BMC Pulmonary Medicine

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Lymphatic malformations involving the thorax in children: a retrospective cohort study

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Abstract

Background Lymphatic malformations (LMs) involving the thorax are rare, with limited clinical understanding. We aimed to summarize the classification, clinical features, treatment, and prognosis of thoracic LMs, and to improve disease management and patient outcomes.

Methods Clinical data and follow-up data obtained from 42 patients with thoracic LMs were reviewed retrospectively at a single center in China.

Results Patients were classified into 7 types: 1 with macrocystic LM, 3 with infancy primary chylothorax, 4 with primary lymphedema (PL), and 34 with complicated lymphatic anomalies (CLAs), including 18 with generalized lymphatic anomaly (GLA), 8 with kaposiform lymphangiomatosis (KLA), 6 with central conducting lymphatic anomaly (CCLA), and 2 with Gorham–Stout disease. The specific clinical manifestations included chylothorax (50%), white foamy/jelly-like sputum (47.6%), and plastic bronchitis (7.1%). Imaging findings revealed interlobular septal thickening in 20 patients (47.6%) and ground-glass opacity in 13 (31.0%). Improvements were observed in 16 patients with CLAs who were administered sirolimus, 2 with GLA who were administered sirolimus and bevacizumab, 1 with KLA who was administered trametinib, 6 with CCLA who underwent surgery, 3 with infancy primary chylothorax following dietary treatment, and 1 with macrocystic LM following sclerotherapy. Stabilization occurred in 7 patients (3 with CLAs and 4 with PL) postsurgery. Progression or death was observed in 4 patients with GLA and 3 patients with KLA.

Conclusions Different types of thoracic LMs have similar clinical features and imaging manifestations but vary in terms of treatment and prognosis.

Keywords Complicated lymphatic anomalies, Generalized lymphatic anomaly, Chylothorax, Sirolimus

Background

Lymphatic malformations (LMs) are a group of diseases characterized by abnormal lymphatic tissue development and often present in childhood [1]. LMs involving the thorax can present as various diseases, such as mediastinal masses, interstitial lung disease, plastic bronchitis, recurrent pneumonia, chylothorax, and bronchiectasis [2]. Historically, the term "diffuse pulmonary lymphangiomatosis" was used to diagnose LMs involving the chest [3, 4]. However, with the increasing understanding of lymphatic disorders, this definition has been found to be inaccurate. The classification system of LMs was revised by the International Society for the Study of Vascular Anomalies (ISSVA) in 2014 and 2018 [5, 6]. Subsequent studies have further introduced a definition for complex lymphatic abnormalities (CLAs), including generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA), central conducting lymphatic anomaly

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(CCLA), and Gorham–Stout disease (GSD) [7]. Distinct types of LMs exhibit differences in clinical features and outcomes. Given the rarity of thoracic LMs, most available data come from case reports and small series.

In this study, we conducted a retrospective analysis of the largest cohort to date, comprising 42 patients with thoracic LMs, summarizing their classification, clinical manifestations, imaging findings, treatment approaches, and prognosis. These findings aim to enhance our understanding of the disease and improve disease management and prognosis.

Methods

Patient cohort

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Ethics Committee of Beijing Children's Hospital ([2022]-E-163-Y). As this study was based on routine clinical data and does not contain any data that can identify individuals, the requirement for informed consent was waived by the Ethics Committee. Therefore, the requirement for informed consent was waived. We retrospectively analyzed the records of patients diagnosed with lymphatic malformations, chylothorax, diffuse pulmonary lymphangiomatosis, or lymphedema, who were treated at the National Clinical Research Center for Respiratory Diseases, Beijing Children's Hospital, Beijing, China, between June 2014 and June 2024. Patients with secondary causes or incomplete clinical data were excluded, resulting in a final sample size of 42 patients.

Patient classification

The following classifications were performed according to ISSVA guidelines and previous literature reports [6, 8–10].

1. Common (cystic) LMs: Solitary lesions, further subdivided into macrocystic, microcystic, or mixed cystic LMs based on the size of the cysts.
2. GLA: Multifocal LMs frequently affecting bone, liver, spleen, the mediastinum, and the lungs.
3. KLA: a subtype of GLA with a poor prognosis, characterized histologically by spindled endothelial cells, and clinically diagnosed by symptoms including hemorrhagic effusions, thrombocytopenia, and severe consumptive coagulopathy.
4. GSD: Overlapping with GLA but distinguished by severe osteolysis, including cortical osteolysis.
5. CCLA: Disorders affecting the central lymphatic channels, either as an independent entity or associated with one of the other LMs.
6. Primary lymphoedema (PL): Lymphedema in the limbs and external genitals, which can be confirmed by lymphoscintigraphy.
7. Infancy primary chylothorax: primary chylothorax presenting during infancy in the absence of the aforementioned lymphatic abnormalities, an additional classification that we defined.

Chylous effusion was diagnosed on the basis of the following four criteria: (1) pale yellow or chylous appearance; (2) nucleated cells predominantly lymphocytes (> 80%); (3) negative bacterial culture; and (4) positive ether test or elevated triglycerides (> 1.1 mmol/L). Hemorrhagic effusion was diagnosed when the effusion hematocrit was greater than 50% of that in the peripheral blood. Thrombocytopenia was defined as a platelet count less than 100 × 10^9/L, hypofibrinogenemia was defined as a fibrinogen level less than 1.5 g/L, and elevated D-dimer was defined as a test result exceeding 0.5 g/L.

Results

Demographic and classification

A total of 42 patients (19 males and 23 females) were included. The median age at onset was 5.4 years, ranging from birth to 14.6 years. All patients with PL exhibited limb edema immediately after birth. The median age at the time of admission to our hospital was 8.8 years, ranging from 0.1 to 14.7 years. Among them, 14 patients visited our hospital due to disease progression or recurrence after a stable period of 2 to 13 years. None of the parents had LMs. One pair of siblings was simultaneously diagnosed with CCLA and included in this study. The classifications of the 42 patients were as follows: macrocystic LM (at the base of the lung, $n = 1$), PL ($n = 4$), infancy chylothorax ($n = 3$), and CLAs ($n = 34$), including GLA ($n = 18$), KLA ($n = 8$), CCLA ($n = 6$), and GSD ($n = 2$).

Among 42 patients, 11 (26.2%) with GLA/GSD were confirmed by histopathological examination, showing irregular lymphatic vessel proliferation and dilation, along with positive immunostaining for D2-40. Thirty-one (73.8%) patients were clinically diagnosed based on typical clinical manifestations and characteristic imaging findings, with other diseases ruled out. The clinical manifestations included chylous effusion, plastic bronchitis (PB), and lymphedema. Imaging findings included multiple cystic lesions shown by magnetic resonance imaging (MRI), interlobular septal thickening and osteolytic lesions observed via computerized tomography (CT), as well as abnormal morphology and reflux of the thoracic duct demonstrated by lymphoscintigraphy and/or lymphangiography.

All 8 patients with KLA were clinically diagnosed based on their medical history and laboratory test results. Among them, 2 did not experience hemorrhagic effusions, thrombocytopenia, or coagulation dysfunction in the early stage of the disease; these symptoms gradually

emerged 1 to 3 years after being diagnosed with GLA, and the diagnosis was later revised to KLA.

Clinical features

Thirty-three (78.6%) patients had chronic cough, 20 (47.6%) had white foamy or jelly-like sputum, and 3 (7.1%) had bronchial cast-like sputum and PB. Dyspnea was observed in 32 patients (76.2%), with severity ranging from exertional dyspnea to nocturnal awakenings due to a sensation of suffocation. Recurrent respiratory infections were noted in 16 patients (38.1%), wheezing in 10 (23.8%), and hemoptysis in 2 (4.8%). Physical examination revealed malnutrition in 22 patients (52.4%, median body mass index: 14.5 ± 1.3 kg/m^2) and scoliosis/funnel chest/pectus carinatum in 9 patients (21.4%). In terms of complications, 34 patients (81.0%) had pleural effusion (chylothorax, 50%), 19 (45.2%) had pericardial effusion, 4 (9.5%) had deep vein thrombosis, and 2 (4.8%) had pathological fractures. Additionally, 1 patient had a congenital atrial septal defect, 4 had seroperitoneum, 7 had edema (including 4 with PL), and 1 had protein-losing enteropathy.

Among 42 patients, 36 (85.7%) presented with chest symptoms as the initial manifestation, whereas 6 (14.3%) did not. Specifically, 1 patient with GSD had no obvious clinical symptoms, and the lung and bone lesions were discovered incidentally via CT during an evaluation for pneumonia; 1 with KLA initially presented with abdominal LMs, and subsequently developed mediastinal lesions and pleural effusion 2 years later; and 4 with PL presented with thoracic lesions 1 to 13 years after the onset of limb edema.

Imaging findings

All patients (100%) underwent CT scans, and 10 (23.8%) underwent contrast-enhanced CT scans. Imaging findings (Fig. 1) showed diffuse mediastinal lesions with or without hilar involvement in 26 patients (61.9%), interlobular septal thickening in 20 (47.6%), multiple osteolytic lesions in 20 (47.6%), pleural thickening in 17 (40.5%), persistent ground-glass opacities in 13 (31.0%), and peribronchovascular interstitial thickening in 13 (31.0%). Further enhanced CT examination revealed tortuous and dilated blood vessels in the lesions of 9 patients (2 in the mediastinum and 7 in the chest wall soft tissue), suggesting local lymphatic-venous mixed malformations. Nineteen patients (45.2%) underwent enhanced MRI scans, which identified mediastinal soft tissue lesions and pulmonary nodular shadows in 12 patients, as well as multiple cystic lesions in the abdominal cavity and spleen in 15 patients.

Among 32 patients receiving peripheral lymphoscintigraphy (Fig. 2), 28 (87.5%) showed radioactive filling in the thorax and/or pericardium, 23 (71.9%) demonstrated persistent visualization at the left venous angle (including 4 with bilateral venous angle drainage), and 1 (28.1%) exhibited slow or absent lower extremity reflux visualization. Sixteen patients underwent additional direct lymphangiography (Fig. 3), revealing thoracic duct abnormalities: 9 (56.2%) had thoracic duct backflow

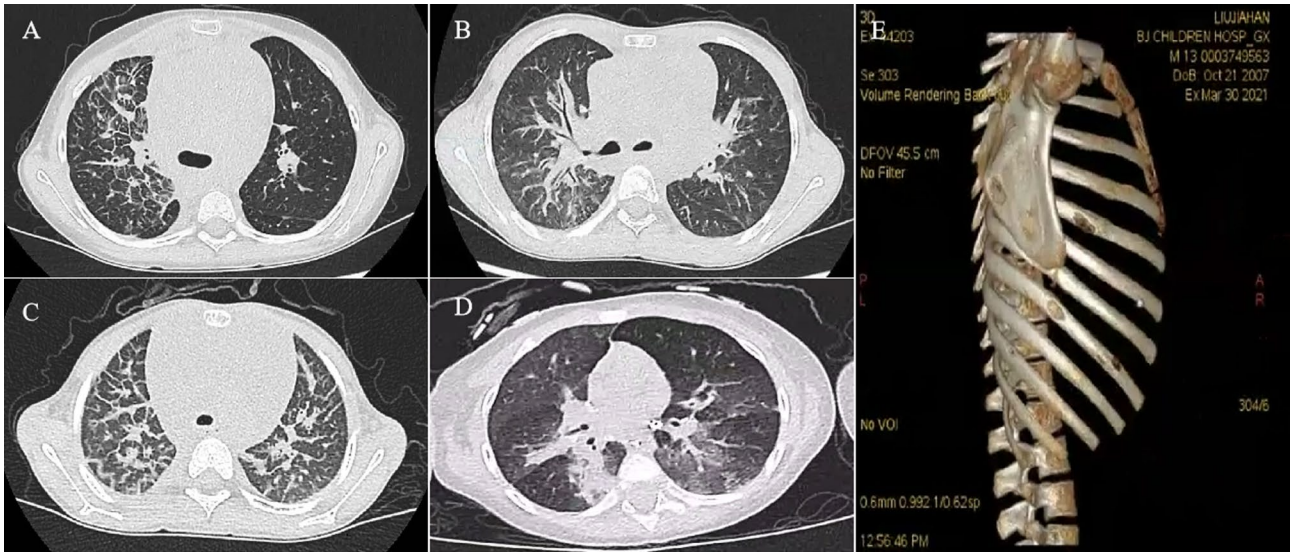

Fig. 1 Radiographic findings of chest high-resolution computed tomography (HRCT) in patients with CLAs. (**A**) In a patient with KLA, HRCT shows interlobular septal thickening of the right lung. (**B**) In a patient with GLA, HRCT shows diffuse mediastinal lesions involving the lung hilum and bilateral bronchial wall thickening. (**C**) In a patient with GLA, who had a 7-year medical history prior to treatment. HRCT shows thickening of the interlobular septum and pleura in both lungs. (**D**) In a patient with CCLA, a bronchial cast was removed by bronchoscopy. HRCT shows multiple ground-glass opacities in both lungs and an increased density in the right bronchus with distal truncation. (**E**) For a patient with GSD, CT bone reconstruction reveals multiple areas of bone destruction in the ribs and scapula

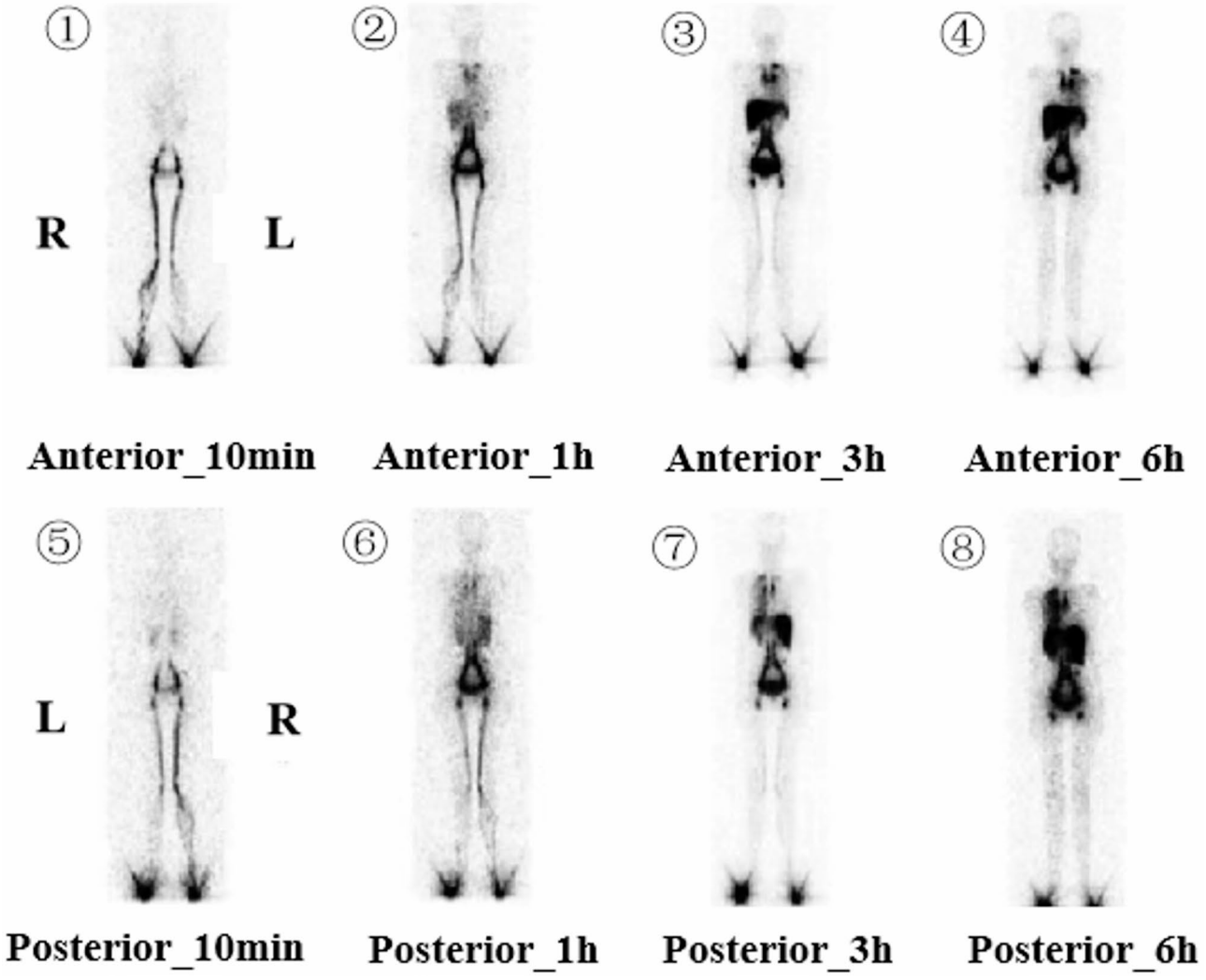

Fig. 2 Imaging findings of lymphoscintigraphy: ①~④ are anterior views, and ⑤~⑧ are posterior views. The imaging agent was injected subcutaneously between the first and second toes, as well as the fourth and fifth toes of both feet. Whole-body imaging was performed at 10 min, 1 h, 3 h, and 6 h, post-injection. Lymphatic return in both lower extremities was slow. The upper mediastinal lymphatic vessels and bilateral venous angles were widened and continuously visualized, suggesting bilateral venous angle drainage and potential obstruction of the thoracic duct outlet

obstruction with intrapulmonary lymphatic reflux (5 cases) and/or retrograde mesenteric lymphatic flow (4 cases), 8 (50%) had outlet obstruction, 4 (25.0%) had thoracic duct dilation, and 3 (18.8%) lacked a normal main thoracic duct.

Laboratory results

Twenty-three patients exhibited abnormal coagulation function, of whom 15 cases were associated with infection or thrombosis, and 8 cases were related to KLA. The 8 patients with KLA had significantly elevated D-dimer levels ranging from 10.271 to 60.402 mg/L and decreased fibrinogen levels ranging from 0.38 to 1.43 g/L. Platelet counts were examined in all patients; among them, 7 patients with KLA had persistent thrombocytopenia, with platelet counts ranging from 9 to 100 × 10^9/L, while 1 patient with KLA had a significant increase in platelet count to more than 900 × 10^9/L after splenectomy.

Among the 34 patients with pleural effusion, 21 (61.8%) had chylous effusions, 8 (23.5%) had chylous-bloody effusions (6 attributed to KLA and 2 to mediastinal lymphatic venous mixed lesions), 2 (5.9%) had bloody effusions secondary to rupture and hemorrhage from chest wall lesions, while the nature of the effusion in the remaining 3 patients (8.8%) could not be determined due to the lack of diagnostic examinations. Among 19 patients with pericardial effusion, pericardiocentesis confirmed chylous effusions in 7 (36.8%) and chylous-bloody effusions in 2 (10.5%), while the nature of the effusion remained undetermined in 10 (52.6%) due to insufficient diagnostic examinations.

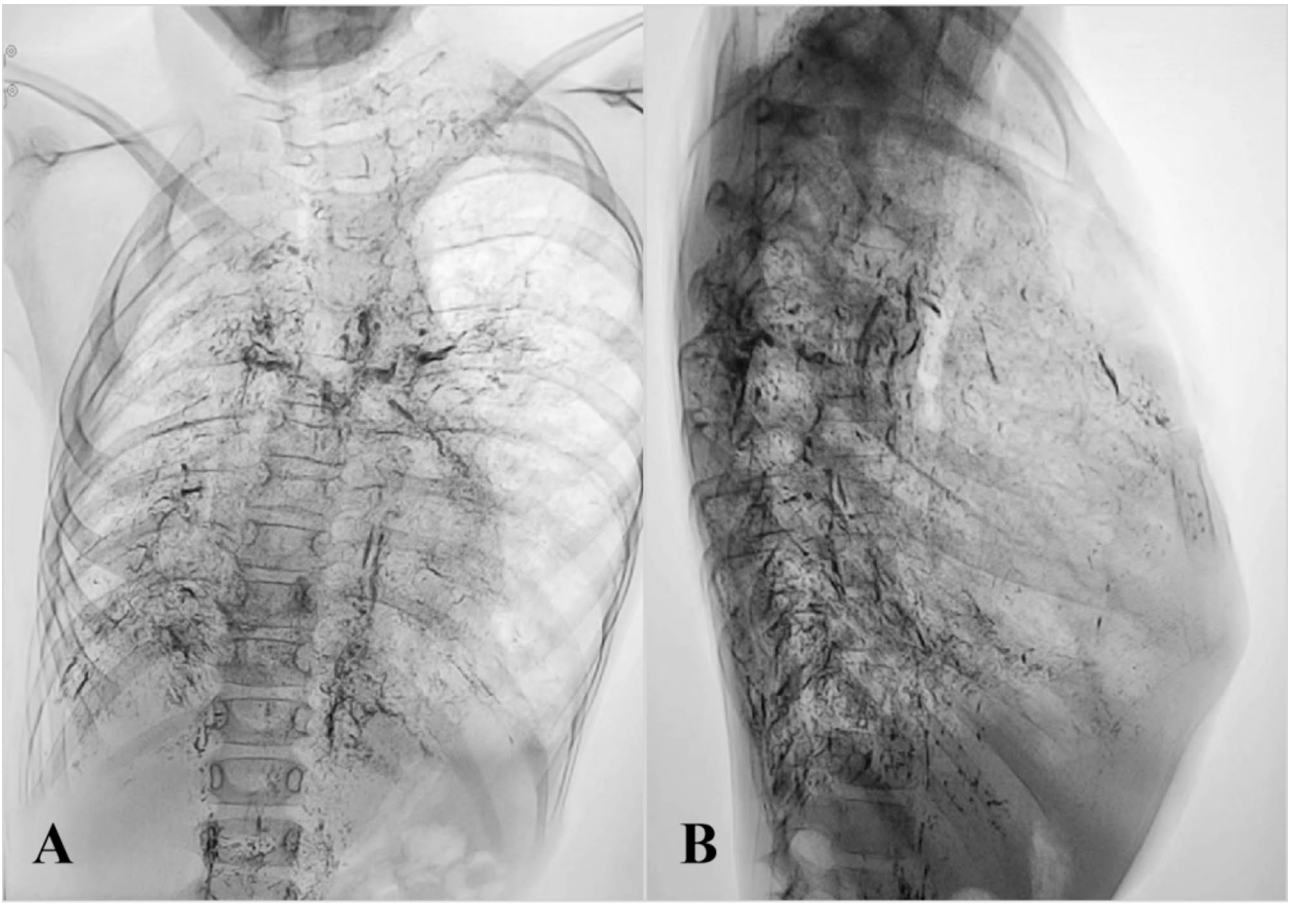

Fig. 3 In a case of GLA, lymphangiography was performed via inguinal lymph node access. The anteroposterior (**A**) and lateral (**B**) views showed hyperplasia and disorder of pulmonary lymphatic vessels, and retrograde flow into lungs

Gene results

Six patients underwent whole exome sequencing (~120X) for germline variants, and 2 with CCLA (siblings) were identified as carriers of an *EPHB4 (*c.778G > A) variant. Three patients underwent somatic mutation testing via plasma cell-free DNA panel sequencing (~7200×), and 1 with KLA received a genetic diagnosis of an *NRAS* (c.182 A > G) mutation with a variant allele frequency (VAF) of 0.70%. Four patients underwent lesional tissue whole exome sequencing for somatic variants (~500X), yielding genetic diagnoses in 2 cases. Specifically, an *NRAS* (c.182 A > G, VAF = 5.00%) mutation was identified in 1 GLA case, and compound heterozygous variants of *KRAS* (c.41T > G, p.V14G/c.37G > C, p.G13R, VAF = 7.70%) were detected in another GLA case.

Treatment and outcome

All patients received dietary modifications, including medium-chain triglycerides (MCT) supplementation and low-fat diets. Twenty-three patients underwent surgical intervention: pleurodesis or thoracic duct ligation for pleural effusion in 7 patients, lymphaticovenous anastomosis in 2, thoracic duct exploration with fibrous adhesiolysis in 10, and sclerotherapy/resection of isolated lesions in 3. Among 34 patients with CLAs, 20 received sirolimus (including 1 KLA case with vincristine combination, 1 GLA and 1 GSD case with bevacizumab combination), while 14 did not due to parental refusal or pre-2018 medication accessibility constraints at our center.

Of 20 patients treated with sirolimus, 16 (80%) exhibited clinical improvement, characterized by reduced cough frequency, decreased sputum production, alleviated dyspnea severity, and partial or complete resolution of pleural effusion; 2 achieved clinical and radiological improvement, specifically manifested as improvement in pulmonary interlobular septal thickening. Notably, 1 patient with CCLA achieved adequate disease control to allow subsequent surgical intervention. Four patients with poor response to sirolimus had the following outcomes: 2 recurrence cases were successfully salvaged with bevacizumab combination therapy; 1 refractory KLA case carrying an *NRAS* mutation improved with trametinib-targeted therapy after sirolimus failure; and 1 KLA case experienced rapid disease progression and eventually died.

Table 1 Thoracic lymphatic malformations

Classification	Number	Clinical features	Treatment	Outcomes
Cystic lymphatic malformations	1	Isolated lesions	Sclerotherapy	Improvement
Complex lymphatic anomalies	34	Symptoms overlap; chylothorax, plastic bronchitis; diffuse mediastinal lesions; interlobular septal thickening	Comprehensive treatment	Overall improvement (80% response rate)
Generalized lymphatic anomaly (GLA)	18	Involvement of thorax, bone, spleen, and soft tissue; combined with CCLA	Sirolimus, bevacizumab, surgery	Improvement/Stabilization/Death
Kaposiform lymphangiomatosis	8	Like GLA; hemorrhagic effusions; consumptive coagulopathy (thrombocytopeni, hypofibrinogenemia, elevated D-dimer); spindled endothelial cells	Sirolimus, trametinib, vincristine, surgery	Improvement/Death
Gorham–Stout disease	2	Like GLA; osteolysis, cortical destruction; pathological fracture	Sirolimus, symptomatic treatment	Improvement in chest lesions, progression in bone lesions
Central conducting lymphatic anomaly (CCLA)	6	Pleural/pericardial/peritoneal effusions; persistent ground-glass opacity on CT, lymphangiography	Mainly depended on surgery, response to sirolimus, diet intervention	Improvement/Stabilization
Primary lymphoedema	4	Chest lesions appeared several years following limb edema; combined with CCLA	Thoracic duct surgery, limb compression decongestive management	Stabilization
Infancy chylothorax	3	Infancy, right chylothorax	Diet intervention	Improvement

Among 14 cases of CLAs without specialized pharmacological treatment, 5 CCLA cases showed clinical improvement following surgery or solely dietary intervention; 3 remained stable (2 GLA cases post-surgery, 1 GSD case under dietary management); 1 GLA case refused treatment and progressed; and 5 cases (3 GLA and 2 KLA) did not improve following surgery and ultimately died.

Additionally, 3 patients with infancy primary chylothorax showed improvement following dietary interventions (feeding with skimmed milk powder, MCT supplementation of 1 g/kg per day with a maximum of 10 g) and remained stable over a follow-up period of 5–10 years. Four PL cases had stable conditions after undergoing thoracic duct surgery and limb lymphatic reconstruction. One patient with macrocystic LM experienced a decrease in the size of the lesion after sclerotherapy. Detailed clinical data are shown in Table 1.

Discussion

In this study, patients were classified into 6 types based on the ISSVA criteria: cystic LMs, GLA, KLA, GSD, CCLA, and PL. Additionally, 3 patients presented with only infant-onset chylothorax without any other organic lesions and achieved long-term remission through dietary treatment alone, indicating a better prognosis compared to previously reported perinatal-onset congenital chylothorax [11, 12]. Thus, we classified these cases as infant chylothorax. In this cohort, CLAs, particularly the GLA type, were most common. CCLA was frequently observed in association with other types. All 4 patients with PL had CCLA. Some studies suggest that PL associated with central lymphatic defects can also be called CLAs [13]. Cystic LMs are common in the head and neck regions and can extend to the mediastinum; however, reports of lesions involving the pleural cavity, as described here, are extremely rare [14, 15].

The clinical manifestations of different types of thoracic LMs were similar and consistent with previous literature, presenting as nonspecific respiratory symptoms [16]. In this study, more than half of the patients experienced coughing with white foamy or jelly-like sputum, and 3 patients even had bronchial cast-like sputum and were diagnosed with PB. The nature of sputum is similar to that of most pleural effusions, characterized as chylous. The mechanism is the leakage of lymph fluid into the airway and pleural cavity through lymphatic vessels beneath the bronchial submucosa, which is referred to as pulmonary lymphatic perfusion syndrome [2]. Notably, PB mainly occurs in patients with secondary pulmonary lymphatic flow abnormalities following the Fontan procedure for a single ventricle [17, 18]. Although primary lymphatic abnormalities causing PB are rare, similar to chylothorax, they represent a specific manifestation that aids in diagnosing thoracic LMs [19].

In terms of imaging, interlobular septal thickening is frequently reported in patients with CLAs and was previously considered a specific manifestation of diffuse pulmonary lymphangiomatosis [20, 21]. In this study, more than 50% of the patients exhibited this imaging sign. Additionally, we identified persistent ground-glass opacity in 13 patients, which may be associated

with lymphatic leakage from the alveolar walls into the alveolar cavity [22]. Notably, 6 patients with CCLA presented with ground-glass opacity without interlobular septal thickening. These findings indicate that persistent ground-glass opacity is also a characteristic imaging feature of thoracic LMs and has significant implications for diagnosing these diseases, particularly CCLA.

LMs are associated with inappropriate activation caused by somatic mutations in genes encoding components of the PI3K (phosphoinositide 3-kinase)/AKT (protein kinase B)/mTOR (mammalian target of rapamycin) and RAS (rat sarcoma)/MAPK (mitogen-activated protein kinase) pathways [23]. *PIK3CA* was mainly detected in cystic LMs and has also been successively identified in various CLAs [24]. Identified somatic mutations found in this study were only located in the RAS pathway. Among them, *NRAS* (c.182 A > G) is a hotspot mutation that has been reported in multiple studies [25]. *KRAS* is another known pathogenic gene for CLAs; however, the complex heterozygous mutation phenomenon observed in our study is relatively rare in previous literature [26]. Additionally, we identified an *EPHB4* variant in a pair of sisters with CCLA, which has been confirmed as a pathogenic gene for CCLA through the zebrafish model [27].

Sirolimus, an mTOR inhibitor, has been widely used to treat CLAs, and trametinib, a MEK inhibitor, has demonstrated efficacy in some cases. In this study, 16 out of 20 patients with CLAs showed clinical improvement after sirolimus treatment, confirming its overall effectiveness in managing CLAs. In addition, one patient harboring an *NRAS* mutation exhibited a positive response to trametinib. These findings were consistent with previous studies [28–31].

Unlike other types of CLAs, CCLA is largely managed surgically and shows inconsistent responses to sirolimus based on previous reports [29, 32, 33]. In this study, one patient with CCLA who developed plastic bronchitis and respiratory failure showed improvement following sirolimus treatment, but ultimately achieved long-term clinical remission through lymphaticovenous anastomosis. Additionally, the chest symptoms in 4 patients with PL were alleviated following thoracic duct fibrous adhesiolysis. For cystic LMs, sirolimus has greater advantages in treating microcystic and mixed cystic types; however, for macrocystic LMs, as observed in this study, sclerotherapy or surgical excision is more advantageous [34, 35].

Conclusions

In conclusion, this study systematically classified thoracic LMs and summarized their clinical phenotypes. While the retrospective nature of the study and the relatively small sample size of each subtype may introduce potential selection bias, our findings reveal commonalities in clinical manifestations and imaging characteristics across subtypes, as well as divergence in treatment approaches and prognoses. These results should enhance our understanding of thoracic LMs and contribute to improvements in early diagnosis, disease management, and prognosis. As research on the molecular mechanisms underlying the disease advances, the correlation between phenotype and genotype is expected to become clearer in the future, providing support for disease management and precision medicine.

Abbreviations

CCLA	Central conducting lymphatic anomaly
CLAs	Complicated lymphatic anomalies
GLA	Generalized lymphatic anomaly
GSD	Gorham–Stout disease
KLA	Kaposiform lymphangiomatosis
LMs	Lymphatic malformations
PL	Primary lymphedema

Acknowledgements

The authors thank the children and their families who participated in this study and all the physicians for their help in accomplishing this work.

Author contributions

W. H., and S. Z. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. H. Y., J. L., and Huimin L. collected data, and carried out the initial analyses. H.X., Hui L., and X. T. coordinated data collection, and carried out the further analyses.

Funding

Not applicable.

Data availability

The data supporting the findings of this study can be provided upon reasonable request to the corresponding author, S. Y.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Ethics Committee of Beijing Children's Hospital ([2022]-E-163-Y). As this study was based on routine clinical data and does not contain any data that can identify individuals, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

Received: 6 February 2025 / Accepted: 12 May 2025
Published online: 17 May 2025

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