



ORIGINAL ARTICLE

Childhood Interstitial Lung Disease in Metabolic Disorders: Prevalence, Genotypic and Clinical Characteristics, and Management Approaches: An Analysis of the Child-Turkey Registry

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ABSTRACT

Objective: Childhood interstitial lung disease (chILD) refers to a rare and heterogeneous group of disorders that can arise from genetic or acquired causes. Interstitial lung involvement due to metabolic diseases is a rare but significant condition among chILD cases.

Methods: This retrospective descriptive study analyzed data from the chILD-Turkey registry, established in November 2021, including patients registered until August 2024.

Results: A total of 28 patients (3.9% of 706 children in the registry) were included, with lysosomal storage diseases (LSDs) accounting for 25 cases (89.3%) and Niemann-Pick disease (NP) being the most common diagnosis ($n = 16$, 57.1%), followed by Gaucher disease (GD) ($n = 7$, 25.0%). The mortality rate during the 3-year follow-up was 10.7% (3/28). Computed tomography (CT) most commonly revealed interlobular septal thickening ($n = 17$, 60.7%). No statistically significant differences in CT findings were observed between symptomatic and asymptomatic patients at the time of diagnosis. The most frequent variant in NP was c.416 T > C in *SMPD1* ($n = 4$, 25%), and in GD, c.1448 T > C was identified in four patients (57.1%). Eight patients (2 NP and 6 GD) received enzyme replacement therapy (ERT). No increase in respiratory support needs was observed under ERT, and one patient showed significant regression in CT findings during follow-up.

Conclusion: chILD in metabolic disorders often progresses insidiously, resulting in delayed diagnosis. While management is mostly supportive, early ERT may improve or stabilize lung disease in selected cases. Further prospective studies are needed to clarify the impact of ERT and substrate reduction therapy (SRT) on long-term pulmonary outcomes.

1 | Introduction

Childhood interstitial lung disease (chILD) refers to a rare and heterogeneous group of disorders that can arise from genetic or acquired causes [1]. Metabolic disorders can affect the respiratory system through various mechanisms, ranging from frequent infections and airway obstruction to widespread interstitial involvement.

Lysosomal storage diseases (LSDs) are the metabolic conditions most commonly associated with chILD [2]. Niemann-Pick disease (NP), types A, B, or AB, along with Gaucher disease (GD), is among the LSDs most commonly associated with chILD. NP types A, B, or AB arise from autosomal recessive genetic mutations in the *SMPD1* gene. In contrast, NP type C is genetically distinct, primarily affects the central nervous system, and differing from the other NP types in both pathophysiology and clinical presentation [3, 4]. GD, an autosomal recessive disorder, results from mutations in the glucocerebrosidase gene [4]. The most common form GD type 1. GD type 2 is associated with rapid disease progression, while GD type 3 begins in early childhood but has a slower course [5].

Although less common than LSDs, amino acid metabolism disorders such as lysinuric protein intolerance (LPI) and prolidase deficiency can also involve the lungs [6, 7]. LPI may cause a spectrum of respiratory findings ranging from silent interstitial changes to pulmonary alveolar proteinosis (PAP) and progressive fibrosis, with symptoms emerging at any age [8]. Prolidase deficiency, though primarily known for dermatologic and infectious features, has also been linked to cystic lung changes and chILD in pediatric case series [9–11].

The onset and severity of chILD, varies among individuals in metabolic disorders [12, 13]. In the early stages, patients could be asymptomatic, but pulmonary involvement is closely associated with prognosis in most metabolic diseases [13, 14].

Recent data from national and international chILD registries have highlighted the rarity yet clinical relevance of metabolic diseases as underlying causes of chILD. While metabolic chILD accounted for 5% of cases in the U.S. registry, 4.1% in Spain, and only 1.2% in the chILD-EU registry, it was extremely rare in the Australian/New Zealand registry, with only a single case of NP type B reported [15–18].

With the implementation of hematopoietic stem cell transplantation, substrate reduction therapy (SRT), gene editing, and enzyme replacement therapy (ERT), the life expectancy of patients with inherited metabolic diseases, particularly those with LSDs, has significantly improved, emphasizing the need for early recognition and treatment of pulmonary involvement.

The Turkish Childhood Interstitial Lung Disease Registry (chILD-Turkey) was established in November 2021 to raise awareness about the disease and improve diagnostic and therapeutic standards [19]. This study aims to analyze data from the chILD-Turkey registry system to assess the prevalence of

metabolic disorders among chILD cases in Turkey, identify specific diagnoses, evaluate survival rates, and define most common genotypes, clinical, and laboratory features as well as treatment strategies.

2 | Methods

2.1 | chILD-Turkey Registry System

The chILD-Turkey registry is a nationwide, web-based data collection platform developed specifically for pediatric interstitial lung diseases. Established in November 2021, it currently includes 29 pediatric pulmonology centers across Turkey [19].

Children suspected of chILD, based on clinical features and the diagnostic criteria by Kurland et al., are included [1]. The registry captures comprehensive data at the time of initial diagnosis and throughout follow-up. Collected data included demographics, clinical presentation, clinical course, pulmonary function tests (PFTs), chest X-ray or computed tomography (CT) imaging, bronchoscopy, lung biopsy, genetic results, and treatment details including respiratory support.

2.2 | Patient Selection and Data Collection

This retrospective, descriptive study utilized data from the chILD-Turkey registry. The analysis included patients registered between November 2021 and August 2024. Diseases were categorized based on the chILD-EU study group classification [16]. The chILD-Turkey registry, which contains data on 706 patients, was used to identify 34 individuals with specific diagnoses. These diagnoses included A415: secondary PAP, and B136: storage diseases. Six were excluded due to non-metabolic diagnoses ($n = 2$) or incomplete clinical data ($n = 4$). The final study cohort included 28 patients from 11 participating pediatric pulmonology centers. Clinical, imaging, and treatment data were extracted from the registry. Chest CT images were re-evaluated by a senior radiologist specialized in chILD.

2.3 | Statistical Analysis

The analysis of data was conducted using the Statistical Program for Social Sciences (SPSS, version 23.0). Descriptive statistics included the calculation of mean and standard deviation (SD) for continuous variables, median and interquartile range (IQR) for non-normally distributed variables, and percentage distributions for categorical variables. The normality of data distribution was assessed using the Shapiro-Wilk test. Chi-square test was used in the analysis of qualitative data. Survival analysis was performed using the Kaplan–Meier method to estimate overall survival and chILD-free survival times. The chILD-free survival time is defined as the duration from birth until the first diagnosis of chILD made by a pediatric

pulmonologist. Median survival times and their 95% confidence intervals (CI) were calculated, and group comparisons were conducted with the Log-Rank test. Values of $p < 0.05$ were considered statistically significant. Graphs and figures were created using GraphPad Prism 10 and designed with Adobe Illustrator 2022.

3 | Results

A total of 28 patients were included, representing 3.9% of the 706 children in the chILD-Turkey registry. The median age was 8.0 years (range: 3–16.6) (Table 1). Of these, 25 (89.3%) had LSDs and 3 (10.7%) had amino acid metabolism disorders. NP was the most common diagnosis ($n = 16$, 57.1%) (Table 2).

Three patients (10.7%) died during the 3-year follow-up, with a median age at death of 6.0 years (range: 3.6–8.1) (Table 1, Figure 1A). Respiratory symptoms at the onset were reported in 20 patients (71.4%), most commonly cough ($n = 15$, 53.6%). The median age at symptom onset was 2.4 years (range: 0.1–10.0), and at diagnosis was 6.1 years (range: 2.1–13.9). Eight patients (28.6%) were asymptomatic, only one had abnormal findings (crackles) on physical examination at the time of diagnosis (Table 2).

The Kaplan-Meier analysis revealed that the median chILD-free survival time was 6.8 years (95% CI: 3.91–9.61) for asymptomatic patients and 5.2 years (95% CI: 3.76–6.64) for symptomatic patients (Log-rank test, $\chi^2 = 2.238$, $p = 0.135$) (Figure 1B). For symptomatic patients, the median time from symptom onset to chILD diagnosis was 2.2 years (0.3–3.9).

chILD was diagnosed by chest CT in 25 patients and by X-ray in 3. The most common CT findings were interlobular septal thickening (60.7%) and ground-glass opacities (GGO) (57.1%) (Figure 2).

3.1 | Lysosomal Storage Diseases: Clinical Characteristics and Management

3.1.1 | Niemann-Pick Disease

A total of 16 patients (57.1%) were diagnosed with NP, with a median age of 7.8 years (range: 3.2–16.6) and chILD diagnosis at 5.1 years (range: 2.3–9.9) (Table 2). Two patients died during follow-up: One was a 3.6-year-old with NP type A on ERT who died due to pneumonia. The other, an 8-year-old with NP type C, had a tracheostomy and died of chronic respiratory failure.

The median symptom onset was 2.1 years (range: 0.1–10.0; $n = 11$). The most common symptom was cough ($n = 9$, 56.3%), followed by shortness of breath ($n = 6$, 37.5%). Crackles ($n = 7$, 43.8%) and persistent tachypnea ($n = 4$, 25%) were the most frequent findings.

A total of five patients were asymptomatic at the time of chILD diagnosis, the majority ($n = 3$, 60%) classified as NP type A/B. Referred for pulmonary screening, these cases were diagnosed via chest CT and radiography.

Chest CTs ($n = 13$) revealed interlobular septal thickening (62.5%) and GGO (43.7%); fibrosis was noted in three cases. Nodular opacities occurred in four patients. Three others (two with NP type A/B and one with NP type C) had only chest

TABLE 1 | Baseline characteristics at initial registry enrollment ($n = 28$).

Characteristic, n (%)	
Gender (male)	16 (57.1%)
Median age, years (IQR)	8.0 (5.8–11.9)
Onset of the ILD diagnosis, median, years (IQR)	6.1 (4.2–8.3)
Death	3 (10.7%)
History	
Consanguinity	22 (78.6%)
Neonatal intensive care admission	5 (17.9%)
Recurrent lower respiratory tract infections	11 (39.3%)
Clinical findings	
Weight z-score (mean $\pm$ SD)	−1.8 ($\pm$ 1.5)
Height z-score (mean $\pm$ SD)	3.5 ($\pm$ 2.2)
Presence of respiratory symptoms at the age of onset	20 (71.4%)
Most common respiratory symptom; cough	15 (53.6%)
Median age at symptom onset, years (IQR)	2.4 (1.1–4.9)
Onset of symptoms with	
Crackles on auscultation	13 (46.4%)
Tachypnea	11 (39.3%)
Retractions	3 (10.7%)
Clubbing	2 (7.1%)
Chest wall anomalies (pectus carinatum)	6 (21.4%)
Extrapulmonary involvement	
Hepatosplenomegaly	20 (71.4%)
Neuromotor system	7 (25.0%)
Structural heart disease	7 (25.0%)
Pulmonary hypertension	2 (7.1%)
Immunodeficiency	2 (7.1%)
Laboratory findings	
FVC predictive %, median (IQR) $n = 5$ (17.9%)	84.0 (63.0–94.5)
DLCO (Adj), $n = 2$ (7.1%)	69–73
Lung biopsy	1 (3.5%)
Flexible bronchoscopy	8 (28.6%)
Treatment	
Disease-specific treatment	11 (39.3%)
ERT	8 (28.6%)
SRT (Miglustat)	3 (10.7%)
Respiratory support	9 (32.1%)
Invasive mechanical ventilation	3 (10.7%)
Non-invasive mechanical ventilation	4 (10.7%)
Oxygen therapy*	2 (7.1%)
Other	

(Continues)

TABLE 1 | (Continued)

Inhaled steroid	4 (14.3%)
Pulse-intravenous steroid**	1 (3.5%)
Oral steroid**	1 (3.5%)

Abbreviations: chILD, Childhood Interstitial Lung Disease; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; ERT, Enzyme Replacement Therapy; FVC pred., Forced Vital Capacity (predicted); SRT, Substrate reduction therapy. *Patients receiving oxygen support only. **During pulmonary exacerbation.

X-rays, which showed diffuse reticulonodular patterns and areas of consolidation.

Bronchoscopy was performed in three patients; one had lipid-laden macrophages (LLMs) in BAL, two had mild tracheomalacia.

PFT was available for two NP type B patients: predited Forced Vital Capacity (FVC) was 84.0% in one (11 years), and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) was decreased (73%) in another (15.5 years).

Genetic data were available for 12 patients. The most common variant was c.416 T > C in *SMPD1*, identified in four males with NP type A/B, none requiring respiratory support. The second most frequent was c.1267 C > T in *SMPD1*, found in two females with NP type A, one of whom died due to pneumonia (Table 3).

The median age for initiating respiratory support was 7.3 years (range: 5.0–9.5). Two patients required tracheostomies and were 24 h invasive mechanical ventilation (IMV)-dependent; one died. Among three patients with NP type B, two used Bi-level Positive Airway Pressure ST (BiPAP) for less than 12 h daily, while one was supplemental oxygen-dependent 24 h a day.

Three NP type C patients received SRT (miglustat). Two of these patients, including one who died, were IMV-dependent and had early symptoms. Miglustat started at 1.5–2.0, and tracheostomies at 6.7–7.1. The third patient required no respiratory support (Table 3).

Two patients (NP type A and A/B) received ERT. One NP type A patient discontinued supplemental oxygen after 4.5 months of ERT but died of pneumonia in the sixth month. The second, NP type A/B, showed clinical stability on ERT at 4-month follow-up. One patient used oral steroids intermittently; two used inhaled corticosteroids regularly.

3.1.2 | Gaucher Disease

A total of seven patients with GD, accounting for 25% of the study population, were identified, including five with type 3. The median age of these patients was 10.0 years (range: 5.0–16.0), and four (57.1%) were male (Table 2). No cases of pulmonary hypertension or hepatopulmonary syndrome were observed.

Two GD patients (28.5%) were asymptomatic at the diagnosis. Both had undergone chest CT as part of the initial evaluation. One was a 16-year-old female with GD type 1, on ERT since age 4, referred at 13.7 years. Chest CT showed diffuse septal thickening and GGO; FVC was 94%, DLCO 69%. The other was a 7-year-old male with GD type 3, also on ERT, with CT showing linear septal thickening and lower lobe GGO.

Among five symptomatic patients, common complaints were cough ($n = 4$) and shortness of breath ($n = 3$). Crackles ($n = 4$)

and tachypnea ($n = 3$) were frequently observed. Clubbing was noted in one case.

Chest CT consistently showed interlobular septal thickening in all seven patients (100%) and GGO in six (85.7%). A diffuse distribution pattern was noted in five cases, and mosaic perfusion in three (42.8%).

Bronchoscopy ($n = 3$) showed LLMs in all, with foamy histiocytes and hemosiderin in two; one had subglottic compression.

One open lung biopsy in a GD type 3 patient revealed foamy histiocytes, hemosiderin, and periodic acid-Schiff (PAS) positivity.

PFTs were performed at the time of diagnosis in three patients. Two had normal predicted FVC values (94% and 95%), including one who showed a decreased DLCO of 69%. The third patient had a reduced FVC of 61%.

Genotypic data were available for five patients. The c.1448 T > C homozygous mutation was the most common, identified in four patients. A patient with the c.1193 G > T homozygous variant was diagnosed with secondary PAP (Table 4).

Six patients were receiving ERT, with a median initiation age of 3 years (range: 8 months–5.4 years). Two patients were diagnosed with GD type 1, and four with type 3. Longitudinal follow-up of a GD type 1 patient demonstrated significant improvement under ERT, with % FVC pred. increasing from 61% to 74% over 6 years, alongside marked reduction in pulmonary involvement on CT imaging (Figures 3 and 4).

Among the four GD type 3 patients, respiratory support was required, including supplemental oxygen or non-invasive mechanical ventilation (NIV). Two patients remained on supplemental oxygen despite ERT, and one developed oxygen need after ERT discontinuation. Another received continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea (OSA).

3.1.3 | Fucosidosis

An 11.8-year-old male with severe neuromotor retardation and recurrent lower respiratory infections since age 3.5 was diagnosed with chILD. At age 6, a tracheostomy was performed after repeated extubation failures during a hospitalization for respiratory distress. Chest CT at age 7 showed GGO and atelectasis (Figure 3H).

3.1.4 | Multiple Sulfatase Deficiency

A 6-year-old male with multiple sulfatase deficiency, neuro-motor retardation, and epilepsy had recurrent infections, swallowing dysfunction, and moderate OSA since infancy. Chest CT at 4.2 years showed GGO, mosaic perfusion, and septal thickening, consistent with chILD. Bronchoscopy revealed laryngopharyngeal reflux and adenoid vegetation. CPAP therapy was initiated for OSA. He died of bacterial pneumonia at age 6.

3.2 | Amino Acid Metabolism Disorders: Clinical Characteristics and Management

3.2.1 | Lysinuric Protein Intolerance

Two female patients with LPI showed distinct respiratory findings. The first had asymptomatic but showed a restrictive

TABLE 2 | Primary diagnoses and age-related characteristics of study participants ($n = 28$).

Primary diagnosis, $n(\%)$	Age, median, years (min.-max)	Onset of the respiratory symptoms, median, years (min.-max)	Onset of the ILD diagnosis, median, years (min.-max.)
Lysosomal Storage Diseases, $n = 25$ (89.3%)	8.0 (3.2–16.6)	2.5 (0.1–10.0), $n = 18$	6.1 (2.1–13.7)
Niemann-Pick, $n = 16$ (57.1%)	7.8 (3.2–16.6)	2.1 (0.1–10.0), $n = 11$	5.1 (2.3–9.9)
Type A, $n = 1$ (3.6%)	3.6	2.0	2.2
Type B, $n = 5$ (17.9%)	7.0 (3.2–15.5)	3.4 (0.1–10.0), $n = 4$	4.4 (2.3–9.9)
Type A/B, $n = 5$ (17.9%)	8.0 (5.8–16.0)	1.4 (0.8–2.2), $n = 2$	5.2 (2.9–8.7)
Type C, $n = 5$ (17.9%)	8.0 (5.2–16.6)	4.5 (1.0–8.1), $n = 4$	6.1 (3.1–7.0)
Gaucher Disease, $n = 7$ (25.0%)	10.0 (5.0–16.0)	2.4 (1.3–8.2), $n = 5$	7.9 (4.4–13.7)
Type 1, $n = 2$ (7.1%)	15.2–16.0	2.4, $n = 1$	9.4–13.7
Type 3, $n = 5$ (17.9%)	5.8 (5.1–10.7)	3.7 (1.3–8.2), $n = 4$	5.2 (3.5–8.9)
Fucosidosis, $n = 1$ (3.6%)	11.8	3.5	7
Multiple sulfatase deficiency, $n = 1$ (3.6%)	6	0.6	4.2
Amino acid metabolism disorders, $n = 3$ (10.7%)	12.1 (3.0–16.3)	4.3 (0.5–8.1), $n = 2$	11.3 (2.4–13.9)
Lysinuric protein intolerance, $n = 2$ (7.2%)	12.1–16.3	8.1, $n = 1$	11.4–13.9
Prolidase deficiency, $n = 1$ (3.6%)	3.0	0.5	2.4

pattern on PFT (FVC: 65%) at 13.9 years, with chest CT revealing interstitial involvement and focal GGO. The second developed shortness of breath and digital clubbing at 8 years. Initial CT was normal, but a follow-up CT at 11.5 years revealed a crazy paving pattern, with bronchoscopy ruling out PAP via negative PAS staining.

3.2.2 | Prolidase Deficiency

A 3-year-old patient diagnosed with prolidase deficiency, born to consanguineous parents, had a history of frequent cough, wheezing, and recurrent lung infections. The patient showed no signs of hypoxia or dyspnea and did not require respiratory support. Chest physiotherapy and inhaled corticosteroids were initiated. Chest CT revealed bilateral mosaic attenuation (Figure 3G).

4 | Discussion

Our study provides a comprehensive evaluation of metabolic diseases associated with interstitial lung involvement, utilizing data from Turkey's chILD national registry. It highlights the clinical, radiological, genotypic, and management aspects of ILD in pediatric cases of metabolic disorders. Beyond well-known associations with NP, GD, and LPI, we also report rare cases of prolidase deficiency, fucosidosis, and multiple sulfatase deficiency.

In our cohort, the prevalence was 3.9%, compared to 1.3% in the USA, 6.7% in Chinese children over 2 years, 4.2% in Spain, and

0.87% in Australia/New Zealand (excluding immunodeficiencies) [17, 20–23]. Consistent with previous reports, NP was the most frequent diagnosis (57.1%) [17, 20].

NP has three types (A, B, and C), each with distinct clinical and pulmonary involvement. Type A is associated with severe neurological impairment and early death, often from respiratory infections by age 2–3. Type B shows milder pulmonary symptoms and longer survival [24]. In our series, the 3-year mortality rate for chILD-related deaths was 10.7%, and both cases were associated with NP. One type A patient died of pneumonia despite initial improvement with ERT, and one type C patient with neurological sequelae died due to severe chILD. While our cohort was limited to children under 18, these early outcomes emphasize the importance of timely pulmonary surveillance. In NP type B and NP type A/B, pulmonary involvement is well-documented, with ILD reported in 66–90% of cases in some series [24, 25]. In a 30-year retrospective study conducted at a single center in Turkey, Gulhan et al. reported a 20.3% ILD prevalence in NP and Gaucher patients [26]. Consistently, NP type B and A/B was the most frequent subgroup in our cohort (35.7%), with no reported deaths and a median age of 8 years. A larger study of NP type B reported ILD-related mortality rates of 27%, predominantly in pediatric cases with a median age of death at 15 years [24]. Differences in follow-up and age distribution limit comparability across studies. Larger multicenter cohorts are needed to clarify long-term outcomes in this group.

GD primarily presents in adulthood with type 1 but may also involve the lungs in 5%–14% of cases, particularly in type 3

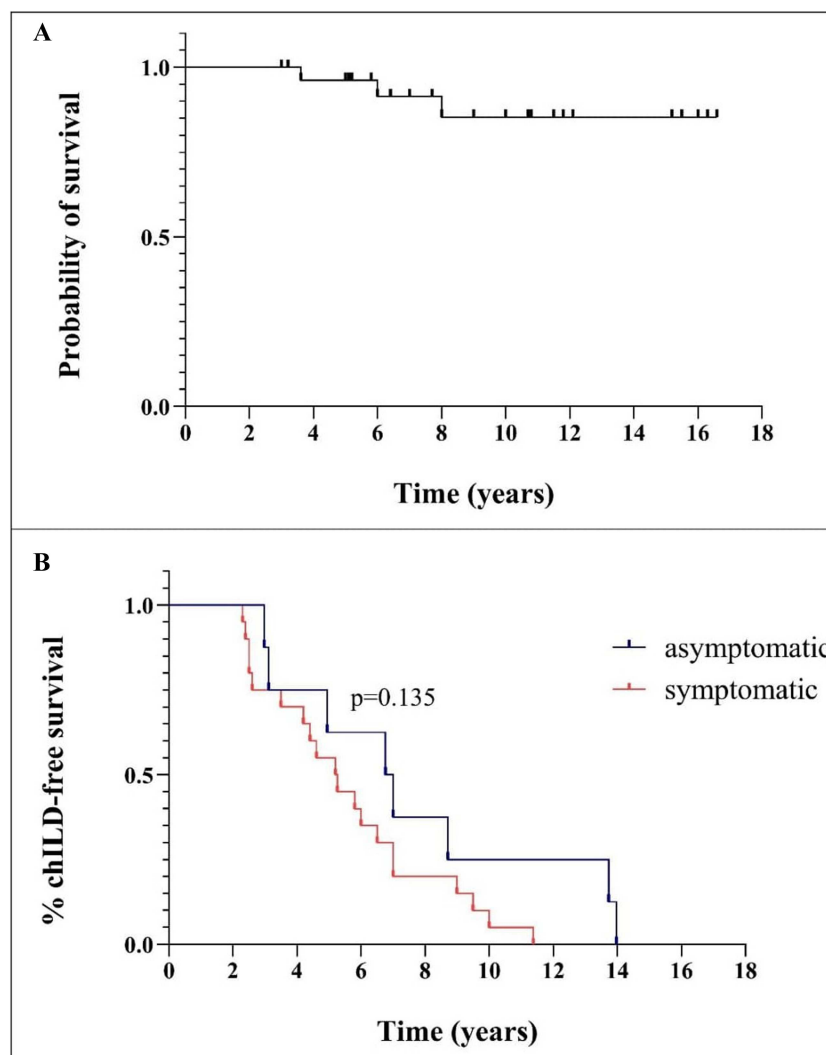


FIGURE 1 | Kaplan-Meier survival analysis showing overall survival (A) and chILD-free survival (B) in children with chILD and metabolic disorders. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ppul.71603)]

[23, 27, 28]. Type 2 is more fatal, with early deaths [4]. In our study, 25% of patients had GD, predominantly types 1 and 3. No type 2 cases were reported.

In our study, we also reported patients with fucosidosis and multiple sulfatase deficiency, which are rarely associated with ILD in the literature. These two disorders are extremely rare LSDs [29, 30]. Although the pathogenesis of both conditions is different, pulmonary involvement is frequently described as recurrent infections, obstructive disease, and central apnea. However, restrictive lung disease is also among the possible manifestations, although its true incidence remains unknown [30–32].

Prolidase deficiency is often reported in the literature with recurrent lung infections, cystic changes, and bronchiectasis, with rare cases also documenting interstitial involvement [7, 33, 34]. LPI is frequently associated with secondary PAP and can also cause ILD [35]. In our study, we observed mild involvement in LPI patients without evidence of PAP.

In the current study, 28.5% of chILD diagnoses were made during chest CT imaging in asymptomatic patients with NP, GD, or LPI. In all but one case, these patients had no

abnormal findings on physical examination and were referred by metabolic specialists to pediatric pulmonologists for pulmonary screening, which led to diagnosis via chest CT. These cases were diagnosed later (median age 6.8 years) than symptomatic ones (5.2 years). Imaging frequently revealed various interstitial changes, even when the FVC values were within normal range. Prior studies have similarly reported clinically silent cases, including NP type B, GD, and LPI, with CT findings ranging from mild to severe [8, 36–38]. Notably, Mendelson et al. found no consistent correlation between CT severity scores and PFT parameters in NP type B, with some patients showing preserved gas transfer despite severe radiologic changes [39]. Collectively, these findings support presymptomatic imaging as a tool to detect early lung pathology potentially missed by PFTs. Although standardized surveillance protocols are lacking, the literature increasingly supports baseline and periodic chest imaging and functional assessments in high-risk metabolic diseases such as NP [40].

Chest CT evaluations in NP predominantly revealed interlobular septal thickening (62.5%) and GGO (43.7%),

mirroring findings from prior studies such as Freitas et al., who reported both in all NP type B patients [37]. Notably, centrilobular nodular opacities, rarely described, were observed in 30.7% of our NP cohort [41]. In contrast, imaging findings in GD were more variable. Previous reports have described features such as interlobular septal and intralobular interstitial thickening, irregular pleural interfaces, and varying degrees of GGO [28, 38, 42, 43]. In our cohort, all had septal thickening and 85.7% had GGO. Mosaic perfusion was seen in 42.8%. Mediastinal or hilar lymphadenopathy, termed “Gaucheroma,” has been described in the literature but was absent in our cohort [44]. Due to the small number of GD cases, these findings may not fully represent the broader radiological spectrum.

Bronchoalveolar lavage revealed LLMs in all GD cases, but only one-third of NP cases, highlighting variability in diagnostic yield. While LLMs may support suspicion of LSDs, they are nonspecific and can also be seen in conditions such as exogenous lipoid pneumonia, aspiration, and vaping-related lung injury [23, 45–47]. Therefore, LLMs should not be used in isolation for diagnosis. Complementary tools such as genetic testing, enzyme assays, and advanced imaging remain essential for accurate diagnosis and disease characterization.

In this registry, the most frequent variant in NP patients was c.416 T > C (25%), associated with mild pulmonary involvement, while a patient with the homozygous c.1267 C > T mutation succumbed to an infection-triggered pulmonary exacerbation despite initial improvement with ERT. These findings align with previous reports linking c.416 T > C to mild symptoms in Turkish NP type B patients and c.1267 C > T to severe early-onset NP type A with significant pulmonary

involvement, particularly in the Arab region [48]. In GD, while homozygous c.1448 T > C (L444P) mutations have been associated with ILD [24], in our series, 57.1% of patients having homozygous L444P mutations [2, 49]. As our registry includes only patients with pulmonary involvement, genotype–phenotype associations should be interpreted cautiously and confirmed by larger studies.

Treatment remains primarily supportive, with limited data on the efficacy of ERT or SRT in improving pulmonary outcomes [50]. Studies indicate that ERT can stabilize pulmonary disease in selected cases of NP type B and GD type 1, though benefits in GD type 3 are unclear [51–54]. In our cohort, one GD type 1 patient showed significant improvement in FVC and CT findings over 6 years. Among NP cases, one type A patient died despite ERT. SRT was used in three NP type C patients, but efficacy assessment was confounded by severe neurological impairment and IMV dependency.

This study has several limitations inherent to registry-based analyses. Data were collected during clinical visits, leading to variability in patient follow-up intervals and hindering longitudinal analysis. Small sample sizes for certain diagnoses limited advanced statistical evaluations. Additionally, the pediatric nature of the cohort and the presence of neurological sequelae likely affected compliance with PFTs. Although the primary aim was to identify metabolic diseases causing chILD, we also assessed respiratory outcomes in patients receiving ERT/SRT based on registry data. However, the lack of detailed information on treatment dosages and schedules limited the analysis of therapeutic effects. Given the young age of the cohort, long-term survival and outcome data remain incomplete, underscoring the need for extended follow-up in future studies.

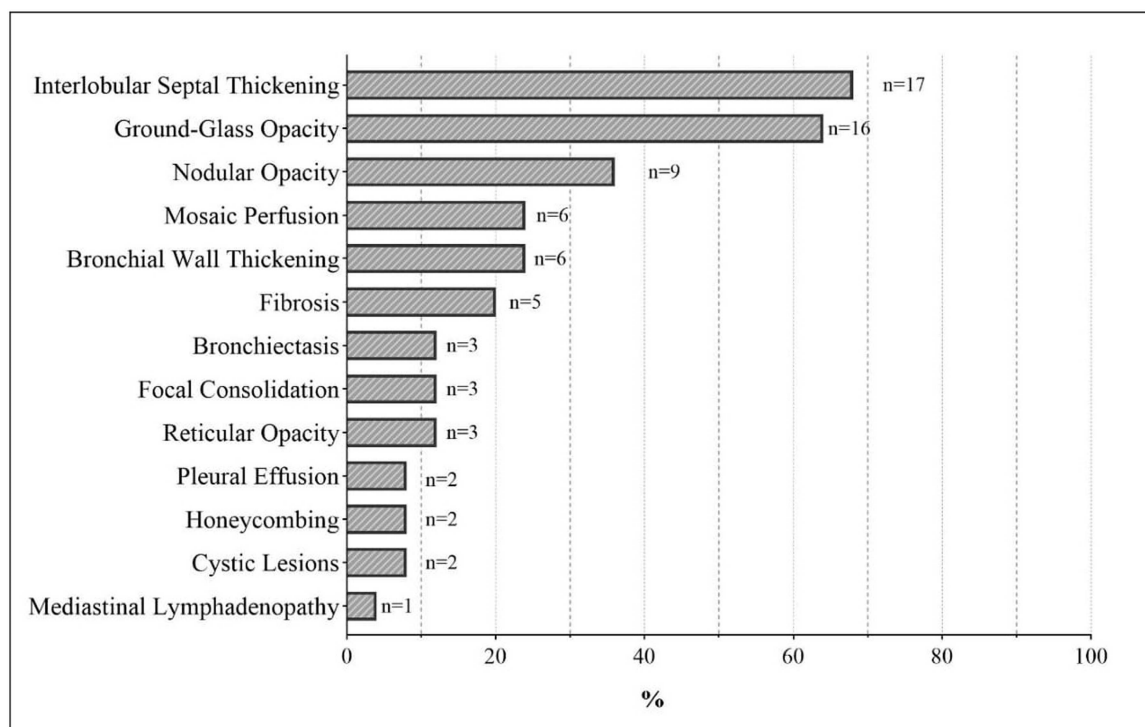


FIGURE 2 | Chest CT findings in patients with chILD and metabolic disorders, $n = 25$.

TABLE 3 | Clinical and radiological features of Niemann-Pick patients according to genotypic classification, $n = 11/16$.

		ERT/SRT			Age at		Respiratory support	
		diagnosis		initiation		Age at initiation		CT
First variant	Second variant	Third variant	Type	Age/Sex	of child (years)	(years)	(years)	
SMPD1	c.416 T > C	c.416 T > C	A/B	16 Male	8.7	—	—	<ul style="list-style-type: none"> • Interseptal thickening • GGO
			A/B	6.4 Male	2.9	6.0	—	<ul style="list-style-type: none"> • Diffuse nodular opacities • Chest X-Ray: Diffuse reticulonodular opacities
			A/B	11.5 Male	5.2	—	—	<ul style="list-style-type: none"> • Interseptal thickening • Diffuse nodular opacities
			B	10.8 Male	6.7	—	—	<ul style="list-style-type: none"> • Interseptal thickening • Reticular opacities
	c.573delT	c.382 G > A	A	3.6 Female	2.3	3.0 (ERT)	2.3–3.3 years (Oxygen support for < 12 h per day)	<ul style="list-style-type: none"> • Interseptal thickening, Diffuse GGO • Mosaic attenuation
	c.1267 C > T	c.1267 C > T	A/B	5.8 Female	5.0	—	—	<ul style="list-style-type: none"> • Interseptal thickening • GGO
	c.1652 T > C	c.1652 T > C	A/B	8 Male	4.9	—	—	<ul style="list-style-type: none"> • Interseptal thickening, Diffuse nodular opacities
	c.272 G > A	c.272 G > A	B	3.2 Female	2.4	—	—	<ul style="list-style-type: none"> • GGO
	c.1117 C > T	c.1117 C > T	A/B	7 Female	4.4	—	—	<ul style="list-style-type: none"> • Interseptal thickening • GGO
NPC1	c.1073delT	c.1073delT	NP-C	8 Male	6	1.5 (SRT)	7 (Full-time IMV)	<ul style="list-style-type: none"> • Interseptal thickening • Diffuse nodular opacities
	c. 852del	c. 852del	NP-C	5.2 Female	3.2	—	—	<ul style="list-style-type: none"> • GGO
	c.1468 T > A	c.1468 T > A	NP-C	7.7 Female	2.5	2.5 (SRT)	—	<ul style="list-style-type: none"> • Interseptal thickening • GGO

Note: Five patients without genotypic data in the registry were not included.

Abbreviations: chILD, Childhood Interstitial Lung Disease; CT, Computed Tomography; ERT, Enzyme Replacement Therapy; FVC, Forced Vital Capacity; GGO, Ground Glass Opacification; SRT, Substrate reduction therapy.
*Chest X-ray findings are provided only for the patient without an available CT scan.

TABLE 4 | Clinical and radiological features of Gaucher patients according to genotypic classification $n = 5/7$.

Mutation in GBA1	Type	Age (years)	Sex	Age at diagnosis of child (years)	Symptom at onset	CT	ERT Age at initiation (years)	Respiratory support Age at initiation (years)	FVC pred. %	DLCO (Adj)
c.1448T > C homozygous	1	15.2	Male	2.5	Chronic wet cough	• Interseptal thickening	2.6	—	61	
						• Diffuse GGO				
						• Crazy-paving pattern				
	1	16	Female	13.7	No	• Interseptal thickening	3.9	—	94	69
	3	10	Male	7.1	No	• Diffuse GGO	8 months	—	86	
c.11193G > T homozygous	3	5.8	Male	5.2	• Chronic wet cough • Tachypnea • Retraction	• Focal GGO	5.4	4.1 (Oxygen support < 12 h per day)	—	
						• Interseptal thickening,				
						• Diffuse GGO				
						• Mosaic attenuation				
						• Bronchiectasis				
	3	5	Male	3.5	• Chronic wet cough • Tachypnea • Retraction	• Honeycombing	3.6	3.5 (Oxygen and BIPAP-ST < 12 h per day)		
						• Interseptal thickening				
						• Diffuse GGO				
						• Mosaic attenuation				
						• Crazy paving pattern				

Note: Two patients without genotypic data in the registry were not included.

Abbreviations: BiPAP, Bilevel Positive Airway Pressure; chILD, Childhood Interstitial Lung Disease; CT, Computed Tomography; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; ERT, Enzyme Replacement Therapy; FVC pred., Forced Vital Capacity (predicted); GGO, Ground Glass Opacification.

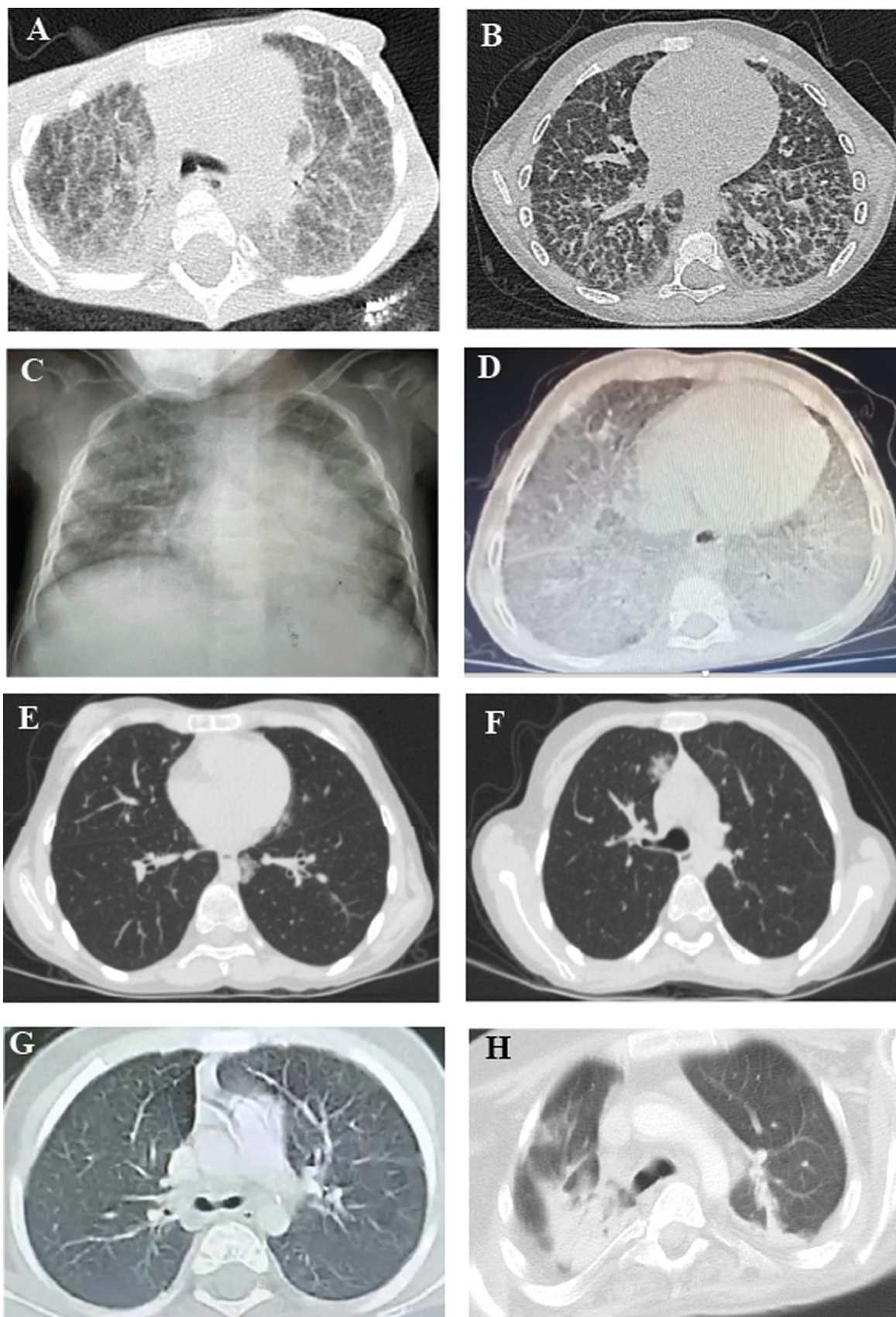


FIGURE 3 | Radiological Findings. (A) GGO, interlobular septal thickening, and focal consolidation in a patient with NP type A. (B) Extensive fibrosis in an asymptomatic NP type A/B patient. (C) Bilateral widespread reticulonodular appearance and consolidation on chest X-ray in a patient with NP type C. (D) Crazy paving pattern in a Gaucher type 3 patient with secondary PAP. (E, F) Focal GGO images in a patient with lysinuric protein intolerance. (G) Mosaic perfusion appearance in a patient with prolidase deficiency. (H) Consolidation, atelectasis, and GGO, in a patient with fucosidosis.

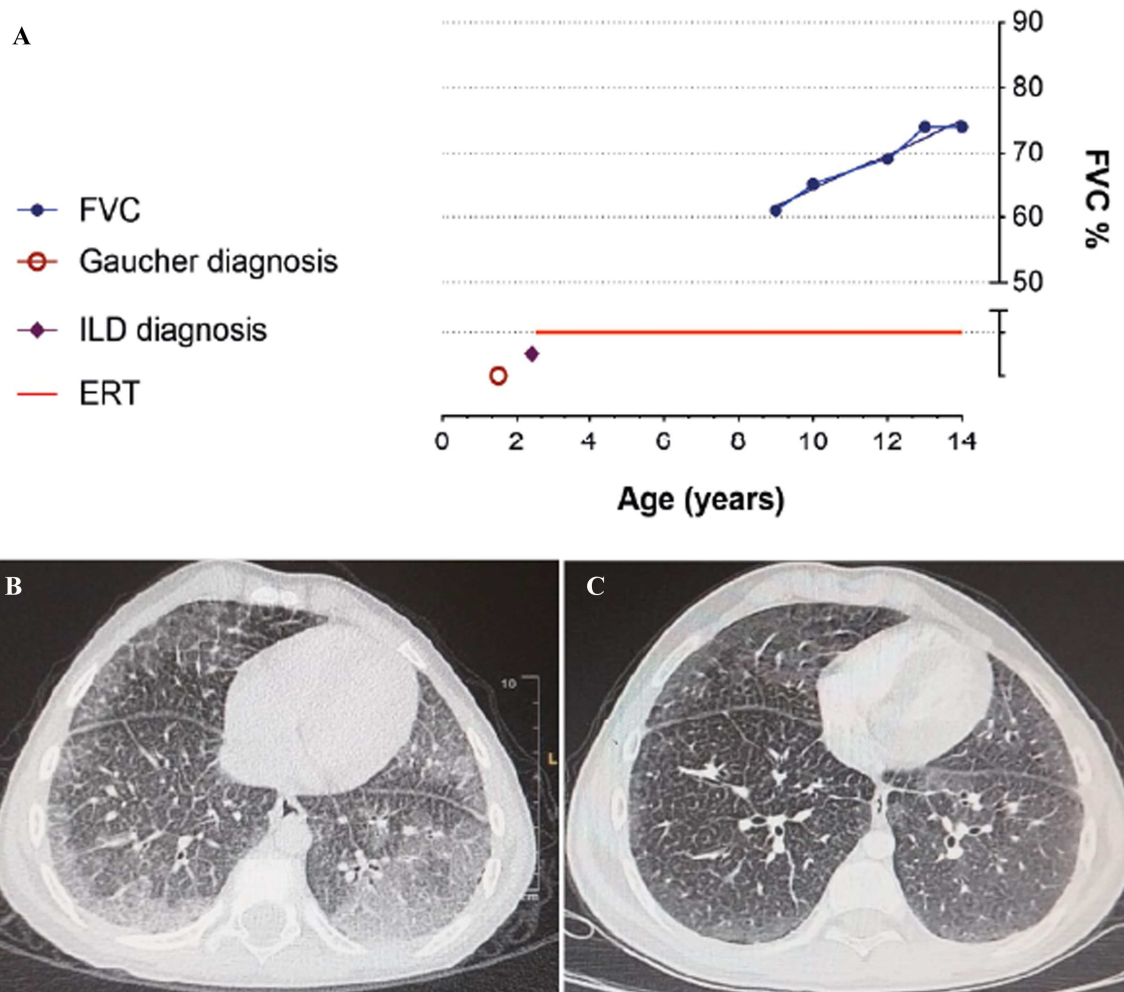


FIGURE 4 | Longitudinal Changes in Pulmonary Function Test and Radiological Findings in a Gaucher Type 1 Patient Under Enzyme Replacement Therapy. (A) GD-1 patient was monitored under ERT, with % FVC values expressed over time. (B) Chest CT at 9 years showed GGO and interlobular septal thickening with a crazy paving pattern. (C) Chest CT at 13 years under ERT showed a significant reduction in GGO and interlobular septal thickening. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ppul.71603)]

5 | Conclusion

Metabolic diseases encompass a broad spectrum of interstitial lung involvement with variable onset and severity. In some patients, pulmonary manifestations may be asymptomatic in the early stages and can be detected through chest imaging. Early referral to pulmonologists and radiological evaluation are crucial for timely diagnosis and close monitoring. Pulmonary management is generally supportive; however, early initiation of ERT has been reported to improve or stabilize pulmonary involvements in selected case series of NP and GD. Further prospective, long-term studies are needed to better understand the impact of ERT and SRT on pulmonary outcomes in these conditions.

Author Contributions

Merve Selçuk Balcı: conceptualization, investigation, methodology, validation, visualization, writing – original draft, writing – review and editing, software, formal analysis, project administration, data curation, supervision, resources. **Fazılcan Zirek:** investigation, data curation. **Handan Kekeç:** investigation, data curation. **Melih Hangül:** investigation, data curation. **Gökçen Kartal Öztürk:** investigation, data curation. **Burcu Çapraz Yavuz:** investigation, data curation. **Gülây**

Bilgin: investigation, data curation. **Beste Özsezen:** investigation, data curation. **Mina Hızal:** investigation, data curation. **Azer Kılıç Başkan:** investigation, data curation. **Ali Özdemir:** investigation, data curation. **Tuğba Ramaslı Gürsoy:** investigation, data curation. **Nazan Çobanoğlu:** investigation, data curation, writing – review and editing. **Tuğba Şişmanlar Eyüboğlu:** investigation, data curation, writing – review and editing. **Nagehan Emirlioğlu:** investigation, data curation, writing – review and editing. **Ahmet Cevdet Ceylan:** investigation, data curation. **Berna Oğuz:** investigation, writing – review and editing. **Diclehan Orhan:** investigation. **Ayşe Ayzıt Kılınç:** investigation, data curation, writing – review and editing. **Saniye Girit:** investigation, data curation, writing – review and editing. **Sevgi Pekcan:** investigation, data curation, writing – review and editing. **Güzin Cinel:** investigation, writing – review and editing, data curation. **Ebru Yalçın:** investigation, writing – review and editing, data curation affiliations. **Nural Kiper:** investigation, funding acquisition, writing – review and editing, data curation, software, supervision, resources affiliations. **Yasemin Gökdemir:** investigation, writing – review and editing, project administration, resources, supervision, data curation, software, validation, visualization, methodology, conceptualization, funding acquisition.

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Ethics Statement

The registry was approved by the central ethics committee at Hacettepe University (GO 20/604), with written confirmations obtained from all 11 participating centers, in accordance with national IRB reliance procedures.

Consent

Written informed consent for data collection was obtained from the legal guardians of the patients.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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