Original article

Predictors of early neonatal mortality in extremely low birth weight infants in a Neonatal Intensive Care Unit over a 10-year period

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Abstract

Background: Early neonatal mortality (ENM) contributes substantially to overall mortality rates. Reliable cause-specific data are valuable; thus, the definition of risk factors provides information on antenatal, perinatal and immediate neonatal management.

Objective: The present study was designed to investigate rates of ENM within extremely low birth weight (ELBW) infants group, to define associated antenatal, perinatal and neonatal factors associated with ENM and also primary causes of early death.

Methods: Case records of consecutive ELBW infants admitted to our Neonatal Intensive Care Unit over a 10-year period were retrospectively surveyed for the deaths up to 7 days postpartum. Logistic regression modeling was used to determine the association of risk factors with ENM.

Results: Infants included (n = 359) were classified into non-survivors (cases, n = 80) and survivors (controls, n = 231) during the first 7 days while non-survivors after 7 days of life (n = 48) were excluded. Survival analysis showed that most of the early deaths occurred within 48 hours postpartum. The overall ENM rate was 25.7%, with no significant variation over time. Predictors as gestational age, birth weight, gender, chorioamnionitis, preeclampsia, intrauterine growth retardation, antenatal steroids administration (ASA), Apgar score at 1 minute, perinatal acidemia and surfactant doses were involved for early death. All results were adjusted for possible confounders. Specifically, until 48 hours of life ASA decreased

odds for death. The main immediate causes of death until the first 48 hours were prematurity and pulmonary hemorrhage, while from 48 hours to 7 days were prematurity and pulmonary insufficiency.

Conclusions: ENM rates occurred mainly during 2 postnatal days, did not show significant improvement over time and as related to certain factors can be modified with simple targeted perinatal policies.

Keywords

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How to cite

Introduction

Extremely low birth weight (ELBW, ≤ 1,000 g) infants, with an incidence of 0.31-1.3% of live births, are at high risk of morbidity and mortality [1-4]. During the last two decades, survival rates of ELBW infants have increased significantly (71.8-87%), due to improved antenatal, perinatal care and increased clinical experience as well, although a lack of progress has been recently reported [5-7]. Approximately 75% of all postnatal deaths occur within the first 7 days of life, while 50% of early neonatal deaths occur within 72 hours of life [2, 3, 6-10]. ELBW infants still account for 50% of all neonatal deaths, despite a 40% reduction in recent years [10, 11]. Hence, early neonatal mortality (ENM), defined as death up to the first 7 days of life, contributes significantly to the overall neonatal mortality.

A better understanding of factors contributing to preterm birth and the need for intensive perinatal care are necessary to increase neonatal survival, by focusing on prevention measures [3,

12]. In addition, the determination of risk factors as predictors of ENM could provide valuable clinical information for more immediate and better management/treatment of ELBW infants.

Various studies have examined predictors affecting early in-hospital mortality among ELBW infants. Shankaran et al. [7] evaluated predictors of early death within the first 12 hours of life and after, while Bacak et al. for neonatal mortality within 28 days of life [13]. Studies have not focused particularly on the critical period of the first 7 days of life and, additionally, there is a dearth of scientific data for this subgroup of neonates in our country. Although studies regarding mortality factors for ELBW infants have been published, there is still a need for data on ENM for every tertiary center in order to develop a model for risk during this critical period [7, 8, 13].

The aim of the present study was to determine the contribution of various factors and develop a model for risk for ENM as well as the causes of early death among ELBW infants in a Neonatal Intensive Care Unit (NICU) over a 10-year period of time.

Patients and methods

Study population

This was a retrospective observational study, evaluating data on ENM for live-born ELBW infants (≤ 1,000 g and ≥ 24 weeks), consecutively admitted to our NICU, between March 2007 and December 2017. Stillborn and < 24 weeks' gestational age (GA) infants were excluded. Case records of enrolled ELBW infants' analysis took place, focusing on the first 7 days of life (0-7 days postpartum). ELBW infants were classified into non-survivors (Group A) and survivors (Group B). Non-survivors were further classified into two subgroups; infants who died during the early neonatal period in the first 7 days of their life (Group A1) with those who died after (> 7 days postpartum) being excluded (Group A2). Cases (Group A1) and controls (Group B) were stratified by GA (< 26 weeks, 26-27 weeks and ≥ 28 weeks) and birth weight (BW) (< 750 g and 750-1,000 g).

Methods

Selected data on predictors potentially associated with ENM were grouped into three categories: antenatal care status, perinatal history

and neonatal characteristics. Antenatal care status data analyzed were conception method, multiple gestation, hypertension (preeclampsia), gestational diabetes, premature rupture of membranes (PROM), chorioamnionitis, mode of delivery, intrauterine growth retardation (IUGR), antenatal steroids administration (ASA), calcium channel blocker tocolytics administration and hospital birthplace (inborn/outborn). Perinatal history data included biophysical profile before birth, delivery room intubation, Apgar score at 1 minute (1-min Apgar) and perinatal acidosis. Neonatal characteristics data analyzed were gender, GA, BW, growth retardation and respiratory distress syndrome (RDS).

The following definitions were used. GA in completed weeks was based on last menstrual period and/or ultrasonographic scans [14]. Perinatal acidosis was defined as cord pH < 7.15 indicative of fetal hypoxia [15]. Abnormal fetal heart rate and/or ultrasonographic assessment of fetal movement, tone, breathing and amnionic fluid with a total score < 6 were identified as pathological biophysical profile [16]. Neonates whose BW was less than the 10th percentile, according to Fenton scale, were classified as small for gestational age (SGA) [17]. PPROM was defined at > 18 hours before birth, ASA as ≥ 2 doses of dexamethasone 24 hours - 7 days before delivery. Criteria for chorioamnionitis diagnosis were fever (> 37.8°C) in combination with ≥ 2 of the following criteria: a) uterine tenderness, b) leukocytosis or increase in serum C-reactive protein (CRP) levels, c) malodorous amniotic fluid and d) fetus tachycardia (> 160 bpm/min).

Finally, immediate causes of early death based solely on clinical criteria (referring to the dominant factor responsible for death, thus excluding probably preventable catastrophic final events such as intraventricular hemorrhage) as reported by Hein and Lofgren and time point during early neonatal period when most deaths occurred, were also analyzed [12].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normal distribution, or median (range) depending on the distribution. Student t-test or Mann-Whitney U test was used to compare continuous variables and Fisher exact test to compare categorical variables. Kaplan-Meier survival analysis was used to define the time point

within 7 days postpartum when the majority of deaths occurred. Crosstabulation analysis was used to calculate the odds ratio (OR) for each factor, comparing cases and controls to evaluate the impact on ENM. Multivariate logistic regression analysis, with the dependent variable being early neonatal death and stratification of risk according to GA and BW, calculated adjusted OR and 95% confidence interval (CI) for each factor.

A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS® 17.0v for Windows® (SPSS Inc., Chicago, Ill, USA).

Results

During the study period (March 2007-December 2017), 5,649 infants were admitted to our NICU. A total number of 365 ELBW infants born in a level III tertiary center (with 90.7% inborn) were included in the study, with GA ranging from 24 to 32 weeks and BW from 340 to 1,000 g. The final study population included 359 infants (6 were excluded due to lack of data for key variables), classified into non-survivors (Group A, n = 128 [35.7%]) and survivors (Group B, n = 231 [64.3%]). Non-survivors were further divided into those infants who died at early neonatal period (Group A1, n = 80 [62.5%]) and after (Group A2, n = 48 [37.5%]).

Infants in Group A1 (cases) were of mean BW 695 ± 164.8 g and mean GA 25.5 ± 1.5 weeks, while in group B (controls) 851 ± 120.6 g and 27.7 ± 2.1 weeks, respectively (p < 0.001). The overall ENM was 25.7%, with no significant variation over the 10-year time period (data not shown). GA-specific ENM rates ranged from 42.1% at < 26 weeks (n = 59/140) to 13.2% at 26-30 weeks (20/151) and 5% at ≥ 30 weeks (n = 1/20), while BW-specific ENM reached 46.8% for infants weighing < 750 g (n = 52/111) and 14% for 751-1,000 g (n = 28/200). GA-specific and BW-specific ENM showed no significant variation over the 10-year time period (data not shown).

Survival analysis showed that the majority of deaths during the 7 days postpartum period, occurred on 48 hours of life (n = 44 [55%]) (**Fig. 1**).

The prevalence of risk factors among group A1 and B newborn groups (early death and alive) was determined, and differences tested with Fisher exact test revealed OR (**Tab. 1**). Predictors as GA, BW, gender, chorioamnionitis, preeclampsia, IUGR, ASA, 1-min Apgar (< 3), perinatal acidemia
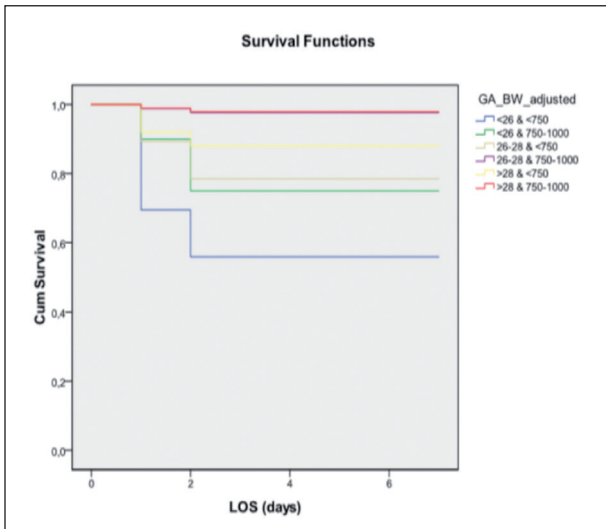
Figure 1. Survival analysis of ELBW during 7 days postpartum.
LOS: length of stay.

and surfactant doses were involved in early death. After adjustment for confounders, low GA, low BW, IUGR and low 1-min Apgar were found to increase while ASA decreased odds for early death (**Tab. 1**). Specifically, during the period until 48 hours, when most deaths occurred, other than GA and BW, only ASA decreased odds for death. The main immediate cause of death based on clinical criteria was prematurity, followed by pulmonary hemorrhage; pulmonary insufficiency due to RDS was responsible for nearly 61.3% (49/80) of early deaths.

Discussion

In this study, a profile of predictors of early neonatal death in ELBW infants admitted in our III level tertiary center during a 10-year period is

Table 1. Predictors for early neonatal death among extremely low birth weight (ELBW) infants, 2007-2017.

		Cases (group A1, n = 80)	Controls (group B, n = 231)	p-value	Crude OR	Adjusted OR
Antenatal care status						
Inborn setting [a]		69 (86.2)	187 (91.2)	ns		
Normal conception [a]		44 (72.1)	99 (58.2)	ns		
Multiple gestation [a]		28 (42.4)	67 (34.7)	ns		
Gravidity (> 2) [a]		23 (34.8)	58 (30.7)	ns		
Preeclampsia [a]		2 (3.1)	22 (11.6)	0.049	0.44 (0.08-1.18)	0.26 (0.04-1.68)
Diabetes [a]		1 (1.7)	9 (4.8)	ns		
PROM [a]		13 (20.6)	35 (18.4)	ns		
Chorioamnionitis [a]		11 (17.5)	17 (8.9)	0.068	1.7 (1-2.8)	1.64 (0.51-5.25)
Mode of delivery	**Vaginal** [a]	9 (13.6)	20 (10.5)	ns		
	CS [a]	57 (86.4)	171 (89.5)	ns		
IUGR [a]		33 (41.8)	61 (28.9)	0.017	1.49 (1-2.18)	5.09 (1.6-16.1) [c]
ASA [a]		47 (58.8)	177 (83.9)	0.001	0.43 (0.3-0.6)	0.36 (0.23-1) [c]
Tocolytics [a]		25 (39.7)	80 (42.1)	ns		
Perinatal history						
Path biophysical profile [a]		17 (28.3)	39 (20.5)	ns		
DRI [a]		59 (90.8)	106 (57)	ns		
Apgar score at 1 minute (< 3) [a]		11 (23.9)	15 (8.7)	0.009	2.32 (1.35-3.98)	2.5 (0.84-7.48) [c]
Apgar score at 5 minutes [b]		7 (2-9)	8 (3-9)	ns		
Perinatal acidemia [a]		13 (20)	12 (6.3)	0.003	2.3 (1.47-3.59)	0.83 (0.18-3.18)
Newborn characteristics						
GA < 26 weeks [a]		59 (73.8)	81 (35.1)	0.001	3.42 (2.2-5.36)	7.35 (2.5-21.5) [c]
BW < 750 g [a]		52 (65)	59 (25.5)	0.001	3.34 (2.2-4.97)	2.88 (1.2-6.8) [c]
Gender (M) [a]		45 (58.4)	90 (41.1)	0.011	1.677 (1.13-2.48)	1.92 (0.81-4.59)
SGA [a]		33 (41.3)	82 (39.8)	ns		
RDS [a]		60 (90.9)	171 (89.5)	ns		
Surfactant doses [b]		1 (0-4)	1 (1-3)	0.001	1.9 (1.26-2.87)	1.58 (0.85-2.95)

OR: odds ratio; ns: not significant; PROM: premature rupture of membranes; CS: cesarean section; IUGR: intrauterine growth retardation; ASA: antenatal steroids administration; DRI: delivery room intubation; GA: gestational age, BW: birth weight; SGA: small for gestational age; RDS: respiratory distress syndrome.
[a] Fisher exact or χ^2 exact t-test accordingly, data presented as n (%); [b] Mann-Whitney U test was used, data presented as median (range); [c] p < 0.05.

provided. Our results elucidated several factors contributing positively or negatively to ENM in two different lifetime periods within the first 7 days postpartum. Specifically, GA, BW, 1-min Apgar, ASA and IUGR were involved in early death after adjustment for confounders.

ENM coefficients are considered to reflect antenatal care (maternal health and/or delivery status), access to high-qualified medical care and public health practices, while late neonatal mortality mainly reflects the quality of in-hospital care [3].

ELBW infants' high morbidity and mortality rates vary considerably, possibly due to differences in the neonatal population, antenatal and/or perinatal care [1]. In our setting, early mortality rates (total, GA-specific, BW-specific) showed no significant variation over the 10-year period time, confirming the already reported lack of progress in effective clinical management of ELBW infants [3, 5].

ENM during the first 7 days of life for the 10-year period time was 25.7%, with approximately 2/3 of all neonatal deaths occurring during this time period. In the majority of cases, death took place during the first 2 days, similarly to other studies [18, 19]. Large variations of early death in tertiary hospitals from 13% up to 73% can be explained by differences in obstetric and neonatal care, specifically for infants < 25 weeks of gestation [20]. The correlation between neonatal mortality and GA, BW has already been pointed out in the literature. Itabashi et al. [21] showed that among perinatal factors affecting survival in very low birth weight infants, GA was the best predictor, with most clinicians accepting 22 weeks as the lowest threshold of viability. In our study, GA < 26 weeks and BW < 750 g were associated with significantly higher ENM, consistent with neonatal mortality rates of ELBW < 27 weeks of gestation ranging between 44-70% in Europe [1, 22]. Our study results in line with Gould et al. findings showed that BW-specific death for ELBW persists after 4 days of life [19] in contrary to Meadow et al., who demonstrated its effect before 3 days of life [18]. Additionally, Philip's study [23] showed that 65% of deaths occurred within 24 hours after birth, while Shankaran et al. study reported that most deaths occur during the first 3 days of life [7].

ELBW outborn in level II or III facilities in our area were directly transported and admitted in our hospital, with no differences found regarding hospital birthplace. Male gender presented as a predictor, although increasing crude odds for early death during both time periods. Gender difference, with increased mortality rates in male neonates (although appearing to lose significance at 27 weeks gestation) mainly due to delayed lung maturation, has already been described in the literature [13, 24, 25]. Still, the biological mechanisms for this difference are not well understood.

Studies have shown that survival in ELBW is associated with cesarean section (CS) performed for fetal distress and transfer to a tertiary center [10, 26]. Obstetric care for death within 24 hours after birth has been found to decrease odds for ENM within 24 hours of life after CS at 0.4, after vaginal breech delivery at 2.3, while increased at 2.6 after birth at a level II [10, 27]. CS was not found to associate with early death in our study, probably due to our specific study sample, comprising of ELBW infants born in a level III tertiary center and physicians' willingness for CS.

Additionally, preeclampsia was found linked to survival as other mostly single-center studies have shown, inconsistent to our ratio study results [13]. This can be explained by increased use of magnesium sulfate for seizure prophylaxis and close surveillance of at-risk pregnancies, although data are lacking from our study.

Delivery room resuscitation in infants born in our tertiary center reflects the severity of antenatal or delivery status but also the importance of substandard intra-uterine environment. Shankaran et al. [7] showed that ELBW infants at the highest risk (BW < 500-750 g, GA < 24 weeks, 1-min Apgar < 3) intubated in the delivery room were more likely to survive, as being stabilized, compared to those who were not intubated [13].

Literature supports evidence that survival in ELBW infants has been improved by surfactant replacement therapy and ASA, as well as advancements in NICU's technologies [1, 8, 18, 21, 28, 29]. In our analysis, ASA showed a clear benefit towards decreased odds for early death until 48 hours of life, when most deaths occurred.

IUGR factor known to increase odds for death was found to associate with higher early mortality rates similar to Bernstein et al. study results [30]. On the other hand, SGA infants did not show better chances for survival as in Tagare et al. and Tyson et al. studies [31, 32]. This non-difference could be attributed to the fact that the majority of ELBW had a high level of hospital care (level III).

The main causes of mortality recorded in our study were extreme prematurity, pulmonary

hemorrhage and pulmonary insufficiency due to RDS quite similar to Patel et al. study [33]. Specifically, immediate causes of death until the first 48 hours were immaturity and pulmonary hemorrhage, from 48 hours to 7 days were immaturity and pulmonary insufficiency.

Limitations of the study were provision of data from a single center, possible inter-observer variation on data collection and no selection of other factors as key variables to be included in the multivariate analysis, probably influencing our results. Variables as socioeconomic status, maternal demographics (i.e., age) and ethnicity despite the fact that all citizens are able to purchase basic health insurance and having direct access to the health care system were also not included.

In conclusion, ENM remained high among ELBW infants of 24-26 weeks and < 750 g. The main predictors for early death were found to be GA, BW, low 1-min Apgar (< 3), ASA and IUGR. Specifically, until 48 hours of life when most deaths occurred, mainly GA, BW and ASA decreased odds for death.

Change in obstetric practices as ASA, improved access to level III perinatal services, use of noninvasive respiratory support and quality improvement initiatives are the main contributors to ELBWs' better outcomes over the past two decades [5, 10]. Additionally, since ENM is the main contributor to overall postnatal mortality, survival may be improved by applying better antenatal and perinatal services, better resuscitation practice and centralization of at-risk deliveries [10].

Developing a model for risk and acknowledgment of predictors and causes of death by physicians and health providers for each specific tertiary center could be used for targeted decision-making interventions to optimize ELBW infants' care and improve survival.

Declaration of interest

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