Cardiology in the Young

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Conjugated hyperbilirubinemia is associated with increased morbidity and mortality after neonatal heart surgery

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Original Article

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Abstract

Background: Cholestasis characterised by conjugated hyperbilirubinemia is a marker of hepatobiliary dysfunction following neonatal cardiac surgery. We aimed to characterise the incidence of conjugated hyperbilirubinemia following neonatal heart surgery and examine the effect of conjugated hyperbilirubinemia on post-operative morbidity and mortality. *Methods:* This was a retrospective study of all neonates who underwent surgery for congenital heart disease (CHD) at our institution between 1/1/2010 and 12/31/2020. Patient- and surgery-specific data were abstracted from local registry data and review of the medical record. Conjugated hyperbilirubinemia was defined as perioperative maximum conjugated bilirubin level > 1 mg/dL. The primary outcome was in-hospital mortality. Survival analysis was conducted using the Kaplan–Meier survival function. *Results:* Conjugated hyperbilirubinemia occurred in 8.5% of patients during the study period. Neonates with conjugated hyperbilirubinemia were more likely to be of younger gestational age, lower birth weight, and non-Caucasian race (all $p < 0.001$). Patients with conjugated hyperbilirubinemia were more likely to have chromosomal and non-cardiac anomalies and require ECMO pre-operatively. In-hospital mortality among patients with conjugated hyperbilirubinemia was increased compared to those without (odds ratio 5.4). Post-operative complications including mechanical circulatory support, reoperation, prolonged ventilator dependence, and multi-system organ failure were more common with conjugated hyperbilirubinemia (all $p < 0.04$). Patients with higher levels of conjugated bilirubin had worst intermediate-term survival, with patients in the highest conjugated bilirubin group (>10 mg/dL) having a 1-year survival of only 6%. *Conclusions:* Conjugated hyperbilirubinemia is associated with post-operative complications and worse survival following neonatal heart surgery. Cholestasis is more common in patients with chromosomal abnormalities and non-cardiac anomalies, but the underlying mechanisms have not been delineated.

Introduction

Neonatal jaundice, generally considered to be benign, is common in the first 2 weeks of life, with unconjugated hyperbilirubinemia comprising most cases. However, cholestatic jaundice with conjugated hyperbilirubinemia in neonates is always considered to be pathologic.[1] In patients without congenital heart disease (CHD), conjugated hyperbilirubinemia can be secondary to a variety of causes including obstructive aetiologies such as biliary infection, genetic or metabolic disorders such as Alagille syndrome, toxins, haemolysis, hypoperfusion, endocrinopathies, or biliary atresia.[2] Conjugated hyperbilirubinemia is also frequently observed in children with CHD, particularly in the post-operative period, with an incidence of up to 24% observed in a recent large series. The aetiology of this hyperbilirubinemia in patients with CHD is unclear but is associated with both worse post-operative outcomes and poor long-term prognosis.[2–4]

Children with conjugated hyperbilirubinemia following heart surgery have a significantly higher odds of mortality and longer length of stay compared to children with normal conjugated bilirubin levels in the post-operative period.[2] These findings appear to be independent of underlying conditions such as genetic syndromes, gestational age, or intraoperative factors such

as the use of cardiopulmonary bypass.[2] Moreover, conjugated bilirubin levels in this subset of patients also appear to be independent of duration of total parental nutrition or heparin use and independent of other markers of liver function such as coagulation factors.[1] As such, conjugated hyperbilirubinemia may help to identify patients at increased risk of a poor outcome following surgery for CHD. We characterised the incidence of conjugated hyperbilirubinemia following neonatal heart surgery, identified patient and clinical risk factors for perioperative conjugated hyperbilirubinemia, and examined the effect of conjugated hyperbilirubinemia on post-operative morbidity and mortality.

Materials and methods

This is a retrospective descriptive study of neonates who underwent surgery for CHD at the Children's Hospital of Philadelphia between January 1, 2010 and December 31, 2020. Exclusion criteria included patients who underwent surgery without the use of cardiopulmonary bypass. Patient- and surgery-specific data were abstracted from local registry data and the medical record. Conjugated hyperbilirubinemia was defined as a maximum conjugated bilirubin level >1 mg/dL observed at any time during the initial hospitalisation. The institutional review board approved this study and granted a consent waiver because the research involved no more than minimal risk to study participants (IRB #21-018796, approval date 7/27/27). The primary outcome was in-hospital mortality. Secondary outcomes included post-operative complications and intermediate-term survival. Patient-specific risk factors including genetic syndromes and demographics were investigated.

Patient characteristics including demographic, clinical, and operative factors were first analysed for the entire cohort. The cohort was then divided into three groups based on the maximum perioperative conjugated bilirubin level: maximum conjugated bilirubin level < 1 mgdL ("no conjugated hyperbilirubinemia"), maximum conjugated bilirubin level 1–10 mg/dL ("mild-moderate conjugated hyperbilirubinemia"), and maximum conjugated bilirubin level > 10 mg/dL ("severe conjugated hyperbilirubinemia"). Morbidity outcomes included post-operative complications such as cardiac failure, sepsis, need for reoperation during the initial hospitalisation, and need for mechanical circulatory support. Abdominal ultrasound reports were examined for patients with conjugated hyperbilirubinemia, and a variety of parameters were extracted including common bile duct diameter, liver and spleen size, and qualitative assessments of liver echotexture. Mortality was assessed first at discharge from the index hospitalisation, and again at 1, 3, and 5 years.

Categorical variables are expressed as counts (percentages) and continuous variables as medians (first quartile-third quartile). Comparisons between the three groups were performed using chi-squared tests for categorical variables and multiple analysis of variance for continuous variables. Mortality was analysed using Kaplan–Meier estimations and compared between cohorts using a log-rank test. All significance tests were two-tailed. Missing information was managed via exclusion. All statistical analyses were performed using STATABE 17.0 (StataCorp LLC, College Station, TX, USA).

Results

Patient characteristics

At our institution, 1267 neonates underwent cardiac surgery for repair of CHD between January 1, 2010 and December 31, 2020. Of these, two had comorbid biliary atresia and were excluded from this analysis. Characteristics of the remaining patients (n = 1265) are presented in Table 1. The majority (n = 743, 58.7%) of patients were male, and most were Caucasian (n = 755, 59.7%). Mean birthweight and gestational age were 3.1 kg and 37.9 weeks, respectively. Preterm birth (<37 weeks) was present in 16.0% (n = 202) of patients. The most common cardiac diagnoses were hypoplastic left heart syndrome (n = 276, 21.8%), transposition of the great arteries (n = 268, 21.2%), and tetralogy of Fallot (n = 124, 9.8%). Genetic syndromes were present in 22.0% (n = 278) of patients. The incidence of perioperative conjugated hyperbilirubinemia, defined as a maximum conjugated bilirubin level ≥ 1 mg/dL, was 8.5% (n = 107) in our cohort. In the minority of patients (n = 15, 14%), the peak observed conjugated bilirubin level occurred pre-operatively. Of patients with perioperative conjugated hyperbilirubinemia, most (n = 90, 84.1%) had maximum conjugated bilirubin levels between 1–10 mg/dL. A minority (n = 17, 15.9%) had maximum conjugated bilirubin levels > 10 mg/dL.

Table 1. Patient characteristics.

Variable	Frequency (%)	
Gender		
Male	743 (58.7)	
Female	522 (41.6)	
Race		
African American	140 (11.1)	
White	755 (59.7)	
Asian	20 (1.6)	
Indian	11 (0.9)	
Other	339 (26.8)	
Preterm birth (<37 wk)	202 (16.0)	
Diagnosis		
Hypoplastic left heart syndrome	276 (21.8)	
Transposition of the great arteries	268 (21.2)	
Tetralogy of Fallot	124 (9.8)	
Truncus	60 (4.7)	
AVSD	30 (2.4)	
VSD	24 (1.9)	
Other	485 (38.3)	
Maximum direct bilirubin		
<1 mg/dL	1158 (91.5)	
1–10 mg/dL	90 (7.1)	
>10 mg/dL	17 (1.3)	
Genetic syndrome (any)	278 (22.0)	
	Median	**IQ_{25}, IQ_{75}**
Gestational age (weeks)	38	37, 39
Birth weight (kg)	3.2	2.7, 2.5
Maximum perioperative conjugated bilirubin	0	0, 0.1

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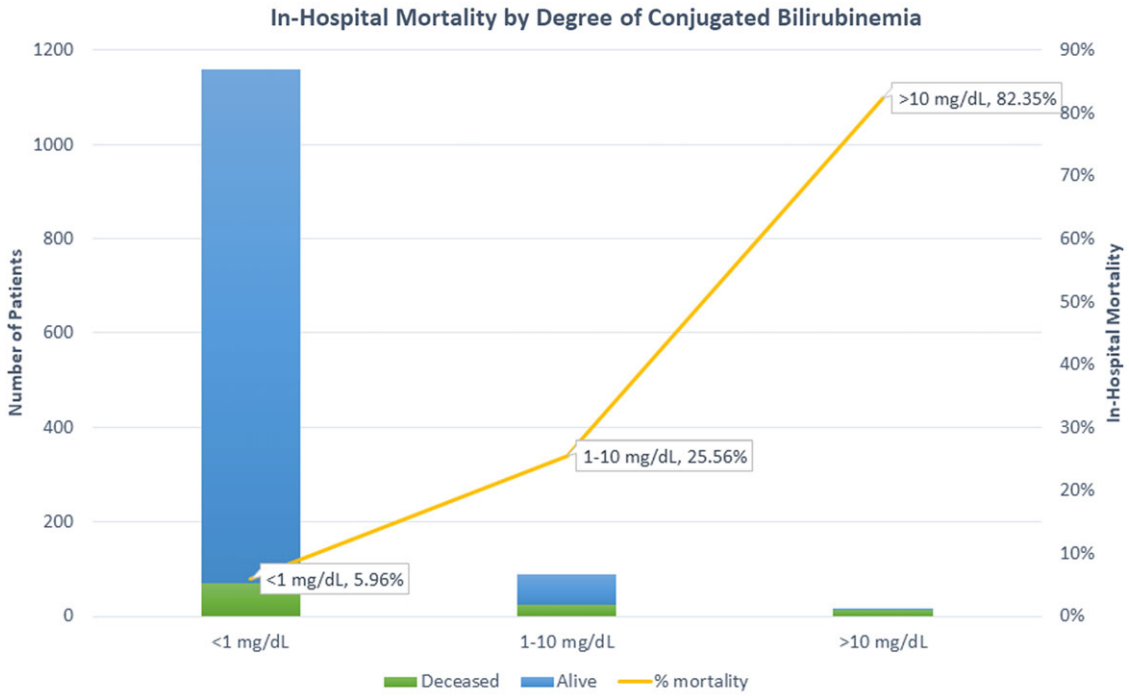

Maximum conjugated bilirubin level	In-hospital mortality (%)	Odds Ratio [95% CI]	p value	Dead (n)	Alive (n)
<1 mg/dL	5.96%			69	1089
1-10 mg/dL	25.56%	5.4 [3.2, 9.2]	<0.0001	23	67
>10 mg/dL	82.35%	73.7 [20.7, 262.4]	<0.0001	14	3

Figure 1. In-hospital mortality by degree of conjugated bilirubinemia.

In-hospital mortality

Overall in-hospital mortality for the cohort was 8.4% (n = 106/1265) (Fig 1). When examined by severity of conjugated hyperbilirubinemia, mortality was lowest among patients without conjugated hyperbilirubinemia (6.0%), increased in patients with mild-moderate conjugated hyperbilirubinemia (25.6%, odds ratio 5.4), and highest in patients with severe conjugated hyperbilirubinemia (82.4%, odds ratio 73.6).

Patient and operative factors associated with conjugated hyperbilirubinemia

Patient and operative characteristics associated with perioperative conjugated hyperbilirubinemia are listed in Table 2. There was no difference in the incidence of perioperative conjugated hyperbilirubinemia based on gender (p = 0.229). Rates of conjugated hyperbilirubinemia varied by gestational age and birthweight, with mild-moderate conjugated hyperbilirubinemia observed most frequently in patients of younger gestational age and lower birthweight (p = <0.001). Patients without conjugated hyperbilirubinemia were more likely to be African American or Caucasian while patients with severe conjugated hyperbilirubinemia were more likely to be of "other" racial categories (p < 0.001). Diagnoses of hypoplastic left heart syndrome and transposition of the great arteries were more commonly encountered in patients without conjugated hyperbilirubinemia as opposed to patients with severe conjugated hyperbilirubinemia who were a more heterogeneous group of "other" diagnoses (p = 0.0020). There was a higher incidence of severe conjugated hyperbilirubinemia in patients with chromosomal abnormalities such as single nucleotide polymorphisms and unnamed variants of unknown significance (47.1% versus 34.4% and 25.7% for severe, mild-moderate, and no conjugated hyperbilirubinemia, respectively; p = 0.03); however, there was no increased risk of conjugated hyperbilirubinemia in patients 22q11, trisomy 18, trisomy 21, or Turner syndromes. Conversely, there was a lower incidence of conjugated hyperbilirubinemia in patients with VACTERL (0.0% versus 0.0% and 6.0% for severe, mild-moderate, and no conjugated hyperbilirubinemia, respectively; p = 0.018). With respect to the presence of extracardiac anomalies, patients with head, cleft lip, brain, and GI tract anomalies were more likely to have severe conjugated hyperbilirubinemia compared to their counterparts (p = 0.011, 0.004, 0.018, and 0.001 respectively).

We also examined perioperative liver function tests to evaluate for concomitant hepatic dysfunction or inflammation as evidenced by perturbation in liver enzymes. We found that there were significant differences in maximum levels of alkaline phosphatase, aspartate aminotransferase, and alanine transaminase among the three patient subgroups, with patients with conjugated hyperbilirubinemia having higher peak perioperative levels of all three enzymes (all p < 0.001). There were no significant differences in perioperative albumin levels among the three groups (p = 0.099).

In addition to patient characteristics, several operative factors were considered. Patients with severe conjugated hyperbilirubinemia more frequently had complicated pre-operative courses, as evidenced by higher rates of pre-operative cardiopulmonary resuscitation (5.9% versus 3.3% versus 0.9% for severe, mild-moderate, and no conjugated hyperbilirubinemia, respectively;

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Table 2. Patient factors associated with perioperative conjugated hyperbilirubinemia and post-operative complications.

	Max conjugated bilirubin<1		Max conjugated bilirubin 1-10		Max conjugated bilirubin>10		
Variable	n	%	n	%	n	%	p-value
Male gender	672	58%	59	65.56	12	70.59	0.2290
Race							<0.0001
African American	121	10%	19	21%	1	6%	0.0060
White	717	62%	33	37%	5	29%	<0.0001
Other	241	21%	28	31%	10%	59%	<0.0001
Diagnosis							
Hypoplastic left heart syndrome	244	21.0%	29	32.2%	3	17.7%	0.0410
Transposition of the great arteries/IVS	162	14.0%	2	2.2%	1	5.9%	0.0040
Other	111	9.6%	11	12.2%	7	41.2%	<0.0001
Chromosomal abnormalities							0.0300
22q11	48	4.2%	3	3.3%	1	5.9%	0.8710
Trisomy 18	1	0.1%	0	0.0%	0	0.0%	0.9550
Trisomy 21	27	2.3%	4	4.4%	1	5.9%	0.3170
Turner	11	1.0%	1	1.1%	0	0.0%	0.9100
Other	210	18.1%	23	25.6%	6	35.3%	0.0490
Genetic syndromes							
CHARGE	8	0.7%	1	1.1%	1	5.9%	0.0530
Heterotaxy	42	3.6%	5	5.6%	0.0%	0.0%	0.4650
VACTERL	7	6.0%	3	3.3%	0.0%	0.0%	0.0180
Other	98	8.5%	11	12.2%	1.0%	5.9%	0.4360
Non-cardiac anomalies							
Bowel atresia	9	0.8%	3	3.3%	0	0.0%	0.0500
Malrotation	25	2.2%	4	4.4%	0	0.0%	0.3070
Head anomalies	21	1.8%	3	3.3%	1	11.8%	0.0110
Cleft lip	5	0.4%	0	0.0%	1	5.9%	0.0040
Brain anomalies	24	2.1%	1	1.1%	2	11.8%	0.0180
CDH	1	0.1%	2	2.2%	0	0.0%	0.0000
Omphalocele	1	0.1%	1	1.1%	0	0.0%	0.0610
GI tract anomalies	6	0.5%	3	3.3%	1	5.9%	0.0010
Pre-operative factors							
Pre-operative CPR	10	0.9%	3	3.3%	1	5.9%	0.0160
Atrioventricular block	3	0.3%	0	0.0%	0	0.0%	0.8700
MCS	15	1.3%	2	2.2%	1	5.9%	0.2280
Persistent shock	15	1.3%	3	3.3%	0	0.0%	0.2560
Resolved shock	46	4.0%	1	1.1%	4	23.5%	<0.0001
Post-operative ECMO	62	5.3%	21	23.3%	9	52.9%	<0.0001
	Median		Median		Median		
Gestational age (weeks)	38		36.5		37.1		<0.0001
Birthweight (kg)	3.12		2.73		2.89		<0.0001
CPB time (min)	84		94		109.5		0.0012
DHCA time (min)	21.7		28.89		32		0.0025

(*Continued*)

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Table 2. (*Continued*)

	Median	Median	Median	
Duration of TPN (days)	11.5	32.8	33.4	<0.0001
Alanine transaminase	27	41	34	<0.0001
Aminotransferase	79	99	213	<0.0001
Alkaline phosphatase	103	117	113	<0.0001
Albumin	3	3.1	2.8	0.099

	Max conjugated bilirubin < 1		Max conjugated bilirubin 1–10		Max conjugated bilirubin > 10		p-value
Post-operative complication	n		%		n		%
Arrhythmia	94	8.2%	29	33.0%	9	52.9%	<0.0001
Cardiac failure	37	3.2%	9	10.2%	1	5.9%	0.0040
Chylothorax	50	4.4%	11	12.5%	1	5.9%	0.0030
Mediastinal infection	7	0.6%	3	3.4%	0	0.0%	0.0160
Open sternum	197	17.2%	36	40.9%	9	52.9%	<0.0001
Pulmonary HTN crisis	2	0.2%	2	2.3%	2	11.8%	<0.0001
Pleural effusions	78	6.8%	10	11.4%	1	5.9%	0.2710
Post-op MCS	74	6.5%	27	30.7%	12	70.6%	<0.0001
Reoperation for bleeding	72	6.2%	12	13.6%	2	11.8%	0.0230
Seizure	94	8.2%	16	18.2%	10	58.8%	<0.0001
Sepsis	31	2.7%	8	9.1%	6	35.3%	<0.0001
Stroke	123	10.7%	11	12.5%	6	35.3%	0.0060
Temporary dialysis	2	0.2%	2	2.3%	3	17.7%	0.0000
Tracheostomy	16	1.4%	2	2.3%	2	11.8%	0.0030
Unplanned catheterisation	147	12.8%	20	22.7%	4	23.5%	0.0170
Unplanned reoperation	67	5.9%	18	20.5%	3	17.7%	<0.0001
Wound infection	4	0.4%	2	2.3%	0	0.0%	0.0400
None	356	31.1%	5	5.7%	0	0.0%	<0.0001

ECMO = extracorporeal membrane oxygenation; GI = gastrointestinal; AVSD = atrioventricular septal defect; VSD = ventricular septal defect; IVS = interventricular septum; CDH = congenital diaphragmatic hernia; CPR = cardiopulmonary resuscitation; DHCA = deep hypothermic circulatory arrest; HTN = hypertension; MCS = mechanical circulatory support.

$p = 0.016$) and resolved shock (23.5% versus 1.1% versus 4.0% for severe, mild-moderate, and no conjugated hyperbilirubinemia, respectively; $p = 0.0000$). There was no difference in rates of heart block, pre-operative mechanical circulatory support, or persistent shock among the three groups. However, patients with conjugated hyperbilirubinemia did have longer bypass (109.5 versus 94 versus 84 minutes, $p = 0.001$) and circulatory arrest times (32 versus 29 versus 22 minutes, $p = 0.003$) compared to their counterparts without perioperative conjugated hyperbilirubinemia. Patients with perioperative conjugated hyperbilirubinemia had longer duration of total parental nutrition administration compared to those without (11.5 versus 32.8 versus 33.4 for no, mild-moderate, and severe conjugated hyperbilirubinemia, respectively; $p = 0 < 0.001$).

Finally, we examined the timing of peak perioperative conjugated bilirubin level relative to the date of surgery and, for patients who died, the date of death (Supplemental Table 1). When the interval between peak conjugated bilirubin level and date of surgery was investigated, a statistically significant difference between subgroups was identified ($p < 0.0001$). Patients with severe conjugated hyperbilirubinemia had a longer interval between surgery and peak conjugated bilirubin level compared to patients with no conjugated hyperbilirubinemia or conjugated hyperbilirubinemia of mild-moderate severity (0 versus 6 versus 17 days, respectively). Among patients who died, there was no difference in timing of conjugated hyperbilirubinemia, but there was a trend toward shorter interval between peak conjugated hyperbilirubinemia and date of death in patients with severe conjugated hyperbilirubinemia (28 versus 28 versus 2 days, respectively).

Ultrasound data

For the subset of patients with conjugated hyperbilirubinemia, the electronic medical record was queried for abdominal ultrasound reports and a variety of parameters were extracted. Ultrasound data was available for 58 patients (Supplemental Table 2). Notably, there was no difference in mean common bile duct (CBD) diameter between patients with mild-moderate and severe conjugated hyperbilirubinemia, and CBD diameter was normal in both groups (mean 0.97 and 0.96 cm, respectively, $p = 0.84$). There were also no differences in liver or spleen size between the two groups. When qualitative assessments of liver echotexture were examined, the

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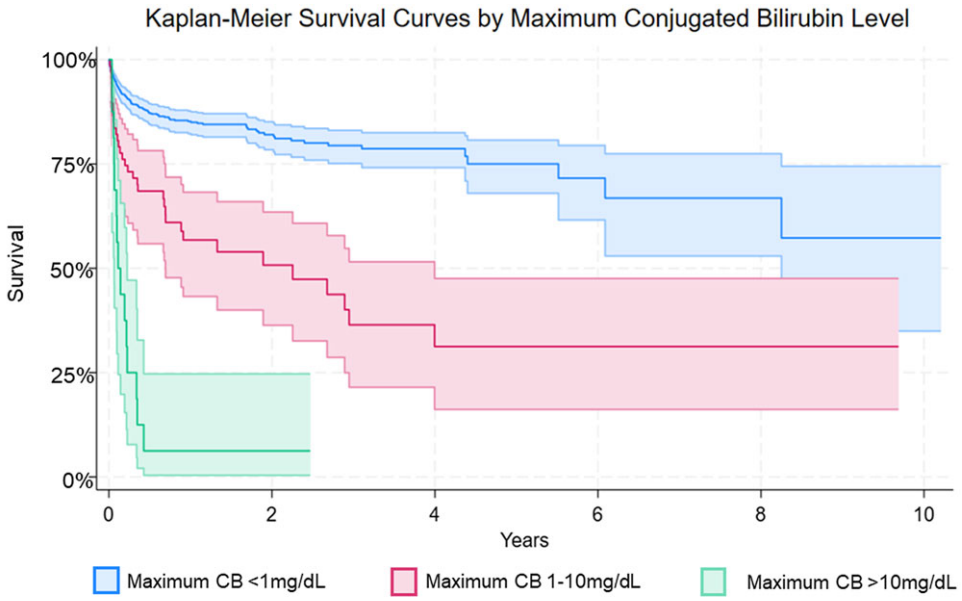

Maximum Conjugated Bilirubin	1-year survival	3-year survival	5-year survival
<1mg/dL	85.2%	79.4%	75.0%
1-10 mg/dL	56.8%	36.5%	31.2%
>10mg/dL	6.3%	0%	0%

CB = conjugated bilirubin; Shaded areas represent 95% confidence intervals

Figure 2. Kaplan–Meier survival curves by maximum conjugated bilirubin level.

majority (89 and 92% of patients with mild-moderate and severe conjugated hyperbilirubinemia, respectively) were found to be normal; only two patients were found to have intrahepatic masses and two additional patients had echotexture suggestive of inflammation/hepatitis. Biliary tree obstruction secondary to bile duct plug was noted in one patient with mild-moderate conjugated hyperbilirubinemia. Finally, vascular abnormalities were exceedingly rare, with only three noted in our cohort: one patient with an IVC leftward of the aorta, one patient with interrupted IVC with azygous continuation, and one patient with abnormal orientation of the superior mesenteric artery relative to its vein.

Post-operative complications

As shown in Table 2, patients with severe conjugated hyperbilirubinemia had higher rates of a variety of post-operative complications, including arrhythmia, delayed sternal closure, pulmonary hypertensive crises, need for post-operative mechanical circulatory support, seizure, sepsis, stroke, temporary dialysis, and ventilator dependence requiring tracheostomy (all $p < 0.05$). Additionally, unplanned reintervention such as cardiac catheterisation or reoperation was more commonly encountered in patients with any degree of conjugated hyperbilirubinemia (both $p < 0.02$).

Survival

Finally, we evaluated the impact of perioperative conjugated hyperbilirubinemia on short- and intermediate-term mortality utilising last known vital status from the electronic medical record and/or local registry data. Kaplan–Meier survival curves for the three groups are presented in Figure 2. Perioperative conjugated hyperbilirubinemia has a significant impact on both short- and intermediate-term survival with 1-, 3- and 5-year survival rates of 6.3, 0, and 0% in the severe conjugated hyperbilirubinemia group; compared to 85.2, 79.4, and 75% in the no conjugated hyperbilirubinemia group (log-rank $p = 0 < 0.001$). Patients with mild-moderate conjugated hyperbilirubinemia also had decreased short- and intermediate-term survival compared to patients without, with 1-, 3-, and 5-year survival rates of 56.8, 36.5, and 31.2% respectively.

Discussion

Perioperative conjugated hyperbilirubinemia occurs not infrequently in neonates undergoing surgery for CHD, with a reported incidence of up to 24% in recent large series.[1] While the underlying mechanisms are incompletely understood, what is clear is that conjugated hyperbilirubinemia, particularly when severe, is associated with increased morbidity and mortality in this patient population.[1,2,4] In this observational study, we have demonstrated that conjugated hyperbilirubinemia is associated with increased in-hospital mortality, greater incidence of post-operative complications, and decreased short- and intermediate-term survival following neonatal cardiac surgery. Moreover, we have identified that patients at risk of developing perioperative conjugated hyperbilirubinemia tend to be more medically complex, comprising a group of children with heterogeneous cardiac diagnoses, often comorbid chromosomal abnormalities or extracardiac anomalies, and who have longer intraoperative bypass or circulatory arrest times.

Conjugated hyperbilirubinemia in children who have undergone surgery for CHD appears to be a marker for poor outcome; with a reported five-fold increased risk of post-operative mortality and four-fold increased length of stay compared to patients with normal bilirubin levels.[2] In a recent analysis of 242 patients who underwent surgery for CHD, conjugated hyperbilirubinemia was present in 24% of patients post-operatively, and even low levels of conjugated bilirubin (average 3 mg/dL) were associated with poor post-operative outcomes. Moreover, these findings were independent of underlying patient factors (e.g. genetic anomaly, presence of biliary atresia, gestational age, demographics) and surgery-

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specific factors (cardiopulmonary bypass time, use of ECMO, use of inotropes).[2]

In the adult cardiac surgery population, hyperbilirubinemia is present in up to 25% of patients in the post-operative period and has been correlated with severity of right heart failure, severity of tricuspid regurgitation, elevated right atrial pressure, hypotension, hypoxaemia, total parental nutrition administration, blood transfusion, and longer cardiopulmonary bypass times.[1] It is hypothesised that the observed hyperbilirubinemia results from two simultaneous processes: (1) increased filling pressured leading to hepatic congestion and altered bile secretion into bile ducts by hepatocytes and (2) decreased perfusion pressure resulting in ischaemia and centrilobular necrosis.[1] However, in adults, this hyperbilirubinemia tends to be transient, peaking within the first 3 days following surgery, and with most cases resolving spontaneously within 1 week.

In our cohort of 1265 neonates undergoing surgery for CHD over a 10-year period, perioperative conjugated hyperbilirubinemia was not uncommon, occurring in 8.5% of all patients. Our results confirm the findings of previous studies that demonstrate an increased risk of in-hospital mortality in patients with conjugated hyperbilirubinemia. Compared to patients without conjugated hyperbilirubinemia, patients with conjugated hyperbilirubinemia are at significantly increased risk of death during the index hospitalisation, with a five-fold increased risk of death in patients with mild-moderate conjugated hyperbilirubinemia compared to patients with conjugated bilirubin levels <1 mg/dL. Interestingly, however, we found that this effect persisted into the intermediate term, with significantly reduced survival rates at 3 and 5 years post-operatively. In patients with mild-moderate conjugated hyperbilirubinemia following their initial neonatal operation, 3- and 5-year survival was nearly half (36.5% and 31.2%, respectively) that of peers without conjugated hyperbilirubinemia (3- and 5-year survival rates of 79.4% and 75.0%, respectively). Taken together, these findings suggest that conjugated hyperbilirubinemia occurring perioperatively renders patients more vulnerable to mortality in the neonatal period and may have some lasting physiologic effect that decreases their likelihood of survival in the long term.

In addition to illuminating the impact of conjugated hyperbilirubinemia on short- and intermediate-term mortality, our findings have also identified a subset of patients who are at increased risk of conjugated hyperbilirubinemia. Not surprisingly, medically complex patients are at increased risk of perioperative conjugated hyperbilirubinemia, including patients with comorbid chromosomal abnormalities, skeletal and visceral anomalies, and premature or low birthweight infants. Additionally, patients with more complicated operative courses are more likely to have elevated conjugated bilirubin levels perioperatively. Notably, while other series have failed to demonstrate an association between bypass and circulatory arrest times and conjugated hyperbilirubinemia, both were significantly associated with conjugated hyperbilirubinemia in our cohort. Our findings did confirm a longer mean duration of total parental nutrition administration in patients with conjugated hyperbilirubinemia, which some have hypothesised contributes to bile duct congestion via hepatocellular injury induced by phytosterol administration. Interestingly, we did identify significant elevations in liver function tests including aminotransferase, alanine transaminase, and alkaline phosphatase among patients with conjugated hyperbilirubinemia, suggesting concurrent hepatic inflammation or synthetic dysfunction. That said, these findings should be interpreted with caution as we have not examined the timeline of enzyme disturbance relative to onset and peak of conjugated hyperbilirubinemia in this patient population.

When timing of conjugated hyperbilirubinemia relative to the date of surgery was examined, we found a significantly longer interval between date of surgery and peak conjugated hyperbilirubinemia in the patients with severe conjugated hyperbilirubinemia compared to those with no conjugated hyperbilirubinemia, or those with mild-moderate conjugated hyperbilirubinemia. Among the patients who died, there was no difference in interval between peak conjugated hyperbilirubinemia and date of death. Taken together, these findings have several potential implications. In patients with severe conjugated hyperbilirubinemia, extremely high levels of conjugated bilirubin may be a predictor of impending mortality. However, in patients with no conjugated hyperbilirubinemia or mild-moderate conjugated hyperbilirubinemia, even early increases in conjugated bilirubin, either pre- or post-operatively, may be a marker of long-term poor outcome. In this way, conjugated hyperbilirubinemia can be informative in risk discussions with families. Finally, to our knowledge our study is the first to illuminate the morbidity associated with perioperative conjugated hyperbilirubinemia in neonates, who are at increased risk for a plethora of complications including sepsis, seizure, ventilator dependence, renal failure, reoperation, cardiac failure, and need for post-operative mechanical circulatory support.

In the 58 patients with conjugated hyperbilirubinemia for whom imaging of the biliary tree was available, ultrasound did not identify anatomic biliary obstruction. This finding suggests that conjugated hyperbilirubinemia is related to an undefined functional abnormality, rather than obstruction of the biliary system. Common bile duct dilation was exceedingly rare, as were abnormalities in liver echotexture or vasculature. There was a trend toward larger spleen size in the severe conjugated hyperbilirubinemia group, and there was a higher degree of increased gallbladder wall thickness observed in patients with severe conjugated hyperbilirubinemia. However, these findings should be interpreted with caution as abdominal ultrasound data was not available for all patients with conjugated hyperbilirubinemia in our study.

This study is subject to the regular limitations of a large, observational cohort study. Moreover, the cohort spans a decade of clinical experience, over which time technical and medical aspects of surgical and critical care management have improved, the effects of which cannot be directly measured. Additionally, our study does not specifically include an analysis of hemodynamic or echocardiographic data which may illuminate underlying mechanisms of ventricular dysfunction, which could contribute to the development of perioperative conjugated hyperbilirubinemia via hepatic congestion. Finally, this study does not consider drug or nutrition administration; a more detailed analysis of the association between medication/nutrition formulation and perioperative conjugated hyperbilirubinemia is the subject of future analyses.

In our large single-institution analysis of neonates who underwent surgery for CHD, conjugated hyperbilirubinemia was present in 8.5% of all patients. Among patients with perioperative conjugated hyperbilirubinemia, both short- and intermediate-term mortality was increased compared to patients without conjugated hyperbilirubinemia. Patients with conjugated hyperbilirubinemia tend to be more medically complex, have more complicated clinical courses both pre- and intraoperatively, and are much more

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likely to suffer from post-operative complications such as sepsis, reoperation, cardiac failure, and ventilator dependence. When imaging of the biliary tree was performed clinically, there was no evidence of anatomic obstruction suggesting a functional abnormality. Future studies are necessary to elucidate underlying mechanisms and to guide clinical management.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123004158

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