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# Does active treatment in infants born at 22–23 weeks correlate with outcomes of more mature infants at the same hospital? An analysis of California NICU data, 2015–2019

Shalmali Bane<sup>1</sup>, Matthew A. Rysavy<sup>2</sup>, Suzan L Carmichael<sup>3,4</sup>, Tianyao Lu<sup>3,5</sup>, Mihoko Bennet<sup>3,5</sup>, Henry C Lee<sup>3,5</sup>

<sup>1</sup>Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA, USA 94306

<sup>2</sup>Department of Pediatrics, McGovern Medical School, University of Texas Health Science Center, Houston TX 77030

<sup>3</sup>Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA 94305

<sup>4</sup>Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford CA, USA 94306.

<sup>5</sup>California Perinatal Quality Care Collaborative, Stanford, California, USA 94306

# Abstract

**Objective:** To investigate whether hospital rates of active treatment for infants born at 22–23 weeks is associated with survival of infants born at 24–27 weeks.

**Study Design:** We included all liveborn infants 22–27 weeks of gestation delivered at California Perinatal Quality Care Collaborative hospitals from 2015–2019. We assessed (1) the correlation of active treatment (e.g., endotracheal intubation, epinephrine) in 22–23 week infants and survival until discharge for 24–27 week infants and (2) the association of active treatment with survival using multilevel models.

**Result:** The 22–23 week active treatment rate was associated with infant outcomes at 22–23 weeks but not 24–27 weeks. A 10% increase in active treatment did not relate to 24–25 week (adjusted OR: 1.00 [95% CI: 0.95–1.05]), or 26–27 week survival (aOR: 1.02 [0.95–1.09]).

**Conclusion:** The hospital rate of active treatment for infants born at 22–23 weeks was not associated with improved survival for 24–27 week infants.

Corresponding Author: Shalmali Bane, sbane@stanford.edu.

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# Introduction

Of approximately 380 000 preterm ( 36 weeks' gestation) live births in the US in 2019, 27 301 (7.1%) were extremely preterm, defined as births at 22–28 weeks of gestation.<sup>1</sup> While extremely preterm births represent less than 1% of total births in the US, the infant mortality rate in this population is 100 times higher than births at 37 weeks or more gestation (208 per 1 000 live births as compared to 2 per 1 000 live births).<sup>2</sup>

Among infants born extremely preterm, mortality and morbidity, as well as recommendations for treatment, vary by gestational week.<sup>3,4</sup> The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine guidelines from 2017 recommend different care for infants born at <22 weeks, 22 weeks, 23 weeks, and >23 weeks.<sup>5</sup> Sociodemographic and medical characteristics are associated with the rate of maternal and neonatal interventions in this population.<sup>6</sup> Importantly, there are differences in practice among hospitals with regards to the initiation of potentially lifesaving interventions to infants born at 22–23 weeks that explain some of the between-hospital differences in mortality and morbidity for these infants.<sup>7</sup>

It has been hypothesized that the approach to caring for infants born at 22–23 weeks could impact mortality and morbidity rates for older infants at that same hospital. Some have speculated that the provision of intensive care to infants born at 22–23 weeks may confer experience, protocol development, and improved skill for caring for older high-risk infants; however, current evidence for this is mixed<sup>8,9</sup>. The aim of this study was to investigate whether hospital rates of active treatment, defined as any potentially lifesaving intervention following birth, for infants born at 22–23 weeks' gestation, was associated with outcomes of infants born at 24–27 weeks in a contemporary population-based U.S. cohort.

# Methods

#### Dataset.

Our study used data submitted by neonatal intensive care unit (NICU) members of the California Perinatal Quality Care Collaborative (CPQCC), a statewide network of California's NICUs that maintains a population-based dataset of perinatal variables and outcomes.<sup>10,11</sup> Over 90% of NICUs in California are members of the CPQCC. Common variables are based on definitions developed by the Vermont Oxford Network. This study was approved by the Institutional Review Board of Stanford University.

#### Cohort.

The cohort included all liveborn infants at 22–27 weeks' gestation delivered at CPQCC member hospitals 2015–2019 (Figure 1). Infants with severe congenital malformations (defined as one or more of the listed congenital abnormalities per CPQCC Data Manual<sup>12</sup>) or missing relevant data were excluded. All infants born outside of the CPQCC network (regardless of whether they received subsequent treatment at a CPQCC hospital) were excluded, as our analysis attributed treatment to the birth hospital. All infants born at hospitals with 10 total births between gestational ages of 22–27 over the study period were included in the analysis (N = 8,802 infants at 122 hospitals). For hospital-level analyses,

only hospitals with 5 births at 22-23 weeks during the study period were included (N = 88 hospitals).

#### Exposure.

The primary exposure was the hospital rate of active treatment administered to infants born at 22–23 weeks' gestation at that hospital. We adapted the definition of active treatment from prior literature using variables available in the CPQCC database.<sup>7,13</sup> We defined an infant to have received active treatment if they received any of the following interventions: endotracheal intubation; continuous positive airway pressure (CPAP) or noninvasive positive-pressure ventilation (NIPPV) for infants that survived >12 hours; epinephrine or cardiac compressions in the delivery room. Hospital rates were computed as the proportion of infants born at 22–23 weeks at the hospital during the study period who received active treatment.

#### Outcome.

The study outcome was the hospital rate of survival to discharge. Infants born at a CPQCC network hospital were followed until discharge, including any transfers to CPQCC network hospitals. The study outcome was attributed to the birth hospital regardless of postnatal transfer. The primary outcome was defined as survival until discharge, including subsequent delivery-related admission or transfers. Analyses were conducted with infants stratified into 3 groups: 22–23 weeks, 24–25 weeks, and 26–27 weeks.

The secondary outcome was survival without any of the following major morbidities: severe retinopathy of prematurity (ROP) (defined as infants receiving an eye examination and whose worst stage or ROP was 3 or having ROP surgery), chronic lung disease (defined as oxygen use at 36 weeks or discharge at 34–35 weeks with supplemental oxygen), necrotizing enterocolitis (diagnosed at surgery or postmortem examination or clinically using the following criteria: 1 or more of the following clinical signs: bilious gastric aspirate or emesis, abdominal distension, or blood in stool, and 1 or more of the following radiographic findings: pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum), nosocomial infection (defined as a late bacterial infection, including coagulase-negative Staphylococcus, or fungal infection after day 3), severe intracranial hemorrhage (defined as a grade 3 or 4 using the Papile criteria on or before day 28)<sup>14</sup>, or cystic periventricular leukomalacia (on cranial ultrasound, computed tomography, or magnetic resonance imaging).<sup>15</sup>

#### Statistical Analysis.

We assessed correlation of hospital rates of active treatment in infants with gestational ages of 22–23 weeks and the following for infants with gestational ages of 22–23 weeks, 24–25 weeks and 26–27 weeks: survival, survival without major morbidity, cesarean section rate and rate of antenatal steroid use. Correlation as assessed using scatter plots and estimation of an R statistic R statistic. We assessed the relationship of hospital-level of active treatment in infants aged 22–23 weeks with infant-level survival using a multi-level logistic regression model with a random intercept with patients clustered by hospital and a logit link. Models were developed separately for the following gestational age groups: 22–23 weeks, 24–25

weeks, and 26–27 weeks. Odds ratios presented are for 10% increases in the rate of active care. All models were adjusted for the following maternal and infant covariates that have been shown to be related to birth outcomes: maternal age (<25 years, 25–35 years, >35 years), maternal diabetes (of any type or severity), maternal hypertension (includes diagnosis of hypertension, chronic or pregnancy-induced, eclampsia, and preeclampsia), infant sex, birth weight, small for gestational age status (defined as an infant with birth weight <10<sup>th</sup> percentile for gestational age<sup>16</sup>), gestational plurality (singleton or multiple), antenatal steroid exposure (at any time prior to birth), mode of delivery (cesarean section as compared to spontaneous or operative vaginal birth).<sup>7–9</sup>

As a sensitivity analysis, we ran the models above with the exposure alternatively defined as the number of actively treated infants as opposed to rate; ORs are presented for a 3-unit increase in the number of 22–23 week infants actively treated. This was to assess if the absolute volume of infants had a different effect than the frequency. Statistical analysis was performed with SAS, version 9.4 (Cary, NC, USA); PROC GLIMMIX was used for the models.

#### Data and Code Availability:

Data are available upon request and completion of requirements from CPQCC. Code is also available upon request.

# Results

The cohort included 8 802 infants from 122 hospitals with gestational ages 22 to 27 weeks. Infant characteristics by gestational age at birth are provided in Table 1. In this population, 1 603 infants were born at 22–23 weeks (18.2%), 3 045 at 24–25 weeks (34.6%), and 4 154 at 26–27 weeks (47.2%). Hospital rates of active treatment for infants aged 22–23 weeks ranged from 0% to 100%, with a median rate of 57% (Appendix Figure 1). Among hospitals with 5 births at 22–23 weeks during the study period (n = 88), 65.9% of hospitals were community hospitals, 21.6% were regional hospitals, 9.1% were non-California Children's Services hospitals, and 3.4% were intermediate hospitals.<sup>17</sup>

In a crude analysis, without adjusting for differences in patient characteristics among hospitals, hospital level of active treatment was highly correlated with survival in the 22–23 week cohort (R = 0.69 [95% CI: 0.56–0.79), p < 0.001) and modestly correlated with survival without morbidity (R = 0.21 [95% CI: 0.00–0.40], p = 0.05). Levels of active treatment in the 22–23 week cohort were not correlated with any hospital-level infant outcomes in either the 24–25 weeks of gestation cohort or the 26–27-week cohort (Figure 2; Appendix Table 1). Similarly, active treatment was highly correlated with the rate of cesarean section and antenatal care in 22–23 week infants, but not in either of the older cohorts (Appendix Figure 2).

In a model adjusting for differences in patient characteristics among hospitals, a 10% increase in rate of active treatment rate was associated with an increase in survival for the 22–23 week population (adjusted OR [aOR]: 1.22, 95% CI:1.12–1.33) but was not associated with an increase in survival for the 24–25 week (aOR: 1.01, 95% CI: 0.95–

1.07) or 26–27 week populations (aOR: 1.02, 95% CI: 0.94–1.11; Table 2). No association between rate of active treatment and survival without morbidities were observed for any of the populations. Excluding antenatal steroids from our fully adjusted model had no substantial effect on the relationship between postnatal active treatment rate and infant outcomes (Appendix Table 2).

Among hospitals in our sample, the absolute volume of 22–23 week infants actively treated ranged from 0 to 56, with a median of 6. Adjusted ORs from the sensitivity analysis using absolute volume of infants actively treated were similar to the main analysis using the hospital rate of active treatment (Table 2).

# Discussion

In this retrospective cohort study of hospitals in California, we found that hospital rates of active treatment in infants of 22–23 weeks gestational age were not associated with improved odds of survival or survival without morbidity in infants born at 24–27 weeks of gestation. Rate of active treatment in the 22–23 week population was associated with increased odds of survival in the same population; however, this effect was not observed for the outcome of survival without morbidity. A sensitivity analysis using the absolute volume of infants actively treated as opposed to hospital rate of active treatment showed similar results.

Providing intensive care to babies born at 22–23 weeks would require some similar knowledge, skills, teamwork, and environmental support needed for very preterm babies born at slightly higher gestational age groups. On the other hand, infants born at the earliest gestational ages may require unique care strategies that recognize these patients' smaller size and ontogenetic differences.<sup>18</sup> Centers caring for a higher volume of high acuity patients has been shown to be associated with decreased mortality for very preterm infants in the NICU.<sup>19,20</sup> The subset of patients born at 22–23 weeks would represent the highest risk patients in this broader cohort with the highest need for intensive care and risk for the most adverse outcomes.

Previous research has shown that differences in hospital practice regarding active treatment for 22–24 week infants explains some of the between-hospital variability in outcomes for these populations.<sup>7</sup> While it is possible that the approach to caring for infants born at 22–23 weeks could impact mortality and morbidity rates for older infants at that same hospital—for example, through conferring experience, protocol development, and improved skill for caring for high-risk infants—our findings in a statewide California network of NICU's do not support this hypothesis for the outcomes of survival and survival without morbidity as defined in our study.

A study using data from 2002–2008 found that aspects of treatment in the 22–24 week population (antenatal corticosteroids, c-section, and resuscitation) were associated with improved outcomes including death within 120 days for infants born at 25–27 weeks (OR: 0.85, 95% CI: 0.74–0.97 for antenatal corticosteroids, 0.84 [95% CI: 0.68–1.05] for cesarean delivery, and 0.89 [95% CI: 0.78–1.02] for resuscitation).<sup>8</sup> This study included only U.S.

academic centers and differs from our study by time period, geography, and definitions of active treatment. Another study from 2011 using data from France assessed whether "intensity of perinatal care" (defined as the ratio of the number of infants admitted to the NICU to the number of these infants delivered) at 24–26 weeks related to outcomes of infants born at 27–28 weeks of gestation.<sup>9</sup> Like our study, that study showed no difference in outcomes.

This study has several strengths, including the use of a large population-based and recent dataset reflecting a time period during which there has been increased resuscitation for babies born at 22–23 weeks and with large variations in practice. CPQCC data are widely used for quality improvement and research to support clinical practice.<sup>10,21–24</sup> However, our study has several limitations. These include that our particular definition of active treatment might not represent the range of care provided by hospitals, that we did not examine outcomes aside from survival and survival without morbidity and that we had insufficient sample size to examine survival without specific individual morbidities. Moreover, our data do not include post-discharge outcomes, which reflect on the quality of neonatal intensive care.

In this study, we found the rate of active treatment in infants of 22–23 weeks of gestational age was not associated with improved survival or survival without morbidity in infants born at 24–27 weeks of gestational age. Advancing healthcare delivery for both groups will require common and targeted discovery efforts in research and strategies for quality improvement.

# Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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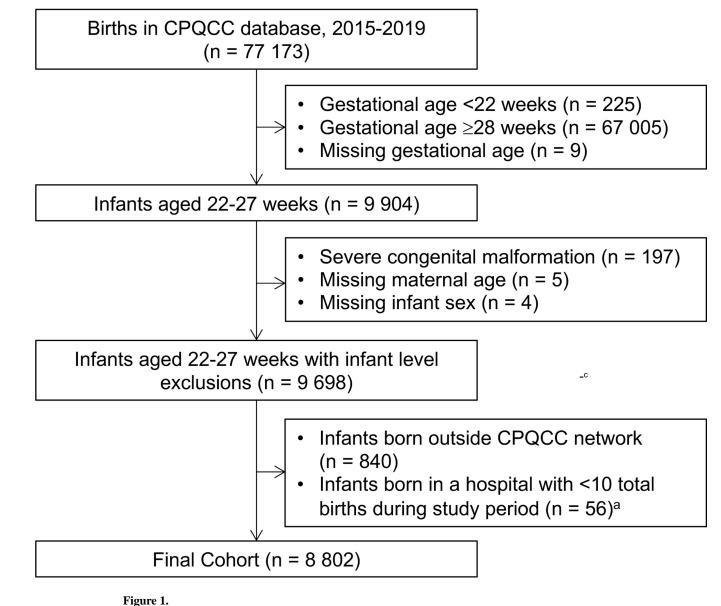
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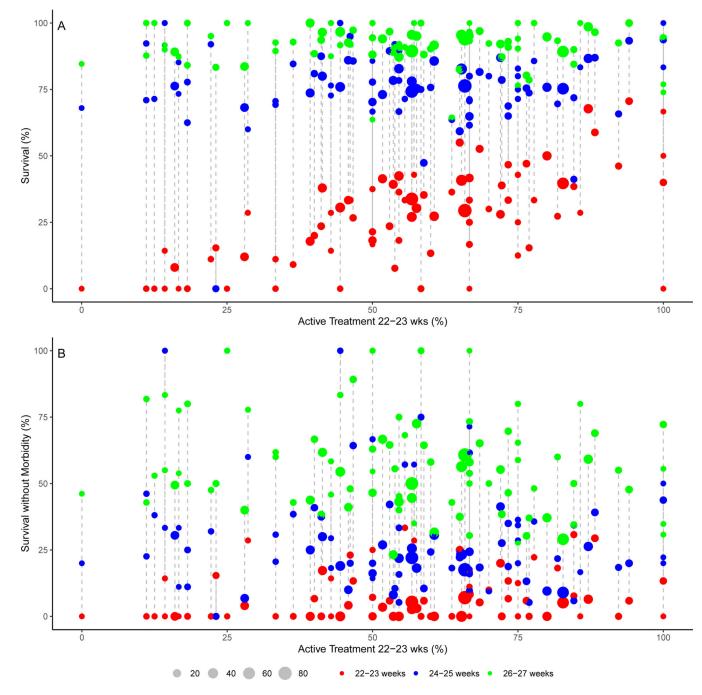
Cohort Selection Process, CPQCC 2015-2019

<sup>a</sup> Of the 134 hospitals, after exclusions for gestational age, severe congenital malformations, missing data and infants born outside CPQCC network, a total of 47 hospitals were excluded due to inadequate number of births.

Abbreviations: CPQCC, California Perinatal Quality Care Collaborative.

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#### Figure 2.

Comparison of Hospital Rates of 22–23 Week Infant Active Treatment and Outcomes of Interest by Gestational Age, CPQCC 2015–2019  $(N = 88)^a$ 

(A) Survival (B) Survival without morbidity

Abbreviations: CPQCC, California Perinatal Quality Care Collaborative.

<sup>a</sup>Bubble size corresponds to unit delivery volume for 22-23 week infants

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# Table 1.

Descriptive Characteristics of Infants and Mothers by Infant Gestational Age: CPQCC hospitals, California 2015–2019 (N = 8 802)

Chamataniation	22–23	22–23 weeks	24-25	24–25 weeks	26–27	26–27 weeks
Unaracteristics	<b>N</b>	(N = 1 603)	<b>N</b>	(N = 3 045)	<b>N</b>	(N = 4 154)
	Z	%	Z	%	Z	%
Maternal Age						
<25 years	347	21.6%	656	21.5%	768	18.5%
25–35 years	948	59.1%	1 752	57.5%	2 425	58.4%
>35 years	308	19.2%	637	20.9%	961	23.1%
Maternal Complication						
Diabetes	126	43.2%	333	36.4%	593	34.1%
Hypertension	166	56.8%	583	63.6%	1 148	65.9%
Infant Sex						
Female	739	46.1%	1 436	47.2%	1 998	48.1%
Male	864	53.9%	1 609	52.8%	2 156	51.9%
Birth Weight						
<500g	489	30.5%	195	6.4%	65	1.6%
500–1000g	1 110	69.2%	2 786	91.5%	2 563	61.7%
>1000g	4	0.2%	64	2.1%	1 526	36.7%
Plurality						
Singleton	1 235	77.0%	2400	78.8%	3 237	77.9%
Multiple	368	23.0%	645	21.2%	917	22.1%
SGA						
Yes	174	10.9%	334	11.0%	480	11.6%
No	1 429	89.1%	2 711	89.0%	3 674	88.4%
Delivery Mode						
Vaginal <sup>a</sup>	1 105	68.9%	906	29.8%	1 117	26.9%
Cesarean	498	31.1%	2 139	70.2%	3 037	73.1%
Antenatal Steroids						
Yes	943	58.8%	2 757	90.5%	3 851	92.7%
No	660	41.2%	288	9.5%	303	7 3%

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Abbreviations: CPQCC, California Perinatal Quality Care Collaborative; SGA, small for gestational age.

 $^{a}$ Compared to vaginal delivery, which included spontaneous and operative vaginal birth.

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Relationship between 22–23 Week Infant Active Treatment Rate and infant outcomes, by Gestational Age, CPQCC 2015–2019 (n = 8 802)

Population						
	N (%)	OR <sup>a</sup> (95% CI)	aOR <sup>b</sup> (95% CI)	N (%)	$OR^a$ (95% CI) a $OR^b$ (95% CI)	aOR <sup>b</sup> (95% CI)
Main Analysis	Main Analysis - % of Active Treatment $^{\mathcal{C}}$	$\Gamma$ reatment $^{c}$				
22-23 weeks	474 (29.6)	22–23 weeks 474 (29.6) 1.34 (1.25, 1.44)	1.22 (1.12, 1.33)	100 (6.3)	1.19 (1.02, 1.38) 1.04 (0.88, 1.22)	1.04 (0.88, 1.22)
24-25 weeks		2 320 (76.5) 1.00 (0.95, 1.05)	1.01 (0.95, 1.07)	751 (24.7)	$0.95\ (0.88,1.03)$	0.94 (0.87, 1.02)
26–27 weeks	3 793 (91.5)	3 793 (91.5) 1.02 (0.95, 1.09)	$1.02\ (0.94,1.11)$	2170 (52.4)	0.96 (0.91, 1.02)	0.96 (0.90, 1.02)
Sensitivity An	ıalysis – number	Sensitivity Analysis – number of 22–23 week infants actively treated $^d$	nts actively treated $^d$			
22-23 weeks	474 (29.6)	22–23 weeks 474 (29.6) 1.11 (1.06, 1.17)	1.08 (1.02, 1.13)	100 (6.3)	0.99 (0.91, 1.07) 0.94 (0.85, 1.03)	$0.94\ (0.85,1.03)$
24-25 weeks	2 320 (76.5)	2 320 (76.5) 1.01 (0.98, 1.04)	$0.94\ (0.89,\ 0.98)$	751 (24.7)	751 (24.7) 1.01 (0.97, 1.04) 0.94 (0.89, 0.98) 1.01	$0.94\ (0.89,\ 0.98)$
26–27 weeks	3 793 (91.5)	26–27 weeks 3 793 (91.5) 1.03 (0.99, 1.07)	$0.97\ (0.94,1.01)$	2 170 (52.4)	0.97 (0.94, 1.01) 2 170 (52.4) 1.04 (0.99, 1.09) 0.98 (0.94, 1.01)	0.98 (0.94, 1.01)

 $^{\mathcal{C}}$ OR presents 10% increase in rate of active care

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 $^{d}$  OR presents 3-unit increase in number of infants actively treated