Neonatal Outcomes at Extreme Prematurity by Gestational Age Versus Birth Weight in a Contemporary Cohort

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Abstract

Objective The aim of the study is to describe the rates of neonatal death and severe neonatal morbidity in a contemporary cohort, as well as to evaluate the predictive value of birth gestational age (GA) and birth weight, independently and combined, for neonatal mortality and morbidity in the same contemporary cohort.

Study Design We performed a secondary analysis of an international, multicenter randomized controlled trial of delayed umbilical cord clamping versus umbilical cord milking in preterm infants born at 23 $^{0/7}$ to 31 $^{6/7}$ weeks of gestation. The current analysis was restricted to infants delivered <28 weeks. The primary outcomes of this analysis were neonatal death and a composite of severe neonatal morbidity. Incidence of outcomes was compared by weeks of GA, with planned subanalysis comparing small for gestational age (SGA) versus non-SGA neonates. Multivariable logistic regression was then used to model these outcomes based on birth GA, birth weight, or a combination of both as primary independent predictors to determine which had superior ability to predict outcomes.

Results Of 474 neonates in the original trial, 180 (38%) were included in this analysis. Overall, death occurred in 27 (15%) and severe morbidity in 139 (77%) neonates. Rates of mortality and morbidity declined with increasing GA (mortality 54% at 23 vs. 9% at 27 weeks). SGA infants ($n = 25$) had significantly higher mortality compared with non-SGA infants across all GAs ($p < 0.01$). There was no difference in the predictive value for neonatal death or severe morbidity between the three prediction options (GA, birth weight, or GA and birth weight).

Conclusion Death and severe neonatal morbidity declined with advancing GA, with higher rates of death in SGA infants. Birth GA and birth weight were both good predictors of outcomes; however, combining the two was not more predictive, even in SGA infants.

Keywords
- extreme prematurity
- fetal growth restriction
- intrauterine fetal growth restriction
- neonatal outcomes
- prematurity

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Key Points

- We performed a secondary analysis of multicenter randomized clinical trials.
- The study included only extremely preterm neonates <28 weeks.
- We provide rates of neonatal morbidity in a contemporary cohort.

Approximately 0.5% of all deliveries occur prior to 28 weeks' gestational age (GA),[1] yet these extremely preterm deliveries account for a significant proportion of neonatal morbidity and mortality.[2,3] Although advances in the care of these neonates have led to improved outcomes, the management of these pregnancies remains challenging. Providers are faced with the complex decisions of which interventions (e.g., corticosteroids, fetal monitoring) are appropriate, if and when delivery is indicated, and which modes of delivery to consider. These decisions are further compounded in the setting of fetal growth restriction.

While estimates of GA have traditionally been the main driver of determining if and when intervention is appropriate,[3–7] it is also commonplace to incorporate estimated fetal weight (EFW) in this decision, with some centers using an EFW of 400 to 500 g as a cut-off below which fetal intervention is not offered.[8,9] However, it is important to acknowledge that estimates of GA or EFW can be imprecise,[2,10] especially for extremely preterm gestations, where the error in ultrasound of 1 to 2 weeks may make the difference in decisions about intervention.[3,11]

Having an understanding of the outcomes of these neonates is of utmost importance for parental counseling and shared-decision making. Current counseling often utilizes the National Institutes of Health and Human Development (NICHD) Neonatal Research Network calculator, which, when originally developed, used data that is now >15 years old.[12] It is noteworthy that the findings have since been validated in a cohort of infants born between 2013 and 2016.[13] However, given major advances in neonatal care, current estimates of the likelihood of survival and of severe morbidity are needed.[2,3] Thus, we sought to describe the rates of neonatal death and severe neonatal morbidity in a contemporary cohort. In addition, we also aimed to evaluate the predictive value of birth GA and birth weight, independently and combined, for neonatal mortality and morbidity in the same contemporary cohort.

Materials and Methods

We performed a secondary analysis of an international, multicenter, randomized controlled trial (association of umbilical cord milking vs. delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants; ClinicalTrials.gov Identifier: NCT03019367).[14] The trial was supported by a grant (1R01HD088646–01A1) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The original trial was designed to determine whether umbilical cord milking was noninferior to delayed umbilical cord clamping among preterm infants born at 23 to 31 completed weeks of gestation. The primary outcome of the trial was a composite of death or severe (grade III or grade IV) intraventricular hemorrhage. Patients were enrolled from nine sites in the United States, Canada, and Europe, and the study was approved by the institutional review board or research ethics committee at each site. Between June 2017 and September 2018, 474 (of a planned 1,500) infants were enrolled. The study was terminated early due to the finding of a significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group (8% in the umbilical cord milking group vs. 3% in the delayed umbilical cord clamping group; risk difference 5% [95% CI 1–9%]; $p = 0.02$). Ongoing studies are following these children long-term.

The current analysis was restricted to those neonates who were delivered at extremely premature GAs, which we defined as delivery at $23^{0/7}$ to $27^{6/7}$ weeks' gestation. Dating of the pregnancy was determined by the following criteria: ultrasound up to $13^{6/7}$ weeks of gestation or assisted reproductive technology (ART) dating if ART was used to achieve pregnancy. If neither of these were available, then the best obstetric estimate at the time of delivery was used. Exclusion criteria were the same as those used in the original trial: major congenital anomalies, suspected or confirmed aneuploidy, placental abruption, transplacental incision, umbilical cord prolapse, fetal hydrops, morbidly adherent placenta with bleeding, placenta previa with bleeding, monochorionic multiple gestation, and inability to return for 24-month neurodevelopmental testing. In addition, infants in whom resuscitation was not planned were excluded.

The primary outcomes of this analysis were neonatal death and a composite of severe neonatal morbidity. We chose to include neonatal death both separately and in our composite outcome, as this is an important component of counseling families about the overall prognosis for their infant. Our neonatal composite outcome (severe morbidity) included the following components: neonatal death, cardiopulmonary resuscitation in the delivery room, use of cardiac inotropes, intraventricular hemorrhage (any grade), necrotizing enterocolitis (stage ≥2), retinopathy of prematurity, periventricular leukomalacia, spontaneous intestinal perforation, cerebellar hemorrhage, use of oxygen at 36 weeks corrected, and requirement for exchange transfusion. In addition to looking at any grade of intraventricular hemorrhage, we also looked at severe intraventricular hemorrhage (grades III or IV) separately. The diagnosis of intraventricular hemorrhage was based on a diagnosis made by a pediatric radiologist at each participating site. Any grade II or higher intraventricular hemorrhage was

adjudicated by two independent pediatric radiologists or neuroradiologists who were not affiliated with any of the participating study centers. The diagnosis of necrotizing enterocolitis was based on the Bell staging criteria,[15] and neonates with Bell stage ≥ 2 were included in outcome ascertainment. This included neonates were treated either medically or surgically. The diagnoses of periventricular leukomalacia and cerebellar hemorrhage were based on a diagnosis made on ultrasound or magnetic resonance imaging performed prior to hospital discharge. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for GA. All outcome assessments were performed by original trial team members.

Summary statistics are presented for baseline maternal, delivery, and neonatal characteristics, overall and by SGA status with comparisons made using the Student's *t*-test, Chi-square test, or Fisher's exact test as appropriate. Trends in primary outcomes across weeks of GA were assessed using the Cochran-Armitage trend test. SGA and non-SGA infants were compared using Chi-square or Fisher's exact tests as appropriate. In addition, multivariable logistic regression was used to model our outcomes based on GA at birth, birth weight, or a combination of both as primary independent predictors, with the following covariates considered in the model: race, ethnicity, parity, maternal diabetes, chorioamnionitis, presence of labor prior to delivery, duration of rupture of membranes prior to delivery, mode of delivery, and infant gender. Receiver operator characteristics curves (ROC) and areas under the curve (AUC) were determined for the three models. AUCs were compared with contrast matrices[16] to determine if birth GA, birth weight, or a combination of both had superior ability to predict outcomes. In addition, this same analysis was performed in a subgroup of SGA infants. All hypothesis tests were considered statistically significant at the 0.05 α level. Statistical analyses were performed using SAS v9.4 software (SAS Institute Inc., Cary, NC).

Results

Of 474 neonates in the parent trial, 180 (38%) were included in this analysis. The baseline characteristics of our sample are presented in ►Table 1. The median GA at delivery was 25.9 (interquartile range 24.5–27.0) weeks, and the median birth weight was 790 (interquartile range 652.5–916.0) g. Twenty-five (14%) neonates were SGA. The majority, 68% ($n = 123$), of neonates were born by cesarean. However, 66% ($n = 119$) had exposure to labor prior to delivery. Corticosteroids were administered prior to delivery in 89% ($n = 160$), and antenatal magnesium sulfate was given in 76% ($n = 137$).

►Table 2 and ►Fig. 1 show the incidence of neonatal death and adverse neonatal outcomes, both overall and by GA at birth in weeks. Overall, neonatal death occurred in 27 (15%) neonates, and the composite of severe neonatal morbidity occurred in 139 (77%). All infant mortalities occurred within 230 days of delivery (range: 0–230 days post-delivery); for a median of 11 days and with 90% of mortalities occurring within 55 days. As shown in ►Table 2, the most common components of the composite outcome were use of cardiac inotropes (43%), use of oxygen at 36 weeks corrected (38%), and intraventricular hemorrhage (37%). Rates of neonatal death and the composite of severe morbidity both declined with increasing GA ($p < 0.01$ for each), with neonatal death occurring in 54% of neonates delivered at 23 $^{0/7}$ to 23 $^{6/7}$ weeks of GA compared with 9% of those delivered at 27 $^{0/7}$ to 27 $^{6/7}$ weeks. The composite morbidity occurred in 100% of infants who were born at 23 $^{0/7}$ to 23 $^{6/7}$ weeks' gestation but decreased to 62% of those born at 27 $^{0/7}$ to 27 $^{6/7}$ weeks. The rates of the individual components of the composite outcome at each week of GA are shown in ►Table 2.

Table 1 Maternal and neonatal characteristics at baseline

Characteristic	$n = 180$
Maternal age, years	30.1 ± 5.6
Race	
White	86 (48%)
Black or African American	30 (17%)
Asian	19 (10%)
Other	15 (8%)
Unknown or not reported	30 (17%)
Ethnicity	
Hispanic	50 (28%)
Non-Hispanic	109 (60%)
Unknown or not reported	21 (12%)
Parity	1 (0–1)
Diabetes mellitus[a]	22 (12%)
Hypertensive disorder of pregnancy	37 (21%)
Chorioamnionitis	81 (45%)
Cesarean delivery	123 (68%)
Gestational age at birth, weeks	25.9 (24.5–27.0)
Birth weight, grams	790.0 (652.5–916.0)
Small for gestational age	25 (14%)
Male gender	92 (51%)
Presence of labor prior to delivery	119 (66%)
Duration of rupture of membranes prior to delivery, hours	81 (9–411)
Antenatal corticosteroids	160 (89%)
Antenatal magnesium sulfate	137 (76%)

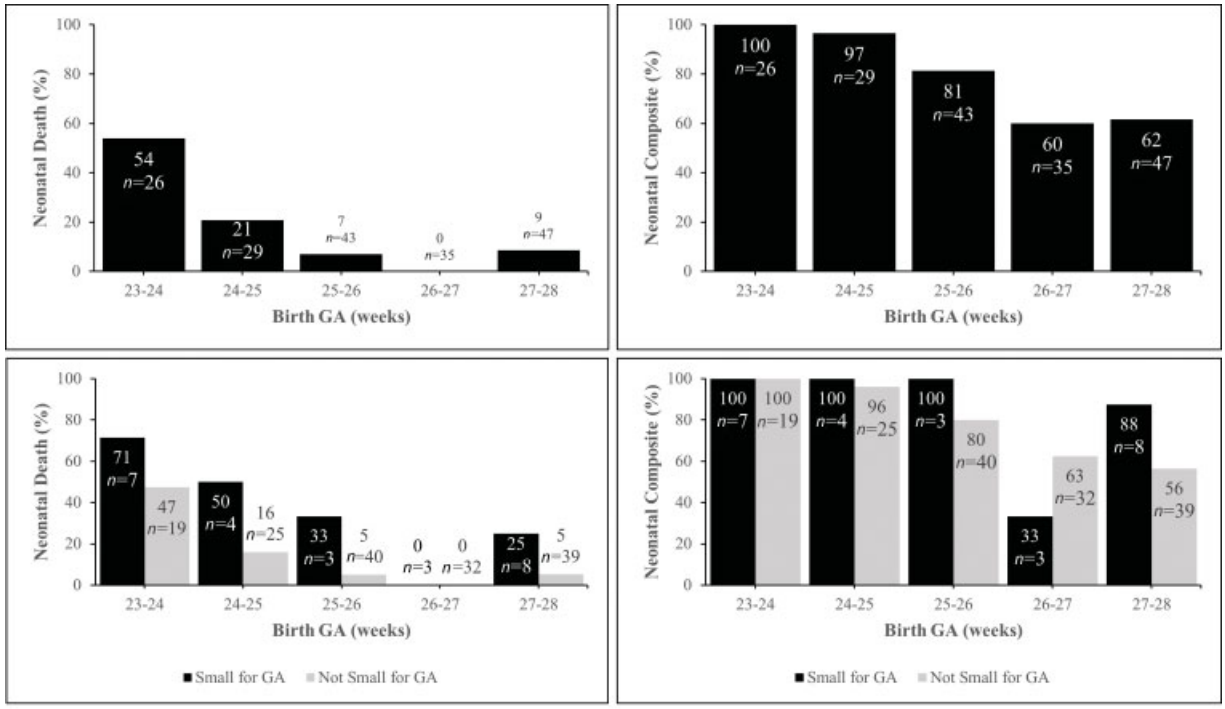
Note: Data are mean ± SD, median (interquartile range), or *n* (%) unless otherwise specified.
[a]Includes either gestational diabetes mellitus or preexisting diabetes mellitus.

In our analysis comparing SGA to non-SGA infants, baseline characteristics are presented in ►Table 3. Compared with the non-SGA cohort, neonates who were SGA were more likely to be born to mothers of higher parity (median 1.5 [interquartile range 0.5–2.0] vs. 0.5 [interquartile range 0.0–1.0], $p < 0.01$) and who had a hypertensive disorder of pregnancy (48 vs. 16%, $p < 0.01$). In addition, they were less likely to be exposed to labor prior to delivery (48 vs. 69%, $p < 0.01$) and had a marginally shorter duration of rupture of

Table 2 Incidence of adverse neonatal outcomes overall and by weeks of gestational age (GA) at birth

Outcome	Overall ($n = 180$)	23°–23^6 wk ($n = 26$)	24°–24^6 wk ($n = 29$)	25°–25^6 wk ($n = 43$)	26°–26^6 wk ($n = 35$)	27°–27^6 wk ($n = 47$)	*p*-Value[a]
Neonatal death	27 (15%)	14 (54%)	6 (21%)	3 (7%)	0 (0%)	4 (9%)	<0.01
Neonatal composite	139 (77%)	26 (100%)	28 (97%)	35 (81%)	21 (60%)	29 (62%)	<0.01
Neonatal death	27 (15%)	14 (54%)	6 (21%)	3 (7%)	0 (0%)	4 (9%)	<0.01
CPR in delivery room	12 (7%)	4 (15%)	3 (10%)	3 (7%)	0 (0%)	2 (4%)	0.03
Use of cardiac inotropes	77 (43%)	16 (62%)	20 (69%)	23 (53%)	7 (20%)	11 (23%)	<0.01
Any intraventricular hemorrhage	66 (37%)	15 (58%)	13 (45%)	16 (37%)	7 (20%)	15 (32%)	0.01
Severe intraventricular hemorrhage[b]	25 (14%)	9 (36%)	4 (16%)	5 (20%)	3 (12%)	4 (16%)	<0.01
Necrotizing enterocolitis	14 (8%)	1 (4%)	5 (17%)	6 (14%)	0 (0%)	2 (4%)	0.17
Retinopathy of prematurity	31 (17%)	6 (23%)	14 (48%)	8 (19%)	3 (9%)	0 (0%)	<0.01
Periventricular leukomalacia	20 (11%)	4 (15%)	6 (21%)	6 (14%)	1 (3%)	3 (6%)	0.02
Spontaneous intestinal perforation	5 (3%)	3 (12%)	1 (3%)	0 (0%)	1 (3%)	0 (0%)	0.02
Cerebellar hemorrhage	5 (3%)	0 (0%)	1 (3%)	2 (5%)	0 (0%)	2 (4%)	0.62
Use of oxygen at 36 wk corrected	69 (38%)	9 (35%)	15 (52%)	22 (51%)	11 (31%)	12 (26%)	0.07
Requirement for exchange transfusion	2 (1%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0.45

Abbreviation: CPR, cardiopulmonary resuscitation; GA, gestational age.
Note: Data are *n* (%) unless otherwise specified.
[a]*p*-Values are obtained from Cochran-Armitage trend test for the association of GA at birth (binned into weeks) with each morbidity.
[b]Includes grade III and grade IV intraventricular hemorrhage.



[a]Neonatal composite includes neonatal death, CPR in delivery room, use of cardiac inotropes, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), intestinal perforation, cerebellar hemorrhage, use of oxygen at 36 weeks corrected, and requirement for exchange transfusion

Fig. 1 Rates of neonatal death and neonatal composite outcome by gestational age (GA) at birth, with bottom panel small for gestational age (SGA) to non-SGA neonates.

Table 3 Maternal and neonatal characteristics at baseline in small for gestational age (SGA) vs. non-SGA neonates

Characteristic	SGA ($n = 25$)	Non-SGA ($n = 155$)	p-Value
Maternal age, years	29.9 ± 6.0	30.2 ± 5.5	0.84
Race			0.47
White	11 (44%)	75 (48%)	
Black or African American	8 (32%)	22 (14%)	
Asian	1 (4%)	18 (12%)	
Other	1 (4%)	14 (9%)	
Unknown or not reported	4 (16%)	26 (17%)	
Ethnicity			0.48
Hispanic	7 (28%)	43 (28%)	
Non-Hispanic	17 (68%)	92 (59%)	
Unknown or not reported	1 (4%)	20 (13%)	
Parity	1.5 (0.5–2.0)	0.5 (0.0–1.0)	<0.01
Diabetes mellitus[a]	3 (12%)	19 (12%)	0.88
Hypertensive disorder of pregnancy	12 (48%)	25 (16%)	<0.01
Chorioamnionitis	7 (28%)	74 (48%)	0.06
Cesarean delivery	19 (76%)	104 (67%)	0.37
Gestational age at birth, weeks	25.3 (23.9–27.1)	25.9 (24.7–27.0)	0.30
Birth weight, grams	585.0 (471.0–670.0)	815.0 (690.0–940.0)	<0.01
Male gender	14 (56%)	78 (50%)	0.47
Presence of labor prior to delivery	12 (48%)	107 (69%)	<0.01
Duration of rupture of membranes prior to delivery, hours	78 (36–122)	83 (9–421)	0.05
Antenatal corticosteroids	24 (96%)	136 (88%)	>0.99
Antenatal magnesium sulfate	22 (88%)	115 (74%)	0.29

Note: Data are mean ± SD, median (interquartile range), or *n* (%) unless otherwise specified.
[a]Includes either gestational diabetes mellitus or preexisting diabetes mellitus.

membranes prior to delivery (median 78 [IQR 36–122] hours vs. 83 [IQR 9–421] hours, $p = 0.05$). Rates of antenatal corticosteroid administration and magnesium sulfate administration were not statistically different in SGA compared with non-SGA infants. There was no difference in rates of SGA between the umbilical cord milking and delayed cord clamping groups; this finding was consistent when controlling for GA ($p = 0.37$).

In comparing outcomes in SGA ($n = 25$) versus non-SGA neonates (►Table 4), neonatal death occurred more frequently in neonates that were SGA (40 vs. 11%, $p < 0.01$). However, the composite outcome of severe morbidity was not statistically significantly different (88 vs. 75%, $p = 0.17$). Other than neonatal death, the individual components of the composite neonatal outcome were also not statistically different between groups (►Table 4). In ►Fig. 1 (bottom panel), rates of neonatal death and the neonatal composite outcome by GA at birth in SGA versus non-SGA infants are shown. SGA infants had significantly higher neonatal mortality across each week of GA at birth ($p < 0.01$). However, the composite outcome of severe neonatal morbidity was not significantly different between SGA and non-SGA infants ($p = 0.24$).

Lastly, ROC curves analyzing birth GA, birth weight, or a combination of birth GA and birth weight for prediction of outcomes are shown in ►Fig. 2. For the outcome of neonatal death, the AUC was 0.85 for birth GA, 0.85 for birth weight, and 0.86 for the combination of birth GA and birth weight. These AUCs were not different when comparing the predictive value of birth GA to birth weight ($p = 0.95$) or when comparing the predictive value of birth GA to the combination of both birth GA and birth weight ($p = 0.44$). When examining the predictive value of these models for the prediction of the composite neonatal severe morbidity, the AUCs were 0.81, 0.80, and 0.81 for birth GA, birth weight, and the combination of both, respectively. Similarly, there was no statistical difference in these models, with a p-value of 0.63 for birth GA versus birth weight and a p-value of 0.62 for birth GA versus the combination of birth GA and birth weight. In the analysis of 25 (14%) SGA infants, there was similarly no difference in the predictive value based on birth GA, birth weight, or a combination of both for either primary outcome (►Fig. 3).

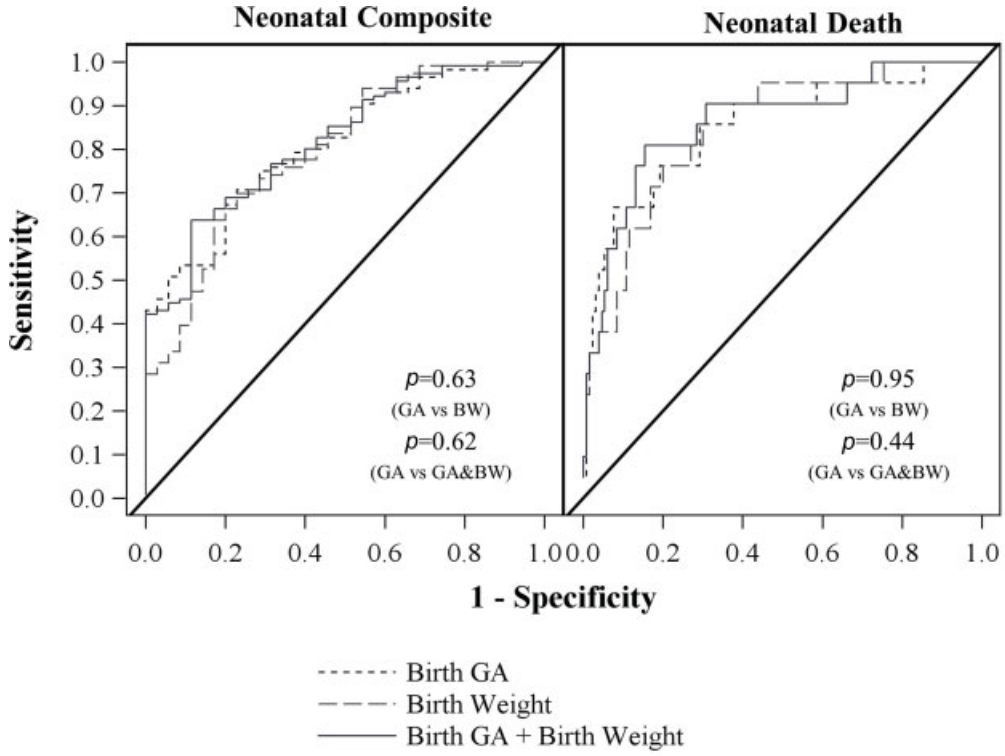
Discussion

In this secondary analysis, we affirmed that neonatal death and a composite of severe morbidity declined with advancing GA; however, we offer updated survival and morbidity estimates at GAs previously considered previable. Interestingly,

Table 4 Incidence of adverse neonatal outcomes in small for gestational age (SGA) vs. non-SGA neonates

Outcome	SGA ($n = 25$)	Non-SGA ($n = 155$)	*p*-Value
Neonatal death	10 (40%)	17 (11%)	<0.01
Neonatal composite	22 (88%)	117 (75%)	0.17
Neonatal death	10 (40%)	17 (11%)	<0.01
CPR in delivery room	1 (4%)	11 (7%)	0.56
Use of cardiac inotropes	13 (52%)	64 (41%)	0.34
Any intraventricular hemorrhage	9 (36%)	57 (37%)	0.94
Severe intraventricular hemorrhage[a]	4 (16%)	21 (14%)	0.74
Necrotizing enterocolitis	3 (12%)	11 (7%)	0.41
Retinopathy of prematurity	5 (20%)	26 (17%)	0.71
Periventricular leukomalacia	3 (12%)	17 (11%)	0.87
Spontaneous intestinal perforation	2 (8%)	3 (2%)	0.09
Cerebellar hemorrhage	0 (0%)	5 (3%)	0.37
Use of oxygen at 36 wk corrected	10 (40%)	59 (38%)	0.65
Requirement for exchange transfusion	0 (0%)	2 (1%)	0.57

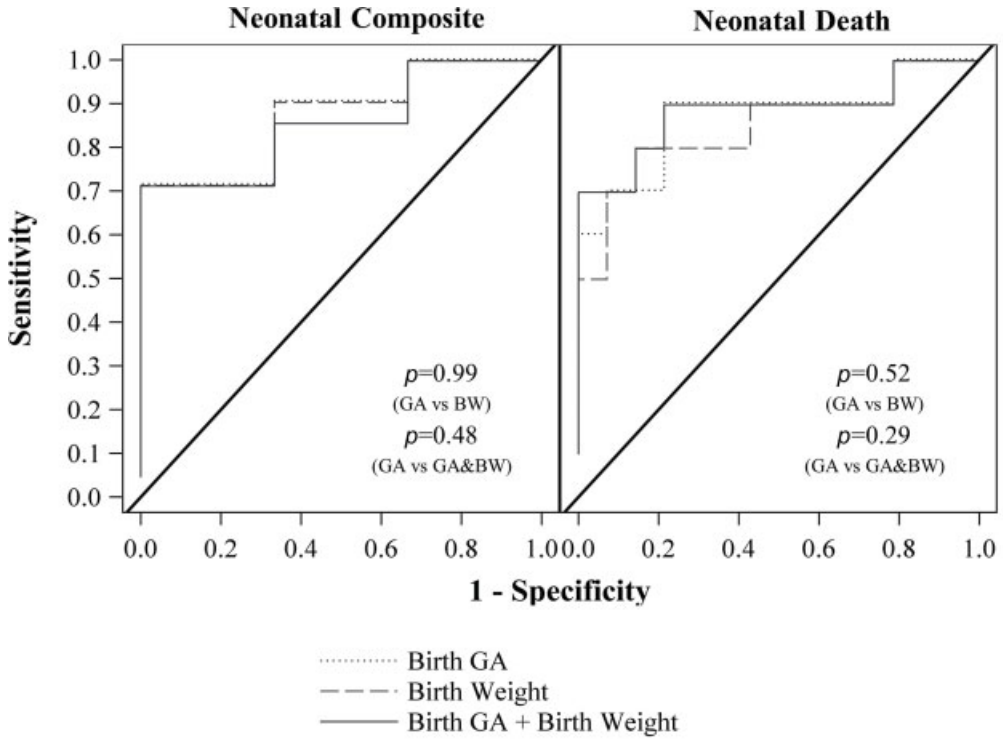
Abbreviation: CPR, cardiopulmonary resuscitation.
Note: Data are *n* (%) unless otherwise specified.
[a]Includes grade III and grade IV intraventricular hemorrhage.



[a]Neonatal composite includes neonatal death, CPR in delivery room, use of cardiac inotropes, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), intestinal perforation, cerebellar hemorrhage, use of oxygen at 36 weeks corrected, and requirement for exchange transfusion

Fig. 2 Receiver operator characteristics (ROC) curves for neonatal death and neonatal composite morbidity based on birth gestational age (GA), birth weight (BW), and a combination of gestational age and birth weight (GA&BW).

the rates of neonatal death and composite morbidity were slightly higher at $27^{0/7}$ to $27^{6/7}$ weeks than they were at $26^{0/7}$ to $26^{6/7}$ weeks, which we attribute to an overall small sample size. In a subanalysis of SGA neonates, neonatal death was higher in SGA than in non-SGA infants. However, composite severe neonatal morbidity was similar. In examining which model best predicts these outcomes, birth GA or birth weight were both good predictors of our outcomes. However, combining



[a]Neonatal composite includes neonatal death, CPR in delivery room, use of cardiac inotropes, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), intestinal perforation, cerebellar hemorrhage, use of oxygen at 36 weeks corrected, and requirement for exchange transfusion

[b]A small random offset was added to the ROC lines in this figure to distinguish those which are overlapping.

Fig. 3 Receiver operator characteristics (ROC) curves in small for gestational age (SGA) neonates for neonatal death and neonatal composite morbidity based on birth gestational age (GA), birth weight (BW), and a combination of gestational age and birth weight (GA&BW).

the two was not more predictive than either alone, even in SGA infants.

Although prior studies have described estimates of neonatal outcomes after early preterm delivery,[3,17–20] there are limited contemporary data. A 2017 consensus statement from the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine acknowledges that these models "may not provide estimates with an accuracy equivalent to that initially reported."[2] As data routinely used in counseling was generated nearly 15 years ago, we report outcomes more reflective of contemporary practice over a single year (2017–2018) derived from a multinational trial. We show a significant improvement in neonatal survival and morbidity in very early preterm gestations beyond what is often used to counsel patients based on available data. The 2002 ACOG Practice Bulletin "Perinatal Care at the Threshold of Viability"[21] presents mortality rates ranging from 70% at 23 weeks (54% in our study) to 10% at 27 weeks (9% in our cohort). More recently, the 2017 ACOG Consensus "Periviable Birth"[2] describes survival rates of 23 to 27% for infants born at 23 weeks (46% in our cohort) and 67 to 76% at 25 weeks (93% in our cohort). However, even this recent publication is guided by data from 2003 to 2011.[17,19,22,23] Comparing our morbidity estimates is more challenging, as morbidities and the length of follow-up are heterogenous between studies. For instance, Stoll et al[19] showed rates of necrotizing enterocolitis of 12% at 23 weeks and 10% at 27 weeks and oxygen use at 36 weeks of 73% at 23 weeks and 34% at 27 weeks. These and other studies[24–27] are in contrast to our data showing significantly lower estimates of these outcomes between 23 and 25 weeks, which are likely reflective of contemporary advances in neonatal care.

When comparing birth weight to GA, Tyson et al studied over 4,000 infants born at 22 to 25 weeks and found that, for each 100-g increment in birth weight, there was a reduction in death and neurodevelopmental impairment similar to that associated with a 1-week increase in GA.[11] More recently, Bader et al showed that not only was birth GA strongly associated with mortality, so was birth weight.[20] These data highlight the importance of considering characteristics other than just GA. In regard to growth restriction in the setting of extreme prematurity, outcome data are limited. In a study evaluating 43 infants with growth restriction between 26 and 28 weeks, Lees et al reported the rate of neonatal death was 19%, and severe neonatal morbidity was 51%.[28] Although these numbers from a larger cohort are more optimistic than those we report between 26 and 28 weeks, it is noteworthy that there were no fetuses <26 weeks, a large focus of our study. Our data describe these outcomes at even earlier GAs—during which severe morbidity and mortality are clearly higher—within the

scope of up-to-date neonatal practice. However, despite the known associations between SGA infants and increased morbidity and mortality at these early GAs, we failed to find any additional predictive benefit of adding birth weight to GA to predict the incidence of these outcomes.

We acknowledge that our study is not without limitations. Although these data are from a randomized trial, our outcomes of neonatal death and severe neonatal morbidity were not the primary outcome of the original trial. Therefore, we report an observational study of these outcomes. Although we performed logistic regression analyses, our study is also subject to residual confounding. Further, although we have data on antenatal corticosteroids and magnesium sulfate, we do not have data on the length of time or number of doses that were administered prior to delivery. We are also unable to account for differences in practice patterns at different centers. In addition, our data regarding weight are based on actual birth weight, not EFW, which is the information that is readily available when counseling the patient before delivery. Estimates of fetal weight were not available in this dataset. However, birth weight is highly reliable, while EFW has a potential error of 1 to 2 weeks. Given that birth weight and GA were equally predictive of outcomes (and the combination not more predictive), it is likely that GA alone is more predictive than any EFW and should be used (perhaps with knowledge of growth restriction) to guide pregnancy management. It is also important to note that some patients will opt against resuscitation at a periviability, and these neonates are not included in our analysis. Lastly, we note that our small sample size, particularly in the SGA cohort, may not be sufficient to detect smaller but clinically significant differences. This small sample size may also explain why outcomes were worse at 27 weeks, which may not be generalizable to all populations and thus needs further evaluation.

The strengths of our study include the multicenter diverse population from a randomized trial that enrolled participants from 2017 to 2018, a timeframe short enough that there were not significant changes in neonatology practice. Further, this data also reflects current neonatology practices. In addition, although extremely preterm neonates are at risk of several morbidities, we chose to focus on those that are the most severe. Lastly, our outcomes, which were objective in nature, were centrally validated by a team of research staff.

In summary, we present updated estimates for neonatal death and severe morbidity in a contemporary patient population. This area warrants additional evaluation in a larger cohort so that providers can effectively counsel patients for informed decision making.

Note

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Conflict of Interest

None declared.

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