VILNIUS UNIVERSITY
MEDICAL FACULTY

Medicine

Institute of Clinical Medicine, Clinic of Cardiovascular Diseases

Subojhan Kandeepan, 6th Year, Group 7

INTEGRATED STUDY MASTER'S THESIS

Lymphatic Hypertension Complications in Fontan Patients. Literature Review

Supervisor: **Prof. Dr. Virgilijus Tarutis**

The Head of the Department/Clinic: **Prof. dr. Sigita Glaveckaitė**

Vilnius, 2025

Subojhan.kandeepan@mf.stud.vu.lt

Table of Contents

1. Summary

Fontan Surgery is established as a definitive palliative medical care for single-ventricle congenital heart disease. This intervention method involves in transporting systemic venous blood to the pulmonary arteries and avoiding the non-functional ventricle. Fontan surgery was first done by Francis Fontan in 1971. Since its invention, the procedure has undergone many changes and alterations in order to enhance and optimize hemodynamic and reduce Fontan surgery-associated morbidity. Even with the advancement of the procedure, long-term survivors often develop severe lymphatic and venous pressure-related complications such as lymphatic hypertension which leads to chylothorax, plastic bronchitis, and protein-losing enteropathy (PLE), these conditions exacerbate morbidity and have an impact in the rate of mortality.

This literature review comprehensively reviews the evolution of Fontan surgery, underlining the advancement in Fontan surgical methods, and understanding the complexity of post-Fontan surgical outcomes, as well as the complications related to lymphatic hypertension in Fontan patients. Furthermore, it analyses the challenges of diagnosing and managing lymphatic complications that arise after Fontan surgery. Detailed analysis of lymphatic system's anatomy and physiology, post-Fontan surgical complications of lymphatic system, assessment of surgical advancements and exploration of diagnostic modalities and treatment of lymphatic hypertension in Fontan patients are included in the objective of this literature review. Despite its important role in the management of univentricular heart disease, the Fontan procedure requires a multidisciplinary approach to manage its multi-system post-surgical complications. Ongoing advances in diagnostic techniques and treatment methods are important to consider in better outcomes in Fontan patients. Additionally, understanding the interplay between increased systemic venous pressure and impaired lymphatic function will be vital for establishing targeted treatment to reduce the post-surgical complications in Fontan patient.

2. Keywords

Congenital heart disease (CHD), Fontan surgery, Chylothorax, Plastic Bronchitis (PB), Protein-losing enteropathy (PLE), Dynamic-contrast magnetic resonance lymphangiography (DCMRL), Heart transplantation.

3. Introduction

The way to treat congenital heart disease for patients with single ventricles is called Fontan surgery. It is a palliative treatment method performed on single-ventricle patients who are

excluded from consideration for repair of biventricular heart. This way of surgical technique involves redirecting the systemic venous blood straight to the pulmonary arteries, without a dependence of the ventricle and effectively bypassing the ventricle[1]. But, After Fontan surgery, the patients continue to face notably increased risk for morbidity and mortality[2]. Because of its modified hemodynamic arising from Fontan circulation, it may lead to complications, for example, lymphatic hypertension. Lymphatic hypertension in Fontan patients is critical and complicated condition. It leads to altered hemodynamics, elevated venous pressure, impaired lymphatic drainage, lymphangiectasia, and lymph leakage. The complications mainly affecting the lymphatic system include protein-losing enteropathy (PLE), edema, pleural effusion, ascites and plastic bronchitis (PB)[3]. There have been many innovations and developments in diagnosing lymphatic complications in Fontan patients throughout the years and it involves a combination of clinical evaluation, invasive imaging procedures. Magnetic resonance lymphangiography (MRL) has become an important tool in visualizing lymphatic flow and identifying abnormal lymphatic drainage. Intranodal lymphangiography (IL), dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL), liver lymphangiography, these helps to find the diagnosis and appropriate therapeutic approach[4].

The purpose of this thesis is to comprehensively understand the post-surgical complications following Fontan surgery, with a special focus on the lymphatic system. The objectives are to assess the progress in surgical techniques for the past decades, establish the interrelation between elevated systemic venous pressure and lymphatic dysfunction and to explore the diagnostic techniques for lymphatic hypertension complication in Fontan patients along with specific treatment strategy to reduce the post-surgical complications. Additionally, this study also describes the pathophysiology and clinical presentation for each complication presented in the lymphatic hypertension in Fontan patients.

4. Literature search strategy & Methods.

In this study, I conducted a literature review to explore about the lymphatic hypertension complication in Fontan patients. To ensure the sincerity of this literature review, I have used variety of databases to gather articles that are relevant to this study. The primary databases used in this study are PubMed, SpringerLink, Science direct (Elsevier), Google Scholar and Sage Journals. To assess the recent studies and data appropriate to lymphatic hypertension

complications in Fontan patients, the above-mentioned databases was crucial. Corresponding to the core theme of this thesis most of the resources used in this thesis were published within the last 10 years, excluding the history and evolution of the Fontan procedure, which exceed the typical academic guidelines of referencing literature within last 10 years. This exclusion was imperative to provide a comprehensive understanding of development of Fontan surgical technique over the decades. Therefore, these references are essential in this thesis to capture the Fontan procedure progression since 1971.

This thesis written in a form of literature review and intended to collect and analyse existing studies on lymphatic hypertension complication in Fontan patients. Therefore, this study required paraphrasing and quoting from multiple sources, including academic journals, medical literature, and digital databases. I have put every effort to ensure appropriate citing of all sources and paraphrased content. However, vast amount of existing literature in medical field and medical terminology may result in some similarities in wording with the original texts, such instances remain academic and reflecting established medical research.

In order to maintain meticulous approach, I used various search term in different configurations: ‘’Lymphatic hypertension complication in Fontan patients”, ‘’Fontan surgery”, ‘’Congenital heart disease”, ‘’Diagnosis and treatment of Lymphatic hypertension complication in Fontan patients”, ‘’Chylothorax in Fontan patients”, ‘’Plastic bronchitis in Fontan patients”, ‘’Protein-losing enteropathy in Fontan patients”, ‘’Treatment strategy in lymphatic hypertension in Fontan patients”, aortopulmonary collaterals in Fontan patients and Heart transplantation for Fontan patients”. Furthermore, I have attached images in the thesis which were used from articles and books that have been used and referred in this thesis, except one attached image [Figure 11] which is adopted from a YouTube video to show the specific treatment technique.

5. Introduction to Congenital Heart Defects, Focusing on Single-Ventricle Defects.

Single-ventricular congenital heart disease occurs when only a single ventricle is fully established, resulting in a medically complex clinical situation. The estimated incidence of single-ventricular congenital heart disease occurs from 0.08 to 0.4 per 1,000 births. Single-ventricle congenital heart disease covers different morphological diagnoses, examples include

hypoplastic left heart syndrome (HLHS) (25% to 67% of single-ventricular conditions), tricuspid atresia (15 to 24%), and double inlet left ventricle (14-18%)[1]. The pathophysiology of different morphological types in single ventricle defects is defined by the inefficiency of the heart to distribute blood effectively through a two-chambered system, and this deformity results in a drastic physiological burden. This condition requires a number of surgical interventions, ultimately ending in the Fontan procedure.

6. Single ventricle congenital heart disease (CHD) and its Morphology

A normal ventricle comprises three primary structures Inlet, Outlet, and Apical trabecular component. Ventricles in malformed hearts present with the apical structure, and it is considered as the major consistent feature within the ventricular cavity and is defined by a pattern of coarse trabecular presented on the right and accompanied by fine trabecular pattern on the left. A ventricle is still characterized by the presence of the apical component, even though it lacks the inlet and outlet components.

Classification and description of congenital heart disease are based on the sequential segmental analysis method, emphasizing a structured approach involving seven key steps: Atrial situs, Atrioventricular connection, Ventriculo-arterial connection, Ventricular morphology, Ventricular topology, Associate anomalies, Cardiac position[5]. This step aids in systematically defining the complexities of congenital heart conditions. For the univentricular heart, the analysis distinguishes between:

1. Univentricular atrioventricular connections: This condition describes the atrial chambers connecting to a single ventricular cavity and is further characterized by the presence of either one atrioventricular valve as seen in tricuspid atresia or in mitral atresia. Or in the double inlet to the right or left ventricle, where it is two atrioventricular valves. Unbalanced atrioventricular septal defect falls in this category also.
2. Biventricular atrioventricular connections: This condition describes the atrial chambers connected with both ventricular cavities as seen in Pulmonary atresia with intact ventricular septum, usually with one normal and one hypoplastic ventricle in a single outlet truncus arteriosus, in Tetralogy of Fallot and double outlet

ventriculoarterial connection in the setting of two well-developed ventricles. Balanced atrioventricular septal defect falls in this category also[5].

Among the single ventricle CHD, Hypoplastic left heart syndrome (HLHS) is characterized by a wide-ranging group of congenital cardiac anomalies caused by underdevelopment of the left-sided cardiac structure. It includes Mitral atresia related to aortic atresia or stenosis, small left ventricle and a small ascending aorta that cannot aid to the systemic circulation. In such condition the right ventricle is functionally dominant and deliver entire systemic blood flow through ductus arteriosus. The sufficient mixing of blood from systemic return (deoxygenated) and from pulmonary venous (oxygenated) at the atrial level are important for survival. The subtypes of left ventricular morphology in HLHS are:

- Virtual/slit-like left ventricle which has no true cavity often seen in mitral atresia and aortic atresia [Fig 1a] [5].
- Miniature left ventricle, which is small, near normal with a thickened parietal wall limiting cavity size [Fig 1b] [5].
- Small wall left ventricle with endocardial fibroelastosis which is a thickened parietal wall with fibroelastic deposits seen in aortic stenosis or atresia and mitral stenosis [Fig 1c] [5].
- Dilated left ventricle due to mitral regurgitation with paradoxical left ventricular dilatation. resulting in large left atrium with compression of the right atrium [Fig 1d][5].

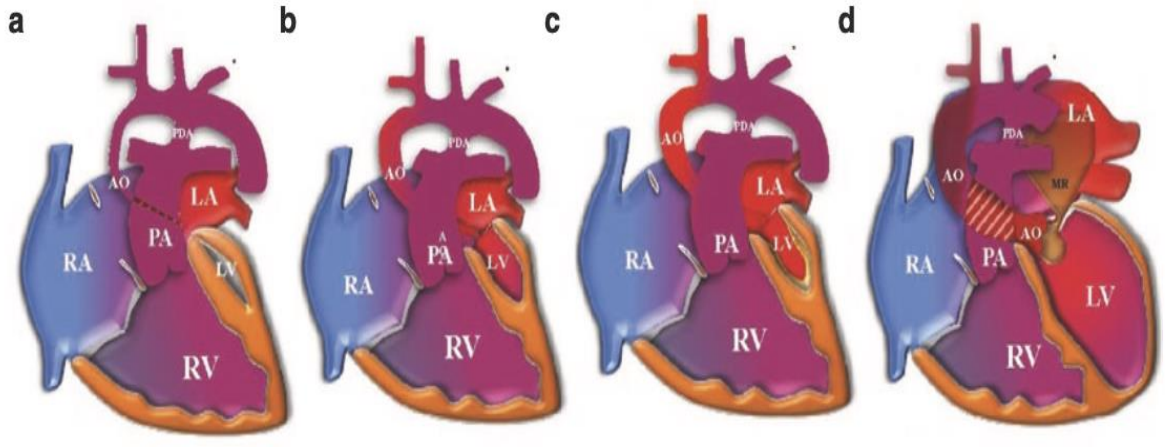

Figure 1. Left ventricular morphology in HLHS [5]. *(Adapted from:* Clift P, Dimopoulos K, Angelini A, editors. Univentricular Congenital Heart Defects and the Fontan Circulation: Practical Manual for Patient Management [Internet]. Cham: Springer International Publishing; 2023 [cited 2024 Oct 22]. Available from: https://link.springer.com/10.1007/978-3-031-36208-8)

7. The need of the Fontan Procedure in Congenital Heart Disease (CHD).

Single or Uni-ventricle congenital heart disease poses severe cardiac malformations where the heart fails to establish its compulsory chambers, and it is characterized by the shortage development of one of the heart's two ventricles, resulting in a situation where only one chamber is tasked with supporting the body's systemic circulation. This created a need for complex surgical intervention.

The Fontan procedure, which was innovated in 1971, has become the standard treatment method for these patients and it is the final stage in the surgical management for patients with single-ventricle cardiac anomalies. The aim of the Fontan procedure is to establish a pathway for systemic venous blood to reach pulmonary arteries from the inferior vena cava and superior vena cava, effectively bypassing the absent or dysfunctional ventricle, thereby reducing cyanosis and preventing significant hypoxemia, preventing or reducing the risk of pulmonary hypertension by maintaining low pulmonary artery pressures, establishing non-obstructed systemic circulation, avoiding immediate need for heart transplantation, and expanding the patient's lifespan. To acquire Total Cavo-pulmonary Connection (TCPC) in Fontan surgery, usually a three-stage Fontan surgical approach is used. This approach drastically reduces surgical mortality reaching less than 2% in recent years[5,6]

7.1 First stage procedure:

The first stage of the procedure is performed in the first days or weeks of life. The surgical strategy is determined by the patient's physio-pathological condition, which based on the morphology of the underlying cardiac defect. The surgical strategies utilized in the first stage of the procedure are: systemic-to-pulmonary artery shunt, pulmonary artery banding, Damus-Kaye-Stansel (DKS) or Norwood procedures[5].

7.1.2 Systemic-to-pulmonary artery shunt

This method is used when there in inadequate pulmonary blood flow, for example: Hypoplastic right heart syndrome (HRHS) and tricuspid atresia. The techniques used in this procedure are:

- Central shunts: anastomosis between ascending aorta and the right pulmonary artery-Waterston shunt. The descending aorta and the left pulmonary artery- Potts shunt.

- Modified Blalock-Taussig shunt: connection between right or left subclavian artery and the ipsilateral pulmonary artery by placing a polytetrafluoroethylene (PTFE) vascular prosthesis.
- Sano shunt: anastomosis between right ventricle and pulmonary artery by placing PTFE vascular prosthesis[5] [Fig 2].

7.1.3 Pulmonary Artery Banding

This method is performed when there is a presentation of pulmonary over circulation (For example: double inlet single ventricle unbalanced atrioventricular septal defect). This method is achieved by applying a synthetic band over the main pulmonary trunk to reduce pulmonary artery pressure, increase systolic blood pressure, and reduce systemic oxygenation to 80-85%[5].

7.1.4 Damus-Kaye-Stansel (DKS) or Norwood procedures.

This method is indicated for systemic outflow tract obstruction, and it is usually seen in HLHS, which involves the reconstruction and modification of the aortic arch by allowing systemic circulation to bypass the systemic flow obstruction and to establish a modified pulmonary flow through a systemic-pulmonary artery by a Modified Blalock-Taussig shunt or Sano shunt as shown in [Fig 2] [7].

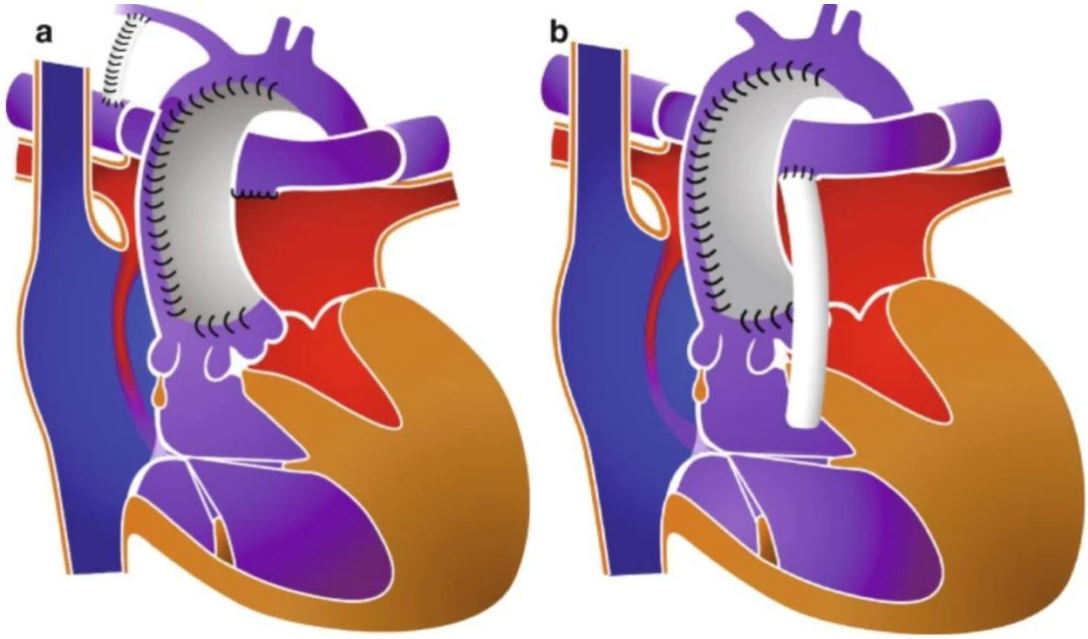

Figure 2. Illustration of (a) Norwood procedure and (b) Sano shunt [7]. *(Adapted from: Cheung Y fai. Congenital and Paediatric Acquired Heart Disease in Practice [Internet]. Singapore: Springer Nature Singapore; 2023 [cited 2025 Mar 18]. Available from: https://link.springer.com/10.1007/978-981-99-2862-0)*

7.2 Second stage procedure:

This stage is performed usually at 6 months of age, using the Bidirectional Glenn shunt procedure where the superior vena cava is anastomosed directly to the right pulmonary artery, thereby improving the systemic oxygenation by decreasing the desaturated blood that could mix with oxygenated blood and reducing the overload of the single ventricle by bypassing the single ventricle to enhance ventricular efficiency. Previously established central or BT shunts are closed, and Sano shunt is usually left open[5].

7.3 Third stage procedure:

The third and final staged procedure is performed normally between 2-4 years of age. The Fontan circulation completion initially involves rerouting inferior vena cava blood into the pulmonary artery.

8. The History, Evolution, and Modification of the Fontan procedure.

This specific surgical procedure represents a turning point in the surgical treatment of congenital heart diseases, especially for the patients with single-ventricle physiology. The Fontan procedure was first introduced in the year 1971 by Francis Fontan and Eugene Baudet, when they published a *''Surgical repair of Tricuspid Atresia"*[8]. This procedure was aimed at giving a surgical solution for patients with tricuspid atresia, a congenital defect where the right atrioventricular valve is either absent or inadequately developed. But this achievement stands on the contribution of several others who were already working towards establishing the Fontan procedure. Rodbard and Wagner, in their landmark research in 1949, demonstrated that, it is possible to directly connect the right atrial appendage to the main pulmonary artery to avoid the right ventricle. This demonstration showed that adequate pressure in the right atrium ensures antegrade flow into the main pulmonary artery[9].

In 1954, Warden and associates conducted staged surgeries, where they first established tricuspid stenosis to generate right atrial enlargement and hypertrophy, followed by an anastomosis between the right atrial appendage to the pulmonary artery. This procedure expected to be the prospective method for the treatment of tricuspid atresia. Moreover, classic Glenn procedure considered as a crucial element of the Fontan surgery. It was established by Glenn in 1958[10]. He performed an anastomosis between the superior vena cava with right pulmonary artery in a 7-year-old boy with the physiology of a single-ventricle[11]. The Fontan operation became a

reality only after a decade of Glenn procedure. The article written by Fontan and Baudet stated that *''A new surgical procedure has been used which transmits the whole vena cava to the left heart''*[8], which describes as the right atrium directs the inferior vena cava blood to the left lung. In 1973, independently from Fontan and Baudet, Kreutzer and associates introduced a surgical method for tricuspid atresia by using a homograft between right atrium (RA) and the main pulmonary artery (MPA), so called atriopulmonary Fontan [Fig 3] without including a Glenn connection or an inferior vena cava (IVC) valve[12]. One more alteration was involving the neo-septation of the right atrium creating a lateral tunnel Fontan [Fig 3]. This method proved to be beneficial for cases when the heart which exhibit dominant left and small right ventricles often linked with left or common atrioventricular valve atresia.

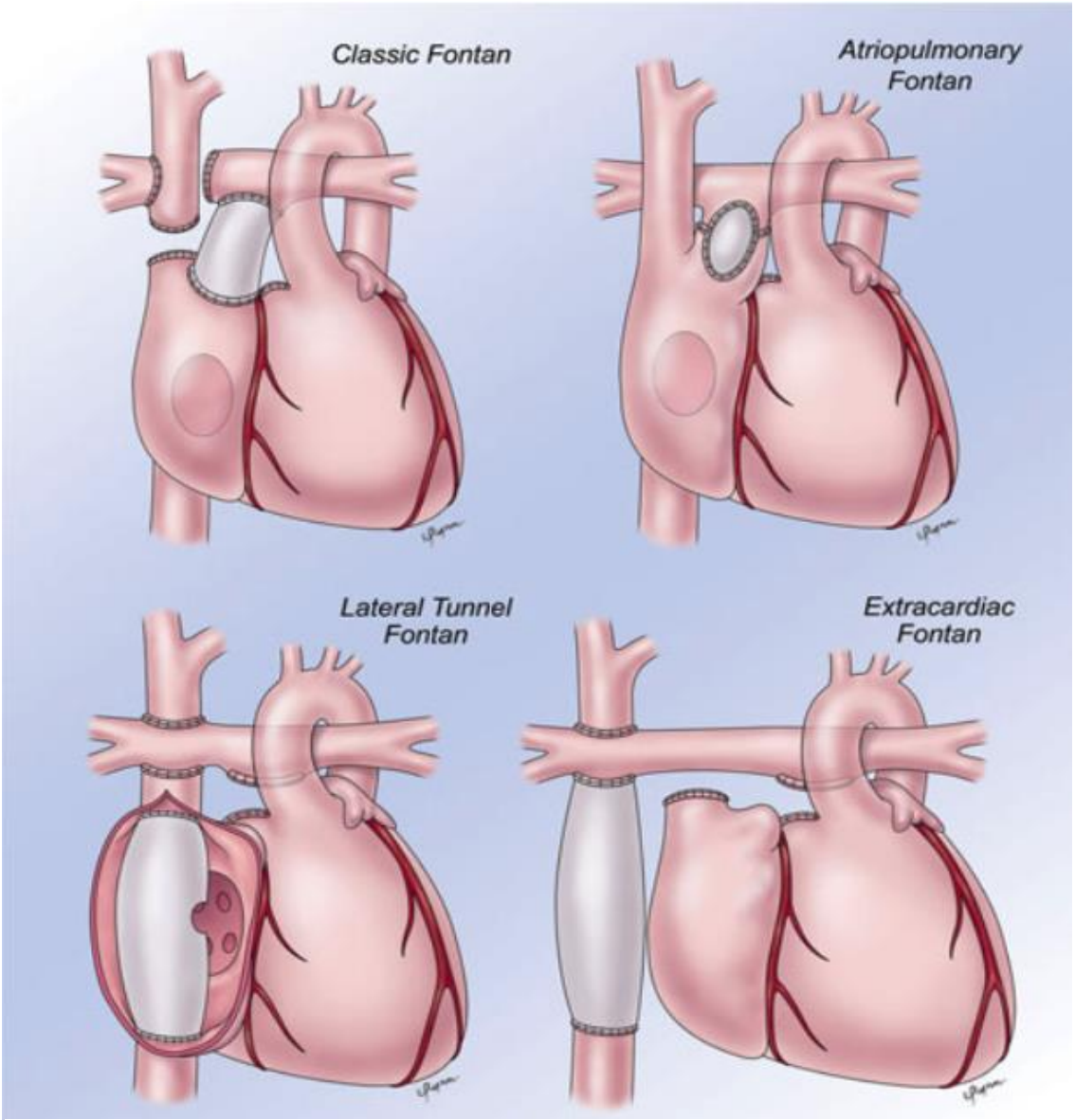

Figure 3. Variation of Fontan circulations. Classic Fontan, Atriopulmonary connection, Lateral tunnel Fontan, Extracardiac Fontan [15]. *(adapted from:Elder RW, Wu FM. Clinical Approaches to the Patient with a Failing Fontan Procedure. Curr Cardiol Rep. 2016 May;18(5):44.)*

Marcelletti et al. significantly advanced cardiac surgery by establishing the extracardiac total cavopulmonary connection (TCPC) or extra-cardiac Fontan[Fig 3][13], with conduit connecting the inferior vena cava directly to pulmonary artery branch [Fig 3]. This method avoids the requirement of suture lines within the atrium. As of now, cardiac surgeons are choosing extra cardiac Fontan or lateral tunnel based on the morphological peculiarities of particular patient, personal judgments and the practices of their institutions.[11]

9. Hemodynamics of Fontan Circulation.

After the Fontan completion, systemic venous return is directly connected to the pulmonary arteries, without the direct ventricular pumping function. This establishment utilizes the residual kinetic energy of postcapillary phase blood, to propel it through the lungs. This circulation relies only on the gradient in pressure between the systemic and pulmonary postcapillary vessels.[14]. However, it can lead to systemic venous congestion and hypertension because of hindrance in pulmonary flow and generally ends in reduced cardiac output, in situation of both during exercise and at rest. Elevated systemic venous pressure and chronically low cardiac output are the two inherent characteristics of the Fontan circulation and are the primary causes of what is known as Fontan failure[14].

The Fontan neo portal system consists of several important elements of the Fontan circuit. Its key components are the venoarterial Fontan connection, pulmonary arteries, capillaries, pulmonary veins, and the venoarterial Pathways. Any impairment within the portal system will dramatically affect the output of the Fontan circuit. This might include stenosis, hypoplasia, vasoconstriction, pulmonary vascular disease, loss, or exclusion of large or micro vessels turbulence and flow collision, flow mismatch, and obstruction by external compression, all of these will severely affect the Fontan circuit's efficiency. The reduced cardiac output in the neo-portal system can be partially alleviated through Fontan fenestration; this method allows blood to bypass some of the pulmonary vasculatures, leading to increased cardiac output and decreased venous congestion. On the other hand, this method will lower arterial oxygen saturation [14].

10.Survival Rates and Long-Term Outcomes of Fontan Patients.

Although most patients' single-ventricle surgical pathway ends with the Fontan procedure, the anatomy of these patients varies significantly. Older Fontan patients often had a morphologic left ventricle (LV) related to either tricuspid atresia or double inlet left ventricle. However, with the introduction of the Norwood procedure for hypoplastic left heart syndrome, an increasing number of patients now have a morphologic right ventricle (RV) functioning as the systemic ventricle. Still, some patients with complex intracardiac anatomy undergo Fontan palliation. The Fontan procedure has evolved over time and undergone many modifications, originally its purpose to serve as a direct anastomosis of the right atrial appendage to the pulmonary artery. The modern techniques of the Fontan procedure offer either extracardiac (EC) or lateral tunnel (LT) modifications [15].

Patients who have undergone the Fontan procedure have shown remarkable improvements in survival rates and long-term outcomes over recent years. A retrospective longitudinal cohort study was done by utilizing data from Australian and New Zealand (ANZ) Fontan registry to examine out comes of patient who underwent Fontan operation between 1975 and 2016 titled *''Reintervention and Survival in 1428 patients in the Australian and New Zealand (ANZ) Fontan Registry,"*[16] which states that about 30% of the 1428 patients underwent at least one reintervention after the Fontan surgery[16]. Survival rates for patients who underwent reintervention after ten years of Fontan surgery were 73%, and 96% was for those who did not require any reintervention. Thirty years after Fontan surgery, the survival rate was 51% for those who required reintervention compared to 83% for those without reintervention.

Another cross-sectional study titled as *''Survival data and predictors of functional outcome an average of 15 years after the Fontan procedure: The pediatric heart network Fontan cohort''*[17], collected from 546 Fontan survivors aged 11.9 ± 3.4 years, evaluated the current transplant-free survival data of all subjects 6.8 ± 0.4 years post Fontan,. followed Fontan patients for an average of 15 years post-Fontan, the interim transplant-free survival rate over seven years was approximately 95%. This study shows the notable aspects of the success of current surgical management in expanding the survival and quality of life for Fontan patients[17].

A lot of various factors, including the notable type of Fontan surgery, the presence of comorbidities, and complications after Fontan surgery, like arrhythmias and organ dysfunction

impact the long-term outcomes of Fontan patients. Several complications, such as Protein-losing enteropathy (PLE), plastic bronchitis, and liver cirrhosis are big fears that affect long-term survival and quality of life. This complication needs long-term follow-up and management. The ANZ Fontan registry points out that many Fontan patients require reintervention to maintain effective circulation which can notably influence long-term outcomes[16]. Early prenatal intervention in single-ventricle congenital heart disease in prenatal diagnosis has been associated with improved outcomes. Additionally, the presence of other cardiac or extracardiac anomalies complicates the post-surgery recovery and results in decreased survival rates[18].

11.Lymphatic Anatomy and Physiology

The lymphatic system is involved in very specific physiological functions. The vessels of the lymphatic system engage in maintaining a fluid balance within the extracellular space by circulating back filtered proteins and fluids into the vasculature[19]. In general, the lymphatic system is important for fluid equilibrium maintenance, as it gets fluid from the peripheral organs and tissue, channelling it centrally through thoracic duct for proper drainage.

The lymphatic system consists of numerous small, thin-walled capillaries, the lymphatic system branches, and interconnects across most tissues parallel to systemic capillaries [Fig 4].

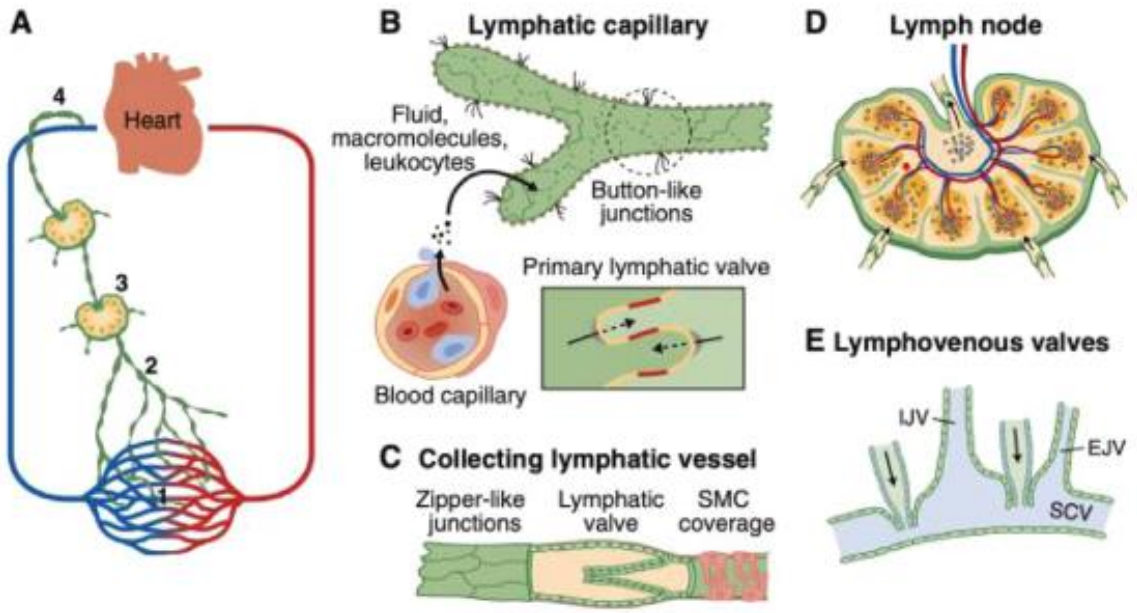

Figure 4. This image shows the lymphatic system. (A) The lymphatic system (B) Flow of lymphatic fluid through the lymphatic capillaries. (C) Lymphangions consist of zipper-like junctions, unidirectional lymphatic valves, and contractile smooth muscle cells (SMC). (D) Lymph nodes. (E) Lymphovenous valves where the lymphatic fluid drains via the subclavian vein [20]. *(Adapted from: RochéRodríguez M, DiNardo JA. The Lymphatic System in the Fontan Patient—Pathophysiology, Imaging, and Interventions: What the Anesthesiologist Should Know. J Cardiothorac Vasc Anesth. 2022 Aug;36(8):2669–78)*

Capillaries of the lymphatic system are made up of a single layer of endothelial cells, that allows the transport of fluid to the lymphatic vasculature from the interstitium. Larger collecting vessels known as ‘’lymphangion’’ are where these branching capillary networks empty their drainage. Lymphangions are characterized by their thick walls consisting of smooth muscle and contain one directional valve that direct lymph flow toward the lymph nodes. Lymphangions’s smooth muscle produces contraction to drive fluid upwards, and the retrograde flow is prevented by the unidirectional valves. The lymphatic fluid then passes through lymph nodes continues into larger lymphatic vessels and drains into the thoracic duct or the right lymphatic duct and eventually into the central venous system[20]. Fluid from the lower extremities, the liver, and mesentery is primarily accumulated in the cisterna chyli. Compared with other organs, the liver's and the intestine's contribution to the thoracic duct flow is close to 40%. The lungs and heart also drain their lymphatic fluid into the thoracic duct[21].

The thoracic duct (TD) begins at the cysterna chyli, anterior to the first or second lumbar vertebra, and then it moves through the aortic hiatus to the posterior mediastinum between the aorta and azygos vein [Fig 5]. Between the fourth and sixth thoracic vertebrae, the thoracic duct

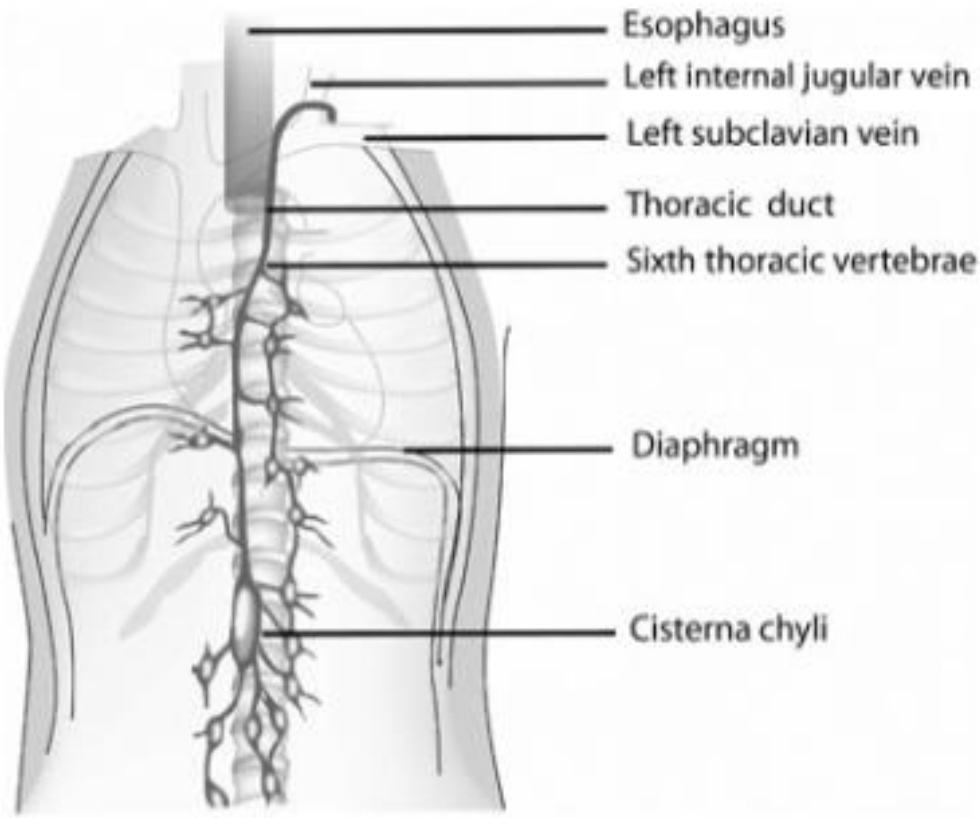

Figure 5. Anatomical relations of thoracic duct [22]. (Adapted from: *Panthongviriyakul C, Bines JE. Post-operative chylothorax in children: An evidence-based management algorithm. J Paediatr Child Health. 2008 Dec;44(12):716–21.)*

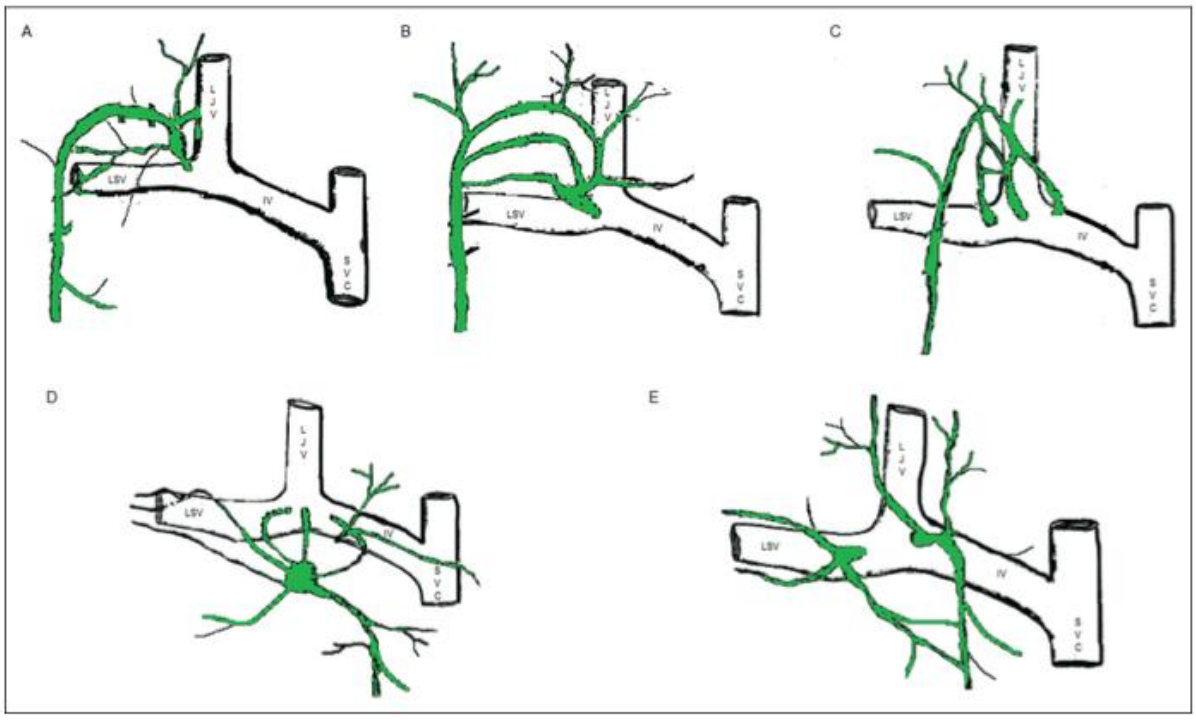

Figure 6. Anatomical variations in thoracic duct drainage. (A) Single inlet. (B) Single inlet featuring multiple archs. (C) Delta inlet. (D) Double inlet structure. (E) Spider-like termination [23]. *(Adapted from: Kreutzer C, Kreutzer G. The Lymphatic System: The Achilles Heel of the Fontan-Kreutzer Circulation. World J Pediatr Congenit Heart Surg. 2017 Sep;8(5):613–23.)*

crosses over the left mediastinum, and it ascends extrapleural along the left side of the esophagus and runs posterior to the aortic arc and left subclavian artery. The duct then extends into the superior mediastinum anterolaterally at the base of the neck and goes down medially to the anterior scalene muscle and then enters the venous system adjacent to the junction of the left internal jugular and subclavian veins[22] [Fig 5].

Approximately 85% of the chyle are carried from the body through thoracic duct excluding the right hemithorax, right head and neck, and right upper extremity, these structures on the right-side drain through the right lymphatic duct into the systemic veins at the intersection of the internal jugular and right subclavian veins, despite the presence of a large degree of anatomical variability [Fig 6]. The thoracic duct (TD) drains into the posterior region of the intersection between the subclavian and left jugular veins. Location of a valve before its drainage, stops blood flow from entering the thoracic duct [23]. The lymphatic network works independently of any central pump, similar to the cardiovascular system, which can contribute to a contractile force. Transportation of the lymphatic fluid primarily depends on pressure gradients, negative pressure exerted by the thorax during inspiration, and diastole. Adequate transport of lymph is facilitated by the contractile force within lymphangions to a lesser extent, by external compression due to surrounding tissues, especially with the support of skeletal muscle contraction [20].

12.Pathophysiology of Lymphatic System in Fontan Patient.

Changes in Starling forces cause lymphatic dysfunction in patients with Fontan physiology. The modified Starling equation describes the pressure in the subgycocalyx space as the major force opposing fluid filtration to the interstitial space from capillaries. This subgycocalyx space plays a noteworthy role in separating the capillary network from the interstitial space. The glycocalyx stops the passage of molecules which are bigger than 70 kDaltons through its mesh structure composed of glycoproteins and proteoglycans, and this supports interstitial oncotic pressures by inhibiting the movement of plasma proteins and other molecules[20]. Increased systemic venous pressure generates the pressure gradient which is crucial to maintain pulmonary blood flow and cardiac output. This increased venous pressure results in a change in Starling forces and leads to interstitial fluid accumulation [Fig 7]. Decreased plasma oncotic pressure also contributes to the accumulation of fluids because of protein deficiency, especially hypoalbuminemia. Also, Inflammation plays a major role in increasing the permeability of the glycocalyx and increasing the subglycocalyx oncotic pressure[20].

When the glycocalyx layer loses its integrity, interstitial oncotic pressure becomes an important part of the net filtration, and all these factors contribute to the alteration in Starling forces in Fontan patients, resulting in the occurance of pleural effusions, ascites, and Protein-losing enteropathy (PLE) [Fig 8]. The liver is responsible for generating 25% to 50% of lymph that moves through the thoracic duct and is especially sensitive to shifts in hydrostatic pressure[20]. The production of lymph mainly arises from the hepatic sinusoids and is proportional to the hydrostatic pressure inside the liver's sinusoidal microcirculation. Due to this, increased hepatic afterload from chronically increases inferior vena cava pressure and hepatic congestion correlates with increased lymph production and high dependence on lymphatic drainage.

This increased lymph production sustains macromolecular transport when sinusoidal hepatocellular exchange capacity is compromised as a result of Fontan-associated liver disease. In Fontan patients, hepatic venous portal and lymphatic drainage may also be compromised by impaired diaphragm function. Hepatic venous flow in this patient is mainly dependent on diaphragmatic function during inhalation and the diaphragm must remain intact to prevent the reversal portal venous flow during exhalation[20].

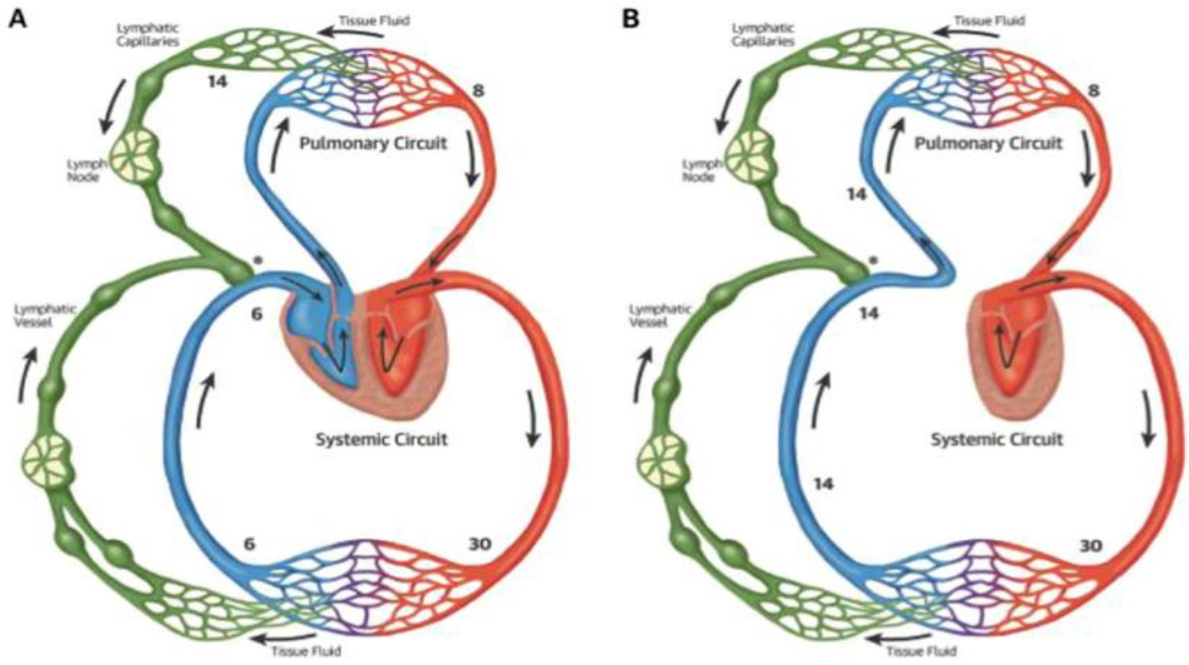

Figure 7. The lymphatic vascular system is shown in both biventricular circulation (A) and the Fontan circulation (B). The number indicates typical mean pressures (mmHg) for each type of circulation. In the Fontan system (B), Pulmonary lymphatic fluid drain through the thoracic duct must occur at a pressure that is equal to or higher than its production rate. Resulting in interstitial fluid accumulation [20]. *(Adapted from: RochéRodríguez M, DiNardo JA. The Lymphatic System in the Fontan Patient—Pathophysiology, Imaging, and Interventions: What the Anesthesiologist Should Know. J Cardiothorac Vasc Anesth. 2022 Aug;36(8):2669–78)*

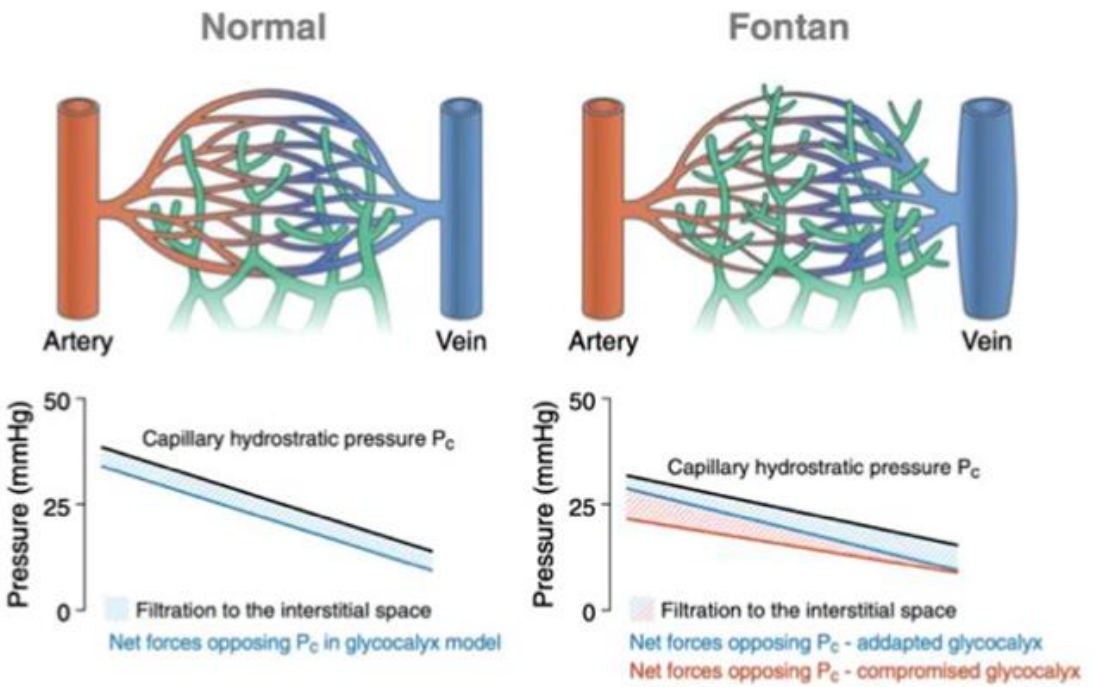

Figure 8. Comparing capillary filtration in normal biventricular circulation with that in the Fontan circulation. The glycocalyx regulates capillary and interstitial oncotic pressures. In Fontan circulation, the raised systemic venous pressure alters the Starling forces. Favouring fluid movement into the interstitial space. Hydrostatic fluctuations may prompt the glycoalyx to adjust and minimize filtrations, or alternatively if the structure is compromised, filtration increases[20]. *(Adapted from: RochéRodríguez M, DiNardo JA. The Lymphatic System in the Fontan Patient—Pathophysiology, Imaging, and Interventions: What the Anesthesiologist Should Know. J Cardiothorac Vasc Anesth. 2022 Aug;36(8):2669–78)*

Chronic elevation in systemic venous pressure and reduced cardiac output results in endothelial dysfunction, which in turn leads to direct capillary leak and places more demands on the lymphatic system for clearing fluid from the interstitial space. Direct injury to the thoracic duct may occur during surgical procedures and result in impairment of lymphatic drainage. Nevertheless, with the challenges implied in the lymphatic system, it is no wonder that adaptive changes occur. In Fontan patients, this adaption leads to dilated lymphatic vessels along with abnormal collateral formation due to impaired drainage and increased interstitial fluid volume. Additionally, Fontan patients are present with a 17% reduction in lymphatic pumping pressure within lymphangions, but it is compensated by a 62% elevation in contractile frequency[20]. This compensatory adaptation is thought to arise from adrenergic stimulation, due to increased sympathetic tone and circulating catecholamines in Fontan patients. Moreover, advanced imaging and catheterization studies of the thoracic duct in Fontan patients have shown that the size of the thoracic duct is increased leading to the incompetence of lymphatic valves often associated with increased lymphatic pressure which results in complications of effective lymphatic drainage and management of lymph-related condition[20]

13.Clinical Presentations of Lymphatic Hypertension in Fontan Patients.

Patients who have undergone Fontan surgery experience lymphatic hypertension. Lymphatic hypertension is a complication, which arises from the Fontan surgery's outcome on hemodynamics, which then, truly modifies lymphatic function and flow. Generally, lymphatic vessels play a notable role in regulating extracellular fluid haemostasis and absorbing dietary fats from the small intestine, thereby, supporting immune system. Dysfunction in this system can arise from modified capillary starling forces, capillary leakage, lymphatic congestion. This condition can lead to chronic issues such as lymphatic congestion, this can define as edema, pleural effusion, chylothorax, plastic bronchitis, and protein-losing enteropathy. The pathophysiology is made up of modified capillary dynamics and elevated systemic venous pressure that breach normal lymphatic drainage and leads to lymph accumulation. This elevated venous pressure results in a shift in starling forces and leads to interstitial fluid accumulation of fluid which resulting in shortage of protein, notably hypoalbuminemia. Throughout the years, there have been many invention regarding imaging techniques for lymphatic dysfunction and ultimately they have advanced, such as MR lymphangiography, and have improved the diagnosis and management of lymphatic complications in Fontan patients[20].

Table 1. Complications related to lymphatic dysfunction in Fontan patients.

Complication	Pathophysiology
Chylothorax & Pleural effusions	Accumulation of fluid in the pleural cavity, commonly occurring after surgery and can be due to trauma to thoracic duct or its branches and due to imbalances in lymph fluid production and drainage.
Peripheral edema	Occurs in case of inadequate drainage leading to fluid accumulation in the extremities
Ascites	Accumulation of fluid in the peritoneal cavity, often associated with hepatic dysfunction or increased hepatic lymph production in Fontan patient.
Plastic Bronchitis (PB)	Formation of fibrinous cast in the airways, which can lead to airway obstruction. Associated with abnormal lymphatic flow from the thoracic duct to lung tissues
Protein-Losing Enteropathy (PLE)	Increased gastrointestinal protein loss leading to serious malnutrition and immune deficiencies. Connected to elevated central venous pressure causing intestinal leakage.

14.Chylothorax

Table 2. Composition of chyle [22].

Composition of Chyle	
Total Protein Albumin	22-60 g/L (>30g/L) 12-42 g/L 11-31 g/L
Total Lipid Triglyceride Cholesterol	4-60 g/L >plasma levels <plasma levels
Glucose	48-200 mg/dL
Electrolytes Sodium Potassium Chloride Calcium	 104-108 mEq/L 3.8-5.0 mEq/L 85-130 mEq/L 3.4-6.0 mEq/L

Disruption in lymphatic drainage perhaps leads to complications in Fontan patients and one of the complications is Chylothorax. The actual definition of Chylothorax is knowns as lymphatic fluid accumulation in the pleural space that results in case of any injury to the thoracic duct due to surgery or trauma and in the instance of congenital abnormality, malignancy, infections, or syndromes, such as Down, Noonan, and Turner. Given the growing and increasing complexity of cardiothoracic surgery in infants and children, post-operative chylothorax has become the main and first cause of chylothorax in specialized paediatric hospitals, hugely influencing the morbidity and higher duration of hospital stays. In the last two decades, the reported incidence of chylothorax after surgery ranged between 2% and 5%[24]. Lymphocytes, glucose, lipids, protein, and electrolytes were found as a massive concentration in the chyle contents, means that prolonged or more loss of chyle can result in protein-energy malnutrition, electrolyte abnormalities, and disturbances in immune function. There are some surgeries that have been conducted in proximity to the thoracic duct, including cardiothoracic, mediastinal, oesophageal, pleuropulmonary, and diaphragmatic surgeries, which might result in chylothorax[20].

The occurrence of chylothorax after a cardiothoracic surgery has inclined over the past years due to the intricacy of cardiac surgery and a higher occurrence of chylothorax can be seen after surgeries like the Fontan procedure, tetralogy of Fallot repair, or heart transplantation [20,24,25].

Lymph flow into venous system gets obstructed when central vein thrombosis or increased central venous pressure takes place. Which in turn lead to enlargement and rupture of the thoracic duct or its tributaries. Straight after surgery if the chylothorax appears, it typically shows any injuries to the thoracic duct, but in case of gradual appearance of chylothorax after surgery could denote central venous thrombosis or hypertension. Procedures such as Fontan along with bicavopulmonary anastomosis, are known to elevate the risk of high central venous pressure. Alteration of the Fontan operation including a fenestration procedure targeting to reduce central venous pressure in the postoperative period. Even with these modifications, fenestration has not proven efficacious in reducing the length of pleural effusion, pointing out that additional influences such as age and cardiac structure and function may be involved. Use of central venous catheters for administering medication or providing parenteral nutrition might also develop central venous thrombosis. In cases of chylothorax arising from such central venous thrombosis or hypertension results in prolonged and extensive loss of chyle [26].

Table 3. Pathophysiology and its proposed mechanism in chylothorax.

Mechanism	Pathophysiology
Trauma	Most reported cases are due to direct injuries to the thoracic duct or its branches.
Increased central venous pressure	Elevated venous pressure in the superior vena cava after single-ventricle palliation surgeries such as Fontan and Glenn are associated with chylous leakage due to increased pressure in intrathoracic lymph system

Table 3. *(Continued)* Pathophysiology and its proposed mechanism in chylothorax.

Central venous thrombosis	In patients with congenital heart disease, thromboembolic disease is a frequent complication. This mechanism involves in blockage of thoracic duct drainage, resulting in an obstruction in chyle flow into the venous system.

14.1Complications Stemming from Chylothorax

The growing complexity of cardiothoracic surgery in infants and children post-operative chylothorax is associated with increased morbidity and mortality risk. Chylothorax, marked by of lymphatic fluid accumulation in the pleural space and results in a significant amount of chyle loss may have consequences in several other systems.

- Respiratory: The accumulation of chylous fluid in the area of pleural space worsens the restrictive lung disease, and will end in respiratory insufficiency, also leading to an extended period of mechanical ventilation.
- Nutritional: Chyle has an abundant amount of protein, which carries protein and also a decent amount of lipids, which are more than 60% dietary fats traveling to the bloodstream through the thoracic duct, this will result in a catabolic state and protein energy malnutrition in patients with chylothorax because of abundant loss of proteins and lipids during fluid extraction.
- Immunological: The risk of infections increases with chylothorax, due to secondary depletion of lymphocytes and hypogammaglobulinemia.
- Hematologic: Increased risk of hemorrhagic complications due to loss of fibrinogen and prothrombin have been observed in patients with chylothorax. Antithrombin depletion from chyle can cause a notable drop in the activity of antithrombin in plasma and it can also lead to higher risk for thrombosis.
- Metabolic: This patient can suffer from hypovolemia, electrolyte disturbances (hyponatremia and hypocalcemia), and metabolic acidosis as a result of losing fluids, proteins, and electrolytes through chylous drainage[25].

14.2 Diagnosis of Chylothorax

Imaging modalities such as chest radiography can confirm the presence of a pleural effusion and it supports identifying the underlying causes of chylothorax but has limited value in detecting the specific diagnosis of chylothorax. Thoracic ultrasound similar to chest radiography, has limited value and unable to differentiate between chylothorax and other pleural effusion. CT and MRI play supportive roles in identifying the underlying causes and evaluating the lymphatic system[27].

Pleural fluid analysis is an essential diagnosis method for chylothorax with the support of various thoracic imaging techniques to identify the main cause of chylothorax. 22-24% of classic descriptions of milky or opalescent fluid in the pleural space do not occur frequently to meet the diagnostic criteria of chylothorax and it is important to consider other differential diagnoses based on gross appearance [27]. Detection of chylomicrons plays a key role in pleural fluid analysis, usually through triglyceride and cholesterol measurement. Pleural fluid with a triglyceride level more than 110mg/dL and cholesterol level less than 200mg/dL indicates chylothorax [27]. It is crucial to observe nutritional status because it can impact the pleural fluid triglyceride levels, complicating the diagnosis of chylothorax and it is essential to test for lipoprotein electrophoresis in such conditions. The most sophisticated diagnostic tool which could be used in chylothorax in Fontan patients is dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL), and intranodal lymphangiography, which help to indicate the specific etiology and mechanism of chylothorax by imaging lymphatic flow [28] [Fig 9].

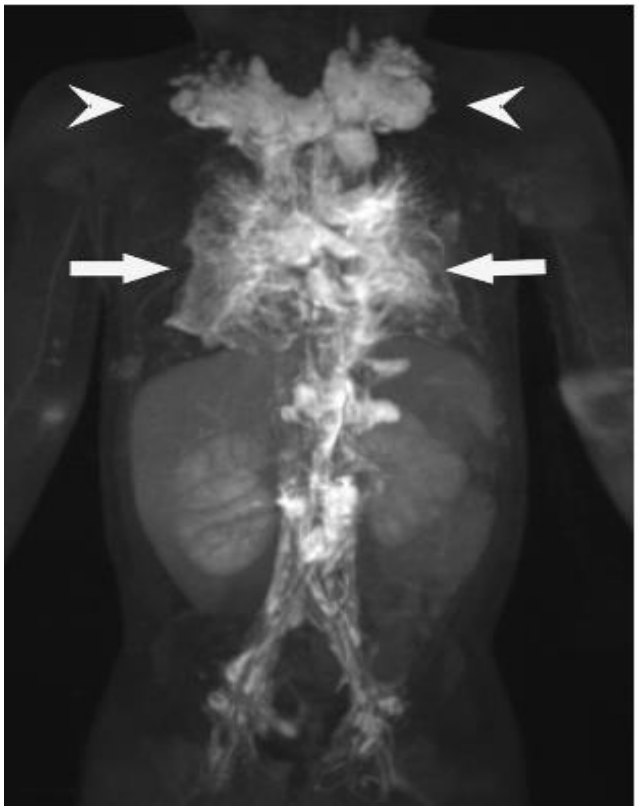

Figure 9. DCMLR, maximum intensity projection image shows a patient with abnormal lymphatic perfusion of both the mediastinum and lungs (arrow). Lymphatic flow is directed from the thoracic duct into the lungs via multiple abnormal lymphatic networks in the chest, with extensive cervical lymphatic networks also visible (arrowheads) [28]. *(Adapetd from: Savla JJ, Itkin M, Rossano JW, Dori Y. Post-Operative Chylothorax in Patients With Congenital Heart Disease. J Am Coll Cardiol. 2017 May;69(19):2410–22.)*

14.3 Management of chylothorax

Usually, initial management of chylothorax involves pleural drainage to alleviate respiratory distress and to prevent the accumulation of fluid and this can be done by thoracocentesis. Chemical pleurodesis can be used in case of failed conservative management and it is achieved by using agents such as talc, tetracycline, bleomycin, and hypertonic glucose [27,29].

The main aim of the initial management strategies is to decrease intestinal lymphatic flow and it can often be successfully treated conservatively. Medium-chain triglycerides (MCT) enter the portal circulation directly and associated with minimal formation of chylomicron. Therefore, it reduces lymph flow in the thoracic duct. MCT-enriched diet and parenteral nutrition have shown no significant differences in clinical outcomes [22]. Although the effectiveness of MCT-enriched diets and parenteral nutrition has not been extensively studied for children with postoperative chylothorax. When there is no high central venous pressure presented, an MCT-enriched oral diet is considered to avoid the risks accompanied by parenteral nutrition, such as sepsis and vein thrombosis, and support the gut barrier function. If this method is effective, chylous leakage typically gets better within the first weeks and stops by the end of the second week. But if the chylous drainage is not improved after the first week, the MCT-enriched diet should be discontinued and recommended to switch the treatment to parenteral nutrition. Patients who have high central venous pressure due to increased right-sided cardiac pressure or central venous thrombosis generally respond poorly to nutritional treatment and might need surgical intervention[22].

Both somatostatin, and octreotide have been used to treat chylothorax since 1990, notably octreotide has been given in cases of unresponsiveness to nutritional therapy or when nutritional treatment has failed. Treatment with somatostatin, a 14 amino-acid peptide stops the release of hormone release and is present in many areas of the body, notably in the central nervous system and gastrointestinal tract. Octreotide, on the other hand, is a synthetic analog of somatostatin is different from Octreotide and Somatostatin has a longer half-life and can be given intravenously or subcutaneously. The usage of somatostatin and octreotide has been very successful in managing patients with venous thrombosis and central venous hypertension. The dosage for somatostatin begins at 3.5 mg/kg/h and can increase to 12 mg/kg/h[22,30]. While, octreotide starts at 0.5 mg/kg/h, and can reach up to 10 mg/kg/h. Effects of treatment are generally seen within 5-6 days, and the typical treatment duration is 10-18 days[22]. Regards to side effects

include cutaneous flash, flu-like symptoms, and gastrointestinal disturbances, with more serious complications like necrotizing enterocolitis that have been reported with octreotide. Regular monitoring and liver thyroid functions and blood glucose should be observed during treatment to avoid potentially serious side effects[22].

15. Plastic Bronchitis

Plastic Bronchitis (PB) is a post-Fontan complication characterized by the production of thick, tenacious cast in the lumen of the airway. It has recently been specified as ‘’a pulmonary lymphatic disorder’’ with the features of proteinaceous material leakage into the airways, which is in the shape of casts and accompanied by wheezing, airway obstruction, and respiratory distress[31]. The casts can often be large, rubbery, cohesive, and are cellular, containing inflammatory components and fibrin. It contains infiltrates of B lymphocytes, neutrophils, and sometimes eosinophils. Cast formation was described 30 years ago in Fontan patients, initially reported at a 4% incidence. More recent data from the Australia and New Zealand Fontan Registry (ANZFR) show a lower occurrence below 1%. However, the patient survey indicates a higher occurrence (8%-14%) of reported casts or plugs, suggesting potential underdiagnosis [32].

Patients with a history of prolonged chest tube drainage at superior cavopulmonary anastomosis or Fontan, postsurgical chylothorax, and postoperative ascites are connected to a higher incidence of plastic bronchitis (PB). Also, the early onset of PB is associated with chest tube drainage of 14 or more days. All these risk factors indicate that lymphatic system disruption is an important factor in the pathogenesis of PB. The average duration time between Fontan surgery and the first onset of PB is typically 2 to 3 years, but there are some cases with acute presentation of PB shortly after surgery[33]. PB is rare in adult patients. The symptoms often consist of dyspnea, cough, fever, wheezing, and acute respiratory failure due to severe airway obstruction. Symptoms like cough and wheezing may or may not accompany cast expectoration. The frequency of expectoration is variable in patients with PB, one-third of patients experience it every few days, and one-half experience it every few weeks. Physical examination may reveal reduced breath sounds and/or wheezing. The condition often leads to multiple hospital stays in most patients with PB due to the chronicity and challenging management. The occurrence of cast formation is thought to be influenced by underlying lymphatic and hemodynamic abnormalities rather than the characteristics of the cast or the existence of infection[33]. Further, the early onset

of PB has been linked with a higher risk of mortality. In single-ventricle patients presenting with chronic cough and suspected asthma symptoms that do not respond to bronchodilators, it is important to consider the diagnosis of PB. There are no specific criteria for diagnosing PB, rather it primarily involves clinical observation and visualization of an airway cast either after being coughed up or seen during bronchoscopy[33].

15.1 Pathophysiology of PB

The lymphatic vasculature serves as a unidirectional transport system that extends to the systemic circulation in the thorax and neck. When the fluid reaches the collecting lymphatic vessels, contractions in the lymphatic vasculature move the fluid forward, and the intraluminal valve prevents possible backflow. Increased lymphatic central venous pressure is seen in patients with Fontan circulation, leading to elevated lymphatic afterload and congestion. This congestion can disrupt the lymphatic fluid flow, potentially causing dilation, reduced vessel contractility, and diminished lymphatic valves. This condition results in a depressed functional lymphatic reserve capacity compared to healthy individuals. Studies analyzing airway casts have demonstrated that they consist of proteinaceous lymphocytic components comprising neutrophils[33]. Observation also shows signs of complement pathway activation and necrosis, implying inflammation and potential infection are demonstrated in the formation of cast. Nonetheless, on bronchoalveolar lavage, one third of viral and bacterial infection have been identified. Inflammation aids in lymphangiogenesis and possibly supports the development of abnormal lymphatic collaterals[34]. These collaterals might create more supply routes for lymphatic fluid into the airways. Once the routes are created, they are preserved open by continuous lymphatic flow as the congested lymphatic system prefers rerouting of flow to the low-pressure airways[33]. In a large cohort study involving 635 Fontan patients titled ‘*’Impact of aortopulmonary and venous collaterals on the onset of plastic bronchitis after the Fontan procedure”*[35] identified a number of clinical and anatomical factors significantly associated with onset of PB among the 635 patients who underwent total cavoplumonary connection (TCPC). In total, PB was observed in 15 patients (2.4%), with median duration to onset of 1.1 years after TCPC. Univariate analysis revealed that the presence of dominant right ventricle (P=. 031), HLHS (P= .003), anomalous pulmonary venous connection (P= .044), post-TCPC chylothorax (P< .001), post-TCPC aortopulmonary collaterals (APCs) (P< .001), and post-TCPC venovenous collaterals (VVCs) (P= -003) were significantly correlated with an increased risk of PB[35].

15.2 Diagnosis of PB

Initial diagnosis of PB relies mainly on patient's clinical evaluation and imaging study particularly chest X-rays. Lymphatic imaging is an important tool for diagnosing and treating PB. Noncontract magnetic resonance lymphangiography with heavily weighted T2 magnetic resonance imaging is being used to identify lymphatic abnormalities that are linked with more critical postoperative results. Dynamic-contrast magnetic resonance lymphangiography (DCMRL) is the choice of technique for more detailed assessment, especially for diagnosing and treating patients with PB [36].

This technique is achieved by injecting contrast agents into lymph nodes to visualize lymphatic fluid movement and possible obstruction. To assess the central lymphatic system, intranodal lymphangiography (IN-DCMRL) is used. Most patients with PB show unilateral or bilateral pulmonary lymphatic perfusion in IN-DCMRL, which is known as pulmonary lymphatic perfusion syndrome (PLPS) [33].

15.3 Management of PB.

Initial management focuses on symptomatic therapies directed toward airway clearance. For patients with suspected PB, the initial management involves hospital admission for the patient's stabilization, evaluation, and initiation of treatment. Cardiac catheterization is important to assess Fontan circulation hemodynamics. Treatment of PB in patients with Fontan circulation involves three important categories, and they are 1. Facilitating cast expectoration 2. Reduce the central venous pressure (CVP) by using pulmonary vasodilators, diuretics, and creation of fenestration. 3. consideration of lymphatic intervention for conditions like pulmonary lymphatic perfusion syndrome (PLPS). Therapies reported effective in reducing patient symptoms and hypoxemia during the acute phase of PB are chest physiotherapy, fibrinolytic, bronchodilators, mucolytics, and heparin inhalation. In the case of chronic PB, the success of the treatment has been additionally with macrolide antibiotics, hypertonic saline, and vibration vests. When conservative therapies fail lymphatic intervention serves as the next-line treatment. In patient with suspected PB, Catheter-based interventions are necessary to be performed in order to address the reversible causes of lymphatic failures, such as pulmonary artery stenosis, superior or inferior caval stenosis, or to reopen closed fenestration between the extracardiac conduit and right atrium. Despite the wide range of management and interventional treatment heart transplantation remains a last resort option [33,37].

16.Protein-Losing Enteropathy (PLE)

PLE is defined as when there is a loss of enteric protein, which leads to hypoalbuminemia, lymphopenia, hypogammaglobulinemia, and depletion of clotting factors. The incidence of PLE after Fontan palliation ranges from 3% to 13%. According to the Australia and New Zealand Fontan Registry (ANZFR), the median time for PLE onset after Fontan surgery is 5.0 years, typically occurring within a decade of Fontan operation. In comparison, a cohort study from the Mayo Clinic stated a mean age of 18.9 ± 11.0 years, noting that this group of patients had their initial Fontan procedure at a later average age (10.1 ± 10.8 years) and during earlier age[33]. PLE has been linked with various univentricular heart structures and different Fontan types. Initial studies reported a predominance of single left ventricular (LV) morphology. Anyhow, recent studies from ANZFR show 58% of patients had a single right ventricular (RV) morphology, which reflects the improved survival rates among children with hypoplastic left heart syndrome[33]. The ANZFR study analyzed the outcomes of 51 cases of PLE and 7 cases of PB and reported many risk factors, including RV morphology correlated with hypoplastic left heart syndrome, older age at Fontan, and extended durations of pleural effusions following the procedure. Survival of PLE has been improved from 50% at 5 years after diagnosis to 88 at 5 years in a recent study from the Mayo Clinic[38]. Higher Fontan pressure, higher pulmonary vascular resistance, decreased ventricular function, lower cardiac index, lower mixed venous saturation, and patients diagnosed with New York Heart Association functional class >2 all has been associated with decreased survival rate. The study found sepsis was the primary cause of death, reflecting the immune deficiency correlated with this diagnosis. However, there was no correlation between ventricular morphology and survival [33,38].

PLE is described as ‘’the state of abnormal increase in protein loss through the intestines, which is measured by high faecal alpha-1 antitrypsin (A1AT) levels or through nuclear scintigraphy using technetium-99m-labeled albumin and this condition can either be present with or without symptoms or manifest of hypoalbuminemia < 3.5 g/dL and total protein (<6 g/dL), followed by symptoms such as edema, abdominal distention or discomfort, diarrhoea, or various effusions (ascites, pleural, or pericardial effusions)”[33]. The earlier interpretation of PLE studies was difficult to interpret due to incoherent definitions. The occurrence of false negatives arising from primary protein loss in the stomach and the occurrence of false positives arising from patients with diarrhoea not caused by PLE [33].

Clinical presentation of PLE may come out soon after Fontan surgery, for example within months; this situation often corresponds to abnormal hemodynamic conditions such as Fontan pathway obstruction, atrioventricular valve regurgitation, or stenosis, elevated pulmonary vascular resistance, or dysrhythmia, including junctional rhythm with loss of atrioventricular synchrony. Initial symptoms can include fluid overload and low serum albumin levels following suspected viral infections, with the incidence of diarrhoea. This condition can more over lead to peripheral and central swelling, in the face, hands, and feet, along with ascites. Patients in this condition might become immunocompromised, increasing their susceptibility to both bacterial and viral infections. When intestinal protein loss progresses, the nutritional deficit may start to appear, leading to severe malnutrition. These patients are at risk for dehydration, mainly loss of electrolytes, and tend to respond poorly to deadly acute bacterial infections[33].

16.1 Pathophysiology of PLE

Patients with the Fontan procedure generally exhibit increased central venous pressure (CVP) and lymphatic congestion. Studies in non-human animals reported that blocking the intestinal lymphatics leads to inflammation[39]; this condition results in lymphangiogenesis, a condition that forms new lymphatic vessels. Moreover, lymphangiectasia, a condition known as dilation of lymph vessels, is very often noted in the intestinal walls of patients with PLE. Chronic systemic inflammation in humans compromises the endothelial glycocalyx layer (EGL) of the vasculature, enhancing its permeability and filtration. Since Fontan patients typically show persistently high levels of inflammatory markers such as tumour necrosis factor-alpha (TNF-a), EGL's integrity is impacted due to TNF-a. This damaged EGL, combined with a congested lymphatic system can lead to edema, further inflammation, and the growth of new lymphatic vessels. Eventually, these abnormal lymphatic vessels can burst and leak into the intestine. In the liver, which normally contributes 25% to 50% of the lymphatic fluid drainage through the thoracic duct, elevated CVP leads to hepatic congestion and, additionally, increased hydrostatic pressure in the sinusoids. Lymphatic production from the liver emerges mainly from the sinusoids, which leads to lymphatic production but leads to impaired drainage due to elevated CVP and lymphatic congestion. This may lead to lymphatic fluid either leaking into the abdomen (ascites) or forming abnormal pathways to the low-pressure intestinal lumen[20]. Also, abdominal and liver-augmented images have been reported with the help of DCMRL, in the DCMRL image the fenestrations are presented in the most parts of duodenum in PLE patients[40].

Table 4. Evaluation of PLE

Assessment Category	Evaluation
Cardiovascular Assessment	Imaging: ECG and MRI to assess pathway of Fontan, function of valve and ventricular, and presence of fenestrations. Cardiac Catheterization: to exclude Fontan pathway obstruction, measure pathway pressure, pulmonary vascular resistance and rule out intra-atrial restriction.
Renal and GI Assessment	Urinalysis: to exclude proteinuria.
Laboratory Tests	Serum albumin, Faecal A1AT Additional tests: serum prealbumin, total protein, immunoglobulins, CBC with differential electrolytes, renal function, liver function thyroid function and iron studies.

16.2 Diagnosis of PLE

The primary diagnosis of PLE should be considered in patients with clinical signs such as hypoproteinaemia, diarrhoea, and peripheral edema. PLE usually shows decreased levels of serum albumin and globulins. Alpha-1- antitrypsin is a sensitive diagnostic marker and it is increased in PLE. It can be measured from blood sample and 24-hour stool collection to evaluate the amount of alpha-1- antitrypsin concentration. Usually, the normal clearance value is less than <24 ml/24 hours, whereas values exceeding 56 ml/24 hours are typically observed in patients experiencing diarrhoea[33]. Clearance values of alpha-1- antitrypsin exceeding the normal level strongly suggest PLE. It is important to note that of alpha-1- antitrypsin concertation is not helpful in case of identifying the exact location of the intestinal protein loss.

The main imaging technique for patients with PLE is called Intrahepatic DCMRL (IH-DCMRL). The specialty of IH-DCMRL is that it will show the connections between the liver and the duodenal wall with leaks into the duodenal lumen in all patients with PLE and congenital heart disease [Fig 10][41]. Intranodal DCMRL (IN-DCMRL) primarily displays lymphatic flow from

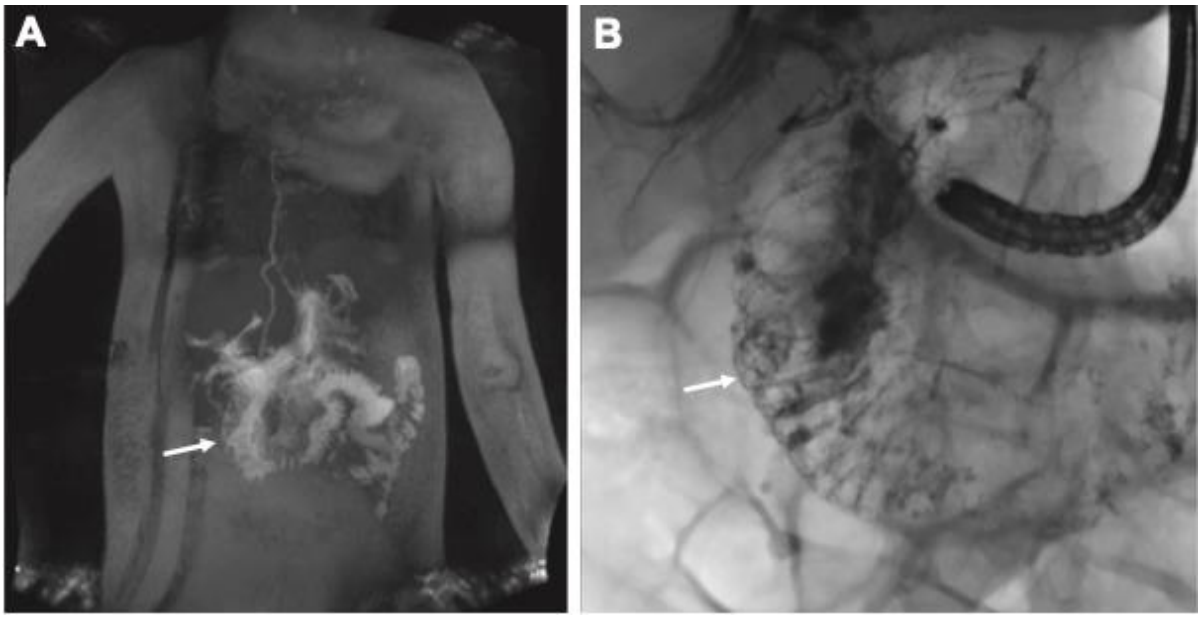

Figure 10. (A) Coronal view of IH -DCMRL shows leak of contrast into duodunel lumen (B) Fluoroscopy image after glue embolization of preduodenal lymphatic networks[33]. *(Adapted from: Mackie AS, Veldtman GR, Thorup L, Hjortdal VE, Dori Y. Plastic Bronchitis and Protein-Losing Enteropathy in the Fontan Patient: Evolving Understanding and Emerging Therapies. Can J Cardiol. 2022 Jul;38(7):988–1001.)*

the lower extremities to the cisterna chyli and thoracic duct but fails to display lymph flow from the liver and mesentery, typically showing no abnormalities. However, in the case of thoracic duct occlusion, IN-DCMRL shows lymph flows to the intestines. For patients in remission from PLE or those with asymptomatic PLE, it can exhibit perfusion of the duodenal wall without any leakage into the lumen of duodenum [33].

16.3Management of PLE

The initial approach for patients with PLE requires hospital admission for a full diagnostic work-up, treatment initiation, and monitoring response therapy. The management of PLE is devoted to nutritional management, reduction of CVP by controlling the Fontan pathway, and use of diuretics and pulmonary vasodilators, anti-inflammatory therapy, and lymphatic interventions in order to avoid leakage of hepatic lymph into the duodenum.

Table 5. Management of PLE[34]

Management	Details
Nutritional Management	High-protein (<2 g/kg/day), low-fat (<25% of calorie intake) diet with medium-chain triglyceride supplements to reduce enteric protein loss, manage malnutrition and optimize growth[33].
Pharmacological Treatments	Usage of diuretics for fluid overload, Spironolactone, an aldosterone receptor antagonist, may decrease loss of potassium and have anti-inflammatory effects. Usage of Sildenafil have effect of lowering the pulmonary vascular resistance and lower the CVP. Budesonides have lower systemic effect due to first pass metabolism. Studies have shown that dopamine infusion have influence on lymphatic vessel contractility, based on its effects on lymphatic receptors.
Immunological Support	Immunoglobulin supplementation for immune deficiency and to improve oncotic pressure, administered intravenously or subcutaneously.
Surgical Intervention	Creating connection like the innominate vein to the common atrium for lymphatic complications, use of grafts and separation of major hepatic veins from inferior vena cava to reduce pressure and improve flow.
Catheter Intervention	Detailed assessment of hemodynamic and cardiac rhythm to find and treat obstructions or valvular issues.
Transplantation	Early referral for transplantation assessment in cases of moderate or severe ventricular dysfunction, considered as a last resort.

Table 5. *(Continued)* Management of PLE[34]

	Studies demonstrates similar post-transplantation outcomes for Fontan patients with and without PLE.

17.MRI Imaging of Lymphatic hypertension in Fontan patients.

Due to their small size and variable location, lymphatics are challenging to evaluate. Lymphangiography, using X-rays, CT, or MRI after injecting contrast into lymphatic channels, is the traditional method to study abnormalities of lymphatic circulation. MRI is rapidly becoming an essential for thoracic duct evaluation, particularly non-contrast T2-weighted MR lymphatic mapping, a non-invasive method capable of clearly visualizing the duct and its branches. However, it only shows static anatomic information[42]. The T2-weighted MR lymphangiogram method has shown lymphangiectasia and lymphatic collateralization in patients with single ventricle palliation and significant dilation of peri bronchial lymphatics in those with plastic bronchitis. T2 MR images of the thorax in Fontan patients have been used to demonstrate four types of abnormalities of lymphatic depending on their anatomical location. Recently, lymphatic imaging involved pedal lymphangiography and lymphoscintigraphy[42]. In pedal lymphangiography, isosulfan blue is injected into the space between the toes, followed by an incision on the dorsum of the foot to access lymphatic vessels by injecting lipiodol, an oil-based contrast injected to view the central lymphatics[20].

Dynamic contrast MR Lymphangiography (DCMRL), established by Dori et al. at The Children's Hospital of Philadelphia, reveals dilated thoracic duct lymphatic channels with abnormal retrograde contrast flow directed towards the pulmonary carnia and hilium, enabling the features of five distinct lymphatic flow patterns into pulmonary parenchyma or bronchi. This condition is termed Pulmonary Lymphatic perfusion Syndrome by Dori et al. Intranodal Dynamic Contrast Magnetic Resonance Lymphangiography (IN-DCMRL) is performed by injecting gadolinium-based contrast agents, similar to the intranodal lymphangiography (IL) method[20]. However, in IL the choice of contrast agent is lipiodol and in IN-DCMRL is a gadolinium-based contrast agents, which is less viscous, allowing deeper and more detailed contrast penetration into the lymphatic system[20]. This technique improves the visualization of the lymphatics in real time and delivers three-dimensional, high-resolution images. Compared to IL the IN-DCMLR provides finer details and makes it predominant for finding lymphatic leakage and lymphatic flow disorders. An advanced imaging technique called Intrahepatic

DCMRL (IH-DCMRL) involves in evaluation of the structure and flow of the liver's lymphatic system by injecting gadolinium into the liver followed by MR imaging to assess liver anatomy and lymph flow. This technique provides good three-dimensional imaging and excellent distal contrast distribution[20,42]. It is also useful in visualizing lymphatic leakage into the duodenal lumen in patients with PLE compared to IN-DCMRL. Due to this reason, IH-DCMRL is now the recommended technique for describing lymphatic abnormalities in patients with PLE and ascites. Another choice to Pedal lymphangiography is Intranodal lymphangiography; and it is currently considered the primary imaging method to view and assess the central lymphatic structures. This procedure involves injecting lipiodol into the inguinal lymph nodes via intermittent fluoroscopy under the guidance of ultrasound. This method makes sure excellent opacification of the central lymphatic system and the thoracic duct in fluoroscopy-guided interventional procedures. It is especially very effective in visualizing lymphatic perfusion of the lung parenchyma along with bronchoscopy in patients with plastic bronchitis (PB). But the use of lipiodol has some notable risks, such as uneven distribution of contrast and potential embolization into the central nervous system in patients with hepatopulmonary syndromes, pulmonary arteriovenous malformations, or right-to-left intracardiac shunts. Scintigraphy, using radiolabelled isotopes like indium 111-labeled transferrin, technetium 99-labeled human serum albumin, or technetium dextran, remains the most sensitive and reliable non-invasive imaging technique for PLE. It can also be used with chromium 51 and iodine 125 conjugated to serum proteins for definitive diagnosis and has demonstrated dilated thoracic duct and perihilar lymphangiectasia[42].

18. Treatment strategies in patients with Lymphatic hypertension complications in Fontan patients.

The management of Fontan patients, particularly those with complications associated with lymphatic system abnormalities. This specific condition creates a space for innovative and effective treatment strategies. The lymphatic complication, which often presents as chylothorax, plastic bronchitis, or protein-losing enteropathy (PLE), can highly affect patient outcomes after Fontan procedures. Treatment strategies like pharmacological methods, decompression of the thoracic duct, and heart transplantation are thoroughly assessed. Anyhow, the main use of advanced imaging techniques such as lymphangiography, plays an important for both diagnosis and therapy to ensure a decision regarding the management of post Fontan complications.

18.1 Pharmacological therapy

Pharmacological treatment in Fontan patients aims to treat the physiological effects and to prevent and treat complications that arise from Fontan procedures. These treatment strategies aim for univentricular function, remodelling, and systemic vascular resistance. Targeted treatment is to reduce the pulmonary vascular resistance. Focusing on agents like phosphodiesterase-5 enzyme inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (bosentan, ambrisentan), and prostacyclin (iloprost). Recent studies, regarding patients with Fontan circulation, explore nine studies with a total of 267 patients, in those, 8 patients having pulmonary vasodilators where 4 with sildenafil, 3 with bosentan, and 1 with iloprost, indicate potential benefits on exercise capacity and hemodynamic[43].

18.2 Closing of Aortopulmonary collaterals in Fontan patients.

Aortopulmonary collaterals (APCs) often emerges as an unpredictable source of pulmonary blood flow in single-ventricle physiology and observed in any stage of surgical palliation: including prior and post Fontan procedure. APCs may support better arterial oxygen saturation by increasing pulmonary blood flow, particularly before the total cavopulmonary connection in order to reduce cyanosis. However, they may result in volume load on the single systemic ventricle and increase pulmonary artery pressure[44].

In a large cohort study involving 635 Fontan patients titled ‘*’Impact of aortopulmonary and venous collaterals on the onset of plastic bronchitis after the Fontan procedure”*[35], explores the role of aortopulmonary collaterals (APCs) in contributing to the development of plastic bronchitis. The study revealed that APCs were identified in 45% of patients, with notably increased occurrence rate in post-Total cavopulmonary connection (TCPC), suggesting a key risk factor for the development of plastic bronchitis. Management of APCs included transcatheter embolization (coiling) [Fig 11] or surgical ligation. To achieve APCs closure, management methods were implemented at different stages – prior to the bidirectional cavopulmonary shunt 2% of the cases, prior to TCPC 10%, and post-TCPC 11% of the cases[35]. These management methods are crucial in order to reduce the adverse effects of APCs, including reducing the pulmonary artery pressure and volume load of the systemic ventricle, thereby preventing the development of plastic bronchitis and potentially improving patient outcomes.

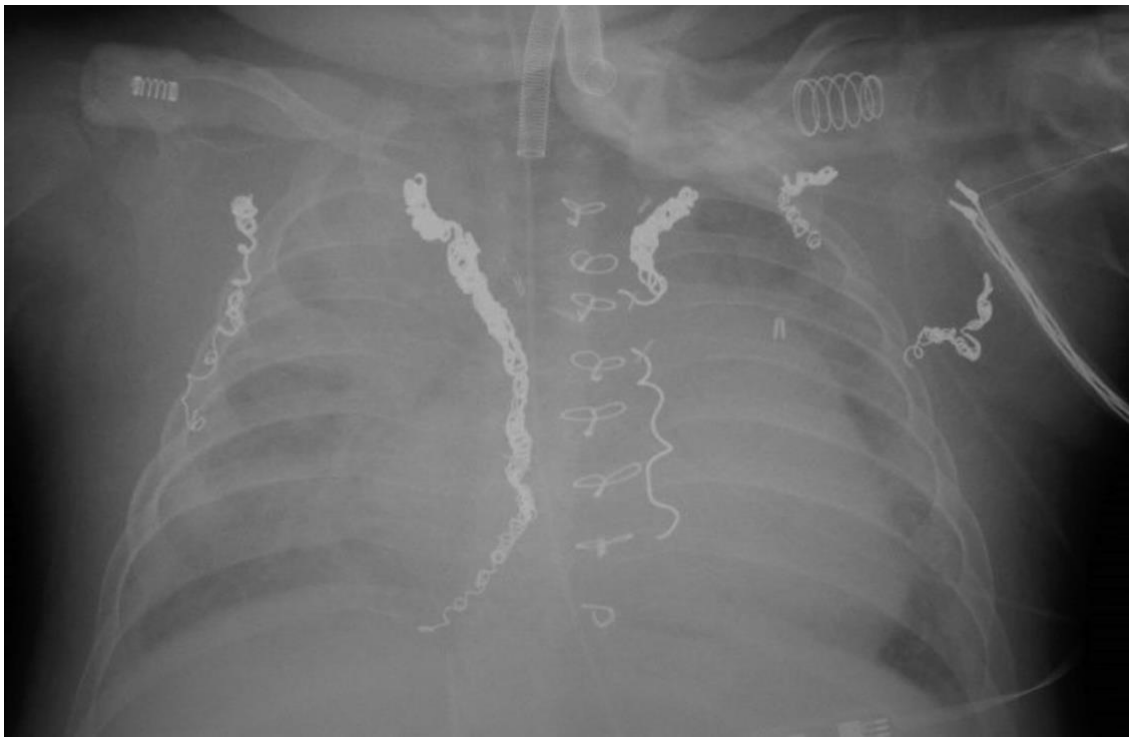

Figure 11. The APC closure involves a transcatheter embolization using coils. DrOrtmannCICU. Aortopulmonary collaterals [Internet]. YouTube; 2023 Dec 19 [Cited 2025 Mar 18] [47]. Available from: https://www.youtube.com/watch?v=wPjr0AWM5xs . Image from video 4 min 21 sec.

18.3 Occlusion of lymphatic collaterals in Fontan patients.

Percutaneous selective lymphatic embolization is the preferred main therapeutic management in Fontan patients with PB. It is a minimally invasive technique to occlude abnormal lymphatic vessels. Inguinal Intra nodal Lymphoangiography is aiding in identifying and occluding the targeted lymph vessel. Lipiodol injection is supporting to find the vessels and they are occluded due to the high viscosity of the lipiodol agent. In patients with chylothorax, the standard treatment has developed into Percutaneous embolization of lymphatic collaterals, which involves getting access to TD through transabdominal or transvenous which is then embolized with a combination of micro coils and N-butyl cyanoacrylate glue. [20]. In patients with PLE selective or targeted embolization involves in sealing leaking lymphatic channels. Multiple embolization agents such as tiny metal coiled, or special glue which are inserted catheter to effectively halt leakage close off the lymphatic vessels which are abnormal[43].

18.4 Surgical Decompression of Thoracic Duct

Thoracic duct (TD) decompression is targeted to alleviate lymphatic afterload by diverting TD to a lower pressure venous chamber. Surgical TD decompression is accomplished with an innominate vein (InV) turn-down procedure, where the InV is redirected to flow into the lower-

pressure common atrium, effectively easing the lymphatic load. This treatment strategy not only reduces pressure in the lymphatic system but also provides ‘’diastolic suctioning’’ of lymph and also enhances cardiac preload at the cost of a right-to-left shunt and potential desaturation[45]. This surgery is considered for patients with type-4 retrograde lymphatic flow who have not responded to six months of medical management. This procedure requires cardiac catheterization and DCMRL to confirm TD anatomy and drainage, usually necessitating cardiopulmonary bypass and consisting of direct anastomosis. Post-surgery, patients are monitored for a few days to ensure arterial saturation is between 80%-85% range. In case of a drop in arterial saturation, the left internal jugular vein might be banded via an incision at the left neck to adjust flow[20]. Moreover, the benefit of InV turn-down anastomosis is that it facilitates access to the common atrium for further interventions. However, the potential effects of rerouting lymphatic flow directly into the systemic circulation, bypassing the lungs require more studies[45].

18.5 Heart Transplantation

Heart transplantation is the conclusive treatment that rectifies Fontan physiology and is utilized for patients with deteriorating Fontan circulation. Research from extensive cohort studies demonstrates between 1.6% and 3.6% of Fontan patients eventually end up in heart transplants[1]. The post-transplant survival rate for these patients is typically worse compared with other congenital heart diseases, with five-year survival rates ranging from 60% to 67%[46].

19.Conclusion

To conclude, this review of lymphatic hypertension complications in Fontan patients highlights the intricate nature of modified hemodynamics, lymphatic abnormalities, and their repercussive clinical presentations. The Fontan procedure, which was first developed as a life-saving procedure for univentricular heart disease, has evolved drastically in the last few years, but it also happens to alter the lymphatic and venous pressures, which leads to a series of physiological challenges that expose patients to series of post-surgical complications, mainly lymphatic hypertension. This condition presents itself with many complicated and chronic issues like, Chylothorax, plastic bronchitis, and protein losing-enteropathy, which affects the long-term lives of these patients and also alters their quality of life negatively. Discoveries in diagnostic methods especially in magnetic resonance lymphangiography has been essential in improving our knowledge also managing these lymphatic abnormalities.

The connection between elevated systemic venous pressure and lymphatic dysfunction is most importantly underlined in this review, this correlation results in notable obstacles in treating the fragile balance of pressures in Fontan circulation, in which small disturbances can lead to serious clinical manifestations. Therefore, the treatment method is not only focused on relieving the symptoms, but the main aim is also to take note of the major changes in the lymphatic flow and pressure dynamics. From intervention through surgery to optimize lymphatic drainage to pharmacological methods to the symptomatic treatments and managing the complications. Hence, when the Fontan procedure stays to be an important intervention for patients having single-ventricle physiology, its wide collection of lymphatic complications needs cross-disciplinary methods of care, highlighting the requirement for ongoing advancement in medical and surgical treatment plans. The aim is to upgrade the quality of patient outcomes by a stronger understanding of Fontan physiology and its effects of the lymphatic system, leading to more efficient and specific interventions.

20.References

1. Van Der Ven JPG, Van Den Bosch E, Bogers AJCC, Helbing WA. State of the art of the Fontan strategy for treatment of univentricular heart disease. F1000Research. 2018 Jun 27;7:935.

2. Marshall KH, D'Udekem Y, Sholler GF, Opotowsky AR, Costa DSJ, Sharpe L, et al. Health-Related Quality of Life in Children, Adolescents, and Adults With a Fontan Circulation: A Meta-Analysis. J Am Heart Assoc. 2020 Mar 17;9(6):e014172.

3. Dittrich S, Weise A, Cesnjevar R, Rompel O, Rüffer A, Schöber M, et al. Association of Lymphatic Abnormalities with Early Complications after Fontan Operation. Thorac Cardiovasc Surg. 2021 Dec;69(S 03):e1–9.

4. Tomasulo CE, Chen JM, Smith CL, Maeda K, Rome JJ, Dori Y. Lymphatic Disorders and Management in Patients With Congenital Heart Disease. Ann Thorac Surg. 2022 Apr;113(4):1101–11.

5. Clift P, Dimopoulos K, Angelini A, editors. Univentricular Congenital Heart Defects and the Fontan Circulation: Practical Manual for Patient Management [Internet]. Cham: Springer International Publishing; 2023 [cited 2024 Oct 22]. Available from: https://link.springer.com/10.1007/978-3-031-36208-8

6. Becker K, Uebing A, Hansen JH. Pulmonary vascular disease in Fontan circulation—is there a rationale for pulmonary vasodilator therapies? Cardiovasc Diagn Ther. 2021 Aug;11(4):1111–21.

7. Cheung Y fai. Congenital and Paediatric Acquired Heart Disease in Practice [Internet]. Singapore: Springer Nature Singapore; 2023 [cited 2025 Mar 18]. Available from: https://link.springer.com/10.1007/978-981-99-2862-0

8. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971 May 1;26(3):240–8.

9. Rodbard S, Wagner D. By-passing the Right Ventricle. Exp Biol Med. 1949 May 1;71(1):69–70.

10. Glenn WWL. Circulatory Bypass of the Right Side of the Heart: Shunt between Superior Vena Cava and Distal Right Pulmonary Artery —Report of Clinical Application. N Engl J Med. 1958 Jul 17;259(3):117–20.

11. Talwar S, Marathe SP, Choudhary SK, Airan B. Where are we after 50 years of the Fontan operation? Indian J Thorac Cardiovasc Surg. 2021 Jan;37(Suppl 1):42–53.

12. Kreutzer G, Galíndez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg. 1973 Oct;66(4):613–21.

13. Marcelletti C, Corno A, Giannico S, Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. J Thorac Cardiovasc Surg. 1990 Aug;100(2):228–32.

14. Gewillig M, Goldberg DJ. Failure of the Fontan Circulation. Heart Fail Clin. 2014 Jan;10(1):105–16.

15. Elder RW, Wu FM. Clinical Approaches to the Patient with a Failing Fontan Procedure. Curr Cardiol Rep. 2016 May;18(5):44.

16. Daley M, Du Plessis K, Zannino D, Hornung T, Disney P, Cordina R, et al. Reintervention and survival in 1428 patients in the Australian and New Zealand Fontan Registry. Heart. 2020 May;106(10):751–7.

17. Atz AM, Zak V, Mahony L, Uzark K, Shrader P, Gallagher D, et al. Survival Data and Predictors of Functional Outcome an Average of 15 Years after the Fontan Procedure: The Pediatric Heart Network Fontan Cohort: Fontan Follow-up. Congenit Heart Dis. 2015 Jan;10(1):E30–42.

18. Liu MY, Zielonka B, Snarr BS, Zhang X, Gaynor JW, Rychik J. Longitudinal Assessment of Outcome From Prenatal Diagnosis Through Fontan Operation for Over 500 Fetuses With Single Ventricle-Type Congenital Heart Disease: The Philadelphia Fetus-to-Fontan Cohort Study. J Am Heart Assoc. 2018 Oct 2;7(19):e009145.

19. Udink Ten Cate FEA, Tjwa ETTL. Imaging the Lymphatic System in Fontan Patients: Toward Robust Quantification of Functional and Structural Abnormalities in Single Ventricle Physiology. Circ Cardiovasc Imaging. 2019 Apr;12(4):e008972.

20. RochéRodríguez M, DiNardo JA. The Lymphatic System in the Fontan Patient—Pathophysiology, Imaging, and Interventions: What the Anesthesiologist Should Know. J Cardiothorac Vasc Anesth. 2022 Aug;36(8):2669–78.

21. Dori Y, Smith CL. Lymphatic Disorders in Patients With Single Ventricle Heart Disease. Front Pediatr. 2022;10:828107.

22. Panthongviriyakul C, Bines JE. Post-operative chylothorax in children: An evidence-based management algorithm. J Paediatr Child Health. 2008 Dec;44(12):716–21.

23. Kreutzer C, Kreutzer G. The Lymphatic System: The Achilles Heel of the Fontan-Kreutzer Circulation. World J Pediatr Congenit Heart Surg. 2017 Sep;8(5):613–23.

24. Mery CM, Moffett BS, Khan MS, Zhang W, Guzmán-Pruneda FA, Fraser CD, et al. Incidence and treatment of chylothorax after cardiac surgery in children: Analysis of a large multi-institution database. J Thorac Cardiovasc Surg. 2014 Feb;147(2):678-686.e1.

25. Zuluaga MT. Chylothorax after surgery for congenital heart disease. Curr Opin Pediatr. 2012 Jun;24(3):291–4.

26. McCulloch MA, Conaway MR, Haizlip JA, Buck ML, Bovbjerg VE, Hoke TR. Postoperative Chylothorax Development Is Associated with Increased Incidence and Risk Profile for Central Venous Thromboses. Pediatr Cardiol. 2008 May;29(3):556–61.

27. Bhatnagar M, Fisher A, Ramsaroop S, Carter A, Pippard B. Chylothorax: pathophysiology, diagnosis, and management—a comprehensive review. J Thorac Dis. 2024 Feb;16(2):1645–61.

28. Savla JJ, Itkin M, Rossano JW, Dori Y. Post-Operative Chylothorax in Patients With Congenital Heart Disease. J Am Coll Cardiol. 2017 May;69(19):2410–22.

29. Zhang K, Li C, Zhang M, Li Y. Treatment of Chylothorax complicating pulmonary resection with hypertonic glucose Pleurodesis. J Cardiothorac Surg. 2021 Dec;16(1):149.

30. Cannizzaro V, Frey B, Bernetbuettiker V. The role of somatostatin in the treatment of persistent chylothorax in children. Eur J Cardiothorac Surg. 2006 Jul;30(1):49–53.

31. Alsaied T, Rathod RH, Aboulhosn JA, Budts W, Anderson JB, Baumgartner H, et al. Reaching consensus for unified medical language in Fontan care. ESC Heart Fail. 2021 Oct;8(5):3894–905.

32. Schumacher KR, Stringer KA, Donohue JE, Yu S, Shaver A, Caruthers RL, et al. Fontan-Associated Protein-Losing Enteropathy and Plastic Bronchitis. J Pediatr. 2015 Apr;166(4):970–7.

33. Mackie AS, Veldtman GR, Thorup L, Hjortdal VE, Dori Y. Plastic Bronchitis and Protein-Losing Enteropathy in the Fontan Patient: Evolving Understanding and Emerging Therapies. Can J Cardiol. 2022 Jul;38(7):988–1001.

34. Telinius N, Hjortdal VE. Role of the lymphatic vasculature in cardiovascular medicine. Heart. 2019 Dec;105(23):1777–84.

35. Osawa T, Schaeffer T, Schmiel M, Hoa Nguyen Cong MB, Niedermaier C, Heinisch PP, et al. Impact of aortopulmonary and venovenous collaterals on the onset of plastic bronchitis after the Fontan procedure. J Thorac Cardiovasc Surg. 2025 Apr;169(4):1070-1079.e3.

36. Dori Y, Keller MS, Rome JJ, Gillespie MJ, Glatz AC, Dodds K, et al. Percutaneous Lymphatic Embolization of Abnormal Pulmonary Lymphatic Flow as Treatment of Plastic Bronchitis in Patients With Congenital Heart Disease. Circulation. 2016 Mar 22;133(12):1160–70.

37. Gossett JG, Almond CS, Kirk R, Zangwill S, Richmond ME, Kantor PF, et al. Outcomes of Cardiac Transplantation in Single-Ventricle Patients With Plastic Bronchitis: A Multicenter Study. J Am Coll Cardiol. 2013 Mar;61(9):985–6.

38. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical Outcomes and Improved Survival in Patients With Protein-Losing Enteropathy After the Fontan Operation. J Am Coll Cardiol. 2014 Jul;64(1):54–62.

39. Breslin JW, Yang Y, Scallan JP, Sweat RS, Adderley SP, Murfee WL. Lymphatic Vessel Network Structure and Physiology. In: Prakash YS, editor. Comprehensive Physiology [Internet]. 1st ed. Wiley; 2018 [cited 2025 Mar 6]. p. 207–99. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cphy.c180015

40. Brownell JN, Biko DM, Mamula P, Krishnamurthy G, Escobar F, Srinivasan A, et al. Dynamic Contrast Magnetic Resonance Lymphangiography Localizes Lymphatic Leak to the Duodenum in Protein-Losing Enteropathy. J Pediatr Gastroenterol Nutr. 2022 Jan;74(1):38–45.

41. Smith CL, Liu M, Saravanan M, Dewitt AG, Biko DM, Pinto EM, et al. Liver lymphatic anatomy and role in systemic lymphatic disease. Eur Radiol. 2022 Jan;32(1):112–21.

42. Menon S, Chennapragada M, Ugaki S, Sholler GF, Ayer J, Winlaw DS. The Lymphatic Circulation in Adaptations to the Fontan Circulation. Pediatr Cardiol. 2017 Jun;38(5):886–92.

43. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, et al. Evaluation and Management of the Child and Adult With Fontan Circulation: A Scientific Statement From the American Heart Association. Circulation [Internet]. 2019 Aug 6 [cited 2024 Oct 29];140(6). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000696

44. Schmiel M, Kido T, Georgiev S, Burri M, Heinisch PP, Vodiskar J, et al. Aortopulmonary collaterals in single ventricle: incidence, associated factors and clinical significance. Interact Cardiovasc Thorac Surg. 2022 Jul 9;35(2):ivac190.

45. Hraška V. Decompression of Thoracic Duct: New Approach for the Treatment of Failing Fontan. Ann Thorac Surg. 2013 Aug;96(2):709–11.

46. Mauchley DC, Mitchell MB. Transplantation in the Fontan Patient. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2015;18(1):7–16.

47. DrOrtmannCICU. Aortopulmonary collaterals [Internet]. YouTube. 2023. Available from: https://www.youtube.com/watch?v=wPjr0AWM5xs

21. Attachments

22. Warranty

Vilniaus universiteto studijuojančiojo, teikiančio baigiamąjį darbą, GARANTIJA

Vardas, pavardė: Subojhan Kandeepan
Padalinys: Medicinos fakultetas
Studijų programa: Medicina
Darbo pavadinimas: Lymphatic Hypertension Complication in Fontan patients. Literature Review
Darbo tipas: Pagrindiniu studiju baigiamasis darbas

Garantuoju, kad mano baigiamasis darbas yra parengtas sąžiningai ir savarankiškai, kitų asmenų indėlio į parengtą darbą nėra. Jokių neteisėtų mokėjimų už šį darbą niekam nesu mokėjęs. Šiame darbe tiesiogiai ar netiesiogiai panaudotos kitų šaltinių citatos yra pažymėtos literatūros nuorodose.

Aš,Subojhan Kandeepan, patvirtinu (pažymėti) ☑

I, Subojhan Kandeepan, confirm (check)

WARRANTY of Vilnius University Student Thesis

Name, Surname: Subojhan Kandeepan
Faculty: Faculty of Medicine
Study programme: Medicine
Thesis topic: Lymphatic Hypertension Complication in Fontan patients. Literature Review
Thesis type: Final Master Thesis

I guarantee that my thesis is prepared in good faith and independently, there is no contribution to this work from other individuals. I have not made any illegal payments related to this work. Quotes from other sources used in this thesis, directly or indirectly, are indicated in literature references.

Patvirtinu, kad baigiamasis darbas yra pateiktas į Vilniaus universiteto studijų informacinę sistemą.
I declare that this thesis is submitted to the Vilnius University Study Information System.

Subojhan Kandeepan		***02/05/2025***
(vardas, pavardė / *name, surname*)	(parašas / *signature*)	(data / *date*)