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ORIGINAL RESEARCH

Lymphatic Disorder Management in Pediatric Patients With Congenital Heart Disease in European Pediatric Cardiology Centers: Current Status, Disparities, and Future Considerations

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BACKGROUND: Lymphatic disorders such as protein-losing enteropathy, plastic bronchitis, and chylothorax are important complications of the Fontan circulation and ultimately result in an increased risk of early death. Several European centers are now performing lymphatic procedures. The aim of this study is to map the extent of these lymphatic disorders and treatments provided across European pediatric cardiology centers.

METHODS AND RESULTS: A survey was circulated to 49 European pediatric cardiology centers consisting of 37 questions including a mix of binary, categorical, and continuous variables. Thirty-one centers (63%) participated in the study, performing a median of 250 (interquartile range, 178 - 313) cardiopulmonary bypass procedures per year. Chylothorax emerged as the most prevalent lymphatic disorder followed by protein-losing enteropathy and plastic bronchitis. The most common diagnostic investigation method was noncontrast magnetic resonance lymphangiography (52%). Eleven centers (35%) conducted lymphatic interventions with a median of 3 (interquartile range, 1 - 4) procedures per year and 12 (interquartile range, 5 - 15) interventions in total per center.

CONCLUSIONS: This study confirms the rarity of and variation in treatment approaches for lymphatic disorders across Europe. With at least 11 centers offering lymphatic interventions, the adoption of these procedures is on the rise in Europe. To improve the quality of care and treatment outcomes for these complex patients, it is crucial to consider evidence-based lymphatic diagnostics, interventional lymphatic procedures, and the centralization of services in Europe.

Key Words: congenital heart disease ■ imaging modalities ■ lymphatic disorders ■ lymphatic interventions ■ MRI

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CLINICAL PERSPECTIVE

What Is New?

- Novel findings from this study show that lymphatic interventions have been implemented in at least 11 pediatric cardiology centers across Europe.

What Are the Clinical Implications?

- The clinical implications of these findings indicate an increased awareness and emerging possibilities to treat patients with lymphatic disorders in Europe.
- Moving forward, further investigation is necessary to assess the long-term outcomes of these interventions and to inform best practices that could potentially revise current treatment guidelines for these rare but serious conditions.

Nonstandard Abbreviations and Acronyms

DCMRL	dynamic contrast magnetic resonance lymphangiography
MRL	magnetic resonance lymphangiography
PB	plastic bronchitis
PLE	protein-losing enteropathy

Despite substantial advancements in the treatment and management of the Fontan circulation, a palliative surgical option for children born with a univentricular heart, this circulation inevitably leads to elevated central venous pressures, causing venous congestion and reduced cardiac output.[1–3] Multiple complications have been related to these pathophysiological changes including liver congestion, cyanosis, thromboembolism, renal dysfunction, and lymphatic complications such as protein-losing enteropathy (PLE), plastic bronchitis (PB), and chylothorax, ultimately resulting in an increased risk of morbidity and premature death.[4–10] Chylothorax, characterized by the leakage of lymphatic fluid into the pleural cavity, has been reported with an incidence of 7% to 24%, occurring following either surgical repair or nontraumatic causes.[11–14] PLE, characterized by the abnormal loss of lymphatic fluid into the lower-pressure enteral lumen, and PB characterized by the leakage of lymphatic fluid into the airways resulting in the formation of exudative airway casts, are rare but severe complications with incidence rates ranging from 3% to 18% and 4%, respectively.[15–21] However, recent surveys of patients with Fontan circulation have reported a higher proportion of patients (14%–24%) experiencing coughing and expectorating casts or plugs, indicating a possible underdiagnosis of patients with PB.[20] These conditions result in considerable morbidity and have high mortality rates after diagnosis, with reported 5-year survival ranging from 50% to 88% of patients.[16,17,21]

Until recently, the management of lymphatic complications was limited due to a poor understanding of the pathogenesis of these diseases. Various medical treatments have been widely used for symptom relief.[22–24] However, in recent years, due to the development of new lymphatic imaging techniques, lymphatic interventions have been introduced in the management of these complications.[8,9,21,25,26] Children's Hospital of Philadelphia has been at the forefront globally in performing lymphatic interventions on these patients.[27–29] As a result, Children's Hospital of Philadelphia has become a referral center for numerous institutions seeking advanced care for their patients. Despite this progress, the evidence supporting these interventions has been limited to case reports, case series, or expert opinions. In recent years, reports have emerged from different centers in Europe, indicating that these lymphatic interventions are now being offered and performed in Europe as well.[30–37] However, comprehensive data on the extent of availability and use of these advanced diagnostic and therapeutic techniques across European pediatric cardiology centers remain limited. This study aims to fill this critical knowledge gap by mapping the current status and number of European centers performing lymphatic interventions.

The aim of this study was to investigate lymphatic disorders associated with congenital heart diseases by providing an overview of the number of patients with lymphatic complications, the current state of imaging, and the treatment options available in Europe. By exploring this novel and highly specialized area within congenital heart disease, we hope to improve the overall care provided to these patients.

METHODS

This study was an exploratory study based on a survey distributed to 49 European centers specializing in pediatric cardiology. The survey included a total of 37 questions designed to investigate practices related to the diagnosis and treatment of lymphatic disorders in pediatric cardiology (Data S1). The survey was distributed electronically using a secure platform designed for academic research, maximizing accessibility and participation. Reminder emails were sent to maximize response rates. The questions consisted of a mix of binary, categorical, and continuous variables. The binary questions were primarily used to confirm participant consent and the presence of specific procedures at the centers. Categorical questions categorized the frequency of cases of chylothorax with options such as

"1–5, 6–10, 11–15, >15." Continuous variables required numerical input, for example, asking for the annual number of cardiopulmonary bypass procedures or the total number of patients with the different lymphatic disorders (PLE and PB). Due to the rarity of PLE and PB, we chose to include the total number of cases per center without defining the exact time frame. However, for chylothorax, which is a more common complication, we asked for the total number of cases per year.

Data are presented as counts or percentages, and means or medians as appropriate, ensuring data uniformity across all points of analysis. As the majority of the data were nonparametric, we primarily reported the median value and its interquartile range (IQR) to show the data dispersion. Additionally, when dealing with predefined categorical limits (eg, <10, >15), we consistently opted for the immediate value below or above, respectively. This approach has been consistently implemented across all data points to maintain uniformity. Data supporting the findings are available from the corresponding author upon reasonable request. The first author and corresponding author had full access to all the data in the study and take responsibility for its integrity and the data analysis. Ethical approval was not required since the survey solely consisted of administrative data (eg, numbers of procedures, patients, and outcomes), and thus no patient sensitive data were included.

RESULTS

Of 49 centers invited to participate in the questionnaire, responses were received from 31 centers (63%). Among these, 5 centers were from the United Kingdom; 3 from the Netherlands and Italy; and 2 from Belgium, Germany, Romania, Spain, and Sweden. Additionally, 1 center each from Denmark, Estonia, Finland, France, Iceland, Ireland, Latvia, Lithuania, Norway, and Switzerland participated. A median of 250 (IQR, 178 - 313) cardiopulmonary bypass procedures in pediatric patients with congenital heart disease are performed per year per center. The total number of cardiac surgeries and interventions associated with congenital heart disease across these 31 centers are illustrated in Figure 1.

All 31 centers concurred to centralizing expertise in lymphatic intervention procedures across Europe. Twenty-three centers (74%) expressed interest in referring patients to other European centers with expertise in lymphatic interventions. Eight centers (28%) showed no interest in referring patients, primarily due to their own center's capability to perform these interventions. When asked about the number of specialized centers needed in Europe, 14 (45%) suggested 1 to 3 centers, 9 (31%) suggested 4 to 6 centers, and 4 (14%) suggested ≥6 centers.

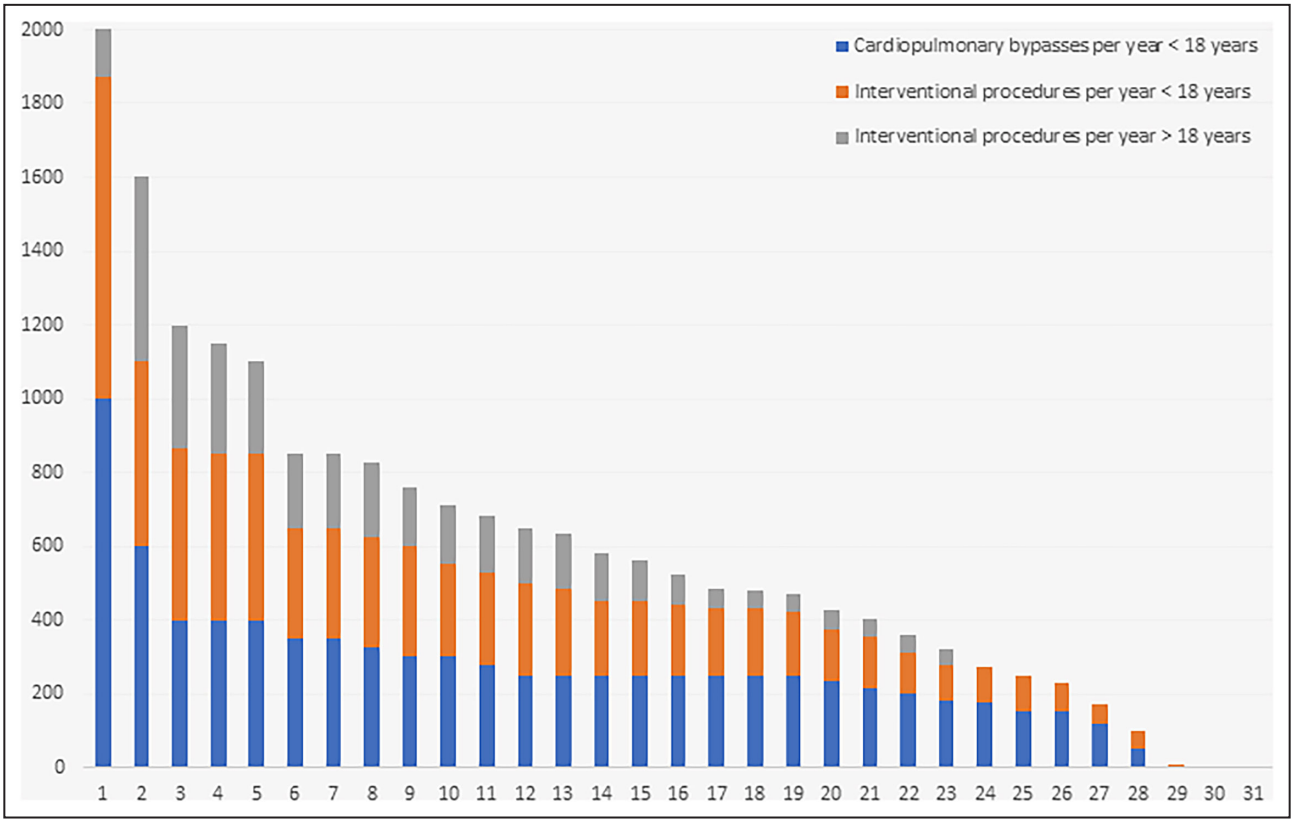

Figure 1. Congenital cardiac interventions and surgery in 31 participating centers in Europe.

Lymphatic Interventions

Among the 31 centers included, 11 centers (35%) reported conducting lymphatic interventions (eg, lymphatic embolization, surgical, or catheter-based Hraska interventions), with a median of 3 (IQR, 1 - 4) procedures per year and 12 (IQR, 5 - 15) interventions in total per center. The total number of interventions performed per year and in total per center are depicted in Figure 2. One center reported conducting repeated procedures, occurring in approximately one third of cases. In 7 centers, lymphatic interventions were conducted by teams comprising both radiologists and pediatric cardiologists, with 3 of these centers collaborating with a visiting team. In 3 centers, interventional radiologists solely conducted these interventions, while in 1 center, the interventions were performed exclusively by a visiting team.

Lymphatic Imaging Modalities

An overview of the current imaging modalities and screening methods used across the 31 centers are provided in Table. When examining for lymphatic abnormalities, 17 centers (55%) used magnetic resonance lymphangiography (MRL), with all centers employing noncontrast MRL using heavily weighted T2 sequence. Additionally, 41% of the centers used dynamic contrast magnetic resonance lymphangiography (DCMRL) for further diagnostic evaluation. Less than 16% of the centers routinely performed noncontrast MRL in all patients either before the Fontan procedure or during the transition to adult services. None of the centers routinely performed DCMRL nor radiographic lymphangiography before the Fontan procedure. Moreover, 13% of the centers screened patients with noncontrast MRL before the Fontan procedure, while 23% of the centers screened only selected patients.

Lymphatic Disorders

When investigating lymphatic disorders associated with congenital heart disease, chylothorax emerged as the most prevalent disorder, with a median caseload per year of 8 (IQR, 3 - 8) patients per center and an incidence of 2.9%. Meanwhile, the median number of total cases involving PLE and PB across the centers were 5 (IQR, 1 - 10) and 2 (IQR, 0 - 4), respectively (Figure 3). A diet high in medium-chain triglycerides (eg, Monogen) was the preferred treatment for chylothorax in 29 centers (94%), with 23 centers (74%) administering this for multiple weeks. Octreotide and total parenteral treatment were used by 23 (74%) and 20 (65%) centers, respectively. In terms of investigating for PLE, plasma albumin levels and stool samples were used by 30 (97%) and 25 (81%) centers, respectively. Imaging was used by less than half of the centers when investigating for PLE; 13 centers (42%) performed noncontrast MRL, 10 centers (32%) performed DCMRL, and contrast radiographic lymphangiography was performed by only 5 centers (16%).

The many available treatment options for PLE across the centers are provided in Figure 4. Only 10 centers (32%) employed lymphatic interventions as treatment for PLE. Among these, 2 centers performed both surgical and catheter-based Hraska decompression, while 1 center performed only catheter-based Hraska decompression. Two centers solely conducted surgical Hraska decompression, with 1 center performing it during the Fontan procedure when anatomically feasible. Lymphovenous anastomosis was performed by only 1 center. Physiotherapy and Mucolycin were used by 18 (58%) and 16 (52%) centers, respectively, when treating patients with PB, while lymphatic embolization and bronchial lavage were employed across 11 centers (35%) each.

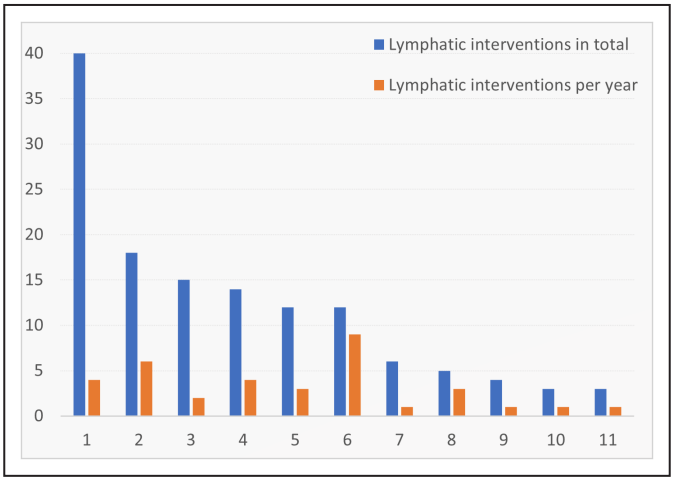

Figure 2. Lymphatic interventions performed per center.

Table. Imaging Strategies Across the European Centers

	Number of centers, n (%)
Lymphatic diagnosis using MRL	17 (55)
• Noncontrast MRL	17 (55)
• DCMRL	12 (39)
Routinely performed noncontrast MRL before Fontan procedure	5 (16)
Routinely performed DCMRL before Fontan procedure	0
Routinely performed radiographic lymphangiography before Fontan procedure	0
Routinely performed noncontrast MRL before transition to adult services	4 (13)
Screening noncontrast MRL in all patients before Fontan procedure	4 (13)
Screening noncontrast MRL before undertaking Fontan procedure in selected patients	7 (23)

DCMRL indicates dynamic contrast magnetic resonance lymphangiography; and MRL, magnetic resonance lymphangiography.

DISCUSSION

For decades, the treatment and management of lymphatic disorders in patients with involvement of a single ventricle have been limited.[1,25] However, recent advancements in imaging technology have led to the introduction of new therapeutical approaches for these complex conditions.[9,25,26] Our study presents the current number of lymphatic disorders and lymphatic interventions performed throughout the 31 European centers included in this study. Despite this progress, the evidence supporting these strategies is often limited to case reports, case series, or expert opinions. While some centers have reported promising short to midterm treatment outcomes for lymphatic interventions, the absence of controlled studies is notable.[27,36–38] Furthermore, indications for such lymphatic interventions have likely varied among centers, leaving the ultimate role of lymphatic interventions in the treatment of these patients yet to be conclusively determined.

When considering the reported number of patients with chylothorax per year in this study, it is crucial to recognize that these figures encompass all cases in pediatric patients with congenital heart disease, rather than exclusively those with Fontan circulation. Data from the Pediatric Cardiac Critical Care Consortium registry and the Pediatric Health Information System databases indicate that the overall incidence of chylothorax in pediatric patients after congenital heart surgery or heart transplantation ranges from 1.5% to 7.6% and 2% to 3.8%, respectively.[13,39] Among the 31 centers involved in this study, the incidence of chylothorax varied from 0.5% to 8.5%, with a median incidence of 2.9%. Consequently, the reported numbers are consistent with previously reported data.

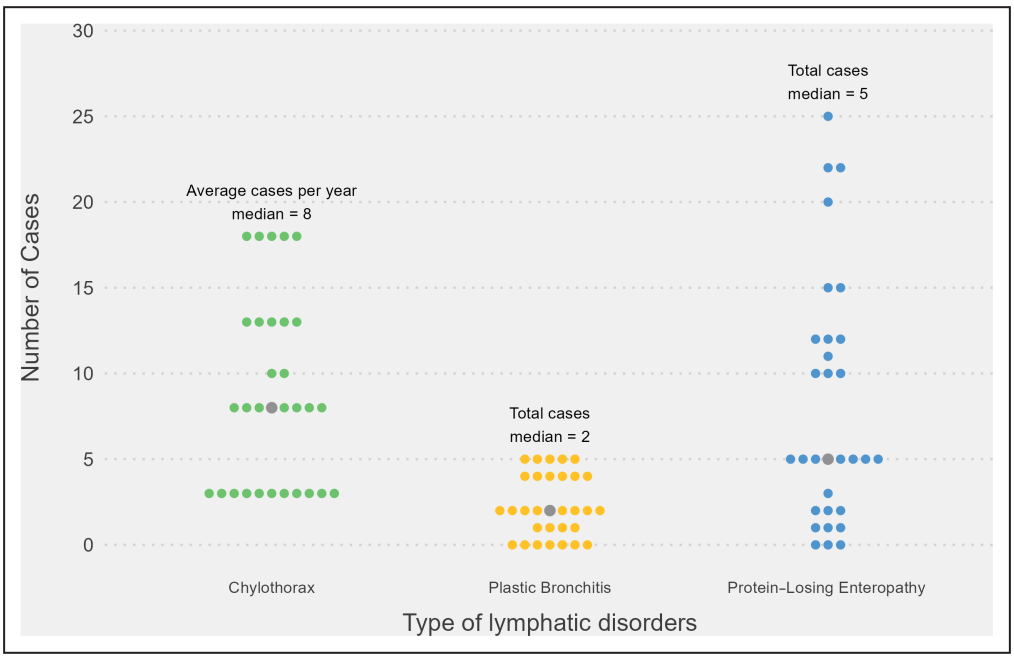

Figure 3. Lymphatic disorders and their occurrence.
Chylothorax is presented as average cases per year, with a median of 8 (IQR, 3 -8) patients per center per year. Plastic bronchitis and protein-losing enteropathy, presented as total cases across all centers over an undefined number of years due to their low incidence, were found to have medians of 2 (IQR, 0 - 4) and 5 (IQR, 1 - 10), respectively. IQR indicates interquartile range.

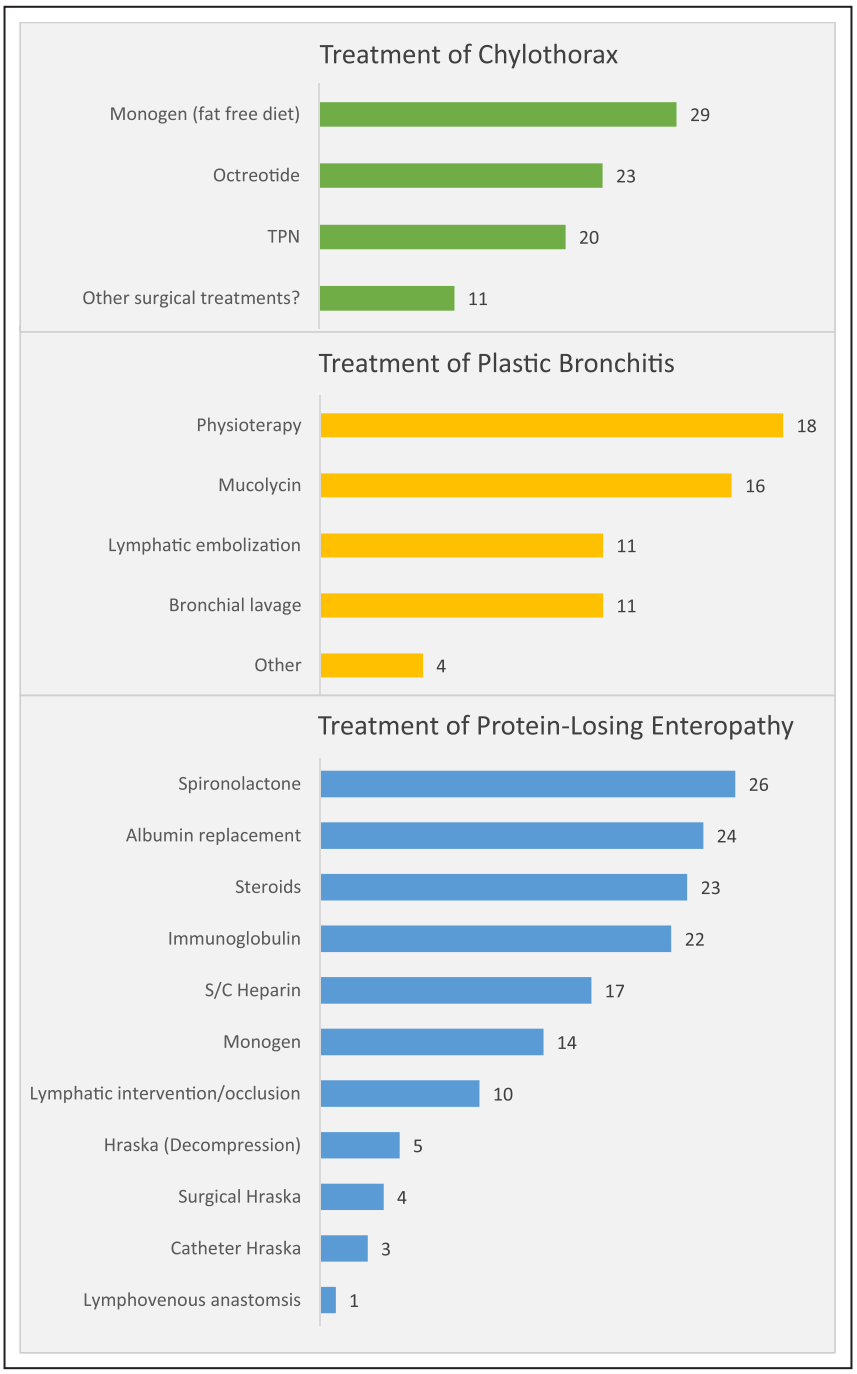

Figure 4. Lymphatic disorders and their treatments across the 31 European centers.
Other surgical treatments for chylothorax indicates 3 thoracic duct ligation, 2 pleurodesis, and 1 pleura adhesion; for the remaining 6 centers, this was not specified. Other treatments for plastic bronchitis: plasminogen-activator inhalation, alteplase when available, and finally surgical Hraska during the Fontan procedure. TPN indicates total parenteral nutrition.

As clinicians gain a deeper understanding of the lymphatic system and its complications, it is evident that this patient population is growing, with patients presenting with a diverse variety of lymphatic-associated complications. The current management of lymphatic disorders involves patient-tailored medical, interventional, and surgical strategies requiring a multidisciplinary approach.[8,9] Conducting lymphatic interventions requires specialized medical personnel including 1 or 2 interventional pediatric cardiologists or radiologists, an anesthesiologist/

intensivist, magnetic resonance imaging (MRI)/echocardiogram/ultrasound experts, gastroenterologist or bronchoscopist, surgeon, and specialist nurses.[40] Additionally, specialized equipment, which may include a hybrid catheterization–MRI laboratory or a cardiac catheterization laboratory and MRI scanner physically close to each other, are required. Our study reveals that several centers have started performing lymphatic interventions in Europe. However, there is considerable variability in the treatment options available across the different centers.

Current Diagnostic and Treatment Recommendations for Lymphatic Disorders

Current diagnostic and treatment recommendations for lymphatic disorders were initially outlined by Dori et al[41] from Children's Hospital of Philadelphia in 2022 with the latest updated recommendations published in a recent review article by Bauer et al in 2023.[9] Noncontrast MRL, using heavily weighted T2 sequences to image slow-moving nonbloody fluids such as lymphatic fluid, has demonstrated a strong correlation between high-grade thoracic lymphatic abnormalities and poor Fontan outcomes (Figure 5).[26,42,43] It is a fast and noninvasive diagnostic tool suitable for inclusion during routine cardiac MRI and has previously been suggested as a screening tool for all thoracic lymphatic abnormalities in patients with single-ventricle involvement before Fontan completion.[41,42,44] Currently, our study shows that only 4 of the 31 included centers perform MRL screening in all patients before the Fontan procedure. Additionally, it is recommended that all patients with suspected lymphatic abnormalities undergo cardiac catheterization to exclude systemic obstruction and assess hemodynamics. If symptoms persist despite optimized medical treatment and percutaneous procedures addressing potential obstructions, DCMRL is recommended as the gold standard method to evaluate the lymphatic system and its flow characteristics (Figure 6). This minimally invasive testing technique involves dynamic and static contrast-enhanced MRI following ultrasound-guided and radiographically guided contrast injections at different access points:

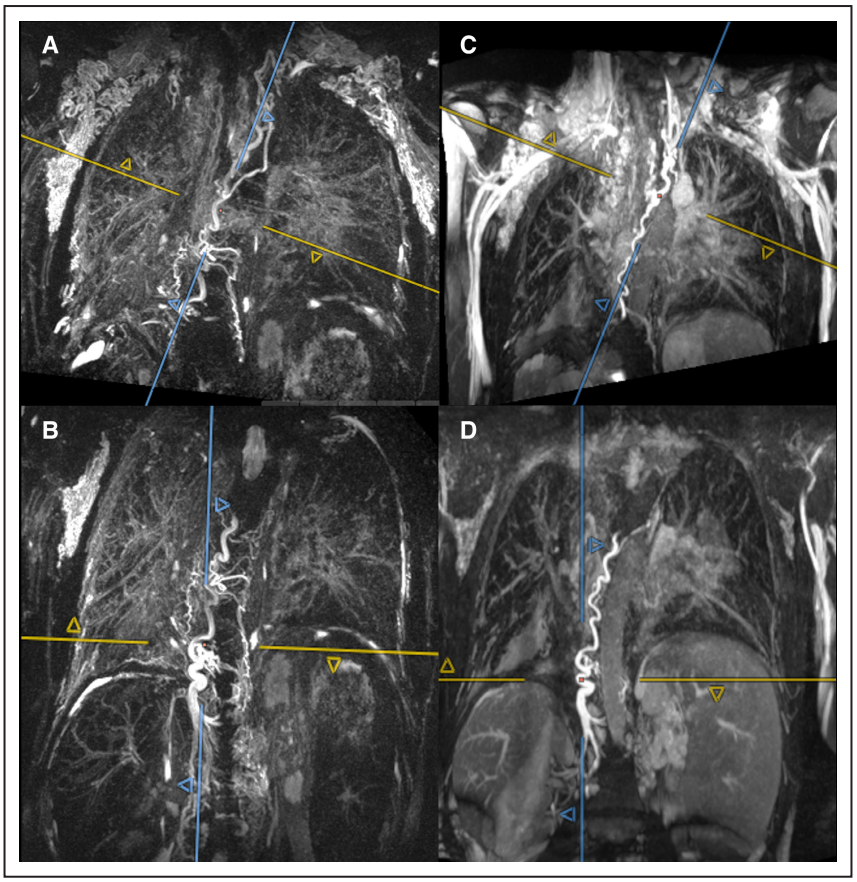

Figure 5. Noncontrast MRL.
Multiplanar reconstructions from heavily T2-weighted noncontrast MRL show a dilated and tortuous thoracic duct (**A, B**). The thoracic duct is also well seen on 3-dimensional SSFP images (**C, D**). MRL indicates magnetic resonance lymphangiography; and SSFP, steady-state free precession.

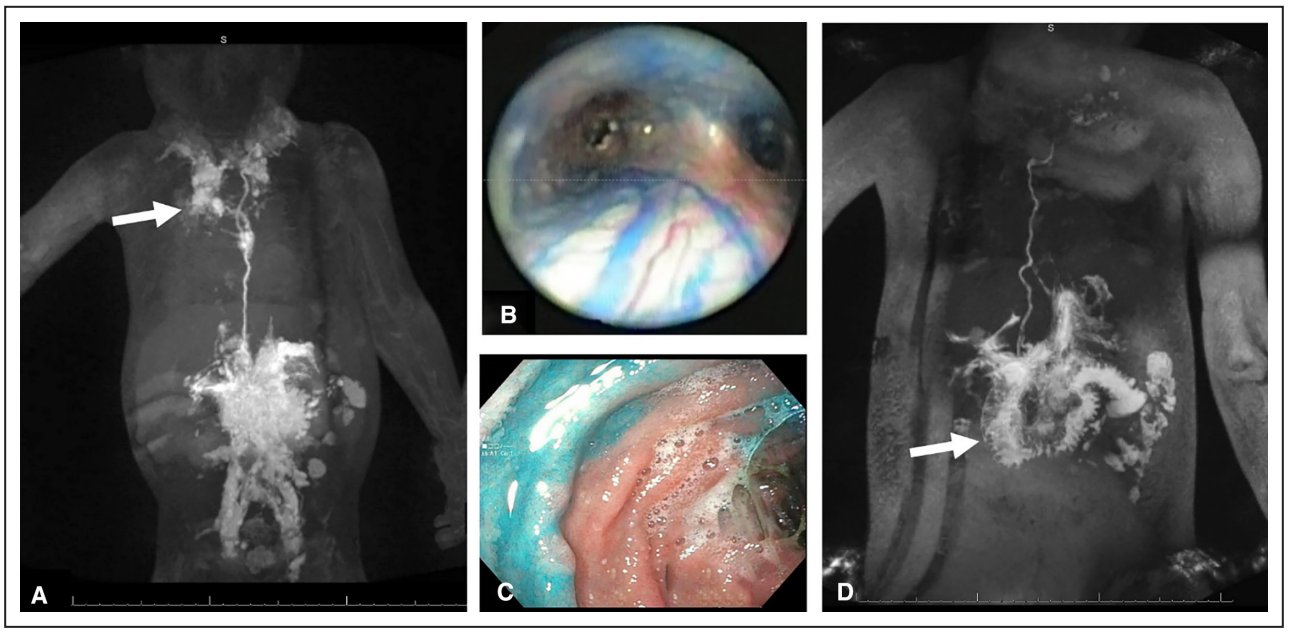

Figure 6. DCMRL.
A, Intranodal DCMRL demonstrating mediastinal and bilateral pulmonary lymphatic perfusion syndrome more on the right (arrow). **B**, In a patient with PB, blue dye injection into the TD demonstrated dilated peribronchial lymphatic networks. **C**, Blue dye injection into the liver demonstrating leak into the duodenal lumen. **D**, Intrahepatic DCMRL demonstrating leak into the duodenal lumen characteristics of PLE (arrow). Reproduced from Dori et al[41] under the terms and conditions of the Creative Commons Attribution (CC-BY) license (https://creativecommons.org/licenses/by/4.0/). DCMRL indicates dynamic contrast magnetic resonance lymphangiography; PB, plastic bronchitis; PLE, protein-losing enteropathy; and TD, thoracic duct.

intranodal DCMRL for central lymphatics, intrahepatic DCMRL for hepatosystemic lymphatics, and intramesenteric DCMRL for peritoneal/mesenteric lymphatics.[26,41] Since contrast is visible only in parts of the lymphatic system within the contrast pathway, different access points are used depending on the clinical presentation. This diagnostic examination can be followed by appropriate lymphatic intervention while the patient is still under general anesthesia. Lymphatic intervention can be categorized into those aimed at occluding abnormal lymphatic ducts (using glue, coils, or a combination) and those intended to decompress the entire lymphatic system (surgical or catheter-based Hraska interventions).[25] Based on case series and case report studies, algorithms have been proposed for the diagnostic evaluation and treatment of patients with chylothorax, PLE, PB, and multicompartment disorders, defined as lymphatic perfusion abnormalities involving at least 2 compartments, including the thorax, abdomen, and soft tissue. A more detailed description and flowcharts can be found elsewhere.[9,41]

Centralizing Lymphatic Interventions: Challenges and Considerations

It is important, however, to highlight that not all centers have the capability to provide diagnostic MRL or DCMRL due to a lack of equipment, experience, and/or expertise in interpreting and evaluating the scans. Consequently, the current diagnostic suggestions and treatment algorithms mentioned above may not be feasible for all centers. Moreover, the included centers in this study perform a relatively low number of lymphatic interventions annually with a median of 3 (IQR, 1 - 4) interventions per year and 12 (IQR, 5 - 15) interventions performed in total by each center. Considering the intricacy of these procedures and the need for a significant number of medical personnel, the question arises: How many centers should be entrusted with performing these procedures? Should each center have its own specialized units dealing with lymphatic complications? Centralization of these highly specialized treatments may warrant detailed consideration. Gathering expertise in a selected number of centers could potentially improve treatment outcomes by ensuring that medical professionals accumulate sufficient experience and proficiency in managing these complex cases. Moreover, centralization may facilitate collaboration and knowledge-sharing among experts, leading to advancements in treatment protocols and patient care. However, centralization may also present challenges, particularly regarding service accessibility, resources, and local expertise, which may potentially impact timely diagnosis and initial management. Centralization may strain the resources of the designated centers, potentially leading to longer waiting times and increased

health care costs. Additionally, patients may face logistical and financial obstacles in accessing centralized centers, especially if they are located far from their place of residence or in a different country.

Patients traveling within the European Union or European Free Trade Association countries can use the S2 form (formerly known as E112 form) to receive health treatment in another EU or European Free Trade Association country. The form is issued by the individual's health insurance authority and must be submitted to the health insurance authority in the country where treatment is sought. This facilitates access to health care services across borders within the European Union and European Free Trade Association, ensuring equitable treatment for patients seeking medical care abroad.

Ultimately, the decision regarding the optimal number of centers performing these complex specialized procedures should be assessed by a thorough evaluation of various factors, including patient needs, health care infrastructure, and resource allocation. Pursuing a balance between centralized expertise and patient accessibility will be crucial in ensuring that all patients with congenital heart disease with lymphatic complications receive high-quality care.

Limitations

This study was isolated to European centers, and although we received responses from 31 centers, the response rate was only 63%. The nonresponding centers invited to participate varied in size, ranging from small to large centers, and were based in several European countries. The demographic and operational characteristics of these centers, such as patient volume, facility resources, and specialization in pediatric cardiology, mirrored those of the centers that participated in the survey. Therefore, we believe that their noninvolvement does not introduce a bias to the results of our survey. While the specific reasons for nonparticipation, despite repeated requests, remain complex and varied, they are beyond the scope of this study. Only few centers from the largest countries in Europe responded to our survey. Our study, therefore, does not represent population-based data from England and the rest of the continental Europe. However, data from the 5 Nordic countries, the Baltic countries, and Ireland represent entire populations. The lack of representation from larger European centers could potentially lead to a skewness in the reported data toward overrepresenting smaller and less specialized centers performing lymphatic interventions themselves. Additionally, being an explorative questionnaire study, one unavoidable limitation is response bias. The responses may have been affected by social desirability bias, recall bias, or other factors influencing the reliability and validity of the collected data. Furthermore, our survey, which primarily captured administrative data, faces limitations in data granularity. This underscores the necessity to consider potential demographic and clinical variations that could influence the management and treatment outcomes of lymphatic disorders in pediatric patients. These variations may include factors like the number of compartments involved in a lymphatic disorder. For instance, multicompartment disorders are inherently more complex and require a broader treatment approach compared with one-compartment disorders like PB. Such variations extend beyond the scope of our study, and future research should integrate both demographic and clinical variables to deepen our understanding of treatment efficacies for these disorders.

CONCLUSIONS

In conclusion, this study is the first to provide valuable insights into the management of lymphatic complications in patients with congenital heart diseases across a large cohort of European pediatric cardiology centers. Chylothorax was found to be the most prevalent lymphatic disorder with a median caseload per year of 8 patients followed by PLE and PB with a median number of total cases of 5 and 2 patients per center, respectively. Seventeen of the 31 included centers performed noncontrast MR lymphangiography while 12 centers performed dynamic contrast MRL. Eleven centers offered lymphatic interventions, while only 5 of these performed Hraska decompression. Notably, the adoption of lymphatic interventions is on the rise in Europe, highlighting the urgency for the development of standardized, evidence-based protocols and the centralization of expertise. Centralization could enhance treatment efficacy due to the technical complexity and the typically low volume of procedures at individual centers. However, such centralization must be balanced against considerations of patient accessibility and the efficient allocation of health care resources. The necessity for ongoing research is evident, especially in evaluating the diagnostic management and long-term outcomes of these interventions. We acknowledge the exploratory nature of our study and recommend that future research incorporate detailed data on demographics and clinical variations across a larger patient population to better understand the impact of confounding variables. Future studies will be crucial in defining best practices and may lead to changes in current treatment algorithms for these rare, yet severe, conditions.

ARTICLE INFORMATION

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Supplemental Material

Data S1. Supplemental Methods

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