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Daily mortality of infants born at less than 30 weeks' gestation

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ABSTRACT

Background: Few studies have reported odds of mortality for hospitalized premature infants stratified by postnatal age and adjusted for severity of illness. Our objective was to examine day-by-day mortality of premature infants in a large multicenter cohort of infants, adjusted for demographics, severity of illness, and receipt of therapeutic interventions.
Methods: This was a multicenter cohort study of infants cared for in 362 neonatal intensive care units with a shared clinical data warehouse from 1997 to 2013. We included all inborn infants born at 22–29 weeks' gestational age with available mortality discharge data. We report the point prevalence of survival to hospital discharge stratified by gestational and postnatal age.
Results: We identified 64,896 infants, of whom 55,348 (85%) survived to hospital discharge. Survival increased with gestational and postnatal age, until infants reached a postmenstrual age of approximately 37 weeks, after which survival began to decrease. Overall survival increased over time (80% in 1997 to 88% in 2013, $P < .001$).
Conclusions: Given the known association between gestational age and postnatal age, survival predictions should be adjusted for both covariates.

1. Introduction

One in three premature infants with an extremely low birth weight (ELBW; <1000 g) who are admitted to a neonatal intensive care unit (NICU) will not survive to hospital discharge [1]. Lower gestational age (GA) and need for therapeutic interventions are associated with increased mortality [1–3].

Mortality prediction is an essential tool to guide parental counseling and treatment of premature infants. Prediction of in-hospital mortality based on infant characteristics at birth including GA, birth weight, sex, singleton birth, and receipt of antenatal steroids has been well established [3]. These variables are included in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) outcome estimator, which generates a range of possible survival probabilities with or without neurodevelopmental impairment, based on these infant characteristics [4]. An important limitation of this prediction tool is its exclusion of infants >25 weeks' GA and focus on risk prediction immediately after birth.

In-hospital mortality decreases significantly if an infant survives the first 3 days of life [5]. As a consequence, studies have incorporated infant characteristics obtained after birth and have attempted to predict in-hospital mortality at different postnatal ages (PNAs) [6,7]. These studies have focused on the characteristics of the prediction model and the relative importance of individual predictor variables. Other studies have reported on the actual day-by-day survival of infants but have not reported risk adjusted predictions [8].

The purpose of our study was to describe the daily point prevalence of survival to hospital discharge of premature infants in a large multicenter cohort of infants, adjusted for GA. We hypothesized that increasing GA and PNA were associated with decreased in-hospital mortality.

2. Methods

2.1. Data source

We used a database derived from electronic medical records and daily progress notes generated by clinicians on all infants cared for by the Pediatrix Medical Group in 362 NICUs in North America from 1997 to 2013. Data on multiple aspects of care were entered into a shared

Abbreviations: DOL, day of life; ELBW, extremely low birth weight; FiO2, fraction of inspired oxygen; GA, gestational age; NICU, neonatal intensive care unit; NRN, Neonatal Research Network; PNA, postnatal age; SGA, small for gestational age.

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electronic medical record to generate admission and daily progress notes and discharge summaries. Information regarding maternal history, demographics, medications, laboratory results, diagnoses, and procedures was then transferred to the Pediatrix Clinical Data Warehouse for quality improvement and research purposes [9]. We included infants 22–29 weeks' GA cared for at one hospital and discharged between 1997 and 2013. We excluded outborn infants, those transferred to another hospital, and those with severe congenital anomalies (Fig. 1). The study was approved by the Duke University Institutional Review Board.

2.2. Definitions

We defined mortality as death prior to discharge from the NICU or 120 days, whichever was first, and described GA in weeks and PNA in days. Antenatal steroid exposure was defined as maternal exposure to steroids during pregnancy. We defined daily inotropic support as the need for any inotropic medication (epinephrine, dopamine, dobutamine, amrinone, milrinone, and norepinephrine) on a given day. Daily oxygen support was defined as the highest fraction of inspired oxygen (FiO_2) administered on a given day, and we categorized the variable as follows: 21%, 22% to 30%, or >30%. We defined small for gestational age (SGA) as previously described [10].

2.3. Statistical analysis

The unit of observation for this analysis was an infant day in the NICU. We censored observations after 120 days of life due to the small sample size and heterogeneous nature of infants hospitalized after that time. We used summary statistics including medians and 25th and 75th percentiles to describe continuous variables, and frequency counts and percentages to describe categorical variables. We compared infant characteristics between survivors and non-survivors using chi-square tests of association and Wilcoxon rank sum tests.

We calculated point prevalence of survival to NICU discharge by GA and birth year, and compared mortality prior to NICU discharge over time stratified by GA using the Cochran–Armitage test for trend. We calculated point prevalence of survival to NICU discharge stratified by GA at prespecified postnatal time points (day of life [DOL] 7, 30, 60, 90, and 120). An infant was included in the denominator for point prevalence calculation if the child was still hospitalized on that day, and the infant was excluded if discharged, alive or dead, prior to that day. We conducted all analyses using Stata 13.1 (College Station, TX) and considered a $P < .05$ statistically significant.

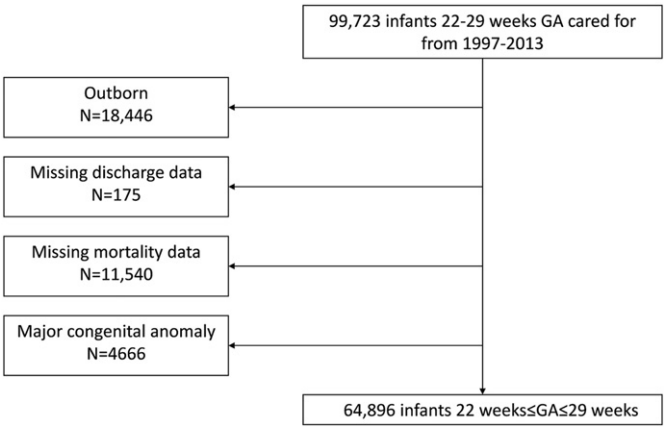

Fig. 1. Study population.

3. Results

Of the 64,896 infants included in our study, 55,348 (85%) survived to hospital discharge. Median (25th, 75th percentile) GA and birth weight were higher in survivors compared to non-survivors (GA: 28 weeks [26, 29] vs. 24 weeks [23, 26], $P < .001$; birth weight: 1000 g [800, 1200] vs. 650 g [546, 794], $P < 0.001$). Survivors were less likely to be SGA or male, and more likely to have received antenatal steroids and be born via cesarean section (Table 1). Median PNA at death was 6 days (1, 19) and 90% of deaths occurred in the first 41 days of life. On the day of death, 93% of infants received mechanical ventilation and 87% received $FiO_2 > 30\%$, but only 35% received inotropes.

Survival increased with GA from 71/485 (15%) for infants born at 22 weeks' gestation to 15,308/15,689 (98%) for infants born at 29 weeks' gestation (Table 1). Survival to hospital discharge increased with PNA (Table 2 and Fig. 2). This increase was more pronounced in lower GA infants and most significant in the first week of life: overall survival on DOL 0 was 85% compared to 92% on DOL 7, 97% on DOL 30, 98% on DOL 60, 98% on DOL 90, and 95% on DOL 120. Survival reached a peak and started to decline as infants aged and remained hospitalized. Survival was highest at a PNA corresponding to a postmenstrual age (PMA) of roughly 37 weeks: DOL 105 for 22-week GA infants (PMA = 37 weeks); DOL 107 for 23-week GA infants (PMA = 38 2/7 weeks); DOL 89 for 24-week GA infants (PMA = 36 5/7 weeks); DOL 77 for 25-week GA infants (PMA = 36 weeks); DOL 68 for 26-week GA infants (PMA = 35 5/7 weeks); DOL 56 for 27-week GA infants (PMA = 35); DOL 49 for 28-week GA infants (PMA = 35 weeks); and DOL 36 for 29-week GA infants (PMA = 34 1/7 weeks). Mortality for the 4239 infants hospitalized for ≥120 days was 5.4%, with a median PNA at death in this subgroup of 161 days (142, 189).

Overall survival increased over time from 477/599 (80%) in 1997 to 4589/5221 (88%) in 2013 ($P < .001$ from Cochran–Armitage test for trend). When analyzed separately by GA, this trend was significant for all infants (all $P < .01$) except for the 22-week GA cohort ($P = 0.08$). The latter finding may be related to the smaller sample size (n = 485 infants) in the 22-week GA cohort.

4. Discussion

We conducted the largest (to our knowledge) study of daily survival to hospital discharge in premature infants. Overall survival was 85% and

Table 1
Demographics.

	Survived n = 55,348	Died n = 9548
Gestational age (weeks), No./No. (%)		
22	71/485 (15)	414/485 (85)
23	1152/3223 (36)	2071/3223 (64)
24	3596/6121 (59)	2525/6121 (41)
25	5587/7256 (77)	1669/7256 (23)
26	7319/8502 (86)	1183/8502 (14)
27	9573/10,330 (93)	757/10,330 (7)
28	12,742/13,290 (96)	548/13,290 (4)
29	15,308/15,689 (98)	381/15,689 (2)
Birth weight (g), No./No. (%)		
<500	715/2110 (34)	1395/2110 (66)
500–750	10,127/15,750 (66)	5623/15,750 (34)
751–1000	17,083/19,061 (90)	1978/19,061 (10)
1001–1500	25,528/26,374 (97)	846/26,374 (3)
>1500	1854/1893 (98)	39/1893 (2)
SGA, No./No. (%)	6139/8401 (73)	2262/8401 (27)
Male, No./No. (%)	28,593/34,091 (84)	5498/34,091 (16)
Antenatal steroids, No./No. (%)	46,126/52,519 (88)	6393/52,519 (12)
Cesarean section, No./No. (%)	38,734/44,870 (86)	6136/44,870 (14)
5-min Apgar score, No./No. (%)		
0–3	1834/3616 (51)	1782/3616 (49)
4–6	9192/12,373 (74)	3181/12,373 (26)
7–10	43,460/47,818 (91)	4358/47,818 (9)

SGA, small for gestational age.