ORIGINAL ARTICLE

Between-Hospital Variation in Treatment and Outcomes in Extremely Preterm Infants

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ABSTRACT

BACKGROUND

Between-hospital variation in outcomes among extremely preterm infants is largely unexplained and may reflect differences in hospital practices regarding the initiation of active lifesaving treatment as compared with comfort care after birth.

METHODS

We studied infants born between April 2006 and March 2011 at 24 hospitals included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Data were collected for 4987 infants born before 27 weeks of gestation without congenital anomalies. Active treatment was defined as any potentially lifesaving intervention administered after birth. Survival and neurodevelopmental impairment at 18 to 22 months of corrected age were assessed in 4704 children (94.3%).

RESULTS

Overall rates of active treatment ranged from 22.1% (interquartile range [IQR], 7.7 to 100) among infants born at 22 weeks of gestation to 99.8% (IQR, 100 to 100) among those born at 26 weeks of gestation. Overall rates of survival and survival without severe impairment ranged from 5.1% (IQR, 0 to 10.6) and 3.4% (IQR, 0 to 6.9), respectively, among children born at 22 weeks of gestation to 81.4% (IQR, 78.2 to 84.0) and 75.6% (IQR, 69.5 to 80.0), respectively, among those born at 26 weeks of gestation. Hospital rates of active treatment accounted for 78% and 75% of the between-hospital variation in survival and survival without severe impairment, respectively, among children born at 22 or 23 weeks of gestation, and accounted for 22% and 16%, respectively, among those born at 24 weeks of gestation, but the rates did not account for any of the variation in outcomes among those born at 25 or 26 weeks of gestation.

CONCLUSIONS

Differences in hospital practices regarding the initiation of active treatment in infants born at 22, 23, or 24 weeks of gestation explain some of the between-hospital variation in survival and survival without impairment among such patients. (Funded by the National Institutes of Health.)

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THE DECISION TO INITIATE OR FORGO potentially lifesaving treatment in infants who are born near the limit of viability is extremely difficult.[1,2] Clinicians recognize that in some cases, the infant is too immature for treatment to be effective, whereas in other cases, treatment is clearly indicated. Yet, in many cases, it is unclear whether treatment is in the infant's best interest.[3,4]

Although factors such as the infant's birth weight and sex, plurality of birth (singleton vs. multiple), and exposure to antenatal glucocorticoids affect the prognosis of extremely preterm infants,[5,6] many groups still make recommendations about active treatment that are based primarily on gestational age at birth.[2,7-12] Active intervention for infants born before 22 weeks of gestation is generally not recommended, whereas the approach for infants born at or after 22 weeks of gestation varies. In the United States, both the American Academy of Pediatrics (AAP) and the American Congress of Obstetricians and Gynecologists (ACOG) recommend that clinicians and families make individualized decisions about treating extremely preterm infants on the basis of parental preference and the most recent data available regarding survival and morbidity.[4,13]

Counseling of families who are facing an extremely preterm birth is complicated by wide variation in outcomes. In two studies, survival estimates range from 1 to 52% among infants born at 23 weeks of gestation and from 31 to 67% among infants born at 24 weeks of gestation.[14,15] Reported rates of neurodevelopmental impairment among children who were born extremely preterm also vary significantly.[16]

The recent summary of a workshop held by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the Society for Maternal–Fetal Medicine, the AAP, and the ACOG on extremely preterm birth suggests that variation in reported outcomes may, in part, reflect differences in hospital practices regarding the initiation of either active treatment or comfort care.[2] To investigate this possibility and its implications, we analyzed data collected for infants who were born at hospitals included in the NICHD Neonatal Research Network (NRN) to identify variation in hospital rates of active treatment and the relationship between active treatment and outcomes at 18 to 22 months of corrected age.

METHODS

We studied infants who were born between April 1, 2006, and March 31, 2011, at 24 hospitals included in the NRN. The NRN consists of clinical centers of various sizes and in several U.S. regions, with diverse patient demographics, clinical practices, and outcomes.[17,18] Hospitals included in the study analysis contributed data for the entire study period.

We collected data for liveborn infants who were born before 27 weeks of gestation, including those who died in the delivery room. Data were collected for infants born before 22 weeks of gestation if they weighed 400 g or more; there was no minimum birth weight for infants born at or after 22 weeks of gestation. A total of 213 infants with recognized syndromes or major congenital malformations were excluded, because factors besides prematurity may have influenced the prognosis and treatment decisions for these infants. Three additional infants were excluded owing to missing data about interventions administered in the delivery room.

DATA COLLECTION

Trained research personnel at each hospital obtained data for all liveborn infants.[19] Demographic and clinical information was extracted from medical records. Gestational age at birth was determined by identifying the dates of the mother's last menstrual period and examining fetal ultrasound images, or if those methods were unavailable, by estimation after birth.[20] Birth weight for gestational age was compared with sex-specific growth curves.[21]

The institutional review board at each participating site approved NRN in-hospital and follow-up protocols. Written informed consent from a parent or guardian was obtained for the follow-up protocol at 20 hospitals and for the in-hospital protocol at 2 hospitals. For all other hospitals, the institutional review board approved a waiver of consent. The second and fourth authors had full access to all data and were responsible for the data analysis and reporting.

ACTIVE TREATMENT

Infants were considered to have received active treatment if they received any of the following interventions: surfactant therapy, tracheal intubation, ventilatory support (including continuous

positive airway pressure, bag–valve–mask ventilation, or mechanical ventilation), parenteral nutrition, epinephrine, or chest compressions. We focused on the specific decision to initiate or forgo active treatment after birth and thus did not include obstetrical treatment or later decisions to withdraw treatment (after an infant's response to treatment could be gauged) in our definition.

OUTCOMES

Data on survival and neurodevelopmental impairment were collected at 18 to 22 months of corrected age. Neurodevelopmental assessment was performed by annually certified examiners and consisted of a structured neurologic examination and developmental and behavioral tests, which have been described previously.[22,23] Severe impairment was defined as a cognitive or motor score on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) of less than 70 (i.e., >2 SD below the scale mean; mean [±SD], 100±15), severe cerebral palsy, a Gross Motor Function Classification System (GMFCS) level of 4 or 5 (on a scale of 0 [normal] to 5 [most impaired]), bilateral blindness (visual acuity, <20/200), or severe hearing impairment that cannot be corrected with bilateral amplification. Moderate impairment was defined as a Bayley-III cognitive or motor score of 70 to 84, (i.e., 1 to 2 SD below the scale mean), moderate cerebral palsy, or a GMFCS level of 2 or 3. Bayley-III motor scores were ascertained beginning in 2010; all other criteria were assessed throughout the study period. Because impairment is a risk only for infants who survive, we used the following outcomes in our models: survival, survival without severe impairment, and survival without moderate or severe impairment.

STATISTICAL ANALYSIS

We used the chi-square test or Fisher's exact test (if the cell size was <5) to compare the differences in demographic and clinical characteristics between infants who received active treatment and those who did not. We calculated overall rates of active treatment (percentage of all infants who received active treatment) by gestational age at birth in both days and weeks. We used Wilson's method to derive 95% confidence intervals.[24]

We used multivariable multilevel logistic-regression models to assess clustering of active treatment at the hospital level, by gestational age at birth, after accounting for differences in patient characteristics. Models included infant-level receipt of active treatment as a binary outcome and were adjusted for characteristics that were known before or shortly after birth, including the infant's birth weight (in grams), sex, plurality of birth (singleton vs. multiple), and 1-minute Apgar score (≤3 vs. >3) and the mother's age (≤19 years vs. >19 years), race (white, black, or other), ethnic group (Hispanic vs. non-Hispanic), enrollment in private health insurance (yes vs. no), receipt of prenatal care (≥1 visit vs. no visits), receipt of antenatal glucocorticoids (yes vs. no), and status with respect to hypertension (including pre-existing hypertension, gestational hypertension, preeclampsia, and eclampsia) (yes vs. no), insulin-dependent diabetes (yes vs. no), and chorioamnionitis (yes vs. no). We calculated the intraclass correlation coefficient (ICC) statistic, which represents between-group variation as a proportion of all variation of a dependent variable when data are analyzed by group (e.g., hospital). Using the models described above, we calculated the ICC for active treatment (i.e., the proportion of variation in active treatment that was attributable to an infant's hospital of birth) by gestational age at birth.[25]

To determine how hospital practices regarding the initiation of active treatment in extremely preterm infants relate to the outcomes of survival and survival without impairment by gestational age at birth, we compared pairs of multilevel logistic-regression models for each of the three specified outcomes.[25] In these models, the infant was the unit of analysis and the outcome was the dependent variable. Each pair of models consisted of one model that included the hospital rate of active treatment (percentage of infants at a given hospital who received active treatment) as a second-level predictor and one model that did not; the ICC was calculated for each model. The between-hospital variation for a given outcome that could be attributed to the hospital rate of active treatment was calculated as 1 – [(ICC of model including hospital rate of active treatment) ÷ (ICC of model not including hospital rate of active treatment)].[25] To account for differences in patient characteristics among hospitals, models were adjusted for the covariates listed previously. For each participating hospital, risk-adjusted outcomes were calculated on the basis of these

models by means of the marginal method of regression adjustment.[26]

In addition, we considered the possibility that hospital volume may explain some of the between-hospital variation in outcomes; this possibility has been proposed previously.[27,28] Sensitivity analyses were performed to evaluate whether hospital volume of extremely preterm births during the study period modified the effect of hospital rates of active treatment on outcomes.

Multilevel modeling was performed using Stata/MP software, version 13.0 (StataCorp). All other analyses were performed using SAS software, version 9.3 (SAS Institute). Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

INFANT CHARACTERISTICS

A total of 4987 infants born at 24 hospitals were included in the study (range, 32 to 489 infants per hospital), of whom 4329 (86.8%) received active treatment (Table 1). Infants who did not receive active treatment after birth were more likely to be small for gestational age and to have 1-minute Apgar scores of 3 or lower; they were less likely to have been exposed to antenatal glucocorticoids or to have been delivered by cesarean section. Methods of active treatment varied by gestational age at birth (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Active treatment was administered to 22.1% (95% confidence interval [CI], 18.1 to 26.8) of infants born at 22 weeks of gestation, 71.8% (95% CI, 68.5 to 74.9) born at 23 weeks of gestation, 97.1% (95% CI, 96.0 to 98.0) born at 24 weeks of gestation, 99.6% (95% CI, 99.1 to 99.8) born at 25 weeks of gestation, and 99.8% (95% CI, 99.4 to 100.0) born at 26 weeks of gestation. Among infants born at 22 or 23 weeks of gestation, overall rates of active treatment were significantly higher among infants born on the last 2 days of the gestational week than among those born earlier during the same week (Fig. 1).

Outcomes were known for 4704 children (94.3%) at 18 to 22 months of corrected age (Table 2). Among those who received active treatment and whose outcomes were known at follow-up (4046 children), 65.0% survived, 56.1% survived without severe neurodevelopmental impairment, and 40.8% survived without moderate or severe neurodevelopmental impairment. Detailed outcomes for children who survived are described in Table S2 in the Supplementary Appendix. All infants who did not receive active treatment (658 infants) died within 24 hours after birth.

Two of 129 infants born before 22 weeks of gestation who weighed 400 g or more received active treatment. These patients were born at 21 weeks 0 days and at 21 weeks 4 days, at different hospitals. All infants born before 22 weeks of gestation died within 12 hours after birth.

VARIATION IN HOSPITAL RATES OF ACTIVE TREATMENT

Among infants born at 22, 23, or 24 weeks of gestation, hospital rates of active treatment varied widely (Fig. S1 in the Supplementary Appendix). The interquartile ranges for hospital rates of active treatment were 7.7 to 100% among infants born at 22 weeks of gestation, 52.5 to 96.5% among infants born at 23 weeks of gestation, and 95.2 to 100% among infants born at 24 weeks of gestation. Most hospitals provided active treatment to all infants born at 25 or 26 weeks of gestation (interquartile range, 100 to 100%); 5 of 24 hospitals provided active treatment to all infants born at 22 through 26 weeks of gestation.

Results from multilevel models indicated that the initiation of active treatment clustered at the hospital level. The proportion of variation in hospital rates of active treatment that was attributable to the infant's hospital of birth was 71% (ICC, 0.71; 95% CI, 0.45 to 0.88), 38% (ICC, 0.38; 95% CI, 0.21 to 0.58), and 25% (ICC, 0.22; 95% CI, 0.06 to 0.57) for infants born at 22, 23, or 24 weeks of gestation, respectively, after adjustment for patient demographic and clinical factors. There was no significant variation in hospital rates of active treatment among infants born at 25 or 26 weeks of gestation.

RELATIONSHIP OF ACTIVE TREATMENT TO OUTCOMES

Overall rates of survival, survival without severe impairment, and survival without moderate or severe impairment were 5.1% (interquartile range, 0 to 10.6), 3.4% (interquartile range, 0 to 6.9), and 2.0% (interquartile range, 0 to 0.7), respectively, among children born at 22 weeks of gestation and were 23.1% (interquartile range, 0 to

Table 1. Mother and Infant Characteristics.*

Variable	Infants Born at 22 Wk of Gestation		Infants Born at 23 Wk of Gestation		Infants Born at 24 Wk of Gestation		Infants Born at 25 Wk of Gestation		Infants Born at 26 Wk of Gestation	
	Active Treatment (N=79)	No Active Treatment (N=278)	Active Treatment (N=542)	No Active Treatment (N=213)	Active Treatment (N=1119)	No Active Treatment (N=33)	Active Treatment (N=1257)	No Active Treatment (N=5)	Active Treatment (N=1330)	No Active Treatment (N=2)
Mother										
≤19 Yr of age — %	17.7†	12.6	13.3	13.6	12.7	15.2	11.4	20.0	11.4	0.0
Enrolled in private insurance — %	24.1	37.1‡	41.9	36.6	39.9	42.4	40.3	40.0	39.9	50.0
Received prenatal care — %	89.9	93.5	94.3	89.7‡	94.7	97.0	94.7	100.0	95.1	100.0
Race and ethnic group — %§										
White non-Hispanic	22.8	35.6‡	34.1	30.5	38.4	36.4	40.3	40.0	37.1	50.0
Black non-Hispanic	62.0	37.1‡	45.9	31.0‡	38.7	24.2	37.9	20.0	36.3	50.0
White Hispanic	7.6	20.1‡	12.5	27.2‡	14.4	30.3‡	14.6	0.0	16.8	0.0
Black Hispanic	1.3	1.1	0.9	1.4	1.1	0.0	0.8	0.0	1.4	0.0
Had insulin-dependent diabetes — %	1.3	2.9	2.4	3.8	5.2	6.1	4.5	20.0	4.7	0.0
Had hypertension — %¶	12.7	7.9	11.1	8.9	17.2	15.2	22.9	40.0	24.4	50.0
Had chorioamnionitis — %	32.9	29.1	23.8	25.8	22.5	45.5‡	19.3	60.0	18.0	0.0
Infant										
Male sex — %	45.6	53.6	53.0	54.9	51.6	60.6	53.1	80.0	50.5	0.0
Singleton birth — %	68.4	68.0	72.3	67.6	74.8	72.7	76.5	100.0	75.8	100.0
1-Minute Apgar score ≤3 — %	83.5	83.8	70.8	80.3‡	56.8	87.9‡	48.1	100.0‡	41.7	100.0
Median birth weight — g (interquartile range)	510 (466–580)	484 (435–526)	586 (526–640)	545 (492–600)	655 (580–720)	600 (555–687)	750 (670–872)	658 (595–680)	860 (750–960)	870 (820–921)
Small for gestational age — %	3.8	5.4	2.8	10.3‡	7.3	21.2‡	8.0	20.0	7.4	0.0
Exposed to antenatal glucocorticoids — %‖	27.8	4.7‡	67.5	25.8‡	90.4	69.7‡	90.1	60.0	88.4	50.0
Full course	10.1	1.4	37.8	12.2	64.0	39.4	63.1	60.0	62.9	50.0
Partial course	17.7	3.3	29.3	12.7	25.9	30.3	26.7	0.0	25.1	0.0
Delivered by cesarean section — %	11.4	2.9‡	26.4	2.8‡	63.1	21.2‡	68.7	0.0	70.3	0.0

* Statistical tests were conducted to compare infants who received active treatment and those who did not receive active treatment by gestational age at birth. Because there was a small number of infants born at 25 or 26 weeks of gestation who did not receive active treatment, formal statistical comparisons were made only among infants born at 22, 23, or 24 weeks of gestation. A total of 129 infants who were born before 22 weeks of gestation were not included.
† Maternal age was missing for 1 infant born at 22 weeks of gestation who received active treatment.
‡ P<0.05.
§ Race and ethnic group were self-reported.
¶ Hypertension includes preexisting hypertension, gestational hypertension, preeclampsia, and eclampsia.
‖ Data on exposure to a full or partial course of antenatal glucocorticoids are not available for all subjects. Therefore, the sum of the values for the full course and partial course rows may not equal the total value.
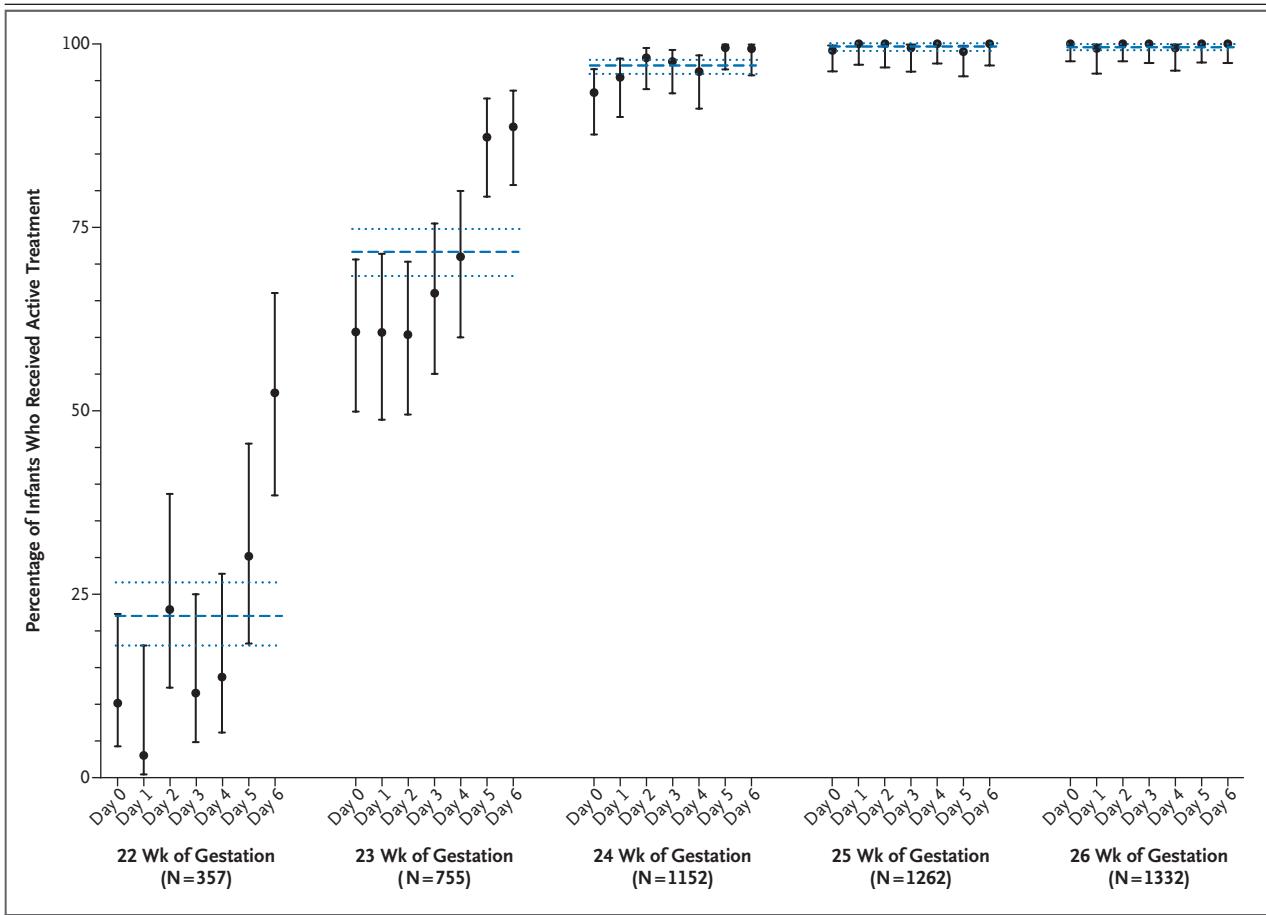
Figure 1. Rates of Active Treatment by Gestational Age at Birth.

Point values represent the mean percentage, across all hospitals, of infants born at a given gestational age (in weeks and days) who received active treatment. Vertical bars represent 95% confidence intervals. Blue dashed lines indicate the mean rate of active treatment among infants born during a given week of gestation, and blue dotted lines indicate 95% confidence intervals.

50.0), 15.4% (interquartile range, 0 to 33.3), and 9.0% (interquartile range, 0 to 14.6), respectively, among those born at 22 weeks of gestation who received active treatment. Overall rates of survival, survival without severe impairment, and survival without moderate or severe impairment were 81.4% (interquartile range, 78.2 to 84.0), 75.6% (interquartile range, 69.5 to 80.0), and 58.5% (interquartile range, 51.6 to 65.4), respectively, among children born at 26 weeks of gestation and were similar among those born at 26 weeks of gestation who received active treatment. The discrepancy between outcomes for all children and outcomes for those who received active treatment decreased with increasing gestational age at birth (Table 2).

Figure 2 shows the relationship of hospital rates of active treatment to risk-adjusted outcomes for children born at 22, 23, or 24 weeks of gestation. Multilevel models did not converge when children born at 22 weeks of gestation and those born at 23 weeks of gestation were considered separately, and thus children born at either 22 or 23 weeks of gestation were included in the same model. Among children born at 22 or 23 weeks of gestation, the hospital rate of active treatment accounted for a majority of the between-hospital variation in outcomes (78% of the variation in survival, 75% of the variation in survival without severe impairment, 41% of the variation in survival without moderate or severe impairment), after adjustment for patient clinical and demographic factors; this relationship was attenuated among those born at 24 weeks. Among children

Table 2. Crude Outcomes by Gestational Age at Birth.*

Outcome	All Infants		Infants Who Received Active Treatment	
	Overall Rate†	Hospital Rate‡	Overall Rate†	Hospital Rate‡
	mean (95% CI)	median (interquartile range)	mean (95% CI)	median (interquartile range)
22 Wk of gestation				
Survival	5.1 (3.2–7.9)	3.4 (0.0–10.6)	23.1 (14.9–34.0)	21.1 (0.0–50.0)§
Survival without severe impairment	3.4 (1.9–5.9)	0.0 (0.0–6.9)	15.4 (8.8–25.4)	5.0 (0.0–33.3)§
Survival without moderate or severe impairment	2.0 (0.9–4.1)	0.0 (0.0–0.7)	9.0 (4.3–17.9)	0.0 (0.0–14.6)§
23 Wk of gestation				
Survival	23.6 (20.7–26.9)	24.8 (10.3–32.1)	33.3 (29.4–37.5)	30.8 (23.8–37.1)
Survival without severe impairment	17.9 (15.3–20.9)	16.8 (7.3–25.2)	25.2 (21.7–29.2)	25.0 (15.1–28.0)
Survival without moderate or severe impairment	11.3 (9.2–13.9)	8.7 (3.6–13.4)	16.0 (13.1–19.4)	14.2 (6.7–18.9)
24 Wk of gestation				
Survival	54.9 (51.9–57.8)	53.7 (45.4–65.9)	56.6 (53.6–59.5)	58.0 (47.2–66.8)
Survival without severe impairment	44.7 (41.7–47.7)	44.3 (37.1–54.5)	46.1 (43.1–49.1)	44.3 (38.2–56.2)
Survival without moderate or severe impairment	30.0 (27.3–32.8)	30.0 (18.4–33.3)	30.9 (28.2–33.8)	30.5 (18.7–33.6)
25 Wk of gestation				
Survival	72.0 (69.4–74.5)	71.2 (65.7–79.5)	72.3 (69.7–74.8)	71.7 (65.7–79.5)
Survival without severe impairment	61.1 (58.3–63.8)	59.3 (54.7–64.3)	61.4 (58.5–64.1)	59.9 (56.2–64.5)
Survival without moderate or severe impairment	44.3 (41.5–47.2)	46.0 (34.9–51.7)	44.5 (41.7–47.4)	46.5 (35.0–51.7)
26 Wk of gestation				
Survival	81.4 (79.2–83.6)	81.0 (78.2–84.0)	81.6 (79.3–83.7)	81.3 (78.9–85.7)
Survival without severe impairment	75.6 (73.2–78.0)	75.7 (69.5–80.0)	75.7 (73.3–78.1)	76.4 (70.8–80.3)
Survival without moderate or severe impairment	58.5 (55.8–61.3)	58.9 (51.6–65.4)	58.6 (55.9–61.4)	59.8 (53.6–67.0)

* CI denotes confidence interval.
† Overall rate is the percentage of all infants regardless of hospital of birth.
‡ Hospital rate is the percentage of infants calculated separately for each of the 24 hospitals, which were included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.
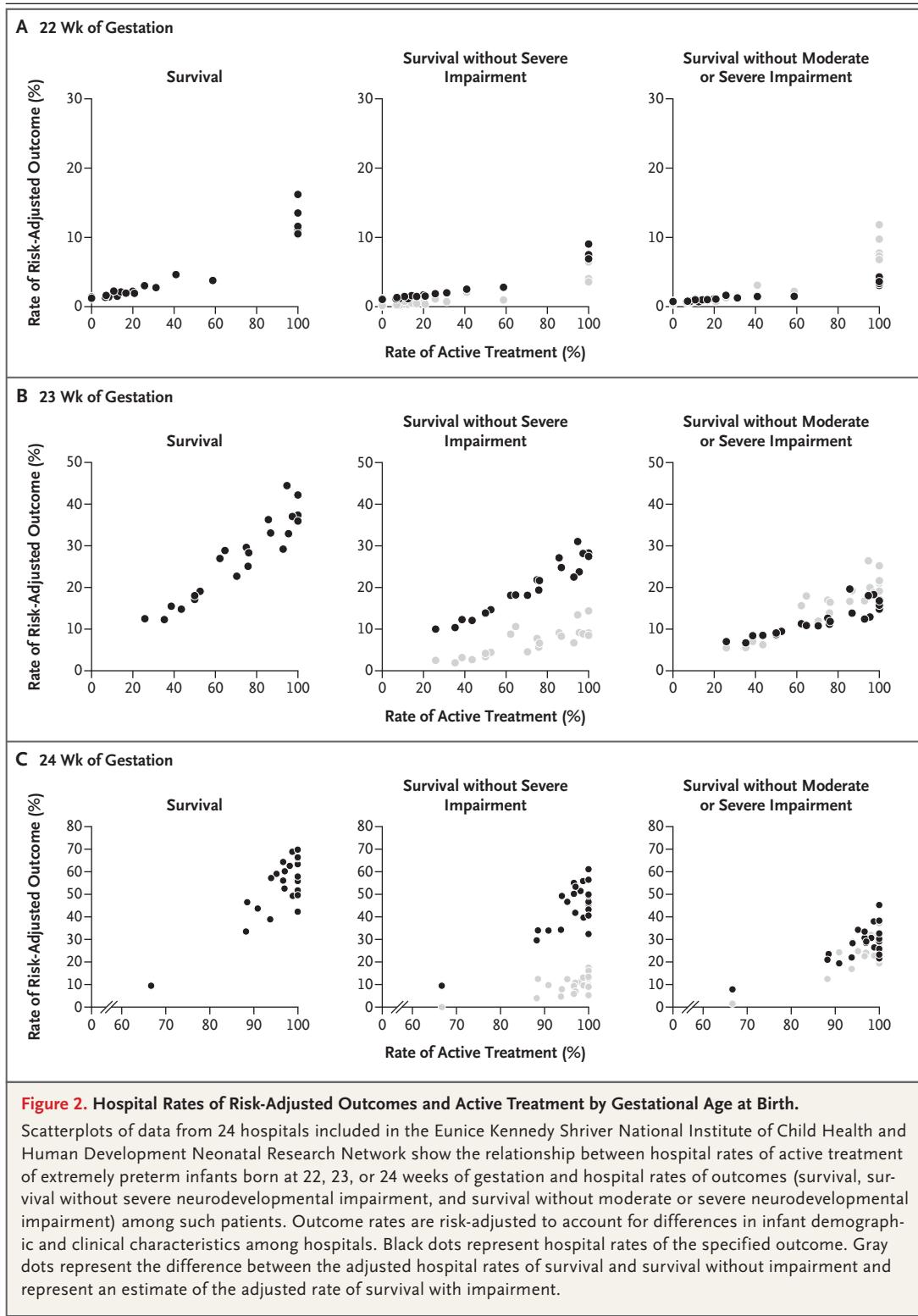§ Because 4 hospitals did not resuscitate any infants born at 22 weeks of gestation, the medians and interquartile ranges at this gestational age were calculated for 20 hospitals.

born at 25 or 26 weeks, hospital rates of active treatment did not account for between-hospital variation in outcomes (Table 3). Furthermore, there was no significant relationship between hospital volume of extremely preterm births and survival outcomes in any of our models (P>0.8 for all comparisons), and hospital volume of extremely preterm infants did not significantly mod-

ify the relationship between hospital rates of active treatment and outcomes.

DISCUSSION

In this cohort of extremely preterm infants born at U.S. hospitals included in the NICHD NRN, we found significant between-hospital variation

Figure 2. Hospital Rates of Risk-Adjusted Outcomes and Active Treatment by Gestational Age at Birth.

Scatterplots of data from 24 hospitals included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network show the relationship between hospital rates of active treatment of extremely preterm infants born at 22, 23, or 24 weeks of gestation and hospital rates of outcomes (survival, survival without severe neurodevelopmental impairment, and survival without moderate or severe neurodevelopmental impairment) among such patients. Outcome rates are risk-adjusted to account for differences in infant demographic and clinical characteristics among hospitals. Black dots represent hospital rates of the specified outcome. Gray dots represent the difference between the adjusted hospital rates of survival and survival without impairment and represent an estimate of the adjusted rate of survival with impairment.

Table 3. Relationship between Hospital Rates of Active Treatment and Variation in Outcomes by Gestational Age at Birth.*

Outcome	Model Not Including Hospital Rate of Active Treatment	Model Including Hospital Rate of Active Treatment	Proportion of Variation in Outcomes Attributable to Hospital Rate of Active Treatment	P Value
	ICC (95% CI)	ICC (95% CI)	%	
22 or 23 Wk of gestation				
Survival	0.13 (0.05–0.29)	0.03 (0.01–0.15)	78	<0.001
Survival without severe impairment	0.07 (0.02–0.24)	0.02 (0.01–0.23)	75	<0.001
Survival without moderate or severe impairment	0.06 (0.01–0.25)	0.04 (0.01–0.22)	41	0.02
24 Wk of gestation				
Survival	0.08 (0.03–0.16)	0.06 (0.02–0.13)	22	0.01
Survival without severe impairment	0.07 (0.02–0.14)	0.05 (0.02–0.13)	16	0.02
Survival without moderate or severe impairment	0.05 (0.02–0.13)	0.04 (0.01–0.12)	15	0.08
25 Wk of gestation				
Survival	0.03 (0.01–0.11)	0.03 (0.01–0.10)	1	0.26
Survival without severe impairment	0.03 (0.01–0.09)	0.03 (0.01–0.09)	0	0.74
Survival without moderate or severe impairment	0.05 (0.02–0.12)	0.05 (0.02–0.12)	1	0.31
26 Wk of gestation				
Survival	0.05 (0.02–0.15)	0.05 (0.02–0.15)	1	0.26
Survival without severe impairment	0.03 (0.01–0.10)	0.03 (0.01–0.10)	0	0.41
Survival without moderate or severe impairment	0.04 (0.01–0.09)	0.03 (0.01–0.09)	0	0.79

* The intraclass correlation coefficient (ICC) represents the proportion of variation in outcomes that was attributable to an infant's hospital of birth, after accounting for demographic and clinical characteristics. Because of rounding, the values for the proportion of between-hospital variation in outcomes that is attributable to the hospital rate of active treatment cannot be directly calculated from this table using the formula given in the text. P values refer to the significance of the hospital rate of active treatment as a continuous variable to predict the outcome.

in the rates of initiating potentially lifesaving treatment after birth. Differences in hospital rates of active treatment among children born at 22, 23, or 24 weeks of gestation explained a large portion of the variation in hospital rates of survival and survival without severe impairment and explained a lesser portion of the variation in hospital rates of survival without moderate or severe impairment.

Best obstetrical estimates of gestational age for most pregnancies (except those conceived through in vitro fertilization) have a margin of error of at least 5 days,[29] and error may be greater for pregnancies resulting in extremely preterm birth.[30,31] Yet, we found that rates of active treatment among infants born at the end of 22 or 23 weeks of gestation were significantly higher than the rates among infants born earlier during the same weeks. Our findings suggest that physicians and families may "round up" when considering gestational age in the decision to initiate potentially lifesaving treatment.

Hospitals at which active treatment was more often initiated had higher rates of risk-adjusted survival both with and without impairment than did hospitals at which active treatment was less

frequently initiated. However, differences in hospital rates of active treatment did not account for all variation in outcomes. Among hospitals that initiated treatment for 100% of infants born at 24 weeks of gestation, for example, rates of risk-adjusted survival still varied from 42.4 to 69.9%. Further research is needed to identify other factors contributing to the variation in outcomes.

In our study, we assessed important outcomes using data collected for a large prospective cohort of liveborn infants with a high follow-up rate to provide information about the scope of between-hospital variation in care for extremely preterm infants in the United States. Although composite outcomes for severe and moderate impairment were necessary to make statistical comparisons, their components do not have equivalent importance to patients or their families, and this should be taken into consideration in interpreting our results. Moreover, standardized Bayley-III scores at 18 to 22 months of corrected age may not fully predict developmental outcomes later in childhood.[32-34]

Other limitations of our study are that our models may not have accounted for some clinical and demographic factors associated with between-hospital variation in outcomes and that we do not have sufficient data to construct a denominator of all births — both live births and stillbirths — at participating hospitals.

Neurodevelopmental impairment is an outcome of particular concern to patients, families, and clinicians when considering whether to initiate or forgo treatment in extremely preterm infants. Perceptions of the risk of impairment significantly influence decisions about initiating treatment in infants born at early gestational ages.[35] Although we found that decisions to initiate active treatment cluster at the hospital level for infants born at 22, 23, or 24 weeks of gestation, we are unable to determine whether between-hospital variation resulted from clustering of family preferences, hospital culture, hospital policy, or other factors. We do not have information regarding when (i.e., before or after birth) or how decisions about the initiation of active treatment were made and cannot determine whether variation in rates of active treatment resulted from differences in understanding of possible outcomes or from varying perspectives regarding the value of survival as compared with the risk of impairment.

Hospital-level outcomes data that are used to counsel families about the benefits and burdens of initiating treatment are influenced by local approaches to initiating treatment. Outcome statistics that are derived from populations that include large numbers of infants who did not receive active treatment may seem to support decisions to forgo future treatment, resulting in a "self-fulfilling" prognosis.[36-38] For transparency and accuracy, it is important to take into account whether the infants included in outcome statistics received active treatment when using those data to counsel families.[39]

Our results highlight considerable variation in hospital practices regarding the initiation of active treatment in infants born at 22, 23, or 24 weeks of gestation. Differences in practices regarding the initiation of active treatment in extremely preterm infants appear to explain a large portion of the between-hospital variation in survival among such patients and a substantial but lesser portion of the variation in survival without neurodevelopmental impairment.

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