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Original Article

Worse outcomes and distinct clinical features in infants with necrotizing enterocolitis and congenital heart disease

Yan Liao, Xiaobi Liang, Yan Guo, Ye Lu, Xumei Liu, Shan Li, Shangqiu Tang, Li Wang, Jianru Li

Heart Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China

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Abstract: Objective: This study aimed to compare the clinical characteristics and outcomes in infants with necrotizing enterocolitis (NEC) with and without congenital heart disease (CHD) and to further evaluate the impact of isolated patent ductus arteriosus (PDA) on NEC severity. Methods: A retrospective cohort study involving 165 infants diagnosed with NEC at our center from January 2015 to April 2025 was conducted. Patients were stratified into two groups: those with CHD (n=75) and those without CHD (n=90). Demographic, clinical, laboratory, and outcome data were collected. Intergroup comparisons were performed using nonparametric and chi-square tests. Univariate and multivariate logistic regression analyses were employed to identify factors associated with severe outcomes. Results: Compared with infants without CHD, infants with CHD had significantly younger gestational ages (median [IQR]: 30.2 [28.5-32.1] vs. 32.5 [31.0-34.0] weeks, P<0.01) and birth weights (1250 [980-1500] vs. 1580 [1350-1820] grams, P<0.01), longer durations of respiratory support (15 [10-25] vs. 8 [5-12] days, P<0.01), longer hospital stays (45 [35-60] vs. 32 [25-40] days, P<0.01), and greater mortality (28.0% vs. 11.1%, P<0.01). Notably, the severity of NEC (Bell's stage II/III) did not differ significantly between infants with isolated PDA and those with other forms of CHD (65% vs. 68%, P=0.82). Multivariate analysis revealed lower serum albumin levels and thrombocytopenia at onset as potential early indicators for adverse outcomes in the CHD group. Conclusions: NEC in infants with CHD is associated with a more severe clinical course and poorer prognosis. Compared with other CHD types, the presence of isolated PDA does not confer an additional risk for more severe NEC.

Keywords: Neonatal necrotizing enterocolitis, congenital heart disease, NEC

Introduction

Neonatal necrotizing enterocolitis (NEC) is a common neonatal gastrointestinal disease and a leading cause of morbidity and mortality in neonates, particularly among preterm infants [1-5]. Its pathogenesis involves a complex interplay of intestinal immaturity, microbial dysbiosis, and compromised mucosal barrier function, often triggered by ischemic injury. While the majority of cases (90%) occur in premature infants, the remaining 10% affect full-term infants [2, 6]. In infants with CHD, the incidence of NEC is notably high, ranging from 3% to 11%, with mortality rates reported between 13% and 57% [7, 8]. This variant, often termed CHD-associated NEC (CHD-NEC), is thought to arise primarily from mesenteric hypoperfusion due to altered systemic hemodynamics, positioning it as a pathophysiologically unique entity compared with classic prematurity-associated NEC [9]. However, the clinical profile and determinants of outcomes in CHD-NEC patients have not been fully delineated. The literature presents conflicting evidence; some studies report significantly increased mortality in patients with CHD-NEC compared with those with NEC without CHD [9, 10], while others find no such difference [1, 11]. Crucially, the effects of specific CHD types, particularly the role of isolated patent ductus arteriosus (PDA), a common lesion with significant hemodynamic consequences, on NEC severity remain poorly investigated. Furthermore, reliable early diagnostic markers for identifying CHD infants at the highest risk for severe NEC are lacking.

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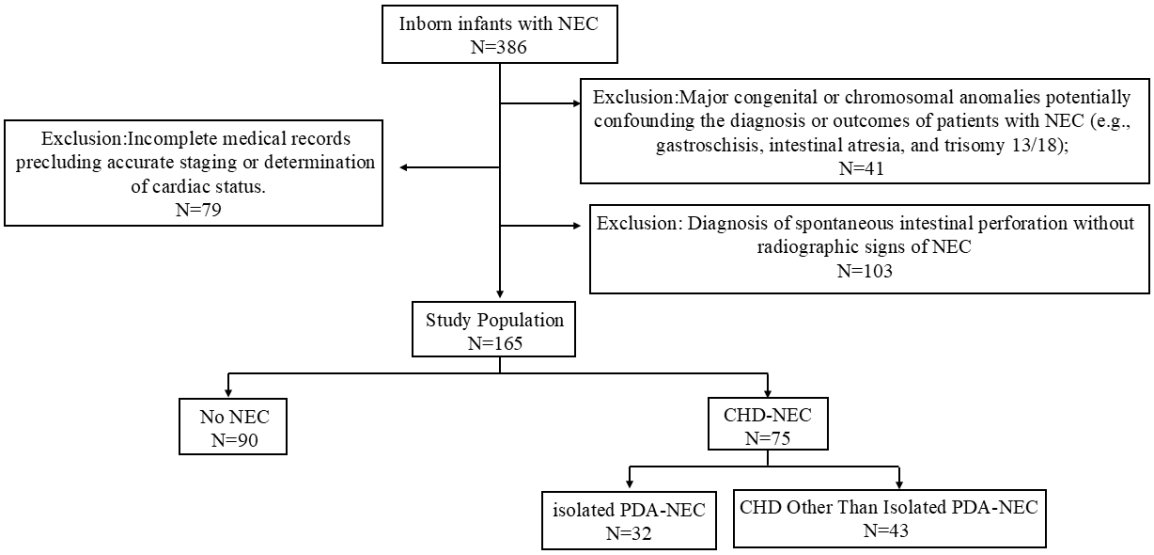

Figure 1. The Patient Flow Diagram. A total of 386 infants with a diagnosis of NEC were initially identified between January 2015 and April 2025. Of these, 221 infants were excluded for the following reasons: 41 were excluded due to major congenital or chromosomal anomalies potentially confounding the diagnosis or outcomes of patients with NEC (e.g., gastroschisis, intestinal atresia, and trisomy 13/18); 103 were excluded due to diagnosis of spontaneous intestinal perforation without radiographic signs of NEC; and 79 were excluded due to Incomplete medical records precluding accurate staging or determination of cardiac status. Consequently, 165 infants met all inclusion criteria and constituted the final study cohort, among that, there were 75 patients with CHD, 32 had an isolated moderate-to-large patent ductus arteriosus (PDA), while 43 had a significant cardiac anomaly that was associated or independent of a PDA.

Therefore, a clearer understanding of the clinical course and prognostic factors specific to NEC in the CHD population is urgently needed to guide risk stratification and management. This retrospective cohort study aimed to (1) comprehensively compare the clinical characteristics, management course, and outcomes between preterm infants with NEC and CHD and those without CHD; (2) evaluate whether the presence of isolated PDA confers a different risk profile for NEC severity than other CHD types; and (3) explore potential early laboratory indicators associated with adverse outcomes in patients with CHD-NEC. By addressing these gaps, our findings provide valuable insights into early recognition and tailored clinical intervention in this vulnerable population.

Methods

Study design and patient selection

This was a single-center, retrospective cohort study conducted at Guangzhou Women and Children's Medical Center. The study protocol was approved by the Institutional Review Board/Ethics Committee of Guangzhou Women and Children's Medical Center (No. 089A01). The requirement for informed consent was waived.

Cohort identification

To efficiently identify the study population, we first screened all infants diagnosed with necrotizing enterocolitis (NEC) who were admitted to our neonatal intensive care unit (NICU) between January 2015 and April 2025. Patients were identified using the International Classification of Diseases (ICD) code for NEC ([ICD-10 P77.1]).

Inclusion criteria

From this initial NEC cohort, infants were included for final analysis if they met all of the following criteria: 1. NEC diagnosis was confirmed by modified Bell's staging criteria [12], requiring both clinical signs and radiographic evidence. 2. Availability of a definitive cardiac status assessment: A complete echocardiogram report or cardiology consultation note was required to reliably determine the presence or absence of congenital heart disease (CHD) (**Figure 1**).

Exclusion criteria

Infants were excluded if any of the following applied: 1. Major congenital or chromosomal anomalies potentially confounding the diagnosis or outcomes of patients with NEC (e.g., gastroschisis, intestinal atresia, and trisomy 13/18); 2. Diagnosis of spontaneous intestinal perforation without radiographic signs of NEC; 3. Incomplete medical records precluding accurate staging or determination of cardiac status (**Figure 1**).

Study groups

The included NEC patients were then stratified into two cohorts on the basis of the presence or absence of CHD documented prior to NEC onset: 1. CHD-NEC group (exposed): NEC infants with any echocardiographically confirmed congenital heart disease. 2. Non-CHD-NEC group (unexposed): NEC infants with a normal echocardiogram, confirming that there was no structural heart disease.

Within the CHD-NEC group, a prespecified subgroup analysis was conducted to compare two distinct phenotypes: 1. Isolated PDA subgroup: Infants whose only cardiac anomaly was a hemodynamically significant patent ductus arteriosus (PDA), with no other major structural heart defects. 2. Other CHD subgroup: Infants with significant congenital heart disease other than or in addition to a PDA (e.g., septal defects, coarctation of the aorta, and total anomalous pulmonary venous connection).

This subgroup comparison was motivated by prior literature suggesting that compared with NEC associated with more complex cardiac lesions, NEC in the context of an isolated PDA might have a distinct pathophysiology and clinical course.

Data extraction and management

A standardized electronic data collection form was developed and piloted. To ensure accuracy and minimize bias, two independent researchers (Liao Yan and Liang Xiaobi) who were blinded to the study's analytical hypotheses extracted all the data from the electronic medical records (EMR). Any discrepancies between the two extractors were resolved through discussion or, if necessary, adjudication by a senior attending neonatologist (Li Jianru and Wang Li).

The extracted data encompassed the following domains:

1. Demographics and perinatal characteristics: Gender, gestational age, birth weight, Apgar scores at 1, 5 and 10 minutes, and mode of delivery.

2. NEC characteristics and management: Age at NEC diagnosis, Bell's stage at diagnosis and maximum stage during hospitalization, and need for and type of surgical intervention.

3. Cardiac status: Presence and specific type of congenital heart disease (CHD). As defined in the patient selection criteria, patients with only a tiny-to-small patent ductus arteriosus (PDA) or a patent foramen ovale (PFO) were classified under the non-CHD group for analysis, as these are considered normal physiological variants in neonates without hemodynamic significance [9].

4. Laboratory parameters: Biochemical data from the onset of NEC symptoms until clinical recovery or surgery were recorded. These included serial measurements of the leukocyte count, platelet count, hemoglobin level, serum albumin level, fibrinogen level, C-reactive protein (CRP) level, lactate level, pH, pO_2, and pCO_2. Both the values at NEC diagnosis and the most abnormal values (peak or nadir) during the acute phase were extracted for analysis.

5. Outcomes: Mortality and complications, including intestinal perforation, short bowel syndrome, wound dehiscence, sepsis, recurrent NEC, intestinal stricture, and the need for enterostomy.

Outcome measures

On the basis of clinical relevance and literature, the outcomes were specified as follows:

Primary outcome: A composite outcome of severe NEC, defined as either progression to Bell's stage III (with pneumoperitoneum) or the need for surgical intervention (laparotomy).

Secondary outcomes: 1. All-cause in-hospital mortality. 2. NEC-related complications (as listed in Section 2.2). 3. Duration of intensive care

Table 1. Types and frequencies of CHDs in the group of 75 infants with NEC

CHD	n	Additional Defects
Isolated PDA	32	-
CoA	7	4PDA; 2VSD, PDA; 1VSD, PDA, PFO
Tetralogy of fallot	6	6PDA
TAPVC	5	4ASD; 1PFO
Aortopulmonary window	4	2PDA, ASD; 2PFO
PA/IVS	4	4PDA
PA/VSD	3	3PDA
PS	3	3PDA, PFO
DORV	3	2PFO, 1PDA/ASD
VSD	3	1PFO; 2PDA, PFO
ASD	3	3PDA
PAPVC	1	1ASD
SA/SV	1	1PS

CoA, coarctation of the aorta; VSD, ventricular septal defect; TAPVC, total anomalous pulmonary venous connection; PA/IVS, pulmonary atresia with intact ventricular septum; PA/VSD, pulmonary atresia with ventricular septal defect; PS, pulmonary stenosis; ASD, atrial septal defect; PAPVC, partial anomalous pulmonary venous connection; SA/SV, single atrium/single ventricle; DORV, double outlet right ventricle; PFO, patent foramen ovale; PDA, patent ductus arteriosus.

support (e.g., days of mechanical ventilation). 4. Total length of hospital stay.

Statistical analysis

The data were analyzed using SPSS statistics 23 (IBM Corp. Armonk, New York, N.Y., USA). The Student's t test and Chi-square test were used for parametric and nonparametric continuous variables between patients with NEC with or without CHD, using the mean ± standard deviation for normally distributed data or the median (minimum-maximum) for nonnormally distributed data. *P* values <0.05 were considered to indicate statistical significance. Missing data were deleted pairwise. Categorical variables were compared using the Chi-square test or Fisher's exact test, while continuous variables were compared using the Student's t test or the Chi-square test. Univariate and multivariate logistic regression analyses were performed for each outcome, with adjustments for birth weight, gestational age and age at diagnosis. The CHD group was divided into the hsPDA group and the other CHD group, excluding the isolated PDA group, with corresponding analyses conducted in these subgroups. Risk was expressed as an odds ratio (OR) with 95% confidence intervals.

All the statistical analyses were performed using IBM SPSS Statistics (version 23.0; Armonk, NY, USA). A two-tailed *p* value <0.05 was considered to indicate statistical significance.

Missing data

The extent of missing data for each key variable was assessed. In the primary analysis, cases with missing data for variables included in a specific model were excluded pairwise. The potential impact of missing data was considered in the interpretation of the results.

Results

CHD characteristics

The various types of congenital heart defects are presented in **Table 1**. Among the 75 patients with CHD, 32 had an isolated moderate-to-large patent ductus arteriosus (PDA), while 43 had a significant cardiac anomaly that was associated with or independent of a PDA. These anomalies included ventricular septal defects (VSDs), atrial septal defects (ASDs), coarctation of the aorta (CoA), total anomalous pulmonary venous connection (TAPVC), partial anomalous pulmonary venous connection (PAPVC), pulmonary atresia with an intact ventricular septum (PA/VSD), a double outlet right ventricle (DORV), an aortopulmonary window, pulmonary atresia with an intact ventricular septum (PA/IVS) and a single atrium/single ventricle (SA/SV), as shown in **Table 1**.

Patient characteristics

There were large differences among the CHD-NEC and PT-NEC groups in terms of sex, gestational age, birth weight, Apgar score, age at diagnosis of NEC, NEC stage, need for surgery, mortality rate, average hospitalization period and use of respiratory support (**Table 2**). Both cohorts were predominantly male. Compared with the CHD group (NEC diagnosis at a mean of 35 days), the PT group presented with an NEC diagnosis at a mean of 11 days, which was

Table 2. Demographic and clinical comparisons of patients with and without congenital heart disease (CHD)

	CHD-NEC N=75	PT-NEC N=90	*p* value
Gender (M)	39 (52%)	69 (76.67%)	0.001
Average gestational age (weeks)	31.27±4.34	33.72±3.61	<0.001
Average birth weight (g)			0.003
<1000 g	19 (25.33%)	7 (7.78%)	
1000-1500 g	25 (33.33%)	22 (24.44%)	
1501-2500 g	18 (24%)	36 (40%)	
>2500 g	13 (17.33%)	25 (27.78%)	
Apgar score at			
1 min	8 [7, 9]	9 [9, 10]	<0.001
5 min	9 [8, 10]	9 [9, 10]	<0.001
10 min	9 [9, 10]	10 [10, 10]	<0.001
Delivery method			0.771
Vaginal	30 (40%)	34 (37.78%)	
C-section	45 (60%)	56 (62.22%)	
Age at diagnosis (days)	35.29±14.16	11.04±7.37	<0.001
Bell's criteria classification			<0.001
IA	4 (5.33%)	14 (15.56%)	
IB	5 (6.67%)	8 (8.89%)	
IIA	14 (18.67%)	36 (40%)	
IIB	13 (17.33%)	14 (15.56%)	
IIIA	14 (18.67%)	12 (13.33%)	
IIIB	25 (33.33%)	6 (6.67%)	
Surgical intervention for NEC	67 (89.33%)	38 (42.22%)	<0.001
NEC mortality rate	18 (24.00%)	4 (4.44%)	<0.001
The average hospitalization period	56 [33, 97]	25 [16, 35]	<0.001
The average respiratory supporting time	26 [13, 63]	2 [0, 8]	<0.001

a significantly earlier timepoint (P<.001). The average gestational age was also greater in the PT group than that in the CHD group ([31.27±4.34] vs. [33.72±3.61] weeks, P<.001). Additionally, the distribution of Bell's stage in this group ranged extensively from a predominant stage IIIB (CHD) to an IIA (PT) (33.33% vs. 40%, P<.001). The delivery mode did not significantly differ between the groups. The incidence of surgical intervention (89% vs. 42%, P<.001) and mortality rates (24% vs. 4%, P<.001) significantly increased.

In addition, the clinical characteristics of infants with and without CHD were compared, and more importantly, patients with CHD were classified into two subgroups: those with isolated moderate-to-large patent ductus arteriosus (hsPDA group) and those with more complex cardiac lesions (CHD group other than isolated PDA). The average gestational age of infants in the CHD group other than the isolated PDA group was significantly greater than that in the hsPDA group ([32.86±4.18] vs. [29.14±3.63] weeks, P<.001). Moreover, the birth weights of infants in the CHD group, but not in the isolated PDA group, were significantly greater than those in the hsPDA group (P<.004). A difference in the distribution method was also discovered between the two subgroups (P=.045), with a higher proportion having undergone cesarean section in the CHD group than that in the isolated PDA group. However, there were no significant differences between the two subgroups in terms of sex, Apgar score, age at NEC diagnosis, NEC stage, NEC surgical intervention, NEC mortality, average hospitalization period or average respiratory support time (**Table 3**).

Table 3. Demographic and clinical comparison of patients with NEC with isolated PDA and those with CHD other than isolated PDA

	Isolated PDA-NEC N=32	CHD Other Than Isolated PDA-NEC N=43	*p* value
Gender (M)	16 (50%)	23 (53.49%)	0.765
Average gestational age (weeks)	29.14±3.63	32.86±4.18	<0.001
Average birth weight (g)			0.004
<1000 g	14 (43.75%)	5 (11.63%)	
1000-1500 g	11 (34.38%)	14 (32.56%)	
1501-2500 g	5 (15.63%)	13 (30.23%)	
>2500 g	2 (6.25%)	11 (25.58%)	
Apgar score at			
1 min	8 [6, 9]	8 [7, 9]	0.677
5 min	9 [8, 10]	9 [9, 10]	0.616
10 min	9 [9, 10]	9 [9, 10]	0.750
Delivery method			0.045
Vaginal	17 (53.13%)	13 (30.23%)	
C-section	15 (46.88%)	30 (69.77%)	
Age at diagnosis (days)	35.47±12.4	35.16±15.48	0.927
Bell's criteria classification			0.943
IA	1 (3.13%)	3 (6.98%)	
IB	2 (6.25%)	3 (6.98%)	
IIA	6 (18.75%)	8 (18.60%)	
IIB	7 (21.88%)	6 (13.95%)	
IIIA	6 (18.75%)	8 (18.60%)	
IIIB	10 (31.25%)	15 (34.88%)	
Surgical intervention for NEC	29 (90.63%)	38 (88.37%)	1.000
NEC mortality rate	8 (25%)	10 (23.26%)	1.000
The average hospitalization period	63 [27, 108]	54 [35, 89]	0.403
The average respiratory supporting time	25 [14, 69]	28 [12, 59]	0.479

Data are presented as the mean ± S.D. (for normally distributed data) or the median (range) (for nonnormally distributed data).

Laboratory findings

Leukocyte and CRP levels were significantly greater in the CHD group than those in the PT group (10.3 [7.8, 16.2] vs. 7.8 [5.3, 11.2], P<.001; 55.7 [16.2, 90.4] vs. 10.8 [3.6, 30.1], P<.001, respectively). In contrast, the levels of thrombocytes and hemoglobin were lower in the CHD group than those in the PT group (131 [100, 183] vs. 305 [259, 379], P<.001; 108 [93, 121] vs. 115 [102.8, 139], P=0.013, respectively). The albumin and fibrinogen levels in the CHD group decreased (25 [21.3-27.9] vs. 33.4 [31.2, 35.7], P<.001; 2.4 [1.8, 4.0] vs. 3.2 [2.3, 4.2], P=0.006, respectively). The CHD group had lower pH values and higher pCO_2 levels than those in the PT group (7.36 [7.31, 7.42] vs. 7.32 [7.37, 7.36], P<.001; 5.6 [4.7, 7.2] vs. 4.5 [3.9, 5.4], P<.001, respectively). Serum pO_2 and lactate levels were similar between the groups. The biochemical data are shown in **Table 4**. In addition, no significant differences were observed among CHD types, such as those in the isolated PDA group and the hsPDA group, shown in **Table 5**.

Outcomes

Univariate analyses indicated that neonates with CHD had better short- and long-term outcomes with respect to NEC than those without CHD, as shown in **Table 6**. In particular, compared with the PT group, the CHD group had significantly greater risks of perforation (OR: 6.57 [95% CI: 3.23-13.34]), stricture development (OR: 2.45 [95% CI: 1.20-5.04]), stoma requirements (OR: 5.93 [95% CI: 2.39-14.78]),

Table 4. Biological data between patients with and without congenital heart disease (CHD)

	CHD-NEC	PT-NEC	*p* value
Leukocytes (×10^9/L)	10.3 [7.8, 16.2]	7.8 [5.3, 11.2]	<0.001
Thrombocytes (×10^9/L)	131 [100, 183]	305 [259, 379]	<0.001
CRP (mg/L)	55.7 [16.2, 90.4]	10.8 [3.6, 30.1]	<0.001
Hemoglobin (mmol/L)	108 [93, 121]	115 [102.8, 139]	0.013
Albumin (g/L)	25 [21.3, 27.9]	33.4 [31.2, 35.7]	<0.001
Fibrinogen (g/L)	2.4 [1.8, 4.0]	3.2 [2.3, 4.2]	0.006
pH	7.36 [7.31, 7.42]	7.42 [7.37, 7.46]	<0.001
pO_2 (kPa)	9.1 [7.3, 10.7]	9.7 [8.4, 12.0]	0.061
pCO_2 (kPa)	5.6 [4.7, 7.2]	4.5 [3.9, 5.4]	<0.001
Lactate (mmol/L)	2.4 [1.2, 3.6]	2 [1.3, 3.0]	0.311

Data are presented as the mean ± S.D. (for normally distributed data) or the median (range) (for nonnormally distributed data).

Table 5. Biological data comparison of patients with NEC with isolated PDA and those with CHD other than isolated PDA

	Isolated PDA-NEC	CHD Other Than Isolated PDA-NEC	*p* value
Leukocytes (×10^9/L)	9.6 [5.1, 15.5]	11.6 [9, 16.4]	0.069
Thrombocytes (×10^9/L)	131.5 [79, 190]	131 [105, 180]	0.781
CRP (mg/L)	60.2 [17.2, 95.6]	54.9 [15.6, 89.2]	0.630
Hemoglobin (mmol/L)	99.5 [94.3, 114.5]	113 [93, 143]	0.069
Albumin (g/L)	25.6 [21.7, 27.9]	23.7 [21.1, 27.6]	0.343
Fibrinogen (g/L)	2.4 [1.9, 3.9]	2.4 [1.8, 4.1]	0.979
pH	7.34 [7.27, 7.40]	7.39 [7.33, 7.43]	0.048
pO_2 (kPa)	9.4 [7.5, 11.6]	9 [7.3, 10.3]	0.301
pCO_2 (kPa)	5.9 [4.8, 7.5]	5.4 [4.5, 6.5]	0.179
Lactate (mmol/L)	2.4 [1.1, 4.0]	2.4 [1.4, 3.6]	0.756

Data are presented as the mean ± S.D. (for normally distributed data) or the median (range) (for nonnormally distributed data).

Table 6. Risk of NEC-specific outcomes for subjects with and without CHD

Outcome	NEC With CHD (N=75), n (%)	NEC Without CHD (N=90), n (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)[a]	Multivariate OR (95% CI)[b]
Perforation (post-NEC)	44 (58.7%)	16 (17.88%)	6.57 (3.23-13.34)*	2.94 (1.20-7.16)*	1.78 (0.40-7.95)
Short bowel syndrome	9 (12%)	5 (5.56%)	2.32 (0.74-7.25)	0.50 (0.11-2.30)	0.35 (0.03-4.09)
Wound dehiscence	7 (9.33%)	0 (0%)	Not estimable[c]	Not estimable[c]	Not estimable[c]
sepsis	18 (24%)	3 (3.33%)	6.79 (2.19-21.10)*	1.49 (0.27-8.41)	2.91 (0.13-65.47)
Recurrent NEC	5 (6.67%)	5 (5.56%)	1.21 (0.34-4.36)	0.38 (0.06-2.29)	2.05 (0.13-32.08)
Stricture	26 (34.67%)	16 (17.78%)	2.45 (1.20-5.04)*	2.33 (0.93-5.84)	3.13 (0.64-15.28)
Need for stoma	25 (33.33%)	7 (7.78%)	5.93 (2.39-14.78)*	4.27 (1.28-12.32)*	6.42 (1.23-33.60)*
Death from NEC	17 (22.7%)	4 (4.44%)	6.30 (2.02-19.68)*	2.61 (0.49-14.05)	1.21 (0.06-23.75)

[a]Multivariate model including birth weight and gestational age. [b]Multivariate model including birth weight, gestational age, and age at diagnosis. [c]OR cannot be estimated due to the 0 occurrence of wound dehiscence in the NEC without CHD group. *P<0.05.

sepsis (OR: 6.79 [95% CI: 2.19-21.10]), and NEC-related mortality (OR: 6.30 [95% CI: 2.02-19.68]). There was also a trend toward an increased risk of recurrent NEC (OR: 1.21 [95% CI: 0.34-4.36], short bowel syndrome (OR: 2.32 [95% CI: 0.74-7.25], and wound dehiscence (OR

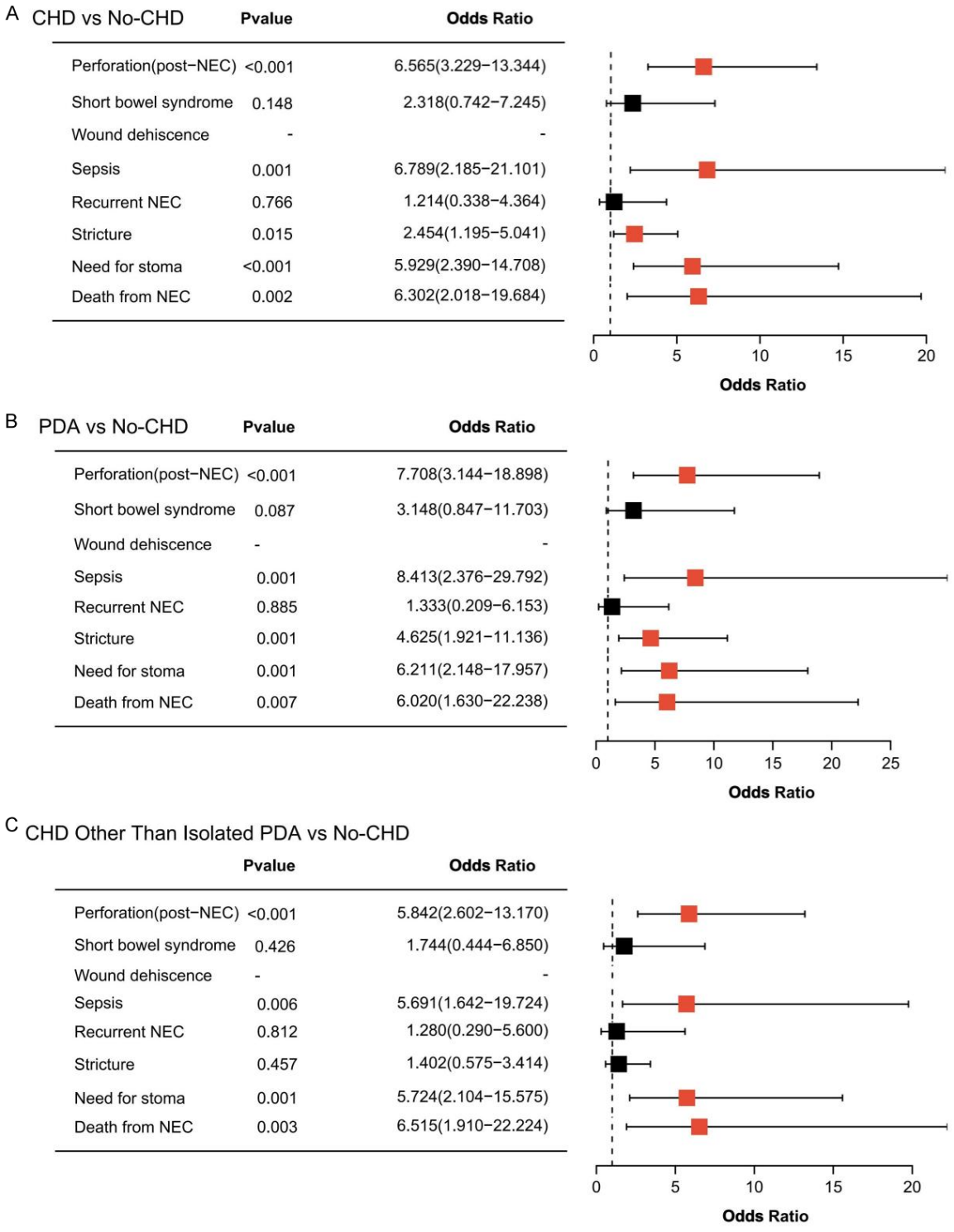

Figure 2. Comparison of Univariate Risk (OR) of NEC-Specific Outcomes for All Subjects with CHD, for Isolated Medium-to-Large PDA, and for CHD Other Than Isolated PDA. A: CHD vs. No-CHD; B: PDA vs. No CHD; C: CHD Other Than Isolated PDA vs. No CHD.

not estimable because there were 0 cases of SBS in the PT-NEC group); however, these associations did not meet statistical significance, as shown in **Figure 2A**. Taken together, these

data indicated a trend toward an increased risk of NEC-associated death and morbidity in the context of CHD.

Similar findings were found for the prediction of NEC according to the results of univariate regression analysis of CHD subgroups, such as the hsPDA group and CHD group, but not for the isolated PDA subgroup. Compared with the PT-NEC group, both the combined group and the multiple-site group had substantially increased risks of complications, including perforation, sepsis, the need for stoma formation, and mortality from NEC (P<.05 for both). There was also a trend toward higher rates of developing short bowel syndrome, recurrent NEC, and intestinal stenosis; however, this difference failed to reach statistical significance, as shown in **Figure 2B**.

Multivariate analysis revealed that CHD-NEC was associated with an increased risk of perforation, sepsis, stricture, need for stoma and death from NEC and lower odds of recurrent NEC and short bowel syndrome. The multivariate model adjusted for age at diagnosis significantly increased the probability of stoma requirement. Furthermore, the risk of sepsis, recurrent NEC and stricture increased without statistical significance, whereas the risk of perforation, SBS and mortality decreased, as shown in **Figure 2C**.

Discussion

Our study confirms and extends the well-established association between congenital heart disease (CHD) and adverse outcomes in patients with necrotizing enterocolitis (NEC). Consistent with the study by Pickard et al. [11], which showed a severe increase in mortality risk for NEC infants with CHD, our cohort demonstrated significantly higher mortality, longer respiratory support, and extended hospitalization in CHD-NEC infants compared with non-CHD infants [11]. This, along with broader evidence, includes a large single-center study reporting an odds ratio of 7.39 for in-hospital death in preterm infants with CHD [2, 10, 11]. The more severe clinical course we observed underscores that CHD is not merely a comorbidity but a primary driver of NEC severity, supporting the concept of “cardiogenic NEC” as a distinct clinical entity with a unique pathophysiology centered on mesenteric hypoperfusion [2, 13-16].

The most significant and novel finding of our analysis pertains to the role of an isolated patent ductus arteriosus (PDA). In contrast to the assumption that PDA might exacerbate NEC severity through diastolic “steal” phenomena, our data revealed no significant difference in the risk of severe NEC between infants with isolated PDA and those with other forms of CHD. These findings are in direct agreement with the conclusions of Pickard et al. [11], who also reported that isolated PDA was not an independent risk factor for mortality or surgical intervention in their multivariable model. This finding suggests that within the high-risk context of established NEC in CHD infants, the specific contribution of an isolated PDA to disease progression may be overshadowed by the overarching hemodynamic instability common to all cardiac lesions.

Many researchers have clarified the influence of PDA on the hemodynamic and systemic transition in the neonatal stage [11, 17, 18]. The pathophysiological rationale for our findings likely lies in the shared hemodynamic vulnerability of all infants with CHD who develop NEC. While a hemodynamically significant PDA can cause systemic diastolic runoff and reduced postductal blood flow, other complex cardiac lesions (e.g., single-ventricle physiology, left-sided obstructive lesions) induce equally severe or worse states of low cardiac output and systemic hypoperfusion. A study by Diez et al. [14] provided compelling evidence that compared with preterm infants without cardiac disease, both the PDA-NEC subgroup and the CHD-NEC subgroup exhibited significantly impaired intestinal perfusion and dramatically higher odds of extensive bowel necrosis, indicating a common final pathway of ischemic injury [14]. Therefore, during the acute crisis of NEC, the dominant driver of intestinal injury in all infants with CHD may be this shared state of compromised systemic and splanchnic perfusion, potentially masking any incremental risk attributable to the specific hemodynamics of an isolated PDA. This unified hemodynamic insult hypothesis could explain why, in our cohort and others, the presence of an isolated PDA did not confer additional prognostic weight once NEC was established.

Some studies have reported a possible relationship between increasing rates of cesarean section and the incidence of NEC [19]. We analyzed the mode of delivery of neonates in the CHD group and PT group. The results revealed that the CHD group, especially children with complex congenital heart disease, was more likely to be delivered by cesarean section, whereas the PT group had a higher probability of natural delivery; however, there was no significant difference between the two groups.

In this report, the diagnostic markers in these children were investigated. In line with the findings of previous studies [1, 20], we observed that children with chronic heart disease and necrotizing enterocolitis (CHD-NEC) had more severe inflammatory reactions, with elevated WBCs and CRP levels. These findings suggest that inflammatory responses might be involved in the pathogenesis of CHD-NEC. In addition, lower platelet counts were significantly associated with poor survival in patients with NEC. We discovered significantly lower platelet counts in the CHD cohort compared with the PT cohort, which were associated with mortality in the CHD cohort. In addition, we found that the albumin content in the CHD group was significantly lower than that in the PT group. We speculated that the decreased platelet counts and albumin levels represented unique markers of NEC and that the degree of decrease was significantly correlated with poor prognosis.

The current study is limited by its single-center retrospective nature and small number of patients. Further larger-sized or multicenter studies are expected to validate the outcomes of NEC in infants with CHD.

Conclusions

Our analysis revealed certain characteristic differences between infants with NEC who have CHD and those with traditional NEC. Compared with those with normal NEC, preterm infants with NEC who have congenital heart disease had younger gestational ages, lower birth weights, longer durations of respiratory support and hospital stay, worse prognoses, and higher mortality rates. Notably, the prevalence of NEC did not significantly differ between patients with isolated patent ductus arteriosus (PDA) and those with knee-deep congenital heart disease excluding PDA. In addition, serum albumin levels and thrombocytopenia might be potential early diagnostic markers for NEC in preterm infants with congenital heart disease. However, owing to the retrospective nature of the analysis and the small sample size, some of the findings should be further explored. Studies with larger sample sizes or multicenter designs are needed to better understand this patient group.

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Disclosure of conflict of interest

None.

Address correspondence to: Jianru Li and Li Wang, Heart Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China. Tel: +86-020-38076586; E-mail: ljr1622@163.com (JRL); wangli-1227@163.com (LW)

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