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Risk Factors for Post-NICU Discharge Mortality Among Extremely Low Birth Weight Infants

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Abstract

Objective—To evaluate maternal and neonatal risk factors associated with post-neonatal intensive care unit (NICU) discharge mortality among ELBW infants.

Study design—This is a retrospective analysis of extremely low birth weight (<1,000 g) and <27 weeks' gestational age infants born in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network sites from January 2000 to June 2007. Infants were tracked until death or 18–22 months corrected age. Infants who died between NICU discharge and the 18–22 month follow-up visit were classified as post-NICU discharge mortality. Association of maternal and infant risk factors with post-NICU discharge mortality was determined using logistic regression analysis. A prediction model with six significant predictors was developed and validated.

Results—5,364 infants survived to NICU discharge. 557 (10%) infants were lost to follow-up, and 107 infants died following NICU discharge. Post-NICU discharge mortality rate was 22.3 per 1000 ELBW infants. In the prediction model, African-American race, unknown maternal health insurance, and hospital stay ≥120 days significantly increased risk, and maternal exposure to intra-partum antibiotics was associated with decreased risk of post-NICU discharge mortality.

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The authors declare no conflicts of intreset.

Conclusion—We identified African-American race, unknown medical insurance and prolonged NICU stay as risk factors associated with post-NICU discharge mortality among ELBW infants.

Keywords

extremely preterm infants; discharge; mortality; predictive model

Advances in perinatal care such as antenatal corticosteroids and exogenous surfactant therapy have resulted in improved survival of extremely low birth weight infants <1000 grams (ELBW) to NICU discharge.[1] The Victorian Infant Collaborative Study Group noted improved survival rate of ELBW infants up to two years of age from 25% in 1979–80 to 56.2% in 1991–2.[2] The NICHD Neonatal Research Network (NRN) has also demonstrated increased survival of ELBW infants in the 1980's to 1990's.[3] From 2000–2005, the U.S. infant mortality rate has reached a plateau at ~ 6.71 infant deaths per 1000 live births.[4] Thus, despite the improved survival to NICU discharge for ELBW infants, extreme prematurity still contributes disproportionately to the overall U.S. infant mortality rate. In the NICHD NRN, Stoll el. al. also reported a lack of progress in reducing both morbidity and mortality rates among ELBW infants.[5] Multiple studies have examined the predictors of early death and survival to NICU discharge among ELBW infants,[1, 6–9] however, information on risk factors for post-NICU discharge mortality is scarce. Factors that may affect post-NICU discharge mortality may be very different from factors that are known to affect risk of in-hospital mortality among ELBW infants.

In 2004, the median post-NICU discharge mortality for ELBW infants among 16 centers of the NICHD NRN was 3% with a range of 0–6%.[10] However, risk factors that may impact mortality after NICU discharge among ELBW infants were not explored in this study. Infant mortality has been linked to maternal health, quality and access to medical care, socioeconomic conditions and public health practices.[11] Identification of risk factors associated with post-NICU discharge mortality among ELBW infants may lead to intervention programs that may improve the overall infant mortality rate. Our hypothesis was that the risk of death following NICU discharge among ELBW infants might be related to lower maternal socio-economic status (SES), male sex, African-American race and selected neonatal morbidities. Therefore, the objectives of this study were: 1) to determine the rate of post-NICU discharge mortality in a recent cohort of ELBW infants; 2) to evaluate the different maternal and neonatal risk factors that may significantly impact post-NICU discharge mortality among ELBW infants; and 3) to develop a predictive model for post-NICU discharge mortality using significant maternal and neonatal risk factors.

Methods

This study was a retrospective cohort analysis of prospectively collected data from the NICHD NRN Generic Database Registry. Infants were included if they were born in one of the participating NRN sites between January 2000 and June 2007, with birth weight <1000 grams and gestational age <27 weeks. Trained research personnel collected maternal demographic and infant clinical data from NICU admission to discharge. Each center's Institutional Review Board approved the data collection procedures. All infants in the cohort were encouraged to attend the 18–22 months follow-up visit by phone calls and incentives. Infants who died between NICU discharge and the follow-up visit were classified as post-NICU discharge mortality. Infants who were alive at the 18–22 months follow-up visit were classified as the follow-up group.

The primary outcome was the rate of post-NICU discharge mortality among ELBW infants at 18–22 months corrected age. Predictor variables include selected maternal and infant risk

factors that we speculated may be associated with post-NICU discharge mortality. The mean age of death and days from NICU discharge to death were also determined. Causes of death were not reported as this information has not been included in the NRN database since 2005.

Statistical Analysis

The infants were grouped into those who survived to NICU discharge and were alive at 18 months follow-up, those who were lost to follow-up between discharge and 18 months and those who were known to have died after NICU discharge. The first step in the analysis compared maternal and infant characteristics between the infants in the analysis cohort (alive at 18 months follow-up and post-NICU discharge mortality group) and the lost to follow-up group. This was followed by analysis of similar variables between the group of infants alive at follow-up and those in the post-NICU discharge mortality group. Fisher exact or Chi-square test was used to compare categorical variables between groups. Student`s t-test or Wilcoxon rank-sum test was used to compare continuous variables between groups. A P value of <0.05 was considered significant. Variables that were significantly different between the post-NICU discharge mortality and the follow-up group were entered into the univariate logistic regression analysis to evaluate risk of post-NICU discharge mortality. We decided a priori to create a prediction model and then validate the model. Significant predictors for post-NICU discharge mortality were entered into the final multiple logistic regression model using 66% of the data set (selected randomly) followed by validation of the model with the remaining 34% of the data. The results were presented as odds ratio (OR) with 95% confidence intervals (CI) and the predictive ability of the model was measured using a receiver operating characteristic (ROC) curve. Statistical analyses were performed using SAS statistical software version 9.2.

Results

There were 5,364 infants discharged from the NICU; 557 (10%) infants were lost to follow-up and data on their survival status were not available. Of the 4,807 infants included in the analysis cohort, 107 (2.2%) infants died following discharge from the NICU. There were 4,700 infants who survived and were seen for the 18–22 month follow-up visit. post-NICU discharge mortality occurred at a median age (mean ± SD) of 228 (290 ± 176) days and at a median (mean ± SD) of 100 (151 ± 158) days from NICU discharge. There was no seasonal variation of deaths in the post-NICU discharge mortality group (data not shown).

Compared with the analysis cohort, mothers in the lost to follow-up group were younger, single and have Medicaid or unknown health insurance and were less likely to have prenatal care or a complete course of antenatal steroids ($P < .05$). Infants who were lost to follow-up had higher birth weight and postnatal steroid use but had a lower incidence of NEC and home oxygen use compared with the analysis cohort ($P < .05$).

In comparison with mothers in the follow-up group, mothers in the post-NICU discharge mortality group were younger, single, African-American, had less than a high school education and were less likely to have received intra-partum antibiotics or have private medical insurance (Table I; $P < .05$). Infants in the post-NICU discharge mortality group had higher prevalence of BPD, ROP (≥ Stage 3) and home oxygen use; had longer duration of mechanical ventilation and hospital days and had more individuals living with them in the household compared with those infants who were alive at follow-up (Table II; $P < .05$). Although the median discharge weight was similar between the two groups, the average weight gain per day was higher in the follow-up group compared with the post-NICU discharge mortality group ($P = 0.003$). The median post-menstrual age (PMA) at discharge

was also significantly higher among the post-NICU discharge mortality group compared with the follow-up group (43.6 vs. 39.9 weeks, $P < .0001$).

In the univariate logistic regression analysis (data not shown), maternal factors such as age <24 years, Medicaid insurance, African-American race, single marital status and less than high school education showed significantly increased odds of having an infant with post-NICU discharge mortality ($P < 0.05$). Exposure to maternal intra-partum antibiotics was associated with decreased post-NICU discharge mortality ($P < .05$). Infant predictors that showed increased odds of post-NICU discharge mortality were presence of BPD, ROP, home oxygen use, duration of ventilator use (per week), hospitalization ≥120 days and living with ≥4 individuals in the household ($P < .05$).

As shown in Table III, predictors included in the model were the following: African-American race, maternal age, health insurance, intrapartum antibiotics administration, infants' hospital stay (in days) and home oxygen use. The post-NICU discharge mortality prediction model showed significantly increased odds of post-NICU discharge mortality with African-American race, unknown health insurance and infants' hospital stay ≥ 120 days. Maternal exposure to intra-partum antibiotics remained protective for post-NICU discharge mortality. Maternal age, as well as infant discharge home on oxygen did not affect post-NICU discharge mortality in the final model. The validation of the post-NICU discharge mortality prediction model generated an ROC curve with an area under the curve (AUC) of 0.758 (Figure). Variables with missing data ranged from 0.3% to 5.4%.

Discussion

Among infants in the study cohort, post-NICU discharge mortality occurred at a rate of 22.3 per 1000 ELBW infants discharged from the hospital. In the prediction model of post-NICU discharge mortality, African-American race, infant's hospitalization ≥120 days and unknown health insurance remained significantly associated with increased risk for post-NICU discharge mortality, and maternal intra-partum antibiotic use was associated with decreased risk for post-NICU discharge mortality.

In the only other study evaluating death after NICU discharge among very low birth weight infants (VLBW), Kugelman et al reported a post discharge mortality rate of 7.5 per 1000 discharges in the post neonatal period (28 days to 1 year of age).[12] We report on smaller infants (<1000 g) and evaluates post-NICU discharge mortality over a longer period of time (up to 18–22 months corrected age).

Risk factors for infant mortality in the U.S. as well as mortality in the post neonatal period have been evaluated in other studies and have been shown to be related to social conditions.[13, 14] Singh et al examined the U.S. infant mortality rate that included VLBW infants from 1969–2001 and noted that the highest post neonatal mortality occurred in the most deprived group and in mothers with < 12 years of education.[14] The National Center for Health Statistics reported a more than 3-fold difference in infant mortality rate among non-Hispanic Black women compared with women of other racial backgrounds.[4] In a review by Bryant et al on the racial/ethnic disparities in obstetric outcomes, non-Hispanic Black women tended to have worse pregnancy and maternal outcomes.[11] Similarly, our findings showed that mothers of infants in the post-NICU discharge mortality group were predominantly African-American and more likely to have a less than high school education or to have private health insurance.

Studies on the potential genetic contributions to racial disparities in pregnancy and infant outcomes have expanded over the years as well. Hitti et al demonstrated an association of lower genital tract infection with preterm delivery of low birth weight infants among

African-American women but not in other racial groups.[15] A population based study in Atlanta by Schuchat et al showed that both early-onset and late-onset GBS disease were more common among Black infants than non-Black infants.[16] Recently, a population based surveillance of early-onset sepsis (EOS) performed by Weston et al demonstrated that Black preterm infants had the highest incidence of EOS and case fatality rate compared with non-Black term infants.[17] Racial background certainly is a non-modifiable risk factor; however, efforts should be made to identify and correct the non-genetic factors that account for the disadvantage of certain racial groups. We suggest improving educational status of childbearing women and also the accessibility and quality of health care, which can be anticipated to eventually improve the rate of post-NICU discharge mortality.

Maternal intra-partum antibiotics exposure was associated with decreased risk for post-NICU discharge mortality in both the univariate analysis and in the prediction model. Although, there was no significant difference in the incidence of clinical chorioamnionitis between the post-NICU discharge mortality and follow-up group (Table I), we speculate that histological chorioamnionitis may be under diagnosed. Chorioamnionitis has been associated with adverse neonatal outcomes in preterm infants[18, 19] and can be subclinical in as high as 50% of preterm deliveries.[20] Administration of intra-partum antibiotics in non-laboring women with preterm premature rupture of membranes (PPROM) also has been shown to prolong the latency of pregnancy and trend towards improved perinatal mortality.[21] Similarly, Stoll et al showed that mothers who did not receive intra-partum antibiotics were significantly more likely to deliver within 2 hours of admission than those who received antibiotics.[22] In the presence of chorioamnionitis, early intra-partum antibiotic therapy is associated with a reduction in maternal morbidity and neonatal infectious morbidity.[21] Because we did not have information on the time of admission to the hospital for the mothers in our registry, we are unable to speculate why intra-partum antibiotics was protective against post-NICU discharge mortality.

Neonatal morbidities such as BPD, brain injury, severe ROP and late-onset infection/NEC are common complications of extreme prematurity. These morbidities strongly predict the risk of NICU death or neurodevelopmental impairment at 18–22 months corrected age.[23, 24] Kugelman et al noted that post-discharge mortality occurring in the post neonatal period among VLBW infants was independently associated with congenital malformations, neonatal seizures, NEC and BPD.[12] Our analysis showed that among neonatal diagnoses, respiratory morbidities, severe ROP and prolonged hospital stay were associated with increased odds of post-NICU discharge mortality in the unadjusted analysis. In the prediction model, however, only hospitalization ≥ 120 days remained associated with increased risk of post-NICU discharge mortality. Prolonged hospital stay is associated with illness severity in these ELBW infants. Specific medical complications may no longer be significant in a model that accounts for all of them using this surrogate.

The strengths of this study include a large and fairly recent cohort of infants with diverse racial and socio demographic backgrounds. The rate of lost to follow-up at 18–22 months was only 10%. We also noted that mothers in the lost to follow-up group have a high risk social profile, whereas their infants had fewer neonatal morbidities. Limited access to health care may explain this lack of compliance for follow-up. Because there is limited information on risk factors associated with post-NICU discharge mortality among ELBW infants, this study and the prediction model serve as a guide for practitioners to identify high-risk infants in their practice. The prediction model has an AUC of 0.758, predicting 3 out of 4 cases correctly.

The limitations of the study are the registry's occasional missing data and the lack of information about the causes of post-NICU discharge mortality. Missing data, specifically

for important predictors (maternal education, health insurance status and number of people living in the household) may have biased the results of the study. Collecting information on socio demographic status is often a challenge and such information may have been at best, a rough measure of a person's socioeconomic well-being. Information on the cause of post-NICU discharge mortality was not collected and could have provided us important additional insight.

In conclusion, we have identified specific perinatal and socioeconomic risk factors associated with post-NICU discharge mortality among ELBW infants. African-American race, poor socioeconomic factors such as limited or no access to health insurance and prolonged hospital stay increase post-NICU discharge mortality. These data may be used to design postnatal interventions that are targeted to decrease post-NICU discharge mortality. The association of decreased risk for post-NICU discharge mortality and use of maternal antibiotics requires validation in future studies.

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Abbreviations

NRN	Neonatal Research Network
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
ROP	Retinopathy of prematurity
ELBW	Extremely low birth weight
SES	Socioeconomic status
BPD	Bronchopulmonary dysplasia
IVH	Intraventricular hemorrhage
PVL	Periventricular leukomalacia

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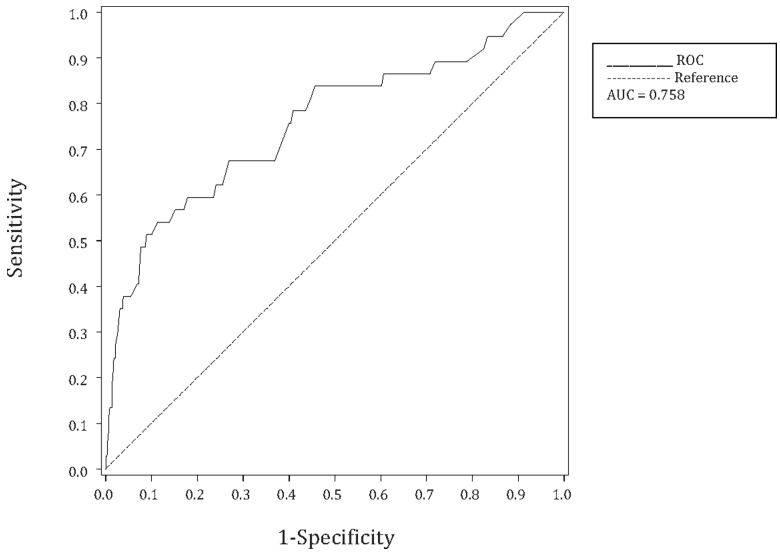

Figure 1.
ROC for P-NDM Prediction Model.

Table 1

Maternal Clinical Characteristics of the Follow-up vs. P-NDM Group

	Alive at Follow-up (n=4700)	P-NDM (n=107)	*P*-value*
Maternal age, mean (SD)	27.2 (6.5)	25.0 (6.9)	< .01**
African-American race, %	42.3	59.8	< .01**
Gravidity, median (Q1, Q3)	2 (1, 4)	2 (1, 4)	0.72#
Parity, median (Q1, Q3)	2 (1, 3)	2 (1, 3)	0.07#
Education[2] < HS diploma, %	27.4	40.7	< .01**
Marital Status, single[1], %	51.9	71.4	< .01**
Prenatal care, %	93.5	89.7	.18
Antenatal steroids, complete course, %	46.0	41.5	.41
Chorioamnionitis[3], clinical, %	4.2	4.7	.81+
Intra-partum antibiotics[4], %	72.1	60.8	.01**
PIH[5]/Eclampsia, %	18.2	22.4	.32
Antepartum Hemorrhage	20.8	17.8	.52
Health Insurance			
Medicaid, %	60.7	58.9	< .01**
Private or mix[6], %	35.1	11.2	
Unknown[7], %	4.2	29.9	

** *P*-value less than 0.05 is considered significant.

* Unless otherwise noted, *P*-values were from continuity-adjusted chi-square tests of 2×2 tables, or Pearson chi-square tests of larger tables.

P-value is from a Wilcoxon rank-sum test.

+ *P*-value is from a Fisher's exact test.

1 Married, single or unknown.

2 ≥ or < high school degree.

3 Presence of maternal temperature of ≥ 37.8°C plus ≥ 2 of the following criteria: (1) uterine tenderness; (2) malodorous vaginal discharge; (3) maternal leukocytosis (white blood cell count of >15,000 cells/mm3; and (4) fetal tachycardia (>160 beats/min]

4 Any antibiotics used during the admission resulting to delivery.

5 Systolic pressure ≥140 mm Hgor a diastolic pressure ≥90 mmHgontwo occasions 2 to 24 hours apart

6 Some mix of private insurance and public insurance.

7 Method of payment is not yet known at the time of data collection.

Table 2

Infant Clinical Characteristics of the Follow-up vs. P-NDM Group

	Alive at Follow-up (n=4700)	P-NDM (n=107)	*P*-value*
Gestational age[1], wks, mean (SD)	25 (1)	24.8 (1)	0.21
Birth weight, g, mean (SD)	746 (130)	724 (143)	0.09
Male Sex, %	49.4	54.2	0.38
Surfactant administration, %	89.5	89.7	1.00
Mechanical ventilator days, mean (SD)	36 (28)	51 (34)	< .01**
BPD[2] (O_2 at 36 wks PCA), %	57.0	71.0	< .01**
Home O_2 Use, %	32.7	50.5	< .01**
Postnatal steroid use, %	24.6	29.5	0.29
Grade III-IV IVH[3], %	15.9	19.4	0.39
ROP stage III or greater, %	29.4	40.2	0.02**
Proven NEC[4], %	9.5	11.3	0.65
Late onset sepsis[5], %	45.7	54.2	0.09
Late onset meningitis[5], %	4.6	1.9	0.24
Hospital days[6], median (Q1, Q3)	103 (86, 125)	126 (96, 159)	< .0001**#
Discharge Weight, g, median (Q1, Q3)	2525 (2145, 2965)	2500 (2255, 3095)	0.335#
Avg weight gain (g)/day, median (Q1, Q3)	17.5 (14.1, 20.8)	15.4 (11.4, 20.2)	0.003**#
PMA at Discharge, wks, median (Q1, Q3)	39.9 (37.9, 42.7)	43.6 (38.9, 48.4)	<.001**#
Living arrangement at discharge[7]			
≤ 2 individuals, %	4.9	5.3	0.06
3 or 4 individuals, %	57.3	44.0	
> 4 individuals, %	37.8	50.7	

** *P*-value less than 0.05 is considered significant.

* Unless otherwise noted, *P*-values were from continuity-adjusted chi-square tests of 2×2 tables, or Pearson chi-square tests of larger

P-value is from a Wilcoxon rank-sum test.

[1] Determined by best obstetric estimate.

[2] Oxygen use at 36 weeks postmenstrual age.

[3] Defined based on Papile's classification.

[4] Defined by Bell's staging.

[5] Based on culture proven blood and cerebrospinal fluid infection.

[6] Calculated as the number of days between birth and the final known status date. This also includes the time spent at another hospital or chronic care facility.

[7] Planned living arrangement for the infant at discharge was classified as ≤ 2, 3–4 and > 4 individuals living in the household.

Table 3

Logistic Regression Model of Predictors Associated with P-NDM

Predictor	Odds Ratio	95% CI	*P*-value
African-American race	1.95	(1.16, 3.29)	0.012
Maternal age			
< 24 vs. 24–35	1.54	(0.89, 2.66)	0.302
> 35 vs. 24–35	1.22	(0.53, 2.82)	
Insurance[1]			
Medicaid vs. private[2]	1.65	(0.76, 3.57)	<.0001
Unknown vs. private insurance	14.23	(6.07, 33.37	
Intra-partum antibiotics	0.53	(0.32, 0.87)	0.013
Discharged home on oxygen	1.19	(0.71, 2.00)	0.509
Hospitalization (days)			
≥ 120 vs. < 120	2.78	(1.59, 4.85)	0.0003

[1]Missing data - 4.8% of study cohort.

[2]This category included private insurance or a mix of public and private insurance.