Changes in Survival Patterns of Very Low-Birth-Weight Infants From 1980 to 1993

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Objective: To determine changes in survival patterns among very low-birth-weight (<1500 g) infants between 1980 and 1993.

Methods: The records of 12,960 infants treated in nine perinatal intensive care centers in Florida were analyzed on the basis of survival (discharged alive from hospital) according to four independent variables: birth weight, race, sex, and transport status. Survival curves were generated using log linear regression techniques for each race by sex by transport status group.

Results: Race, sex, and transport status correlated significantly with survival; survival percentages were higher among black infants, female infants, and infants transported to the perinatal intensive care centers than among white infants, male infants, and those admitted initially to the tertiary care centers. After 1985, 95% of neonates with birth weights between 1200 and 1500 g survived.

In addition, survival of 500- to 550-g transported black male infants increased from zero to near 80% during the 13-year period; that of 500- to 550-g inborn white female infants rose from 35% to 70%.

Conclusions: These results illustrate the value of taking into account race, sex, and transport status in efforts to understand the contribution that neonatal intensive care of extremely low-birth-weight infants makes to the lowering of infant mortality, and of using multivariable statistical procedures to generate predicted survival probabilities for different subpopulations. These probabilities can be applied to (1) predicting survival for specific subgroups of extremely low-birth-weight infants, and (2) helping physicians develop clinical guidelines for extending care to infants at the threshold of viability.

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Numerous recent studies have reported that neonatal survival rates for very low-birth-weight (VLBW) (<1500 g) infants increased during the 1980s, especially among the extremely low-birth-weight (ELBW) (<1000 g) subgroup. Improved survival is an international phenomenon. Reductions in neonatal mortality of about 20% to 30% have been reported by researchers in Australia, the Netherlands, and Finland. These changes have been attributed to a number of factors: (1) greater numbers of high-risk pregnant women enrolled in prenatal care programs; (2) expanded availability of neonatal intensive care units; (3) advances in ventilator technology; (4) increased use of artificial surfactant; and (5) the continuing option of therapeutic abortion.

In the United States, the occurrence of VLBW is 1.2% of all births. However, it is three times higher for black infants compared with white infants, and both neonatal and infant mortality rates for black infants continue to be more than twice that of white infants. Differences in survival among VLBW male and female infants continue to be documented, with female infants surviving at higher rates than male infants.

To assess trends in survival of VLBW infants in Florida for different combinations of the risk factors race, sex, birth weight, and transport status, we designed a historical prospective study of the state’s Regional Perinatal Intensive Care Centers (RPICC) program for premature and sick infants that has been in place since 1980. The study was designed to analyze changing patterns of neonatal mortality in a large population of infants of VLBW
SUBJECTS AND METHODS

STUDY DESIGN

Data on 12,960 neonates were obtained from a computerized data collection system at each of the nine participating NICUs in Florida.\textsuperscript{22,23} The records of VLBW infants (500 to 1500 g) entering neonatal intensive care units between July 1, 1980, and March 30, 1993, were analyzed for the effects of race, sex, birth weight, and transport status on hospital survival. Infants who died in the delivery room were not included in this study because detailed information about them was not systematically collected until the beginning of the current decade, and information about neonates who were not transferred to an NICU was not available.

To determine the extent of changes in survival among neonates of the lowest birth weights during the 13-year study period, data were analyzed in 50-g increments. The data are also presented in the traditional format of 250-g increments and grouped into three periods. However, the data were analyzed on a year-by-year basis for each 50-g birthweight category. Descriptive statistics for the entire sample and for subgroups are given in Table 1. Multiple births were excluded from the sample.

STATISTICAL ANALYSIS

For each race by sex by transport status combination, we modeled the probability of mortality as a log linear function of birth weight (BW), age (Y), year squared (Y^2), birth weight times year (BW×Y), and birth weight times year squared (BW×Y^2). The quadratic term Y^2 was included because we anticipated that there might be a curvilinear, not simply a linear, relation between year and birth weight: BW×Y and BW×Y^2 are terms for first- and second-order interactions of birth weight and year. Birth weight was categorized and coded 1, 2, 3, 4, etc., up to and including 20, with numbered categories representing the midpoint of the intervals 500 to 549, 550 to 599, 600 to 649, 650 to 699, etc., up to 1500 g, respectively. Twelve-month periods were represented as 1, 2, 3, etc., up to 13, representing the fiscal years: July 1 to June 30, 1980-1981, 1981-1982, etc., up to 1992-1993, respectively.

A log linear regression model was chosen because in a previous analysis of data for the nine perinatal intensive care centers, we corroborated findings of other research that such a model fit survival data in low-birth-weight infants better than the usual logistic model.\textsuperscript{24} Because preliminary analyses indicated the presence of complex interactions, separate models were fit for eight separate race by sex by transport status groups. The analysis was conducted to estimate the effects of birth weight and time on the probability of mortality (P_0) (see equation below), but for illustration purposes curves were generated representing percent survival—that is, 1 minus the probability of in-hospital mortality.

Stepwise modeling results suggested that the second-order interaction term, BW×Y^2, could be dropped from all eight models (because it did not increase the models' goodness of fit) but that the other variables were significantly related to mortality for at least one group. Thus, the final models fitted were of the following form:

$$\log(P_0) = b_0 + b_1BW + b_2Y + b_3Y^2 + b_4BW×Y$$

where b_0 is the intercept and b_1, b_2, b_3, and b_4 are the coefficients for the independent variables.

Models were fitted using a statistical software package (Generalized Linear Interactive Modeling).\textsuperscript{25} To illustrate the relationships of probability of survival to time, we fixed birth weight in the equations for probability of mortality at values corresponding to the midpoint of 50-g intervals from 500 to 1000 g and to the midpoint of 100-g intervals from 1000 to 1500 g; we graphed the probability of survival (and multiplied by 100 to express as percent) vs. time for each BW (Figure 1 and Figure 2). Similarly, to illustrate relationships of probability of survival to birth weight, we set year to values corresponding to the midpoints of the periods 1982-1983, 1983-1986, 1988-1989, and 1991-1992, and graphed the probability of survival vs. birth weight for each time period (Figure 3).

The coefficients for each of the equations used to generate the survival curves are given in Table 2. Included in Table 2 are the scaled deviance values which, when divided by their degrees of freedom, provide a measure of the models' goodness of fit. Scaled deviance values less than their degrees of freedom indicate adequate fitting models. Note that all eight models provided adequate fits.

from 1980 to 1993. The resulting cell sizes for constituent subgroups were large enough so that complex relations between the independent variables and outcome, involving second order interactions, could be investigated.

RESULTS

OVERALL EFFECTS

In the preliminary analysis, significant main effects were found for each of the independent variables: race, sex, and transport status (P < .001 for all). Like other geographically defined populations, our investigation of neonatal intensive care units in Florida demonstrated the following: (1) overall survival for VLBW infants increased during the last 13 years; (2) black infants survived at higher rates than white infants in the same birth-weight category; (3) female infants survived at higher rates than male infants in all birth-weight categories; and (4) transported infants survived at higher rates than inborn infants in all birth-weight categories.

TEMPORAL EFFECTS

Figure 1 illustrates changes in survival over time for each of the eight different subgroups (race by sex by transport status) of ELBW infants for the 10 selected birth-weight categories less than 1000 g described in the "Subjects and Methods" section. The curves indicate different patterns of survival for each of the eight race by sex by
transport status groups. For example, inborn white female infants of the lowest birth-weight category (500 to 550 g) recently reached 70% survival, whereas the percent survival for inborn black male infants, although it has risen from 0% to 20%, was 50 percentage points below that of white female infants in the same birth-weight category.

Figure 2 contains plots of the survival probability for the five selected birth weights (from 1001 to 1500 g in 100-g increments) across the continuum of 13 years. All groups in the top third of VLBW categories (1200 to 1500 g) exceeded the 90% survival level. The two sets of graphs illustrate increased survival in birth weight and in the case of the 500- to 1000-g subgroup a survival advantage for transported infants.

**BIRTH-WEIGHT EFFECTS**

Figure 3 presents fitted curves for four 12-month periods (selected to illustrate an early, two middle, and one recent time period for the 13-year study span). These curves plot percent survival as a function of birth weight.

The graphs for inborn infants generally confirm previously published findings about Florida’s inborn low-birth-weight population. Two years of additional data in the present study confirmed the previous patterns of survival: Female infants and black infants survived at higher rates than male infants and white infants at ELBW. In the first of the four time periods studied, no black infants with birth weights between 500 and 550 g survived; in the fourth time period, survival for this subgroup was approximately 20%.

**TRANSPORT EFFECTS**

Transported infants consistently had higher percent survival than inborn infants across the 13-year study span (Figure 1). Survival for transported black male infants weighing between 500 and 550 g increased from 0% to near 80% between 1980 and 1993. The improvement for transported white male infants in the same birth-weight category was not as dramatic: from 50% to near 70%. A similar difference in improvement among the two races was noted among transported female infants, but it was
not as large as among male infants. In the 500- to 550-g birth-weight group, survival of black female infants rose from 30% to 60% between the first (1980-1981) and the last year (1992-1993); survival among white female infants of the same birth-weight group also improved, from 30% to near 80%. During the entire time period, the survival of black female infants averaged over all birth-weight groups was 11% greater than that of white male infants (84.3% vs 73.3%).

Figure 1 illustrates major differences in percent survival among the inborn and transported infants weighing less than 1000 g. During the most recent year for which we report data (1992-1993), 80% of the smallest black male infants (500 to 550 g) who had been transported were discharged alive from the tertiary neonatal intensive care centers. In general, in the transport group the race and sex effects on survival were less pronounced: black infants had slightly higher survival but both white and black infants exceeded 95%, once birth weight exceeded 1200 g. The advantage in survival for female infants was not found in the transport group.

**COMMENT**

The 12,960 neonates in our study were drawn from nine tertiary care hospitals in Florida, representing the largest study reported to date (to our knowledge) of survival of neonates of VLBW (<1500 g). Our sample yielded large enough cell sizes so that all combinations of the independent variables could be analyzed for possible interaction effects. Also, the number of neonates was sufficient to enable us to study birth weight by 50-g increments, rather than the customary 250-g increments used in most other studies of VLBW infants. In addition, the 13-year period was longer than any other studies of neonatal survival by birth weight known to us, offering a closer look at long-term patterns of survival.

The survival of neonates weighing less than 1500 g at birth rose from 76.5% between 1980 and 1985 to 84.1% between 1990 and 1993. The greatest improvement in survival occurred in infants weighing less than 750 g. In the five subgroups between 500 and 750 g (defined by 50-g increments), the subgroup having the lowest birth weight, 500 to 550 g, had the greatest improvement in survival, an increase of 29.5%. Fifty-six percent of these infants were discharged alive from perinatal intensive care units between 1990 and 1993.

Our study yielded important details about factors affecting survival other than birth weight. Between 1990 and 1993, for example, survival in the lowest birth-weight group (500 to 550 g) was 56.1%. Within this group, however, a wide range of survival rates became apparent. For example, only 20% of inborn black male infants weighing 500 to 550 g survived compared with 80% for transported black female infants. Between 1980 and 1993, survival of these transported male black infants increased from 0% to 80%; among female infants, from 20% to 80%. Among inborn infants, survival of white female infants in the lowest birth-weight category has doubled (from 35% to 70%).
The finding of a survival advantage for transported infants is contrary to the experience reported by a number of other centers, and may be the result of a selection bias. Physicians attending preterm births may have chosen not to recommend for transport the most medically fragile infants, choosing instead to send healthier, more robust infants likely to survive transport or those who might benefit from complex surgery. Another type of selectivity also may have been in place: the RPCICs were and are aligned with another state-supported program that operates clinics for patients with high-risk obstetrical conditions. Women likely to present complications of labor and delivery would be recommended for admission to tertiary care centers before giving birth, thus reducing the gravity of conditions among infants remaining to be chosen for transport.

In 1991, the National Institute of Child Health and Human Development Neonatal Research Network Centers reported an overall survival of 34% for infants weighing 501 to 750 g for 1987-1988. That is the same overall rate achieved at RPCIC from 1980 to 1985 (see Table 1, which also gives a 48% overall survival for this same birthweight group during 1985 to 1990). The National Institute of Child Health and Human Development study did not break down its sample into race, sex, and transport status subgroups, although these variables have a pronounced effect on survival. The practice of presenting aggregated data makes it difficult for researchers in the field of neonatal medicine to compare their state or regional variations with the findings of a national sample. Data presented by subgroups are also needed in clinical settings for estimating probability of survival for individual neonates. In addition, survival information by this kind of specificity may help physicians develop clinical guidelines for extending care to infants at the threshold of viability.

The survival among all inborn male infants, black and white, weighing 500 to 550 g at birth, was only 20% in the last time period of the study (1990 to 1993). In contrast, survival for inborn white female infants of the same birth weight was 70% and for black inborn female infants, 30%. Our data confirm the findings of other investigators that, at any given low birth weight, male infants are less likely to survive than female infants.

Although infants of VLBW account for only 1.4% of all live births in Florida, most of the state's neonatal deaths occur in infants weighing less than 1000 g at birth. Because approximately half of all infants with VLBW were treated in the nine perinatal intensive care centers from which our data were drawn, we believe that the expanded capabilities of these centers and improvements in technology and treatment contributed to the overall lowering of neonatal mortality in Florida—down from 9.7 per 1000 live births in 1980 to 5.6 per 1000 in 1993. Concurrently, the US neonatal mortality rate declined from 8.5 to 5.4 per 1000. Thus, by having achieved a 40% drop in its neonatal mortality rate, Florida has been able to close the gap between its rate and the national average.

Table 2. Coefficients for Equations Used to Generate Survival Curves for Each Race by Sex by Transport Status Subgroup

<table>
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<tr>
<th>Race/Sex</th>
<th>Transport Status</th>
<th>( b_0 ) (Constant)</th>
<th>( b_1 ) (BW)</th>
<th>( b_2 ) (Y)</th>
<th>( b_3 ) (Y^2)</th>
<th>( b_4 ) (BW×Y)</th>
<th>Scaled Deviance Value dk=225</th>
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<tr>
<td>B/M</td>
<td>I</td>
<td>0.6398</td>
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<td>(0.2104)</td>
<td>(0.0177)</td>
<td>(0.0533)</td>
<td>(0.0035)</td>
<td>(0.0023)</td>
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<tr>
<td>B/M</td>
<td>T</td>
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<td>(0.3861)</td>
<td>(0.0321)</td>
<td>(0.1083)</td>
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<td>W/M</td>
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<td>(0.4226)</td>
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<td>(0.0339)</td>
<td>(0.1081)</td>
<td>(0.0075)</td>
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The SE of the estimate is in parentheses. I indicates inborn; T, transported; \( b_0 \), intercept; \( b_1 \) to \( b_4 \), coefficients for the independent variables; BW, birth weight; Y, year; Y^2, year squared; and BW×Y, birth weight times year.

The results of this study have a bearing on two important questions: (1) did Florida, after 13 years' experience in implementing regionalized perinatal intensive care, significantly improve the survival of VLBW infants? and (2) how has the threshold of viability for ELBW infants changed? The people of Florida can be assured that their state's support of regionalized perinatal care centers has been rewarded by an increase in the survival of premature infants. It is also clear from this study that the range of viability has continuously been enlarging. Our results point out that neonatal survival must be considered in light of race, sex, transport status, and birth.
weight. Increased knowledge of the subgroups of neonates at greatest risk can assist practitioners involved in neonatal care in their approach to treatment and communication with family members.

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