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ORIGINAL RESEARCH

Association between congenital heart disease and parenteral nutrition–associated liver disease in neonates: A retrospective cohort study

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Abstract

Objective: Infants receiving parenteral nutrition (PN) are at increased risk of PN-associated liver disease (PNALD), which can lead to hepatic fibrosis. Congenital heart disease (CHD) represents a risk factor for hepatic fibrosis, so this study sought to better understand whether infants with CHD were at elevated risk of PNALD when receiving long-term PN.

Study Design: This study includes a retrospective cohort of infants at a level IV neonatal intensive care unit from 2010 to 2020 who received long-term PN during the first 8 weeks of life. A time-varying Cox survival model was used to model risk of PNALD between infants with and without CHD, adjusted for demographics, surgical intervention, and PN exposure, using a 5000-iteration bootstrap estimation. Secondary analyses evaluated risk against discrete CHD diagnoses, and sensitivity analysis was performed on the magnitude and quantity of direct bilirubin laboratory measurements making up the PNALD definition.

Results: Neonates with CHD were found to be at higher risk for PNALD during or soon after long-term PN exposure. A pattern of increasing association strength with increasing bilirubin threshold suggests infants with CHD may also experience higher degrees of injury.

Conclusions: This work offers a step in understanding how diagnoses can be factored into neonate PN prescription. Future work will explore modifications in lipid profiles and timing to mitigate risk in patients with CHD.

KEYWORDS
liver disease, neonates, outcomes research/quality, parenteral nutrition

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CLINICAL RELEVANCY STATEMENT

Neonates who require long-term parenteral nutrition (PN) are at high risk for developing PN-associated liver disease (PNALD). When prescribing PN, care teams consider risk factors related to an infant's birth status (eg, gestational age, birth weight), clinical status (eg, need for gastrointestinal surgeries, infections), and PN itself (eg, lipid type, duration), but variability in PNALD outcomes suggests a need to consider additional risk factors. This paper presents a retrospective cohort study of infants receiving PN to assess differences in baseline risk. It identifies an association between infants with congenital heart disease and increased risk for development and magnitude of direct hyperbilirubinemia.

INTRODUCTION

Parenteral nutrition (PN) is a life-sustaining therapy that can meet the nutrition needs of infants born with a low birth weight, premature, or with conditions that preclude enteral feeds. However, up to 40%–60% of infants receiving long-term PN develop PN-associated liver disease (PNALD).[1] PNALD is a pathologic diagnosis characterized by cholestasis, inflammation, steatosis, and hepatic fibrosis, which can progress to end-stage liver disease.[2–4]

Factors that increase the risk of developing PNALD include elements of birth status (prematurity, low birth weight, small for gestational age status), clinical history (gastrointestinal disorders, surgeries, bloodstream infections), and PN usage (lack of enteral feeding before starting PN, duration of PN, excess or deficiency of macronutrients and micronutrients).[2,5–9] PNALD risk is also related to the lipid component of PN, as evidenced by the impact of fish oil–containing lipid emulsions.[10,11] Even accounting for known risk factors, substantial heterogeneity remains in identifying which infants develop PNALD, suggesting consideration of additional factors may be required to fully contextualize patient risk.

One such factor, implicated in the development of liver disease but not currently considered in the development of PNALD, is the comorbid diagnosis of congenital heart disease (CHD). Although current evidence in neonates is limited,[12] in adolescents and adults with CHD, cardiac hepatopathy is mediated by right heart insufficiency leading to hepatic congestion.[13] Children with CHD can develop congestive cardiac hepatopathy and hepatic fibrosis, particularly if they have undergone the Fontan operation.[14]

To date, it is unclear whether CHD represents a meaningful risk factor in the development of neonatal PNALD. To fill this knowledge gap, we measured the association between occurrence of PNALD and diagnosis of CHD, as defined by a contemporary classification system specific to neonatal outcomes. We hypothesized that neonates with PN exposure and a diagnosis of CHD would be more likely to develop PNALD, as compared with infants without CHD.

METHODS

Study design

This retrospective cohort study includes infants admitted to the Children's Mercy Kansas City (CMKC) Level IV neonatal intensive care unit (NICU) between January 1, 2010, and January 1, 2020. The study cohort and protocol were approved by the Children's Mercy Institutional Review Board (#11120563) with a waiver of consent.

Definition of CHD

CHD was defined per Norman et al.[15] These conditions were categorized as severe or minor CHD, with severe further subdivided into three categories: category A (defects that primarily compromise systemic output), category B (defects that create sustained cyanosis), and category C (diagnoses resulting in congestive heart failure (CHF) and pulmonary overcirculation). A complete listing of diagnoses in each category can be found in Table 1.

Definition of PNALD

Based on current literature, PNALD was defined as a serum direct bilirubin ≥2 mg/dl in infants with at least 14 days of PN exposure, and without comorbid diagnosis of secondary disease known to cause neonatal cholestasis.[4,9,16–21]

Data and study cohort

For each infant, clinical and patient-level data were extracted from the electronic medical record, including demographics, all direct bilirubin laboratory values, and diagnoses. Given billing codes' reliability,[22] we obtained diagnoses reported to Children's Hospitals Neonatal Consortium, which are manually reviewed by database/quality improvement specialists in the Division of Neonatology. Pharmacy-level PN administration times were extracted from the medication administration record.

Inclusion criteria

All infants admitted to the CMKC NICU during the study period who received at least one dose of PN were considered for inclusion, provided their clinical record had at least one laboratory measurement of direct bilirubin and at least one diagnosis before discharge. Should infants have multiple admissions to the NICU, only the initial admission was considered.

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TABLE 1 Norman categories of CHD.

Norman A (compromised systemic output)	Norman B (creates sustained cyanosis)	Norman C (manifest in CHF)	Norman minor CHD
HLHS with MS, MA, AS, AA Aortic valve stenosis Coarctation of aorta Hypoplastic aortic arch Interrupted aortic arch Mitral valve stenosis Supravalvar aortic stenosis	Hypoplastic right heart syndrome Tricuspid atresia (with or w/o pulmonary atresia) Transposition of the great vessels – D-TGA – With intact ventricular septum – With VSD – L-TGA – Other TGA Ebstein's anomaly Pulmonary artery stenosis – Supravalvar – Branch (not PPS) Pulmonary atresia – Intact ventricular septum Pulmonary valve stenosis Tetralogy of fallot – Pulmonary stenosis – Pulmonary atresia – Complete AV canal – Type unknown Tricuspid stenosis Absent pulmonary valve TAPVR – Type unknown – Type I (supracardiac) – Type II (intracardiac) – Type III (infradiaphragmatic/infracardiac) – Type IV (mixed)	Other complex CHD – LV only – RV only Double-outlet RV Truncus arteriosus—all types AV canal – Complete balanced – Intermediate transitional – Partial unbalanced	Complete heart block congenital Cardiomyopathy Patent ductus arteriosus Right aortic arch ASD VSD Systemic vein (SVC, IVC) anomalies

Abbreviations: AA, aortic atresia; AS, aortic stenosis; ASD, Atrial septal defect; AV, atrioventricular; CHD, congenital heart disease; CHF, congestive heart failure; D-TGA; dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; IVC, inferior vena cava; L-TGA, levo-transposition of the great arteries; LV, left ventricle; MA, mitral atresia; MS, mitral stenosis, PPS, peripheral pulmonary stenosis; RV, right ventricle; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; VSD, ventricular septal defect; w/o, without.
Adapted with permission from Norman et al[15] tab. 8.

Exclusion criteria

Logistical

Infants who received PN or had direct bilirubin measured before admission to the NICU were excluded to remove potential biases that may result from the inclusion of infants with significant medical management outside of the NICU. These were infants with severe congenital conditions who were first admitted to the pediatric intensive care unit (PICU) for surgery or when infants were transferred to CMKC from another medical facility.

Diagnoses

To ensure our analysis focused on liver disease associated with PN only, infants with congenital and/or acquired conditions associated with direct hyperbilirubinemia were excluded. For example, biliary atresia (the most common cause of direct hyperbilirubinemia in infants) is complicated by CHD in 6.3%–15% of affected patients.[12,23–25] A complete list of excluded conditions can be found in Supporting Information: Supplementary Table S1. Infants without recorded diagnoses were excluded. Infants who required extracorporeal membrane oxygenation were excluded, as this procedure is known to impact liver functioning. Lastly, although hypoplastic left heart syndrome (HLHS) represents a significant

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CHD diagnosis, local management requires transfer to pediatric intensive care for Norwood surgery around the sixth day of life (DOL). These patients recover outside of the NICU and are subject to PN protocols that may be different from those of other patients in the study. We excluded these infants to make a conservative estimate of the proposed association and minimize bias introduced by interunit management.

PN exposure

Infants with <14 days of PN exposure within a 21-day window were excluded to account for intermittent administration. We also required infants to start PN (first day of the window) within the first 8 weeks of life to reduce bias introduced by infants requiring PN late in their NICU encounter. As recent studies have identified injury as early as 7 days,[26] we created two sensitivity analysis cohorts, modifying the 14-day definition used throughout the main text, requiring 7 days of PN within a 14-day window and 21 days of PN within a 28-day window.

Injury window

With respect to the direct bilirubin values used for PNALD diagnosis, we sought to ensure that laboratory tests were within a timeframe relevant to PN administration. Thus, we focused only on laboratory results that occurred after PN exposure (day 14, 7, or 21, based on sensitivity analysis). Laboratory results recorded later than 28 days after the final day of PN administration were excluded, as we sought to safeguard against capturing elevated values related to conditions acquired weeks or months after PN was completed. Although this may miss late-developing cholestasis, we aimed to take a conservative approach to identifying PNALD vs other forms of cholestasis.

Statistical analyses

As PNALD can occur at any point during the observation window and not all administration and/or laboratory data may be relevant in determining overall odds of incidence, we used time-to-event survival models (Cox proportional hazard) to estimate association between CHD (Norman categories A, B, and C combined into a single broad CHD binary indicator for each infant) and PNALD as a hazard ratio compared with infants without CHD. As duration of PN administration and PNALD are directly related, we introduced a culminate time-varying covariate for days of PN exposure, starting from the beginning of the observation through the 28-day period after the final PN administration to account for potentially differing odds of PNALD on days without PN administration. Additionally, recent works have identified hyperbilirubinemia in postoperative patients with CHD, outside of any PN exposure.[27] To account for potential bias from such interventions, a second time-varying covariate was added as a binary flag: a value of 0 for preoperative days and 1 for all days after the surgical intervention of an infant if relevant.

The model was adjusted for demographics and first DOL receiving PN. Owing to heavy right tails, birth weight was log-transformed. DOL PN initiation was found to violate the promotional hazard assumption and was stratified into "early" (representing whose PN began on DOL ≤7) and "late" (DOL > 7).

To assess robustness of the relationships between PN, CHD, and PNALD, we performed a sensitivity analysis of the PNALD definition. First, we varied the minimum threshold for cholestasis, ranging from the usual 2 mg/dl up to and including 5 mg/dl by increments of 1. Second, we assessed the impact of requiring more than one laboratory test at a given threshold. A single spurious laboratory value could introduce bias, and bilirubin testing is known to be subject to measurement variance.[28] We evaluated thresholds of two or more and three or more values at or above a particular bilirubin threshold to be classified as having PNALD; in these cases, the "event" date used by the Cox model represented the second or third date the threshold was met, resulting in 12 total combinations.

All regressions were run using a bootstrap evaluation to better estimate the direction and magnitude of the relationship. In each iteration, data were sampled with replacement and were stratified by the proportion of PNALD in respective original data. Models were then fit on the resampled data and the coefficient for the respective CHD indicator variable stored. Although rare, coefficients for any model that did not converge were ignored, and the sample was redrawn without counting the iteration. As a best practice from recent statistical literature, *P* values were not computed. Rather, the mean coefficient was taken from the sampling distribution as an effect size, and 95% CIs were computed. For completeness, the analysis was repeated, including infants with only Norman + minor CHD into the CHD binary indicator (defined as having any Norman category A, B, or C + Norman minor, as found in in Table 1).

Association to individual diagnoses

We then quantified the magnitude and directionality of associations between PNALD and each of the congenital heart diagnoses to better understand which component of the definition contributed to the relationship. Given the co-occurrence between many CHD conditions, each diagnosis was modeled as a binary feature within an independent Cox model, maintaining adjustment for the complete set of demographics and PN factors as detailed in the primary analysis for each model.

Infrequent diagnoses (<1% of the cohort) were combined into an "other" category. Models were again estimated using a 5000-iteration bootstrap, and 95% CIs were estimated around the diagnosis coefficient. All analyses were run using Python 3.8, Pandas 1.2.4, NumPy 1.20.1, and Lifelines 0.26.4.[29–32]

RESULTS

In total, 8977 infants were admitted and discharged to the CMKC NICU within the 10-year study period. Of these, 52.6% ($n = 4718$) received at least 1 day of PN. Following exclusion criteria, 568 infants were retained in the 14-day PN cohort, with 1283 and 326 infants in the 7-day and 21-day PN sensitivity analysis cohorts, respectively. Approximately 13% of infants had at least one CHD diagnosis (Norman A, B, or C).

For the primary cohort (14-day PN exposure), exclusion counts for each criterion can be seen in the Consolidated Standards of Reporting

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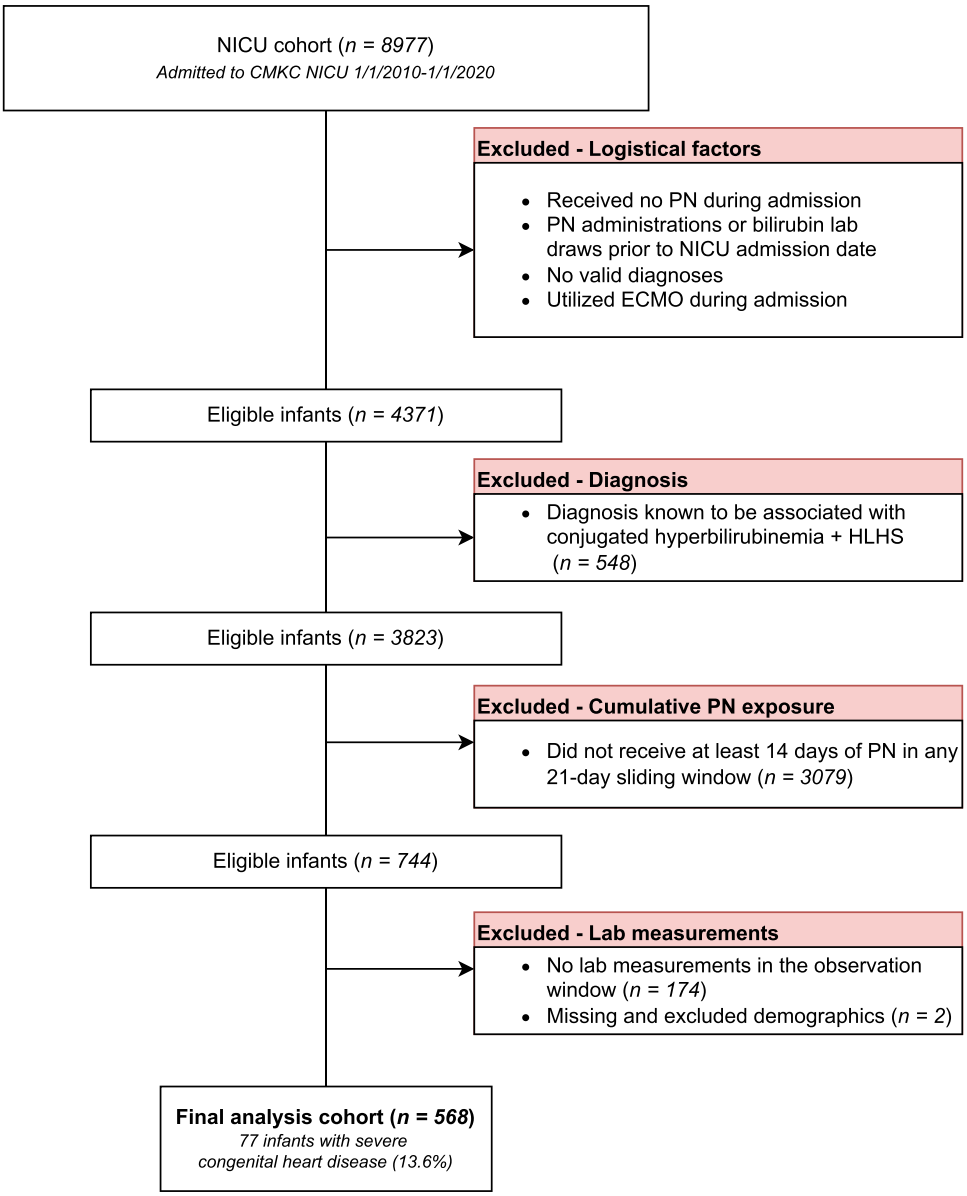

FIGURE 1 Inclusion and exclusion criteria for 14-day PN cohort. CMKC, Children's Mercy Kansas City; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; lab, laboratory; NICU, neonatal intensive care unit; PN, parenteral nutrition.

Trials (CONSORT) diagram (Figure 1), and demographic details are provided in Table 2. Results for sensitivity analysis of 7- and 21-day PN cohorts can be found in the supporting information.

Association of CHD and PNALD

Figure 2 presents the results from the primary analysis, representing the mean bootstrapped hazard ratio estimate and corresponding 95% CI between infants with CHD compared with those without CHD. An analogous analysis for Norman minor conditions can be found in Supporting Information: Supplementary Figure S1.

A diagnosis of CHD was generally associated with a higher hazard of experiencing PNALD during the observation window. There is a clear pattern of increasing association strength with increasing bilirubin threshold, suggesting infants with CHD have higher bilirubin values than their non-CHD peers have and are thus at greater risk for PNALD. To assess this finding, a post hoc analysis was performed, in which a linear model was fit in the same bootstrapping procedure with the dependent variable of the highest direct bilirubin recorded for an infant during the observation window, and adjusted again for age, sex, birth weight, DOL that PN was started, and total number of days receiving PN. A binary flag was also added to indicate whether the infant had undergone surgery. This revealed a positive association between maximum direct bilirubin level and CHD diagnosis. At the most conservative PNALD criteria (one or more laboratory tests showing bilirubin 2 mg/dl), correlation coefficients for CHD with and without Norman minor diagnosis were 0.66 (95% CI, 0.31–1.00) and 1.26 (95% CI, 0.69–1.86), respectively.

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TABLE 2 Cohort demographics.

	Overall	No CHD	CHD
n	568	491	77
GA, mean (SD)	31 wk 2 d (5 wk 3 d)	30 wk 5 d (5 wk 2 d)	35 wk 2 d (3 wk 6 d)
BW, mean (SD), g	1719.016 (1012.259)	1640.303 (1021.812)	2220.935 (785.878)
Sex, *n* (%)			
Female	250 (44.014)	215 (43.788)	35 (45.455)
Male	318 (55.986)	276 (56.212)	42 (54.545)
Race, *n* (%)			
White	339 (59.683)	279 (56.823)	60 (77.922)
Black	127 (22.359)	124 (25.255)	3 (3.896)
Hispanic	62 (10.915)	52 (10.591)	10 (12.987)
Other	26 (4.577)	24 (4.888)	2 (2.597)
Unknown	14 (2.465)	12 (2.444)	2 (2.597)
Delivery type, *n* (%)			
Cesarean	360 (63.380)	318 (64.766)	42 (54.545)
Vaginal	205 (36.092)	171 (34.827)	34 (44.156)
Unknown	3 (0.528)	2 (0.407)	1 (1.299)
DOL PN, mean (SD)	5.873 (10.950)	5.843 (11.040)	6.065 (10.421)
Total PN days, mean (SD)	18.960 (21.579)	18.458 (21.574)	22.156 (21.476)
Surgery, *n* (%)			
No	238 (41.901)	209 (42.566)	29 (37.662)
Yes	330 (58.099)	282 (57.434)	48 (62.338)
Norman A, *n* (%)			
No	528 (92.958)	491 (100.000)	37 (48.052)
Yes	40 (7.042)		40 (51.948)
Norman B, *n* (%)			
No	535 (94.190)	491 (100.000)	44 (57.143)
Yes	33 (5.810)		33 (42.857)
Norman C, *n* (%)			
No	547 (96.303)	491 (100.000)	56 (72.727)
Yes	21 (3.697)		21 (27.273)
Any CHD, *n* (%)			
No	491 (86.444)	491 (100.000)	
Yes	77 (13.556)		77 (100.000)

Abbreviations: BW, birth weight; CHD, congenital heart disease; DOL, day of life; GA, gestational age; PN, parenteral nutrition.

Association of individual diagnoses with PNALD

Table 3 illustrates the hazard ratios and CIs for individual diagnosis of the Norman classification scheme. Notably, even at the typical definition of a single direct bilirubin measurement of >2 mg/dl, two diagnoses were found to be strongly associated with increased risk. From the severe categories, this includes coarctation of the aorta and, when considering minor diagnoses, atrial septal defects. Although several additional diagnoses provide bootstrapped point estimates that suggest increased risk for PNALD across the range of sensitivity analyses for its definition, we refrain from additional commentary on these, given wide CIs. We also note, for the 14- and 21-day cohorts,

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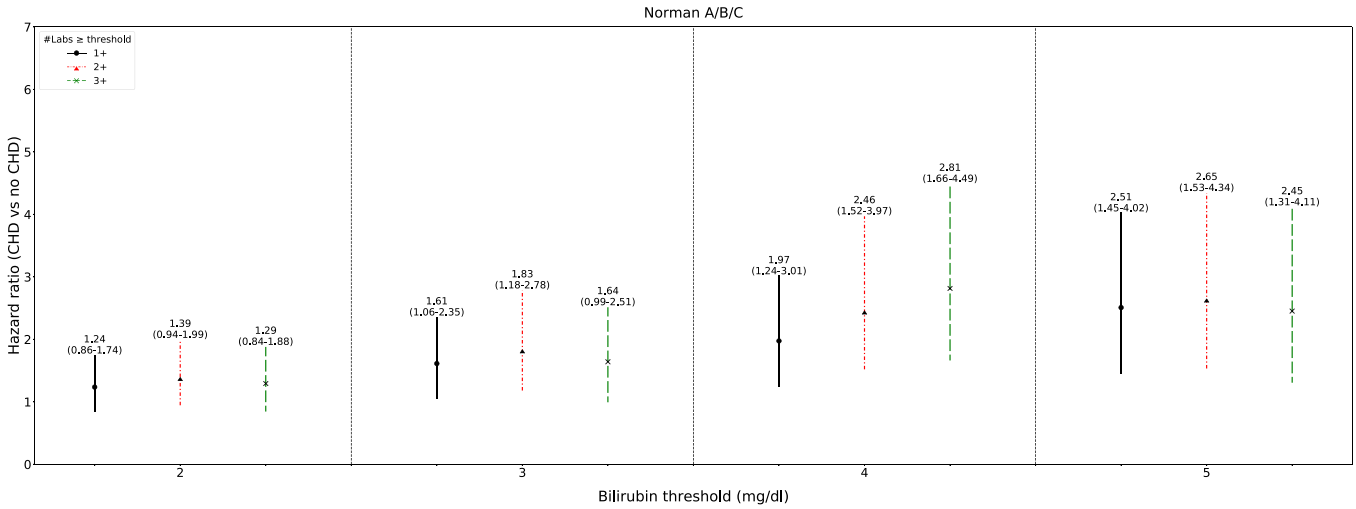

FIGURE 2 Hazard ratio and 95% CI for parenteral nutrition–associated liver disease (PNALD) in patients with CHD (reference level: no CHD) across a range of definitions for PNALD, considering CHD as only diagnoses within the Norman A, B, and C categories for the 14-day cohort. Each panel represents a configuration of the PNALD definition as a sensitivity analysis. Each major cell captures a specific bilirubin threshold (2–5 mg/dl). Within each cell, the results we provide the results for increasing the minimum number of laboratory values (one to three) required to be at or above the threshold (#Labs ≥ threshold) to have the infant be labeled as having PNALD. CHD, congenital heart disease.

the small cohort of patients with interrupted aortic arch had a low incidence of PNALD; as such, when stratified bootstrapping was performed for this effect size, these same patients were often selected and thus created the appearance of a highly confident low-risk cohort. Additional studies are needed to improve generalizability of this cohort.

DISCUSSION

This study presents evidence of an increased risk for PNALD in infants with CHD. Infants with CHD often require PN to meet elevated protein and energy needs.[33] However, PN administration can cause liver disease in a dose-dependent manner.[34] Based on established associations between CHD and biliary dysfunction,[35,36] we hypothesized that the underlying pathophysiology of infants with CHD may predispose patients to liver injury, resulting in higher observed odds of PNALD.

We found an increased risk of PNALD in infants diagnosed with CHD who received prolonged PN, even after excluding other conditions predisposing to direct hyperbilirubinemia. Moreover, hazard ratios between infants with and without CHD continue to increase with direct bilirubin threshold, with minimal difference at 2 mg/dl to a much larger difference between odds of PNALD at a higher threshold. This suggests infants in the non-CHD cohort may be equally likely to reach this level of injury, but not more likely, or that bilirubin levels may more commonly naturally fluctuate higher than 2 mg/dl because of other clinical factors not captured in this study.

Confidence in the conclusions drawn from these analyses strengthened as similar patterns were found when more than a single laboratory measurement was required for a PNALD diagnosis, suggesting a reliable PNALD diagnosis rather than a spurious laboratory result. As expected, there was a widening of CIs at the highest bilirubin levels and in definitions requiring three laboratory values. This was likely due to small sample sizes for these configurations. However, our sensitivity analysis exploring criteria requiring only 7 days of continuous PN usage (with a larger sample size) displays similar patterns.

We speculate that increased risk of PN exposure may be related to compromised right heart function, which, in turn, leads to an increased pressure gradient between portal venous and cardiopulmonary circulation, resulting in hepatic venous congestion and injury. However, additional studies are needed to confirm this pathophysiology. The wide CIs for several of the conditions in this work suggest that increased multi-institutional sample sizes are needed to isolate high-risk conditions from those with potentially unaccounted-for confounding in patient condition or care.

It is our hope that by identifying high-risk conditions a priori, PN protocols can be developed to prevent PNALD rather than treat the injury. Treatment of PNALD primarily consists of increasing enteral nutrition and decreasing PN. However, in cases for which this is not possible (eg, short bowel syndrome), decreasing exposure to soybean-based lipid formulations and instead using fish oil–containing lipid emulsions may result in fewer adverse events[37] and aid in resolving liver injury.[38,39] Starting such compounds earlier may be a reasonable approach in infants known to be at high risk. PN cycling may prevent or treat PNALD as well, but it is not often practiced in NICUs. However, more studies are needed because it is not known whether these approaches are efficacious in patients with both CHD and PNALD.

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TABLE 3 HRs and CIs of parenteral nutrition–associated liver disease risk for infants modeled at the diagnosis level.

	Diagnoses	Bilirubin threshold, mg/dl	One or more laboratory tests, HR (95% CI)	Two or more laboratory tests, HR (95% CI)	Three or more laboratory tests, HR (95% CI)
Norman A	Coarctation of aorta	2	0.81 (0.3–1.27)	0.99 (0.47–1.45)	0.74 (0.1–1.26)
		3	0.93 (0.34–1.43)	1.16 (0.55–1.67)	1.14 (0.39–1.72)
		4	1.16 (0.53–1.69)	1.42 (0.76–2.03)	1.52 (0.73–2.23)
		5	1.49 (0.82–2.09)	1.79 (1.08–2.45)	1.46 (0.33–2.28)
	Hypoplastic aortic arch	2	0.53 (−0.37 to 1.26)	0.48 (−0.63 to 1.39)	0.67 (−0.56 to 1.62)
		3	0.7 (−0.39 to 1.52)	0.79 (−0.48 to 1.68)	0.81 (−0.56 to 1.82)
		4	0.97 (−0.26 to 1.84)	1.51 (0.31 to 2.48)	1.44 (−0.01 to 2.44)
		5	1.19 (−0.09 to 2.11)	1.57 (0.16–2.45)	1.35 (−16.19 to 2.38)
	Interrupted aortic arch	2	−17.66 (−18.77–−16.97)	−17.63 (−18.31 to −16.62)	−17.59 (−18.05 to −16.46)
		3	−17.47 (−17.98 to −16.36)	−16.82 (−17.86 to −16.02)	−16.6 (−17.65 to −15.63)
		4	−16.67 (−17.74 to −15.84)	−16.35 (−17.2 to −15.21)	−16.3 (−16.86 to −15.04)
		5	−16.37 (−17.1 to −15.3)	−16.14 (−16.75 to −14.95)	−15.78 (−16.81 to −14.98)
Norman B	Pulmonary valve stenosis	2	0.12 (−0.95 to 0.94)	0.32 (−0.85 to 1.16)	0.42 (−0.68 to 1.29)
		3	0.49 (−0.64 to 1.34)	0.52 (−0.99 to 1.44)	0.44 (−16.83 to 1.42)
		4	0.74 (−0.6 to 1.72)	1.0 (−0.42 to 1.94)	0.79 (−16.59 to 1.79)
		5	0.74 (−16.63 to 1.72)	−0.17 (−17.57 to 0.89)	0.03 (−16.92 to 0.93)
Norman C	Double-outlet right ventricle	2	0.26 (−0.57 to 0.86)	0.3 (−0.87 to 1.01)	0.45 (−0.74 to 1.23)
		3	0.41 (−0.65 to 1.06)	−0.37 (−17.8 to 0.55)	−0.07 (−17.54 to 0.79)
		4	0.26 (−16.73 to 1.02)	0.12 (−17.35 to 1.04)	0.34 (−16.8 to 1.28)
		5	0.19 (−16.98 to 1.04)	0.45 (−16.83 to 1.34)	0.65 (−16.65 to 1.56)
Norman minor	Atrial septal defect	2	0.45 (0.1–0.77)	0.35 (−0.05 to 0.7)	0.37 (−0.07 to 0.73)
		3	0.71 (0.31–1.07)	0.53 (0.05–0.95)	0.57 (0.05–1.01)
		4	0.64 (0.13–1.04)	0.57 (0.01–1.04)	0.51 (−0.13 to 1.0)
		5	0.61 (0.06–1.06)	0.56 (−0.12 to 1.08)	0.61 (−0.12 to 1.14)
	Patent ductus arteriosus	2	−0.07 (−0.34 to 0.19)	−0.1 (−0.39 to 0.19)	0.01 (−0.3 to 0.31)
		3	−0.08 (−0.4 to 0.22)	−0.04 (−0.41 to 0.3)	0.19 (−0.19 to 0.55)
		4	0.11 (−0.26 to 0.46)	0.24 (−0.15 to 0.61)	0.37 (−0.06 to 0.77)
		5	0.24 (−0.16 to 0.63)	0.25 (−0.2 to 0.69)	0.52 (0.04 to 1.0)
	Ventricular septal defect	2	0.35 (−0.04 to 0.69)	0.01 (−0.46 to 0.4)	−0.14 (−0.67 to 0.28)
		3	0.4 (−0.05 to 0.78)	0.23 (−0.32 to 0.66)	0.02 (−0.71 to 0.53)
		4	0.17 (−0.42 to 0.65)	0.28 (−0.43 to 0.78)	0.23 (−0.56 to 0.78)
		5	0.21 (−0.52 to 0.74)	0.57 (−0.18 to 1.12)	−0.0 (−1.21 to 0.63)
	Systemic vein anomalies	2	0.55 (−0.71 to 1.52)	0.7 (−0.46 to 1.61)	0.9 (−0.44 to 1.75)
		3	0.52 (−16.21 to 1.44)	0.32 (−16.85 to 1.42)	0.59 (−16.64 to 1.65)
		4	0.99 (−15.76 to 1.87)	0.72 (−16.57 to 1.84)	0.97 (−16.48 to 2.03)
		5	0.81 (−16.6 to 1.87)	1.13 (−16.35 to 2.17)	1.22 (−16.16 to 2.17)
Other	Other Dx	2	0.06 (−0.42 to 0.5)	0.07 (−0.48 to 0.53)	−0.02 (−0.65 to 0.48)
		3	0.4 (−0.12 to 0.85)	0.47 (−0.14 to 0.96)	0.28 (−0.48 to 0.84)

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TABLE 3 (Continued)

Diagnoses	Bilirubin threshold, mg/dl	One or more laboratory tests, HR (95% CI)	Two or more laboratory tests, HR (95% CI)	Three or more laboratory tests, HR (95% CI)
	4	0.5 (−0.13 to 1.06)	0.61 (−0.12 to 1.19)	0.75 (0.01–1.36)
	5	0.84 (0.13–1.4)	0.65 (−0.13 to 1.26)	0.52 (−0.46 to 1.15)

Abbreviations: Dx, diagnosis; HR, hazard ratio.

Limitations

Given the retrospective, observational nature of this study, there are several limitations that should be considered. First, there is currently no universally agreed-upon clinical definition for PNALD.[3] Definitive diagnosis often requires pathology evaluation, which is uncommon in practice owing to risks related to liver biopsy and the possibility of false negative diagnoses.[40] Rather, current literature typically considers a direct bilirubin value of ≥2 mg/dl as cholestasis, yet emerging studies suggest this threshold may not be appropriate given the normal distribution of direct bilirubin levels and their percentage of total bilirubin based on DOL.[41] The sensitivity analysis we present around a range of bilirubin thresholds from 2 to 5 mg/dl should aid in improving the reliability of study results. Finally, the definition of PNALD is often a diagnosis of exclusion. Although steps were taken to exclude comorbid diagnoses and surgical procedures known to impact hepatic function, it is challenging to disentangle the course of care for neonates with CHD, which may impact bilirubin levels (eg, medication usage and blood transfusions), from the impact of the underlying CHD pathology. As such, there may exist uncontrolled variance that could be standardized across future prospective work.

Second, all data were collected from a single clinical center and likely reflect local institutional practices, including the use of specific lipids and/or timing of use as well as decreased variability across respective diagnoses represented in this study, which necessarily limits generalizability.

Third, the classification of CHD is structured using the Norman categories, which represent anatomic groupings. It is possible that other functional groupings better explain the association between CHD and elevated bilirubin in neonates exposed to PN.

Finally, owing to institutional practices for HLHS, infants with HLHS were excluded from this study because of their extended time in the PICU and surgical intervention. This, in turn, reduces the sample size of participants with Norman category A CHD and may impact the overall effect size if comparing Norman categories.

CONCLUSION

This study identifies CHD as an important and independent risk factor in the development and magnitude of direct hyperbilirubinemia associated with PN use. In the absence of definitive treatment options, patients with CHD would benefit from increased surveillance to identify PNALD earlier and from other mitigating strategies such as early adoption of alternative lipid emulsions or PN cycling. Moreover, an understanding of PNALD risk extends beyond direct injury—as postoperative PN has previously been associated with direct hyperbilirubinemia in children with CHD—and, in turn, was associated with increased mortality and prolonged length of hospital stay.[42] Further studies are needed to explore the impact of these mitigating strategies and to evaluate long-term developmental and clinical outcomes.

AUTHOR CONTRIBUTIONS

Keith Feldman, Christopher R. Nitkin, and Ryan Fischer conceptualized the study. Keith Feldman, Alexandra Oschman, Ayan Rajgarhia, and Yasasvhinie Santharam collected and curated the data. Keith Feldman and Yasasvhinie Santharam performed analyses. Keith Feldman, Yasasvhinie Santharam, Alexandra Oschman, Christopher R. Nitkin, Ayan Rajgarhia, and Ryan Fischer interpreted results. All authors contributed to the writing of the manuscript and approved the final draft.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available, as they contain detailed aspects of personal health information but are available upon request to the corresponding author.

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SUPPORTING INFORMATION

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