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Unimpaired Outcome in Extremely Low Birth Weight Infants at 18–22 Months

Regina A. Gargus, MD¹, Betty R. Vohr, MD^{2,3}, Jon E Tyson, MD⁴, Pamela High, MD^{3,5}, Rosemary D. Higgins, MD⁶, Lisa A. Wrage, MPH⁷, and Kenneth Poole, PhD⁷

¹University of Arkansas Medical Sciences, Little Rock, AR

²Women and Infants Hospital

³The Warren Alpert Medical School of Brown University

⁴University of Texas Houston Medical School

⁵Hasbro Children's Hospitals

⁶Neonatal Research Network, National Institute of Child Health and Human Development

⁷RTI International

Abstract

Background—To identify among extremely low birth weight (≤ 1000 grams) live births, the percent of infants who are unimpaired at 18–22 months corrected age.

Methods—Unimpaired outcome was defined as both Bayley-II MDI and PDI Scores ≥ 85 , a normal neurological exam, normal vision, normal hearing and normal swallowing and ambulating. Outcomes at 18–22 months were determined for 5250 (86%) of 6090 ELBW inborn infants. Group comparisons were made and regression models were developed to identify factors associated with unimpaired outcome.

Results—Of the 5250 infants whose outcome was known at 18 months, 850 (16%) were unimpaired, 1153 (22%) had mild impairments, 1147 (22%) had moderate to severe neurodevelopmental impairments and 2100 (40%) had died. Unimpaired survival rates varied by birth weight from $<1\%$ for infants ≤ 500 grams to 24% for infants 901–1000 grams for all live births. The regression model to predict unimpaired survival versus death or impairment for live births ($n=5250$) identified that 25.3% of the variance was derived from infant factors present at birth including female gender, higher birth weight, singleton, and small for gestation, and less than 2% was explained either by maternal demographic factors or selected obstetric interventions. For the 3232 infants discharged from the NICU, the unimpaired survival rate was 26%. The regression model to predict unimpaired survival for discharged infants identified that most of the variance was derived from combined effects of major neonatal morbidities, neonatal interventions, and maternal demographics (15.7%) and only 8.5% was derived from infant factors present at birth.

Conclusions—Although $<1\%$ of ELBW live births ≤ 500 grams survive free of impairment at 18 months this increases to almost 24% for infants 901–1000 grams. Female gender, singleton, higher birth weight, absence of neonatal morbidities, private health insurance and White race increase the likelihood of unimpaired status.

Corresponding Author: Betty R. Vohr, M.D., Women and Infants Hospital, 101 Dudley Street, Providence, Rhode Island 02905, Phone: 401-274-1100, FAX: 401-453-7571, Betty_Vohr@brown.edu.

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Keywords

Extremely low birth weight; outcomes; neurodevelopmental impairment

There is extensive literature documenting improved survival of ELBW infants over the past two decades.(1–10) Improvements in the effectiveness of antenatal, perinatal and neonatal care (11–14) have been associated with improved survival. Rates of major neurodevelopmental impairment in ELBW survivors have varied between 15–40% and have remained relatively unchanged.(15–19) Most ELBW studies do not distinguish between normal outcome (unimpaired) and mild impairments. Understanding the factors associated with unimpaired survival in ELBW infants may help to direct future management.

The objective of this study was to determine the percentage of unimpaired survival in ELBW infants and to identify the associated perinatal, neonatal and social-environmental characteristics at 18–22 months corrected (CA). It was hypothesized that survival with unimpaired outcome for ELBW at 18–22 months is predicted by fewer neonatal morbidities and higher socio-economic status.

METHODS

A total of 6090 inborn ELBW (401–1000 grams) infants (including delivery room deaths) cared for in one of 19 National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers who were admitted between January 1, 1998 and December 31, 2001 were included. There were 886 (14.5%) deaths by 12 hours, an additional 1132 (18.6%) deaths by discharge, and 82 (1.3%) known post discharge deaths for a total of 2100 (34.4%) deaths by 18 months. Of the 3990 (65.5%) survivors, 3345 (84%) were seen, 645 (16%) were lost to follow-up, 195 had incomplete assessments and could not be placed in one of the study groups, and 3150 were fully evaluated. Therefore, the study cohort with complete outcomes and death data consisted of 5250 infants (3150 evaluated and 2100 deaths). The discharged alive cohort consisted of 3232 infants (3150 evaluated and 82 post discharge deaths).

Comparison of the children seen with the 645 children lost revealed the lost had a higher gestational age (26.6 ± 2 versus 26.2 ± 2 weeks, $p < 0.0001$), less grade 3–4 IVH (6.9% versus 9.9%, $P < 0.02$) and less ≥ 3 stage ROP (18.8% versus 22.8%, $p < 0.04$). A comparison between the 3150 children seen and the 195 with incomplete follow-up revealed that those with incomplete assessments were more likely to be multiples (29.7% versus 22.3%, $p < 0.02$).

Infants were classified as unimpaired if they had both Bayley-II(20) MDI and PDI Scores within 1 standard deviation of the mean, and normal neurological exam, vision, hearing, functional ability for swallowing by parent report, and ambulation. Infants were classified as having mild impairments if they had any of the following: Bayley MDI or PDI between 70 and 84, mild cerebral palsy (CP), mild other neurological findings, or minor sensory impairments (glasses, transient conductive hearing loss, unilateral hearing loss, unilateral blindness). Severe neurodevelopmental impairment (NDI) was defined as any of the following: Bayley MDI < 70 , Bayley PDI < 70 , moderate to severe cerebral palsy, bilateral blindness or bilateral hearing loss requiring amplification.

The maternal and neonatal data were prospectively collected by trained study personnel from birth to death, hospital discharge, or 120 days of hospitalization. The study was approved by the Institutional Review Board at each center, and verbal or written consent was obtained.

Neonatal characteristics and morbidities included chronic lung disease (CLD) (supplemental oxygen at 36 weeks or discharge), early sepsis (≤ 72 hours) and late onset sepsis (> 72 hours)

(positive blood culture), necrotizing enterocolitis (NEC) (Bell's classification stage II A or higher), intraventricular hemorrhage (IVH) grade 3–4 (maximum grade by 28 days by Papile classification), cystic periventricular leukomalacia (PVL) (head ultrasound examination 2 weeks after birth), retinopathy of prematurity (ROP grade 3 or greater), length of ventilation and length of hospitalization. Alexander(21) growth curves were used to establish birth weight appropriate for gestation and small for gestation (< 10th percentile).

A comprehensive evaluation and medical and social history previously described was completed at 18–22 months CA.(18) The Amiel-Tison(22) neurological examination was performed by certified examiners. Cerebral palsy was defined as a nonprogressive central nervous system disorder with abnormal muscle tone in at least one extremity and abnormal control of movement and posture which interfered with age appropriate activities.(18) CP was classified mild if the child was able to walk with an assistive device, moderate if the child could sit independently or with support, but an assistive device was required for ambulation, and severe if the child was unable to sit with support. Deaf was defined as hearing loss requiring bilateral amplification and hearing impairment as unilateral sensorineural or conductive hearing loss or bilateral transient conductive hearing loss. Visual impairment was defined as lack of normal vision including use of corrective lenses and blind with corrected vision of less than 20/200 in both eyes.

The Bayley Scales of Infant Development–II (BSID-II)(20) was administered by certified examiners and a mental developmental index (MDI) and psychomotor developmental index (PDI) were derived based on CA. Scores of 100+/- 15 represent the mean +/- 1 standard deviation (SD) and a score < 70 indicates significant delay. Children who could not be assessed due to severe developmental delay were assigned scores of 49.(18) Anthropometrics were obtained using standard techniques. Centers for Disease Control gender specific growth charts were used.

Statistical Analysis

Associations between neurodevelopmental status (unimpaired, mild, or NDI groups) and maternal and child characteristics and morbidities were explored. Unadjusted analyses of overall associations between these variables and neurodevelopmental status were assessed using Chi Square tests for categorical variables and ANOVA for continuous variables. Multiple comparison procedures developed by Zar(23) and Dunnett(24) were used for pairwise comparisons between groups. Adjusted results were obtained using a binary logistic regression model for the two level outcomes: survival to 18 months or death, and nominal logistic regression models for the three level outcome: unimpaired survival, mildly impaired survival, and impaired survival or death, with the last group chosen as the reference group. Variables considered for each model were clustered by order of appearance and then entered into the model using a forward stepwise selection procedure. Variables with a p-value of < 0.10 from each step were retained prior to consideration of the next cluster. Second order terms for continuous variables were also considered in the model to test for a non-linear relationship between the predictor variable and the outcome. Results were expressed as the proportion of variation explained by each cluster in the fitted model using the max-rescaled R-square.(25) Clusters for the models included 1. social and demographic, 2. infant biologic factors, 3. obstetric interventions, 4. important neonatal morbidities and 5. important neonatal interventions. Analyses were completed at RTI International, Research Triangle Park, North Carolina.

RESULTS

The cohort of 5250 infants consisted of 850 (16%) unimpaired, 1153 (22%) mildly impaired, and 1147 (22%) with NDI at 18–22 months CA and 2100 (40%) deaths. The maternal

characteristics are shown in Table 1. Mothers of unimpaired, mildly impaired and NDI infants were more likely to have received antenatal steroids and be delivered by C-section than mothers of infants who died. Mothers of unimpaired and mildly impaired infants were more likely to have a higher level of education and private insurance than mothers of infants with NDI. In addition, mothers of unimpaired infants were more likely to be married and Caucasian than mothers of infants with NDI.

Infant characteristics and morbidities are shown in Table 2. Both unimpaired and mildly impaired infants had greater birth weight and head circumference, were more likely to be female and have lower rates of the common neonatal morbidities compared to the NDI and died groups. Compared to infants with NDI, unimpaired infants also had greater birth length and higher gestational age, and both unimpaired and mildly impaired infants had fewer days to regain birth weight, less ventilation, and shorter hospitalization.

Child outcomes are shown in Table 3. Based on our study design the unimpaired group had normal outcomes. The Bayley scores for the unimpaired group ranged from average to superior; 4% had MDI scores >115 and 5% had PDI scores > 115. Approximately 1% of children in the mild group had Bayley scores in the above-average range. Within the NDI group 5.6% had an MDI in the average range and 16.6% had a PDI in the average range. Moderate to severe CP was present in 18.4% of the NDI group although almost half were walking independently, 81% had normal swallowing and 72% were feeding independently. The number of impairments ranged from 1 to greater than 3. Of the mildly impaired infants, 53% were classified based on a single factor (10% PDI<85, 33% MDI<85, 10% mild motor problems, and <1% other), 32% for 2 factors, and 15% for 3 or more factors. Of the infants with NDI, 56% were classified on a single factor (11% PDI<70, 41% for an MDI <70, 4% other) 28% for 2 factors, and 16% for 3 or more factors. The mild group was doing well functionally with 85% as independent walkers, 96% with normal swallowing and 92% feeding independently. The unimpaired and mild groups had better growth and were less likely to have growth parameters <10th % compared to the NDI group. The unimpaired group was least likely to have a head circumference <10% or symmetric growth restriction.

Results of the logistic regression models with clustered, forward stepwise regression are shown in Table 4. All variables entered into the regression models are shown. Variables retained in the final model are shown in bold; variables dropped from the model prior to consideration of the next cluster had a $p>0.1$. In model one the outcome modeled was survival to 18 months (versus death) for 5250 infants. The total R-square of 0.4175 indicates that a total of 41.8% of the variance was explained by the final model. The largest contributor to the model was the cluster of infant factors present at birth (female, birth weight, singleton, and SGA) which contributed 37% of the variance. Maternal social and demographic factors provided a minor contribution of 0.54% of the variance above and beyond the factors present at birth. Maternal interventions studied contributed an additional 4.2% of the variance.

Model 2 shows the regression which modeled the three level outcomes at 18 months of unimpaired survival, mildly impaired survival, and impaired survival or death, for the total birth cohort of 5250 infants. The same clusters of variables were entered as model 1. The largest contributor to the model was again the cluster of infant factors present at birth which contributed 25.3% of the variance. Maternal social and demographic factors provided a minor contribution of 1.9% of the variance; however this was almost 4 times greater than in the model for death. Only maternal environmental factors differed in effects between the unimpaired or mildly impaired survival versus NDI or death. White race and married differentiated only unimpaired survival from NDI or death whereas maternal age ≥ 20 years differentiated only mildly impaired survival from NDI or death. The model explained 29% of the variance.

Model three shows the regression that modeled the three level outcome of unimpaired survival, mildly impaired survival, versus NDI or death at 18 months for the subset of 3232 infants alive at discharge for whom death or developmental outcomes are known. A neonatal morbidities cluster and neonatal intervention cluster were added. Infant factors present at birth contributed 8.5% of the variance compared to 37% in Model 1. Maternal social and demographic factors provided an increased contribution of 3.6% of the variance which was substantially greater than in the model for death. Major neonatal morbidities and interventions contributed an additional 5.6% and 6.6% of the variance, respectively. Maternal pregnancy related interventions were no longer significant. Whereas the majority of differences were significant for both unimpaired and mild impairment versus NDI or death, white race and SGA differentiated only unimpaired survival versus NDI or death. The final model explained a total of 24.2% of the variance.

Figure 1 and Figure 2 show the distribution of outcomes of death, unimpaired, mild, and NDI status in increments of 100 grams birth weight and 1 week of gestation for the total birth cohort of 6090 infants and includes incomplete follow-up and lost to follow-up. There is a steady decrease in the death rate from 85.2% for infants ≤ 500 grams to 9.9% for infants 901–1000 grams and a steady increase in the percent unimpaired from 0.9 % (5 infants) at ≤ 500 grams to 24.3% (279 infants) at 901–1000 grams (13.9% for total cohort). The death rate decreases from 82.4% at ≤ 23 weeks to 17.3% at 26 weeks whereas the unimpaired rate increases from 1.2% at ≤ 23 weeks to 17.2% at 26 weeks and continues in the range of 20 to 25% at higher gestations. The NDI rate among the 6090 infants is 14%.

DISCUSSION

The outcomes described in the study are presented as a percent of 3 different cohort denominators: the discharged cohort (N=3150), all infants discharged from the NICU alive and seen at 18 months CA; the birth cohort (N=5250), all births, deaths in the NICU and known outcomes at 18 months CA; and third, the total cohort (N=6090), all births, deaths, and infants evaluated including those lost to follow-up or with incomplete data. Rates of unimpaired infants in the 3 cohorts were 27%, 16%, and 14%, clearly demonstrating the importance of defining a cohort when interpreting data or counseling families. It is apparent that if the infant survives and is discharged from the NICU the likelihood of an unimpaired outcome is higher than at the time of birth.

Our first two regression models predicting survival and unimpaired survival for this cohort included only maternal and infant characteristics known at birth. Infant characteristics present at birth provided by far the largest contribution (37%) to model 1 in which the outcome was survival. Infant characteristics are therefore important when counseling families prior to or shortly after delivery. This finding is similar to the by Tyson et al report for the NICHD Neonatal Network.(26) Singleton and female have previously been shown to be associated with better outcomes.(27,28) The contributions of antenatal steroids and cesarean section (4.2%) and maternal demographics (0.5%) to this model were significantly less than infant characteristics. Regression model 2 includes the same birth cohort but models the outcome unimpaired survival or mildly impaired survival at 18 months versus NDI or death. The relative importance of the model clusters changes. Compared to model 1 for survival, the contributions of infant characteristics (37 to 25% of the variance) and maternal interventions (4.2 to 1.6%) decrease whereas the contribution of maternal demographics (0.54 to 1.9%) increases; Infant characteristics, however, remain the most important contributor to both models.

Our hypothesis that higher SES and fewer neonatal morbidities would predict neurodevelopmental outcome was confirmed in model 3 which included only discharged infants. White race, maternal age, and private insurance contributed 3.6%, absence of neonatal

morbidities 5.5% and neonatal interventions 6.5% for a total contribution of 15.7%. . . The contribution of infant characteristics decreased to 8.5% variance in this model. The prediction of improved neurodevelopmental outcome by decreased severity of illness and higher SES is consistent with the literature.(10,29) Private health insurance was significant in model 3 and differentiated both unimpaired and mildly impaired from NDI or death. The SES factors provided a minimal contribution (.54% variance) to death in Model 1 and increased in importance when developmental status is the outcome (3.6% variance in Model 3) whereas maternal pregnancy interventions become less important. This suggests that adequate resources, namely health insurance, have an increasing impact after discharge in determining unimpaired outcome. All of the neonatal morbidities in our cluster are known to be associated with NDI (9,18,30–34) and it is not surprising that their absence was associated with unimpaired outcome.

Children with NDI have high rates of academic failure. Many studies have reported that ELBW children who escape NDI remain at significant risk of requiring education supports.(35–38) Our findings suggest that concerns about future risk of academic difficulties should be expanded to include the 37% of ELBW children with mild impairments. The cohort children with mild impairments had a mean MDI more than 1 SD below the mean, and increased rates of minor neurological impairments. Most 18 to 24 month reports of outcomes of ELBW infants cluster children with mild impairments and “normal” outcome. This may account for some of the “hidden disability” (35–39) identified at school age. Long term follow-up is needed to answer this question.

Failure to thrive with growth parameters below the 10% was 3 times more likely in the NDI group than the unimpaired group. However, even in the unimpaired group, 50% of children had weight below the 10th % at 18 to 22 months. These findings support the ongoing need for continued surveillance of nutritional intake after discharge.(40,41)

Many studies in the past have traditionally used NDI as a primary outcome and compare results to a composite comparison group that includes children with both mild impairments and unimpaired status. We propose it is important to separate infants who are unimpaired from infants with mild impairments, particularly to assess the need for support services. The school-age outcomes of children with unimpaired status at 18–22 months are unknown. Reports of school age outcomes among ELBW infants have identified increased rates of learning disabilities despite normal intellectual functioning and no sensory or neurological impairments. (42) (43)

Strengths of this multi-center study include a large cohort and standardized protocols. Limitations are that 16% of children did not have complete follow-up data, and term controls were not included.

It was encouraging that 27% of 3150 ELBW infants discharged and assessed at 18–22 months were unimpaired. Whereas infant factors present at birth are strongly associated with an increased likelihood of survival for ELBW live births, unimpaired survival for infants discharged from the NICU is also highly associated with the absence of major neonatal morbidities and interventions, White race and private health insurance. Appropriate counseling should be offered to families at the time of delivery and at the time of discharge, and continued research is needed to identify maternal and neonatal interventions that improve the likelihood of unimpaired survival.

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Abbreviations

ELBW	extremely low birth weight
CP	Cerebral Palsy
CA	corrected age
NICU	neonatal intensive care unit
MDI	mental developmental index
PDI	psychomotor developmental index
NDI	neurodevelopmental impairment
NICHHD	National Institute of Child Health and Development
BPD	bronchopulmonary dysplasia
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity

Appendix

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18-22 Month Outcomes by Birth Weight in ELBW

Figure 1.
Outcomes in 100 gram increments for 6090 ELBW infants.

18-22 Month Outcomes by Gestational Age in ELBW

Figure 2.

Outcomes in 1 week of gestation increments for 6090 ELBW infants.

Table 1
Maternal Characteristics of Infants with Known Outcomes at 18–22 months CA

Characteristic N=5250	Unimpaired 850(16%)	Mild 1153(22%)	NDI 1147(22%)	Died 2100(40%)	p-value ²
% Antenatal Care	94.6	94.4	93.2	92.3	0.06
% Antenatal Steroids	87.5**	85.8**	83.3**	56.1	<.0001
% C-Section	65.9**	62.4**	61.3**	35.1	<.0001
Maternal Age					
% <20	14.8	12.9**	16.1	18.5	<.0001
% 20–29	47.6	47.2	50.0	49.6	
% 30+	37.5**	39.9*,**	33.8	31.9	
% Married	54.0*,**	46.8**	41.9	42.0	<.0001
Maternal education:					
% < 12 yrs	24.2*	27.2*	32.2	N/A	<.0001
% 12 yrs	29.1	28.5	31.0		
% Partial college	21.3	24.4*	19.8		
% College degree	25.4*	19.8	17.0		
Medical Insurance					
% Medicaid	53.0*	61.7*	71.9	N/A	
% Private	36.3*	28.4**	20.3		<.0001
% Both/Other	10.7	9.9	7.9		
Race					
% Black	38.5*,**	46.0	49.7	46.3	<.0001
% White	48.9*,**	36.1	31.6	35.3	
% Hispanic	10.5*,**	15.4	15.3	15.0	
% Other	2.1	2.6	3.4	3.4	

¹ Includes N=886 infants who died within 12 hours and for whom limited data was collected.

² p-value for overall association, Chi Square test;
Significantly different pairwise comparisons (p < .05) indicated by * (vs. NDI) and ** (vs. Died)

N/A information collected only for infants discharged alive.

Table 2

Infant Characteristics and Morbidities

Characteristic N=5250 Mean (SD) or %	Unimpaired 850(16%)	Mild 1153(22%)	NDI 1147(22%)	Died 2100/ (40%)	p- value ²
Birth Weight (g)	824 (124) **, **	794 (135) **, **	751 (138) **, **	622 (143)	<.0001
Birth Length (cm)	34.0 (2.3) **, **	33.4 (2.4) **, **	32.7 (2.5) **, **	30.8 (2.8)	<.0001
Birth HC (cm)	24 (1.5) **, **	23.6 (1.7) **, **	23.3 (1.8) **, **	22.2 (1.7)	<.0001
GA (weeks)	26.7 (1.9) **, **	26.2 (1.9) **, **	25.8 (2.0) **, **	24.0 (2.2)	<.0001
% Singleton	79.3 **, **	78.5 **, **	75.7 **, **	73.9	0.0025
% Female	65.3 **, **	55.9 **, **	45.2 **, **	43.6	<.0001
% AGA	81.3 **, **	84.0 **, **	83.0 **, **	86.1	0.0066
Days to regain birth weight	14 (6.6) *	14.9 (6.7) **, **	16 (7.4) **, **	13.7 (7.1)	<.0001
% CLD	33.4 **, **	44.6 **, **	59.5 **, **	81.2 ⁴	<.0001
% IVH Grade 3–4	5.1 **, **	8.3 **, **	15.0 **, **	34.7	<.0001
% PVL	2.0 **, **	2.3 **, **	7.5 **, **	7.3	<.0001
% Sepsis	29.3 **, **	35.6 **, **	48.7 **, **	39.7	<.0001
% NEC	5.4 **, **	6.6 **, **	11.2 **, **	17.0	<.0001
% ROP ≥ Grade 3	10.5 **, **	21.1 **, **	33.0 **, **	28.9	<.0001
% Postnatal Steroids	26.0 **, **	35.9 **, **	51.3 **, **	25.8	<.0001
Weeks on ventilator	2.0 (2.3) *	3.3 (3.0) **, **	5.3 (4.2) **, **	2.0 (3.5)	<.0001
Weeks in NICU	11.0 (3.7) **, **	13.0 (5.0) **, **	16.5 (7.8) **, **	5.3 (8.2)	<.0001

Characteristic N=5250 Mean (SD) or %	Unimpaired 850(16%)	Mild 1153(22%)	NDI 1147(22%)	Died 2100 ¹ (40%)	p- value ²
Number of Morbidities ³					
0	43.2 ^{*,**}	33.2 ^{*,**}	17.3 ^{**}	7.8	<.0001
1	37.0 ^{*,**}	33.4 ^{**}	30.2 ^{**}	19.6	
2	14.7 ^{*,**}	22.7 ^{*,**}	31.0	35.8	
3 or more	5.1 ^{*,**}	10.8 ^{*,**}	21.5 ^{**}	36.8	

¹ Includes 886 infants who died ≤ 12 hours and for whom limited data were collected.

² p-value for overall association, Chi Square tests for categorical, ANOVA for continuous variables Significantly different pairwise comparisons (p < .05) indicated by * (vs. NDI) ** (vs. Died)

³ Presence of CLD, sepsis, Severe IVH, PVL, or ROP stage 4–5.

⁴ Denominator is 218 infants alive at 36 weeks who subsequently died after 36 weeks

Table 3

Child Outcomes at 18–22 Months CA

Outcomes ² N=3150 N Mean(SD) or %	Unimpaired 850(27%)	Mild 1153(37%)	NDI 1147(36%)	p-value ¹
MDI	97.6 (9.2)	83.4 (10.4)	60.8 (11.6)	N/A
MDI %				
<70	0	0	85.2	N/A
70–84	0	68.4	9.2	
85–115	96.0	30.4	5.6	
116+	4.0	1.2	0	
PDI Score	99.4 (9.1)	88.0 (10.1)	66.5 (16.3)	N/A
PDI %				
< 70	0	0	56.7	N/A
70–84	0	39.9	26.4	
85–115	94.8	59.0	16.6	
116+	5.2	1.1	0.3	
% Vision Impairment, any	0	12.4	25.1	N/A
% Bilateral Blindness	0	0	2.1	N/A
% Hearing Impairment, any	0	1.8	7.7	N/A
% Bilateral Deafness	0	0	4.2	N/A
Neurological Examination category	0	6.4	31.9	N/A
% CP	0	2.3	5.6	
% abnormal tone, no CP	0	33.5	29.5	
% Other abnormality	100	57.9	33.0	
% Normal				
Moderate/Severe CP	0	0	18.4	N/A
% Independent Walker	100	85.2	49.7	N/A
% Normal Swallowing	100	95.5	80.9	N/A

Outcomes ² N=3150 N Mean(SD) or %	Unimpaired 850(27%)	Mild 1153(37%)	NDI 1147(36%)	p-value ¹
% Independent Feeding	97.2 ^{*,**}	91.7 ^{**}	71.9	<.0001
% Weight <10 th %	50.2 ^{**}	45.4 ^{**}	58.2	<.0001
% Length <10 th %	27.4 ^{**}	27.0 ^{**}	46.8	<.0001
% HC <10 th %	16.5 ^{*,**}	21.4 ^{**}	40.2	<.0001
% All growth parameters <10 th %	8.0 ^{**}	9.2 ^{**}	24.2	<.0001

¹ p-value for overall association, Chi Square tests for categorical variables, ANOVA for continuous variables, N/A indicates that the variable was used in the outcome definition; Significantly different pairwise comparisons (p < .05) indicated by * (vs. Mild) ** (vs. NDI)

Table 4

Forward Stepwise Regression Models

Model 1: Outcome: Survival to 18 months (N=5250)			
Cluster	Cluster R-Square ¹	Percent of Total R-Square ²	Cumulative Total R-Square
Maternal age, married, White	0.0054	1.3%	.0054
Female, birth weight, Singleton, SGA	0.3700	88.6%	.3754
Prenatal care, Antenatal steroids, Cesarean section	0.0421	10.1%	.4175**
Model 2: Outcome: Unimpaired Survival or Mildly Impaired Survival at 18 Months; versus. Impaired Survival(NDI) or Death) (N=5250)			
Maternal age, married, White,	0.0199	6.9%	.0199
Female, birth weight, Singleton, SGA	0.2532	87.4%	.2731
Prenatal care, Antenatal steroids, Cesarean section	0.0166	5.7%	.2897**
Model 3: Outcome: At 18 months, Unimpaired Survival or Mildly Impaired Survival versus. Impaired Survival(NDI) or Death; Infants discharged with known outcome (N=3232)			
Maternal age, married, White, private insurance	0.0356	14.7%	.0356
Female, birth weight, Singleton, SGA	0.0849	35.1%	.1205
Prenatal care, Antenatal steroids, Cesarean section	0	0%	.1205
Sepsis, IVH 3–4, PVL, CLD, ROP, NEC	0.0555	23.0%	0.1760
Weeks on mechanical Ventilation, Weeks in NICU, postnatal steroids	.0657	27.2%	0.2417**

Models 1, 2, and 3 **BOLD** significant factors retained in model;

Model 2 All bolded factors are significant for both comparisons except: Maternal age (only for Mildly Impaired), married and White (only for Unimpaired).

Model 3 All Bolded factors are statistically significant for both comparisons except: Maternal age (Neither comparison), White and SGA (Unimpaired versus impaired)

¹ Defined as the proportion of total variation in the outcome explained by the cluster

² Calculated as (Cluster R-Square/Total R-Square) x 100

** Total R-Square