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Predicting Time to Hospital Discharge for Extremely Preterm Infants

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Abstract

As extremely preterm infant mortality rates have decreased, concerns regarding resource utilization have intensified. Accurate models to predict time to hospital discharge could aid in resource planning, family counseling, and perhaps stimulate quality improvement initiatives.

Objectives—For infants <27 weeks estimated gestational age (EGA), to develop, validate and compare several models to predict time to hospital discharge based on time-dependent covariates, and based on the presence of 5 key risk factors as predictors.

Patients and Methods—This was a retrospective analysis of infants <27 weeks EGA, born 7/2002–12/2005 and surviving to discharge from a NICHD Neonatal Research Network site. Time to discharge was modeled as continuous (postmenstrual age at discharge, PMAD), and categorical variables (“Early” and “Late” discharge). Three linear and logistic regression models with time-dependent covariate inclusion were developed (perinatal factors only, perinatal+early neonatal factors, perinatal+early+later factors). Models for Early and Late discharge using the cumulative presence of 5 key risk factors as predictors were also evaluated. Predictive capabilities were compared using coefficient of determination (R^2) for linear models, and AUC of ROC curve for logistic models.

Results—Data from 2254 infants were included. Prediction of PMAD was poor, with only 38% of variation explained by linear models. However, models incorporating later clinical characteristics were more accurate in predicting “Early” or “Late” discharge (full models: AUC 0.76–0.83 vs. perinatal factor models: AUC 0.56–0.69). In simplified key risk factors models, predicted probabilities for Early and Late discharge compared favorably with observed rates. Furthermore, the AUC (0.75–0.77) were similar to those of models including the full factor set.

Conclusions—Prediction of Early or Late discharge is poor if only perinatal factors are considered, but improves substantially with knowledge of later-occurring morbidities. Prediction using a few key risk factors is comparable to full models, and may offer a clinically applicable strategy.

Introduction

Survival rates among even the most premature infants have improved remarkably over the past decades (1–3). However, substantial concerns remain regarding the costs of initial hospitalization for these high-risk infants (4). Resource use during initial hospitalization among extremely preterm infants is complex, determined by multiple factors, and differs markedly among risk groups (5–7). Although there are many costs associated with premature delivery

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during and after initial hospital discharge, length of initial hospital stay is a strong marker for resource utilization in general. (8)

Hospitalization-associated costs are significantly higher, and lengths of stay (LOS) are more than six times greater for extremely preterm infants than for late preterm infants (9,10). Accurate prediction of the length of initial hospitalization could improve long-term complex institutional resource planning, medical provider-insurance company interface, and appropriate counseling for families. Predictive modeling for LOS may also identify modifiable risk factors for prolonged hospitalization, and such information could translate to hospital-based quality improvement initiatives. However, there is little in the literature investigating LOS prediction in this high-risk patient population. Previous analyses have been small single-center studies, included earlier birth cohorts, or broad gestational age ranges (11-13). Other studies have focused on effects of specific morbidities on LOS, or explored variables associated with a pre-specified LOS (14-18). These studies utilized logistic and linear regression to identify risk factors rather than development of true predictive models to compare capabilities of models with differing factor profiles. True predictive models could be used to determine whether length of hospitalization can be predicted with equal accuracy from earlier or later events.

Length of stay is an increasingly pertinent short-term outcome for extremely preterm infants. In this analysis of National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) data, we assessed the continuous outcome of postmenstrual age (PMA) at discharge, and the categorical outcomes “Early Discharge” and “Late Discharge” (defined as lowest and highest quartile PMA) among infants <27 weeks estimated gestational age (EGA) born at and surviving to discharge from a NRN site. We constructed three multivariate predictive models for each LOS-related outcome, including risk factors known at different times during hospitalization in each model, and compared the predictive capabilities of these models. We also developed simplified models based on the presence of 5 key risk factors to assess observed and predicted probabilities of Early or Late discharge, and to compare predictive capabilities of these streamlined models with more complex multivariate models.

Methods

Study design and patient population

This was a retrospective analysis of prospectively collected data from the NICHD NRN Registry. Infants were included if they were born July 1 2002 to December 31 2005, <27 weeks estimated gestational age (EGA), inborn at a NRN site, and survived to discharge to home from a NRN site. Infants were excluded if chromosomal or congenital anomalies were proven or suspected, if they remained in the hospital at 1 year of age, if they were transferred to a non-NRN site, or discharged to a long-term care facility.

Data from NICHD NRN centers that participated during the entire study period were used in the analysis. Each center's Institutional Review Board (IRB) reviewed and approved the data collection procedures. Research nurses collected demographic, perinatal and infant data at each center using common definitions developed by the investigators and described in previous publications (1,2). Estimated gestational age (EGA) was determined by best obstetric estimate. Antenatal antibiotics (AABX) were administration of any antibiotics to the mother during the admission that resulted in delivery. Antenatal steroids (ANS) were defined as administration of any corticosteroids to accelerate fetal lung maturity in the present pregnancy. Surfactant treatment was defined as at least one dose of any surfactant. Intraventricular hemorrhage (IVH) was reported according to the classification of Papile, et. al. (19). Cystic periventricular leukomalacia (cPVL) was diagnosed by cranial ultrasound (CUS). Early sepsis was defined as

culture-proven sepsis in the first 72 hours, treatment with antibiotics for at least 5 days beginning by 72 hours for presumed sepsis regardless of culture result, or culture-proven sepsis from 72 hours to <7 days and treated with at least 5 days of antibiotics. Late sepsis was defined as culture proven sepsis from 7 days of age to discharge and treated with antibiotics for at least five days. Necrotizing enterocolitis (NEC) was modified Bell's classification stage IIA or higher (20). Retinopathy of prematurity (ROP) stage III or greater in either eye was evaluated for this analysis. Bronchopulmonary dysplasia (BPD) was defined as requiring supplemental oxygen or positive pressure ventilation including CPAP at 36 weeks PMA. Postnatal steroids (PNS) were any corticosteroid given for the prevention or treatment of BPD. Surgery performed during NICU stay for patent ductus arteriosus (PDA), NEC, or ROP was noted.

Variable grouping

The variables were grouped based on likely timing during the hospital course, although exact timing of event was not recorded. **“Perinatal”** variables were those known at the time of delivery: NRN center, level of maternal education, mother's insurance, multiple gestation, gender, race, birth weight (≤ 750 g vs. > 750 g), rupture of membranes > 24 hours, ANS, AABX, delivery mode, chest compressions and/or drugs for resuscitation in the delivery room, and Apgar score < 3 at 5 minutes. **“Early Neonatal”** variables included: early sepsis, need for oxygen from 6 hours to at least 24 hours of age, need for respiratory support including mechanical ventilation and/or CPAP at 24 hours of age, pneumothorax, surfactant, indomethacin at < 24 hours of age, diagnosis of PDA, and IVH grade 3 or 4. **“Later Neonatal”** variables included: one or more episodes of late sepsis, NEC, use of conventional or high frequency ventilator (HFV) any time during hospitalization, cPVL, PNS, BPD, stage 3 ROP, shunt or other device for hydrocephalus, and surgery for ROP or NEC or PDA. Because some events and treatments such as sepsis or mechanical ventilation could have occurred at any time or multiple times during hospitalization, they were included as part of the “Later Neonatal” variable set.

Analysis

The study sample was randomly divided into a development sample (1,573 patients, 70%), used to develop models for predicting length of hospital stay; and a validation sample (681 patients, 30%), used to validate the models.

Because the clinical issues and discharge concerns may vary across gestational ages, patients were also grouped by EGA: (1) 22 +0/7 to 24+6/7 weeks EGA, and (2) 25 to 26+6/7 weeks EGA. Gestational age groups were characterized in terms of PMA in days at time of discharge. Discharge groups were then further characterized as categorical outcome variables; “Early Discharge” was defined as membership in the 1st quartile (lowest) of age at discharge, and “Late Discharge” as membership in the 4th quartile (highest) of age at discharge.

Three approaches were used to select and validate models for predicting time to hospital discharge. First, time to discharge was modeled as a continuous variable. We conducted t-tests and analyses of variance to compare length of stay by the perinatal, early neonatal, and later neonatal variables listed above. Variables were included in a series of backward stepwise regression models predicting PMA at discharge with variable retention criterion of $p < 0.10$. To determine how soon after birth we can accurately PMA at discharge, we ran three sets of stepwise regression models which included (1) Perinatal variables only, (2) Perinatal + Early Neonatal variables, and (3) Perinatal + Early Neonatal + Later Neonatal variables. Using the final set of variables, we conducted linear mixed effect models to predict PMA at discharge with NRN center as a random effect to account for clustering of infants within centers.

Second, time to discharge was modeled as a categorical variable. Using the developmental sample, we ran a series of stepwise logistic regression models predicting Early and Late Discharge for the three sets of variables described above. After identifying the final models, we conducted generalized linear mixed effect models to account for clustering within center. We then conducted receiver operating characteristic (ROC) curve analyses using the predicted probabilities from the generalized linear mixed models to predict timing of discharge in the validation sample.

Third, we explored how well the presence of only a few key risk factors predicted time to discharge. To enhance potential clinical applicability, we determined *a priori* to limit analysis to five categorical variables. The following risk factors were used in this analysis: (1) BW <750 g, (2) at least one late sepsis episode or proven NEC, (3) ROP stage 3 or more severe, (4) surgery for PDA, NEC, or ROP, and (5) BPD. Using the development sample, we developed generalized linear models for Early and Late Discharge using the cumulative number of factors present (0 to 5) as predictors. We then used the validation sample to assess the predictive validity of the models based on area under the curve (AUC) of the ROC curves.

Results

Study group

During the study period, 4185 infants <27 weeks EGA were born at one of 16 NRN sites. Figure 1 shows the flow of patients from delivery to inclusion in study group. Of the 4062 infants born at a NRN site, death occurred in 738/922 (80.0%) 22-23 week EGA, 438/984 (44.5%) 24 week EGA, 282/1024 (27.5%) 25 week EGA, and 160/1132 (14.1%) 26 week EGA infants. Of the 2254 patients in the study group, 166 were 22-23 weeks EGA, 516 were 24 weeks EGA, 676 were 25 weeks EGA and 896 were 26 weeks EGA. The number of subjects contributed by each site to the study sample ranged from 65 to 243.

Characterizing time to hospital discharge

Table 1 characterizes PMA at discharge by quartiles for gestational age groups. For 22-24 week EGA infants, 98% of observations fell between 242-473 days PMA at discharge; for 25-26 week EGA infants, 98% of observations fell between 235-409 days PMA at discharge.

Predicting hospital discharge as a continuous variable: PMA in days at discharge

Model statistics for all time-based models as tested on the validation sample (Table 2) demonstrate coefficients (R^2) of less than 0.4, even in models including the complete variable set.

Predicting hospital discharge as Early or Late Discharge

Logistic regression analyses for Early Discharge and Late Discharge, modeled on the development sample, are shown in Tables 3 and 4. For both Early and Late Discharge models, variables statistically significant in early steps of model development did not always remain significant as later occurring variables were added in subsequent steps. Birth weight remained a significant factor in all full models except the 22-24 week Late Discharge model. For 25-26 week EGA models, late sepsis, BPD, PNS, ROP stage 3 and surgery were significantly inversely associated with Early Discharge (Table 3) and positively associated with Late Discharge (Table 4) in full models.

ROC curve analyses were conducted using these final models, validity was tested on the validation sample, and predictive capabilities were compared by AUC of the ROC curve (Table 5). In models including Perinatal variables alone, AUC ranged from 0.56-0.69. There was little difference in predictive capabilities between models that included Perinatal variables alone

and those that included Perinatal+Early Neonatal variables. However in full models including Later neonatal morbidities, AUC was substantially improved and ranged from 0.76 to 0.83.

Predicting Early or Late Discharge by counting the presence of key risk factors

In these analyses, we investigated whether the number of key factors present (from 0-5) could effectively predict discharge category. Table 6 shows the observed rates of Early and Late Discharge by gestational age in each factor count category, results of logistic regression (development sample), and prediction performance in the validation sample. Compared to infants who had none or only 1 risk factor, those with 3 risk factors had a 7- to 8-fold increase in the odds of Late Discharge, while those with 4-5 factors had a 8- to 11-fold increase. Conversely, the odds of Early Discharge were cut in half for infants with only 2 factors compared with those with 0-1 factors. The predicted probabilities for Early and Late Discharge in each of the factor count categories compared favorably with the observed rates in both EGA groups. Furthermore, the validity of the predictive models developed on the number of key factors present as described by the AUC of the ROC curves (validation sample) was similar to that of the full models developed using the full variable set that included Perinatal+Early +Later neonatal factors (Table 5).

Discussion

In this analysis of time to hospital discharge among surviving infants <27 weeks EGA, we found that prediction of exact PMA in days at time of discharge was poor, even in models including the complete variable set. Prediction of Early or Late discharge group was poor if only perinatal variables were considered, but improved substantially with addition of later-occurring events and morbidities. Predictive modeling of Early and Late discharge using the count of a small number of key risk factors was comparable to full regression models. Utilizing a streamlined model may prove to be a practical and clinically applicable predictive strategy.

Length of hospital stay and initial hospitalization costs for this extremely preterm group are grossly disproportionate to their contribution to total preterm admissions. Nationwide, hospital admissions for infants <28 weeks are estimated to account for only 8% of all low birth weight stays, yet incur approximately one-third of the total hospitalization costs for low birth weight hospitalization (9). In a California population-based study, VLBW births accounted for only 0.9% of cases, but 35.7% of hospital costs (21). Development of reliable time to discharge models could be a necessary first step for delineating potentially modifiable risk factors associated with extended stays, which could lead to targeted quality improvement initiatives. Unfortunately, with increasing emphasis on outcomes based evaluation of hospital performance, there may be a temptation to use length of stay as a “quality marker” in and of itself. But there is a grave danger that this approach may lead to unsafe and inappropriately early discharge practices for this extremely high-risk patient population; our analysis should not be used to support such practices. Rather, our findings should encourage implementation of hospital-based programs to avoid the complications associated with prolonged hospital stays.

Our analyses suggest that accurate prediction of exact PMA at discharge is unlikely for this extremely preterm patient population, although prediction of “Early” or “Late” discharge appears to be feasible. The predictive validity of full models was very good to excellent, with point estimates for the AUC of the ROC curves ranging up to 0.83. However, in models including only Perinatal variables, AUC point estimates were as low as 0.64. From both the family and medical provider viewpoints, it would be beneficial if accurate length of stay estimates could be made early in the course of the hospitalization. But, it is clear from all our models indicate that later-observed variables are critical to optimal discharge prediction. Thus, family counseling regarding time to discharge may be neither reliable nor advisable until later

in the hospital stay, and certainly not based on perinatal variables alone. Nevertheless, we believe our findings will help physicians prepare families for longer than anticipated stays in a data-driven fashion, with the occurrence of each risk factor throughout the hospitalization.

Importantly, the predictive capabilities of models using the number of 5 key risk factors present as variables were similar to those of full regression models. Furthermore, these models demonstrated that having a high count or very low count of key adverse variables made membership in the Early or Late discharge groups highly improbable, respectively. For instance, in the 25-26 week group, having 4-5 factors was associated with only a 1% predicted rate of Early discharge, whereas having 0-1 factors was associated with a 10% predicted rate of Late discharge. Other investigators have explored this type of “key factor count” methodology in the context of different outcomes. Schmidt, et. al. (22) reported a linear relationship between the count of 3 neonatal morbidities and death or neurodevelopmental impairment at 18-22 months. Doyle, et. al. (23) reported that survival to 5 years without sensorineural disability was related to the number of four adverse variables experienced during the neonatal hospitalization. Prospective application and testing of such models would be an important next step to establishing their true relevance and validity for hospital discharge prediction.

Our analysis excluded patients that died before discharge. From a global perspective of societal burden due to hospitalization costs, it would be reasonable to evaluate total number of hospital days and total hospitalization costs including both survivors and non-survivors (9,10,21). However our analysis was focused on evaluating whether accurate prediction of time to discharge was possible among extremely preterm infants who would survive. This objective grew from several points of view. From the perspective of family counseling, conversations related to the central questions of survival and LOS are usually directed independently, and those outcomes can be estimated separately. In fact, we found that 91% of 22-24 week EGA deaths and 78% of 25-26 week EGA deaths occurred by 28 days. Furthermore, our analysis demonstrates that knowledge of later morbidities is important to achieving optimal predictive models for time to discharge; many of these morbidities are observed beyond the time point when the great majority of deaths would have already occurred.

There are limitations to our analysis. This analysis includes only inborn patients of centers participating in the NICHD NRN during the study period; thus, our findings may not be generalizable to all institutions. Interpretation of multi-center analyses is also challenging due to care approach differences between sites. Because differences are difficult to precisely quantify, we attempted to address this limitation by controlling for center in our multivariable analyses and models. Optimally, every hospital caring for extremely preterm infants would construct predictive models for its own patient population. However, in our analysis we found that the number of patients contributed to the study sample by individual sites was as low as 65 over the 3 ½ year study period, so it would be difficult for all but the largest centers in the United States to develop robust models. In any case, with respect to resource utilization forecasts, it is likely that most hospitals simply base their budget projections on previous years rather than attempting more complex predictions. We excluded patients who transferred to other hospitals prior to discharge because transfer patterns and access to local intermediate care units were likely to vary and be inconsistent during the study period and among sites, and complete length of stay data were not available for all transferred patients. However, only 7% (179/2444) of survivors were transferred prior to discharge, so the impact of this approach may be limited.

This analysis furthers efforts to understand and better predict length of initial hospital stay among extremely preterm infants. Our findings underscore the difficulty in precise prediction of time to discharge, but provide evidence that estimation of early or late discharge may be

possible with knowledge of later-occurring morbidities. Importantly, several of these morbidities, including late sepsis, BPD, NEC, and surgery during neonatal hospitalization have also been shown to be independently associated with neurodevelopmental impairment in early childhood (24-27). Some of these determinant neonatal factors may be modifiable, resulting in shorter hospital stays and improved outcomes (28). Future research should focus not only on refining and prospectively testing predictive models, but also on interventions to ameliorate in-hospital morbidity to improve short- and long-term outcomes.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Carla M. Bann (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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References

1. Fanaroff AA, Stoll BJ, Wright LL, et al. NICHD Neonatal Research Network. Trends in morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007;196:147 e1–147 e8. [PubMed: 17306659]
2. Lemons JA, Bauer CR, Oh W, et al. NICHD Neonatal Research Network. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics* 2001;107:e1–e8. [PubMed: 11134465]
3. Hintz SR, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. *ADC Fetal and Neonatal* 2005;90:F128–F133.
4. Gilbert WM, Nesbitt TS, Danielsen B. The cost of prematurity: Quantification by gestational age and birth weight. *Obstet Gynecol* 2003;102:488–92. [PubMed: 12962929]
5. Kilpatrick SJ, Schlueter MA, Piecuch R, Leonard CH, Rogido M, Sola A. Outcome of infants born at 24–26 weeks gestation: I. Survival and cost. *Obstet Gynecol* 1997;90:803–808. [PubMed: 9351768]
6. Chan K, Ohlsson A, Synnes A, Lee DSC, Chien LY, Lee SK, Canadian Neonatal Network. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol* 2001;185:220–226. [PubMed: 11483932]
7. Tyson JE, Younes N, Verter J, Wright LL, NICHD Neonatal Research Network. Viability, morbidity and resource use among newborns of 501–800 g birth weight. *JAMA* 1996;276:1645–1651. [PubMed: 8922450]
8. Slonim AD, Marcin JP, Pollack MM. Long-stay patients: Are there any long-term solutions? *Critical Care Medicine* 2003;31:313–314. [PubMed: 12545038]
9. Russell RB, Green NS, Steiner CA, Meikle S, Howse JL, Paschman K, Dias T, Potetz L, Davidoff MJ, Damus K, Petrini JR. Cost of hospitalization for preterm and low birth weight infants in the United States. *Pediatrics* 2007;120:e1–e9. [PubMed: 17606536]
10. Ringborg A, Berg J, Norman M, Westgren M, Jonsson B. Preterm birth in Sweden: What are the average lengths of hospital stay and the associated inpatient costs? *Acta Paediatrica* 2006;95:1550–1555. [PubMed: 17129960]
11. Jijon CR, Jijon-Letort FX. Perinatal predictors of duration and cost of hospitalization for premature infants. *Clin Pediatr* 1995;34:79–85.
12. Zernikow B, Holtmannspotter K, Michel E, Hornschuh F, Groote K, Hennecik KH. Predicting length-of-stay in preterm neonates. *Eur J Pediatr* 1999;158:59–62. [PubMed: 9950310]

13. Profit J, McCormick MC, Escobar GJ, Richardson DK, Zheng Z, Coleman-PHox K, Roberts R, Zupancic JAF. Neonatal intensive care unit census influences discharge of moderately preterm infants. *Pediatrics* 2007;119:314–318. [PubMed: 17272621]
14. Rawlings JS, Scott JS. Postconceptional age of surviving preterm low birth weight infants at hospital discharge. *Arch Pediatr Adolesc Med* 1996;150:260–262. [PubMed: 8603218]
15. Ferlauto JJ, Walker MW, Martin MS. Clinical significant gastroesophageal reflux in the at-risk premature neonate: Relation to cognitive scores, days in the NICU and total hospital charges. *J Perinatol* 1998;18:455–459. [PubMed: 9848760]
16. Eichenwald EC, Blackwell M, Lloyd JS, Tran T, Wilker RE, Richardson DK. Inter-neonatal intensive care unit variation in discharge timing: Influence of apnea and feeding management. *Pediatrics* 2001;108:928–933. [PubMed: 11581446]
17. De Courcy-Wheeler RHB, Wolfe CDA, Fitzgerald A, Spencer M, Goodman JDS, Gamsu HR. Use of the CRIB score in prediction of neonatal mortality and morbidity. *Arch Dis Child Fetal Neonatal Ed* 1995;73:F32–F36. [PubMed: 7552593]
18. Cotten CM, Oh W, McDonald S, Carlo W, Fanaroff AA, et al. Prolonged hospital stay for extremely preterm infant: Risk factors, center differences and the impact of mortality on selecting a best-performing center. *J Perinatol* 2005;25:650–655. [PubMed: 16079906]
19. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a case study of infants with birth weights less than 1500 g. *J Pediatr* 1978;92:529–534. [PubMed: 305471]
20. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin N Am* 1986;33:179–201.
21. Schmitt SK, Sneed L, Phibbs CS. The cost of newborn care in California: A population-based study. *Pediatrics* 2006;117:154–160. [PubMed: 16396873]
22. Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF, et al. TIPP investigators. Impact of bronchopulmonary dysplasia, brain injury and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months. Results of the Trial of Indomethacin Prophylaxis in Preterms. *JAMA* 2003;289:1124–1129. [PubMed: 12622582]
23. Doyle LW, Victorian Infant Collaborative Study Group. Outcome at 5 years of age of children 23 to 27 weeks' gestation: Refining the prognosis. *Pediatrics* 2001;108:134–141. [PubMed: 11433066]
24. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD, NICHD Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–2365. [PubMed: 15547163]
25. Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF, Poole WK, Blakely ML, Wright L, Higgins R, NICHD Neonatal Research Network. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. *Pediatrics* 2005;115:696–703. [PubMed: 15741374]
26. Vohr BR, Wright LL, Poole WK, McDonald SA, NICHD Neonatal Research Network. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation born between 1993–1998. *Pediatrics* 2005;116:635–643. [PubMed: 16143580]
27. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A, TIPP Investigators. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: Results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007;150:229–234. [PubMed: 17307535]
28. Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor HG, Schluchter M, Hack M. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. *Pediatrics* 2007;119:37–45. [PubMed: 17200269]

Abbreviations

NRN	Neonatal Research Network
LOS	length of stay
PMA	postmenstrual age

EGA	estimated gestational age
ROC	receiver operating characteristic
AUC	area under the curve
BPD	bronchopulmonary dysplasia
PNS	postnatal steroids
ROP	retinopathy of prematurity

Figure 1.
Flow of <27-week EGA infants from delivery at a NRN site to inclusion in study group.

Table 1
Postmenstrual age (PMA) in days at discharge categories by gestational age group

Quartile	PMA in days at discharge	N (% in GA group)
22-24 weeks EGA		
1 st quartile	≤ 273 days	177 (26)
2 nd quartile	274-287 days	167 (24)
3 rd quartile	288-311 days	168 (25)
4 th quartile	≥ 312 days	170 (25)
25-26 weeks EGA		
1 st quartile	≤ 260 days	416 (26)
2 nd quartile	261-274 days	385 (24)
3 rd quartile	275-292 days	391 (25)
4 th quartile	≥ 292 days	380 (24)

Table 2
Model statistics for linear mixed effect models of postmenstrual age at hospital discharge (Validation sample)

Variables	Model (EGA group)					
	22-24 weeks			25-26 weeks		
	N	R ²	N	N	R ²	N
Perinatal	203	0.06	477	477	0.08	
Perinatal + Early neonatal	201	0.07	475	475	0.21	
Perinatal + Early + Late neonatal	203	0.23	475	475	0.38	

Table 3
Generalized linear models for Early Discharge by EGA and variable grouping[‡]

Model	22-24 weeks EGA				25-26 weeks EGA			
	Variable	OR	95% CI	P value	Variable	OR	95% CI	P value
Perinatal only	Male	0.45	0.29, 0.71	< .001	Male	0.60	0.45, 0.80	< .001
	BW>750 g	3.23	1.82, 5.71	< .001	BW>750 g	3.92	2.71, 5.67	< .001
	Black*	1.72	1.10, 2.68	.017	Multiple birth	0.67	0.47, 0.97	.035
					Black*	1.59	1.17, 2.16	.003
					CPR, drugs in DR	0.42	0.23, 0.77	.005
Perinatal + Early Neonatal					No insurance [‡]	1.84	1.07, 3.14	.027
	Male	0.45	0.29, 0.71	< .001	Male	0.60	0.44, 0.80	< .001
	BW>750 g	3.09	1.73, 5.53	< .001	BW>750 g	3.95	2.71, 5.75	< .001
	Black*	1.66	1.06, 2.62	.027	Black*	1.52	1.11, 2.09	.009
	Surfactant	0.54	0.26, 1.14	.106	CPR, drugs in DR	0.47	0.25, 0.86	.014
Perinatal + Early+ Late Neonatal	PDA	0.49	0.31, 0.77	.002	No insurance [‡]	0.40	0.29, 0.54	.012
					Respiratory support at 24 hours	2.02	1.17, 3.51	.004
					PDA	0.43	0.12, 1.55	< .001
	Male	0.53	0.33, 0.86	.011	BW>750 g	2.27	1.51, 3.42	< .001
	BW>750 g	2.27	1.20, 4.29	.012	PDA	0.65	0.46, 0.93	.018
	Late sepsis	0.51	0.31, 0.81	.005	HFV	0.45	0.27, 0.77	.003
	BPD	0.21	0.12, 0.35	< .001	Conventional vent	0.55	0.29, 1.01	.055
	Surgery	0.45	0.27, 0.73	.002	Late sepsis	0.51	0.35, 0.73	< .001
					BPD	0.24	0.16, 0.36	< .001
					PNS	0.39	0.18, 0.82	.014
					NEC	0.27	0.08, 0.99	.048
					ROP stage 3	0.27	0.13, 0.59	< .001
					Surgery**	0.36	0.19, 0.66	.001

* Referant value = all non-Black;

[†] Mother's insurance; referant value = Private insurance;

^{**} Surgery for NEC, ROP or PDA;

[‡] All models controlled for clustering within NRN centers. Variable selection was based on backwards stepwise logistic regression and therefore, models may contain different sets of variables

Table 4
Generalized linear models for Late Discharge by EGA and variable grouping**

Model	22-24 weeks EGA				25-26 weeks EGA			
	Variable	OR	95% CI	P value	Variable	OR	95% CI	P value
Perinatal only	BW>750 g	0.36	0.16, 0.78	.010	Male	1.84	1.36, 2.48	< .001
					BW>750 g	0.34	0.25, 0.46	< .001
					5 minute Apgar<3	1.93	0.97, 3.85	.061
					AABX	0.74	0.53, 1.02	.065
					CPR, drugs in DR	1.69	1.01, 2.81	.044
Perinatal + Early Neonatal	BW>750 g	0.30	0.13, 0.68	.004	Male	1.89	1.39, 2.56	< .001
	IVH grade 3 or 4	1.84	1.16, 2.92	.010	BW>750 g	0.34	0.25, 0.46	< .001
					AABX	0.72	0.52, 1.00	.053
					CPR, drugs in DR	1.83	1.14, 2.93	.012
					Respiratory support at 24 hours	3.42	1.18, 9.89	.023
					Pneumothorax	2.84	1.62, 4.97	< .001
					PDA	1.50	1.11, 2.04	.008
Perinatal + Early+ Late Neonatal	HFV	1.71	1.00, 2.94	.052	Male	1.48	1.05, 2.07	.026
	BPD	5.18	2.49, 10.79	< .001	BW>750 g	0.49	0.35, 0.70	< .001
	Surgery†	2.86	1.64, 5.00	< .001	AABX	0.67	0.46, 0.96	.031
					HFV	1.53	1.06, 2.21	.024
					Late sepsis	1.45	1.04, 2.01	.028
					BPD	4.17	2.84, 6.13	< .001
					PNS	1.67	1.06, 2.62	.026
					ROP stage 3	1.69	1.10, 2.56	.014
					Surgery†	2.73	1.85, 4.03	< .001

* AABX=antibiotics

† Surgery for NEC, ROP or PDA

** All models controlled for clustering within NRN centers. Variable selection was based on backwards stepwise logistic regression and therefore, models may contain different sets of variables.

Table 5
Classification Statistics for ROC Models (Validation Sample)

Model	Variables	AUC (95% CI)
22-24 Weeks		
Early Discharge	Perinatal	0.67 (0.59, 0.75)
	Perinatal + Early	0.69 (0.61, 0.77)
	Perinatal + Early + Late	0.83 (0.77, 0.89)
Late Discharge	Perinatal	0.56 (0.48, 0.65)
	Perinatal + Early	0.59 (0.51, 0.68)
	Perinatal + Early + Late	0.76 (0.69, 0.84)
25-26 Weeks		
Early Discharge	Perinatal	0.69 (0.64, 0.74)
	Perinatal + Early	0.72 (0.67, 0.77)
	Perinatal + Early + Late	0.82 (0.78, 0.86)
Late Discharge	Perinatal	0.64 (0.54, 0.70)
	Perinatal + Early	0.69 (0.63, 0.75)
	Perinatal + Early + Late	0.81 (0.77, 0.86)

Table 6
Key factor count models* for Early and Late Discharge: Generalized linear models, observed and predicted probabilities, and model statistics

MODEL # of factors	Observed rate	Predicted rate (95% CI)	OR	95% CI	P	AUC [†]
EARLY DISCHARGE						
22-24 week EGA						
4-5	0.10	0.10 (0.05, 0.17)	0.10	0.05, 0.21	< .001	0.75
3	0.17	0.17 (0.10, 0.26)	0.18	0.10, 0.34	< .001	
2	0.31	0.34 (0.24, 0.45)	0.47	0.27, 0.81	.007	
0-1	0.48	0.52 (0.41, 0.63)	REF			
25-26 week EGA						
4-5	0.01	0.01 (0.00, 0.05)	0.02	0.00, 0.07	< .001	0.77
3	0.10	0.10 (0.03, 0.06)	0.13	0.08, 0.22	< .001	
2	0.23	0.23 (0.17, 0.30)	0.37	0.27, 0.51	< .001	
0-1	0.43	0.44 (0.37, 0.52)	REF			
LATE DISCHARGE						
22-24 week EGA						
4-5	0.37	0.36 (0.26, 0.47)	7.86	3.54, 17.43	< .001	0.76
3	0.38	0.36 (0.27, 0.47)	8.03	3.66, 17.58	< .001	
2	0.16	0.15 (0.09, 0.24)	2.49	1.06, 5.87	.037	
0-1	0.08	0.07 (0.03, 0.13)	REF			
25-26 week EGA						
4-5	0.54	0.55 (0.44, 0.65)	11.13	6.91, 17.93	< .001	0.76
3	0.43	0.43 (0.33, 0.53)	6.85	4.44, 10.56	< .001	
2	0.23	0.21 (0.15, 0.28)	2.87	1.65, 3.70	< .001	
0-1	0.11	0.10 (0.07, 0.14)	REF			

* Variable represents the cumulative number of the following factors present: BW <750 grams; one or more episode of late sepsis or proven NEC; ROP stage 3 or more severe; BPD; surgery for PDA, NEC or ROP. All models controlled for clustering of patients within NRN centers.

[†] Validation sample