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ORIGINAL RESEARCH

Risk Factors of Chylothorax After Congenital Heart Surgery in Infants: A Single-Centre Retrospective Study

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Background: Studies of chylothorax after congenital heart disease in infants are rare. Chylothorax has a higher incidence in infancy, but its risk factors are not well understood.

Objective: The purpose of this study is to investigate the risk factors of chylothorax after congenital heart surgery in infants.

Methods: This retrospective study included 176 infants who underwent congenital heart disease surgery at the Guangdong Cardiovascular Institute, China, between 2016 and 2020. According to the occurrence of chylothorax, the patients were divided into a control group (n = 88) and a case group (n = 88). Univariate and multivariate logistic regression were performed to analyse the incidence and influencing factors of chylothorax after congenital heart surgery in infants.

Results: Between 2016 and 2020, the annual incidence rate fluctuated between 1.55% and 3.17%, and the total incidence of chylothorax was 2.02%. Multivariate logistic regression analysis showed that postoperative albumin ($p = 0.041$; odds ratio [OR] = 0.095), preoperative mechanical ventilation ($p = 0.001$; OR = 1.053) and preterm birth ($p = 0.002$; OR = 5.783) were risk factors for postoperative chylothorax in infants with congenital heart disease.

Conclusion: The total incidence of chylothorax was 2.02% and the annual incidence rate fluctuated between 1.55% and 3.17% between 2016 and 2020. Premature infants, longer preoperative mechanical ventilation and lower albumin after congenital heart surgery may be risk factors for chylothorax. In addition, infants with chylothorax are inclined to be infected, need more respiratory support, use a chest drainage tube for longer and remain longer in hospital.

Keywords: congenital heart surgery, congenital heart disease, postoperative chylothorax, infant, risk factor

Introduction

Chylothorax is a disease caused by the obstruction or leakage of the thoracic duct, resulting in the accumulation of lymphatic fluid in the pleural cavity.[1,2] The causes of chylothorax can be classified into traumatic and non-traumatic. Non-traumatic chylothorax can be caused by malignant lymphoma, pleurisy or cirrhosis. Traumatic chylothorax can be caused by surgical trauma or external injury. Surgical trauma, especially cardiac surgery, is the main cause of traumatic chylothorax.[3] According to reports from the Pediatric Cardiac Critical Care Consortium and the Pediatric Health Information System databases,[4] the overall incidence of chylothorax in paediatric patients following congenital heart surgery or heart transplantation ranges from 2.8% to 3.8%. However, the incidence in China is approximately 3%–5%.[5] Postoperative chylothorax is a rare but serious complication of congenital heart disease (CHD) surgery in infants and

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children.[6–9] However, few studies investigate the incidence rate and influencing factors of postoperative chylothorax in infants, and the current literature reports common postoperative CHD. The main causes of postoperative chylothorax include thoracic duct injury, venous hypertension and venous thrombosis during or after surgery, which can result in nutritional, immunological and haemodynamic disturbances.[10,11] Infants are more susceptible to postoperative chylothorax due to their unstable haemodynamics and small calibre blood vessels and thoracic ducts. Postoperative chylothorax prolongs mechanical ventilation (MV) support and hospital stay, increasing medical costs and the burden on society and families. At present, the treatment of chylothorax is mainly conservative treatment such as a medium- and long-chain fatty acid diet or total parenteral diet, drug treatment (such as octreotide) and surgical intervention, but the efficacy of these methods is imperfect.[12,13] Therefore, identifying potential risk factors and preventing or reducing postoperative chylothorax are important goals.

Materials and Methods

Study Participants

This was a retrospective case-control study. The convenience sampling method was used to select infants who underwent CHD surgery at the Guangdong Cardiovascular Institute, China, between 1 January 2016 and 31 December 2020 as the research participants. According to the occurrence of chylothorax, the patients were divided into a control group (n = 88) and a case group (n = 88) according to the 1:1 matching on the same day (± 7 d), the same weight (± 200 g) and the same sex. The inclusion criteria were as follows: 1) age ≤1 year, 2) surgical operation for CHD and 3) diagnosis of chylothorax according to the criteria of (a) a milky appearance of pleural fluid and positive chylous test, (b) a pleural fluid cell count >1000/L, lymphocyte percentage >80% and erythrocyte count between 50 and 600/mm^3, (c) a pleural fluid fat range of 0.4–6.0 g/dL, a cholesterol range of 65–220 mg/dL and a triglyceride level >110 mg/dL and higher than the serum triglyceride level and (d) a pleural fluid protein range of 2–6 g/dL, an albumin range of 1.2–4.1 g/dL, a globulin range of 1.1–3.1 g/dL and electrolyte levels similar to plasma.[14,15] The exclusion criteria were as follows: 1) non-CHD postoperative chylothorax, such as congenital chylothorax and chylothorax caused by infection, 2) age >1 year and 3) patients with chylous ascites only after CHD. This study obtained the informed consent of the patient's family members and was approved by the hospital's ethics approval committee.

Method

Clinical data, including gestational age (premature delivery: <37 weeks gestational age), preoperative age (d), preoperative weight (kg), diagnosis, preoperative infection status, pulmonary artery pressure, last preoperative albumin (g/L), preoperative MV time (h), preoperative noninvasive ventilation time (h), preoperative oxygenation time (h), cardiopulmonary bypass time (min), delayed chest closure (yes/no), Aristotle score,[16] postoperative infection status, first postoperative albumin (g/L), postoperative MV time (h), postoperative noninvasive ventilation time (h), postoperative oxygenation time (h), other postoperative complications, drainage tube removal time (d) and hospitalisation time (d), were collected for both groups.

Statistical Analysis

The SPSS 26.0 statistical software package was used to analyse the data. The quantitative data of normal distribution were described by mean ± standard deviation (x ± s), and the t-test was used for comparison between groups. Quantitative data with non-normal distribution were described by median and quartile range, and the Mann–Whitney U-test was used for comparison between groups. The count data were described by the number of cases and percentage, and the comparison between groups was performed by the chi-squared test or Fisher exact test. Variables with a p-value of <0.05 in the univariate analysis were included in the multivariate analysis. Multivariate logistic regression was used to analyse the influencing factors. A p-value of <0.05 indicated that the difference was statistically significant.

Results

Baseline Characteristics of the Research Participants

A total of 176 children were included in the study after screening and applying the inclusion and exclusion criteria (Figure 1). Eighty-eight patients were diagnosed with chylothorax, and 88 patients were matched in the control group. There were 60 male children in the case group and the control group. The median weight was 3.6 kg, and the median age of the case group and the control group was 44 d and 44.5 d, respectively. There was no significant difference between the two groups in each variable, and the baseline was comparable ($p > 0.05$).

In the control group, the top three diagnoses were ventricular septal defect (VSD) (28 cases), transposition of the great arteries (TGA) (19 cases) and coarctation of the aorta (10 cases). The top three surgical procedures were VSD closure (24 cases), coarctation repair (11 cases) and congenitally corrected TGA repair (11 cases). The top three diagnoses in the case group were TGA (17 cases), VSD (16 cases) and total anomalous pulmonary venous drainage (TAPVC) (14 cases). The top three surgical procedures were ventricular septal closure defect repair (11 cases), TAPVC repair (14 cases) and congenitally corrected TGA repair (17 cases) (Table 1).

Incidence of Chylothorax After Congenital Heart Surgery in Infants Between 2016 and 2020

Between 2016 and 2020, the Guangdong Cardiovascular Institute, China performed surgery on 4357 children aged <1 year with CHD. The total incidence of chylothorax was 2.02%. The annual incidence rate fluctuated between 1.55% and 3.17% between 2016 and 2020, as shown in Table 2.

Univariate Analysis of Postoperative Chylothorax in Infants

Compared with the control group, the case group had a higher proportion of premature infants (7.95% vs 43.18%, $p < 0.001$), higher preoperative MV time (0 h vs 26.4 h, $p < 0.001$), more preoperative oxygenation time (0 h vs 0 h, $p = 0.002$), higher Aristotle score (7 score vs 9 score, $p = 0.001$), higher postoperative infection (52.3% vs 85.2%, $p < 0.001$), longer

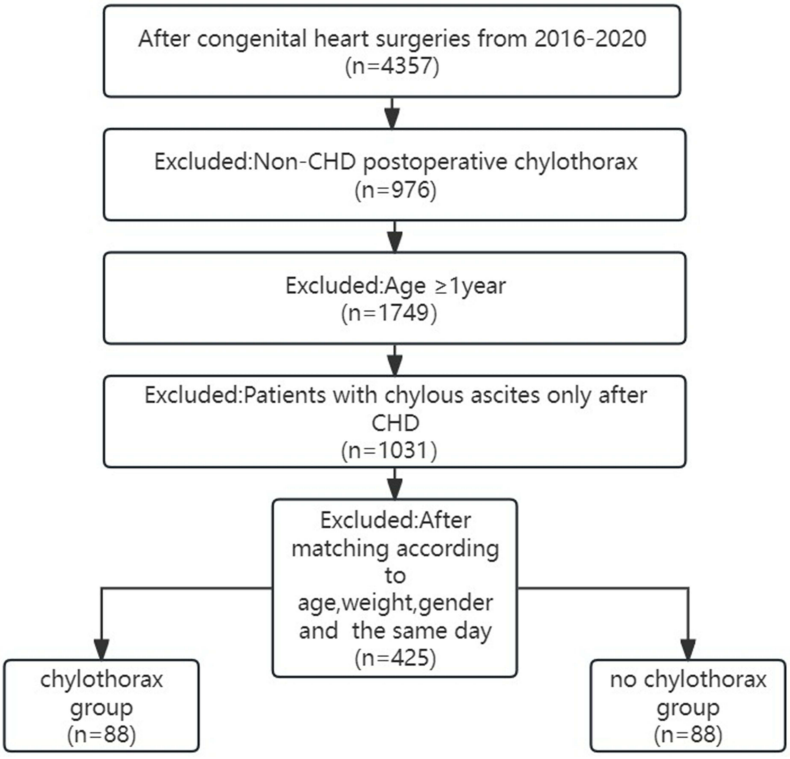

Figure 1 Flow chart presenting the selection of study infants.

Table 1 The Diagnosis and Surgical of 176 Infants

	Non-Chylothorax	Chylothorax	Total
Diagnosis			
VSD	28	15	43
ASD	4	1	5
TGA	19	17	36
CAVC	2	3	5
DORV	2	3	5
PTA	1	0	1
Coronary artery fistula	1	0	1
COA	10	7	17
TOF	3	12	15
TAPVC	7	14	21
PA\PS	4	5	9
Aortic arch dysplasia	4	1	5
HLHS	0	1	1
IAA	0	5	5
Others	3	4	7
Surgical procedures			
Arterial switch repair	8	0	8
TAPVC repair	7	14	21
Coarctation repair	11	0	11
IAA repair	1	6	7
VSD repair	24	16	40
ASD repair	5	0	5
PTA closure	3	0	3
Aortic arch repair	3	9	12
TOF repair	3	11	14
Congenitally corrected TGA repair	11	17	28
Modified Blalock-Taussig shunt	1	3	4
CAVC repair	1	1	2
Others	10	11	21

Abbreviations: VSD, ventricular septal defect; ASD, atrial septal defect; TGA, transposition of the great arteries; CAVC, Total endocardial cushion defect; DORV, double outlet right ventricle; PTA, persistent truncus arteriosus; COA, coarctation of the aorta; TOF, tetralogy of Fallot; TAPVC, complete anomalous pulmonary venous drainage; PA\PS, pulmonary stenosis; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch.

Table 2 Incidence Rate of Chylothorax During 2016–2020

Item	2016	2017	2018	2019	2020	Total
The number of surgery	906	1028	937	823	663	4357
Chylothorax	14	23	15	15	21	88
Incidence rate (%)	1.55	2.24	1.60	1.82	3.17	2.02

postoperative MV time (81.5 h vs 141.5 h, $p < 0.001$), longer postoperative noninvasive ventilation time (0 h vs 57 h, $p < 0.001$), longer postoperative oxygen therapy time (80 h vs 119.5 h, $p = 0.005$), tube drainage time (4 d vs 14 d, $p < 0.001$) and longer hospital stay (20.86 ± 10.55 d vs 34.61 ± 24.33 d, $p < 0.001$). Compared with the control group, preoperative albumin was lower (36.29 ± 5.12 g/L vs 34.43 ± 5.62 g/L, $p = 0.041$) and postoperative albumin was lower (30.01 ± 5.62 g/L vs 27.73 ± 6.69 g/L, $p = 0.016$) in the case group (Table 3). Univariate analysis showed that there were statistically significant differences in preterm birth, preoperative albumin level, preoperative MV time, preoperative oxygenation time, Aristotle score, postoperative albumin level, postoperative infection rate, duration of postoperative respiratory support, duration of catheter drainage and duration of hospitalisation.

Table 3 Univariate Analysis of Postoperative Chylothorax in Infants

Variable	Non-Chylothorax	Chylothorax	X2/t	P-value
Male, n(%)	60 (68.18)	60 (68.18)		
Age[d, median(IQR)]	44.5 (15,109.75)	44 (11.25,111.5)	0.126	0.899
Weight[kg, median(IQR)]	3.6 (3,5.3)	3.6 (3.1,4.85)	0.657	0.512
Premature, n(%)	7(7.95)	38 (43.18)	28.691	<0.001
Birth weight (kg)	3.01±0.48	2.90±0.51	1.485	0.14
Preoperative infection, n(%)	32(36.36)	35(39.77)	0.217	0.641
Pulmonary artery high pressure, n(%)				
No	25(28.41)	25(28.41)	0.845	0.839
Slight	7(7.96)	6(6.82)		
Medium	10(11.36)	14(15.91)		
High	46(52.27)	43(48.86)		
Preoperative albumin(g/L)	36.29±5.12	34.43±5.62	2.057	0.041
Preoperative MV time[h, median(IQR)]	0 (0,0)	26.4 (23.54,32.76)	−4.712	<0.001
Preoperative noninvasive ventilation time[h, median(IQR)]	0 (0,0)	0 (0,13.5)	−0.599	0.55
Preoperative oxygen therapy time[h, median(IQR)]	0 (0,74.25)	0 (0,0)	3.139	0.002
Aristotle score[median(IQR)]	7 (6,9)	9 (7,9)	−3.295	0.001
CPB time(min)	130.42±87.35	134.45±57.37	−0.348	0.729
Delay chest closed, n(%)	26 (29.5%)	38 (43.2%)	3.536	0.060
Postoperative albumin(g/L)	30.01±5.62	27.73±6.69	2.44	0.016
Postoperative infection, n(%)	46 (52.3)	75 (85.2)	22.24	<0.001
Other complications, n(%)	40 (45.5)	49 (55.7)	1.841	0.175
Postoperative MV time[h, median(IQR)]	81.5 (25,155.75)	141.5 (72.25,204)	−3.501	<0.001
Postoperative noninvasive ventilation time[h, median(IQR)]	0(0.51)	57 (9.25,119.5)	−4.692	<0.001
Postoperative oxygen therapy time[h, median(IQR)]	80 (45.25,123.25)	119.5 (53.25,215)	−2.809	0.005
Tube drainage[d, median(IQR)]	4 (3,6)	14 (10,18)	−9.785	<0.001
Hospital stay(d)	20.86±10.55	34.61±24.33	−4.864	<0.001

Abbreviations: IQR, interquartile range; MV, mechanical ventilation; CPB, cardiopulmonary bypass.

Logistic Regression Analysis of Postoperative Chylothorax in Infants

Multivariate logistic regression analysis was used to analyse the occurrence of chylothorax as the dependent variable. Indicators with statistical differences in univariate analysis were included in the analysis. The results showed that preterm infants (OR = 5.783, 95% CI: 1.947–17.180), longer preoperative MV time (OR = 1.053, 95% CI: 1.021–1.086) and lower postoperative albumin (OR = 0.925, 95% CI: 0.859–0.997) were risk factors for postoperative chylothorax in infants. Preoperative albumin level, preoperative oxygenation duration and Aristotle score were not influencing factors of chylothorax in infants ($p > 0.05$) (Table 4).

Table 4 Logistic Regression Analysis of Postoperative Chylothorax in Infants

Variable	B	SE	OR	95% CI	P-value
Premature	1.755	0.556	5.783	(1.947, 17.180)	0.002
Preoperative albumin	0.003	0.042	1.003	(0.923, 1.09)	0.943
Preoperative MV time	0.052	0.016	1.053	(1.021, 1.086)	0.001
Preoperative oxygenation time	−0.004	0.004	0.996	(0.988, 1.004)	0.321
Aristotle score	0.216	0.124	1.241	(0.974, 1.581)	0.081
Postoperative albumin	−0.078	0.038	0.925	(0.859, 0.997)	0.041
Constant	−0.430	2.154	0.651		0.842

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; MV, mechanical ventilation.

Discussion

This study analysed children aged <1 year with chylothorax who underwent congenital heart surgery at the Guangdong Cardiovascular Institute, China, between 2016 and 2020. In this study, we showed that preterm birth, preoperative MV time and low postoperative albumin level are major risk factors for chylothorax after congenital heart surgery in infants. In addition, the annual incidence rate fluctuated between 1.55% and 3.17% between 2016 and 2020, and the incidence of chylothorax in 2020 was 2.02%. This is consistent with Christofe et al,[17] who found that the incidence of chylothorax after congenital heart surgery was 2.10% but lower than Raatz et al,[18] who found a 9.7% incidence of postoperative chylothorax. This may be because our centre has carried out a more mature "prenatal and postnatal integrated model of care for CHD"[19] and increased the mature perioperative management of CHD in children. The cause of postoperative chylothorax may be intraoperative thoracic duct injury and central venous catheter-related blockage[20] caused by elevated venous pressure.

Buckley et al[3] and Resch et al[21] mentioned premature infants, the type of surgery and its complexity, low body weight and height, duration of extracorporeal circulation and X-clamp time and the existence of syndromes (in particular Down's syndrome, Noonan syndrome and Turner syndrome (4–7 times of chylothorax due to lymphangiectasis and spontaneous lymphatic branch abnormalities). Furthermore, secondary chest closure, postoperative sedation and reintubation are associated with chylothorax.[22]

Preterm infants may be at high risk of chylothorax after congenital heart surgery, as was also found by Alarcon et al.[23] This may be due to the increased risk of organ damage as a result of immaturity and the technical challenges of performing surgery on smaller patients. Premature infants with immature intrauterine development and underdeveloped tissues and organs, such as smaller lymphatic vessels, are at increased risk of injury after surgical strikes.[24] The light weight of preterm infants and the thin heart and blood vessels make performing surgical procedures on preterm infants more challenging and prone to intraoperative injuries associated with them.[25] In other words, premature infants have higher systemic venous pressure, which increases the pressure gradient between the lymphatic system and the pleural space, leading to leakage of chyle. Increased lung blood flow and obstruction of lymphatic return will also lead to leakage of lymphatic fluid, causing chylothorax.

This study revealed that a long duration of preoperative MV is a high risk factor for chylothorax. First, MV may increase thoracic pressure and obstruct lymphatic return. The need for sedation and enteral or parenteral nutrition during intubation for MV may lead to lung injury, which also increases the thoracic pressure.[26] Second, MV may cause barotrauma or volutrauma to the lungs, which may damage the lymphatic vessels and cause chyle to leak. Finally, MV may alter the haemodynamics and fluid balance in the thoracic cavity, which may affect the production and reabsorption of chyle.[27]

Our centre has shown that low postoperative albumin is a high risk factor for chylothorax. The relevant literature reported that it could be low protein, low autoimmune function or early postoperative malnutrition, including low food intake and feeding intolerance.[28] The lower albumin level can reduce the pressure of the blood plasma, which increases the leakage of pleural fluid. We found that the preoperative albumin level was low in the case group and the postoperative protein was significantly different between the two groups; that is, the postoperative albumin level was lower in the case group and, therefore, the albumin should be supplemented as early as possible in the postoperative period.

Other related literature reported that the Risk Adjustment for Congenital Heart Surgery (RACHS-1) method was used to score the surgical approach to investigate its effect on postoperative chylothorax.[29] Some studies have shown that the complexity of surgery is a major risk factor for chyle emulsion. The higher the RACHS-1 score is, the higher the complexity of surgery.[3] However, the Aristotle score was used to score the surgical approach at our centre, and the univariate analysis suggested it is a major risk factor for postoperative chylothorax. The multivariate analysis did not show it to be a major risk factor, which may be due to the maturity of the preoperative management model of CHD at our centre or the refinement of the surgical approach.

Infants with chylothorax after congenital heart surgery are more likely to develop postoperative infection, require longer postoperative respiratory support, require a longer postoperative tube drainage time and have longer hospitalisation.[30] After the occurrence of chylothorax, infants with decreased albumin levels and decreased autoimmune function are more susceptible to pathogens, and after infection, early postoperative extubation is delayed and more time is needed for respiratory support, including MV, noninvasive ventilation and oxygenation time. Chylothorax is mainly

manifested by increased pleural effusion, which requires longer drainage time than in postoperative patients without chylothorax.[31] Combining all these factors leads to a prolonged hospital stay for the infants.

The present study has the following limitations. First, it is a single-centre study of patients with postoperative chylothorax in infants with CHD, and the number of cases is small. Second, due to the absence of random sampling, selection bias may occur, leading to a false association between an unrelated feature and the disease. Finally, this was a retrospective study, which may have incomplete data. Therefore, it is important to be alert to the occurrence of postoperative chylothorax after CHD in infants, as well as to other complications.

Conclusion

In summary, the total incidence of chylothorax was 2.02% and the annual incidence rate fluctuated between 1.55% and 3.17% between 2016 and 2020. Preterm birth, preoperative MV time and low postoperative albumin level are risk factors for chylothorax after congenital heart surgery in infants. Therefore, it is important to be alert to the occurrence of chylothorax and other complications after coronary heart disease surgery in infants, which can reduce the mortality rate of infants and reduce the pain and burden of family members. In clinical practice, the occurrence of chylothorax was detected early by paying close attention to the postoperative thoracic drainage of infants born prematurely or receiving long-term MV before surgery. In addition, albumin was actively supplemented after surgery to increase autoimmune function and reduce the occurrence of chylothorax.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Guangdong Provincial People's Hospital. Written informed consent was obtained from all participants' parents or legal guardian.

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Disclosure

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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