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Predictors of mortality in extramural very low birth weight neonates: a prospective observational study

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ABSTRACT

Background: Over the past few decades, the burdens of very low birth weight (VLBW) preterm infants are increasing due to advances in obstetrics and perinatal services. Objectives of the study were to assess predictors of mortality of extramural VLBW neonates.

Methods: Prospective one year cohort study was undertaken on VLBW neonates fulfilling the inclusion criteria at a tertiary institute. Maternal and neonatal demographic data were analyzed.

Results: Male to female ratio was 1.26:1. One hundred and thirty seven (74.9%) neonates had birth weights from 1000-1499 g while 46 (25.1%) had birth weights <1000 g (ELBW) and 90% were preterm. One hundred and sixty five (90.2%) neonates were admitted in early neonatal period. Anaemia was the commonest maternal illness and preeclampsia/eclampsia was the most common obstetric complication. Respiratory distress, temperature instability and lethargy were common clinical presentations. Respiratory distress, sepsis and perinatal asphyxia were common diagnoses on admission. Mortality rate in VLBW neonates was 59.6% and respiratory distress was the commonest cause of death. Male gender (p=0.01), home delivery (p=0.04), vaginal delivery (p=0.05) and positive septic screen (p=0.003) had significantly higher mortality while mode of delivery (aOR 0.27 CI 0.086-0.83 p=0.02) and positive septic screen (aOR 4.0 CI 1.67-9.84 p=0.002) were independent risk factors for mortality.

Conclusions: In extramural VLBW neonates, male gender, home delivery, vaginal delivery and positive septic screen had significantly higher mortality whilst mode of delivery and positive septic screen were independent risk factors for mortality.

Keywords: Morbidity, Mortality, Extramural neonate, Predictors of mortality, Risk factors, Very low birth weight

INTRODUCTION

Despite improving maternal and neonatal health services and intensive care management, the neonatal period carries the greatest risk of death during childhood. Around 6700 neonates died everyday, and one third died on the first day of life. In India, recorded neonatal mortality was 22 in 2019 with interstate, rural-urban variation. Sepsis, prematurity and birth asphyxia are the major causes of neonatal mortality in developing countries, whereas

prematurity and malformations are the major causes in developed countries.⁴ Major causes of neonatal deaths in India are preterm births, neonatal infections, birth asphyxia and congenital malformations.⁵

Due to advances in obstetrics and perinatal services, the burden of very low birth weight (VLBW) preterm infants is increasing over past two decades.^{6,7} Though, VLBW babies constitute only 4-7% of live births, they contribute about 30% to early newborn deaths.⁸ In India, survival of VLBW infant ranges from 61.8-75.4% while it is over 90%

in Japan. 9-11 This is due to poor coverage of health system, shortage of health care providers and poor access to referral services. 12 Prognosis depends not only on birth weight and gestational age, but also on perinatal factors and physiological condition of infants. 13,14

Most previous studies on VLBW neonates have been conducted on hospital-born and neonatal intensive care treated neonates as against outborn neonates who were previously admitted at a different health facility or delivered at home and are sometimes older at the time of admission. ¹⁵⁻¹⁷ Data on such a subgroup treated with suboptimal care in a general paediatric ward is scanty.

Objectives

The objective of the study was to assess the predictors of mortality of extramural VLBW neonates.

METHODS

This prospective observational study was carried out at a tertiary care teaching government referral hospital of central India (Government medical college and hospital, Nagpur, Maharashtra, India) on extramural neonates (delivered outside our hospital premises - at home, government, private hospital), and admitted through either outpatient or emergency department to our institute over a one year period (from May 2016 to April 2017). Approval for study was obtained from the Institutional ethical committee and informed valid consent was obtained from parents. As per hospital policy, extramural neonates were treated in a separate neonatal cabinet in general paediatric ward with facilities like central oxygen pipes, phototherapy units, warmers and bubble continuous positive airway pressure (CPAP) machines.

Inclusion criteria

All extramural neonates of either sex or gestational age with birth weight (mentioned on referral sheet) from 500-1500 g were included in the study.

Exclusion criteria

The exclusion criteria included neonates with birth weights >1500 g or <500 g, neonates with non-documented birth weight, though admission weight is 500-1500 g, neonates with lethal congenital malformations, death within 12 hours of admission and those leaving hospital against medical advice and those not willing to participate in study.

Data were collected following admission from either mother or caregiver in a structured data sheet. Maternal details included age, gravida/parity, antenatal care, obstetric complications, mode and place of delivery, referring person, mode of transport and distance travelled by the neonate. Socioeconomic status of parents was

classified according to the modified Kuppuswammy scale. 18

Neonates were assessed on admission for gestational age by maternal documentation about menstrual history/ultrasound report or new Ballard scoring. Weight was recorded on electronic weighing scale but we included neonates whose birth weight was mentioned on referral sheet. We also recorded axillary temperature by digital thermometer, capillary refill time (>3 seconds considered prolonged), blood sugar (<45 mg/dl considered hypoglycemia) and the neonates were examined for other life threatening events.

Birth asphyxia was considered in the presence of failure to established breathing at birth.

Respiratory distress was diagnosed in presence of at least 2 of the following: respiratory rate >60/min, chest indrawing, and expiratory grunt/groaning.

Meconium aspiration syndrome was diagnosed in presence of two of the following: meconium staining of liquor or staining of nails, umbilical cord or skin; respiratory distress within 1 hour of birth; and radiological evidence of aspiration pneumonitis (atelectasis and/or hyperinflation).

Clinical sepsis was defined as neonate having symptoms or signs of sepsis with maternal risk factors of infection. Probable sepsis was clinical sepsis with positive septic screen and confirmed sepsis was growth of causative organism in blood culture. Early onset sepsis was clinical manifestation of sepsis within 72 hours of birth while late onset sepsis was after 72 hours. Apgar score was noted either from available document or estimated, based on mother's data whether baby cried immediately after birth, details of activity, colour and respiratory effort of newborn after birth.

All neonates were investigated, managed and monitored as per standard treatment protocol. Outcome was assessed in terms of death or survival. Demographic, maternal and neonatal variables were studied as risk factors for mortality.

Statistical analysis

Data were entered into Microsoft excel sheet and analysed using STATA version 14. Continuous variables were presented as mean±standard deviation (SD) and categorical variables as frequencies and percentages. For comparison between survival and non-survival, independent t-test was used for normalized data and Mann-Whitney test for non-normalized data. Categorical variables were compared using Chi-square test and Fischer exact test.

Multiple logistic regression was used to identify significant risk factors of mortality. Adjusted odds ratio

(aOR) and 95% confidence interval (CI) were calculated. p<0.05 was considered significant.

RESULTS

During study period 1038 extramural neonates were admitted, of whom 221 (21.3%) had weights less than 1500 g at time of admission. Of these, 28 were excluded due to non-availability of recorded birth weight; thus, 183 VLBW neonates were included in study. Male to female ratio was 1.26:1. Nineteen (10.4%) neonates had intrauterine growth restriction. A medical officer of primary/ secondary health care level has referred 145 (79.2%) neonates to our hospital. Characteristics of the 183 extramural VLBW neonates participating in study are shown in Table 1. Septic screen was positive in 20.8% neonates and there was a significant difference between survival and non-survival (p=0.003). Average duration of hospital stay among non-survival was significantly shorter compared to survival (p<0.0001).

The socio-demographic and maternal characteristics of participants are shown in Table 2. A booked case is one who has visited the antenatal clinic three or more times. Of the deliveries 176 (96.2%) occurred at primary, secondary or tertiary health care level. None of the 7 neonates who were delivered at home survived.

The clinical characteristics of the 183 extramural VLBW neonates are shown in Table 3. Respiratory distress, temperature instability and lethargy were common clinical presentations.

Morbidity and mortality pattern of extramural VLBW neonates is shown in Table 4. Eight neonates had malformations, three having congenital heart disease and one each having meningocele, cleft lip/palate, hydronephrosis, hypospadiasis and tracheo-oesophageal fistula. Neonate with tracheo-oesophageal fistula and one neonate with cyanotic congenital heart disease succumbed. High case fatality rates were recorded in neonates with respiratory distress, perinatal asphyxia, sepsis and malformations.

Table 1: Neonatal variables of extramural very low weight neonate.

Variables	Total admission (n=183, %)	Survival (n=74, %)	Non-survival (n=109, %)	P value
Gender (male)	102 (55.74)	33 (44.59)	69 (63.30)	0.01
Average duration of stay (days)	6.25±4.73	9.12±4.87	4.30±3.51	< 0.0001
Gestational age				
Preterm	164 (89.62)	63 (85.14)	101 (92.66)	0.07
Term	18 (9.84)	11 (14.86)	07 (6.42)	
Post term	01 (0.54)	00	01 (0.92)	
Weight (grams)	•			
≤999	46 (25.14)	16 (21.62)	30 (27.52)	0.36
1000-1499	137 (74.86)	58 (78.38)	79 (72.48)	
Average distance travel by neonate	87.69±63.18	81.59±63.36	91.84±63.01	0.28
Cried immediately after birth (yes)	142 (77.59)	59 (79.73)	83 (76.15)	0.56
Resuscitation required (yes)	41 (22.40)	15 (20.27)	26 (23.85)	
Type of resuscitation	•			
Bag and mask	35 (19.13)	14 (18.92)	21 (19.27)	0.5
Intubation	6 (3.28)	1 (1.35)	5 (4.59)	0.4
Blood sugar (mg/dl)[mean±SD]	98.98±24.87	98.62±25.69	99.23±24.42	0.8
Serum calcium (mg/dl) [mean±SD]	9.03±0.51	9.07±0.47	9.01±0.54	0.4
Sepsis screen (positive)	38(20.77)	07(9.46)	31(28.44)	0.003
Age at admission (mean±SD)	3.14±4.43	3.44±5.01	2.93±4.00	0.4
Referral person of neonate				
Trained dai	6 (3.28)	1 (1.35)	5 (4.59)	0.21
Accredited social health activist	32 (17.49)	10 (13.51)	22 (20.18)	
Medical officer	145 (79.23)	63 (85.14)	82 (75.23)	

Table 2: Socio-demographic and maternal variables.

Variables	Total admission (n=183, %)	Survival (n=74, %)	Non-survival (n=109, %)	P value
Residence (rural)	120 (65.57)	47 (63.51	73 (66.97)	0.62
Socioeconomic status				

Continued.

Variables	Total admission (n=183, %)	Survival (n=74, %)	Non-survival (n=109, %)	P value
Lower	116 (63.39)	45 (60.81)	71 (65.14)	0.55
Middle	67 (36.61)	29 (39.19)	38 (34.86)	
Availability of health facility (yes)	182 (99.45)	74 (100)	108 (99.08)	1.0
Antenatal care (booked)	172 (93.99)	70 (94.59)	102 (93.58)	0.77
Antenatal care received from				
Primary health centre	61 (33.34)	20 (27.03)	41 (37.61)	0.26
Rural hospital	44 (24.04	22 (29.73)	22 (20.18)	
District hospital	39 (21.31)	18 (24.32)	21 (19.27)	
Teaching institute	39 (21.31)	14 (18.92)	25 (22.94)	
Maternal age (years)		<u> </u>		
18-20	9 (4.92)	4 (5.40)	5 (4.59)	0.44
21-25	144 (78.69)	61 (82.43)	83 (76.15)	
26-30	30 (16.39)	9 (12.17)	21 (19.26)	
Gravida				
Primi	132 (72.13)	51 (68.92)	81 (74.31)	0.42
Multi	51 (27.87)	23 (31.08)	28 (25.69)	
Mode of delivery				
Vaginal	161 (87.98)	61 (82.43)	100 (91.74)	0.05
Caesarean section	22 (12.02)	13 (17.57)	9 (8.26)	
Place of delivery				
Home	7 (3.83)	0	7 (6.42)	0.04
Hospital	176 (96.17)	74 (100)	102 (93.58)	
Maternal diseases (not exclusive)				
Anemia	123 (67.21)	49 (66.22)	74 (6.89)	0.81
Diabetes	4 (2.19)	2 (2.70)	2 (1.83)	1
Hypertension	50 (27.32)	16 (21.62)	34 (31.19)	0.15
Sickle cell disease	1 (0.55)	0	1 (0.92)	1
Hypothyroidism	26 (14.21)	7 (9.46)	19 (17.43)	0.13
Chronic kidney disease	2 (1.09)	1 (1.35)	1 (0.92)	1
Heart disease	1 (0.55)	0	1 (0.92)	1
Obstetric complications				
Gestational diabetes	3 (1.64)	0	3 (2.75)	0.2
Preeclampsia/eclampsia	88 (48.09)	34 (45.95)	54 (49.54)	0.63
Antepartum haemorrhage	11 (6.01)	2 (2.70)	9 (8.26)	0.2
Intrapartum fever	3 (1.64)	2 (2.70)	1 (0.92)	0.56

Table 3: Clinical details of very low weight neonate (not exclusive).

Clinical variables	Total admission (n=183, %)	Survival (n=74, %)	Non-survival (n=109, %)	P value
Lethargy	139 (75.96)	61 (82.43)	78 (71.56)	0.09
Temp instability	150 (81.97)	59 (79.73)	91 (83.49)	0.51
Respiratory distress	170 (92.89)	68 (37.16)	102 (93.58)	0.66
Apnea	70 (3.25)	24 (32.43)	46 (42.20)	0.18
Convulsion	22 (12.02)	8 (10.81)	14 (12.84)	0.67
Cyanosis	36 (19.67)	11 (14.86)	25 (22.94)	0.17
Prolonged CFT	94 (51.57)	32 (43.24)	62 ((56.88)	0.07
Jaundice	11 (6.01)	4 (5.41)	7 (6.42)	0.77

Table 4: Morbidity and mortality pattern of extramural very low weight neonate.

Clinical diagnosis	Total admission (n=183, %)	Survival (n=74, %)	Death (n=109, %)	Case fatality rate (%)
Sepsis	31 (16.94)	13 (17.57)	18 (16.51)	58.06
Prematurity with RDS	116 (63.39)	37 (50)	79 (72.48)	68.1
Perinatal asphyxia	17 (9.29)	07 (9.46)	10 (9.17)	5.82
Neonatal hyperbilirubinemia	11 (6.01)	11 (14.86)	00	-
Malformations	8 (4.37)	06 (8.11)	2 (1.83)	25

Out of 183 VLBW neonates 109 (59.6%) died. Mortality rate in extremely low birth weight neonates (30/46) was 65.2% whereas that in VLBW neonates (79/137) was 57.7%. On univariate analysis, male sex (p=0.01), positive septic screen (p=0.003), home delivery (p=0.04) and vaginal delivery (p=0.05) were significant risk factors for mortality. Mode of delivery and positive septic screen were independent risk factors for mortality in extramural VLBW neonates (Table 5).

Table 5: Risk factors for mortality in extramural very low birth weight neonate (multiple logistic regression).

Variables	Adjusted odds ratio	95% confidence interval	P value
Mode of delivery	0.27	0.086-0.83	0.023
Positive sepsis screen	4.0	1.67-9.84	0.002

DISCUSSION

In the present study, 17.6% VLBW neonates were admitted during the study period which is higher than that reported in the literature. 19,20 This may be because our institute has the largest referral centre in central India catering to a large population. Similar to observations of other authors males outnumbered females. 15,16,19 This may be because of increased biological vulnerability of male neonate and more acceptance of male neonate in rural India. Prematurity is the commonest cause of morbidity and mortality in VLBW neonate. 16,17 Majority of participants in our study too were preterm neonates. Non institutional births constitute a significant proportion of total births in developing countries like India and these neonates were referred to a tertiary institute due to nonavailability of neonatal health services. In our study, although 96.2% of neonates were delivered either at primary or secondary health care level by vaginal route (88%) by paramedical and medical persons, most neonates were referred by medical officer without prior communication. Average distance of travel by neonate was 87.69±63.18 km without health assistant and proper supportive care. Transported neonates may become hypothermic, hypoxic, and/or hypoglycemic which can have serious clinical implications and increase chances of morbidity and mortality due to lack of pre-treatment stabilization and monitoring during their transport. Most studies revealed high morbidity and mortality due to limited transport facilities. 21,22

In this study, though most mothers belonged to lower socio-economic class of rural area, 94% mothers were booked cases and received antenatal care from either primary or secondary health care level. Primiparity was evident in 72.1% mothers and most mothers were in the 21-25 year age-group. Anaemia was the commonest maternal illness followed by hypertension, and preeclampsia/eclampsia was the most common obstetric complication associated with mothers of VLBW neonates. Naskar et al and Su et al reported primipara mother with under-nutrition, belonging to poor socioeconomic status with maternal hypertension to be associated with VLBW babies. 19,23 Identification of maternal risk factors of prematurity by proper antenatal and effective perinatal care is of vital importance for preventing incidence of VLBW babies.

Most participants were admitted with respiratory distress, lethargy, temperature instability, prolonged capillary refill time, apnoea and cyanosis. These may be related to occurrence of cardiovascular collapse, metabolic derangement, and lack of cerebral autoregulation, incomplete development and maturation of lungs. Not only prevention of prematurity but also well-equipped transport with trained health assistant is vitally important to take care of temperature, sugar and oxygenation of VLBW infants during transport, to prevent morbidity and mortality in this subgroup. We observed respiratory distress in 63.4%, sepsis in 16.9%, perinatal asphyxia in 9.5%, neonatal hyperbilirubinemia in 6%, and malformation in 4.4% as the common causes of morbidity. Kumar et al revealed neonatal jaundice as the commonest cause of admission, followed by sepsis and birth asphyxia in outborn neonates while birth asphyxia, sepsis and respiratory distress were reported by Kabilan et al and Lakshmanaswamy et al in their study of inborn VLBW neonates. 15,16,24 We found respiratory distress was the commonest (72.5%) cause of death followed by sepsis (16.5%) in our study. The main cause of death in babies with respiratory distress syndrome was lack of surfactant therapy and non-availability of adequate number of ventilation facilities. Other factors that may have contributed to mortality were overcrowding of patients, inadequate nursing staff leading to loss of quality health care and inadequate referral linkage. Our finding were similar to findings by Tripathy et al while Kumar et al revealed birth asphyxia and sepsis as leading causes of mortality in outborn VLBW neonates. 9,24 Recent study by Brasher et al on outborn extremely low birthweight (ELBW) neonates observed that outborn ELBW infants had increased odds ratio for late onset sepsis compared to inborn neonates. 25

In current study, mortality rate was 59.6%. Survival rate in ELBW neonates was 34.8% and VLBW neonates were 42.3% (Overall survival rate 40.4%). Most studies from India have reported survival rates from 60-75% in VLBW neonates delivered in hospital and managed in wellequipped intensive care but comparative data on outborn neonates treated with suboptimal care is lacking. None of the clinical variables and maternal factors like age, gravida, maternal diseases or neonatal factors like age at admission was significant risk factors for mortality except male sex, home delivery, vaginal delivery and positive septic screen. Ballot et al reported small for gestational age, place of birth, mode/place of delivery, hypothermia at birth, resuscitation at birth and gender as survival determinants in VLBW neonates in public sector hospital while Mukherjee et al revealed gestational age <25 weeks, birth weight <750 g, antenatal steroid administration and resuscitation at birth as risk factors for mortality. 17,26,27 Ruegger et al reported mode of delivery, low gestational age, multiple births, outborn neonate and birth weight as the major survival determinants of VLBW neonates in population based study.²⁸ Chen et al observed that deceased infants had significantly lower gestational age, Apgar score and birth weight in a VLBW cohort.⁶ A study by Zile et al concluded that neonatal mortality was significantly higher in ELBW neonates, gestational age <31 weeks, Apgar score of 6 points at fifth minute, congenital abnormalities and placental abruption while Porta et al concluded multiple pregnancy as a prognostic factor that can slightly increase mortality in VLBW neonates. 29,30 In our study mode of delivery and positive septic screen were independent risk factors for mortality in VLBW neonates.

Limitations

The limitation of the study was that the sample size was small.

CONCLUSION

Mortality rate in extramural VLBW neonates was 59.6% and respiratory distress was the commonest cause of morbidity and mortality. Male, home delivery, vaginal delivery and positive septic screen neonates had significantly higher mortality while mode of delivery and positive septic screen were independent risk factors for mortality in VLBW neonates.

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Institutional Ethics Committee

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