Gestational Age and Outcomes in Critical Congenital Heart Disease

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abstract

BACKGROUND AND OBJECTIVES: It is unknown how gestational age (GA) impacts neonatal morbidities in infants with critical congenital heart disease (CCHD). We aim to quantify GA-specific mortality and neonatal morbidity in infants with CCHD.

METHODS: Cohort study using a database linking birth certificate, infant hospital discharge, readmission, and death records, including infants 22 to 42 weeks' GA without chromosomal anomalies (2005–2012, 2 988 925 live births). The *International Classification of Diseases, Ninth Revision* diagnostic and procedure codes were used to define CCHD and neonatal morbidities (intraventricular hemorrhage, retinopathy, periventricular leukomalacia, chronic lung disease, necrotizing enterocolitis). Adjusted absolute risk differences (ARDs) with 95% confidence intervals (CIs) were calculated.

RESULTS: We identified 6903 out of 2 968 566 (0.23%) infants with CCHD. The incidence of CCHD was highest at 29 to 31 weeks' GA (0.9%) and lowest at 39 to 42 weeks (0.2%). Combined neonatal morbidity or mortality in infants with and without CCHD was 82.8% and 57.9% at <29 weeks and declined to 10.9% and 0.1% at 39 to 42 weeks' GA. In infants with CCHD, being born at 34 to 36 weeks was associated with a higher risk of death or morbidity than being born at 37 to 38 weeks (adjusted ARD 9.1%, 95% CI 5.5% to 12.7%), and being born at 37 to 38 weeks was associated with a higher risk of death or morbidity than 39 to 42 weeks (adjusted ARD 3.2%, 95% CI 1.6% to 4.9%).

CONCLUSIONS: Infants born with CCHD are at high risk of neonatal morbidity. Morbidity remains increased across all GA groups in comparison with infants born at 39 to 42 weeks. This substantial risk of neonatal morbidity is important to consider when caring for this patient population.

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Dr Steurer conceptualized and designed the study together with the other coauthors, performed part of the analyses, and drafted the initial manuscript; Ms Baer conducted part of the analyses and critically reviewed the manuscript; Dr Keller was involved in conceptualizing and designing the study and critically reviewed the statistical analyses; Mr Oltman and Drs Chambers, Norton, Peyvandi, Rand, Rajagopal, and Ryckman were involved in conceptualizing and designing the study and critically reviewed the manuscript; Dr Moon-Grady conceptualized and designed the study together with the co-authors, was involved in the database preparation, and critically revised the manuscript; Dr Jelliffe-Pawlowski conceptualized and designed the study together with the coauthors, supervised the statistical analyses, and reviewed and revised the manuscript; and 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: Critical congenital heart disease (CCHD) and prematurity are among the leading causes of neonatal mortality. Gestational age influences mortality in preterm and term infants with and without CCHD.

WHAT THIS STUDY ADDS: In this population-based cohort study, we assess the impact of gestational age on neonatal morbidities in preterm and term infants with CCHD and compare these results with term and preterm infants without CCHD.

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In the developed world, congenital heart disease (CHD) and prematurity are the 2 leading causes of perinatal and infant mortality.[1,2] CHD is the most common birth defect, with an incidence reported between 0.3% and 0.8%,[3,4] whereas critical CHD (CCHD) has a reported incidence of 0.17%.[5] Despite recently improved outcomes, perinatal mortality in neonates with CHD remains relatively high (9.2% in the Heart Disease and Stroke Statistics of the year 2016),[6,7] and survivors are at risk for complications and long-term sequelae.[6]

Gestational age (GA) is the most significant predictor of mortality in extremely preterm infants without congenital anomalies.[8] Even late preterm infants born at 34 to 36 weeks have a higher risk of death than term infants.[9,10] In several studies, researchers have investigated the relationship between GA and mortality in infants with CHD.[11–13] In all of these studies, the researchers found a significant association extending beyond premature infants: early term infants (37–38 weeks' gestation) with CHD have a higher risk of death than infants born at 39 to 40 weeks' gestation.[11–13] In none of these studies did researchers investigate the relationship between GA and mortality in infants <34 weeks' GA or whether the impact of GA on mortality is quantitatively different in infants with and without CCHD.

It is well known that survivors of preterm birth often suffer from severe neonatal morbidities, including chronic lung disease (CLD), retinopathy of prematurity (ROP), sequelae of necrotizing enterocolitis (NEC), intraventricular hemorrhage, or periventricular leukomalacia (PVL).[14,15] In recent years, changes in neonatal care have decreased the incidence of severe morbidities related to prematurity in infants >25 weeks' gestation.[16] Infants born after 32 weeks' gestation rarely suffer severe neonatal morbidities.[17] However, it is unknown to what extent these major prematurity-related morbidities affect infants with CCHD.

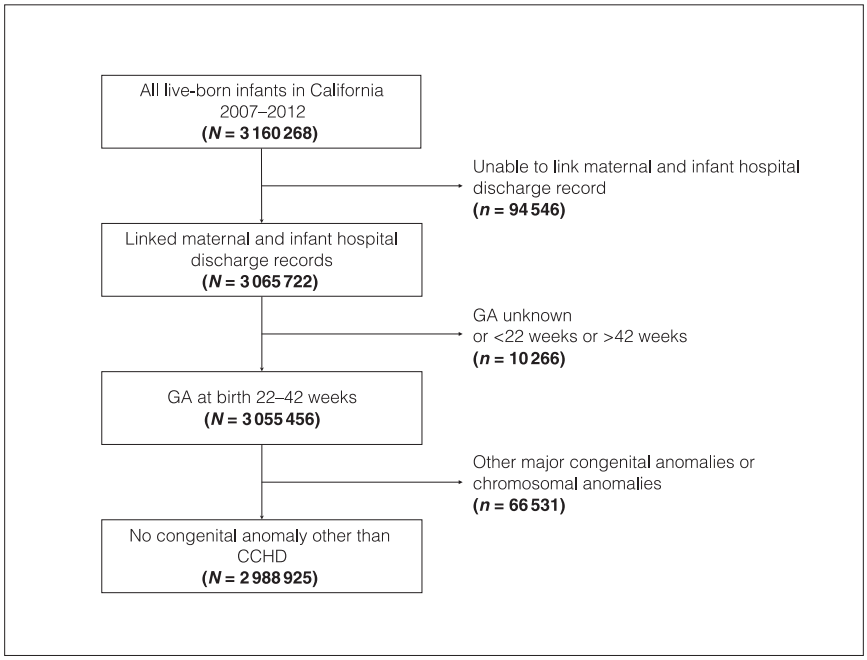

FIGURE 1
Study population.

In this population-based study, we aim to quantify the effect of GA on mortality and neonatal morbidity in preterm and term infants with CCHD and compare these effects with a control group of infants without CCHD.

METHODS

The California Office of Statewide Health Planning and Development maintains a birth cohort database containing 3 160 268 live births from 2007 to 2012. This database includes detailed information on infant characteristics derived from hospital discharge records (birth hospitalization and readmissions), linked to birth and death certificates, from birth to 1 year of age. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).[18] The database has been used in multiple studies examining birth and neonatal outcomes.[19–22]

All live-born infants with GA 22 to 42 completed weeks were included. Infants with known chromosomal abnormalities or major structural birth defects other than CCHD were excluded. Structural birth defects were considered major if they were determined by clinical review to result in mortality or major morbidity and likely to be identified at birth or lead to hospitalization during the first year of life (Fig 1).

Infants with CCHD were identified by ICD-9-CM diagnostic and procedure codes present in the birth, transfer, or readmission records (Supplemental Table 4). For the purpose of this study, CCHD was defined as CHD that is likely to be detected by pulse oximetry screening some or most of the time.[5,23] Primary targets for screening were

hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, transposition of the great arteries, tricuspid atresia, truncus arteriosus, and total anomalous venous return. Secondary targets were coarctation of the aorta, double outlet right ventricle, Ebstein anomaly, and single ventricle. Additionally, we included pulmonary and aortic stenosis requiring intervention during the first year of life.[23]

Two physicians (M.A.S. and A.J.M.-G.) reviewed all cases according to a proposed framework based on morphogenetically similar developmental mechanisms[5,24] to ensure the correct classification of infants with multiple diagnostic or procedure codes. The final diagnosis was reached by consensus. Infants with multiple CCHD codes consistent with heterotaxy were also classified as CCHD.

To adjust for complexity of CCHD, we built 6 severity groups modified from risk adjustment in congenital heart surgery (RACHS)[25] (Table 1). It was impossible to use RACHS in its original form because some surgical details needed for classifications were not available in this database.

TABLE 1 Classification of CCHD (Modified From RACHS)

Modified RACHS	*N*	Mortality, *N* (%)
Any CCHD	6903	866 (12.6)
Modified RACHS 1		
Nonneonatal coarcation	319	33 (10.3)
Modified RACHS 2		
Neonatal coarctation	1055	70 (6.6)
Pulmonary valve anomaly requiring intervention	367	20 (5.5)
Aortic valve anomaly requiring nonneonatal intervention	67	11 (16.4)
TOF	1329	97 (7.3)
DORV	89	6 (6.7)
Nonneonatal TAPVR	95	6 (6.3)
Modified RACHS 3		
TGA without pulmonary stenosis and without VSD	136	22 (16.2)
Nonneonatal Ebstein anomaly	190	8 (4.2)
TOF and AV canal	14	0 (0)
Modified RACHS 4		
Aortic valve anomaly requiring neonatal intervention	60	5 (8.33)
TGA and VSD	547	33 (6.0)
TGA and pulmonary stenosis	164	18 (11.0)
Neonatal TAPVR	181	10 (5.5)
Truncus arteriosus	181	25 (13.8)
Modified RACHS 5		
Neonatal Ebstein anomaly	88	31 (35.2)
Common ventricle	84	12 (14.3)
Tricuspid atresia	116	12 (10.3)
Complex single ventricle	416	78 (23.1)
PA/IVS	52	10 (19.2)
Complex CHD consistent with heterotaxy	368	85 (23.1)
Modified RACHS 6		
HLHS	980	272 (27.8)

AV, atrioventricular; DORV, double outlet right ventricle; PA/IVS, pulmonary atresia with intact intraventricular septum; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

The outcomes assessed were 1-year mortality (determined by the death certificate) and severe neonatal morbidity (determined from ICD-9-CM codes). These included intraventricular hemorrhage greater than grade II (772.13 and 772.14), NEC (777.5), CLD (770.7), and PVL (779.7). 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.

Demographics and clinical characteristics between infants with and without CCHD were compared by using a single logistic regression. The results are presented as odds ratios and 95% confidence intervals (CIs). A χ^2 test was used to compare proportions between 2 groups.

We derived curves for the predicted probability of death or severe neonatal morbidity separately in infants with and without CCHD. To obtain a smooth curve, we fitted restricted cubic splines with 4 predefined knots for GA. GA-specific margins were calculated while adjusting for *z* score for birth weight, sex, multiple gestation, and complexity of CHD (all confounders were kept at their mean values).

Given departure from linearity, we divided GA a priori into 6 clinically relevant categories (extremely preterm [<29 weeks], very preterm [29–31weeks], moderately preterm [32–34 weeks], late preterm [35–36 weeks], early term [37–38 weeks], and term [39–42 weeks]) to investigate the effect of GA on mortality and major neonatal morbidity in infants with CCHD. We calculated crude and adjusted absolute risk differences (ARDs) and 95% CIs to compare mortality and morbidity in infants with CCHD between different GA groups. For the adjusted models, we included a priori predictors that are known to influence mortality and morbidity in preterm infants: *z* score for birth weight, sex, and multiple gestation. Additionally, we adjusted for complexity of CHD (Table 1). The adjusted ARD was obtained by calculating margins while keeping all confounders at their mean value. We performed sensitivity analyses by including infants with noncritical CHD requiring surgical repair in the first year of life (isolated atrial septal defect,

ventricular septal defect, and atrioventricular canal).

To quantify the effect of GA on the difference in mortality and major neonatal morbidity between infants with and without CCHD, we built logistic models allowing for interaction between the presence or absence of CCHD and GA while adjusting for birth weight *z* score, sex, and multiple gestation. The results are presented as ARDs with 95% CIs.

All analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC) and Stata version 14.2 (StataCorp, College Station, TX). The study was approved by the Committee for the Protection of Human Subjects within the California Health and Human Services Agency.

RESULTS

The incidence of CCHD in live-born infants of 22 to 42 weeks' gestation without chromosomal anomalies was 6903 out of 2 968 566 (0.23%) in this population-based cohort. There were an additional 930 out of 7833 (11.9%) infants with CCHD with chromosomal anomalies, all of whom were excluded from this study. Overall, 18.1% (1246 out of 6903) of infants with CCHD were born prematurely (<37 weeks' gestation) compared with 8.4% of infants without CCHD (251 029 out of 2 983 022, $P < .001$). Baseline characteristics of infants with and without CCHD are presented in Table 2. The incidence of CCHD was lowest at 39 to 42 weeks' gestation (4167 out of 2 079 836, 0.2%); it increased with decreasing GA and reached its maximum at 29 to 31 weeks' gestation (0.9%, 163 out of 18 114) before declining to 0.79% (128 out of 16 143) at <29 weeks' gestation.

GA-specific severe neonatal morbidities in infants with and

TABLE 2 Characteristics of Infants With and Without CHD

	Any CCHD, *n* (%)	No CCHD, *n* (%)	OR (95% CI)
Sample	6903	2 983 022	—
Birth weight			
Mean birth weight, g (SD)	3090.7 (733.8)	3306.7 (555.3)	—
SGA	1120 (16.2)	266 133 (8.9)	2.0 (1.9 to 2.1)
LGA	664 (9.6)	293 001 (9.8)	1.1 (1.0 to 1.2)
Mode of delivery			
Cesarean	2942 (42.6)	983 421 (33.0)	1.5 (1.4 to 1.6)
Race			
Non-Hispanic white	1902 (27.6)	787 896 (26.4)	Reference
Hispanic	3235 (46.9)	1 442 117 (48.3)	0.9 (0.9 to 1.0)[a]
African American	355 (5.1)	161 450 (5.4)	0.9 (0.8 to 1.0)
Asian	778 (11.3)	370 399 (12.4)	0.9 (0.8 to 0.9)
Other	633 (9.2)	221 160 (7.4)	1.2 (1.1 to 1.3)
Sex			
Female	2839 (41.1)	1 466 857 (49.2)	0.7 (0.7 to 0.8)
Gestation			
Singleton	6544 (94.8)	2 891 671 (96.9)	Reference
Multiple	359 (5.2)	91 351 (3.1)	1.7 (1.6 to 1.9)
Maternal education, y			
<12	1651 (23.9)	705 119 (23.6)	1.0 (0.9 to 1.1)
12	1789 (25.9)	757 673 (25.4)	Reference
>12	3062 (44.4)	1 409 955 (47.3)	0.9 (0.9 to 1.0)[a]
Payment for delivery			
Private insurance	3180 (46.1)	1 396 651 (46.8)	Reference
Public insurance	3408 (49.4)	1 425 303 (47.8)	1.1 (1.0 to 1.1)[a]
Self-pay	96 (1.4)	60 250 (2.0)	0.7 (0.6 to 0.9)
Other	208 (3.0)	96 074 (3.2)	1.0 (0.8 to 1.1)
Parity			
Nulliparous	2638 (38.1)	1 170 050 (39.2)	1.0 (0.9 to 1.0)
Oligohydramnios	284 (4.1)	82 559 (2.8)	1.5 (1.3 to 1.7)
PROM	524 (92.4)	2 822 613 (94.6)	1.4 (1.3 to 1.6)
Chorioamnionitis	151 (2.2)	66 426 (2.2)	1.0 (0.8 to 1.2)
Maternal age, y			
<18	180 (2.6)	84 536 (2.8)	0.9 (0.8 to 1.1)
18–34	5338 (77.3)	2 358 962 (79.1)	Reference
>34	1384 (20.1)	539 365 (18.1)	1.1 (1.1 to 1.2)
Maternal diabetes			
Any	1048 (15.2)	278 445 (9.3)	1.7 (1.9 to 1.9)
Preexisting	249 (3.6)	24 010 (0.8)	4.8 (4.2 to 5.4)
Gestational	799 (11.6)	254 435 (8.5)	1.5 (1.3 to 1.6)
Maternal BMI[b]			
Underweight	315 (4.6)	144 813 (4.9)	1.0 (0.9 to 1.1)
Normal weight	2924 (42.4)	1 362 968 (45.7)	Reference
Overweight	1647 (23.9)	707 830 (23.7)	1.1 (1.0 to 1.2)[a]
Obese	1423 (20.6)	566 383 (19.0)	1.2 (1.1 to 1.2)
Mental illness	351 (5.1)	95 515 (3.2)	1.6 (1.5 to 1.8)
Smoking during pregnancy	400 (5.8)	134 473 (4.5)	1.3 (1.2 to 1.4)
Illicit drug use	146 (2.1)	49 776 (1.7)	1.3 (1.1 to 1.5)
Hypertension			
Preexisting	125 (1.8)	32 104 (1.1)	1.7 (1.5 to 2.1)
Gestational	158 (2.3)	65 828 (2.2)	1.1 (0.9 to 1.2)
Preeclampsia	405 (5.9)	111 074 (3.7)	1.6 (1.5 to 1.8)
Mortality[c]	866 (12.6)	8161 (0.3)	52.3 (48.5 to 56.3)
GA at birth, wk			
39–42	4167 (60.4)	2 075 669 (69.6)	Reference
37–38	2102 (30.5)	812 515 (27.2)	1.4 (1.3 to 1.5)
35–36	612 (8.9)	156 191 (5.2)	2.1 (1.9 to 2.3)
32–34	343 (5.0)	60 872 (2.0)	2.8 (2.5 to 3.1)
29–31	163 (2.4)	17 951 (0.6)	4.5 (3.9 to 5.3)
<29	128 (1.9)	16 015 (0.5)	4.0 (3.3 to 4.8)

LGA, large for GA; OR, odds ratio; PROM, premature rupture of membranes; SGA, small for GA; —, not applicable.

[a] $P < .05$.

[b] Underweight: BMI <18.5; normal weight: BMI 18.5–24.9; overweight: BMI 25.0–29.9; obese: BMI ≥30.0.

[c] Mortality: death in the first year.

without CCHD are shown in Fig 2. At <29 weeks' GA, at least 1 severe neonatal morbidity was present in 61% of infants with CCHD and 38.5% of infants without CCHD ($P < .001$). This number decreased to 2.7% of infants with CCHD and 0.1% of infants without CHD born at 39 to 42 weeks' gestation ($P < .001$). In the group with CCHD, infants born at 35 to 36 weeks GA had a significantly increased rate of severe neonatal morbidity compared with infants born at early term (37–38 weeks, $P = .001$), and infants born at early term had a significantly increased rate of morbidity compared with infants born at 39 to 42 weeks ($P = .015$). In infants with CCHD, 1-year mortality increased from 8.9% at 39 to 42 weeks' gestation to 41.4% at <29 weeks' gestation (Table 3). The adjusted ARD for mortality showed significant differences between those born at 29 to 31 weeks' and 32 to 34 weeks' gestation (18.3%, 95% CI 9.1%

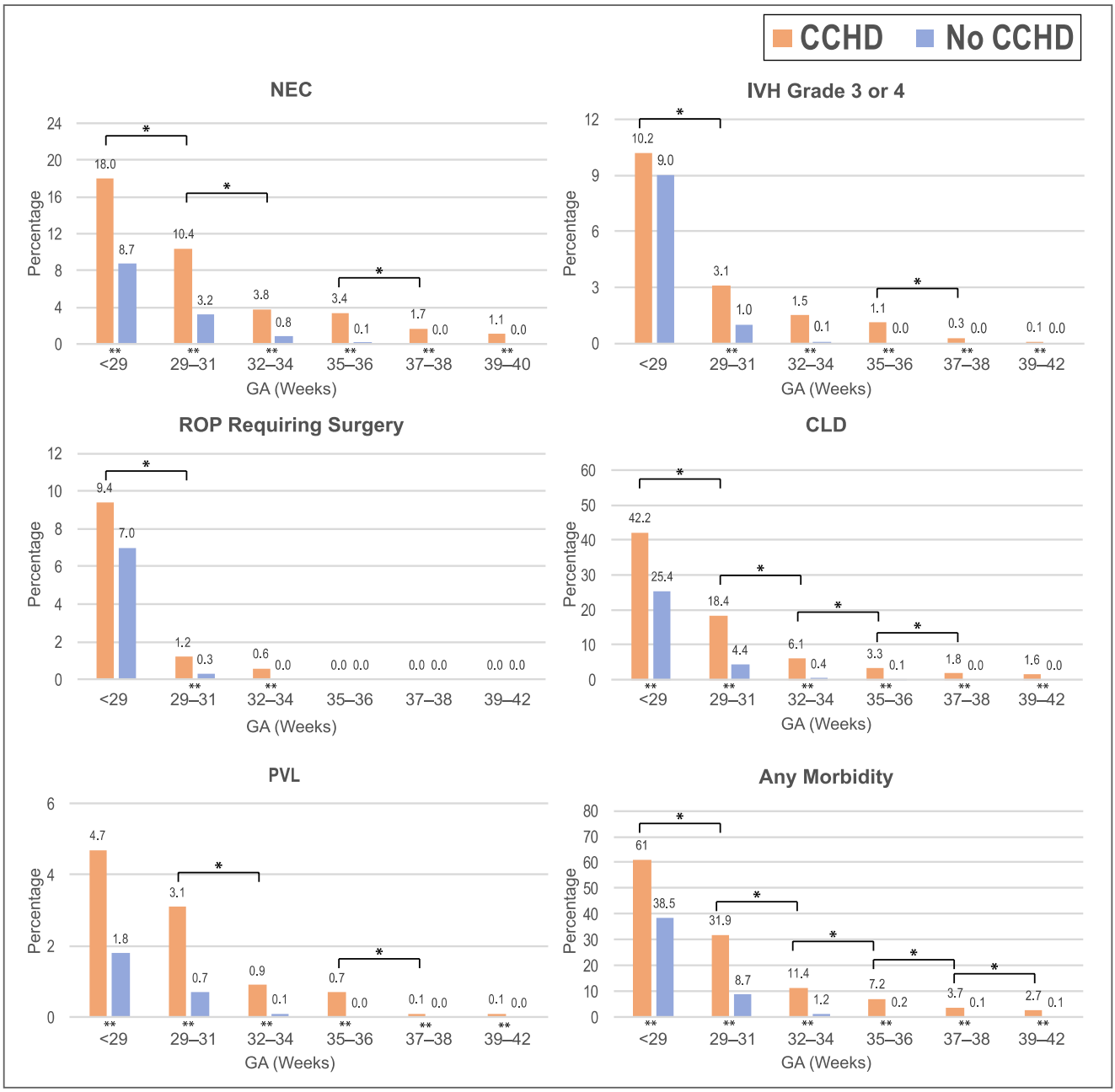

FIGURE 2

GA-specific rates of prematurity-related morbidities in infants with and without CHD. * $P < .05$ for χ^2 of 2 adjacent GA groups. ** $P < .05$ for χ^2 comparing CCHD versus no CCHD. IVH, intraventricular hemorrhage.

TABLE 3 GA-Specific ARD for Mortality- and Prematurity-Related Morbidity in Infants With CCHD

GA (wk)	*n*	Mortality (%)	Crude ARD[a] (95% CI)	Adjusted ARD[a] (95% CI)	Mortality or Morbidity[b] (%)	Crude ARD[a] (95% CI)	Adjusted ARD[a] (95% CI)
39–42	3555	8.9	—	—	10.9	—	—
37–38	2102	12.4	3.5 (1.9 to 5.2)	2.6 (1.1 to 4.0)	15.1	4.2 (2.4 to 6.1)	3.2 (1.6 to 4.9)
35–36	612	18.5	6.0 (2.6 to 9.4)	6.3 (3.1 to 9.5)	24.2	9.1 (5.3 to 12.8)	9.1 (5.5 to 12.7)
32–34	343	20.1	1.6 (−3.6 to 6.8)	3.2 (−2.0 to 8.5)	28.9	4.7 (−1.2 to 10.6)	6.6 (0.6 to 12.6)
29–31	163	33.7	13.6 (5.2 to 22.0)	18.3 (9.1 to 27.6)	53.4	24.5 (15.5 to 33.5)	29.1 (19.8 to 38.5)
<29	128	41.4	7.6 (−3.5 to 18.9)	9.2 (−3.1 to 21.5)	82.8	29.4 (19.4 to 39.5)	28.9 (19.4 to 38.4)

Adjusted ARD: adjusted for CHD complexity (modified from RACHS), birth weight *z* score, sex, and multiple gestation. —, not applicable.

[a] ARD refers to the difference between 2 adjacent GA categories.

[b] Morbidity is defined as either NEC, CLD, PVL, intraventricular hemorrhage grade 3 or 4, or ROP requiring surgery.

to 27.6%), 35 to 36 weeks' and 37 to 38 weeks' gestation (6.3%, 95% CI 3.1% to 9.5%), and 37 to 38 weeks' and 39 to 42 weeks' gestation (2.6%, 95% CI 1.1% to 4.0%) (Table 3). The combined outcome of mortality or severe neonatal morbidity in infants with CCHD was 82.8% at <29 weeks' GA and decreased to 10.9% at 39 to 42 weeks' GA. The adjusted ARD for mortality or severe neonatal morbidity showed a significant difference across all GA categories: the adjusted ARD was 28.9% (95% CI 19.4% to 38.4%) comparing GA <29 weeks with GA 29 to 31 weeks, 29.1% (95% CI 19.8% to 38.5%) comparing GA 29 to 31 weeks with GA 32 to 34 weeks, 6.6% comparing GA 32 to 34 weeks with GA 35 to 36 weeks (95% CI 0.6% to 12.6%), 9.1% (95% CI 5.5% to 12.7%) comparing GA 35 to 36 weeks with GA 37 to 38 weeks, and 3.2% (95% CI 1.6% to 4.9%) comparing GA 37 to 38 weeks with GA 39 to 42 weeks (Table 3). The results of the sensitivity analysis including infants with noncritical CHD requiring intervention revealed an expected slight decrease in mortality and morbidity and only minimal changes in crude and adjusted ARDs (Supplemental Table 5).

In Fig 3, we show adjusted predicted outcome probabilities with 95% CIs for mortality or severe neonatal morbidity in infants with and without CCHD. As can be visually appreciated,

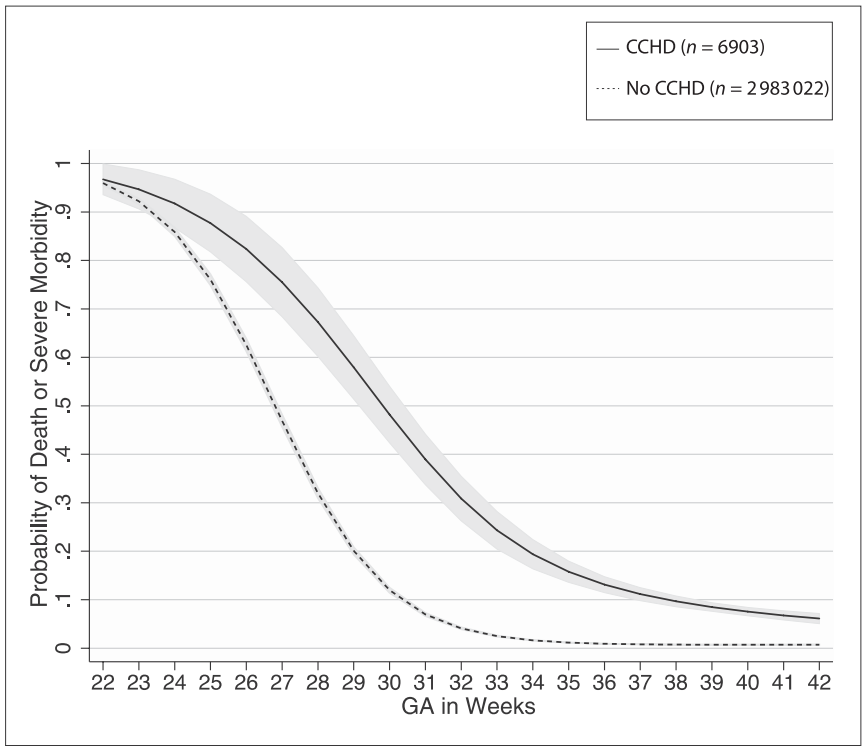

FIGURE 3

Adjusted prediction (with 95% CI) for death or severe morbidity in infants with and without CCHD. Adjusted prediction: adjusted for birth weight *z* score, sex, multiple gestation, and complexity of CCHD; all predictors are kept at means.

the GA-specific differences in outcome between infants with and without CCHD is variable across GA categories, suggesting an interaction between CCHD and GA. The interaction terms were significant for each GA category ($P < .01$ for each term). In Fig 4, we illustrate this effect by showing GA-specific adjusted ARD with 95% CIs comparing outcome probabilities for mortality (Fig 4A) and mortality or severe morbidity (Fig 4B) between infants with and without CCHD. The adjusted ARD is the smallest at GA 39 to 42 weeks, with 7.9% (95% CI 7.1% to 8.8%) for mortality and 9.6% (95% CI 8.7% to 10.6%) for mortality or severe morbidity. The adjusted ARD for both outcomes increases as GA decreases and it is largest at GA 29 to 31 weeks (ARD for mortality: 30.5, 95% CI 23.2 to 37.7; ARD for mortality or morbidity: 42.3, 95% CI 34.5 to 50.1) (Supplemental Table 6).

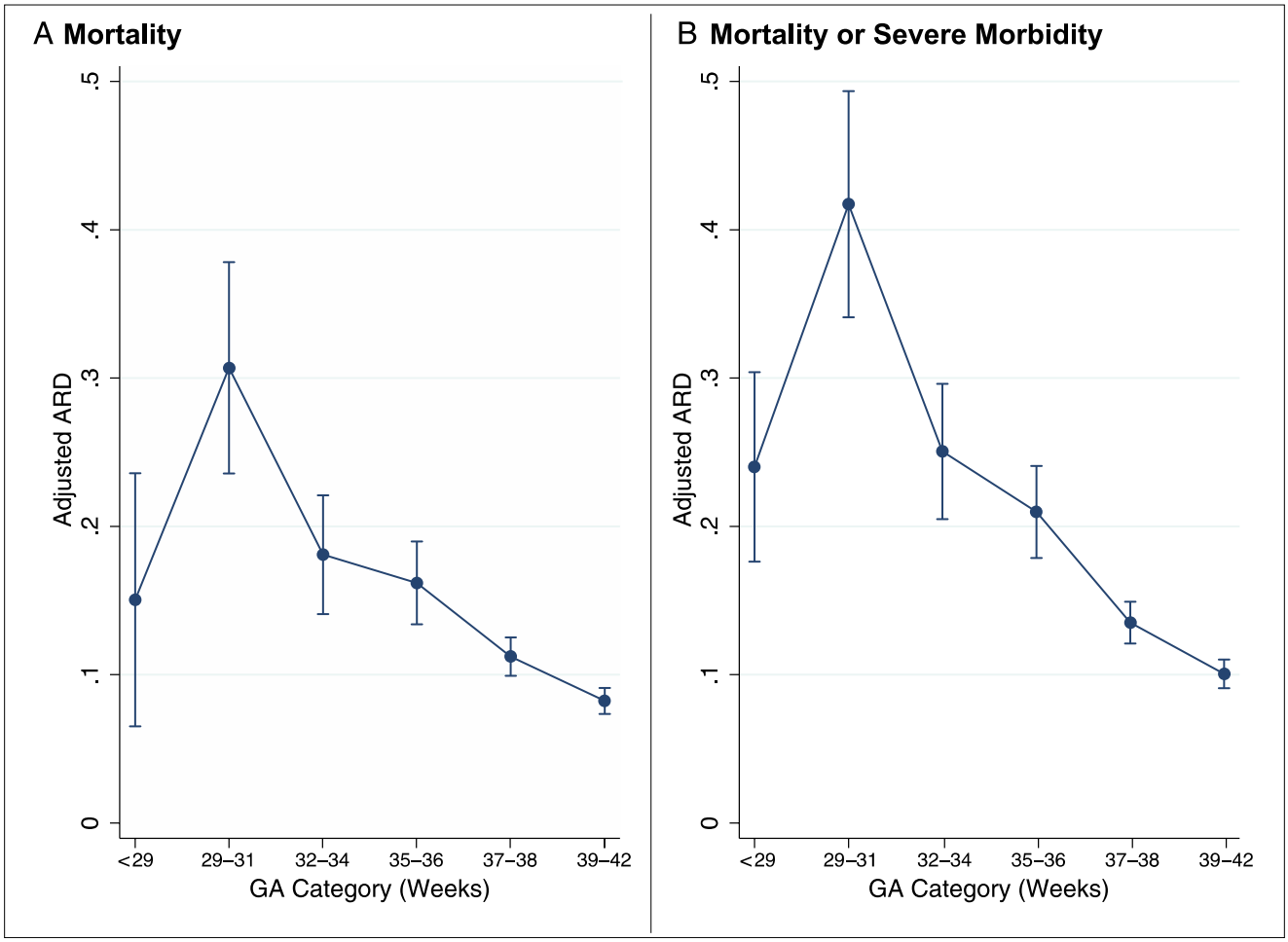

FIGURE 4
GA-specific adjusted ARDs for mortality (A) and mortality- or prematurity-related morbidity (B) in infants with CCHD compared with infants without CCHD.

DISCUSSION

In this cohort study, we analyzed the relationship between GA and mortality or morbidity in infants with CCHD. We found that infants born at 35 to 36 weeks' GA had a higher risk of death or severe neonatal morbidity than infants born at early term (37–38 weeks' gestation, adjusted ARD 9.1%, 95% CI 5.5% to 12.7%) and that early term infants had a higher risk of death or severe neonatal morbidity than infants born at 39 to 42 weeks' gestation (adjusted ARD 3.2%, 95% CI 1.6% to 4.9%). Additionally, we present GA-specific rates for neonatal morbidities in a population-based cohort in infants with CCHD.

Our findings regarding GA and mortality in infants with CCHD are consistent with other studies.[12,13] We show a negative relationship between CCHD mortality and GA group. However, we did not find statistical significance between the categories of <29 and 29 to 31 weeks or 32 to 34 and 35 to 36 weeks. Because the point estimate is consistent with a negative trend, we believe this is mainly a power issue. Cnota et al[13] used an administrative database comparable to ours and demonstrated a negative linear relationship between CHD death rates and GA between 34 and 40 weeks. They used GA in 1-week intervals. Similar to the results of our study, they did not find a significant difference between some GA groups while still showing a negative trend. They did not look at infants born <34 weeks and used mortality as their only outcome. More recently, Costello et al[12] used the database of the Society of Thoracic Surgeons Congenital Heart Surgery to investigate the relationship between GA and outcomes in infants who underwent cardiac surgery. They found that mortality and postoperative complications were more common in late preterm and early term infants when compared with infants born at 39.5 weeks' GA; however, the postoperative complication rate did not progressively increase with earlier GA at birth. The use of a rich clinical database allowed them to perform robust risk adjustments; for example, they were able to adjust for weight at the time of surgery,

a potential source of confounding when assessing the relationship between GA and outcomes.[26,27] The authors attribute their observation that complication rates did not progressively increase with earlier GA at birth to the fact that the Society of Thoracic Surgeons Congenital Heart Surgery database does not capture complications associated with prematurity.[12] With our study, we add important complementary information to the study of Costello et al[12] by providing information on prematurity-related complications in infants with CCHD, wherein we observed the expected progressive increase in noncardiac prematurity-related complications with earlier GA at birth.

In the modern era, changes in neonatal care have decreased the incidence of severe morbidities related to prematurity in infants >25 weeks' gestation.[16] Researchers conducting the EPIPAGE-2 cohort study[17] reported at least 1 major neonatal morbidity in 8.5% of infants born at 29 to 31 weeks and in only 2.1% of infants born at 32 to 34 weeks. These results are similar to the numbers in our cohort of infants without CCHD (any morbidity 8.7% at GA 29–31 weeks and 1.2% at GA 32–34 weeks, respectively, Fig 2). The incidence was significantly higher in the group with CCHD in our study, in which 61% of infants with CCHD born at 29 to 31 weeks' GA and 11.4% of infants born at 32 to 34 weeks' GA had at least 1 major morbidity.

Interestingly, there is an interaction between GA and presence or absence of CCHD with regards to mortality and combined mortality and morbidity. The largest difference of mortality and combined mortality and morbidity between infants with and without CCHD is apparent at 29 to 31 weeks (Figs 3 and 4). Although we expect that infants born extremely premature have a high risk of poor outcome, the relative increase we identified in infants of 29 to 31 weeks (compared with lower GA) is likely due to the fall in the rate of combined mortality and morbidity at 29 to 31 weeks' gestation in infants without CCHD.[17] Thus, our data support the "double jeopardy" of prematurity and CCHD.[1]

The reason for the significantly increased vulnerability for neonatal morbidities in infants with CCHD is most likely multifactorial. There is evidence that certain CCHDs carry an increased risk for the development of NEC-like clinical presentation in term neonates.[28,29] Episodic or chronic decreased mesenteric perfusion related to CHD has been proposed as a potential underlying mechanism.[28,29] This hemodynamic compromise of the mesenteric organs might potentiate the risk of prematurity for developing NEC in infants with CCHD. There are recent findings suggesting that brain maturation in infants with CCHD is delayed.[30,31] The imaging findings in such newborns have been found to be similar to those in premature newborns.[31] This might explain a higher susceptibility to PVL in the perioperative period of late preterm and early term infants with CCHD.

The realization that infants with CCHD are at high risk for severe neonatal morbidities even at more mature GA categories is crucial for physicians taking care of this patient population: There are several preventive strategies available to potentially lessen the burden of prematurity-related morbidity. For example, ROP has been correlated with fluctuations of hyperoxia followed by hypoxia.[32] Avoidance of undesired high and low oxygen saturations in preterm infants has been suggested to prevent ROP.[32] Mainly from adult data, it is known that mechanical ventilation with large tidal volumes or insufficient positive end-expiratory pressure to maintain functional residual capacity can lead to severe lung injury.[33,34] This mechanism has been proposed as an important contributing factor to the development of CLD.[33] Most recently, evidence emerged that antenatal corticosteroids reduce neonatal respiratory morbidity in late preterm infants.[35] A meta-analysis concluded that antenatal steroids can be considered in women undergoing planned cesarean delivery ≤37 weeks.[36] Applying such preventive strategies to late preterm and early term infants with CCHD has the potential to lower the incidence of prematurity-related morbidities in this high-risk patient group (as does optimizing tidal volumes and use of noninvasive assisted ventilation strategies) throughout the neonatal hospitalization.

This study has some important limitations. First, the identification of the cases with CCHD depended on ICD-9-CM codes. Thus, it is possible that we missed cases if the ICD-9-CM coding was incomplete. However, cases were not only captured from the birth hospitalization but also from transfer records and readmission records during the first year of life, further increasing the likelihood of capturing all infants with CCHD.[37] With regards to the classification of CCHD, although 2 physicians independently reviewed every case with multiple codes for CCHD, we cannot exclude the possibility of a misclassification of infants with CHD based on ICD-9-CM codes.[38] Additionally, the lack of data on surgical repair details made the grouping of CCHD according to RACHS or another established surgical classification system challenging, and we ended up modifying the RACHS classification. However, the only purpose of classification and severity grouping of CCHD cases in this study was to ensure that CCHD severity was adjusted for across GA categories,

and we are confident that this goal was achieved. It is also possible that there was some misclassification of the outcomes. However, the morbidity rates of premature infants without CCHD is similar to what has been recently reported in the literature,[17] supporting that the ICD-9-CM and procedure codes adequately capture severe neonatal morbidities. An additional major limitation is the fact that we were unable to control for some potentially important confounders, such as antenatal maternal corticosteroid administration, prostaglandin use, age at surgery, or prenatal diagnosis. Prenatal diagnosis is a potentially important confounder because it might influence prenatal management and therefore GA. Further studies should focus on identifying and quantifying the effect of these confounders.

Physicians caring for neonates with CCHD should be aware of the high incidence of severe neonatal morbidities in this patient population. These findings should be considered in the clinical care of infants with CCHD, and physicians should institute preventive measures whenever possible in both premature and more mature infants. Additionally, the presentation of our results as ARDs facilitates the use of these findings for decisions around the timing of delivery and for counseling parents.

ABBREVIATIONS

ARD: absolute risk difference
CCHD: critical congenital heart disease
CHD: congenital heart disease
CI: confidence interval
CLD: chronic lung disease
GA: gestational age
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
NEC: necrotizing enterocolitis
PVL: periventricular leukomalacia
RACHS: risk adjustment in congenital heart surgery
ROP: retinopathy of prematurity

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