ORIGINAL RESEARCH

Neonatal Outcomes in Very Preterm Infants With Severe Congenital Heart Defects: An International Cohort Study

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***Background*—**Very preterm infants are at high risk of death or severe morbidity. The objective was to determine the significance of severe congenital heart defects (CHDs) for these risks.

***Methods and Results*—**This cohort study included infants from 10 countries born from 2007–2015 at 24 to 31 weeks' gestation with birth weights <1500 g. Severe CHDs were defined by *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth* (*ICD-10*) codes and categorized as those compromising systemic output, causing sustained cyanosis, or resulting in congestive heart failure. The primary outcome was in-hospital mortality. Secondary outcomes were neonatal brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity. Adjusted and propensity score–matched odds ratios (ORs) were calculated. Analyses were stratified by type of CHD, gestational age, and network. A total of 609 (0.77%) infants had severe CHD and 76 371 without any malformation served as controls. The mean gestational age and birth weight were 27.8 weeks and 1018 g, respectively. The mortality rate was 18.6% in infants with CHD and 8.9% in controls (propensity score–matched OR, 2.30; 95% CI, 1.61–3.27). Severe CHD was not associated with neonatal brain injury, necrotizing enterocolitis, or retinopathy of prematurity, whereas the OR for bronchopulmonary dysplasia increased. Mortality was higher in all types, with the highest propensity score–matched OR (4.96; 95% CI, 2.11–11.7) for CHD causing congestive heart failure. While mortality did not differ between groups at <27 weeks' gestational age, adjusted OR for mortality in infants with CHD increased to 10.9 (95% CI, 5.76–20.70) at 31 weeks' gestational age. Rates of CHD and mortality differed significantly between networks.

***Conclusions*—**Severe CHD is associated with significantly increased mortality in very preterm infants. **(*J Am Heart Assoc*. 2020;9:e015369. DOI: 10.1161/JAHA.119.015369.)**

Key Words: cardiac malformation • mortality • newborn infant • preterm birth

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Preterm birth remains the most common cause of death in children younger than 5 years.[1] In particular, those born very preterm, ie, more than 8 weeks before their due date, face a considerable risk of mortality.[2] To disentangle the effects of prematurity from other causes of neonatal death, congenital malformations have been excluded in many studies of preterm mortality.[2–4] By this approach, however, the outcomes for preterm infants with malformations have been left unstudied.

Birth defects are more common in the very preterm than in the general newborn population, and congenital heart defects

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Clinical Perspective

What Is New?

- Irrespective of type of heart defect, very preterm infants with severe congenital heart defects have higher odds for mortality, but not for neonatal brain injury, necrotizing enterocolitis, or treated retinopathy of prematurity, than peers without severe congenital heart defects.

What Are the Clinical Implications?

- Although the outlook for very preterm infants with severe congenital heart defects remains poorer than in peers without congenital heart defects, 4 of 5 of the affected infants survive the neonatal period and without an increased risk for added major neonatal morbidity.

(CHDs) are among the most common types.[5–8] The majority are minor and are associated with an excellent prognosis, but severe CHDs are associated with excess mortality in term infants.[9–11] Less is known about the outlook for very preterm infants with CHDs. Previous studies have indicated significantly lower survival in preterm infants with CHDs than in those without CHDs.[7,9,12–16] Limitations of these studies include older birth cohorts (from 1985 to 2005), low numbers (from 0 to 149 infants born very preterm) with mixed types of CHDs, and little or no information on the association with gestational age (GA) <32 weeks.[7,9,12–15] Three larger studies including live-born infants with birth weights <1500 g reported mortality rates of 44% to 55%[16,17] and an increased risk for necrotizing enterocolitis (NEC) in infants with severe CHD.[18] The reports on mortality (infants born in 1997–2012) included significant proportions of infants with CHDs who were untreated with antenatal corticosteroids (29–35%), who were outborn (21–51%), who were small for GA (42%),[17] and who had genetic syndromes (21%)[16] or extracardiac malformations (35%)[17]—all factors that may affect mortality independent of CHDs.[19–21] Moreover, the mean GA was 28 to 30 weeks and the relationship between CHD and neonatal outcome at the lowest GA remains to be clarified. Finally, there are no reports available from outside of the United States.

The objective of this study was to determine neonatal outcomes for a contemporary cohort of very preterm infants born with severe and isolated CHD by type of CHD, by gestational week at birth, and by country of birth. Our main hypotheses were that severe CHD would be associated with significantly increased risks of mortality and morbidity in very preterm infants, particularly among those with the lowest GA, and that neonatal outcomes would vary between countries.

Methods

Individual data will not be made available to other researchers for purposes of reproducing the results or replicating the procedures because the institutional review boards only permitted aggregated data to be publicly available or published. Analytic methods, however, are presented in this article to assist other researchers in reproducing the results or replicating the procedures.

Setting

The study used data from the International Network for Evaluation of Outcomes in Neonates (iNeo), ie, from neonatal networks in 10 high-resource countries: Australia, New Zealand, Canada, Finland, Israel, Italy, Japan, Spain, Sweden, and Switzerland.[22] The participating networks and the iNeo Coordinating Centre at the Maternal-Infant Care Research Centre, Mount Sinai Hospital in Toronto, Canada, each obtained data sharing agreements and research ethics review and approval for data collection, transfer, and analyses from the local, national institutional ethics committees. Because of the retrospective nature of the study, informed consent from parents was waived.

Data Sources

Individual-level data from the following neonatal networks were included: Australia and New Zealand Neonatal Network (ANZNN), Canadian Neonatal Network (CNN),[23] FinMB (Finnish Medical Birth Register), Neonatal Research Network of Japan (NRNJ),[24] Israel Neonatal Network (INN),[25] Tuscany Neonatal Network (TIN-Toscane online), Spanish Neonatal Network (SEN1500), SNQ (Swedish Neonatal Quality Register),[26] and Swiss Neonatal Network (SwissNeoNet). Previous reports provide details of the proportion of neonates in this data set out of the total number of neonates born in each country.[27] Based on a consensus between all iNeo participants, data collection was standardized and included information on maternal and obstetric variables, neonatal characteristics, treatments, and outcomes. Diagnoses were classified according to the *Ninth* and *Tenth* versions of the *International Classification of Diseases* (*ICD-9* and *ICD-10*, respectively).[28]

Study Population

The study population included all singleton infants admitted to neonatal units between 2007 and 2015 who were very preterm (between 24 and 31 weeks' gestation) and had birth weights <1500 g. The database did not hold information on abortions or stillbirths. In addition, delivery room deaths were not consistently captured across networks and were therefore

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excluded. Multiple pregnancies and neonates with major congenital malformations in addition to CHD were also excluded.

Exposure

In a first step, infants with a diagnosis of any CHD were identified in the iNeo database by a search strategy using *ICD-9* codes 745 to 747 or *ICD-10* codes Q200-Q262. Second, infants with minor CHDs (n=1928); CHD associated with a chromosomal aberration (trisomy 21 [n=9], trisomy 13 or 18 [n=4], or other trisomy or monosomy [n=2]); or additional severe malformations (nervous [*ICD-10* codes Q00–05], digestive [Q39, 41, 42, 44, and 79], or urinary [Q60–61] syndromes [Q74–78, Q86, Q8726, Q894] [n=33 infants total]) were excluded. The study group consisted of the remaining very preterm infants without chromosomal anomaly who had isolated, severe CHD (main exposure). Differentiation between nonsevere and severe CHDs was performed using the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) criteria.[29] A patent ductus arteriosus was not considered as a CHD in this context. A third and final step included the Vermont Oxford Network (VON) categorization[18] of severe CHDs by manifestation: category A comprised defects that primarily compromised systemic output (critical aortic stenosis, coarctation of the aorta, hypoplastic left heart syndrome, and interrupted aortic arch); category B comprised defects that created sustained cyanosis (transposition of the great vessels, tetralogy of Fallot, critical pulmonic stenosis, pulmonary atresia, tricuspid atresia, and total anomalous pulmonary venous return); and category C comprised diagnoses resulting in congestive heart failure (CHF) and pulmonary overcirculation (such as complete atrioventricular canal, double outlet right ventricle, truncus arteriosus, and other single ventricle physiology).

Outcomes

The primary outcome was mortality. Secondary outcomes included a composite of mortality and major neonatal morbidity, and major morbidities analyzed as separate outcomes. Major neonatal morbidity was defined as ≥1 of the following diagnoses: intraventricular hemorrhage grade 3 to 4[30] or cystic periventricular leukomalacia[31]; NEC stages 2 or 3[32]; bronchopulmonary dysplasia (defined as oxygen requirement, with or without mechanical respiratory support, at 36 weeks of postmenstrual age or at time of transfer to level 2 unit)[33]; and treated retinopathy of prematurity.[34]

Covariates

Covariates and potential confounders included advanced maternal age (≥35 years) at delivery of the infant; hypertensive disorder of pregnancy (chronic hypertension, gestational hypertension, preeclampsia, eclampsia, or hemolysis, elevated liver enzymes, low platelet count syndrome); any treatment with antenatal corticosteroids; mode of delivery; delivery outside a tertiary center; GA; infant sex; birth weight *z* score; and country of birth.

Statistical Analyses

Maternal and infant characteristics and outcomes were compared between neonates with and without severe CHD. Frequencies (percentages) or means (SDs) were reported. Differences between groups were assessed with Pearson chi-square tests and Student *t* tests for categorical variables and continuous variables, respectively. Univariate and multivariable logistic analyses were applied for the primary and secondary outcomes. Odds ratios (ORs) with 95% CIs were estimated. The analyses were stratified by CHD manifestation, GA, and network. Finally, propensity score (PS) matching was applied for analysis. The PS for 2 groups was estimated using multivariate logistic regression stratified by network. Matching between infants with CHD and infants without CHD was performed using the SAS macro *match.sas* and was based on a caliper width of 0.2 times the SD of the logit-transformed PS. Within each matched sample, covariates were tested for balance using paired *t* tests for continuous variables and McNemar tests for categorical covariates. The association between severe CHD and neonatal outcome in each matched sample was examined by using generalized estimating

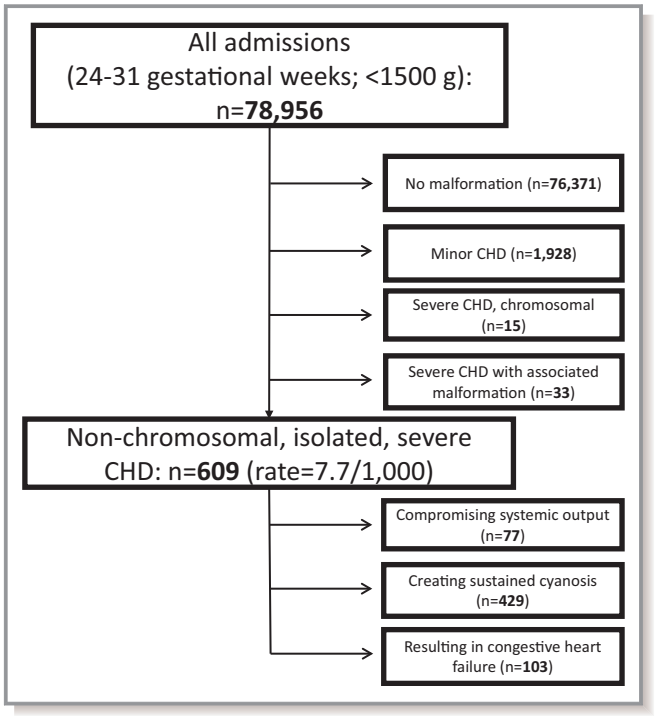

Figure 1. Flow chart: inclusion and severe congenital heart defects (CHDs) by their manifestation in very preterm, singleton infants.

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Table 1. Maternal, Obstetric, and Neonatal Characteristics of Very Preterm Infants With and Without Nonchromosomal, Isolated, Severe CHDs

	Infants With Severe CHD (N=609)	Infants Without CHD (N=76 371)	*P* Value
Maternal characteristics			
Maternal age ≥35 y, n/N (%)	118/448 (26.3)	14 082/59 110 (23.8)	0.21
Hypertensive disorders of pregnancy*, n/N (%)	136/561 (24.2)	16 474/69 194 (23.8)	0.81
Antenatal corticosteroids, n/N (%)	485/599 (81.0)	57 441/74 536 (77.1)	0.02
Cesarean section, n/N (%)	431/608 (70.9)	51 113/75 698 (67.5)	0.08
Neonatal characteristics			
Apgar score <7 at 5 min, n/N (%)	176/598 (29.4)	18 752/74 855 (25.1)	0.01
Gestational age, n/N (%)			
28–31 wk	359/609 (59.0)	43 377/76 371 (56.8)	0.29
<28 wk	250/609 (41.0)	32 994/76 371 (43.2)	
Males, n/N (%)	302/609 (49.6)	39 987/76 337 (52.4)	0.17
Birth weight, mean (SD)			0.12
Grams	1018 (279)	1035 (271)	<0.01
z score	−0.44 (1.07)	−0.25 (0.95)	
Small for gestational age, n/N (%)	139/609 (22.8)	10 948/76 336 (14.3)	<0.01
Outborn, n/N (%)	75/609 (12.3)	7321/76 343 (9.6)	0.02

CHD indicates congenital heart defect; n, number in group; N, total number in category.
*Hypertension in pregnancy includes gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome.

equations with logit linkage and unstructured correlation, and ORs with 95% CIs were estimated. All analyses were conducted using SAS 9.4 (SAS Institute Inc) with a 2-sided significance level of 0.05.

Results

Between 2007 and 2015, there were 78 956 singleton very preterm infants in the database, 76 371 (96.7%) of whom had no malformation and 2585 (3.3%) of whom had a diagnosis of any CHD. Of these, 1928 (2.4%) had nonsevere CHDs, and 609 (0.77%) neonates had nonchromosomal, isolated, severe CHDs. The distribution of the 3 types of severe CHDs is depicted in Figure 1.

Baseline characteristics are reported in Table 1. In comparison with infants without CHDs, infants with severe CHDs were more frequently treated with antenatal corticosteroids, were more often outborn and small for GA, and had a larger proportion with Apgar scores <7 at 5 minutes.

Table 2. Odds for In-Hospital Mortality and for Major Neonatal Morbidity in Very Preterm Infants With Nonchromosomal, Isolated, Severe CHDs

	Infants With Severe CHD (N=609), n/N (%)	Infants Without CHD (N=76 371), n/N (%)	Crude OR (95% CI)	Model 1 Adjusted OR (95% CI)*	Model 2 PS Score–Matched OR (95% CI)†
Mortality	113/609 (18.6)	6815/76 371 (8.9)	2.33 (1.89–2.86)	2.46 (1.95–3.11)	2.30 (1.61–3.27)
Mortality or major morbidity‡	313/583 (53.7)	26 616/72 232 (36.9)	1.99 (1.69–2.34)	2.67 (2.21–3.24)	1.91 (1.53–2.38)
Severe brain injury§	67/580 (11.6)	6868/72 033 (9.5)	1.24 (0.96–1.60)	1.26 (0.96–1.64)	1.10 (0.77–1.58)
Necrotizing enterocolitis	41/606 (6.8)	3595/75 172 (4.8)	1.45 (1.05–1.99)	1.22 (0.88–1.69)	1.21 (0.75–1.95)
Bronchopulmonary dysplasia	185/504 (36.7)	14 680/67 979 (21.6)	2.11 (1.76–2.53)	2.64 (2.14–3.27)	1.82 (1.41–2.34)
Treated retinopathy of prematurity	40/609 (6.6)	5271/76 344 (6.9)	0.95 (0.69–1.31)	1.54 (1.09–2.18)	1.27 (0.81–1.99)

CHD indicates congenital heart defect.
*Model 1: adjusted for gestational age, sex, birth weight *z* score, network, antenatal corticosteroids, mode of delivery, and outborn.
†Model 2: propensity score (PS)–matched odds ratios (ORs), stratified by network.
‡Major neonatal morbidity: intraventricular hemorrhage grade 3 to 4, cystic periventricular leukomalacia, retinopathy of prematurity treatment, or bronchopulmonary dysplasia.
§Severe brain injury: intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia.

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Table 3. Odds for In-Hospital Mortality and for Major Neonatal Morbidity for Category A: Very Preterm Infants With CHDs Compromising Systemic Output

	Infants With Severe CHD (N=77), n/N (%)	Infants Without CHD (N=76 371), n/N (%)	Crude OR (95% CI)	Model 1 Adjusted OR (95% CI)*	Model 2 PS Score–Matched OR (95% CI)†
In-hospital mortality	16/77 (20.8)	6815/76 371 (8.9)	2.68 (1.54–4.65)	3.46 (1.85–6.48)	2.26 (0.97–5.30)
In-hospital mortality or major neonatal morbidity‡	40/75 (53.3)	26 616/72 232 (36.9)	1.96 (1.24–3.08)	3.51 (2.10–5.88)	2.01 (1.08–3.72)
IVH grade 3 or 4 or cPVL	13/75 (17.3)	6868/72 033 (9.5)	1.99 (1.09–3.62)	2.27 (1.21–4.25)	1.95 (0.73–5.21)
NEC	5/77 (6.5)	3595/75 172 (4.8)	1.38 (0.56–3.42)	1.23 (0.49–3.08)	1.69 (0.38, 7.60)
BPD	17/62 (27.4)	14 680/67 979 (21.6)	1.37 (0.78–2.40)	1.77 (0.92, 3.40)	1.69 (0.82–3.46)
ROP (treated)	4/77 (5.2)	5271/76 344 (6.9)	0.74 (0.27–2.02)	2.01 (0.70–5.75)	1.00 (0.23–4.31)

BPD indicates bronchopulmonary dysplasia; CHD, congenital heart defect; cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; PS, propensity score; ROP, retinopathy of prematurity.

*Model 1: adjusted for gestational age, sex, birth weight z-score, network, antenatal corticosteroids, mode of delivery, and outborn.

†Model 2: propensity score (PS)-matched odds ratios, stratified by network.

‡Major neonatal morbidity: intraventricular hemorrhage grade 3-4, cystic periventricular leukomalacia, retinopathy of prematurity treatment, or bronchopulmonary dysplasia.

In-hospital mortality was 18.6% (95% CI, 15.5–21.7%) in infants with severe CHDs and 8.9% (95% CI, 8.7–9.1%) in infants without any CHD ($P<0.001$). The proportion of infants with the composite outcome in-hospital mortality or major neonatal morbidity was 53.7% (95% CI, 49.7–57.8%) in those with CHDs and 36.9% (95% CI, 36.5–37.2%) in controls ($P<0.001$). Infants with CHDs had significantly higher rates of bronchopulmonary dysplasia defined as oxygen dependency at 36 weeks of postmenstrual age, but they did not differ from infants without CHD with regards to odds for severe neonatal brain injury (intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia), NEC, or treated retinopathy of prematurity. After adjustments and PS matching, the ORs for mortality and the composite outcome changed marginally from the unadjusted models (Table 2).

The highest odds for mortality (PS-matched OR, 4.96; 95% CI, 2.11–11.7) and for the composite outcome (PS-matched OR, 2.82; 95% CI, 1.61–4.94) were seen in infants with CHDs manifesting primarily as CHF. The lowest increase in odds for mortality (PS-matched OR, 1.84; 95% CI, 1.20–2.83]) was seen in infants with CHDs manifesting as sustained cyanosis (Tables 3 through 5).

In infants of <27 weeks GA, in-hospital mortality did not differ between infants with (37/165=22.4%; 95% CI, 16.1–28.8%) and without (4653/22 670=20.5%; 95% CI, 20.0–21.0%) severe CHD. From 27 weeks' GA and upwards, mortality decreased significantly more slowly in infants with CHD than in those without; and at 31 weeks' GA, the in-hospital mortality was still 15.1% (95% CI, 7.6–22.7%) in infants with CHD but had decreased to 1.5% (95% CI, 1.2–1.7%) in those without CHD

Table 4. Odds for In-Hospital Mortality and for Major Neonatal Morbidity for Category B: Very Preterm Infants With CHDs Creating Sustained Cyanosis

	Infants With Severe CHD (N=429), n/N (%)	Infants Without CHD (N=76 371), n/N (%)	Crude OR (95% CI)	Model 1 Adjusted OR (95% CI)*	Model 2 PS Score–Matched OR (95% CI)†
In-hospital mortality	66/429 (15.4)	6815/76 371 (8.9)	1.86 (1.43–2.42)	1.86 (1.39–2.50)	1.84 (1.20–2.83)
In-hospital mortality or major neonatal morbidity‡	211/407 (51.8)	26 616/72 232 (36.9)	1.85 (1.52–2.24)	2.28 (1.81–2.86)	1.71 (1.32–2.22)
IVH grade 3 or 4 or cPVL	43/407 (10.6)	6868/72 033 (9.5)	1.12 (0.82–1.54)	1.15 (0.83–1.61)	1.11 (0.71–1.75)
NEC	25/427 (5.9)	3595/75 172 (4.8)	1.24 (0.83–1.86)	1.04 (0.69–1.58)	1.08 (0.59–1.98)
BPD	138/368 (37.5)	14 680/67 979 (21.6)	2.18 (1.76–2.69)	2.55 (1.99–3.26)	1.73 (1.29–2.32)
ROP (treated)	30/429 (7.0)	5271/76 344 (6.9)	1.01 (0.70–1.47)	1.54 (1.03–2.31)	1.39 (0.81–2.38)

BPD indicates bronchopulmonary dysplasia; CHD, congenital heart defect; cPVL, cystic periventricular leukomalacia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; PS, propensity score; ROP, retinopathy of prematurity.

*Model 1: adjusted for gestational age, sex, birth weight z-score, network, antenatal corticosteroids, mode of delivery, and outborn.

†Model 2: propensity score (PS)-matched odds ratios, stratified by network.

‡Major neonatal morbidity: intraventricular hemorrhage grade 3-4, cystic periventricular leukomalacia, retinopathy of prematurity treatment, or bronchopulmonary dysplasia.

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Table 5. Odds for In-Hospital Mortality and Major Neonatal Morbidity for Category C: Very Preterm Infants With CHDs Resulting in CHF

	Infants With Severe CHD (N=103), n/N (%)	Infants Without CHD (N=76 371), n/N (%)	Crude OR (95% CI)	Model 1 Adjusted OR (95% CI)*	Model 2 PS Score–Matched OR (95% CI)†
In-hospital mortality	31/103 (30.1)	6815/76 371 (8.9)	4.39 (2.88–6.70)	5.05 (3.10–8.24)	4.96 (2.11–11.7)
In-hospital mortality or major neonatal morbidity‡	62/101 (61.4)	26 616/72 232 (36.9)	2.72 (1.82–4.07)	4.17 (2.60–6.67)	2.82 (1.61–4.94)
IVH grade 3–4 or cPVL	11/98 (11.2)	6868/72 033 (9.5)	1.20 (0.64–2.24)	1.06 (0.55–2.03)	1.03 (0.44–2.44)
NEC	11/102 (10.8)	3595/75 172 (4.8)	2.41 (1.29–4.50)	1.99 (1.05–3.79)	1.41 (0.54–3.65)
BPD	30/74 (40.5)	14 680/67 979 (21.6)	2.48 (1.56–3.94)	4.22 (2.49–7.16)	2.45 (1.22–4.89)
ROP (treated)	6/103 (5.8)	5271/76 344 (6.9)	0.83 (0.37–1.90)	1.29 (0.53–3.17)	1.00 (0.37–2.68)

CHD indicates congenital heart defect; CHF, congestive heart failure; NEC, necrotizing enterocolitis.
*Model 1: adjusted for gestational age, sex, birth weight *z* score, network, antenatal corticosteroids, mode of delivery, and outborn.
†Model 2: propensity score (PS)–matched odds ratios (ORs), stratified by network.
‡Major neonatal morbidity: intraventricular hemorrhage (IVH) grade 3 or 4, cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP) treatment, or bronchopulmonary dysplasia (BPD).

(Figure 2) (adjusted OR, 10.9; 95% CI, 5.76–20.7). Driven by mortality, a similar trend was observed for the composite outcome stratified on GA (Table 6).

The overall prevalence of severe CHD in the iNeo database was 7.7 per 1000 infants, with a significant network variation from low (1/941=1.06 per 1000 infants in TuscanNN and 70/22 578=3.1 per 1000 infants in NRNJ) to high (152/10 384=14.6 per 1000 infants in CNN and 52/3139=16.6 per 1000 infants in SNQ). The increase in odds for the composite outcome in infants with CHD compared with controls also varied significantly between networks, with adjusted ORs for mortality or major neonatal morbidity (in networks reporting at least 10 infants with CHD who had the composite outcome) ranging from 1.85 (95% CI, 1.26–2.70) in Canada to 29.3 (95% CI, 5.84–146) in Switzerland (Table 7).

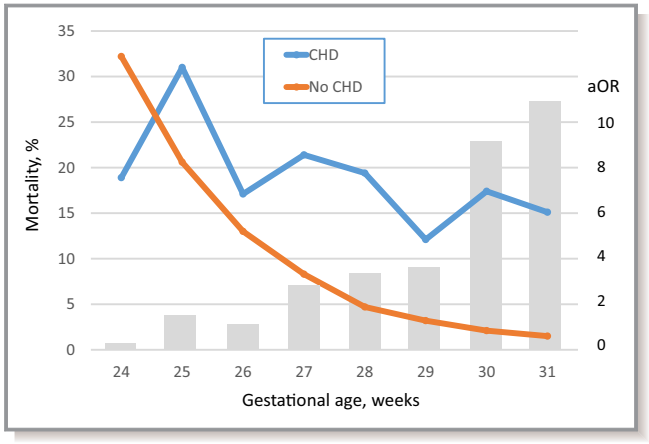

Figure 2. Mortality rates (lines) by gestational age among very preterm infants with or without severe congenital heart defects (CHDs). aOR (grey bars) indicates adjusted odds ratio for mortality.

Survival data by type of severe CHD is presented in Table 8.

Discussion

This study has several important findings. First, very preterm infants with isolated, nonchromosomal, severe CHD exhibited 2 to 3 times higher odds for in-hospital mortality than infants without CHD. Second, infants with CHD also had higher odds for oxygen dependency at 36 weeks' postmenstrual age, whereas proportions with major neonatal brain injury, NEC, and treated retinopathy of prematurity did not differ significantly from infants without CHD. Third, the largest group, ie, those with CHD creating sustained cyanosis, had the most favorable outcomes, whereas CHD creating CHF was associated with the poorest survival. Fourth, while mortality declined with each week of increasing GA in infants without CHD, it remained high in infants with CHD irrespective of GA. Finally, rates and outcomes of severe CHD in very preterm infants varied 10-fold between networks and countries.

Strengths and Limitations

Given the low prevalence of severe CHD, different types of CHD, and the comparatively low incidence of very preterm birth, large sample sizes are required to accurately estimate neonatal risks. iNeo is a collaboration between neonatal networks from high income countries.[35] With detailed information on more than 150 000 infants, the database offers a unique opportunity to assess the impact of rare exposures on rare outcomes. This is the first study of rates of severe CHDs outside of the United States and of associated mortality and morbidity risks in very preterm infants by each gestational

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Table 6. Mortality and Composite Outcome of Mortality or Major Neonatal Morbidity Among Very Preterm Infants With or Without Severe CHDs by Gestational Age

Gestational Age, wk	Infants With Severe CHD, n/N (%)	Infants Without CHD, n/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
	Mortality			
24	7/37 (18.9)	1897/5885 (32.2)	0.49 (0.22–1.12)	0.36 (0.15–0.87)
25	18/58 (31.0)	1567/7602 (20.6)	1.73 (0.99–3.03)	1.63 (0.90–2.94)
26	12/71 (16.9)	1189/9183 (13.0)	1.37 (0.73–2.55)	1.16 (0.61–2.22)
27	18/84 (21.4)	855/10 324 (8.3)	3.02 (1.79–5.11)	2.82 (1.62–4.90)
28	18/93 (19.4)	570/12 024 (4.7)	4.82 (2.86–8.12)	3.43 (1.99–5.93)
29	11/88 (12.5)	391/12 366 (3.2)	4.38 (2.31–8.30)	3.52 (1.81–6.84)
30	16/92 (17.4)	229/10 968 (2.1)	9.87 (5.67–17.2)	9.29 (5.13–16.8)
31	13/86 (15.1)	117/8019 (1.5)	12.0 (6.49–22.3)	10.9 (5.76–20.7)
	Composite outcome: mortality or major neonatal morbidity†			
24	27/36 (75.0)	4825/5749 (83.9)	0.57 (0.27–1.23)	0.53 (0.25–1.16)
25	43/57 (75.4)	5210/7319 (71.2)	1.24 (0.68–2.28)	1.26 (0.68–2.36)
26	51/68 (75.0)	4963/8778 (56.5)	2.31 (1.33–4.00)	2.46 (1.39–4.33)
27	46/82 (56.1)	4028/9861 (40.9)	1.86 (1.19–2.87)	2.03 (1.28–3.22)
28	44/88 (50.0)	3281/11 443 (28.7)	2.49 (1.63–3.79)	2.31 (1.49–3.58)
29	35/83 (42.2)	2282/11 645 (19.6)	2.99 (1.93–4.64)	2.87 (1.82–4.53)
30	36/87 (41.4)	1346/10 138 (13.3)	4.61 (3.00–7.09)	4.39 (2.77–6.95)
31	31/82 (37.8)	681/7299 (9.3)	5.91 (3.75–9.29)	5.68 (3.53–9.15)

CHD indicates congenital heart defect; n, number in group; N, number in category; OR, odds ratio.
*Adjusted for antenatal corticosteroids, mode of delivery, sex, outborn, birth weight *z* score, and network.
†Major neonatal morbidity: intraventricular hemorrhage grade 3 or 4, cystic periventricular leukomalacia, retinopathy of prematurity treatment, or bronchopulmonary dysplasia.

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week and by network. It also provides the most contemporary estimation of neonatal outcomes in very preterm infants with severe CHD. Information on obstetrical and neonatal variables was available, and data were collected according to common preset definitions and standardized protocols, limiting information bias. Mortality and morbidity were adjusted for GA and

Table 7. Composite* Outcome for Very Preterm Infants With and Without Severe CHDs by Neonatal Network

Neonatal Network	Infants With Severe CHD, n/N (%)	Infants Without CHD, n/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)†
ANZNN	65/109 (59.6)	5539/14 371 (38.5)	2.36 (1.60–3.46)	3.48 (1.57–3.91)
CNN	67/152 (44.1)	3401/10 232 (33.2)	1.58 (1.15–2.19)	1.85 (1.26–2.70)
FinMBR	2/5 (40.0)	345/1004 (34.4)	1.27 (0.21–7.66)	0.96 (0.14–6.68)
INN	26/52 (50.0)	1793/5407 (33.2)	2.02 (1.17–3.48)	3.75 (1.99–7.07)
NRNJ	47/70 (67.1)	8673/22 508 (38.5)	3.26 (1.98–5.37)	5.97 (3.36–10.6)
SEN1500	67/130 (51.5)	4652/11 498 (40.5)	1.57 (1.11–2.21)	2.25 (1.51–3.34)
SNQ	29/52 (55.8)	1043/3087 (33.8)	2.47 (1.42–4.29)	3.00 (1.56–5.77)
SwissNeoNet	10/12 (83.3)	904/3184 (28.4)	12.6 (2.76–57.7)	29.3 (5.84–146.5)
TuscanNN	0/1 (0)	266/941 (28.3)	NA	NA
All networks	313/583 (53.7)	26 616/72 232 (36.9)	1.99 (1.69–2.34)	2.65 (2.19–3.21)

ANZNN indicates Australia and New Zealand Neonatal Network; CHD, congenital heart defect; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Registry; INN, Israel Neonatal Network; N, number in category; n, number in group; NRNJ, Neonatal Research Network of Japan; OR, odds ratio; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscany Neonatal Network (Italy).
*Mortality or major neonatal morbidity (defined as intraventricular hemorrhage grade 3 or 4, cystic periventricular leukomalacia, retinopathy of prematurity treatment, or bronchopulmonary dysplasia).
†Adjusted for antenatal corticosteroids, mode of delivery, gestational age, sex, outborn, and birth weight *z* score.

Table 8. Mortality by Type of Severe CHD

Type of Severe CHD	*ICD-9* Code	*ICD-10* Code	Mortality n/N (%)
Category A (defects that primarily compromise systemic output)			16/77 (20.8)
Aortic valve stenosis	746.3	Q230	18/55 (32.7)
Coarctation of the aorta, IAA	747.1	Q251	6/37 (16.2)
HLHS	746.7	Q234	6/11 (54.6)
Aortic atresia, stenosis, hypoplasia	747.22	Q252	3/7 (42.9)
Congenital mitral insufficiency	746.6	Q233	1/7 (14.3)
Congenital mitral stenosis	746.5	Q232	1/3 (33.3)
Category B (defects that create sustained cyanosis)			66/429 (15.4)
Tetralogy of Fallot	745.2	Q213	12/118 (10.2)
TGA	745.1	Q203	18/55 (32.7)
Pulmonary valve atresia	746.01; 746.02	Q220	2/22 (9.1)
Pulmonary artery atresia	743.7	Q255	1/7 (14.3)
Epstein anomaly	746.2	Q225	3/5 (60.0)
Tricuspid atresia	746.1	Q224	1/1 (100)
TAPVR	747.41	Q262	1/1 (100)
HRHS	(Missing)	Q226	0/2 (0)
Category C (diagnoses resulting in CHF and pulmonary overcirculation)			31/103 (30.1)
AVSD	745.69	Q212	17/58 (29.3)
Truncus arteriosus	745.00	Q200	9/32 (28.1)
Double outlet right ventricle	745.11	Q201	6/17 (35.3)
Other single ventricle	745.3	Q204	3/5 (60.0)

AVSD indicates atrioventricular septal defect; CHD, congenital heart defect; CHF, congestive heart failure; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; IAA, interrupted aortic arch; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries.

for other factors that are known to influence outcomes. PS matching added to the robustness of the analyses.

This study also has limitations. The data set did not contain information on antenatal screening or diagnosis of CHD, or on terminations of pregnancy and fetal deaths. Including only live births and not all very preterm births may have led to a conservative bias in estimating mortality rates and risks associated with severe CHD. The iNeo database—like the VON—only included information on infants with birth weights of ≤1500 g. This means that some appropriate- and large-for-gestational-age infants born at 30 to 31 weeks' GA were excluded from the analysis, which could have contributed to a larger proportion of small-for-GA infants in this GA span. However, all analyses were adjusted for birth weight *z* scores. Although several of the networks were population-based, others only included data from hospitals with level III neonatal intensive care units and so some outborn babies may have escaped reporting. The database did not contain information on specific surgical procedures for CHD, potential redirection of care after a postnatal diagnosis of CHD or on organization of care in the 390 hospitals in the 10 iNeo countries. This limits the applicability of the overall associations in counseling families and guiding medical decisions. However, presenting outcome data by type of CHD, for each gestational week and by geographical region, this study provides a higher resolution than previous work. Despite accounting for several important confounders, we cannot exclude the possibility of residual confounding by unmeasured or unknown confounders. The *ICD* codes were not validated against other databases or medical records. In adults, administrative data sets utilizing billing codes for CHD have been reported to be associated with misclassification.[36] However, these misclassifications were mainly a problem for minor CHD. The current study only included severe CHD diagnosed in infancy by expert pediatric cardiologists. Accordingly, significant misclassification should not be a problem in this study. Finally, survival was confined to hospital discharge and did not extend beyond hospital stay.

Comparison With Other Studies

The rate of severe CHD in very preterm infants reported here (7.7 per 1000) is in the same range as that reported from the VON (8.9 per 1000).[17] Another US study from the Pediatrix Medical Group reported an annual rate of 2.2 per 1000 for nonchromosomal major CHD in very preterm infants.[16] This rate is similar to that in the general newborn population, where it is reported to be 2.0 per 1000.[10] Different CHD rates may reflect differences in the set of CHD diagnoses and denominators (live born or neonatal intensive care unit admissions only) chosen. High rates of severe CHD in our study and reported by VON may also reflect referral bias, as these networks consist of a high proportion of tertiary centers. A higher prevalence of cardiovascular malformations in preterm infants than in term infants has been previously reported.[9] So far, it has been difficult to explain the excess CHDs in preterm infants. Although ascertainment bias could be a contributing factor because of more frequent postnatal echocardiographic assessments in very preterm than in term infants, this explanation could only be valid for minor CHDs without clinical manifestations in the neonatal period.

In the majority of infants with CHD, the CHD manifested as sustained cyanosis. Similar or lower proportions of cyanotic

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CHD in preterm infants have previously been reported.[9,17] Inconsistencies in definitions and denominators, as well as in antenatal and postnatal diagnosis and management, make more detailed comparisons difficult.

The mortality in very preterm infants with CHD has previously been reported to vary. The lowest rate was reported in a study of all CHDs (including minor) and the highest rates of ≥44% have been reported in very low-birth-weight infants (<1500 g; GA 22–29 weeks) with severe CHD.[12,15–18] The mortality for infants born at 24 to 29 weeks' GA in iNeo was found to be 20%, ie, less than half of that previously reported. The lowered mortality observed in iNeo could be related to improvements in neonatal and pediatric cardiac care over time,[11] especially considering that the mean GA in our report was 2 weeks lower than in the VON study[17] and similar to that in the Pediatrix study.[16] Differences in case mix and in definitions of severe CHD may also play a role. In VON, serious CHD was defined as any CHD treated before discharge with specific surgical or medical therapy to correct a major anatomic defect or a life-threatening physiologic dysfunction[17] and not, as in iNeo, based on *ICD* codes classified using EUROCAT.[29]

Reassuring for very preterm infants and their families, CHD was not associated with increased risk of major morbidity in a majority of the models. The association with oxygen dependency 36 weeks of postmenstrual age was expected and may reflect cyanotic heart defects and heart failure rather than an increased risk for bronchopulmonary dysplasia. An increased risk for NEC has previously been associated with CHF caused by a complete atrioventricular canal.[18] After adjusting for covariates and potential confounders and also after PS matching, the odds for NEC in the present study were not significantly higher in infants with CHD than in those without CHD. In the subgroup of very preterm infants with CHDs resulting in CHF, however, we note that the NEC rate was 10.8% as compared with 4.8% in controls. This difference did not reach statistical significance, suggesting that limitations in power in our study may have contributed to different conclusions.

Extremely low-birth-weight (401–1000 g) infants with any CHD (28% with atrial or ventricular septal defects) have previously been reported to experience higher mortality (48%) than infants with no birth defect (35%),[15] and, in infants with severe CHD and weighing <750 g at birth, mortality reached 79%.[16] We present the first study reporting CHD-related mortality by each GA week in infants born very preterm outside of the United States. Whereas mortality decreased from 32% at 24 weeks' GA to 1.5% at 31 weeks' GA in infants without severe CHD, there was much less reduction in mortality with increasing GA in infants with CHD. The reasons for such an uncoupling of GA and mortality in very preterm infants are unclear. Higher proportions of outborn infants and lower Apgar scores among infants with severe CHD than in those without CHD may provide some clues of less active care. However, obstetric management (treatments with antenatal corticosteroids and cesarean section) was found to be even more active in infants with CHD than in those without CHD, suggesting that, at least before birth, there was no bias towards redirection of care.

Network variations in rates of severe CHD and in outcomes may have several explanations. The CHD incidence may vary between populations. Variations in the use of antenatal screening and diagnosis, in terminations of pregnancy, and in routines for postmortem examinations may also have played a role in incidence rates. However, high rates of antenatal diagnosis and termination of pregnancy cannot be the only explanation for a low postnatal incidence of severe CHDs in very preterm infants. The highest rate of severe CHD (16.6 per 1000) was found in Sweden—a country with population-based data, with high antenatal detection rates[37] and high abortion rates (>50% for hypoplastic left heart syndrome or single ventricle if antenatally detected[38]). Active management after birth[5] may have been equally important for high postnatal detection rates.

Provided the pregnancy was not terminated, an antenatal diagnosis is likely to have improved the outcome of most CHDs by planned delivery and perinatal management.[39] The proportion of CHDs diagnosed before birth has been reported to vary significantly, from 15%[40] to 69%,[37] but we have no information on the specific rates for the regions and countries participating in iNeo. Differing guidelines for centralization and access to advanced neonatal cardiac surgery within a reasonable time and distance may also be important in explaining the geographical variations in outcome.

Conclusions

In very preterm infants, the added effect of a severe CHD on mortality is pronounced, especially for infants in the upper GA range. Still, overall, 81% of very preterm infants with severe CHD survive the neonatal period—most of them without an increased risk for added major neonatal morbidity. The longer-term outcomes for these patients remain to be studied.

Appendix

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