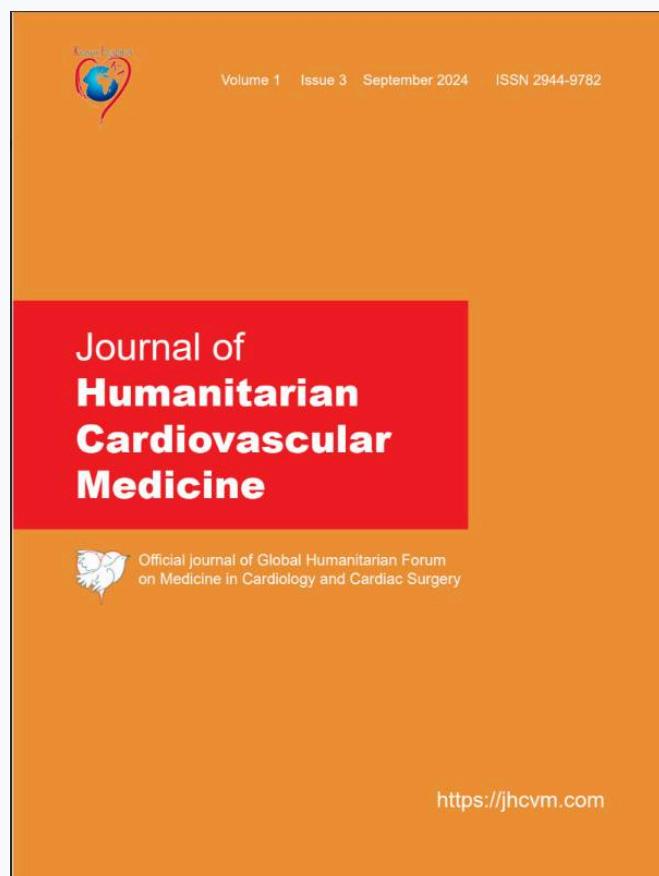


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# Risk Factors for Postoperative Chylothorax Occurrence Following Pediatric Congenital Heart Surgery

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## Keywords

Postoperative chylothorax, chylothorax post pediatric cardiac surgery, pediatric chylothorax

## Abstract

**Objectives:** Chylothorax, a rare but potentially life-threatening complication post congenital heart surgery, warrants early identification of risk factors to implement preventive strategies and timely interventions. This study aims to determine risk factors associated with chylothorax occurrence at our cardiac intensive care unit.

**Methods:** We conducted a nested case control study involving 2042 children who underwent congenital heart surgery at Nhi Dong 1 hospital (Ho Chi Minh city, Vietnam) from Feb 25<sup>th</sup>, 2015 to October 12<sup>th</sup>, 2019. Among these, 38 chylothorax cases were matched by sex and year of surgery to 76 randomly selected control patients. Univariate analysis and logistic regression were performed to identify independent factors associated with chylothorax occurrence after congenital heart surgery.

**Results:** Neonatal cardiac surgery, RACHS-1 risk category  $\geq 3$ , aortic arch repair, the arterial switch operation, prolonged bypass time (median 160 mins vs 87 mins) and aortic clamp time (median 89.5mins vs 51 mins), delayed sternal closure and unexpected reoperation were all associated with postoperative chylothorax occurrence on univariate analysis. Additionally, body weight  $< 4.5$  kg ( $p=0.027$ ), postoperative dysrhythmias ( $p=0.004$ ), and high volume of chest tube output ( $> 10\%$  of total expected blood volume) within the first 6 postoperative hours after cardiac intensive care unit admission ( $p=0.014$ ) emerged as independent risk factors for postoperative chylothorax occurrence with odds ratios and 95% confident interval of 2.78 (1.12-6.87), 3.38 (1.29-8.86) & 3.82 (1.55-9.39), respectively. These factors served as predictors of postoperative chylothorax occurrence with a sensitivity of 42.1%, specificity of 90.8%, positive predictive value of 69.6% and a negative predictive value of 75.8%.

**Conclusions:** High chest tube output within the first 6 postoperative hours, postoperative dysrhythmias, and body weight of  $< 4.5$ kg at surgery significantly increase the risk of postoperative chylothorax in our institution.

Chylothorax occurrence following congenital heart surgery (CHS) is a rare but potentially life-threatening condition<sup>1, 2, 3</sup>. This complication can lead to malnutrition, hospital-acquired infection, a prolonged stay in the Intensive Care Unit (ICU), increased resource utilization, and even death<sup>1, 4, 5</sup>. The primary causes of postoperative chylothorax (POC) can include direct trauma to the thoracic duct or lymphatic vessels during surgery, an increase in venous pressure over intrathoracic lymphatic pressure, or obstruction of lymphatic drainage due to central venous thrombosis or a combination thereof<sup>1, 2, 3, 6, 7</sup>. Several contemporary studies report several risk factors associated with this complication, including the type of procedure, delayed chest closure, low surgical weight, duration of cardiopulmonary bypass and aortic cross-clamping, and the presence of trisomy 21<sup>8, 9, 10, 11</sup>.

In the context of a hospital with limited resources for cardiac surgery, the majority of our procedures involve biventricular repair for a patient population where more than two-thirds present with malnutrition. The occurrence of postoperative chylothorax in our hospital setting also presents a unique set of challenges due to lack of availability of long chain fatty-acid free diet products, as well as inadequate total parenteral nutrition and the risk of hospital acquired infection. By identifying risk factors associated with POC within this specific context, our goal is to equip our ICU team with the knowledge needed for early recognition and a proactive approach to prevent and manage this formidable complication. Timely interventions and preventative strategies are crucial, not only in mitigating the impact of chylothorax on post-operative hospitalization, but also in averting cascading complications that could arise from its prolonged presence.

## Objectives:

This study aims to determine risk factors associated with postoperative chylothorax occurrence at our cardiac intensive care unit.

## Materials & Methods

A nested case-control study was conducted on 2042 children who underwent congenital

heart surgery at Children's Hospital 1 (Ho Chi Minh City, Vietnam) from February 25, 2015, to October 12, 2019.

### Definitions of Cases and Controls

Postoperative chylothorax cases were identified by searching the hospital's Cardiac ICU database, where all major postoperative complications are recorded. The diagnosis of chylothorax was then confirmed by reviewing hospital records. Laboratory diagnostic criteria for chylothorax in our study was a pleural fluid with a triglyceride level greater than 110mg/dl.

After these cases were identified from the cardiac intensive care unit database, control patients who underwent cardiac surgery during the same period but did not develop chylothorax were randomly selected using SPSS 20.0 software. These were matched by gender and year of surgery to chylothorax cases with a 2:1 ratio.

### Inclusion Criteria:

All patients undergoing cardiac surgery at Children's Hospital 1 (February 25, 2015 - October 12, 2019) who developed a postoperative chylothorax during their cardiac ICU stay were included.

### Exclusion Criteria:

Presence of a chylothorax before surgery.

Patients who died in the operating room or less than 24 hours after admission to cardiac intensive care unit.

### Clinical Data Collection

Demographic and clinical data were obtained by reviewing the cardiac intensive care unit database. The collected preoperative and intraoperative information included age, gender, weight, and height at the time of surgery; preoperative diagnosis; details of surgery, such as whether it involved cardiopulmonary bypass (CPB) or not, arch or non-arch repair; bypass time and aortic cross-clamp times (if applicable); surgical complexity categorized by the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) classification and any previous sternotomy or thoracotomy.

Postoperatively, data collection extended to include delayed sternal closure, chest tube output every hour during the first six hours after admission to cardiac intensive care unit, patients with echocardiographic evidence of right ventricular diastolic dysfunction, residual pulmonary valve stenosis, residual right ventricular outflow tract stenosis, postoperative pulmonary hypertension, obstruction of superior vena cava (all of these were diagnosed by clinical signs and confirmed by echocardiography) and any significant postoperative dysrhythmias.

#### Variable definitions:

High chest tube output (CTO): Volume of chest tube output greater than 10% of the patient's expected blood volume within the first six postoperative hours after admission to cardiac intensive care unit.

Postoperative dysrhythmias: Any significant or sustained postoperative dysrhythmias that occurred throughout the study period, confirmed by at least one pediatric cardiac intensivist or pediatric cardiologist, and necessitated intervention. Dysrhythmia patients identified in this study either had junctional rhythm, supraventricular tachycardia, junctional ectopic tachycardia, sinus node dysfunction, or complete heart block during their cardiac intensive care unit course.

Unexpected reoperation: Any chest reoperation during the same admission caused by residual lesions or bleeding was considered an unexpected reoperation.

#### Ethics:

Approval number CS/N1/20/35 by the Scientific Council and Ethics Committee of Children's Hospital 1 was obtained.

#### Statistical Analysis

Microsoft Access was used for data entry, and SPSS version 20.0 for Windows was utilized for data analysis. Descriptive analysis was conducted by calculating frequencies, percentages, medians, and ranges for qualitative and quantitative variables. We performed a bivariate analysis using the Chi-square or Fisher exact test when appropriate. All variables with a  $P < 0.05$  were

introduced into a binary logistic regression analysis to identify independent risk factors for post-operative chylothorax and predict its probability. The threshold of significance was selected as  $P < 0.05$ . Adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) were obtained.

#### Results

Over the course of the study, 2042 cardiac surgeries were performed. Among them, 38 cases of POC were identified and meticulously matched by gender and year of operation to 76 randomly selected control patients. The prevalence of POC varied from 1.28% to 2.46%, averaging 1.86% (**Table 1**).

**Table 1:** Number of cardiac surgery cases and prevalence of POC by year

Year of surgery	Number of cardiac surgical cases	Number of POC cases (%)
2015	325	8 (2.46%)
2016	462	7 (1.52%)
2017	445	8 (1.8%)
2018	420	10 (2.38%)
2019	390	5 (1.28%)
Total	2042	38 (1.86%)

Abbreviations: POC: Postoperative chylothorax

Six patients with chylothorax (15.8%) had non-CPB surgery for coarctation while 3 (3.9%) in the other. There were 5 (13.2%) versus 2 (2.6%) children ( $p=0.04$ ) who underwent unexpected redo surgery due to a significant residual lesion in the same admission (**table 3**). One child required his chest to be reopened for post-surgical bleeding versus none in the control group. The mortality rate was 15.8% ( $n= 6$ ) in the POC group versus 2.6% ( $n=2$ ) in the control group.

**Table 2** outlines the patient demographics (age, weight, gender, and nutritional status) included in this study. There were no statistically significant variations in age, weight, and nutritional status between the two groups.

#### Risk factors of postoperative chylothorax

**Table 3** lists potential risk factors for POC. When considering all demographic variables, the neonatal group exhibited a POC likelihood 5.8 times higher than that of the non-neonatal group.

**Table 2:** Patient demographics

Variables	Statistics	Cases (n= 38)	Controls (n= 76)	P
Age (Day)	Median (IQR; range)	109.5 (456; 1- 3709)	211 (486; 11-4558)	0.074
Weight (Kg)	Median (IQR; range)	5 (4.5; 2-39)	6 (5; 2-53)	0.260
Gender	Male (%)	22 (57.9%)	44 (57.9%)	1
Nutritional status (WHO-2006 classification / BMI for age)	Normal	18 (47.4%)	27 (36%)	0.316
	Mild malnutrition	7 (18.4%)	10 (13.3%)	
	Moderate malnutrition	2 (5.3%)	14 (18.7%)	
	Severe malnutrition	4 (10.5%)	13 (17.3%)	
	Overweight and obesity	7 (18.4%)	11(14.7%)	
Nutritional status (WHO-2006 classification / Weight for length/height)	Normal	16 (43.2%)	26 (37.7%)	0.118
	Mild malnutrition	5 (13.5%)	7 (10.1%)	
	Moderate malnutrition	4 (10.8%)	12 (17.4%)	
	Severe malnutrition	4 (10.8%)	14 (20.3%)	
	Overweight and obesity	8 (21.6%)	10 (14.4%)	

Abbreviations: BMI: Body mass index; WHO: World Health Organization

**Table 3:** Unadjusted associations between risk factors and POC

Characteristic	POC cases (n=38)	Controls (n=76)	Unadjusted Odds ratio and 95% CI	P value
Age groups	Neonates	11 (28.9%)	5 (6.6%)	5.8 (1.8-18.2)
	Infants	16 (42.1%)	46 (60.5%)	
	Children	11 (28.9%)	25 (32.9%)	
Weight at surgery <4.5 kg	17 (44.7%)	19 (25%)	2.4 (1.1-5.5)	0.033
RACHS-1 (median- IQR)	3 (2)	2 (1)		
RACHS-1 score ≥3	22 (57.9%)	23 (30.3%)	3.6 (1.6-8.2)	0.004
Aortic arch repair	12 (31.6%)	8 (10.5%)	3.9 (1.4-10.7)	0.005
Arterial switch operation	9 (23.7%)	4 (5.3%)	5.6 (1.6-19.6)	0.006
Tetralogy correction	13 (34.2%)	16 (21.1%)	1.9 (0.8-4.6)	0.128
Bypass time (Minutes, median, IQR)	160.5 (125)	87 (77)		0.001
Cross clamp time (Minutes, median, IQR)	89.5 (82)	51 (47)		0.005
Delayed sternal closure	14 (36.8%)	4 (5.3%)	10.5 (3.2-35)	0.0005
Unexpected reoperation	5 (13.2%)	2 (2.6%)	5.6 (1-30.4)	0.04
High CTO	19 (50%)	16 (21.1%)	3.8 (1.6-8.7)	0.002
Postoperative dysrhythmias	15 (39.5%)	12 (15.8%)	3.5 (1.4-8.5)	0.005

Abbreviations: CTO: Chest tube output; IQR: Interquartile range; POC: Postoperative chylothorax; RACHS-1: Risk Adjustment for Congenital Heart Surgery-1.

Additionally, POC occurred 2.4 times more frequently in children weighing less than 4.5 kg at the time of surgery compared to those weighing 4.5 kg or more.

While patients following tetralogy of Fallot correction did not display a statistically significant difference in the occurrence of POC between the two groups, the POC group manifested a higher proportion of RACHS-1 scores ≥ 3. Moreover, there were more instances of aortic arch repair and arterial switch operation in the POC group.

Patients undergoing arterial switch surgery had a 5.6 times higher likelihood of POC when compared to other surgeries, whereas patients post aortic arch repair had a 3.9 times higher chance of POC (**Table 3**). Remarkably, POC patients experienced significantly longer bypass and aortic cross-clamp times than those in the control group.

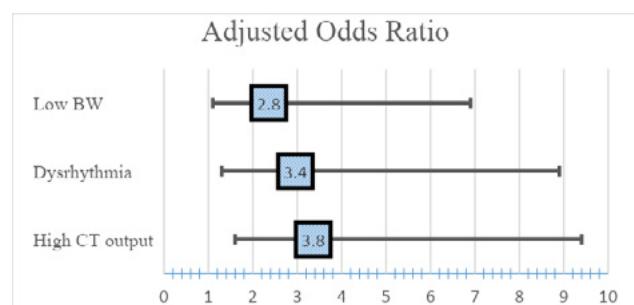
Postoperatively, the univariate analysis identified delayed sternal closure, unexpected reoperation, high CTO, and significant postoperative

dysrhythmias as factors associated with POC. Two patients in our study with complete heart block underwent single chamber permanent pacemaker implantation and experienced persistent POC, unresponsive to aggressive medical or surgical treatment, leading to death from hospital-acquired infection. Additionally, three patients developed superior vena cava (SVC) syndrome during the study period. Among them, two neonates with SVC blockage had prolonged POC and succumbed to infection. The final patient, a 44-day-old baby with post-bypass SVC stenosis developed POC, responded to aggressive medical therapy, and was discharged from the cardiac ICU on postoperative day 29.

To assess the impact of risk factors on the probability of POC, covariates associated with POC in univariate analysis were incorporated into the binomial logistic regression model. Due to the loose-matching data on the variables of gender and year of surgery, we opted for an unconditional logistic regression model. Nevertheless, some risk variables - neonatal age, arterial switch operation, aortic arch repair, delayed sternal closure, and unexpected reoperation - had a small number of patients (< 10 cases) in the control group, rendering them ineligible for inclusion in the logistic regression model. Consequently, only four factors were sequentially added to the model based on the magnitude of the Chi-square association. These factors, in descending order of importance, included: high volume of CTO, RACHS-1 score  $\geq 3$ , significant postoperative dysrhythmia, and weight at surgery  $< 4.5$  kg. Changes to the model were analyzed at each step to identify multicollinearity and model instability. Upon inclusion of the RACHS-1 score  $\geq 3$  in the model, the standard error rose by over 10%, leading to its subsequent removal for improved model precision.

The logistic regression model was statistically significant,  $\chi^2 (3) = 20.837$ ,  $p < 0.0005$ . The model explained 23.2% (Nagelkerke  $R^2$ ) of the variance in POC and correctly classified 74.6% of cases. Sensitivity was 42.1%, specificity was 90.8%, positive predictive value was 69.6%, and negative predictive value was 75.8%. Graph 4.1 shows adjusted odds ratios (aORs) and 95% confidence intervals (95% CI) for risk factors of

POC.



Graph 1: Multivariate postoperative chylothorax risk model

Abbreviations: BW: Body weight; CT: Chest tube.

## Discussion

In this study, we identified risk factors for postoperative chylothorax in infants and children undergoing congenital heart surgery at our resource-limited hospital. While POC was observed in a minority of our patients, it carried significant mortality. Independent risk factors for POC included low body weight at the time of surgery, significant postoperative dysrhythmias, and a high volume of CTO.

The prevalence of postoperative chylothorax in our study population aligns with findings from other recent publications<sup>9, 11, 12, 13</sup>. Nevertheless, reported rates displayed considerable variability, ranging from 0.85% to 15%, primarily due to differences in study design, particularly in case definitions<sup>2, 9, 13, 14</sup>. Notably, Sung Kwang Lee's comprehensive review from 2011 to 2018 revealed a range of POC incidence in children, spanning from 0.34% to 5.32%<sup>15</sup>.

In univariate analysis, we uncovered several potential risk factors, reflecting the complexity of chylothorax development. Factors such as low body weight, neonatal status, high RACHS-1 classification, aortic arch repair, arterial switch operation, prolonged bypass and aortic cross-clamp time, delayed sternal closure, high volume of initial chest tube output, significant postoperative dysrhythmia, and unexpected reoperation were all potential contributors. Our analysis, consistent with prior studies, reinforced established risk factors for POC<sup>2, 8, 12, 16</sup>.

Neonatal cardiac surgeries, known for their complexity, carry a higher risk of chylothorax compared to pediatric patients<sup>2, 8, 17, 18</sup>. In a ret-

rospective study involving 149 cardiac surgeries during the neonatal period, Perez-Perez Alba et al. found that up to 20.8% of their patients developed chylothorax<sup>17</sup>. In our study, neonatal patients demonstrated approximately a six-fold increased risk of POC compared to non-neonatal patients, a finding slightly higher than that reported by Buckley et al.<sup>16</sup>. The diversity in pediatric cardiac surgeries may contribute to varying POC rates among age groups, while the increased incidence in neonates may be attributed to the greater vulnerability of the lymphatic system during these operations<sup>8, 12, 19</sup>.

The complexity of the corrective surgery being performed has also been shown to be a risk factor in the development of POC<sup>2, 9</sup>. It has been reported that a higher RACHS-1 score represents an increased associated risk<sup>9, 19</sup>. Mery et al.<sup>2</sup> observed an increase in POC incidence from 1% in RACHS-1 category 1 cases to 5.2% in more complex RACHS-1 category 5 and 6 patients, with the highest incidence (9.2%) noted among individuals undergoing multiple types of repairs simultaneously. According to the findings of Day et al.<sup>9</sup>, RACHS-1 category 4 is linked with the greatest risk, with an odds ratio that ranges between 2.22 and 2.98. Our study also found patients with RACHS-1 categories  $\geq 3$  exhibited a greater prevalence of POC than those with RACHS-1 categories 1 and 2 in univariate analysis. However, high RACHS-1 score was eliminated from binomial logistic regression model as it might be collinear with weight.

In reviewing the literature, POC is also related to surgeries associated with elevated postoperative systemic venous pressure, such as those in single ventricle surgery, tetralogy of Fallot repair<sup>7</sup>, or procedures involving dissection of the descending aorta (e.g. aortic arch repair), or surgeries requiring a significant vascular anastomosis, as seen in arterial switch operation and heart transplantation<sup>2, 4, 8, 12, 18</sup>. Our univariate analysis revealed a higher likelihood of POC in certain surgical procedures. However, the logistic regression model couldn't assess these variables due to the restricted sample size, which is a limitation of our research.

In logistic regression analysis, we identified

three independent risk factors associated with chylothorax in our pediatric cardiac surgery population. Among these, low body weight at the time of surgery emerged as one of three predictors, highlighting the vulnerability of smaller patients to this postoperative complication. Consistent with findings by Shahzad et al.<sup>19</sup>, our study observed a reduction in the likelihood of developing chylothorax with increasing age and weight. This suggests that as children grow older and gain weight, the risk of thoracic duct injury decreases.

Additionally, the high volume of chest tube output within the first 6 hours post- cardiac ICU admission and the occurrence of significant post-operative dysrhythmias were identified as pivotal contributors to chylothorax development. This slightly differs from Biewer et al.<sup>8</sup> where they found an association between POC and delayed chest closure, prolonged bypass times, the use of anesthesia after the operation, and reintubation from multivariate regression analysis. This discrepancy can be explained by differences in population and sample size. Furthermore, Moza et al.<sup>10</sup> presented a prediction model for the early diagnosis of postoperative pediatric chylothorax, emphasizing a high volume of chest tube output on the first day following sternal closure as a crucial predictor. Our study also used CTO volume measurements, focusing on the day of operation for early POC prediction. This is because we adhere to a practice of initiating enteral nourishment as soon as feasible, often on the night of the operation or the first postoperative day. The majority of our patients undergo chest tube removal in the early phase in their postoperative course, usually by postoperative day 1. Early POC prediction may facilitate the potential withholding of enteral feeding in high-risk individuals, preventing more significant chylothorax effects. Early POC diagnosis leads to swift resolution through effective expedited conservative therapy<sup>10, 20</sup>.

Remarkably, our study identified significant postoperative dysrhythmias as a distinctive risk factor for POC. This observation may be attributed to the potential of postoperative dysrhythmias to induce atrioventricular desynchronization, elevating superior vena cava pressure and hindering lymphatic flow draining to the heart. Instances

of atrioventricular desynchronization, particularly due to a complete heart block and post single chamber permanent pacemaker implantation, suffered persistent POC unresponsive to medical or surgical therapy. Shahzad et al. recently reported a similar association between arrhythmias and an increased incidence of chylothorax but only on univariate analysis<sup>19</sup>.

### Limitations:

Our study had several limitations, primarily stemming from its retrospective nature and reliance on our cardiac ICU database. We only included patients diagnosed and treated for POC within the cardiac ICU, excluding those who developed POC on the ward or after discharge. Consequently, our reported post-surgical POC rate might be underestimated. Despite being based on 5-year data from 2042 patients admitted to our cardiac ICU following cardiac surgery, the relatively small number of POC cases limited the power to assess the association between risks and POC. Some risk factors were identified only through univariate analysis and couldn't be included in the multivariable regression model due to the restricted sample size. Future research should prioritize expanding the sample size and exploring additional risk factors to enhance our understanding of chylothorax etiology in our specific health care context.

### Conclusions

In our resource limited center, the POC rate after congenital cardiac surgery averaged 1.86%. Notably, low weight at surgery, significant postoperative arrhythmias, and high early CTO emerged as key risk factors for POC in our setting. These three parameters can predict the likelihood of POC at our center after cardiac surgery with a sensitivity of 42.1% and a specificity of 90.8%. Our study not only confirms known risk factors but also provides unique insights tailored to resource-limited hospital. These identified risk factors lay the groundwork for targeted interventions and ongoing research, refining our understanding of chylothorax in the context of pediatric cardiac surgery. These findings facilitate early identification high risk children in our cardiac ICU, allowing for the implementation of

preventive strategies and timely interventions to mitigate POC complications and mortality. However, it is crucial to validate our early predictive POC factors through more extensive prospective cohort studies.

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