Outcome Trajectories in Extremely Preterm Infants

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KEY WORDS
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ABBREVIATIONS
AUC—area under the curve
CPAP—continuous positive airway pressure
ELBW—extremely low birth weight
IVH—intraventricular hemorrhage
NDI—neurodevelopmental impairment
NRN—Neonatal Research Network
PMA—postmenstrual age

Dr Ambalavanan provided conception, design, data analysis and interpretation, drafting, and revision of manuscript; Drs Carlo and Tyson provided conception, design, drafting, and revision of manuscript; Mr Langer provided design and data analysis and interpretation; Drs Walsh and Parikh provided conception, design, drafting, and revision of manuscript; Dr Das provided design and data analysis and interpretation; Dr Van Meurs, Shankaran, and Stoll provided drafting and revision of manuscript; and Dr Higgins provided conception, design, drafting, and revision of manuscript. Data collected at participating sites of the National Institute of Child Health and Human Development 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, Dr Das (DCC Principal Investigator) and Mr Langer (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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WHAT'S KNOWN ON THIS SUBJECT: Death or neurodevelopmental impairment in extremely premature neonates can be predicted at birth by considering gender, antenatal steroids, multiple birth, birth weight, and gestational age.

WHAT THIS STUDY ADDS: Prediction of death or neurodevelopmental impairment in extremely premature infants is improved by using information available later during the clinical course. The importance of birth weight declines, whereas that of respiratory illness severity increases with advancing postnatal age.

abstract

OBJECTIVE: Methods are required to predict prognosis with changes in clinical course. Death or neurodevelopmental impairment in extremely premature neonates can be predicted at birth/admission to the ICU by considering gender, antenatal steroids, multiple birth, birth weight, and gestational age. Predictions may be improved by using additional information available later during the clinical course. Our objective was to develop serial predictions of outcome by using prognostic factors available over the course of NICU hospitalization.

METHODS: Data on infants with birth weight ≤1.0 kg admitted to 18 large academic tertiary NICUs during 1998–2005 were used to develop multivariable regression models following stepwise variable selection. Models were developed by using all survivors at specific times during hospitalization (in delivery room [n = 8713], 7-day [n = 6996], 28-day [n = 6241], and 36-week postmenstrual age [n = 5118]) to predict death or death/neurodevelopmental impairment at 18 to 22 months.

RESULTS: Prediction of death or neurodevelopmental impairment in extremely premature infants is improved by using information available later during the clinical course. The importance of birth weight declines, whereas the importance of respiratory illness severity increases with advancing postnatal age. The c-statistic in validation models ranged from 0.74 to 0.80 with misclassification rates ranging from 0.28 to 0.30.

CONCLUSIONS: Dynamic models of the changing probability of individual outcome can improve outcome predictions in preterm infants. Various current and future scenarios can be modeled by input of different clinical possibilities to develop individual "outcome trajectories" and evaluate impact of possible morbidities on outcome. *Pediatrics* 2012;130:e115–e125

Prognostic estimates are necessary in clinical medicine. The prognosis from the time of initial diagnosis may change over time because of disease progression, therapeutic response (or lack thereof), complications, or advancing age. Identification of changes in prognosis may be especially important in critically ill patients. In the NICU, extremely low birth weight (ELBW; birth weight ≤1000 g) infants are at the highest risk of adverse outcomes.[1] Taking into consideration postadmission events in addition to data available at the time of birth/admission supports more informed clinical decision-making and parental discussion and allows evaluation of prognosis at different postnatal ages.

At birth, the probability of death or neurodevelopmental impairment (NDI) in ELBW infants can be estimated considering multiple factors (eg, gender, exposure to antenatal steroids, multiple birth, and birth weight) in addition to gestational age.[1] Five minutes after birth, prediction of death can be improved by adding the Apgar score, which reflects the early care and infant response.[2] Because the risk of mortality is lower if initial resuscitation is successful, and declines over the first few weeks,[3] a prediction made at the time of birth for subsequent death/NDI is an overestimate for mortality if the infant survives beyond this vulnerable period. Conversely, in an infant predicted to have a good outcome at birth, complications such as bronchopulmonary dysplasia or retinopathy of prematurity substantially reduce the probability of a good outcome.[4] The effect of morbidities on subsequent outcome depends partly upon the previous probability up to that point (eg, the effect of a bilateral severe intracranial hemorrhage on the probability of a bad outcome will be larger in an infant with a high predicted probability of good outcome at birth and will be relatively small in an infant with a low predicted probability of good outcome at birth). Although MRI[5] and neurobehavioral assessments[6] may provide additional prognostic information, these are difficult to perform soon after birth in sick ELBW infants.

We hypothesized that a multivariable analysis of clinical data available at birth and at subsequent time points during the hospitalization (7 days, 28 days , and 36 weeks postmenstrual age [PMA]) will improve prognostication for poor outcome (death/NDI, death alone, NDI in survivors) over that at birth for individual ELBW infants.

METHODS

Study Centers and Population

Data from all live-born infants (both inborn and outborn if admitted within 14 days of birth) with a birth weight of 401 to 1000 g born between January 1, 1998, and December 31, 2005 who were admitted to 18 centers of the National Institute of Child Health and Human Development Neonatal Research Network (NRN) were included. All Network centers are academic tertiary care centers. The data analyzed are collected systematically, stored in a database, and used for the surveillance of the care and outcome of high-risk infants in NICUs and for provision of background data to design prospective studies. Patient identity is kept confidential. Data collection for the NRN's prospective data registry was approved by the institutional review boards of all participating institutions. All statistical analyses were performed by the NRN Data Coordinating Center at RTI International (Research Triangle Park, NC).

Data Collection and Analysis

The available data set was randomly divided into a development set (70%) and a validation set (30%). Infants with gestational age <22 weeks (nonviable) or >32 weeks (severe growth retardation if >32 weeks and birth weight ≤1000 g) or with major malformations were excluded. Infants discharged alive but with missing follow-up data were also excluded. NDI was defined as one or more of Mental Developmental Index <70 on Bayley Scales of Infant Development-II, Psychomotor Developmental Index <70, cerebral palsy, blind in both eyes, or needing hearing aids in both ears at follow-up at 18 to 22 months corrected age.[7–9]

Multivariable forward stepwise logistic regression models for predicting death/NDI (the primary outcome), death alone, and NDI in survivors were developed by using clinical data available in the delivery room (birth) and at specified postnatal time points (postnatal age of 7 days or 28 days and 36 weeks PMA) in the development set. Variables that would have been clinically evident at or before each of these time points were evaluated for inclusion in the models at each time point (Table 1). Continuous (eg, birth weight) and categorical data variables (eg, gender) were used unaltered. Ordinal variables (eg, Apgar score) were considered as continuous for ease of analysis.

Models including fewer variables (parsimonious models) were then developed and validated. Variables were included in the final parsimonious model if their contribution to area under the curve (AUC) was ≥0.4%, at $P < .01$ in the initial model. This threshold was empirically set to avoid including statistically significant variables that contributed little to model accuracy. The model at the time of birth included Apgar scores, because the status at birth and response to resuscitation is sometimes included in the decision to continue or withdraw support.

To account for center variation,[7,10] models including center were also developed, which increased the c-statistic (AUC) of the models by ~1%, but did not significantly alter parameter estimates

TABLE 1 Clinical Variables Used at Different Time Points for Model Development and Their Definitions

Variable	Definitions of Clinical Variables
Variables evaluated for time point of birth	
Birth weight	Birth weight in grams
Gestational age	Gestational age in completed weeks by best obstetric estimate
SGA	Small for gestational age (below the 10th percentile). This is determined by the combination of gender, gestational age, and birth weight.
Male gender	Male gender
Multiple gestation	Multiple gestation (twins, triplets, or greater)
Black race	Black, not Hispanic, as reported on obstetric records
Antenatal steroids	Administration of antenatal steroids to accelerate pulmonary maturity
Tocolytics	Tocolytics administered to mother before delivery
Antibiotics	Antibiotics administered to mother before delivery
Antepartum hemorrhage	Antepartum hemorrhage (placenta previa, abruption, or threatened abortion) with vaginal bleeding or retroplacental clot, other than bloody show, after 20 wk of pregnancy
PIH	Hypertension/preeclampsia/eclampsia, as reported on obstetric records
Maternal insurance	Maternal medical insurance: private
Maternal education	Maternal educational level: high school or greater
Outborn	Outborn status
Cesarean delivery	Cesarean delivery (compared with those with vaginal vertex or breech)
Surfactant	Administration of surfactant to infant
1 min Apgar (median; 25–75th)	Apgar score at 1 min
5 min Apgar (median; 25–75th)	Apgar score at 5 min
Delivery room: intubation	Intubation in delivery room
Delivery room: chest compression	Chest compressions in delivery room
Variables evaluated at time point of 7 day (in addition to those evaluated at earlier time points)	
Days on IMV (to day 7)	Days on conventional ventilator in first postnatal week
Days on HFV (to day 7)	Days on high-frequency ventilator in first postnatal week
Days on CPAP (to day 7)	Days on CPAP as the highest level of respiratory support in first postnatal week
Highest Fio_2 on day 7	Highest Fio_2 on the highest level of respiratory support on the seventh postnatal day
Surfactant doses	Doses of surfactant received
IVH grade	IVH Grade[11] diagnosed by cranial ultrasound (assumption made that highest grade of IVH occurs by day 7)
Received antibiotics for >5 d	Received antibiotics for >5 d
Variables evaluated at time point of 28 d (in addition to those evaluated at earlier time points)	
Days on IMV (to day 28)	Days on conventional ventilator in first 28 d if not also on HFV on the same day
Days on HFV (to day 28)	Days on high-frequency ventilator in first 28 d
Days on CPAP (to day 28)	Days on CPAP in first 28 d
Highest Fio_2 on day 28	Highest Fio_2 on 28th postnatal day
PVL	Periventricular leukomalacia
Late onset sepsis	Late onset blood culture-positive infection
Episodes of late-onset culture-negative clinical infection	Number of episodes of late-onset blood culture-negative clinical infection treated with antibiotics for 5 or more days
Days of parenteral feeding (to day 28)	Number of days on total parenteral nutrition in first 28 d
Proven NEC	Stage II or III (Bell staging) necrotizing enterocolitis
Spontaneous GI perforation	Spontaneous gastrointestinal perforation
PDA	Patent ductus arteriosus
PDA requiring treatment	PDA that was managed with medication or surgery
Variables evaluated at time point of 36 wk PMA (in addition to those evaluated at earlier time points)	
BPD: on ventilator or CPAP at 36 wk (%)	Bronchopulmonary dysplasia, on ventilator or CPAP at 36 wk PMA
BPD: on supplemental O_2 but not ventilation or CPAP	Bronchopulmonary dysplasia, on supplemental oxygen at 36 wk PMA
Days on CV (to 36 wk)	Days on conventional ventilator until 36 wk PMA
Days on HFV (to 36 wk)	Days on high-frequency ventilator until 36 wk PMA
Days on CPAP (to 36 wk)	Days on CPAP until 36 w PMA
Highest Fio_2 at 36 wk	Highest Fio_2 on highest respiratory support at 36 wk PMA time point
U/S: vent. size enlarged (day 28 to 36 wk)	Enlargement of cerebral ventricles on cranial ultrasound closest to 36 wk
U/S: PVL or porencephalic cyst (day 28 to 36 wk)	Periventricular leukomalacia or porencephalic cyst on cranial ultrasound closest to 36 wk
Hearing abnormality	Abnormal hearing screen before discharge
ROP: any stage	Retinopathy of prematurity: any stage identified before discharge
ROP: stage 3 or plus disease	Retinopathy of prematurity: stage 3 or plus disease identified before discharge
Steroids for BPD	Corticosteroid administration for BPD

IMV, intermittent mandatory ventilation; PIH, pregnancy-induced hypertension.

of the variables. Therefore, to increase generalizability of the models, only analyses excluding center are presented.

A prediction tool was developed that provides individual estimates of death/NDI (the primary outcome), death alone, and NDI in survivors at 18 to 22 months corrected age at each of the time points. Figure 1 presents 2 examples of risk of death/NDI for 2 hypothetical infants. A Web-based version of this tool is available at https://neonatal.rti.org/.

RESULTS

Patient Characteristics

A total of 14 147 infants with a birth weight of 401 to 1000 g were admitted to NRN centers between 1998 and 2005. We excluded infants with a gestational age <22 weeks (n = 308) or >32 weeks (n = 76) and those with major malformations (n = 573). Additional exclusions were due to transfers (n = 67) and missing or uncertain final status (n = 6) or subjects in the hospital at 1 year (n = 32). Therefore, 13 085 infants were analyzed. Characteristics of the evaluated patients are shown in Table 2. The available number of infants for analysis decreases over time, because death (n = 4448) or loss to follow-up (n = 1005): 2587 infants died between birth and 7 days, 941 died between 7 and 28 days, 488 died between 28 days and 36 weeks PMA, and 432 died between 36 weeks PMA and follow-up (297 before discharge and 135 after discharge). Of infants in the analyzed cohort, 92.3% either died or were evaluated for NDI, with 88% of known survivors seen at 18- to 22-month follow-up. NDI was diagnosed in 2396 of 7632 surviving infants (31.4%).

Models Using Variables in the Delivery Room (Table 3)

For death/NDI, lower birth weight was the major contributor to the model, followed by lower 5-minute Apgar score, male gender, lower gestational age, and no antenatal steroids. The variables in the model for death alone were the same as for death/NDI, although the magnitude of contribution was different. For NDI in survivors, lower birth weight was again the main contributor, followed by male gender, intubation at birth, and being inborn. The model for death alone had a higher AUC (0.84) compared with that for NDI in survivors (AUC 0.66), and the combined death/NDI model had an AUC of 0.78.

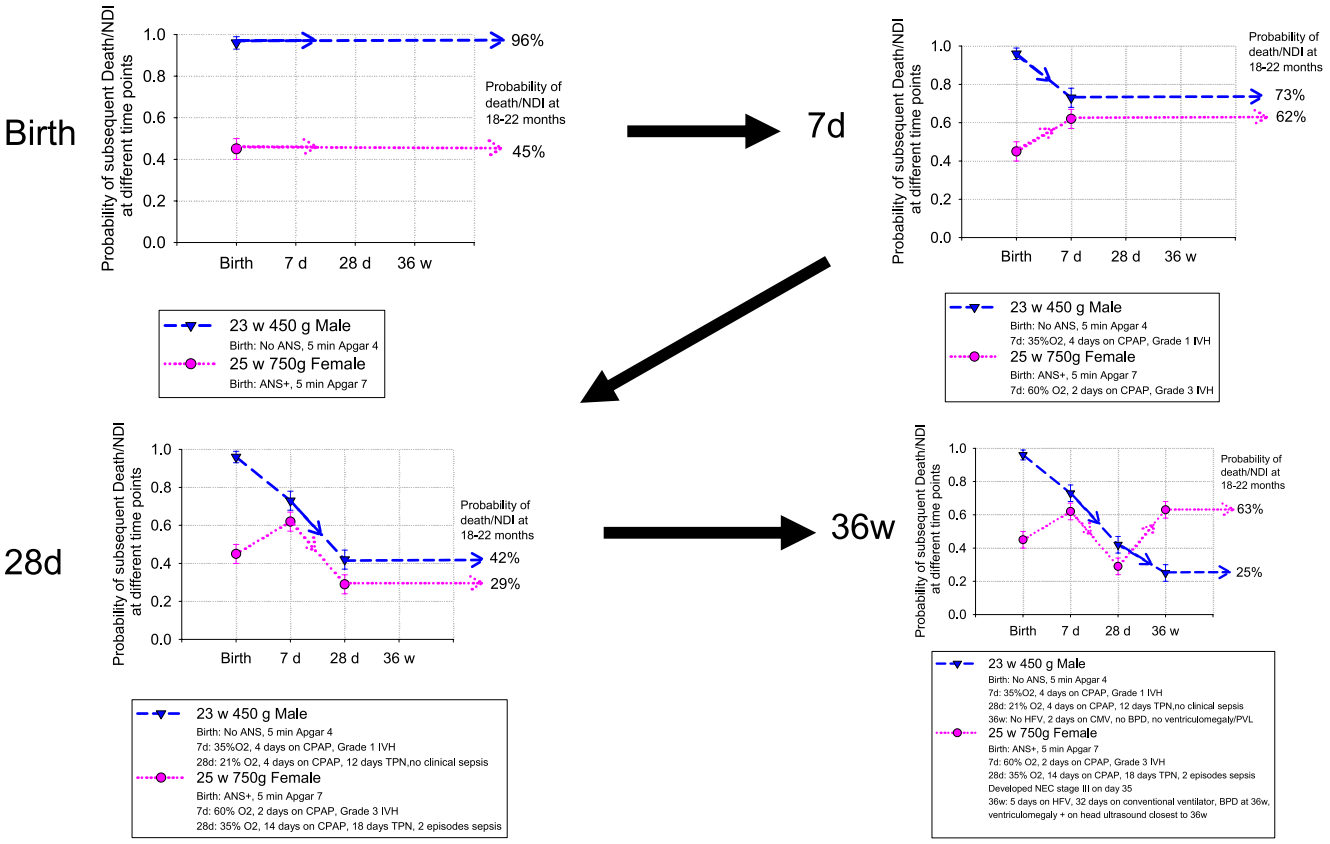

FIGURE 1
Outcome trajectory of 2 hypothetical infants with use of the National Institute of Child Health and Human Development Outcome Trajectory Estimator. The trajectories are shown for a 23-week 450-g male infant (blue triangle) and a 25-week 750-g female infant (pink circle), and have been developed by using the interactive spreadsheet.

TABLE 2 Table of Patient Characteristics (All Enrolled Infants Who Were Evaluated for Death/NDI) That Are Significantly Different by Unadjusted Analysis in Survivors Without NDI, in Comparison With Infants Who Die or Develop NDI

Variable	Overall	Survivors Without NDI	NDI and/or Death	*P* (for Survivors Without NDI vs NDI/Death)
Day 1 variables	*n* = 13 085	*n* = 4991	*n* = 7089	
Birth weight, mean ± SD	738 ± 156	808 ± 130	681 ± 151	<.0001
Gestational age, mean ± SD	25.5 ± 2	26.4 ± 1.9	24.8 ± 1.9	<.0001
SGA, %	15.2	16.5	13.5	<.0001
Male gender, %	50.2	41.9	56.5	<.0001
Black race, %	42.6	40.4	44.5	<.0001
Antenatal steroids, %	73.1	84	64.6	<.0001
Hypertension/PIH, %	23.4	29.8	18.1	<.0001
Outborn, %	11.9	8.5	13.9	<.0001
Cesarean delivery, %	57.3	65.7	50.5	<.0001
Surfactants, %	84	77.2	90.8	<.0001
Intubation	73.6	70.7	75.5	<.0001
1-min Apgar (median; 25–75th)	4 (2–6)	5 (3–7)	3 (1–5)	<.0001
5-min Apgar (median; 25–75th)	7 (5–8)	7 (6–8)	6 (3–7)	<.0001
IMV, %	85.4	88	53.6	<.0001
Day 7 variables	*n* = 10 466	*n* = 4975	*n* = 4499	
Highest Fio_2 on day 7, (mean ± SD)	0.37 ± 0.2	0.33 ± 0.16	0.43 ± 0.23	<.0001
No. days on CPAP (to day 7), (mean ± SD)	1.16 ± 1.8	1.52 ± 2	0.74 ± 1.54	<.0001
IVH grade[11] (diagnosed by day 7), %				<.0001
Grade IV	3.5	1	6.5	
Grade III	2.4	1.4	3.6	
Grade I–II	7.4	11.9	8	
None	86.7	90.7	81.8	
Day 28 variables	*n* = 9353	*n* = 4878	*n* = 3523	
Highest Fio_2 on day 28	0.41 ± 0.23	0.37 ± 0.20	0.49 ± 0.26	<.0001
No. episodes late-onset culture-negative clinical infection	0.88 ± 1.16	0.65 ± 0.93	1.24 ±1.36	<.0001
No. days parenteral feeding (to day 28)	22.1 ± 6.6	20.8 ± 7	24.1 ± 5.2	<.0001
No. days on CPAP (to day 28)	5.01 ± 6.8	6.04 ± 7.3	3.51 ± 5.8	<.0001
36 wk variables	*n* = 7630	*n* = 4029	*n* = 2828	
BPD: on ventilator or CPAP at 36 wk, %	26.8	17.3	41.8	<.0001
No. days on CV (to 36 wk)	23.8 ± 21.1	18.2 ± 17.8	32.4 ± 22.7	<.0001
No. days on HFV (to 36 wk)	3.3 ± 7.9	2.1 ± 5.9	5.3 ± 9.9	<.0001
U/S: ventricular size enlarged (day 28 to 36 wk), %	14.2	8.3	23.3	<.0001
U/S: PVL or porencephalic cyst (day 28 to 36 wk), %	5.3	2.3	9.8	<.0001

P values are from Fisher exact test (2-tailed) for categorical variables and from unadjusted logistic regression for BPD or death for continuous variables. BPD, bronchopulmonary dysplasia; CV, conventional ventilator; HFV, high-frequency ventilator; IMV, intermittent mandatory ventilation; PIH, pregnancy-induced hypertension.

AUCs/misclassification rates in validation models were 0.80/0.28 for NDI/death, 0.84/0.20 for death, and 0.68/0.32 for NDI in survivors.

Models Using Variables at 7 Days of Age (Table 4)

For death/NDI, lower birth weight was the most important contributor, followed by the highest Fio_2 on day 7, male gender, higher intraventricular hemorrhage (IVH) grade,[11] and fewer days on continuous positive airway pressure (CPAP) by day 7. The model for death alone had similar variables (with the exception of days on CPAP), although the order of variables was different and the highest Fio_2 on day 7 was the most important variable. For NDI in survivors, lower birth weight, followed by male gender were the 2 most important predictors. Similar to the time point of birth, the model for death alone had a higher AUC (0.77) compared with that for NDI in survivors (AUC 0.68), and the combined death/NDI model had an AUC of 0.72.

AUCs/misclassification rates in validation models were 0.74/0.32 for death/NDI, 0.77/0.14 for death, and 0.70/0.32 for NDI in survivors.

Models Using Variables at 28 Days of Age (Table 5)

The highest Fio_2 on day 28, followed by the number of episodes of late-onset culture-negative infection (by day 28) and the number of days of parenteral feeding (to day 28) were the top 3 predictors for the models for death/NDI and death alone. The number of episodes of late-onset culture-negative infection (by day 28) followed by more days on high-frequency ventilation and conventional ventilation (by day 28) and male gender were the important predictors for NDI in survivors. At this time point, birth weight did not contribute significantly to the models. These models had similar validity to models at earlier time points with AUCs/misclassification rates in validation models of 0.74/0.30 for death/NDI, 0.80/0.08 for death, and 0.71/0.31 for NDI in survivors.

TABLE 3 Models Using Variables in the Delivery Room (Birth) (n = 8713)

Variable	Time Period When Variable Was Evaluated	AUC c-statistic	% Increase in AUC	OR (95% CI)	*P*
Death/NDI					
Birth weight, g	Birth	0.730		0.67 (0.64–0.70) (per 100 g increase)	<.0001
Apgar score at 5 min	Birth	0.758	2.8	0.83 (0.81–0.85) (per point increase)	<.0001
Male gender	Birth	0.773	1.5	2.00 (1.80–2.22)	<.0001
Gestational age, wk	Birth	0.779	0.6	0.86 (0.83–0.89) (per wk later)	<.0001
Antenatal steroids	Birth	0.783	0.4	0.56 (0.49–0.64) (treated with ANS)	<.0001
Death before discharge					
Birth weight, g	Birth	0.785		0.61 (0.58–0.64)	<.0001
Apgar score-5 min	Birth	0.822	3.7	0.78 (0.76–0.80)	<.0001
Gestational age, wk	Birth	0.834	1.2	0.77 (0.74–0.80)	<.0001
Antenatal steroids	Birth	0.839	0.5	0.49 (0.43–0.56)	<.0001
Male gender	Birth	0.843	0.4	1.67 (1.49–1.88)	<.0001
NDI in survivors					
Birth weight, g	Birth	0.607		0.75 (0.72–0.78)	<.0001
Male gender	Birth	0.640	3.3	1.87 (1.66–2.11)	<.0001
Intubation	Birth	0.654	1.4	1.76 (1.51–2.05)	<.0001
Inborn	Birth	0.659	0.5	1.66 (1.37–2.01)	<.0001

CI, confidence interval; OR, odds ratio.

Models Using Variables at 36 Weeks Postmenstrual Age (Table 6)

The top 3 predictors for death/NDI and NDI in survivors were more days on conventional ventilation (to 36 weeks), days on high-frequency ventilation (to 36 weeks), and ventricular size enlarged on cranial ultrasound. The top 3 variables in the model for death before discharge were highest Fio_2 at 36 weeks, number of episodes of late-onset culture-negative clinical infection, and culture-positive sepsis. AUCs/misclassification rates in validation models were 0.74/0.30 for death/NDI, 0.88/0.03 for death, and 0.72/0.29 for NDI in survivors.

Overall, the AUC of models for NDI in survivors improved over time, from 0.66 in the delivery room, to 0.69 at 28 days, and to 0.72 at 36 weeks. Predictive accuracy at 7 days to 36 weeks for death/NDI was lower than at birth with removal of earlier death from later models.

DISCUSSION

In this study, we demonstrate that various current and future scenarios can be modeled by input of different clinical events to determine changes in

TABLE 4 Models Using Variables at 7 DAYS of Age (n = 6996)

Variable	Time Period When Variable Was Evaluated	AUC c-statistic	% Increase in AUC	OR (95% CI)	*P*
Death/NDI					
Birth weight, g	Birth	0.659		0.71 (0.68–0.74) (per 100-g increase)	<.0001
Highest Fio_2 on day 7	Day 7	0.690	3.1	1.18 (1.14–1.21) (per 10% increase)	<.0001
Male gender	Birth	0.708	1.8	1.88 (1.69–2.10)	<.0001
IVH grade (diagnosis by day 7)	Day 7	0.717	0.9	4.40 (3.04–6.39) grade IV 1.91 (1.33–2.74) grade III	<.0001
Days on CPAP (to day 7)	Day 7	0.724	0.7	0.89 (0.86–0.92) (per 1 d more)	<.0001
Death before discharge					
Highest Fio_2 on day 7	Day 7	0.716		1.28 (1.24–1.32)	<.0001
Birth weight, g	Birth	0.760	4.4	0.62 (0.59-0.65)	<.0001
IVH grade (diagnosis by day 7)	Day 7	0.770	1.0	3.55 (2.65–4.75) grade IV 1.89 (1.31–2.74) grade III	<.0001
Male gender	Birth	0.774	0.4	1.61 (1.40–1.86)	<.0001
NDI in survivors					
Birth weight, g	Birth	0.606		0.82 (0.78–0.86)	<.0001
Male gender	Birth	0.639	3.3	1.76 (1.56–2.00)	<.0001
Days on CPAP (to day 7)	Day 7	0.655	1.6	0.98 (0.93-1.02) (per 1 d more)	.2720
Apgar score at 5 min	Birth	0.662	0.7	0.93 (0.90–0.96) (per point increase)	<.0001
Days on HFV (to day 7)	Day 7	0.667	0.5	1.20 (1.14–1.26) (per 1 d more)	<.0001
Days on CV (to day 7)	Day 7	0.676	0.8	1.11 (1.07–1.14) (per 1 d more)	<.0001

CI, confidence interval; CV, conventional ventilator; HFV, high-frequency ventilator; OR, odds ratio.

TABLE 5 Models Using Variables at 28 Days of Age (n = 6241)

Variable	Time Period When Variable Was Evaluated	AUC c-statistic	% Increase in AUC	OR (95% CI)	P
Death/NDI					
Highest Fio_2 on day 28	Day 28	0.656		1.11 (1.08–1.14) (per 10% increase)	<.0001
Episodes of late-onset culture-negative clinical infection	Day 28	0.680	2.4	1.25 (1.18–1.32) (per episode)	<.0001
Days parenteral feeding (to day 28)	Day 28	0.695	1.5	1.05 (1.04–1.06) (per 1 d more)	<.0001
Days on CPAP (to day 28)	Day 28	0.707	1.2	0.97 (0.96–0.98) (per 1 d more)	<.0001
Male gender	Birth	0.714	0.7	1.69 (1.50–1.91)	<.0001
Birth weight, g	Birth	0.721	0.7	0.83 (0.79–0.87) (per 100-g increase)	<.0001
Death before discharge					
Highest Fio_2 on day 28	Day 28	0.751		1.24 (1.20–1.29)	<.0001
Episodes of late-onset culture-negative clinical infection	Day 28	0.776	2.5	1.22 (1.14–1.31)	<.0001
Birth weight, g	Birth	0.794	1.8	0.81 (0.75–0.87)	<.0001
Days parenteral feeding (to day 28)	Day 28	0.803	0.9	1.10 (1.07–1.13)	<.0001
Days on CPAP (to day 28)	Day 28	0.809	0.6	0.95 (0.92–0.97)	<.0001
NDI in survivors					
Episodes of late-onset culture-negative clinical infection	Day 28	0.610		1.28 (1.21–1.36)	<.0001
Days on CV (to 28 days)	Day 28	0.652	4.2	1.04 (1.03–1.04) (per 1 d more)	<.0001
Days on HFV (to 28 days)	Day 28	0.678	2.6	1.07 (1.06–1.09) (per 1 d more)	<.0001
Male gender	Birth	0.686	0.6	1.53 (1.35–1.73)	<.0001

CV, conventional ventilator; HFV, high-frequency ventilator.

prognosis and evaluate the impact of possible morbidities and/or their therapies on outcomes over time. This serial prediction of outcome over time in individual patients can be expressed as the concept of individual "outcome trajectories" which is more valuable than prognostication at a single, initial time point. This technique may prove useful not only in neonatal intensive care, but also in other clinical situations (eg, traumatic brain injury, malignancies, adult cardiovascular or cerebrovascular disease) when a change in clinical status (acquisition of new clinical signs, diagnostic results, responses to treatments, features of the disease course, or complications) is associated with a change in prognosis. Clinician assessment of outcome is not very accurate. For example, roughly half of all medical ICU adult patients predicted to die in hospital by at least 1 caretaker survived to discharge, and 15% of patients predicted to die by all medical caretakers survived.[12] In a cohort of ventilated ELBW infants, 40% of infants with normal head ultrasound and no prediction of death had an adverse outcome.[13] These studies emphasize the need for more accurate determination of prognosis.

Tyson et al[1] found that the probability of a death or adverse developmental outcome can be better estimated at birth by consideration of multiple risk factors than with the use of a single variable (gestational age). The current study extends these observations by evaluating prediction of outcome at subsequent time points. As noted in the study by Tyson et al,[1] predictive ability was improved by the addition of gender and birth weight. As we found in the current and a previous study,[2] the 5-minute Apgar score was an additional predictor of mortality, which reflects not only condition at birth, but also whether and how effectively resuscitation was provided. Our study suggests that it may be appropriate to assess the response to initial resuscitation in the decision to provide support to extremely premature infants at the threshold of viability, in addition to considering antenatal risk factors. Chiswick[14] stated that the condition of the infant at birth and the response to bag-and-mask ventilation influences the decision on whether to continue intensive care, and subsequent care in the NICU should be considered as a "trial of life," with the option of withdrawing care according to the perceived futility of treatments and the mounting burden of neonatal complications. However, clinician assessment of appearance and response to resuscitation may not be accurate.[15] Our models may help provide additional information on outcome to help in such decision-making.

As expected, the contribution of the different variables to outcome varied with the time period. Surprisingly, the ability to predict death and death/NDI did not improve with increasing postnatal age among infants who avoided early death. We have previously shown that the ability to predict long-term morbidity/death in ELBW infants did not improve significantly over the first week of life,[16] probably because most of the commonly used variables are predictors of early mortality and not longer-term outcome, although the effects of different variables varied with postnatal age. The results of the current

TABLE 6 Models Using Variables at 36 Weeks Postmenstrual Age (n = 5118)

Variable	Time Period When Variable Was Evaluated	AUC c-statistic	% Increase in AUC	OR (95% CI)	P
Death/NDI					
Days on CV (to 36 wk)	36 wk	0.688	—[a]	1.03 (1.02–1.03) (per 1 d more)	<.0001
Days on HFV (to 36 wk)	36 wk	0.706	1.8	1.04 (1.03–1.04) (per 1 d more)	<.0001
U/S: ventricular size enlarged (day 28 to 36 wk)	36 wk	0.719	1.3	1.99 (1.63–2.43)	<.0001
Male gender	Birth	0.728	0.9	1.63 (1.43–1.86)	<.0001
U/S: PVL or porencephalic cyst (day 28 to 36 wk)	36 wk	0.736	0.8	3.33 (2.38–4.67)	<.0001
BPD: on ventilator or CPAP at 36 wk	36 wk	0.741	0.5	1.70 (1.44–2.00)	<.0001
Death before discharge					
Highest Fio_2 on 36 wk	36 wk	0.855	—[a]	1.30 (1.21–1.40) (per 10% increase)	<.0001
Episodes of late-onset culture-negative clinical infection	Day 28	0.873	1.8	1.28 (1.16–1.42)	<.0001
BPD: on ventilator or CPAP at 36 wk	36 wk	0.881	0.8	3.98 (2.39–6.62)	<.0001
Days on CPAP (to 36 wk)	36 wk	0.895	1.4	0.94 (0.92–0.96) (per 1 d more)	<.0001
Episodes of late-onset sepsis (day 28 to 36 wk)	36 wk	0.910	1.5	1.37 (1.20–1.56)	<.0001
Proven NEC (day 28 to 36 wk)	36 wk	0.913	0.3	2.74 (1.63–4.61)	.0001
Days parenteral feeding (to day 28)	Day 28	0.921	0.8	1.13 (1.06–1.21)	.0002
NDI in survivors					
Days on CV (to 36 wk)	36 wk	0.668	—[a]	1.03 (1.02–1.03)	<.0001
U/S: PVL or porencephalic cyst (day 28 to 36 wk)	36 wk	0.685	1.7	3.28 (2.33–4.61)	<.0001
Days on HFV (to 36 wk)	36 wk	0.698	1.3	1.04 (1.03–1.05)	<.0001
Male gender	Birth	0.709	1.1	1.62 (1.42–1.86)	<.0001
U/S:ventricular size enlarged (day 28 to 36 wk)	36 wk	0.716	0.5	1.99 (1.63–2.44)	<.0001

BPD, bronchopulmonary dysplasia; CI, confidence interval; CV, conventional ventilator; HFV, high-frequency ventilator; NEC, necrotizing enterocolitis; OR, odds ratio; PVL, periventricular leukomalacia.

study are consistent with the previous finding, as accuracy of prediction over time remained relatively constant (AUC of 0.72–0.73 for death/NDI) from 7 days of age to 36 weeks PMA. Other investigators have also shown that events occurring during the NICU stay improve prognostic power over information available at birth. Lagatta et al[13] have demonstrated that early NICU therapy improves predictive power for the outcomes of ventilated ELBW infants. Meadow et al[17] showed that illness severity scores and caretaker intuitions became progressively less helpful over time as predictors of death, although intuitions of death were a good predictor of infants who would either die or have impairment at 2 years. Some aspects of the studies by Lagatta et al[13] and Meadow et al,[17] such as the day-to-day changes in prognosis and the use of clinician intuition for prognostication, were not available in our study. However, our study has the advantage of a larger sample size from multiple centers, with more variables being analyzed.

We observed that the models for NDI/death were similar to the models for death alone in the first 28 days, but were similar to the models for NDI in survivors at the 36-week time point, because most death occurs in the first 28 days, whereas NDI accounts for most of the combined NDI/death outcome at 36 weeks. An important finding was that birth weight and other predictors at birth (with the exception of male gender) that are strongly associated with outcome at earlier time points decline in importance with advancing postnatal age (28 days and 36 weeks), whereas the importance of respiratory illness severity and late-onset culture-negative clinical infection (an indicator of overall illness severity) increased over time. Except at the time of delivery, gestational age, when considered along with birth weight and the other variables, did not contribute enough to model predictive ability to be included. This may be because the resolution (in completed weeks, within a relatively narrow range) and accuracy of the gestational age assessment is relatively poor[1,18] in comparison with birth weight. Antenatal steroids were also associated with improved outcome at the time of birth. It is well known that antenatal steroids improve outcomes in preterm infants,[19] and we have recently shown that they are associated with reduced death or NDI even in infants born at 23 to 25 weeks gestation.[20] Above and beyond its effects on other predictors (eg, ventilator days), IVH grade did not contribute significantly to NDI in survivors at any time point, although ventricular enlargement and periventricular leukomalacia /porencephalic cyst at 36 weeks were associated with NDI and

NDI/death. We have previously shown that the addition of data on severe IVH to models with clinical data alone did not improve outcome prediction.[21] Other investigators have also shown that infants with isolated IVH and without associated echolucency and/or ventriculomegaly are only slightly more likely to have cerebral palsy than those with normal ultrasound studies.[22]

Limitations of the study include difficulty in ascertainment of time of onset of some complications. For example, most IVH occurs in the first 3 to 5 days,[23,24] but some infants may have their first cranial sonogram after 7 days, thereby delaying the diagnosis but not actual timing of the morbidity. A second limitation is that, although the follow-up rate is not low, attrition may result in biased estimates of prediction of adverse outcomes. Another limitation is that NDI at 18 to 22 months corrected age may not correlate highly with later impairment. Many ELBW survivors have neurosensory disabilities but become functional young adults.[25,26] We are aware that transitioning NDI assessment from the Bayley II to the Bayley III, since the assessment of infants in this study has led to differences in the magnitude and nature of diagnosed NDI,[27] and outcomes may change with advances in intensive care, requiring updating of these prediction models at a future date. Finally, these estimates reflect outcomes in the NRN during the study period, which may be different from the centers where it is applied.

One risk associated with the development of the prediction models is of creation of "self-fulfilling prophecies," particularly if support is not provided to infants who would otherwise have a reasonable likelihood of a favorable outcome.[28] From the ethical standpoint, the possibility of misclassification indicates that these tools should only aid and not replace clinical decision-making. It has been demonstrated that obstetricians and pediatricians who underestimate neonatal survival are less likely to provide beneficial therapy.[29]

The development of individual "outcome trajectories" enables determination of changes in prognosis over time, and the visual and interactive nature of the Web-based tool is user-friendly, enabling use by clinicians without knowledge of complex statistical approaches. A quantitative approach to perception of risk of outcome and of the effects of various complications or sequelae on longer-term outcome in ELBW infants would be useful to clinicians and parents. Quantification of risk at different time points may also assist researchers who wish to risk-stratify patients for entry into clinical trials and for quality improvement projects.

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