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Poor Outcomes at Discharge Among Extremely Premature Infants

A National Population-Based Study

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Objectives: To assess risk factors and develop a simple estimate method for poor neonatal outcomes for specific groups of extremely premature infants at birth.

Design: Population-based study.

Setting: Israel National Very Low Birth Weight Infant Database.

Participants: Infants born at 23 to 26 weeks' gestation between January 1, 1995, and December 31, 2008.

Intervention: We developed a tool to estimate poor neonatal outcomes for infants born at 24 to 26 weeks' gestation (n=2544) that incorporated factors at birth significantly associated with poor outcomes into a linear regression model.

Main Outcome Measures: Poor neonatal outcomes defined as the composite of mortality or severe neurologic or pulmonary morbidity at discharge from the hospital.

Results: Major factors associated with poor outcomes at 24 to 26 weeks' gestation were gestational age, male sex, sex-specific birth weight percentile, and lack of prenatal steroid therapy. Estimated poor outcomes for January 1, 2000, to December 31, 2008, were calculated as the sum of the percentages determined for each of the 4 parameters: (1) gestational age (26, 25, and 24 weeks; 0%, 17%, and 34%, respectively), (2) birth weight percentile (>75th, 25th-75th, and <25th percentiles; 0%, 13%, and 26%, respectively), (3) lack of prenatal steroids (16%), and (4) male sex (7%). There was also an intercept value of 25%. Estimated poor outcome rates for the 36 subgroups of infants ranged from 25% to 100% and correlated well with observed rates (intraclass correlation coefficient, 0.93).

Conclusions: The combined outcomes of deaths or severe morbidities in the neonatal period of infants born at 24 to 26 weeks' gestation could be simply estimated at birth. The provision of an appropriate and up-to-date estimate of poor neonatal outcomes for specific infants may be useful in counseling families on treatment options for these infants.

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THE OUTCOMES OF EXtremely preterm infants at the time of discharge from neonatal intensive care units have been determined in a number of population-based or large multicenter studies in the past decade.[1-6] Common to all these studies is the use of infants' gestational age (GA) as the basis for reporting the outcomes assessed. However, GA alone does not appear to be an adequate predictor of outcome, and several investigators have looked for additional factors beyond GA present at or before birth that affect the prognosis of extremely premature infants.[7,8] In a population-based study derived from the Israel National Very Low Birth Weight (VLBW) Infant Database, we developed a prediction model and tool for estimating mortality rates of extremely premature infants.[9] In addition to GA, the mortality of infants born at 23 to 26 weeks' gestation could be simply estimated on the basis of 3 additional parameters available at birth: (1) sex-specific birth weight percentile, (2) prenatal steroid therapy, and (3) multiple births. The implications of these findings in relation to current treatment guidelines for extremely preterm infants were considered by Parikh et al,[10] who noted that "there is a need to replace GA-based guidelines with probability-based guidelines to promote decisions to initiate intensive or comfort care that are better informed, more individualized, and less influenced by the frequent errors in assessing GA."[10]

Our ability to predict long-term outcomes is limited at birth, during the first days and weeks after birth, and during prolonged hospitalizations.[11] Extremely low-birth-weight infants are at ongoing risk for medical morbidities and other adverse events that may influence their prognosis.[11-15] Data regarding the risk for major morbidities and mortality in extremely preterm infants are frequently requested by our neonatal and obstetric colleagues as well as by parents. Unimpaired survival of extremely low-birth-weight infants aged 18 to 22 months was strongly associated with the absence of major neonatal morbidities and interventions.[15] Thus, assessment of the risks of major morbidities occurring during the neonatal period and the risk of mortality are of concern to parents and caregivers.[11-15]

Because mortality and major morbidities may be competing outcomes in these infants, we considered that determination of an estimate for the combined outcome of death or major morbidity was the best approach to providing this information. The aims of this study were to assess risk factors and develop a simple way to estimate poor neonatal outcomes including death or severe neonatal morbidity at the time of discharge for specific groups of extremely premature infants.

METHODS

PARTICIPANTS

This study is based on analysis of data collected by the Israel Neonatal Network on VLBW infants (≤1500 g) born in Israel from January 1, 1995, to December 31, 2008. All 28 neonatal departments in Israel are included in data collection to compose the Israel National VLBW Infant Database. All live births of infants born at 23 to 26 completed weeks of gestation were included.[16]

DATA COLLECTION

Data were prospectively collected on a prestructured form and included information on the parents, maternal pregnancy history, antenatal care, details of the delivery, the infant's status at delivery, diagnoses, procedures, complications during the hospital stay, and outcome at discharge.[9] Stillbirths or miscarriages are not reported to the database. Patient information is cross-checked with the Israel national birth registry, and data from any missing infants are requested from the birth hospital. Data are collected on all infants until discharge or death. Birth hospital and patient identification remain confidential by consensus agreement of all participating centers. This study was approved by the Declaration of Helsinki committee of the Sheba Medical Center, Tel Hashomer, Israel.

DEFINITIONS

Definitions used were concordant with those of the Vermont Oxford Neonatal Database manual of operations[17] and have been previously reported in detail.[18] The best estimate of GA was determined by the hierarchy of obstetric measures (ie, last menstrual period, obstetric history and examination, and first-trimester prenatal ultrasonography) and a neonatologist's estimate based on early postnatal physical and neurologic examination findings. Sex-specific birth weight *z* scores and percentiles were determined according to the intrauterine growth charts of Kramer et al.[19] Antenatal steroid therapy was considered as either no treatment or any treatment, which included infants receiving partial or complete courses of therapy. Delivery room resuscitation comprised endotracheal intubation, cardiac massage, and epinephrine administration and did not include mask ventilation or oxygen therapy alone. Infants who died soon after birth without resuscitation or any active respiratory support were defined as having received comfort care. Mortality was considered as death prior to discharge. For the purpose of this study, poor neonatal outcomes were defined as death or severe neurologic or pulmonary morbidities at discharge. Any of the following was considered severe neurologic morbidity: (1) grade 4 periventricular-intraventricular hemorrhage, (2) posthemorrhagic hydrocephalus, (3) periventricular leukomalacia, or (4) grade 4 retinopathy of prematurity. Severe pulmonary morbidity was defined as oxygen supplementation at 40 weeks' postmenstrual age or home oxygen therapy.

STATISTICAL ANALYSIS

Birth weight and birth weight *z* scores for male and female infants were compared using the Wilcoxon rank sum test. Differences in clinical characteristics and outcomes among GA groups were tested by χ^2 and Mantel-Haenszel tests for trends. All tests were 2-tailed, and $P < .05$ was considered statistically significant. Stepwise multivariable logistic regression analyses with a threshold of $P = .05$ for entry and retention in the model were used to determine factors at birth significantly associated with mortality or severe morbidity for each GA group. Variables included in the analyses were (1) birth weight *z* scores,[19] (2) sex, (3) ethnicity (Jewish vs non-Jewish), (4) infertility treatment, (5) prenatal steroid therapy, (6) plurality (multiple vs singleton), (7) maternal hypertensive disorders, and (8) amnionitis.[9] Results are presented as odds ratios (ORs) with the appropriate 95% CIs. Incorporating the significant factors into a linear regression model based on the recent period (2000-2008), we developed a tool for estimating poor neonatal outcomes (death or severe morbidity) for infants born at 24 to 26 weeks' gestation. Parameter estimates were rounded to provide a simple and practical method for estimating poor outcomes for specific groups of infants. The 1-way random effects intraclass correlation coefficient was calculated to evaluate whether the observed and estimated values for poor outcome were correlated and their means were not significantly different.[20] Statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc).

RESULTS

Between January 1,1995, and December 31, 2008, 20 970 VLBW (≤1500 g) infants were recorded in the Israel National VLBW Infant Database, accounting for more than 99% of all live-born VLBW infants in Israel. The study population comprised all 4408 infants of 23 to 26 weeks' gestation. The number of infants by GA and the clinical characteristics of the infants for each GA week are shown in **Table 1**. Morbidity and mortality data are presented in **Table 2**. Mortality, severe neurologic morbidity, and severe respiratory morbidity at discharge decreased significantly with increasing GA. The proportion of infants with poor neonatal outcomes decreased from 97.7% at 23 weeks to 85.4%, 71.0%, and 50.1% at 24, 25, and 26 weeks, respectively ($P < .001$). Because the outcome was poor for almost all infants at 23 weeks' gestation (only

Table 1. Clinical Characteristics of 4408 Infants Born From 1995 to 2008 According to Gestational Age

Characteristic	Gestational Age			
	23 wk (n = 640)	24 wk (n = 1009)	25 wk (n = 1203)	26 wk (n = 1556)
Sex, No. (%)				
Male	367 (57)	561 (56)	668 (56)	848 (54)
Female	273 (43)	448 (44)	535 (44)	708 (46)
Birth weight, median, g				
All infants	570	650	734	850
Male	584	669	750	875
Female	560	625	710	820
P value[a]	<.001	<.001	<.001	<.001
Birth weight *z* score, median				
All infants	−0.077	−0.232	−0.303	−0.202
Male	−0.123	−0.224	−0.340	−0.191
Female	−0.042	−0.256	−0.289	−0.215
P value[a]	.06	.90	.94	.71
Prenatal steroid therapy, No. (%)	156 (25)	506 (51)	729 (61)	1021 (66)
Cesarean delivery, No. (%)	108 (17)	375 (37)	651 (54)	1013 (65)
Multiple births, No. (%)	283 (44)	412 (41)	409 (34)	542 (35)
Delivery room resuscitation, No. (%)	388 (61)	839 (83)	1028 (85)	1258 (81)
Comfort care	226 (35)	68 (7)	20 (2)	7 (0.4)

[a] *P* values reflect comparisons between male and female infants for each gestational week.

Table 2. Mortality and Severe Morbidity Rates in Survivors According to Gestational Age

Mortality or Morbidity	Infants at GA, No. (%)				*P* Value for Trend
	23 wk (n = 640)	24 wk (n = 1009)	25 wk (n = 1203)	26 wk (n = 1556)	
Mortality					
Died	600 (93.8)	742 (73.5)	633 (52.6)	466 (29.9)	<.001
Survived	40 (6.2)	267 (26.5)	570 (47.4)	1090 (70.1)	<.001
Severe morbidity in survivors					
Neurologic morbidity					
PIVH grade 4	4 (10.0)	23 (8.7)	40 (7.2)	74 (7.0)	.28
PHH	6 (15.0)	22 (8.3)	46 (8.1)	104 (9.5)	.80
PVL	4 (10.5)	38 (14.7)	59 (10.6)	113 (10.9)	.25
ROP grade 4	2 (5.1)	18 (6.8)	8 (1.4)	11 (1.0)	<.001
Any severe neurologic morbidity	12 (30.0)	67 (25.1)	112 (19.6)	206 (18.9)	.01
Respiratory morbidity					
Oxygen therapy at 40 wk	18 (45.0)	63 (23.6)	104 (18.2)	114 (10.5)	<.001
Oxygen therapy at discharge	13 (32.5)	71 (26.6)	92 (16.1)	101 (9.3)	<.001
Any severe respiratory morbidity	21 (52.5)	87 (32.6)	135 (23.7)	144 (13.2)	<.001
Severe neurologic and/or respiratory morbidity	25 (62.5)	120 (44.9)	221 (38.8)	314 (28.8)	<.001
Mortality or severe morbidity	625 (97.7)	862 (85.4)	854 (71.0)	780 (50.1)	<.001

Abbreviations: GA, gestational age; PHH, posthemorrhagic hydrocephalus; PIVH, periventricular-intraventricular hemorrhage; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

15 infants, or 2.3%, were discharged alive without severe morbidity), further analysis included only infants at 24, 25, and 26 weeks' gestation.

FACTORS ASSOCIATED WITH POOR NEONATAL OUTCOMES

Stepwise logistic regression analyses identified factors significantly associated with poor neonatal outcomes for each of the 3 GA week groups. Female infants weighed significantly less than male infants in each GA week (Table 1); therefore, analysis was undertaken including sex-specific birth weight *z* scores instead of birth weight.[19] The factors significantly associated with poor outcomes in all 3 GA week groups were sex-specific birth weight *z* score (ORs, 1.67-2.22 for each unit decrease) and lack of prenatal steroids (ORs, 2.00-2.56). Male sex was significant in the 25 and 26 weeks' gestation groups (ORs, 1.52 and 1.41, respectively). Multiple births were not found to be a significant factor in any of the GA groups. In subsequent analyses, sex-specific birth weight percentiles were considered in 3 percentile groups (<25th, 25th-75th, and >75th percentiles) as determined from the charts of Kramer et al[19] to account for the effect of infants' size at birth (**Table 3**).

Table 3. Birth Weight Percentiles According to Gestational Age and Sex[9a]

Birth Weight, Percentiles	Birth Weight at GA, g			
	23 wk	24 wk	25 wk	26 wk
Male				
<25th	<520	<615	<700	<790
25th-75th	520-675	615-780	700-900	790-1030
>75th	>675	>780	>900	>1030
Female				
<25th	<500	<575	<650	<735
25th-75th	500-630	575-740	650-860	735-985
>75th	>630	>740	>860	>985

Abbreviation: GA, gestational age.
[a]Calculation of sex-specific birth weight percentiles was based on data from Kramer et al[19] rounded to the nearest 5 g. The *z* scores for the percentiles are the following: less than –0.674 for lower than the 25th percentile; –0.674 to 0.674 for the 25th to 75th percentiles; and greater than 0.674 for higher than the 75th percentile.

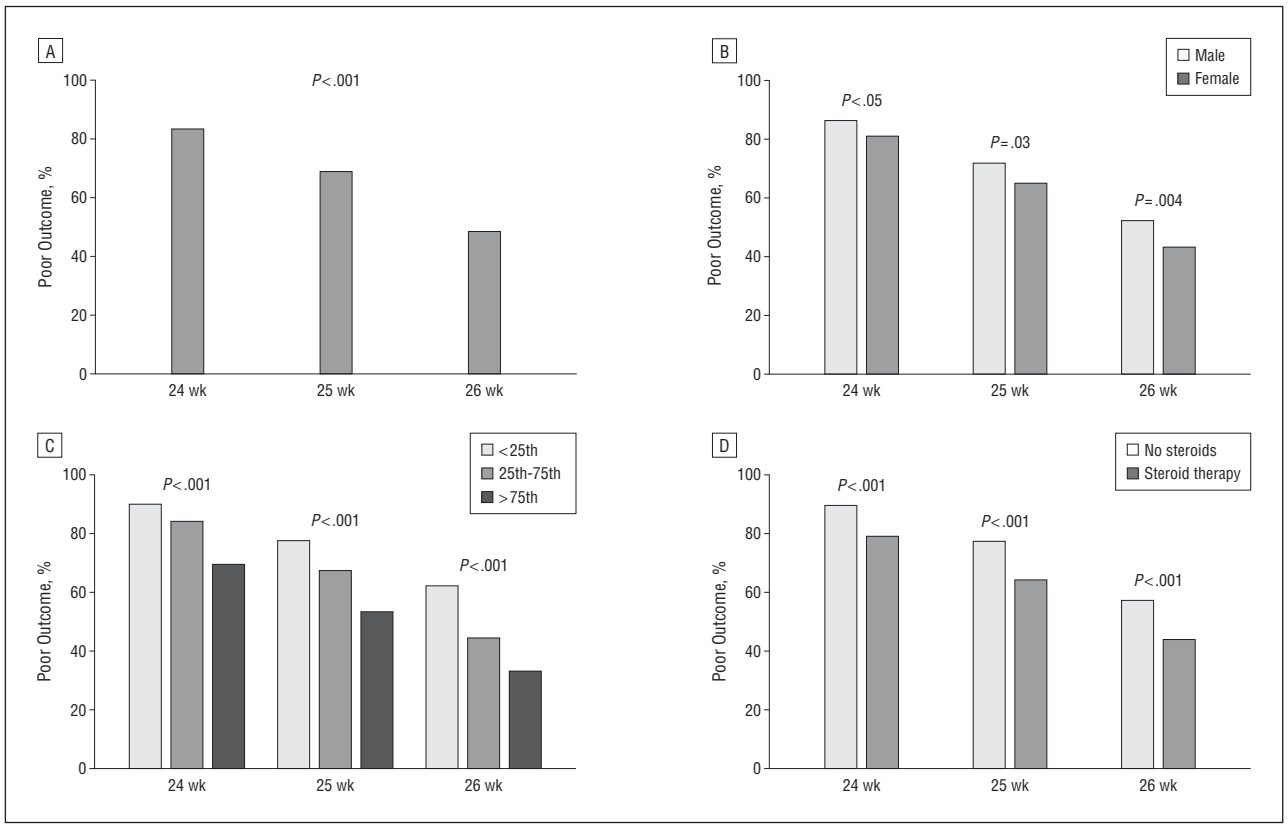

Figure. Combined poor outcomes of death or severe morbidity for infants born at 24 to 26 weeks' gestation (n=2544) between 2000 and 2008 by gestational age (A), sex (B), birth weight percentile (C), and prenatal steroid therapy (D).

OBSERVED POOR NEONATAL OUTCOME RATES

Poor neonatal outcome rates improved significantly ($P<.001$) for infants born at 24 to 26 weeks' gestation between January 1, 2000, and December 31, 2008 (64.1%) compared with between 1995 and 1999 (70.7%). Thus, further analyses for more recent data were performed on data from the 2544 infants born between 2000 and 2008. The percentage of infants with poor outcomes by GA in the recent period are shown in the **Figure**, A. In each GA week, significantly lower rates of poor outcomes were present in female vs male infants (Figure, B) ($P<.05$) with increasing birth weight percentile group (Figure, C) ($P<.001$) and with prenatal steroid therapy (Figure, D) ($P<.001$). Poor outcomes were similar for singleton and multiple infants in each GA week.

ESTIMATION OF POOR NEONATAL OUTCOME

On the basis of these analyses, we developed a model for estimating the rates of poor neonatal outcomes using data from 2000 to 2008 (n=2544). The model was based on 4 predictors of poor outcomes: (1) GA (24, 25, and 26 weeks), (2) sex-specific birth weight percentile group (<25th, 25th-75th, and >75th percentiles) (Table 3), (3) prenatal steroid therapy (any or none), and (4) sex,

Table 4. Multivariate Linear Regression Analysis of Rates of Combined Poor Outcome of Mortality or Severe Morbidity at Discharge of 2544 Infants Born at 24 to 26 Weeks' Gestation From 2000 to 2008

Predictor	Parameter Estimate (95% CI)	*P* Value	Rounded Estimate, %
Decrease per 1 wk in GA	16.6 (13.2-19.9)	<.001	17
Decrease per 1 level in BW	13.0 (9.6-16.4)	<.001	13
No prenatal steroid therapy	16.4 (10.9-21.9)	<.001	16
Male	6.7 (1.2-12.2)	.02	7
Intercept	24.6 (17.8-31.3)	<.001	25

Abbreviations: BW, birth weight; GA, gestational age.

thereby enabling the estimation of mortality or severe morbidity for 36 specific subgroups of infants ($3 \times 3 \times 2 \times 2$). The parameter estimates and rounded estimates of the model as determined by linear regression analysis are shown in **Table 4**. Estimated poor outcomes were calculated as the sum of the percentages determined for each of the 4 parameters: (1) GA (26, 25, and 24 weeks; 0%, 17%, and 34%, respectively), (2) birth weight percentile (>75th, 25th-75th, and <25th percentiles; 0%, 13%, and 26%, respectively), (3) lack of prenatal steroids (16%; $P < .001$); and (4) male sex (7%). The intercept value was 25%. The intraclass correlation coefficient between the observed and estimated poor outcomes was 0.93 (95% CI, 0.82-0.94), indicating a high level of agreement between observed and estimated rates. Estimated poor outcome rates for the 36 subgroups of female and male infants ranged from 25% to 100% (**Table 5**). For example, a male infant born with a birth weight of 800 g at 25 weeks' gestation who received prenatal steroid therapy has a cumulative poor outcome risk of 17% for 25 weeks' GA, 13% for birth weight in the 25th to 75th percentile group, 0% for prenatal steroid therapy, 7% for male sex, and 25% intercept (Table 4). His estimated poor outcome rate is thus 62% (or easily determined by obtaining the percentile group from Table 3 and the estimated rate from Table 5). For comparison, the observed poor outcomes in this group of infants was 66% (99 of 151 infants). For the 2 groups with an estimated rate for poor outcomes of 100%, the observed rates were 96% (23 of 24 infants) for male infants and 100% (24 of 24 infants) for female infants.

COMMENT

Our population-based study shows that the combined poor outcomes of death or severe morbidity at discharge of infants born at 24 to 26 weeks' gestation were significantly influenced by 3 parameters available at birth in addition to GA: (1) sex, (2) sex-specific birth weight percentile, and (3) prenatal steroid therapy. Our model for estimating poor outcomes showed cumulative risk of 17% for each GA week less than 26 weeks, 13% for each birth weight percentile group below the 75th percentile (25th to 75th and <25th percentiles), 16% for no exposure to prenatal corticosteroid therapy, and 7% for male sex. The percentage of infants with poor outcomes at discharge decreased significantly with each GA week. However, within each of these GA groups, the estimated rates for poor outcomes varied considerably, depending on the presence of these additional parameters. The estimated poor outcomes ranged from 59% to 100% for infants born at 24 weeks' gestation, 42% to 91% at 25 weeks' gestation, and 25% to 74% at 26 weeks' gestation. These results strongly suggest that GA alone should not be used to estimate the likelihood of survival without major neonatal morbidity among extremely preterm infants.

Our study supports the finding of Tyson et al,[7] who challenged the use of a GA threshold alone in deciding whether to administer intensive care to extremely premature infants. They concluded that 4 factors in addition to GA can predict survival without neurodevelopmental impairment for infants aged 18 to 22 months who received intensive care: (1) male sex, (2) lack of antenatal corticosteroids, (3) lower birth weight, and (4) multiple vs singleton birth. In our study and in accordance with other studies,[7,8,21] male sex was a risk factor for poor outcomes. An excess risk (OR, 2.31) for supplemental oxygen at 40 weeks' postmenstrual age was reported among male infants in the EPICure study.[1] This may explain the significant impact of male sex on outcomes noted in our study. In agreement with recent studies,[7,8] we showed that prenatal steroids were independently associated with better outcomes, including mortality and morbidity. The better outcomes for infants who received prenatal corticosteroids may result at least in part from their use when the obstetricians are committed to optimizing outcomes.[22] Singleton birth had no effect on the combined outcomes of death or severe morbidity in our study. Mercier et al[23] also found that plurality did not affect outcomes, and no difference in survival between preterm singletons and twins was suggested when controlled for birth weight and GA by others.[3,24] Draper et al[25] found an unexpected better outcome for multiple births. These findings are in contrast to other studies, where plurality had a negative effect on outcomes.[1,7,8,11,26]

Although the major neonatal morbidities included in a number of population-based or large multicenter studies varied considerably, the presence of respiratory and neurologic morbidities was usually considered.[1-6] For the purpose of this study, poor neonatal outcomes included the presence of severe neurologic or pulmonary morbidities that have been associated with poor long-term neurodevelopmental outcomes.[23,27-37] The clinical usefulness of the individual risk estimates is, however, limited by their relatively modest predictive accuracy.[38] For example, Schmidt et al[13] showed that 53% of infants who developed bronchopulmonary dysplasia had a favorable 18-month outcome. Therefore, in defining severe morbidity, we elected

Table 5. Estimated Percentage of Poor Outcome at Discharge[a]

Birth Weight Percentile by Sex	Prenatal Steroids	Poor Outcome at GA, %		
		26 wk	25 wk	24 wk
Female				
>75th	Yes	25	42	59
	No	41	58	75
25th-75th	Yes	38	55	72
	No	54	71	88
<25th	Yes	51	68	85
	No	67	84	100
Male				
>75th	Yes	32	49	66
	No	48	65	82
25th-75th	Yes	45	62	79
	No	61	78	95
<25th	Yes	58	75	92
	No	74	91	100

Abbreviation: GA, gestational age.

[a] Poor outcome at discharge is considered to be mortality or severe morbidity. The infants were born at 24 to 26 weeks' gestation. The estimated rates are based on GA, birth weight percentile, and prenatal steroid therapy.

to focus on infants at the highest risk by using the most severe definitions for neurosensory and pulmonary morbidities. For example, for pulmonary morbidity, we included only infants who received oxygen supplementation at 40 weeks' postmenstrual age or at discharge. Infants with bronchopulmonary dysplasia discharged with oxygen therapy (but not those breathing room air) had lower developmental scores at 2 years compared with those without bronchopulmonary dysplasia,[26] and home oxygen therapy correlated with motor outcomes at a mean age of 9.9 years.[1] For ultrasonographic signs that may indicate probable brain injury,[33,34] Schmidt et al[13] included echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, ventriculomegaly with or without intraventricular hemorrhage, and grade 3 and 4 periventricular-intraventricular hemorrhage, while we used grade 4 periventricular-intraventricular hemorrhage, posthemorrhagic hydrocephalus, or periventricular leukomalacia. Including infants with only the most severe neonatal morbidities may allow for more specific counseling for parents.

Our study is unique in being a national population-based analysis comprising data on more than 99% of VLBW births in Israel and including recent data. It represents a solid database for assessment of perinatal risk factors for mortality and severe morbidity in this group of infants, therefore providing useful information for the counseling of families on treatment options for these infants. Our study, similar to the EPICure study,[1] reports on all live births rather than neonatal intensive care unit admissions, with the advantage of possible estimation of poor outcomes just prior to delivery but the disadvantage of not considering delivery room care separately (willingness to treat and immediate viability of the infant) and neonatal intensive care unit care (potential medical improvements and limitations and short- and long-term outcome measures).

A number of limitations should be considered when assessing the results and implications of this study. The study was observational in design, and variations in obstetric as well as neonatal attitudes could influence clinical practice and outcomes. The improving accuracy of sonographic birth weight estimation shortly before birth in the small fetus remote from term may enable the use of estimated fetal weight as a proxy for birth weight in such models.[39] However, use of estimated fetal weight for prenatal counseling requires further validation. Finally, our model estimates poor outcomes at discharge from the neonatal intensive care unit. We have not undertaken long-term neurodevelopmental assessment of our own cohort; hence, it cannot be construed that all infants discharged with severe morbidities will have significant developmental handicaps. However, as discussed, we selected the most severe neonatal morbidities in our definition of poor outcomes considering the results of recent studies of developmental follow-up of very preterm infants.[11-13,23,27-37] In developing this model, we used the complete national data set and hence a separate population sample was not available for the purpose of validating the model. Despite this limitation, our analysis showed a high level of agreement between observed and estimated poor outcome rates. Our study reflects recent Israeli data and may be limited in its applicability to populations in other countries that use different policies and ethical approaches with different medical resources and capabilities. These results may help in creating poor outcome estimation tools for other populations that will adopt the principles of our model using their own mortality and morbidity data.

The combined poor outcomes of death or severe morbidity in the neonatal period of infants born at 24 to 26 weeks' gestation could be simply estimated on the basis of 4 parameters available at birth: (1) GA, (2) sex, (3) sex-specific birth weight percentile, and (4) prenatal corticosteroid therapy. This study's findings are complementary to our previous study;[9] we provide additional information regarding neurologic and pulmonary outcomes and present a more comprehensive and realistic

estimation for poor neonatal outcome. The provision of appropriate and up-to-date estimates of poor neonatal outcomes for specific groups of infants may be useful in counseling families on treatment options for these infants.

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