RESEARCH PAPER

Predictors of Mortality and Major Morbidities in Extremely Low Birth Weight Neonates

KANYA MUKHOPADHYAY, DEEPAK LOUIS, RAMA MAHAJAN, AND PRAVEEN KUMAR

From the Neonatal Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Correspondence to: Dr Kanya Mukhopadhyay, Additional Professor (Neonatology), Department of Pediatrics, PGIMER, Chandigarh, India. kanyapupul@yahoo.com

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Objectives: To determine predictors of mortality and morbidity in extremely low birth weight neonates (ELBW) from a developing country

Study design: Prospective observational study.

Setting: Level III neonatal unit in Northern India.

Subjects: Neonates <1000g born and admitted to intensive care during study period were enrolled. They were analyzed based on survival and development of major morbidity. Multivariable logistic regression model was used to determine independent risk factors.

Outcome: Mortality and major morbidity (one or more of the following: Bronchopulmonary dysplasia (BPD), Retinopathy of Prematurity (ROP) requiring laser, grade III or IV intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and necrotizing enterocolitis (NEC) stage III) during hospital stay.

Results: Of 255 ELBW neonates born, 149 received optimal care, of which 78 (52%) survived and 57 (39%) developed morbidities. Mean birth weight and gestational age were 29.1±2.6 weeks and 843±108g. Major causes of mortality were sepsis (46%), birth asphyxia (20%) and pulmonary hemorrhage (19%). Birth weight ≤800g [OR (95% CI)-3.51 (1.39-8.89), *P*=0.008], mechanical ventilation [4.10 (1.64-10.28), *P*=0.003] and hypotensive shock [10.75 (4.00-28.89), *P*<0.001] predicted mortality while birth weight ≤800g [3.75 (1.47-9.50), *P*=0.006], lack of antenatal steroids [2.62 (1.00-6.69), *P*=0.048), asphyxia [4.11 (1.45-11.69), *P*=0.008], ventilation [4.38 (1.29-14.79), *P*=0.017] and duration of oxygen therapy [0.004 (1.001-1.006), *P*=0.002] were the predictors of major morbidities.

Conclusions: Low birth weight, mechanical ventilation and hypotensive shock predicted mortality in ELBW neonates while low birth weight, lack of antenatal steroids, birth asphyxia, ventilation and duration of oxygen therapy were predictors for major morbidity.

Keywords: ELBW neonate, India, Mortality, Morbidity, Predictors, Survival.

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Survival of extremely low birth weight neonates (ELBW) is on a rising trend. This has been attributed to advances in perinatal and neonatal care especially with the use of antenatal steroids, ventilation and surfactant therapy. Fanaroff, *et al.* [1] reported outcomes of very low birth weight neonates (VLBW) from NICHD neonatal network (1997 to 2002) and compared it with two previous epochs. They found an increasing survival of ELBW neonates during 1997-2002 compared to the previous epochs. Similar trend has been reported by other groups [2,3].

Studies from developed countries have focused on identifying risk factors for mortality in preterm population [4-6]. However, there is dearth of similar data from developing countries. Tagare, *et al*. [7] recently reported 56% survival among ELBW neonates from a level III neonatal unit in India. Narayan, *et al*. [8] observed a survival of 49% in the ELBW group from Northern India. They found that lower birth weight and gestational age, asphyxia, air leak syndrome, sclerema, seizures and acute renal failure were the risk factors for mortality. But neither of them reported major morbidities or associated risk factors.

Since neonatal care has changed significantly in the last decade, it becomes relevant to study ELBW neonates and their outcomes in the present scenario. Hence we planned this study to look at the various risk factors affecting mortality and major morbidities among ELBW neonates.

METHODS

This prospective study was conducted in a level III neonatal unit of a teaching hospital in Northern India between January 2009 and March 2011. All intramural neonates >23 weeks and between 400-999g birth weight were consecutively enrolled after obtaining informed consent from parents. Exclusion criteria included presence of life threatening malformations. All antenatal and natal details were recorded in a predesigned, structured proforma. Gestational age was based on

maternal last menstrual period, urine pregnancy test and early ultrasound and when dates were not reliable, ultrasound based assessment was used and confirmed postnatally by New Ballard Score [9]. Small for gestational age (SGA) was defined when birth weight was <10th centile in Lubchenco's intrauterine growth charts [10]. These neonates were followed till death or discharge. The study was approved by the Institute Ethics Committee.

After initial stabilization, these neonates were shifted to intensive care unit depending on the availability of beds and parental consent. Those who were not shifted were provided compassionate care in delivery room. Neonates with respiratory distress syndrome received early rescue surfactant and nasal continuous positive airway pressure (CPAP). Those failing CPAP were given a trial of nasal intermittent positive pressure ventilation (NIMV) before initiating mechanical ventilation. Prophylactic surfactant was not used. Trophic feeding was initiated at the earliest and transitioned to full feeds depending on tolerance. Vitamin A was not used as a standard therapy in our unit. Blood culture by BACTEC method was used for bacterial isolation in neonates with suspected sepsis and antibiotics were initiated in them. Echocardiography was performed for identification of hemodynamically significant patent ductus arteriosus (PDA) in symptomatic babies and in all ventilated babies within first 24 hours, if they remained asymptomatic [11]. Persistent pulmonary hypertension of newborn (PPHN) was defined on the basis of labile oxygen saturation, pre and post-ductal oxygen saturation difference of >10% or pre- and post-ductal partial pressure of arterial oxygen (PaO_2) difference of >20mmHg in the presence of echocardiographic evidence of PPHN [12]. Hypotensive shock was defined as per Zubrow's charts when systolic and/or diastolic blood pressure (BP) was <5th centile for the particular gestational age, weight and postnatal age [13]. Packed red blood cell transfusion was given when PCV <35% in sick neonates and <21% in asymptomatic neonates [14].

Risk factors for mortality as well as major morbidities were pre-defined. Cause of mortality was assigned by two independent experienced physicians in the unit, not involved in the active management of the neonate.

Major morbidity was defined as the composite of one or more of the following: Bronchopulmonary dysplasia (BPD), Retinopathy of Prematurity (ROP) requiring laser therapy, grade III or IV intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and NEC stage III. BPD was defined based on the NICHD criteria of receiving treatment with oxygen >21% for at least 28 days [15]. IVH was graded using Volpe's classification [16]. NEC was defined as per modified Bell's staging [17].

Statistical analysis: To determine the association between each risk factor and outcome, chi-square test was used for categorical variables and independent t test was used for normally distributed continuous data and Mann- Whitney U test for skewed data. Those risk factors that were significant on univariate analysis (P<0.05) were entered in to a forward stepwise multivariable logistic regression model and independent risk factors were determined. To adjudge the model with the best fit, Hosmer-Lemeshow goodness-of-fit test was used and a P value >0.05 was considered as good fit. Any association between the risk factors was tested using correlation. Survival at discharge was estimated by the method of Kaplan and Meier. Risk of death was compared across the groups defined by the each of the independent predictors using the log-rank test. P value <0.05 was considered significant.

RESULTS

Of the 255 ELBW infants born during the study period, 149 were admitted to the intensive care. The remaining could not be transferred either due to non-availability of beds or lack of consent from parents due to financial constraints. 78 (52%) of them were discharged alive. 3 neonates discontinued therapy during the ICU stay, but were included for analysis. The baseline characteristics of the cohort are shown in ***Table* I**.

TABLE I BASELINE CHARACTERISTICS OF THE STUDY SUBJECTS (N = 149)

Characteristics	*No. (%)*
Gestational age (wks)*	29.1 (2.6) (Range 23-36)
Birth weight (g)	843 (108) (Range 446-997)
Males	78 (52)
Multiple gestation	29 (19)
SGA	77 (52)
Received antenatal steroids	111 (74)
PROM	40 (27)
Delivered by LSCS	48 (32)
Umbilical artery AEDF/REDF	37 (25)
Medical illness in mother	33 (22)
Obstetric problems in mother	127 (85)
Apgar at 1 min#	6 [3, 7]
Apgar at 5 min#	8 [6, 9]
Age at intensive care# (hrs)	10 [2.5, 27]

** mean (SD) #median [IQR]. SGA – small for gestational age, PROM-premature rupture of membranes, LSCS – lower segment cesarean section, AEDF/REDF-absent/reversed end diastolic flow.*

Of the 68 neonates that died, 9 (13%) died in the first 24 hours, 35 (51%) died between 2 to 7 days, 18 (26%) between 8 and 28 days and 6 (9%) beyond 28 days. The predominant causes of mortality were sepsis (46%), perinatal asphyxia (20%) and pulmonary hemorrhage (19%). Others included extreme prematurity (6%), pulmonary artery hypertension (4%), apnea (3%), aspiration pneumonia (1%) and NEC (1%).

For the purpose of analysis, those neonates who discontinued care (n=3) were grouped under those who died. Univariate analysis for mortality is depicted in ***Web Table* I**. The final model with the best fit is given in ***Table* II**. There was no significant correlation between any of the variables in the regression model (all correlation coefficients were <0.8). This model had an internal prediction accuracy of 83% and model fitted the data well (Hosmer-Lemeshow goodness-of-fit, P=0.52). The C statistic of the model was 0.82 (95% CI 0.75-0.89, P<0.001).

Kaplan Meier survival curves till discharge were made for each independent predictor (***Fig.* 1**). Survival of neonates in the birth weight category >800g versus ≤800g [60% (95% CI-50-68%) *vs*. 44% (95% CI-33-56%), P=0.028], those without and with shock [75% (95% CI-66-85%) *vs*. 24% (95% CI-16-33%), P<0.001], those not mechanically ventilated *versus* ventilated [73% (95% CI-64-83%) *vs*. 31% (95% CI-21-40%), P<0.001] were statistically different.

Fifty seven neonates (39%) developed major morbidities. These were BPD in 19 neonates (33%), Grade III or IV IVH in 39 neonates (68%), PVL in 8 neonates (14%), NEC stage III in 4 neonates (7%) and ROP requiring laser therapy in 2 neonates (3%). The final model with the best fit is given in ***Table* III**. Further, there was no significant correlation between any of the variables in the regression model (all correlation coefficients were <0.8). This model had an internal prediction accuracy of 77% and model fitted the data well (Hosmer-Lemeshow goodness-of-fit, P=0.31). The statistic of the model was 0.74 (95% CI 0.65-0.83, P<0.001).

TABLE II MULTIVARIABLE LOGISTIC REGRESSION MODEL FOR PREDICTION OF MORTALITY

Risk factor	*Adjusted odds ratio (95% CI)*	*P value*
Birth weight ≤800g	3.51 (1.39-8.89)	<0.01
Requiring invasive ventilation	4.10 (1.64-10.28)	<0.01
Shock	10.75 (4.00-28.89)	<0.01

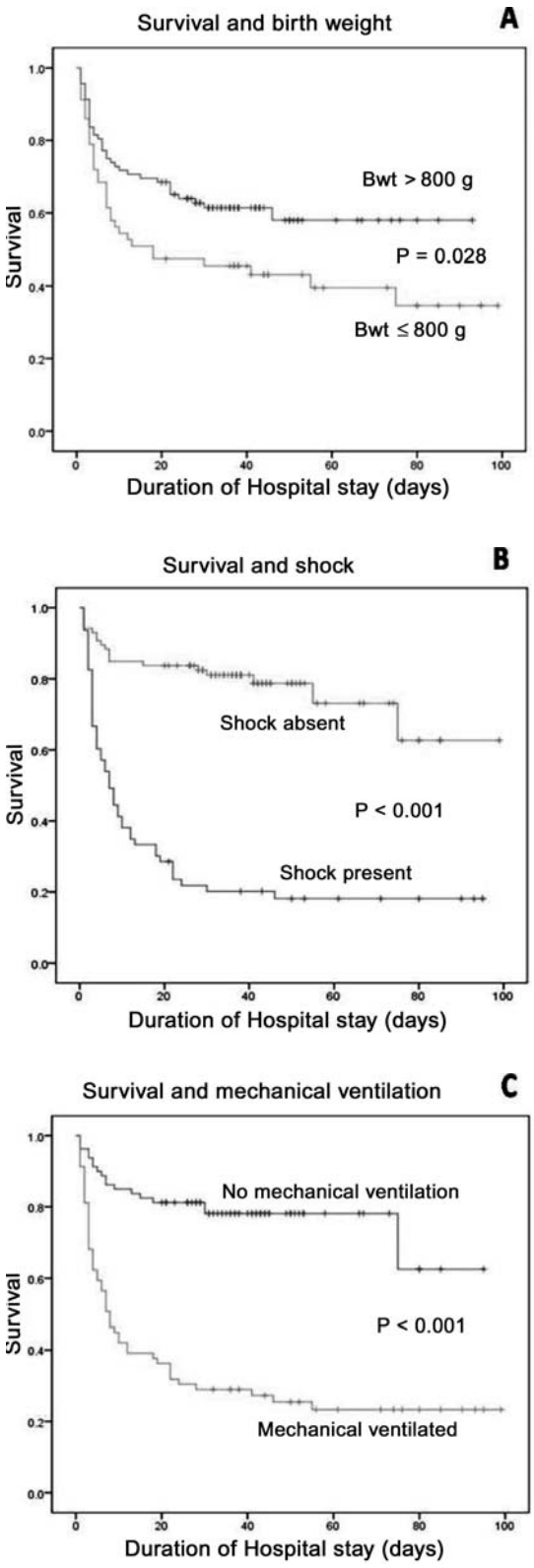

FIG. 1 *Kaplan Meier survival curves in ELBW neonates based on birth weight category (Panel A), shock (Panel B) and mechanical ventilation (Panel C).*

TABLE III MULTIVARIABLE LOGISTIC REGRESSION MODEL FOR PREDICTION OF MAJOR MORBIDITY

Risk factor	*Adjusted odds ratio (95% CI)*	*P value*
Birth weight ≤800g	3.75 (1.47-9.50)	<0.01
Not received antenatal steroids	2.62 (1.00-6.79)	<0.05
Asphyxia	4.11 (1.45-11.69)	<0.01
Ventilated	4.38 (1.29-14.79)	<0.05
Duration of oxygen (h)	1.004 (1.001-1.006)	0.002

DISCUSSION

We found that birth weight, hypotensive shock and mechanical ventilation independently predicted mortality in ELBW neonates while birth weight, lack of antenatal steroids, birth asphyxia, ventilation and duration of oxygen therapy predicted major morbidities in them.

The association between low birth weight and poor outcomes has been well established in western literature. Fanaroff, *et al.* [1] reporting NICHD network data showed that every 100g reduction in birth weight was associated with increasing mortality. The fact that we had more growth restricted babies in our study might be the reason for gestational age not emerging significant in our analysis. Other authors have also found higher mortality in their neonates <750g and <28 weeks gestation [7,8].

We found hypotensive shock as the risk factor with highest odds for mortality. Hypotension is common among ELBW neonates and is strongly associated with mortality [18-20]. A retrospective study showed that septic shock had a 28-day mortality of 40% and 71% mortality among ELBW neonates [19]. The neonatal mortality in our ELBW neonates with shock was 75%. The probable reason is that sepsis was the major cause of mortality in our cohort and might have contributed to the etiology of shock. Similar high rates of sepsis have also been reported previously [7,8]. They found that sepsis accounted for 20-41% of mortality among ELBW neonates, while it was 46% in our study.

Ventilation increased the odds of both dying and major morbidity in our ELBW population. The possible mechanism is through ventilator associated pneumonia (VAP). VAP is more common in babies who are intubated compared to those on non-invasive ventilation [21]. Ventilation *per se* can lead to IVH in preterms with RDS by causing fluctuation in cerebral blood flow velocity (CBFV). A study on neonates <1500g showed that 91% of them with fluctuating CBFV pattern developed IVH compared to only 26% with stable CBFV pattern [22]. In addition, mechanical ventilation can impede central venous return and can cause raised intracranial pressure. It can further lower the cardiac output [23]. All these factors can lead to hypoperfusion of the periventricular white matter in the premature brain. ELBW neonates getting ventilated longer have been shown to have a higher incidence of cerebral palsy [24,25].

We also found that neonates with birth asphyxia had three times the odds for developing major morbidity. Perinatal asphyxia can predispose to brain injury by various mechanisms: increased cerebral blood flow due to impaired vascular autoregulation, increase in central venous pressure, decrease in cerebral blood flow due to hypotension and due to the possible role of endogenous vasodilators [26]. Further, ischemia affects the vulnerable periventricular white matter.

Duration of oxygen therapy was another predictor of major morbidities. Hyperoxia inhibits lung and vascular growth resulting in low volume lungs and causes interstitial edema by increasing capillary permeability. This forms the basis why some authors consider oxygen toxicity as the principal cause of BPD [27]. Oxygen mediated free radical injury also plays a role in causing BPD, IVH and PVL. Its role in causing ROP has remained controversial even though recent studies show that targeting lower oxygen saturations may reduce its incidence in preterm infants [28].

Ours is the first prospective study with adequate sample size in a developing country setting looking at predictors of mortality and morbidities in ELBW neonates. All neonates who were enrolled were followed till death or discharge without loss to follow up. The regression models showed good internal prediction accuracies. We also provided separate survival curves for neonates with each of these independent risk factors that will help treating physicians in prognostication of these neonates. However, our drawback was that we did not use a clinical score at baseline for assessing the severity of illness in these neonates. Being a referral centre along with very high patient turn over, a significant proportion of neonates were not shifted or shifted late to the intensive care area. Our results may not be generalizable to those who did not get admitted to the NICU.

Contributors: KM: conceptualized the study, supervised data collection and reviewed the manuscript; DL: Analyzed data and prepared the manuscript; RM: Collected data; PK: Critically reviewed the manuscript.

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WHAT THIS STUDY ADDS?

- Sepsis, asphyxia and pulmonary hemorrhage were the major causes of mortality in ELBW neonates.
- Low birth weight, mechanical ventilation and hypotensive shock were independent predictors of mortality among them.
- Low birth weight, lack of antenatal steroids, asphyxia, any ventilation and duration of oxygen therapy were predictors of major morbidity among ELBW neonates.

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