842 (2.13 to 6.93)	<0.0001	3.07 (1.56 to 6.03)	0.001
Sepsis pathway followed					
Yes	No	0.785 (0.26 to 2.35)	0.6649		
Drug shortages					
Yes	No	1.43 (0.51 to 4.00)	0.4958		
Appropriate antibiotics prescribed					
No	Yes	1.679 (0.89 to 3.19)	0.1128		
Blood culture sent					
Yes	No	0.784 (0.42 to 1.47)	0.4467		
Clinical pathway availability					
Yes	No	2.176 (0.77 to 6.12)	0.1408		

*Birth weight categories collapsed for analysis given small numbers.
C-section, caesarean section; HIE, hypoxic ischaemic encephalopathy.

revealed that sepsis, ELBW status, HIE, critical illness and infants born at home were each associated with an increased risk of all-cause mortality (table 2). In the multivariate model, we found that critical illness and birth at home were independently associated with all-cause mortality. Interestingly, LBW status (1500–<2500 g) was independently associated with a decreased risk of mortality.

Risk factors for sepsis-related death

More than half of infants (140, 61.14%) were diagnosed with sepsis at least once during their NNU admission.

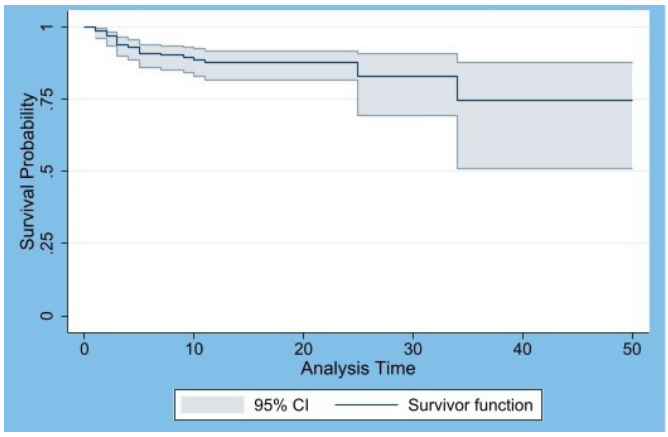

Figure 3 Kaplan-Meier survival curve for sepsis cohort. Analysis time is in days.

Of these, 21 (15%) had EOS and 119 (85%) had LOS. Many of the clinical characteristics of this subcohort were similar to those of the full cohort, including sex, percentage of home births, delivery type and presence of comorbidities (see table 1). Critical illness was noted in 49 (35%) patients, and blood cultures were sent in 100 (79.37%) patients. In terms of location, a significantly higher proportion of the sepsis cohort were admitted to the NICU or premature wing of the NNU. Significantly, more infants met criteria for preterm status and LBW. As expected, significantly more deaths from infection were noted in the sepsis cohort.

Approximately 20% (n=25) of infants with sepsis died before discharge (see figure 3), accounting for 53.2% all deaths in the full cohort. Our univariate subanalysis of the sepsis cohort revealed that ELBW and critical illness were associated with an increased risk of death. These findings persisted in the multivariate model, with both critical illness and ELBW status being independent predictors of death from infection (see table 3).

DISCUSSION

Neonatal mortality in the full cohort

Overall, neonatal mortality was 47 of 207 (22.7%) for a rate of 227 per 1000 live births. Independent risk factors for all-cause mortality included neonates who were classified as critically ill on admission and being born at home.

This proportion of deaths is similar to what has been reported in other LMIC NNUs in sub-Saharan Africa. In Ethiopia, a retrospective observational study over a 3-year period showed a death rate of 709 of 4182 (19%) in hospitalised neonates.[18] Here, risk factors for death included infants transported from home/other facilities, an inverse correlation between birth weight and risk of death, and an association between death and congenital malformations. The presence of intrapartum-related complications, likely analogous to HIE, was also a risk factor.[18] In Uganda, one study demonstrated a mortality rate for all infants in a special care baby unit as 22.1%, with prematurity and its complications accounting for the majority of deaths.[19] However, in Eritrea, a study in a similar NNU revealed a death rate of 66 per 1000 live births despite similar burden of sepsis and comparable population characteristics.[20] In neighbouring South Africa, neonatal mortality in infants admitted to NNU has been reported to be significantly less at an estimated 12%.[21] While PMH serves as a tertiary referral centre and is thus likely to admit a high volume of critically ill infants, the significantly higher mortality rate is concerning, particularly when compared with neighbouring geographical regions with similar patient populations. Moreover, it is notable that the death rate has not significantly improved since last reported one decade prior at 25%, whose birth weight and overall comorbidities illustrated a similar distribution to our cohort.[6] With a large proportion of deaths being associated with potentially preventable conditions, particularly considering that many neonates at highest risk of death are being appropriately classified as critically ill at the time of admission, there is an urgent need to educate staff on risk stratification of this high-risk population, and to focus on resource allocation at time of admission, in order to optimise chances for survival of critically ill neonates.

Protective effect of LBW status

In the full cohort analysis, our results indicate that infants born meeting criteria specifically for LBW status were significantly less likely to die when compared with NBW infants. Notably, our cohort had low mortality in general in this category with just 1 of 60 (1.67%) of LBW infants and 13 of 54 (24%) of VLBW infants experiencing death compared with 11 of 20 (55%) of ELBW infants and 21 of 94 (22.34%) of NBW infants. This birth weight corresponds to gestational age of 32–37 weeks or moderate-late preterm status. As this group of infants is typically of lower acuity and admitted primarily for nutritional needs, we hypothesise that this contributed to their survival benefit. This benefit was also observed, although to a lesser effect, in VLBW infants, with a reduced magnitude of protection likely related to the inherent additional physiological comorbidities associated with their birth weight category. Time to death in LBW infants was significantly less in infants at extremes of age in that both NBW and ELBW infants were more likely to die in the first 48 hours of hospitalisation compared with VLBW infants. For example, of the NBW and ELBW infants who died, 12 of 21 (57%) and 4 of 11 (37%) occurred in the first 48 hours which is significantly more than the 1 of 13 (8%) of VLBW infants who died in the first 48 hours. While the single death in LBW group also happened during this time period, it signals that those at extremes of age are at higher risk of mortality in general. It must also be noted that, depending on resource availability, institutional policy may be to not give invasive ventilatory support to ELBW infants that may not be deemed viable given their weight and/or gestational age.[22] If they survive birth, mortality will consequently be higher in this group that will universally be admitted to the NNU.

Table 3 Risk factors for mortality in sepsis cohort

Variable	Reference	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Birth weight*					
Extremely low birth weight (<1000 g)	Normal birth weight (>2500 g)	4.301 (1.47 to 12.61)	0.0078	3.60 (1.11 to 11.71)	0.033
Low birth weight (1000–<2500 g)		0.783 (0.28 to 2.17)	0.6384	0.96 (0.32 to 2.88)	0.946
Sepsis pathway followed					
Yes	No	0.79 (0.22 to 2.79)	0.709		
Blood culture sent					
Yes	No	0.532 (0.21 to 1.37)	0.1916		
HIE					
Yes	No	1.178 (0.49 to 2.84)	0.716		
Maternal illness at time of delivery					
Yes	No	0.841 (0.195 to 3.62)	0.8163		
Congenital deformity					
Yes	No	1.692 (0.39 to 7.02)	0.477		
Sex					
Male	Female	0.834 (0.37 to 1.88)	0.6618		
HIV exposure					
Yes	No	0.5 (0.15 to 1.69)	0.2657		
Born at home					
Yes	No	2.556 (0.59 to 11.08)	0.2098		
Mode of delivery					
C-section	Vaginal	0.532 (0.198 to 1.43)	0.21		
Critically ill					
Yes	No	3.517 (1.54 to 8.04)	0.003	2.39 (1.0 to 5.77)	0.05
Sepsis pathway followed					
Yes	No	0.786 (0.22 to 2.79)	0.709		
Drug shortages					
Yes	No	1.80 (0.53 to 6.09)	0.35		
Appropriate antibiotics on admission					
No	Yes	1.90 (0.82 to 4.38)	0.13	0.58 (0.25 to 1.35)	0.207
Blood culture sent					
Yes	No	0.532 (0.21 to 1.37)	0.19		

*Birth weight categories collapsed for analysis given small numbers.
C-section, caesarean section; HIE, hypoxic ischaemic encephalopathy.

Neonatal mortality from sepsis

Our study revealed a high proportion of deaths that were attributable to infection. Of the subcohort of patients with a diagnosis of sepsis at least once in hospital stay, 25 of 140 (18%) died, which means that 25 of 47 (53%) of all deaths in the cohort were determined to be infectious in aetiology. A subanalysis of these infants was performed with independent risk factors for death including critical illness and ELBW status.

A systematic review evaluating mortality among neonates with sepsis or severe infection in LMICs reported rates ranging from 14% to 36%.[23] In this review, both prematurity and low birth weight were significantly associated with mortality .[24 25] A study in Zambia investigating risk factors for neonatal sepsis revealed a very high mortality rate of 43%; however, authors noted that an outbreak of *Klebsiella* was likely present during the study period when the infection-related mortality rate jumped from 29% to 47%, in addition to observing an increase in all-cause mortality on the unit. Anecdotally, such outbreaks have been present on PMH NNU intermittently yet were not present during the study period.

Critical illness as a risk factor

Neonates meeting our criteria as being critically ill at time of admission were significantly more likely to experience

all-cause mortality (HR 3.19, 1.63 to 6.25) and infection-related mortality (HR 3.43, 1.32 to 8.91). A large cohort study investigating the risk factors for neonatal death in rural Karnataka, India observed that in infants who died by day 28, significantly more had received bag mask ventilation, oxygen, CPAP (continuous positive airway pressure) and mechanical ventilation compared with those who did not.[26] While no formalised severity illness score has been broadly used in LMICs, likely due to the heterogeneity of patient populations and available resources, our ability to accurately diagnose those at risk of death can and should be leveraged to focus efforts on staffing and resources for this incredibly high-risk cohort.

Extreme prematurity as a risk factor

Although ELBW status was not associated with death in the multivariable model for the full cohort, our study did reveal it to be an independent predictor of mortality in our sepsis cohort. The association of sepsis with prematurity has been well described previously, with LOS approximately 2.7 times more likely to develop in LBW infants compared with other neonates.[27] In a report from the National Institute of Child and Human Development Neonatal Research Network, birth weight and gestational age were the strongest predictors for LOS, with 54% of ELBW infants born under 25 weeks' gestation experiencing at least one episode of culture-proven LOS compared with just 7% of those born after 32 weeks.[28] A systematic review evaluating mortality among neonatal populations in low-resource settings also revealed prematurity and LBW to be significantly associated with mortality.[23] The reasons for the increased risk of associated mortality include a combination of relative immune compromise given poorly developed mechanical and mucosal barriers, increased frequency of invasive procedures including vascular access devices and mechanical ventilation, prolonged hospitalisation which increases the risk of nosocomial infection, and infectious comorbidities such as enterocolitis that lead to frequent antibiotic exposure, thus promoting development of multidrug-resistant organisms.[29]

LIMITATIONS

Maternal records were reviewed on admission to the NNU for signs of abnormal prenatal labs and infection at time of delivery. However, full review of prenatal care throughout pregnancy was not available to us. Outcome data were missing for 10% of the cohort. While documentation overall was comprehensive compared with other LMIC settings, it was at times delayed or missing, and blood culture results were often delayed in terms of reporting. Drug shortages were inquired about daily but may have been underestimated. This study was performed at a national referral hospital which receives the highest risk deliveries and sickest newborn babies in Southern Botswana. Hence, findings are reflective of this setting but may be less generalisable to a primary or district hospital in Botswana.

CONCLUSIONS

High rates of neonatal mortality were noted in our study, similar to those reported in an identical population in the same NNU a decade prior. Risk factors for all-cause mortality included critical illness and being born at home. Specifically, for those dying from sepsis, presence of critical illness and ELBW status were risk factors for mortality. Our findings are generalisable to other tertiary care NNUs throughout LMIC settings, particularly in Southern Africa, where urgent interventions are needed to improve survival rates and to prioritise care for critically ill infants at time of admission, particularly those born at home and/or of ELBW.

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Contributors EK, AS and SC conceived the study and its design. EK, MH, KBS and MC performed data collection and entry. EK, SC, AS and LB assisted with interpretation and data analysis. EK drafted the manuscript. EK, MH, MC, LB, KBS, UM, LM, TA-M, AS and SC reviewed the results, provided critical feedback, approved the final version of the manuscript and agree to be accountable for all aspects of the work ensuring integrity and accuracy. EK is responsible for the overall content as the guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval As this study involved human participants, it was approved by the institutional review boards of PMH, the Health Research and Development Committee of Botswana's Ministry of Health, the University of Botswana, the Children's Hospital of Philadelphia and the University of Pennsylvania (Ref: PMH 5/79(403-1-2018).

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