Journal of the Saudi Heart Association

Volume 35 | Issue 2 Article 4

2023

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Recommended Citation

Shahzad, Muhammad; Alheraish, Yasser abdulrhman; Algethami, Bushra ; Machado, Patricia ; Beheri, Reem Mohamed Essa; Mohamed, Gamal; Khouqeer, Fared; and Halees, Zohair Al (2023) "Incidence and risk factors for chylothorax after pediatric heart surgeries: retrospective analysis of a large institution database," *Journal of the Saudi Heart Association*: Vol. 35 : Iss. 2 , Article 4.
Available at: https://doi.org/10.37616/2212-5043.1341

ORIGINAL ARTICLE

Incidence, Risk Factors and Effective Treatment Strategies for Chylothorax After Pediatric Heart Surgeries: Retrospective Analysis of Large Database in Single Institution

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Abstract

Background: **Risk factors for postoperative chylothorax in children who had cardiothoracic procedures are not always clear. Due to complex course in post-operative care, It's always challenging to find the risk factors, and their management.**

Objective: **The aim of our study was to identify the incidence, risk factors and effective treatment approaches for chylothorax after pediatric heart surgery.**

Methods: **Children who had the cardiac surgery and subsequently developed chylothorax were included in the study. The ratio of the experimental group to the control group was 1:2. Decannulations of extracorporeal membrane oxygenation (ECMO) were not included in the analysis of patient outcomes. For each patient, we keep track of their age, weight, gender, syndrome, RACH-1 scoring, fluid balance, bypass time, clamp time, redo operations, open or close heart surgeries, and rhythm difficulties. Care logs were kept for every single therapy that was administered. Primary outcome was chylothorax, with secondary outcomes included time in the intensive care unit (ICU), length of hospital stay (LOS), and death.**

Results: **5210 surgeries were performed in six years. 96 patients developed the chylothorax with incidence of 1.8%. In chylothorax group, mean weight was 6.7 ± 4.2, while mean age was 11.7 ± 15.2. Clamp time was 74.5 ± 53.5 versus 39.9 ± 13.7. Mean bypass time was 128.34(76.25) versus 84.3 ± 25.1 with an odds ratio 1.02 (Z test 0.0001). Six (6.3%) children with chylothorax had redo cardiac surgeries in the same admission (p-value 0.01) while none in other. Five (5.2%) cases got operated by thoracotomy, three from left side. Mean Chest tube duration was 10 ± 7.8 days versus 3.8 ± 2.4 in control group. (p-value 0.02). chylothorax resolved (mean resolving time = 4 days) in 76 (79.2%) children with monogen formula. Two patients receive midodrine with no significant effect. Four children underwent surgical repair for chylothorax.**

Conclusion: **Bypass time linearly increasesincidence of chylothorax. Younger age, low weight, syndromic children, redo operations, non-open-heart surgeries, and arrhythmias also contribute to this. Gender, fluid balance, and RACHS-1 Scoring were not significant. While further research and testing are required for the use of midodrine. However, the low-fat formula of Monogen has proven to be an effective treatment.**

Keywords: Chylothorax, Risk factors, Cardiac surgery, Children, Complications, Outcome

Received 9 May 2023; revised 30 May 2023; accepted 7 June 2023.
Available online 30 June 2023

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https://doi.org/10.37616/2212-5043.1341

1. Introduction

Chylothorax is a postoperative complication that can occur in children following cardiothoracic surgeries. It causes nutritional, metabolic, and immunological problems, which in turn can result in deep vein thrombosis (DVT), sepsis, malnutrition, and ultimately increased hospital stays and a relatively high mortality rate [1,2]. It has been estimated that 1.1% of children suffer with chylothorax after cardiac surgeries. The first three days after the beginning of feed were marked by the highest occurrence of the condition [3]. Its prevalence has been estimated to be between 2% and 5% in several studies [4].

Chylothorax is associated with thoracic duct injuries during surgical procedures. Lymphatic dysplasia has been suggested as a possible role in the development of chylothorax in syndrome children. Additional risk factors for postoperative chylothorax include: central vein thrombosis and elevated systemic venous pressure above that of the thoracic duct [5,6]. Chylothorax occurs more frequently after some operations, including Fontan, and vascular ring repair [7].

There are several protocols for the care of chylothorax, but none of them are standardized. Both surgical and non-surgical methods can be used to treat the condition. Conventional non-surgical treatments might include to keep none per oral (NPO), beginning the feeding process with medium-chain fatty acids, receiving an infusion of octreotide, other drugs like etilefrine hydrochloride, octreotide, and midodrine. Octreotide is an extended-release form of the somatostatin analog. It reduces the amount of lymph fluid that is excreted while acting directly on vascular somatostatin receptors [8,9]. In circumstances when medicinal therapy is unsuccessful, surgical procedures such as pleurodesis (either chemical or mechanical), thoracic duct ligation (TDL), or the installation of pleuroperitoneal shunts may be contemplated [2].

Chylothorax has a direct influence on the outcome, such as the duration of stay in the intensive care unit (ICU), the length of stay in the hospital, cost, and mortality, with varying results based on the patient's age, diagnosis, and the complexity of the treatment [10,11]. A number of studies have documented varying rates of occurrence of postoperative chylothorax in paediatric patients who had heart surgery. As a result, the purpose of this study was to make use of a large amount of data to assess the prevalence of chylothorax in children following cardiac procedures, as well as the risk factors associated with it, and the short-term outcomes.

Abbreviations:

ECMO	Extracorporeal Membrane oxygenation
ICU	intensive care unit
MCT	Medium Chain Triglyceride
NPO	none per oral
RACHS	Risk Adjustment for Congenital Heart Surgery 1
SPSS	Statistical Package for the Social Sciences
TPN	total parental nutrition
TDL	thoracic duct ligation

2. Materials and method

In this observational retrospective study, all patients in pediatric age group who underwent congenital heart surgery or heart transplant from January 2016 to June 2021 were included. 5290 surgeries were performed in the respective period. 80 cases were excluded who underwent decannulations as ECMO weaning. 5210 patients who had corrective or palliative cardiac surgery were included in the database. The incidence of chylothorax was calculated as a percentage of children who had chylothorax over the total number of surgeries in a defined period. We created a control group in ratio of 1:2 for comparing the risk factors. The Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) score was assigned during an inpatient admission within the study period. If a patient underwent multiple procedures in the same entry, the operation with the highest risk number was appointed as the RACHS score. Respective data for each operation were included in the case of numerous surgeries. Ethical Committee approved the study with RAC # 2,211,206. The informed consent was resigned from the institutional review board (IRB) because of the study's retrospective nature.

Charts were reviewed for all patients who met the inclusion criteria. Any patient who had chylothorax was enrolled for study. In our institution, chylothorax is suspected after the appearance of a milky drain in the chest drainage tube after starting feed. Then it is confirmed with a biochemical test based on the following definition: elevated triglyceride (>1.1 mmol/L) [2]. In other institutions, there is additional microscopic confirmation with lymphocyte predominance (>80%), but elevated triglyceride is still an essential entity to be present [12]. Chylothorax duration was defined as the time interval from the day of diagnosis till the last day without effusion and drain. We calculate the cumulative

days in case of multiple chest drains insertions. In addition, we recorded the cardiac lesion, primary procedure, syndromic or not, bypass time, aortic cross clamp time, postoperative day of development of chylothorax, the status of the chest open or close in ICU, thoracotomy or open heart procedures, and presence of arrhythmia (regardless of the type of arrhythmia), fluid balance and duration of chylothorax. Fluid overload was defined as a cumulative balance >10% from admission to the intensive care unit at 72 h of admission. We calculated the fluid proportion by using the following equation: (total fluid intake-total fluid output) (L)/body weight (kg) × 100 [13]. We also distinguished which treatment strategy was effective in chyle resolution, like low-fat diet (monogen diet), intravenous octreotide infusion, midodrine, or surgical procedure. In addition, we evaluated total parental nutrition (TPN) duration in days till chyle responds to treatment, ICU and hospital stay in days, surgical procedure for chylothorax, and mortality. We defined mortality as in-hospital death in these chylothorax patients.

As a quality boost program, our institution had a standard management protocol. Once a patient has a pleural effusion on Chest X-ray after surgery or milky flow in the existing drain, the initial management consists of drainage and sampling of the pleural fluid to confirm the clinical diagnosis. Then, we stop the general diet for age and commence the Medium Chain Triglyceride (MCT) diet available as a monogen formula. Pleural drain volume is noted daily, and the catheter is removed if it is less than 3 ml/kg/day. We start the octreotide if there is continuous drainage even after 2 weeks over monogen therapy. Midodrine, as over-the-counter medicine recently added in formulary for chylothorax if the patient is poorly responding to octreotide infusion. In our protocol, surgery is indicated if there is persistent excessive drainage of chyle (>10 ml/kg/day) or over a long (2–4 weeks) period.

The results were expressed as numbers and percentages. We categorized the age into four groups according to age at admission: neonates (<30 days), infants (1–12 months), 13–24 months, and more than 25 months. Univariate analysis was performed for all variables in case and control groups. Continuous variables were summarized as median with interquartile range, while Categorical and ordinal variables are abridged as frequency and percentages, respectively. The Means of variables in two Groups was performed with the t-test and chi-square test (SPSS program Version 23). Odds ratio were calculated with 95% CI. A p-value <0.05 was considered to be statistically significant. A multivariate logistic regression analysis was performed with pre-and postoperative parameters.

3. Results

In six years, 5290 palliative and corrective surgeries were performed. We excluded the 80 cases who underwent decannulations as ECMO weaning. A total of 5210 palliative and corrective surgeries were performed. Among them, 96 patients developed chylothorax. 200 children were selected as a control group. There were 21 (21.9%) neonates with chylothorax versus 14 (7%) in control. Most of patients were below 10 kg, 80 (83.3%) with chylothorax versus 133 (66.5%) with non-chylothorax. There was no significant difference in gender in both groups. (p-value 0.49) Twenty children had down syndrome (20.8%) while 06 (03%) children in the control group. (p-value 0.001) Six (6.3%) children with chylothorax had redo cardiac surgeries in the same admission (p-value 0.01) while none in other. There were 11 (11.5%) versus 1 (0.5%) child who came as open chest in CSICU (P-value 0.00). For children who got operated by thoracotomy on either right or left side, there were five (5.2%) cases versus four (2%) (p-value 0.12). Seven (7.3%) children had arrhythmias versus two (1%) in the control group. (p-value 0.006) Fluid overload was rare in our population; most patients had a negative fluid balance of n = 120 (40.5%) as (p-value 0.17). Table 1.

While in risk stratification, patients with RACHS score1 were 10 (10.4%) versus 38 (19%), RACHS score2 34 (35.4%) versus 148 (74%), score3 24 (25%) versus 06 (3%), score4 10 (10.4%) versus 06 (03%), score5 03 (3.1%) versus 01 (0.5%), score6 11 (11.5%) versus 01 (0.5%), while uncategorized patients were 4 (4.2%) versus no patient. Table 2.

96 patients developed the chylothorax with incidence of 1.8%. In chylothorax group, mean weight was 6.7 ± 4.2, while mean age was 11.7 ± 15.2. There were 46 (47.9%) males with little female predominance. Clamp time was 74.5 ± 53.5 versus 39.9 ± 13.7 and bypass time 128 ± 76 versus 84.3 ± 25.1. (p-value 0.01) Mean Chest tube duration was 10 ± 7.8 days versus 3.8 ± 2.4 in control group. (p-value 0.02) Chylothorax was observed between 1st and 25th postoperative days with mean Chyle duration 5.8 ± 3.0 days. Mean chyle appearance day was 4.83 ± 4.03 with peak incidence at 3rd post op day. Tables 3–4.

Among 96 chylothorax patients, 76 (79.1%) children respond to monogen (medium triglyceride chain milk) feed. The mean response time was 8.3 days. 20.8% had persistent chylothorax that did not respond to first-line treatment over two weeks. TPN

Table 1. Univariate analysis in chylothorax and non-chylothorax group.

Variable	Chylothorax n = 96	Non Chylothorax n = 200	p-value
Weight in kg			
2–10	80 (83.3%)	133 (66.5%)	
More than 10	16 (16.7%)	67 (33.5%)	0.003
Age			
Less than month	21 (21.9%)	14 (07%)	–
1–12 month	47 (49%)	81 (40.5%)	0.015
13–24 month	16 (16.7%)	77 (38.5%)	0.0001
More than 25 months	12 (12.5%)	28 (14%)	0.010
Gender			
Female	50 (52.1%)	106 (53%)	–
Male	46 (47.9%)	94 (47%)	0.882
Down syndrome			
Yes	20 (20.8%)	06 (03%)	0.00
No	76 (79.2%)	194 (97%)	
Other syndrome			
Yes	04 (4.2%)	00	0.01
No	92 (95.8%)	200 (100%)	
Surgeries in same admission			
Yes	06 (6.3%)	00	0.01
No	90 (93.8%)	200 (100%)	
Fluid Balance			
Negative	44 (45.8%)	76 (38.1%)	–
Positive	20 (20.8%)	62 (31%)	0.067
Euvolumic	32 (33.3%)	62 (31%)	0.691
chest closure status			
Open	11 (11.5%)	0 (0%)	0.0001
Close	85 (88.5%)	200 (99.5%)	
Thoracotomy			
Yes	05 (5.2%)	04 (02%)	0.12
no	91 (94.8%)	196 (98%)	
Arrhythmias			
Yes	07 (7.3%)	02 (01%)	0.006
no	89 (92.7%)	198 (99.8%)	
Mortality			
Yes	03 (3.1%)	0(0%)	0.03
No	93 (96.9%)	200 (100%)	

was used in 18 (18.8%) children. In 16 (16.7%) children, chyle resolve with octreotide infusion. Mean octreotide days were 14.6 ± 9.4, with infusion days from 7 to 38 days maximum. A total of four (4.1%) children underwent surgery, one thoracic duct ligation, and three diaphragmatic fistula. 2 cases received the midodrine and both underwent fistula formation. ICU and hospital stay time was 21 ± 30 (4–197) days and 31 ± 43 (7–302) days, respectively. Three patients died during their hospital stay (3.1%). Figure 1.

4. Discussion

Our research led us to the conclusion that the incidence of chylothorax is 1.8%, and it began most frequently on the third postoperative day. We hypothesize that chylothorax is linked to factors such as a young age, a low weight, a long clamp time, a short pump time, an open chest, arrhythmias, and repeated surgical procedures. Although the majority of patients diagnosed with chylothorax exhibited a negative fluid balance, this finding did not reach statistical significance. The majority of patients have shown improvement as a result of the monogen treatment, and four patients have undergone surgery to relieve the chylothorax.

In the population that we were studying, a total of 5210 procedures, both palliative and corrective, were carried out over the course of six years. The prevalence of chylothorax was found to be 1.8% during the course of our research. In a large database study that took place over eight years, the incidence was found to be 2.8% [10]. The frequency in our study is somewhat higher than the incidence of 1.1% reported in a previous article by czobor RN et al. [3] This little high incidence in our study might be attributed to the complexity of operations. It has been found that 29.2% of our study sample had a RACHS-1 score of 4 or above. In addition, there were four patients who did not fit any of the categories; two of these patients had received heart transplants, while the other two were received ECMO. Following surgery, eleven patients (11.5%) had open chests, which is also considered to be a statistically significant risk factor for chyle leakage. (p-value 0.001) It is widely known that chylothorax can show up anywhere from the first to the tenth day after a surgery [4]. The most significant increase in incidence was seen on the third postoperative day in the current investigation.

According to our findings, chylothorax is negatively associated with both advancing age and increasing body weight. The likelihood of developing chylothorax reduced with both increasing age

Table 2. Comparison of RACHS scoring in chylothorax and non-chylothorax group.

RACHS 1 SCORE	Chylothorax	Non chylothorax	Odds ratio (95% CI)	p-value
1	10 (10.4%)	38 (19%)	–	0.001
2	34 (35.4%)	148 (74%)	1.58 (0.75–3.37)	0.231
3	24 (25%)	06 (03%)	15.03 (3.52–64.2)	0.0001
4	10 (10.4%)	06 (03%)	2.73 (0.65–11.55)	0.022
5	03 (3.1%)	01 (0.5%)	1.53 (0.61–13.55)	0.003
6	11 (11.5%)	01 (0.5%)	4.13 (1.65–15.55)	0.004
7, uncategorized	04 (4.2%)	00	–	–

Table 3. Characteristics of quantitative and qualitative variables of chylothorax patients.

Variables		Median (IQR)
Chyle appearance day		03 (2–5.5)
Octreotide days		10 (8.75–16.25)
Chyle duration		03 (2–7.75)
Midodrine Given	Yes	02 (2.08)
	No	94 (97.92)
Chyle resolve Monogen	Yes	76 (79.17)
	No	20 (20.83)
TPN	Yes	18 (18.75)
	No	78 (81.25)
Chyle resolve Octreotide	Yes	16 (16.67)
	No	02 (2.08)
Surgery for Chylothorax	Yes	04 (4.17)
	No	92 (95.83)

and weight. As children got older than 12 months, the risk dropped by 25%. It has been hypothesized that as one gets older and puts on more weight, the likelihood of chyle duct injury decreases [1].

In the event that chylothorax is encountered, a higher RACHS-1 score represents increased associated risk. It has been said that its Risk adjustment for Congenital Heart Surgery (RACHS) score for group 1 is 0%, while its score for groups 5 and 6 is 5.6% [14]. In the population that we studied, we discovered that 29.2% of cases had a RACHS-1 score of four or more. These cases included complex surgeries such as the repair of the hypoplastic or interrupted aortic arch, complex arterial switch operations, and neonatal aortic valve operations in group 4, while truncus arteriosus repair tumbled into group 5, and the Norwood operation for hypoplastic left heart syndrome plunged into group 6 respectively. It has been determined that the complicated nature of the surgery is a permanent risk factor in the progression of chylothorax. According to the findings of Day TG et al., RACHS-1 group 4 is linked with the greatest risk, with an odds ratio that ranges between 2.22 and 2.98 [15]. However, in our multivariate study, we discovered that the RACHS-1 score is not always a consistent component in the development of chylothorax. Table 5.

According to the researches, the genetic component poses a substantial threat [16]. It occurs as a result of changes in vascular pathways and lymphatic dysplasia, both of which are characteristic with certain syndromes, the most notable of which being down syndrome, Turner's syndrome and Noonan syndrome [17]. We reported a total of twenty children with Down syndrome, which accounts for 20.8% of the total, whereas the control group only included six children, which accounts for 3%. (p-value 0.001) In light of this, we conducted a multivariate regression analysis in our study and found similar results. Table 5.

The majority of patients in our research group who had chylothorax also had negative fluid balance, however this finding had no direct connection with chylothorax. At 72 h postoperative duration, 45.8% of patients had a negative fluid balance, whereas in the control group, 38.1% children had shown a negative fluid balance. Both groups had mostly a negative fluid balance, indicating the poor relation with occurrence of chylothorax. Despite the fact that an excessive amount of fluid has been identified as a risk that is connected with acute renal damage and inadequate cardiac output, it still has to be regulated for overall outcome [18]. Perry and his colleagues looked into the possibility of a link between fluid balance and chylothorax, but they came up with no positive conclusion [5]. Given that fluid overload is a well-known risk factor for extended periods of mechanical breathing, longer lengths of hospital stays, and fatality So, it is possible that in the future, research study with a subject of an association for chylothorax with fluid overload may be conducted at a broad level.

In univariate analysis, the bypass time was associated with the development of chylothorax, and that remain significant on logistic regression. This has not been shown clearly in previous literature. We found that bypass time was 128 ± 76 with median time of 120 min. With increasing bypass time, there is more chances of chylothorax. Non-open-heart surgeries had insignificance as univariate factor but has been

Table 4. Comparison of quantitative variables in chylothorax and non-chylothorax group.

Variables	Chylothorax n = 96 Mean (SD)	Non Chylothorax n = 200 Mean (SD)	Odds ratio (95% CI)	p-vlaue
Weight	6.75(4.24)	8.64(4.09)	0.88(0.83, 0.94)	0.0001
Age	11.72(15.27)	15.27(12.09)	0.98(0.95, 0.99)	0.001
Clamp time	74.57 (53.56)	39.95(13.77)	1.04(1.03,1.05)	0.002
Bypass time	128.34(76.25)	84.3(25.19)	1.02(1.01, 1.03)	0.003
ICU days	21.26(30.03)	5.34(3.27)	1.34(1.24, 1.46)	0.0001
Hospital days	31.92(43.21)	10.97(5.39)	1.18(1.13, 1.23)	0.02
Chest Tube duration	10.44(7.83)	3.87(2.49)	1.43(1.29, 1.59)	0.0001

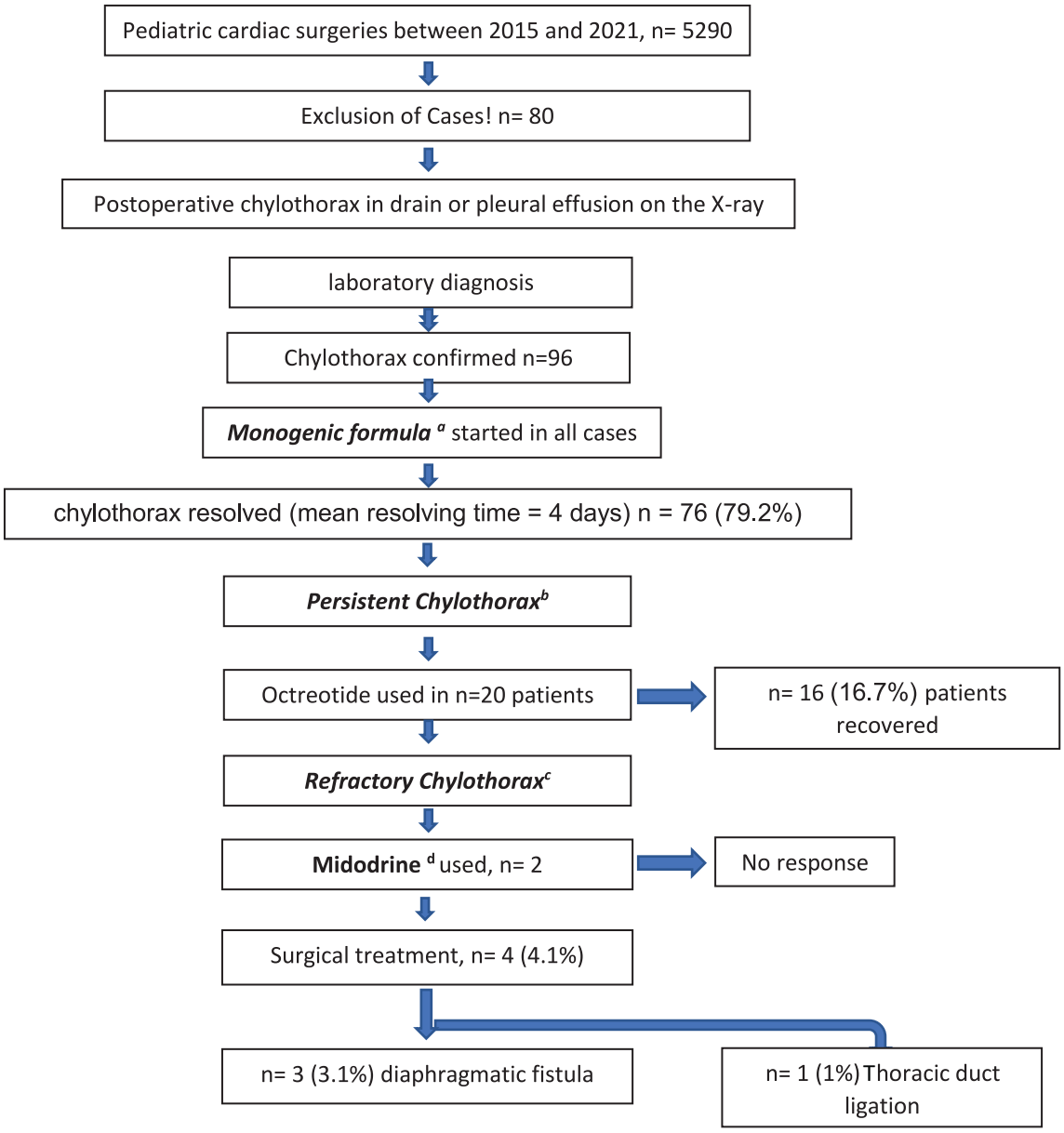

Fig. 1. Treatment algorithm for post cardiac surgery chylothorax. a. A formula, low in long chain triglycerides and high in medium chain triglycerides. b. Chylothorax that not resolved after 2 weeks of monogen therapy. c. Chylothorax that not respond after one week of octreotide therapy. d. midodrine, an α1-adrenergic agonist that causes vasoconstriction of the lymph system, reducing chyle flow.

Table 5. Multivariable logistic regression analysis.

	Odds ratio (95% confidence interval)	p-value
Weight Digits	0.91(0.72, 1.14)	0.409
Age Digits	1.02 (0.95, 1.09)	0.518
Gender	1.12 (0.51, 2.43)	0.78
Down Syndrome	12.39 (3.91, 39.22)	0.02
Fluid Balance		
positive	1.24 (0.47, 3.27)	0.668
euvolemic	1.17 (0.49, 2.78)	0.72
Non-open-heart Surgeries	25.96 (3.29, 204.92)	0.002
RACHS-1	1.28 (0.73, 2.26)	0.388
Bypass Time	1.02 (1.01, 1.02)	0.001

found a major contributor in incidence of chylothorax on logistic regression. Table 5.

Our study showed that medium-chain fatty acid treatment with a monogen diet was effective in 76 (79.2%). The mean response time was 8.3 days. We never use the prophylactic monogen diet irrespective of the complexity of procedures and risks because, in children, brain myelination is dependent on equilibrated nutrition, including fatty acids. Our response is comparable to another study which showed 71% efficacy [6].

TPN was used in 18 (18.8%) children. In our institute, TPN is not started as a treatment for

chylothorax but rather as a supportive tool to fulfill the nutrition requirement. TPN has been linked with many complications such as thrombosis, central line infections, hyperglycemia, and liver and kidney injury. There may be associated complications related with TPN, but our main focus of study was on chylothorax risk factors [19].

In 16 (16.7%) children, chyle resolve with octreotide. Mean octreotide days were 14.6 ± 9.4, with infusion days from 7 to 38 days maximum. It is a long-acting somatostatin analog given either subcutaneous or intravenous that operates unswervingly on vascular somatostatin receptors and lessens lymph fluid emission. Additionally, by increasing splanchnic arteriolar resistance and decreasing intestinal blood flow, octreotide indirectly reduces lymphatic flow. Within 30 min of infusion, it gained the peak serum concentration. In our study, all children received the Intravenous Octreotide. Two patients received midodrine, an α1-adrenergic agonist that causes vasoconstriction of the lymph system and may reduce the chyle flow. Chyle output only decreased temporarily after initiating midodrine, but it remained to drain. We prescribed the midodrine 2.5 mg, Q12 hourly, and continued for 1 and half months. Some case reports are related to a substantial decrease in chyle output in which the midodrine dose was 1 mg, Q8 hourly [20,21]. In our study, both children underwent surgery. A total of four (4.1%) children had surgery for chylothorax, including one thoracic duct ligation and three diaphragmatic fistulae.

Although chylothorax has been observed with certain risk factors, still it's unclear to predict preoperatively which patient is more vulnerable. There may be a role of lymphangiogram to rule out the anatomical variations, but that is not practically possible due to cost-effectiveness, ICU care, and hospital stay. Although, in future we may look for most effective and comfortable means by building a scoring system to intimate the risk for chylothorax.

5. Limitations

There are few limitations in our study. First, it was a retrospective analysis with the possibility of missing the data in the documentation review. There is a lack of documentation at some points as single or multiple pump runs. We calculate our findings of all patients and the chylothorax group separately as a comparison. Furthermore, this is a single-center study, and a larger cohort might enable us to draw additional clues regarding specific results.

6. Conclusion

Chylothorax is a frequently encountered problem in pediatric cardiac surgical ICU. Increasing bypass time causes a linear rise in its incidence. Younger age, Low weight, Syndromic patients, redo surgeries, non-open-heart surgeries and arrhythmias are also associated factors. Gender, Fluid balance, and RACHS-1 Scoring showed insignificant association. Monogen is an effective therapy, while midodrine needs further investigation and trials.

Author contribution

Conception and design of Study: MS, YAA, RMEB, BA, PM, GM, FK, ZAH. Literature review: MS, YAA, RMEB, BA, PM, GM, FK, ZAH. Acquisition of data: MS, YAA, RMEB, BA, PM, GM, FK, ZAH. Analysis and interpretation of data: MS, PM, FK. Research investigation and analysis: MS, PM, GM. Data collection: BA, PM. Drafting of manuscript: MS, YAA, RMEB, GM, FK. Revising and editing the manuscript critically for important intellectual contents: YAA, RMEB, GM. Data preparation and presentation: MS, YAA, PM, GM. Supervision of the research: MS, YAA, GM, FK. Research coordination and management: MS, YAA, RMEBT.

Conflict of interest

There is no conflict of interest.

Acknowledgement

This work was not possible without the help of heart center research team.

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