Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study

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abstract

OBJECTIVES: To assess the rates of mortality and major morbidity among extremely preterm infants born in California and to examine the rates of neonatal interventions and timing of death at each gestational age.

METHODS: A retrospective cohort study of all California live births from 2007 through 2011 linked to vital statistics and hospital discharge records, whose best-estimated gestational age at birth was 22 through 28 weeks. Major morbidities were based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. Survival beyond the first calendar day of life and procedure codes were used to assess attempted resuscitation after birth.

RESULTS: A total of 6009 infants born at 22 through 28 weeks' gestation were included. Survival to 1 year for all live births ranged from 6% at 22 weeks to 94% at 28 weeks. Seventy-three percent of deaths occurred within the first week of life. Major morbidity was present in 80% of all infants, and multiple major morbidities were present in 66% of 22- and 23-week infants. Rates of resuscitation at 22, 23, and 24 weeks were 21%, 64%, and 93%, respectively. Survival after resuscitation was 31%, 42%, and 64% among 22-, 23-, and 24-week infants, respectively. Improved survival was associated with increased birth weight, female sex, and cesarean delivery ($P < .01$) for resuscitated 22-, 23-, and 24-week infants.

CONCLUSIONS: In a population-based study of extreme prematurity, infants ≤24 weeks' gestation are at highest risk of death or major morbidity. These data can help inform recommendations and decision-making for extremely preterm births.

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Dr Anderson was responsible for study conception and design, analysis and interpretation of data, and drafting and revising the article for critically important intellectual content; he had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Baer, Partridge, Kuppermann, Franck, Rand, Jelliffe-Pawlowski, and Rogers were responsible for study conception and design, analysis and interpretation of data, and drafting and revising the article for critically important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Extremely preterm infants (22–28 weeks' gestation) are at high risk of death and morbidity. In recent years, more infants born at 22 to 24 weeks' gestation are being resuscitated instead of receiving comfort care only.

WHAT THIS STUDY ADDS: In our population-based study, extremely preterm infants remain at risk for death and major morbidity, with 22- to 25-week gestation infants being at highest risk. We report rates of resuscitation and timing of death for 22- to 28-week gestation infants.

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With advances in perinatal and neonatal care, more infants are surviving at earlier gestational ages.[1–3] However, the rates of mortality and severe neonatal morbidity increase with decreasing gestational age.[4–6] This trend is consistent across studies, but the absolute rates of mortality and morbidity vary most markedly for those infants born at the earliest gestational weeks.[1,4–14] Similarly, resuscitation practices at <26 weeks vary greatly by country, hospital, and practitioner[4,9,11,15] because there is no consensus on a precise "limit of viability" (defined as anywhere between 22 and 26 weeks).[16–18]

The summary from a 2013 joint workshop held by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists acknowledged the wide variation in practices and outcomes for infants born at <26 weeks' gestation. The workshop recommended that new population-based obstetric and newborn cohort studies investigate neonatal resuscitation practices and outcomes of extremely preterm infants.[19] Data from a recent Neonatal Research Network (NRN) publication support the concept that there is a broad range of practices and outcomes at these gestational ages in the United States.[11] Although population-based data are available for some countries,[1,4,5] comparable data in the United States are limited.[13,20]

The primary aim of the present study was to assess the rates of mortality and major morbidity among extremely preterm infants (22–28 weeks' gestation) born in California, by using data collected from 2007 through 2011 by the California Office of Statewide Health Planning and Development (OSHPD). We also examined the rates of neonatal interventions and timing of death for each gestational week between 22 and 28 weeks.

METHODS

The OSHPD birth cohort database contains detailed information on maternal and infant characteristics derived from linked hospital discharge, birth certificate, and death records, including all records for the mother and infant from 1 year before birth to 1 year after birth. Birth certificates also include information on prenatal care and select antenatal conditions. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).[21] The study population consisted of all live born infants in California from 2007 through 2011 (Fig 1). Of the 16 295 infants born at a gestational age between 22 and 28 weeks, 7519 had linked birth certificate and hospital discharge records. Gestational age was determined by best obstetric estimate from ultrasound and/or last menstrual period. The cohort included infants with a birth weight within 4 SDs of the mean gestational age according to gender-specific growth curves[22]; infants with chromosomal abnormalities or major structural birth defects were excluded.[23] Structural birth defects were considered "major" if determined by clinical review as causing major morbidity and mortality that would likely be identified at birth or lead to hospitalization during the first year of life.

The NICU level of care was defined by the California Children's Services Department certification as intermediate-level

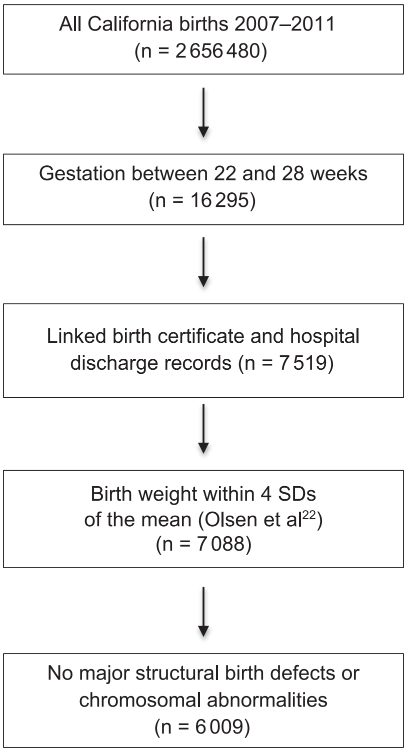

FIGURE 1
Sample selection.

(short-term ventilatory assistance), community-level (long-term ventilatory assistance, limited surgical procedures), or regional-level (full range of neonatal intensive care services, including neonatal surgeries) NICUs.[24] For the purposes of the present study, the NICUs not certified by the state were designated as "no NICU."

Mortality measures were derived from linked death certificates and death discharge information within the birth cohort file. Death in the cohort was presented utilizing daily survival curves for each gestational age. Mortality rates after discharge were also reported.

ICD-9-CM codes in the hospital discharge record were used for maternal hypertension (642), diabetes mellitus during pregnancy (775.0, 250, 648.0, and 648.8), and chorioamnionitis (762.7 and 658.4). Major neonatal morbidities were similarly based on ICD-9-CM codes and included grade III or IV intraventricular hemorrhage (IVH) (772.13 and 772.14), necrotizing enterocolitis (NEC) (777.5), bronchopulmonary dysplasia (BPD) (770.7), sepsis (771.81), and periventricular leukomalacia (PVL) (779.7). All 3-digit codes include the more detailed 4-digit codes (eg, 642 also includes 642.0, 642.1, and 642.2). Retinopathy of prematurity (ROP) surgical procedure codes (14.2, 14.5, 14.7, and 14.9) were used to capture the most severe forms of ROP because ICD-9-CM coding did not adequately capture ROP staging. Morbidities were described among survivors according to gestational age for each condition.

Life-sustaining interventions in this analysis were based on ICD-9-CM procedure codes in the hospital discharge records, and they included noninvasive mechanical ventilation (93.9), continuous invasive mechanical ventilation (96.7), cardiopulmonary resuscitation (99.6), insertion of an endotracheal tube (96.04), or other intubation of the respiratory tract (96.05). The cohort was divided into 2 groups: those who survived ≤1 calendar day and those who survived past the first calendar day of life. Infants who did not survive past the first calendar day of life were classified as "resuscitation attempted" if their record had at least 1 of the aforementioned procedure codes. All infants who survived past the first calendar day of life were assumed to have had life-sustaining interventions until time of death or discharge, and thus were also classified as "resuscitation attempted."

All analyses were performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC). A bivariate analysis compared individual perinatal characteristics and maternal demographic characteristics in the survivors and nonsurvivors for whom resuscitation was attempted by using the χ^2 test for categorical variables and Student's *t* test for continuous variables. Methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the California Health and Human Services Agency.

RESULTS

A total of 6009 infants born at 22 through 28 weeks of gestation were included in this retrospective cohort study (Table 1). Mean birth weight increased with each increasing gestational week, from 489 g at 22 weeks to 1116 g at 28 weeks. More than one-half of the entire cohort was male (53%), and 79% of the births were singleton. Cesarean delivery occurred with increasing frequency from 22 weeks (14%) to 28 weeks (73%). A majority of all 22- to 28-week deliveries occurred at a community-level NICU (58%).

Twenty-eight percent of all extremely preterm infants died within the first year of life. Among the infants born at 22, 23, and 24 weeks, survival to 1 year of age was 6%, 27%, and 60%, respectively (Fig 2) and increased further for each 1-week increase in gestational age, from 78% at 25 weeks to 94% at 28 weeks. Seventy percent of all deaths in our cohort occurred in those infants born at 22 through 24 weeks' gestation; 62% of these deaths occurred in the first day of life, 83% in the first week of life, and 94% in the first 27 days of life. Of the 489 infants born at 25 to 28 weeks who did not survive, 22% died on the first day of life, 49% in the first week of life, and 76% in the first 27 days of life. After 6 days of life, the rates of survival remained high (>90%) across all gestational ages. The rate of survival in the postneonatal period (28–365 days) was even higher (>95%) across all gestational ages. Only 1.3% of all deaths in the first year of life (n = 22) occurred after discharge from the intensive care nursery.

Major neonatal morbidities, including grade III or IV IVH, PVL, NEC, BPD, sepsis, or ROP surgery, were common for all survivors of extreme prematurity, especially at 22 through 24 weeks (Table 2). Approximately 8% of all survivors in our cohort had grade III or IV IVH, with 22-week survivors being at highest risk for this complication (38%). Slightly more than 2% of all extremely preterm infants had PVL; 22- and 23-week infants had ~3 times the rate of PVL compared with 24- to 28-week infants. Approximately 7% of the infants born at 22 to 28 weeks' gestation had NEC. However, surviving 22- and 23-week infants were the most likely to develop NEC (14% and 19%, respectively). The rate of BPD decreased with each 1-week increase in gestational age, ranging from 66% among 22-week survivors to 20% among 28-week survivors. Rates of sepsis decreased with each increasing gestational week, from 69% of 22-week survivors to 42% of 28-week survivors. Nearly 10% of the cohort had ROP that required surgical intervention. Surviving infants born at 22 through 24 weeks' gestation were at the highest risk of having ROP surgery (>1 in 4); at 23 weeks, 36% of survivors required ROP surgery. More than 80% of surviving infants <26 weeks' gestation had at least 1 major morbidity. Furthermore, infants who were born before 24 weeks' gestation were the most

TABLE 1 Perinatal and Maternal Demographic Characteristics

Characteristic	Gestation at Birth, wk							
	22 (*n* = 450)	23 (*n* = 602)	24 (*n* = 766)	25 (*n* = 796)	26 (*n* = 933)	27 (*n* = 1070)	28 (*n* = 1392)	22–28 (*N* = 6009)
Birth weight, g								
Mean	488.7	582.4	659.8	768.4	869.5	1002.7	1116.1	852.9
SD	101.2	94.3	121.2	144.6	172.4	206.1	240.8	273.7
Male	52.7	54.2	51.7	55.2	51.6	53.7	53.2	53.2
Singleton birth	75.6	80.1	80.0	82.8	80.9	78.8	75.6	78.7
Cesarean delivery	13.6	38.4	65.0	67.2	68.4	70.2	72.9	62.1
No prenatal visits	4.4	4.5	3.4	2.3	3.3	1.5	2.3	2.8
Hypertension	4.4	3.8	11.2	13.3	19.3	22.2	25.9	16.9
Diabetes mellitus	6.9	7.0	10.2	8.0	10.6	10.3	11.9	9.8
Chorioamnionitis	18.9	22.1	17.8	12.6	14.2	10.9	8.8	13.7
Race/ethnicity								
White, non-Hispanic	15.1	17.1	18.3	18.7	20.5	21.8	22.7	20.0
Hispanic	51.6	55.3	51.4	52.3	53.1	52.2	51.4	52.3
Black	9.8	8.5	10.6	9.4	7.1	8.5	7.7	8.6
Asian	13.8	11.1	11.5	11.3	10.8	9.4	11.1	11.1
Other	9.8	8.0	8.2	8.3	8.6	8.0	7.0	8.1
Maternal age, y								
<18	3.8	5.2	4.3	6.0	5.9	4.2	3.7	4.7
18–34	75.8	76.9	73.5	72.6	71.8	75.0	72.4	73.6
>34	20.2	17.9	22.2	21.4	22.3	20.6	23.8	21.6
Maternal education, y								
<12	25.8	30.9	27.7	30.0	31.5	28.9	28.2	29.1
12	26.4	24.9	24.4	22.9	24.0	25.5	23.6	24.4
>12	38.4	37.2	43.0	42.8	39.7	40.5	43.3	41.0
Insurance status								
Private insurance	42.7	41.4	41.5	42.3	41.3	43.9	45.9	43.1
Medi-Cal	49.8	50.3	50.3	50.5	50.1	49.1	47.6	49.4
Other	7.6	8.8	8.2	7.2	8.7	7.0	6.5	7.5
Birth hospital NICU level								
No NICU	22.9	20.9	18.3	15.3	17.7	15.9	17.7	17.9
Intermediate	4.0	5.5	3.7	3.1	3.9	3.0	2.7	3.5
Community	58.0	58.5	55.6	60.3	58.0	59.8	57.5	58.3
Regional	15.1	15.1	22.4	21.2	20.5	21.3	22.0	20.4

Data are presented as % unless otherwise indicated.

likely to have >1 major morbidity (69% of 22-week infants, and 66% of 23-week infants).

Resuscitation was attempted in 21% of infants born at 22 weeks, whereas 64% of infants born at 23 weeks and 93% of infants born at 24 weeks had resuscitation attempted. When examining survival after attempted resuscitation, the rate of survival to 1 year at 22, 23, and 24 weeks was 31%, 42%, and 64%, respectively (Table 3). After 24 weeks, the rates of survival after attempted resuscitation ranged from 80% at 25 weeks to 95% at 28 weeks. Survival after attempted resuscitation increased with every 1-week increase in gestational age, with the largest 1-week increase in survival occurring between 23 and 24 weeks. Survival without major morbidity after attempted resuscitation also increased with every 1-week increase in gestational age, from 4% at 22 weeks to 44% at 28 weeks.

Bivariate comparisons of perinatal characteristics and maternal demographic characteristics for survivors and nonsurvivors for whom resuscitation was attempted (Tables 4 and 5) revealed that a higher mean birth weight and female sex were each highly associated with increased survival among 22- to 24-week and 25- to 28-week infants ($P < .001$). Cesarean delivery was associated with increased survival in 22- to 24-week infants (64% vs 57%; $P = .007$), but decreased survival in 25- to 28-week infants (70% vs 76%; $P = .003$). When comparing hospital of birth for survivors and nonsurvivors after attempted resuscitation at 22 to 24 weeks, more were born in a hospital with a regional NICU (20% vs 15%; $P = .031$). Among all resuscitated 22- to 28-week infants, more survivors than nonsurvivors were born at a hospital with a regional NICU (21% vs 17%; $P = .001$), and more nonsurvivors than survivors were born at hospitals with an intermediate-level NICU (5% vs 3%; $P = .034$). In addition, increased survival after resuscitation was

TABLE 2 Major Morbidity in Survivors

Major Morbidity	Gestational Age, wk							
	22 (*n* = 29)	23 (*n* = 162)	24 (*n* = 458)	25 (*n* = 621)	26 (*n* = 801)	27 (*n* = 971)	28 (*n* = 1309)	22–28 (*N* = 4351)
Any major morbidity	25 (86.2)	145 (89.5)	393 (85.8)	498 (80.2)	572 (71.4)	602 (62.0)	706 (53.9)	2941 (67.6)
IVH, grade III or IV	11 (37.9)	26 (16.1)	60 (13.1)	72 (11.6)	65 (8.1)	52 (5.4)	40 (3.1)	326 (7.5)
PVL	2 (6.9)	10 (6.2)	15 (3.3)	18 (2.9)	18 (2.3)	17 (1.8)	19 (1.5)	99 (2.3)
NEC	4 (13.8)	30 (18.5)	63 (13.8)	70 (11.3)	87 (10.9)	86 (8.9)	87 (6.7)	427 (6.7)
BPD	19 (65.5)	94 (58.0)	243 (53.1)	284 (45.7)	298 (37.2)	287 (29.6)	258 (19.7)	1483 (34.1)
ROP requiring surgery	8 (27.6)	58 (35.8)	121 (26.4)	112 (18.0)	77 (9.6)	34 (3.5)	19 (1.5)	429 (9.9)
Sepsis	20 (69.0)	108 (66.7)	283 (61.8)	341 (54.9)	388 (48.4)	429 (44.2)	543 (41.5)	2112 (48.3)
>1 Morbidity	20 (69.0)	107 (66.1)	260 (56.8)	276 (44.4)	266 (33.2)	239 (24.6)	213 (16.3)	1381 (31.7)
None	4 (13.8)	17 (10.5)	65 (14.2)	123 (19.8)	229 (28.6)	369 (38.0)	603 (46.1)	1410 (32.4)

Data are presented as *n* (%).

TABLE 3 Survival and Attempted Resuscitation

	Gestational Age, wk							
	22 (*n* = 450)	23 (*n* = 602)	24 (*n* = 766)	25 (*n* = 796)	26 (*n* = 933)	27 (*n* = 1070)	28 (*n* = 1392)	22–28 (*N* = 6009)
Overall survival, *n* (%)	29 (6.4)	162 (26.9)	458 (59.8)	621 (78.0)	801 (85.9)	971 (90.8)	1309 (94.0)	4351 (72.4)
Survived 1 calendar day or less, *n*	378	297	125	57	28	28	23	936
Any ventilation/intubation or CPR, *n* (%)	21 (5.6)	80 (26.9)	70 (56.0)	36 (63.2)	23 (82.1)	21 (75.0)	16 (69.6)	267 (28.5)
Survived past 1 calendar day, *n*	72	305	641	739	905	1042	1369	5073
Any ventilation/intubation or CPR, *n* (%)	48 (66.7)	278 (91.1)	619 (96.6)	723 (97.8)	865 (95.6)	955 (91.7)	1223 (89.3)	4711 (92.9)
Resuscitation attempted, *n* (%)[a]	93 (20.7)	385 (64.0)	711 (92.8)	775 (97.4)	928 (99.5)	1063 (99.3)	1385 (99.5)	5340 (88.9)
Survival after resuscitation, *n* (%)	29 (31.2)	162 (42.1)	458 (64.4)	621 (80.1)	801 (86.3)	971 (91.3)	1309 (94.5)	4351 (81.5)
Survival without major morbidity after resuscitation, *n* (%)	4 (4.3)	17 (4.4)	65 (9.1)	123 (15.9)	229 (24.7)	369 (34.7)	603 (43.5)	1410 (26.4)

[a] Resuscitation attempted = "Survived 1 calendar day or less AND received any ventilation/intubation or cardiopulmonary resuscitation [CPR]" or "Survived past 1 calendar day."

associated with mothers who were white, non-Hispanic (P = .029), >34 years old (P = .001), had >12 years of education (P = .013), and had private insurance (P = .016).

DISCUSSION

In a population-based cohort of infants born between 22 and 28 weeks' gestation, survival to 1 year of life differed substantially according to gestational age. Whereas only 6% of all infants born alive at 22 weeks' gestation survived, 94% born at 28 weeks' gestation survived. Although methods and populations differed somewhat, overall survival data from the California OSHPD data set were comparable to survival reported from the NRN data set in the 2 most recent epochs (2003–2007 and 2008–2012),[11,25] as well as survival data from the California Perinatal Quality Care Collaborative (CPQCC) from 2005 to 2008.[13] Live born survival rates in the California OSHPD cohort were slightly higher than population-based data from the United Kingdom[1] but lower

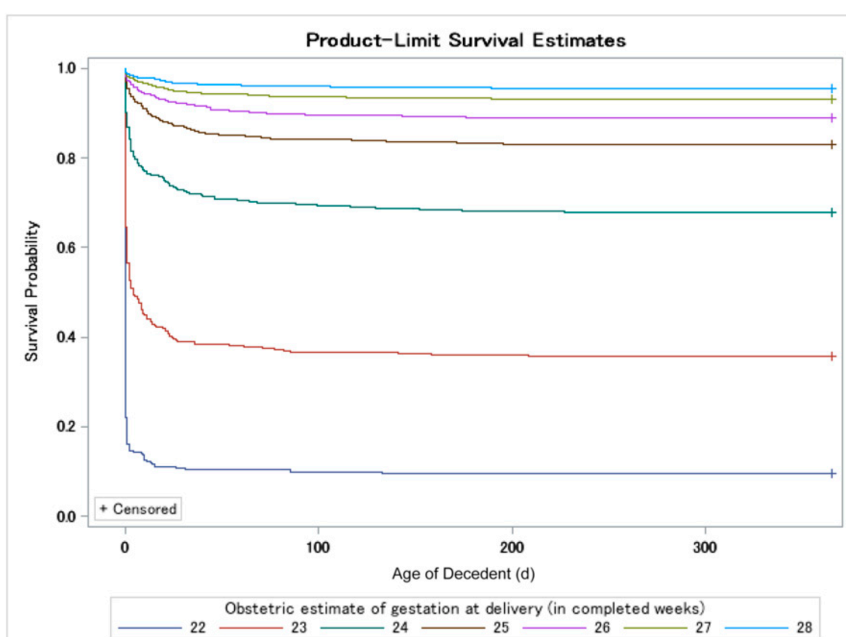

FIGURE 2
Overall survival according to gestational week.

TABLE 4 Perinatal and Maternal Demographic Characteristics Among Survivors and Nonsurvivors for Whom Resuscitation Was Attempted

Characteristic	Gestation at Birth, wk											
	22 (*n* = 93)			23 (*n* = 385)			24 (*n* = 711)			22 to 24 (*n* = 1189)		
	Survivors (*n* = 29)	Nonsurvivors (*n* = 64)	*P*	Survivors (*n* = 162)	Nonsurvivors (*n* = 223)	*P*	Survivors (*n* = 458)	Nonsurvivors (*n* = 253)	*P*	Survivors (*n* = 649)	Nonsurvivors (*n* = 540)	*P*
Birth weight, g[a]												
Mean	529.5	527.5	.004	611.7	580.6	.001	685.0	633.3	<.001	662.7	599.0	<.001
SD	85.1	106.8		94.2	88.9		119.4	109.9		117.4	107.4	
Male[b]	17 (58.6)	29 (45.3)	.234	77 (47.5)	132 (59.2)	.023	210 (45.9)	154 (60.9)	<.001	304 (56.8)	315 (58.3)	<.001
Singleton birth[b]	26 (89.7)	46 (71.9)	.058	134 (82.7)	176 (78.9)	.354	369 (80.6)	206 (81.4)	.781	529 (81.5)	428 (79.3)	.330
Cesarean delivery[b]	13 (44.8)	18 (28.1)	.114	85 (52.5)	118 (52.9)	.931	318 (69.4)	169 (66.8)	.469	416 (64.1)	305 (56.5)	.007
No prenatal visits[b]	2 (6.9)	2 (3.1)	.406	9 (5.6)	12 (5.4)	.941	13 (2.8)	10 (4.0)	.421	24 (3.7)	24 (4.4)	.515
Hypertension[b]	2 (6.9)	2 (3.1)	.406	6 (3.7)	9 (4.0)	.868	54 (11.8)	24 (9.5)	.347	62 (9.6)	35 (6.5)	.054
Diabetes mellitus[b]	2 (6.9)	3 (4.7)	.662	10 (6.2)	19 (8.5)	.389	58 (12.7)	16 (6.3)	.008	70 (10.8)	38 (7.0)	.025
Chorioamnionitis[b]	5 (17.2)	13 (20.3)	.728	39 (24.1)	45 (20.2)	.361	94 (20.5)	37 (14.6)	.052	138 (21.3)	95 (17.6)	.112
Race/ethnicity[b]												
White, non-Hispanic	6 (20.7)	4 (6.3)	.037	27 (16.7)	34 (15.3)	.706	87 (19.0)	41 (16.2)	.354	120 (18.5)	79 (14.6)	.076
Hispanic	16 (55.2)	33 (51.6)	.747	92 (56.8)	135 (60.5)	.461	235 (51.3)	137 (54.2)	.468	343 (52.9)	305 (56.5)	.211
Black	1 (3.5)	12 (18.8)	.049	18 (11.1)	12 (5.4)	.038	45 (9.8)	30 (11.9)	.398	64 (9.9)	54 (10.0)	.937
Asian	4 (13.8)	7 (10.9)	.693	12 (7.4)	21 (9.4)	.487	53 (11.6)	28 (11.1)	.839	69 (10.6)	56 (10.4)	.884
Other	2 (6.9)	8 (12.5)	.419	13 (8.0)	21 (9.4)	.635	38 (8.3)	17 (6.7)	.451	53 (8.2)	46 (8.5)	.827
Maternal age, y[b]												
<18	3 (10.3)	3 (4.7)	.304	8 (4.9)	14 (6.3)	.576	16 (3.5)	15 (5.9)	.128	27 (4.2)	32 (5.9)	.163
18–34	17 (58.6)	54 (84.4)	.007	123 (75.9)	174 (78.0)	.628	334 (72.9)	188 (74.3)	.690	474 (73.0)	416 (77.0)	.113
>34	9 (31.0)	7 (10.9)	.017	31 (19.1)	35 (15.7)	.377	108 (23.6)	50 (19.8)	.241	148 (22.8)	92 (17.0)	.014
Maternal education, y[b]												
<12	13 (44.8)	19 (29.7)	.155	54 (33.3)	80 (35.9)	.605	121 (26.4)	80 (31.6)	.140	188 (29.0)	179 (33.2)	.120
12	5 (17.2)	18 (28.1)	.260	43 (26.5)	59 (26.5)	.985	108 (23.6)	61 (24.1)	.874	156 (24.0)	138 (25.6)	.546
>12	9 (31.0)	22 (34.4)	.752	58 (35.8)	73 (32.7)	.531	211 (46.1)	99 (39.1)	.074	278 (42.8)	194 (35.9)	.015
Insurance status[b]												
Private insurance	11 (37.9)	20 (31.3)	.527	60 (37.0)	88 (39.5)	.629	196 (42.8)	100 (39.5)	.397	267 (41.1)	208 (38.5)	.358
Medi-Cal	16 (55.2)	42 (65.6)	.335	88 (54.3)	116 (52.0)	.655	219 (47.8)	137 (54.2)	.106	323 (49.8)	295 (54.6)	.095
Other	2 (6.9)	2 (3.1)	.406	14 (8.6)	19 (8.5)	.996	43 (9.4)	16 (6.3)	.156	59 (9.1)	37 (6.9)	.158
Birth hospital NICU level[b]												
No NICU	4 (13.8)	9 (14.1)	.972	28 (17.3)	49 (22.0)	.256	85 (18.6)	47 (18.6)	.995	117 (18.0)	105 (19.4)	.533
Intermediate	1 (3.5)	3 (4.7)	.785	12 (7.4)	9 (4.0)	.150	13 (2.8)	11 (4.4)	.286	26 (4.0)	23 (4.3)	.827
Community	20 (69.0)	41 (64.1)	.645	101 (62.4)	138 (61.9)	.927	254 (55.5)	150 (59.3)	.324	375 (57.8)	329 (60.9)	.272
Regional	4 (13.8)	11 (17.2)	.680	21 (13.0)	27 (12.1)	.802	106 (23.1)	45 (17.8)	.095	131 (20.2)	83 (15.4)	.031

Data are presented as *n* (%) unless otherwise indicated.

[a] Calculated by using *t* test.

[b] Calculated by using χ^2 test.

TABLE 5 Perinatal and Maternal Demographic Characteristics Among Survivors and Nonsurvivors for Whom Resuscitation Was Attempted

	Gestation at Birth, wk					
	25 to 28 (*n* = 4151)			22 to 28 (*n* = 5340)		
	Survivors (*n* = 3702)	Nonsurvivors (*n* = 449)	*P*	Survivors (*n* = 4351)	Nonsurvivors (*n* = 989)	*P*
Birth weight, g[a]						
Mean	983.0	842.1	<.001	935.3	709.3	<.001
SD	232.9	246.2		247.4	220.1	
Male[b]	1950 (52.7)	226 (59.2)	.008	2254 (51.8)	581 (58.8)	<.001
Singleton birth[b]	2921 (78.9)	341 (76.0)	.149	3450 (79.3)	769 (77.8)	.284
Cesarean delivery[b]	2579 (69.7)	343 (76.4)	.003	2995 (68.8)	648 (65.5)	.043
No prenatal visits[b]	92 (2.5)	3 (0.7)	.015	116 (2.7)	27 (2.7)	.910
Hypertension[b]	782 (21.1)	94 (20.9)	.926	844 (19.4)	129 (13.0)	<.001
Diabetes mellitus[b]	397 (10.7)	37 (8.2)	.104	467 (10.7)	74 (7.6)	.003
Chorioamnionitis[b]	421 (11.4)	44 (9.8)	.318	559 (12.9)	139 (14.1)	.309
Race/ethnicity[b]						
White, non-Hispanic	789 (21.3)	97 (21.6)	.887	909 (20.9)	176 (17.8)	.029
Hispanic	1929 (52.1)	234 (52.1)	.997	2272 (52.2)	549 (54.5)	.195
Black	301 (8.1)	37 (8.2)	.936	365 (8.4)	91 (9.2)	.409
Asian	390 (10.5)	51 (11.4)	.593	459 (10.6)	107 (10.8)	.804
Other	293 (7.9)	30 (6.7)	.357	346 (8.0)	76 (7.7)	.778
Maternal age, y[b]						
<18	179 (4.8)	20 (4.5)	.721	206 (4.7)	52 (5.3)	.489
18–34	2687 (72.6)	343 (76.4)	.086	3161 (72.7)	759 (76.7)	.009
>34	833 (22.5)	85 (18.9)	.085	981 (22.6)	177 (17.9)	.001
Maternal education, y[b]						
<12	1085 (29.3)	136 (30.3)	.667	1273 (29.3)	315 (31.9)	.107
12	893 (24.1)	109 (24.3)	.943	1049 (24.1)	247 (25.0)	.567
>12	1542 (41.7)	177 (39.4)	.365	1820 (41.8)	371 (37.5)	.013
Insurance status[b]						
Private insurance	1632 (44.1)	182 (40.5)	.152	1899 (43.7)	390 (39.4)	.016
Medi-Cal	1802 (48.7)	236 (52.6)	.117	2124 (48.8)	531 (53.7)	.006
Other	269 (7.3)	31 (6.9)	.780	328 (7.5)	68 (6.9)	.473
Birth hospital NICU level[b]						
No NICU	618 (16.7)	78 (17.4)	.716	735 (16.9)	183 (18.5)	.226
Intermediate	109 (2.9)	21 (4.7)	.047	135 (3.1)	44 (4.5)	.034
Community	2174 (58.7)	270 (60.1)	.567	2549 (58.6)	599 (60.6)	.253
Regional	801 (21.6)	80 (17.8)	.062	932 (21.4)	163 (16.5)	.001

Data are presented as *n* (%) unless otherwise indicated.
[a] Calculated by using *t* test.
[b] Calculated by using χ^2 test.

than population-based data from Sweden[5] and multicenter data from Japan.[9]

In our OSHPD cohort, more than two-thirds of all infants who survived to 1 year of age had major morbidity. For every 1-week decrease in gestational age from 28 weeks, the percentage of infants with ≥2 major morbidities increased. IVH, PVL, BPD, NEC, sepsis, and ROP have all been associated with neurodevelopmental impairment.[26–30] Other studies have shown higher rates of cerebral palsy, cognitive impairment, and behavioral problems among those born at very early gestations,[31–34] thus putting extremely preterm infants with major neonatal morbidities at high risk for significant impairment later in life.

The rates of attempted resuscitation at 22 to 24 weeks in our study were similar to several publications from the same time period. EPICure2 reported on the proportion of live born infants for whom stabilization was withheld at birth.[1] NRN considered infants to have received active treatment if they received certain interventions: surfactant therapy, tracheal intubation, ventilator support, parenteral nutrition, epinephrine, or chest compressions.[11] CPQCC categorized infants as having received intensive care if they were mechanically ventilated.[13] Most other published studies on mortality of extremely preterm infants have not reported whether resuscitative measures or active treatment were attempted or withheld,[5,9] and thus they were not suitable for direct comparison. There was a slightly higher rate of resuscitation or active treatment at 23 weeks in EPICure2 and NRN (83% and 72%, respectively) compared with CPQCC and OSHPD (both 65%), but the ranges of attempted resuscitation or active treatment at 22 weeks (21%–27%) and 24 weeks (93%–97%) were relatively similar in all 4 studies. When comparing survival after resuscitation, the California OSHPD and CPQCC data both showed a higher percentage of 22- to 25-week infants surviving after resuscitation (28%–32% at 22 weeks, 42%–43% at 23 weeks, 64% at 24 weeks, and 80%–81% at 25 weeks) compared with the EPICure2 (7%, 23%, 42%, and 67%) and NRN (23%, 33%, 57%, and 72%) data. The differences in survival may reflect the variations in the definitions of resuscitation or active treatment in each study, or variations in resuscitative and neonatal practice at the individual, hospital, or regional level.

The NRN study reported significant between-hospital variation in treatment initiation of extremely preterm infants, which accounted for a large portion of the variation in hospital survival.[11] It is possible that the differences in resuscitation practices and mortality may extend beyond hospital variability and may represent regional variability. Previous studies have explored or proposed individual decision-making in resuscitation of extremely preterm infants,[35,36] whereas other studies have examined more "macro" differences in resuscitation practice and subsequent outcomes at the hospital or country level.[37–39] Population-based studies and analyses are needed to gain a better understanding of the determinants of, and extent to, which regional practice variations underlie these mortality rate differences.

Differences in perinatal characteristics and maternal demographic characteristics between resuscitated survivors and nonsurvivors, such as increased birth weight and female sex, demonstrate favorable predictors for survival, as previously described by Tyson et al.[12] However, in the present study, singleton birth was not associated with a statistically significant increase in survival. The majority of extremely preterm births in our cohort occurred in hospitals with a community-level NICU, which conferred no survival benefit, whereas an increase in survival was seen in infants born at a hospital with a regional-level NICU, which has been reported in other studies.[20,40] In addition, several sociodemographic factors were associated with survival after resuscitation, including white, non-Hispanic mothers, maternal age >34 years, maternal education >12 years, and private insurance. Maternal race, education, and income have all been previously reported as important factors in neonatal outcomes,[41–44] but further studies are needed to examine how these factors may affect survival.

A major strength of this research is that it is a large population-based study with mortality and major morbidity outcomes up to 1 year of age. We demonstrated that linked statewide statistics (by using discharge diagnoses, birth certificates, and death records) may be used to construct meaningful population-based outcome data on extremely preterm infants. There are some limitations to using statewide data, however. The most recent linked data we can access are through 2011. Also, we are reliant on ICD-9-CM coding for diagnoses and procedures. In extrapolating whether extremely preterm infants received life-sustaining interventions after birth, we were reliant on a limited number of procedure codes. Considering that extremely preterm infants who do not receive life-sustaining interventions after birth typically die within the first day of life,[1,11] it seemed reasonable to deduce that infants who survived beyond the first calendar day of life did receive resuscitation or life-sustaining interventions, regardless of ICD-9-CM procedure code for ventilation, intubation, or cardiopulmonary resuscitation. Unfortunately, our data file was unable to adequately capture antenatal steroid exposure, which has been shown to be highly associated with increased survival in this population.[3,12,13] An additional limitation of the OSHPD data is that approximately one-half of the 22- to 28-week births did not have linked birth certificate and hospital discharge records, and were not included in the study cohort. Although reasons for this absence are not clear given that the linkage was completed by OSHPD staff, considering that our study's resuscitation rates and survival numbers are similar to other recently published studies,[1,11,13] we do not believe that the observed findings are biased toward those with linked data versus not. Other morbidities are not consistently coded, such as ROP stage, thus likely underestimating morbidity. In contrast, discharge codes may overestimate culture-positive sepsis by including infants treated for culture-negative clinical suspicion of infection. To minimize these effects, we reported data for infants with >1 morbidity. Finally, our study does not capture long-term neurodevelopmental outcomes. Because the major morbidities described here all have been associated with neurodevelopmental impairment, we suspect that high rates of long-term impairment exist, particularly in infants of lower gestational age.

Future population-based studies are needed to examine neurodevelopmental and other outcomes beyond year 1. Multicenter studies of long-term outcomes in the United States[34,45] and Japan[9] have relied on large, within-country academic medical centers. Given that many extremely preterm infants are being cared for in community-level NICUs, these multicenter studies may not adequately reflect the full range of hospital practices and patient populations. Large, population-based studies of neurodevelopmental outcomes in survivors of extreme prematurity have been conducted in the United Kingdom (EPICure),[32,46] Sweden (EXPRESS - Extremely Preterm Infants Study in Sweden),[47] Australia (VICS - Victorian Infant Collaborative Study),[48] and France (EPIPAGE - Etude Epidémiologique sur les Petits Ages Gestationnels).[31] However, there are no population-based studies that have assessed the long-term neurodevelopmental outcomes of extreme prematurity in the United States, which has a health care delivery system different from those in Western Europe, Australia, and Japan.

CONCLUSIONS

Our study provides population-based evidence of survival and timing of death for extremely preterm infants in the first year of life. At the lowest gestational ages (ie, 22 and 23 weeks), less than one-half of infants survive after attempted resuscitation, with two-thirds of survivors having >1 major morbidity. These findings can inform recommendations for the care of extremely preterm infants.

ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CPQCC: California Perinatal Quality Care Collaborative
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
NRN: Neonatal Research Network
OSHPD: Office of Statewide Health Planning and Development
PVL: periventricular leukomalacia
ROP: retinopathy of prematurity

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Survival and Major Morbidity of Extremely Preterm Infants: A Population-Based Study

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