

## Risk factors and early outcomes of chylothorax following congenital cardiac surgery: A single-center experience

*Doğumsal kalp cerrahisi sonrası şilotoraksın risk faktörleri ve erken dönem sonuçları: Tek merkez deneyimi*

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### ABSTRACT

**Background:** This study aims to investigate the incidence and risk factors for chylothorax and to evaluate the effect of chylothorax on the early postoperative outcomes following congenital cardiac surgery.

**Methods:** A total of 1,053 patients (606 males, 447 females; median age: 12 months; range, 3 days to 48 years) who underwent surgery for congenital heart disease at our institute between January 2018 and December 2019 were retrospectively analyzed. Patients with chylothorax were identified and the data of this cohort was compared with the entire study population. Following the diagnosis of chylothorax, a standardized management protocol was applied to all patients.

**Results:** Of 1,053 patients operated, 78 (7.4%) were diagnosed with chylothorax. In the univariate analysis, younger age, peritoneal dialysis, preoperative need for mechanical ventilation, surgical complexity, delayed sternal closure, high vasoactive inotrope score in the first 24 h after operation, residual or additional cardiac lesions which required reoperations were found to be the risk factors for chylothorax ( $p<0.05$ ). In the multivariate analysis, the correlation persisted with only younger age, infections, and peritoneal dialysis requirement ( $p<0.05$ ). In the chylothorax group, ventilation times were longer, and re-intubation and infection rates were higher ( $p<0.05$ ). Although the length of intensive care unit and hospital stay was significantly longer in this patient group, there was no significant association between the development of chylothorax and in-hospital mortality ( $p>0.05$ ).

**Conclusion:** Chylothorax following congenital cardiac surgery is a significant problem which prolongs the length of hospital stay and increases the infection rates. Complex cardiac pathologies which require surgery at early ages and re-operations are risk factors for chylothorax. Although there is no consensus on the most optimal therapeutic strategy, standardizing the management protocol may improve the results.

**Keywords:** Chylothorax, congenital cardiac surgery, postoperative complications.

### ÖZ

**Amaç:** Bu çalışmada doğumsal kalp cerrahisi sonrası şilotoraks sıklığı ve risk faktörleri araştırıldı ve şilotoraksın ameliyat sonrası erken dönem üzerine etkileri değerlendirildi.

**Çalışma planı:** Ocak 2018 - Aralık 2019 tarihleri arasında merkezimizde doğumsal kalp hastalığı nedeniyle ameliyat edilen toplam 1053 hasta (606 erkek, 447 kadın; medyan yaş: 12 ay; dağılım, 3 gün - 48 yıl) retrospektif olarak incelendi. Şilotorakslı hastalar belirlendi ve bu grubun verileri, tüm çalışma popülasyonu ile karşılaştırıldı. Şilotoraks tanısı sonrasında tüm hastalara standardize edilmiş bir tedavi protokolü uygulandı.

**Bulgular:** Ameliyat edilen 1053 hastanın 78'ine (%7.4) şilotoraks tanısı kondu. Tek değişkenli analizde genç yaş, periton diyalizi gereksinimi, cerrahi öncesi mekanik ventilasyon ihtiyacı, cerrahi kompleksite, sternumun geç kapatılması, ameliyat sonrası ilk 24 saatte yüksek vazoaktif inotrop skor, yeniden ameliyat gerektiren ilave veya rezidü kardiyak lezyonlar şilotoraksın risk faktörleri olarak bulundu ( $p<0.05$ ). Çok değişkenli analizde ise, bu ilişki yalnızca genç yaş, enfeksiyonlar ve periton diyaliz gereksinimi ile izlendi ( $p<0.05$ ). Şilotoraks grubunda ventilasyon süresi daha uzun ve yeniden entübasyon ve enfeksiyon oranı daha fazla idi ( $p<0.05$ ). Bu hasta grubunda yoğun bakım ünitesi ve hastanede kalış süresi anlamlı olarak daha uzun olmasına rağmen, şilotoraks gelişimi ve hastane mortalitesi arasında anlamlı bir ilişki gözlenmedi ( $p>0.05$ ).

**Sonuç:** Doğumsal kalp cerrahisi sonrası şilotoraks hastanede kalış süresini uzatan ve enfeksiyon oranını artıran ciddi bir problemdir. Erken yaşta cerrahi gerektiren kompleks kardiyak patolojiler ve yeniden ameliyat gereksinimi şilotoraksın risk faktörleridir. Optimum tedavi protokolüne ilişkin bir konsensüs olmamakla birlikte, tedavi protokollerinin standardize edilmesi sonuçları iyileştirebilir.

**Anahtar sözcükler:** Şilotoraks, doğumsal kalp cerrahisi, ameliyat sonrası komplikasyonlar.

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Chylothorax is the presence of lymphatic fluid in the pleural space. Chylothorax following congenital heart surgery is not uncommon, particularly at centers performing complex congenital cardiac surgeries, and is a challenging problem that prolongs the length of intensive care unit (ICU) and hospital stay. Chylothorax may be the result of a direct injury to the thoracic duct while cannulating superior vena cava for cardiopulmonary bypass (CPB), surgical trauma to the thoracic duct or one of its tributaries during dissection, increased central venous pressure (CVP) exceeding lymphatic pressure after cavopulmonary anastomosis or obstruction of lymphatic drainage by central venous thrombosis.<sup>[1,2]</sup> With chylous drainage, loss of fat, electrolytes, proteins, and lymphocytes may result in immune compromise and malnutrition, fluid accumulation in the pleural space may compress the lungs, disturb respiratory mechanics and may result in prolonged mechanical ventilation (MV).<sup>[2]</sup> Eventually, chylothorax is associated with higher rates of postoperative morbidity and mortality.<sup>[1,3]</sup>

Several studies have attempted to identify potential risk factors for the development of chylothorax after cardiac surgery in children. Some of them have described surgical complexity, increasing CPB times, and the presence of genetic disease as independent risk factors for the development of chylothorax.<sup>[3,4]</sup> In the present study, we aimed to investigate the incidence of chylothorax, evaluate the potential risk factors for chylothorax, and describe the effect of chylothorax on the early postoperative outcomes following congenital cardiac surgery using a standardized treatment protocol.

## PATIENTS AND METHODS

This single-center, retrospective study was conducted at Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Pediatric Cardiac Intensive Care between January 2018 and December 2019. We reviewed the records of a total of 1,053 patients (606 males, 447 females; median age: 12 months; range, 3 days to 48 years) who underwent surgery for congenital heart disease at our institute. The Society of Thoracic Surgeons (STS)/European Association for Cardio-Thoracic Surgery (EACTS), abbreviated as the STAT scoring system, which stratifies congenital heart surgery procedures according to their relative risk of in-hospital mortality was used to assess operative complexity.<sup>[5]</sup> If reoperations were required at the same admission, it was accepted as a single hospitalization. Patients with chylothorax were identified, and the data of this cohort was compared with the entire population to

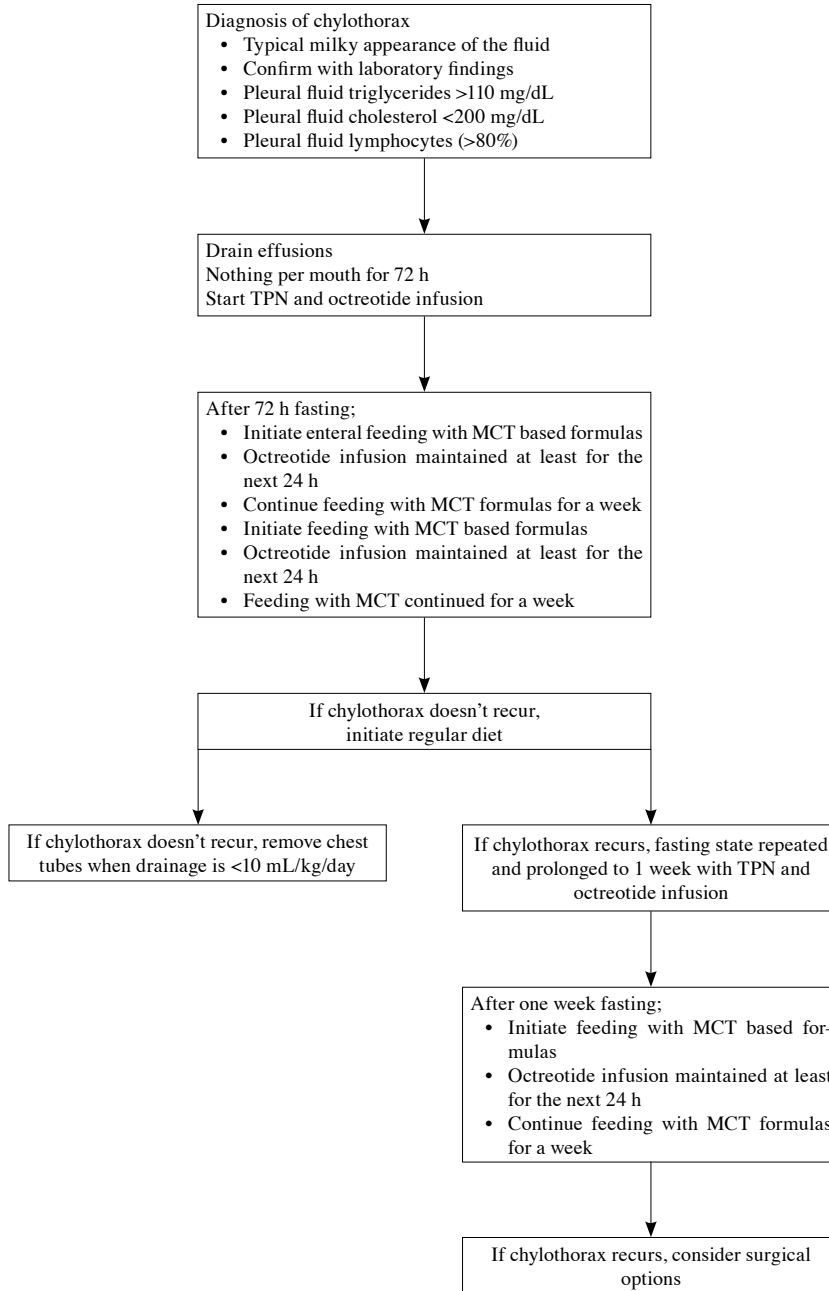
describe risk factors and the impact of chylothorax on postoperative outcomes. Chylothorax was diagnosed by the presence of typical milky appearance of the effusions and confirmed with laboratory analysis (triglycerides >110 mg/dL, total cholesterol levels <200 mg/dL and lymphocytic predominance >80% in the fluid plus sterile cultures). At our unit, according to our experience and the literature data, we standardized the management protocol (Figure 1). We drained the effusions and kept patients *nil per os* for 72 h, simultaneously started total parenteral nutrition (TPN) and octreotide infusion, with a dose range between 5 and 8 µg/kg/h. Without exception, in the fasting state, the milky appearance disappeared, and the amount of drainage decreased significantly. After 72-h fasting, feeding was initiated with medium-chain triglyceride (MCT)-based formulas. Octreotide infusion was continued at least for the next 24 h and, then, stopped and feeding with MCT was maintained for a week. Afterwards, regular diet was initiated. If chylous drainage recurred, the same protocol was repeated, and the fasting state was prolonged to one week. We removed chest tubes, when the output was <10 mL/kg/day with regular diet.

## Statistical analysis

Statistical analysis was performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in median and interquartile range (IQR) or min-max values, while categorical variables were expressed in number and frequency. Age, STAT score and reintervention for primary cardiac pathology were treated as categorical variables. For the comparison, the newborn, STAT-1, and patients who had no intervention groups were designated as the reference categories. Univariate binary logistic regression analysis was applied for each variable to analyze the risk factors for chylothorax. The multivariate model was constructed using binary logistic regression with the backward conditional method. All variables that were significant in the univariate analysis were included, and the final model was reported. The effect of chylothorax on outcomes was analyzed using the chi-square or Fisher exact tests for categorical variables and the Mann-Whitney U test for continuous variables as appropriate. A *p* value of <0.05 was considered statistically significant.

## RESULTS

Of a total of 1,053 patients undergoing congenital cardiac surgeries, 78 (7.4%) were diagnosed with chylothorax. The patients without chylothorax was



**Figure 1.** Chylothorax management protocol.

TPN: Total parenteral nutrition, MCT: Medium-chain triglyceride.

defined as the control group. Demographic and clinical characteristics of the entire study population are shown in Table 1.

The results of the univariate and multivariate regression analyses are shown in Table 2. In the univariate analysis, younger age, lower body weight,

peritoneal dialysis requirement, preoperative need for MV, surgical complexity, delayed sternal closure, high vasoactive inotrope score (VIS) in the first 24 h following operation, residual or additional cardiac lesions which required reoperations and infections were significantly associated with

**Table 1. Demographic and clinical characteristics of patients (n=1,053)**

Variables	n	%	Median	IQR
Age at surgery (month)			12	2-54
Sex				
Female	447	43		
Body weight (kg)			8	4-15
Preoperative mechanical ventilation	84	8		
Type of repair				
Univentricular	231	22		
Biventricular	819	78		
One-and-a-half ventricular	3	0		
Type of incision				
Sternotomy	1024	97.2		
Thoracotomy	29	2.8		
Repeat sternotomy	263	25		
STAT score				
1	148	14		
2	363	35		
3	287	27		
4	213	20		
5	42	4		
Delayed sternal closure	231	22		
Cardiopulmonary bypass time (min)			142	99-187
Cross-clamp time			77	43-116
Cases with chylothorax	78	7.4		
Cases responded to conservative measures	73	93.6		
Cases underwent thoracic duct ligation	5	6.4		

IQR: Interquartile range; STAT: Society of Thoracic Surgeon/European Association for Cardio-Thoracic Surgery.

chylothorax ( $p < 0.05$ ). However, in the multivariate analysis, the correlation persisted with only younger age, infections, and peritoneal dialysis requirement ( $p < 0.05$ ). The chylothorax and control group infection rates were 47% and 13%, respectively. The most commonly documented infection in both groups was ventilator-associated pneumonia (VAP) (Table 2).

There was also a strong tendency in the chylothorax group toward longer ventilation times and higher re-intubation rates ( $p < 0.05$ , Figure 2, Table 3). Although the length of ICU and hospital stay was significantly longer in the chylothorax group ( $p < 0.05$ ), there was no significant association between the development of chylothorax and in-hospital mortality ( $p > 0.05$ ) (Figures 3 and 4, Table 3).

According to correlation of the incidence of chylothorax with the procedural complexity, the

STAT-5 group had the highest risk, with an odds ratio (OR) of 8.05, compared to the STAT-1 group (Table 2). Twenty-nine patients were operated via a thoracotomy incision, and there was no association between thoracotomy incision and the incidence of chylothorax ( $p > 0.05$ , Table 2).

Chylothorax was significantly more frequent following complete atrioventricular septal defect (CAVSD) repair, compared to the rest of the pathologies ( $p = 0.008$ , Table 2). When the surgery involved aortic arch reconstruction, the risk of chylothorax increased significantly ( $p < 0.001$ , Table 2).

All cases with chylothorax responded to conservative management strategy except five (6.4%) cases who required surgical thoracic duct ligation after a median of 14 (IQR: 12 to 20) days following the diagnosis (Table 1).

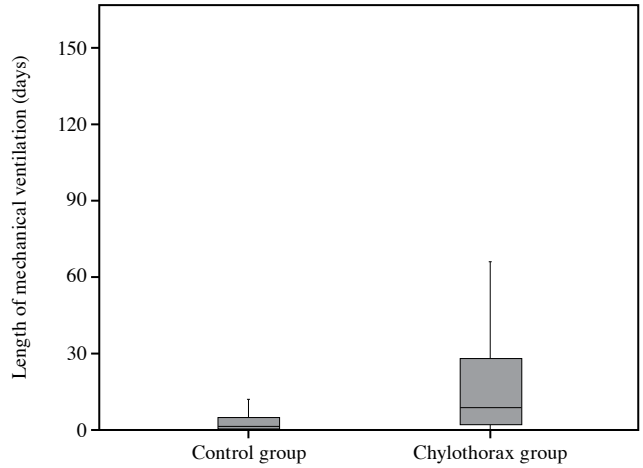
**Table 2. Chylothorax risk factor analysis**

	Control (n=975)				Chylothorax (n=78)				Univariate			Multivariate		
	n	%	Median	IQR	n	%	Median	IQR	p	OR	95% CI for the OR	p	OR	95% CI for the OR
Age at surgery (month)			13	3-56			3	1-12	0.000	0.970	0.955-0.984	0.001	0.973	0.957-0.989
Age group									Reference category					
Newborn, 0-30 days	197	20			28	36			0.517	0.834	0.482-1.443			
Infant, 31 days-1 year	253	26			30	39			0.005	0.414	0.225-0.761			
Young child, 1-6 years	323	33			19	24			0.010	0.073	0.010-0.541			
Older child, 6-12 years	97	10			1	1			0.997	0.000	NA			
Teenager, 12-18 years	78	8			0	0			0.998	0.000	NA			
Adult, >18 years	27	3			0	0								
Sex									0.979					
Female	414	43			33	42								
Body weight (kg)			9	4-16			5	3-8	0.000	0.906	0.863-0.951			
Preoperative mechanical ventilation	70	7			14	18			0.001	2.867	1.530-5.372			
Univentricular	209	21			22	28								
Biventricular	763	78			56	71			0.344					
One-and-a-half ventricular	3	0			0	0								
STAT score									Reference category					
1	145	15			3	4			0.020	4.197	1.258-13.997	0.055	3.413	0.974-11.953
2	334	34			29	37			0.014	4.612	1.369-15.538	0.227	2.207	0.611-7.968
3	262	27			25	32			0.043	3.662	1.041-12.883	0.735	1.261	0.329-4.835
4	198	20			15	19			0.004	8.056	1.922-33.768	0.584	1.551	0.323-7.463
5	36	4			6	8			0.045	0.524	0.279-0.986			
Repeat sternotomy	251	26			12	15			0.192	2.054	0.696-6.058			
Thoracotomy	25	2.6			4	5.1			0.000	2.713	1.683-4.372	0.073	2.132	0.932-4.874
Delayed sternal closure	199	20			32	41			0.001	1.032	1.012-1.051			
Vasoactive inotropic score			13	7-17			17	12-25	0.000					
Aortic arch reconstruction	130	85.5			22	14.5			0.008	2.807	1.324-6.039			
CAVSD repair	43	4.4			9	11.5			0.945					
Levosimendan	36	4			3	4			0.000	4.316	2.622-7.106	0.005	3.032	1.408-6.523
Peritoneal dialysis	116	12			29	37			0.057					
ECMO	96	10			13	17			0.000	6.137	3.788-9.942	0.000	4.930	2.574-9.443
Infection, culture positive	125	13			37	47								

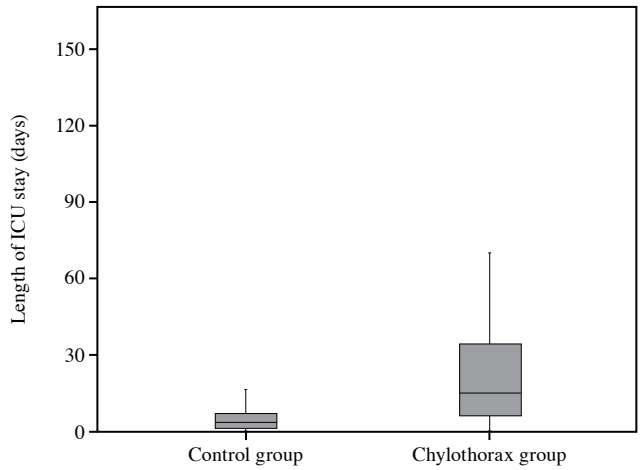
**Table 2. Continued**

	Control (n=975)				Chylothorax (n=78)				Univariate			Multivariate		
	n	%	Median	IQR	n	%	Median	IQR	p	OR	95% CI for the OR	p	OR	95% CI for the OR
<b>Infection site</b>														
VAP	59	47.2			26	70.3								
Bloodstream infection	25	20			4	10.8								
Surgical site infection	32	25.6			4	10.8								
Mediastinitis	7	5.6			2	5.4								
Catheter related bacteremia	2	1.6			1	2.7								
<b>Reintervention for the primary cardiac pathology</b>														
No re-intervention	879	90.2			64	82.1								
Surgery	79	8.1			14	17.9			Reference category					
Only catheter angiography	17	1.7			0	0			0.004	2,481	1,332-4,623	0.998	0,000	NA

IQR: Interquartile range; CI: Confidence interval; OR: Odds ratio; VAP: Ventilator-associated pneumonia; STAT: Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery; CAUSD: Complete atrioventricular septal defect; ECMO: Extracorporeal membrane oxygenation; NA: Non-applicable.

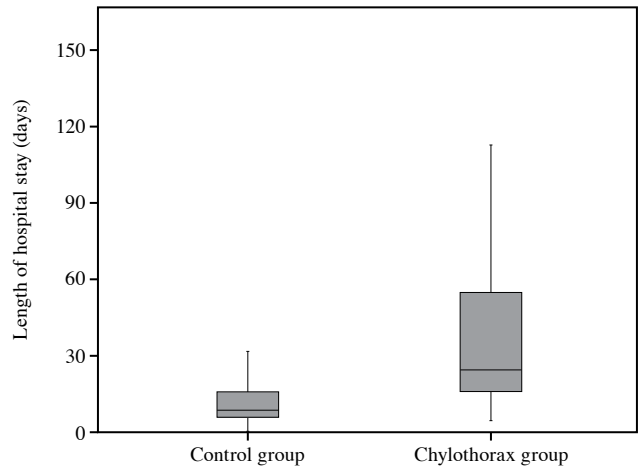


**Figure 2.** Effect of chylothorax on duration of mechanical ventilation.



**Figure 3.** Effect of chylothorax on length of ICU stay.

ICU: Intensive care unit.



**Figure 4.** Effect of chylothorax on length of hospital stay.

**Table 3. Effect of chylothorax on early postoperative outcomes**

	Control (n=975)				Chylothorax (n=78)				p
	n	%	Median	IQR	n	%	Median	IQR	
Re-intubation	168	17			37	49			<0.001
Duration of mechanical ventilation			1	0-5			9	2-28	0.001
Duration of mechanical ventilation (categorical)									
<2 days	574	59			13	17			
2-7 days	203	21			21	28			
8-14 days	111	12			8	11			
>14 days	81	8			33	44			
Duration of ICU stay			4	2-8			13	7-36	<0.001
Duration of hospital stay			9	6-16			25	16-55	<0.001
Mortality	88	9			11	14			0.120

ICU: Intensive care unit.

## DISCUSSION

Our report is one of the largest single-center study in the literature which examines chylothorax. Similar to the previous studies, which had incidences varying from 0.85 to 15.8%,<sup>[2,4,6]</sup> the incidence of chylothorax in our group was 7.4%. Over the years, despite increased experience in surgical procedures, improvements in postoperative care, and a better understanding of the mechanism of chylothorax, the rate of chylothorax seems to have increased, which can be attributed to the increased complexity of pediatric cardiac surgical procedures.<sup>[2]</sup> In our study, the univariate analysis revealed that younger age, peritoneal dialysis requirement, infections, preoperative need for MV, surgical complexity, delayed sternal closure, high VIS in the first 24 h after the operation, presence of residual or additional cardiac lesions which required reoperations, aortic arch reconstructions, CAVSD repairs were associated with chylothorax. However, in the multivariate analysis, only younger age, peritoneal dialysis requirement, and infections were found to be associated with chylothorax. Our study showed that CAVSD repairs constituted an increased risk for chylothorax. This can be easily attributable to the association of CAVSD with Down syndrome, as the association of this syndrome with lymphatic anomalies was previously described.<sup>[7]</sup> Although it did not reach statistical significance, transposition of great arteries (TGA) was the other particular pathology that was found to be associated with chylothorax. In the literature, a tendency to development of chylothorax following TGA repair was reported, and venous clots and lymphatic abnormalities were described as the

underlying mechanisms.<sup>[8]</sup> A higher incidence of chylothorax (11 to 33%) following complex procedures such as Norwood operations, atrioventricular septal defect, TGA, and truncus arteriosus repairs was described.<sup>[3,4,6,9]</sup> In such a way that supports these studies, our study showed the association between the complexity of the procedure and the risk of chylothorax. In the literature, cavopulmonary anastomoses (Fontan and Glenn procedures) were described as risk factors for chylothorax.<sup>[2,10]</sup> Although we had plenty of cases with univentricular palliation (21.9% of the population), we could not show any association between the risk of chylothorax and univentricular palliations. This finding suggests that elevated CVP may not be the major driver for chylothorax in every univentricular palliation.

Younger age was the other factor for the risk of chylothorax.<sup>[11]</sup> Higher incidence in young children may be related to a larger number of lymphatics and lymph nodes that can be disrupted while operating in a limited surgical field. Also, large catheter sizes relative to the vein diameters may occlude the lumen in small children, increase the resistance to thoracic duct drainage, or exacerbate thrombus formation. Upper body central venous lines (CVLs) were found to be associated with postoperative chylothorax in infants after cardiac surgery.<sup>[12]</sup> Conventionally, we used jugular veins for central venous access, and cases in whom femoral veins cannulated were limited in number which precluded a thorough evaluation of the CVL insertion sites in terms of the risk of chylothorax.

The current study showed that residual or additional cardiac lesions, which required reoperations, were

associated with the risk of chylothorax. The incidence of reoperations due to cardiac pathology was 18% for the chylothorax group and 8.1% for the ones who did not have it. Similar to our results, Mery *et al.*<sup>[3]</sup> reported that the incidence of postoperative chylothorax increased, when patients required several cardiac procedures during the same admission.<sup>[3]</sup> This finding emphasizes the importance of detailed evaluation prior to surgery, proper performance of the index surgery, and comprehensive evaluation during the early postoperative period. Baseline echocardiography should be done to assess the adequacy of surgical repair and the presence of residual or additional cardiac lesions. If effusions persist or recur, cardiac catheterization, computed tomography scan, lymphangiography, or magnetic resonance (MR) lymphangiography may help to address the underlying pathology and guide the treatment modality.

With chylous leakage, loss of immunoglobulins, lymphocytes, lipids, and electrolytes may result in a catabolic state, malnutrition, immunosuppression, and hematological complications.<sup>[13]</sup> Large effusions may compromise lung functions, which is particularly substantial in neonates and single ventricle physiology.<sup>[9]</sup> Our data supported most of these findings with the increased incidence of re-intubation, prolonged length of MV days, and prolonged ICU and hospital stay. All these risk factors may have predisposed to increased infection rates.<sup>[10]</sup> Most commonly, we isolated microorganisms from respiratory secretions, which again underlines the importance of VAP in ICUs. In children who had congenital cardiac surgery, a higher VAP rate and its impact on morbidity and mortality were reported previously, and this had an undeniable burden on the ICU course of these particular patients.<sup>[14]</sup> Although chylothorax causes significant morbidity and complicates the recovery, inconsistent with other studies, we found no significant association between chylothorax and mortality.<sup>[1,3]</sup>

In the literature, there is no clear consensus regarding the most optimal management protocol.<sup>[3,11,15]</sup> In general, a stepwise approach is administered, starting with conservative therapy and reserving interventional therapies for refractory cases.<sup>[11,16]</sup> Dietary modifications, either in the form of feeding with MCT formulas or *nil per os*, aim to diminish chyle production to allow spontaneous healing of the injured thoracic duct. Somatostatin and its long-acting synthetic analog octreotide reduce intestinal blood flow and motility to diminish lymph flow in the thoracic duct.<sup>[2,15]</sup> Surgical ligation of the thoracic duct and pleurodesis are the surgical

options.<sup>[17]</sup> Prior to the study period, we used a wide variety of combinations of these therapies. After gaining experience, we realized that utilizing *nil per os* sooner made rapid progression in the amount and duration of effusion. The literature reported that institution of a guideline was associated with improvements in multiple outcomes.<sup>[18]</sup> Therefore, we standardized the management strategy, and this protocol might have improved our results, although it needs further comparative studies to draw more reliable conclusions.

The indications and timing of surgery for refractory chylothorax are yet to be established. Some authors have suggested that it should be considered when chylothorax does not improve within 10 days, while others have recommended surgical intervention when chylous drainage persists after two to five weeks of conservative management.<sup>[19,20]</sup> Over the study period, five patients underwent ligation of the thoracic duct after median 14 (IQR: 12 to 20) days following the diagnosis.

Nonetheless, there are several limitations to the present study. First, it has a single-center, retrospective design, and the data were derived from a pediatric cardiac ICU database; therefore, some cases may have been missed. Second, we were unable to use more sophisticated diagnostic and therapeutic options with lymphangiography or MR lymphangiography. That is why the underlying mechanism could not be delineated, and transcatheter interventions were not performed. Third, data regarding the timing of diagnosis in terms of the cardiac surgical procedure and the location of the chylous effusion, either from the right or left pleura, were missing.

In conclusion, we present one of the largest single-center study in the literature examining the risk factors for chylothorax following congenital cardiac surgery. Our study results showed that the complex congenital cardiac pathologies which needed to be repaired at early ages and residual or additional cardiac pathologies which needed to be operated at the same admission were more likely to result in chylothorax. Chylothorax is a challenging problem with increased infection rates and prolonged ICU and hospital stay. However, there are currently no well-described strategies to prevent it yet and, to date, there is no clear consensus on the most optimal management protocol. Based on our data, we can suggest that implementing a management guideline may improve results, although further studies are warranted.



**Ethics Committee Approval:** The study protocol was approved by the Dr. Siyami Ersek Thoracic Cardiovascular Surgery Training and Research Hospital Ethics Committee (date: 10.11.2022, no: E-28001928-604.01.01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from the parents and/or legal guardians of the patients.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Idea/concept: E.H.Y., N.Y., O.K., M.Ç.; Design: E.H.Y., N.Y., M.Ç.; Data collection: E.H.Y., N.Y.; Analysis: E.H.Y., O.K.; Writing article: E.H.Y., N.Y., O.K., M.Ç.; Critical review: E.H.Y., M.Ç., O.K., N.Y.

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