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Immunodeficiency-Associated Childhood Interstitial Lung Diseases: Data from Türkiye chILD Registry

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Background: Childhood interstitial lung diseases (chILD) and immunodeficiencies are rare, heterogeneous, and clinically challenging disorders.

Aims: To evaluate the clinical and radiological characteristics of immunodeficiency-related chILD using data from the Türkiye chILD Registry (chILD-TR).

Study Design: Retrospective cohort study.

Methods: Patients registered with the B3 code, according to the chILD-European classification, from 18 participating centers were included. Patients were classified into primary immunodeficiency (PID) and secondary immunodeficiency (SID) groups. Demographic, clinical, and radiological variables were compared between the two groups.

Results: Among 667 patients registered in the chILD-TR, 114 (17%) had immunodeficiency-related chILD, including 53 (47%) females. The median current age was 156 months (range: 23–357), the age at symptom onset was 60 months (range: 0–215), and the age at chILD diagnosis was 85 months (range: 2–217). PID was identified in 77 patients (67.6%) and SID in 37 patients (32.4%). The PID group had significantly lower median current age, age at first symptom, and age at chILD diagnosis compared with the SID group ($p < 0.05$). No significant differences were observed in growth z-scores between the groups ($p > 0.05$). A history of hematopoietic stem cell transplantation (HSCT) and a diagnosis of bronchiolitis obliterans (BO) were more frequent in the SID group ($p < 0.05$). The most common computed tomography findings were ground-glass opacities in PID and mosaic perfusion in SID. During follow-up, 14 patients (12.3%) died.

Conclusion: Immunodeficiency-associated chILD encompasses a heterogeneous spectrum of disorders and is associated with increased mortality. Distinct clinical and radiological patterns were observed between PID and SID. These findings underscore the importance of early detection, individualized diagnostic strategies, and ongoing follow-up to improve outcomes in this high-risk population. Recognition of post-infectious BO and following HSCT is critical for timely intervention.

INTRODUCTION

Childhood interstitial lung diseases (chILD) are rare, heterogeneous disorders that primarily affect the lung interstitium but can also involve other pulmonary structures. Clinical presentations vary widely, ranging from mild respiratory symptoms to severe cases resulting in respiratory failure and mortality. Despite their significant clinical impact, chILD remains poorly understood, particularly in children with immunodeficiencies.[1-4]

Primary immunodeficiencies (PIDs) and secondary immunodeficiencies (SIDs) impair immune function, increasing susceptibility to infections, autoimmune disorders, and respiratory complications. In children with immunodeficiency, chILD can contribute substantially to morbidity and may even present as the first manifestation of underlying immune dysfunction. However, data on the association between immunodeficiencies and chILD are extremely limited, complicating diagnosis and management.[5-8]

Although recognition of the link between immunodeficiency and chILD is increasing, key questions regarding the spectrum of lung involvement, diagnostic patterns, and clinical outcomes remain unanswered. To address these gaps, we analyzed nationwide data from the Türkiye chILD Registry (chILD-TR), representing the largest and most comprehensive evaluation of this rare subgroup to date. We hypothesized that chILD associated with PID exhibits distinct demographic, clinical, and radiological characteristics compared with SID-related cases. This study aims to provide detailed demographic, clinical, and radiological data on immunodeficiency-related chILD and to delineate the differences between PID- and SID-related forms of the disease.

MATERIALS AND METHODS

This retrospective cohort study used 2023 data from the chILD-TR. Patient information, including follow-up data on survival status and duration of observation, was collected retrospectively from the national database and supplemented with medical records. The study included all patients with a confirmed immunodeficiency diagnosis (B3 diagnosis code) who were also diagnosed with chILD.

Eighteen centers across Türkiye participated in the study. Each center contributed clinical, radiological, and laboratory data for their patients to the national registry, ensuring the dataset's accuracy and completeness. The chILD-TR, established in November 2021, registers patient data through center coordinators using unique patient codes.

The collected variables included:

- Demographic data: sex, consanguinity, current age, age at symptom onset, age at first admission, follow-up duration, and neonatal history.
- Clinical data: growth z-scores, presenting symptoms, and physical examination findings.
- Radiological data and pulmonary function tests (PFTs): spirometry and diffusion capacity for of the lungs carbon monoxide (DLCO).
- Additional data: genetic analysis results, oxygen support, mechanical ventilation (MV) support, history of hematopoietic stem cell transplantation (HSCT) or other transplantations, and survival status.

Patients were classified into two groups, PID and SID, and their demographic, clinical, and radiological characteristics were compared.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/12-63, date: 23.06.2020). Written informed consent

was obtained from all parents, guardians, or legal representatives for minor participants. Adult participants provided written informed consent for their own participation.

Diagnostic approach to childhood interstitial lung diseases and immunodeficiency

The diagnostic evaluation of children with suspected chILD and immunodeficiency typically follows a stepwise approach. The initial assessment includes a comprehensive medical history, thorough physical examination, and basic laboratory tests targeting immune function. Common immunological tests include measurement of immunoglobulin levels, lymphocyte proliferation assays, flow cytometric analysis of T-, B-, and natural killer cell subsets, neutrophil oxidative burst tests, complement system assessments (CH50/AH50), and cytokine production assays.

High-resolution computed tomography (HRCT) is used to characterize lung patterns and identify interstitial abnormalities. Genetic testing, including targeted gene panels or whole exome sequencing, has become an essential component of the diagnostic workflow, particularly in cases of suspected PID or hereditary lung disorders. In selected patients, flexible bronchoscopy with bronchoalveolar lavage (BAL) aids in excluding infections and analyzing inflammatory cells. Lung biopsy may be indicated if non-invasive investigations do not yield a definitive diagnosis.

This multidisciplinary approach, integrating clinical, radiological, immunological, and genetic evaluations, is consistent with national standards of care and ensures a comprehensive assessment for children at risk of immunodeficiency-related chILD.

Childhood interstitial lung diseases diagnosis classification

All patients with a confirmed diagnosis of chILD who meet internationally established criteria are registered in the chILD-TR. The classification system developed by the chILD-EU study group was applied to categorize diseases in the national registry.

Upon registration, patients are systematically assigned to one of two primary diagnostic categories:

- Diffuse parenchymal lung disease A: Primarily affects infants and includes disorders that typically present within the first two years of life. These conditions are often associated with abnormal lung development or surfactant dysfunction.
- Diffuse parenchymal lung disease B: Can occur at any age and encompasses a broader spectrum of interstitial lung diseases (ILD) that may manifest beyond infancy, including in later childhood or adolescence. This category includes conditions related to systemic diseases, environmental exposures, or immunodeficiencies.[9-11]

Definitions of bronchiolitis obliterans and post-infectious bronchiolitis obliteran

BO is a fibrotic disease affecting the small airways, characterized by concentric narrowing or complete obliteration of the bronchiolar lumen. It is frequently associated with HSCT, immunosuppressive therapies, or underlying pathological conditions. Post-infectious bronchiolitis obliterans (PIBO) is a distinct form of BO that develops following a documented severe lower respiratory tract infection. Adenovirus is the most common causative agent, although other pathogens, including *Mycoplasma pneumoniae*, respiratory syncytial virus, and influenza virus, have also been implicated.[9,11-13]

Primary immunodeficiency diagnosis

PIDs were classified according to the International Union of Immunological Societies system for inborn errors of immunity. PIDs include a broad spectrum of disorders, such as immune dysregulation, congenital defects in phagocyte number or function, antibody deficiencies, combined immunodeficiencies, autoinflammatory syndromes, defects of innate and intrinsic immunity, and bone marrow failure–related disorders.[6]

Secondary immunodeficiency diagnosis

SID was defined in patients with an underlying malignancy or a history of immunosuppressive therapy. The SID group comprised individuals receiving treatment for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), various lymphoma subtypes, or solid tumors, as well as patients who had undergone HSCT or solid organ transplantation and were receiving immunosuppressive regimens. Additionally, patients with immune suppression resulting from long-term corticosteroid therapy, biologic agents, or other immunosuppressive medications were classified as having SID.[8]

Temporal assessment of childhood interstitial lung diseases development in secondary immunodeficiency

In the SID group, chILD developed after the onset of SID, typically following exposure to treatments such as chemotherapy, prolonged corticosteroid therapy, biologic agents, or HSCT. Symptoms or radiologic abnormalities consistent with chILD, as well as pulmonary findings, were observed only after the onset of secondary immunosuppression. None of the patients exhibited chILD-related manifestations prior to these treatments or the diagnosis of SID. Among patients who underwent HSCT, BO was diagnosed when new respiratory symptoms appeared in conjunction with compatible imaging features post-transplantation.

Pulmonary function tests

Spirometry was performed according to the American Thoracic Society/European Respiratory Society Guidelines for pediatric patients. DLCO was measured using the single-breath technique. Results between the 5th and 95th percentiles were considered within normal limits.[14]

High resolution computer tomography evaluation

HRCT scans were acquired at each participating center using standard pediatric thoracic imaging protocols. Although imaging parameters varied across centers, all HRCT images were assessed using consistent radiological criteria to ensure uniform interpretation. Radiological findings were extracted from routine clinical HRCT reports prepared by board-certified radiologists; no standardized scoring system or blinded re-evaluation was applied.

Fan score

The severity-of-illness score developed by Fan and Kozinetz[15] is used for the clinical assessment of patients with chronic ILD. Patients are scored from 1 to 5 based on symptoms, oxygen saturation, and the presence of pulmonary hypertension, with higher scores indicating greater disease severity.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using histograms, probability plots, and the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation, while non-normally distributed data are reported as median (minimum–maximum). Categorical variables are presented as frequencies and percentages. Comparisons between two independent groups were made using the independent samples t-test or Mann–Whitney U test, depending on data distribution. Categorical variables were compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. A p value < 0.05 was considered statistically significant.

RESULTS

In 2023, a total of 667 patients were registered in the chILD-TR, of whom 114 (17%) had immunodeficiency (diagnosis code: B3) and were included in this study. The study flow diagram is presented in Figure 1.

Among the 114 patients with immunodeficiency, 53 (47%) were female and 61 (53%) were male. The median current age was 156 months (range: 23–357), age at first symptom was 60 months (0–215), age at chILD diagnosis was 85 months (2–217), the interval between first symptom and chILD diagnosis was 3 months (0–185), and the follow-up duration for chILD was 47 months (3–204).

The most common presenting symptoms were cough (83, 72.8%), dyspnea (47, 41.2%), tachypnea (44, 38.6%), and cyanosis (40, 35.1%).

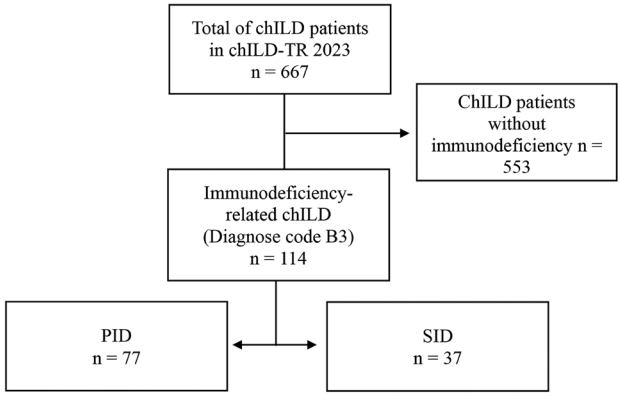

FIG. 1. Flow diagram of the study.
chILD, childhood interstitial lung disease; PID, primary immunodeficiencies; SID, secondary immunodeficiencies; chILD-TR, the Türkiye chILD Registry.

Frequent physical examination findings included crackles (55, 48.2%), rhonchi (31, 27.2%), clubbing (22, 19.3%), decreased breath sounds (20, 17.5%), and retractions (18, 15.8%).

Thirty-five patients were able to perform PFTs. The median values were as follows: forced expiratory volume in 1 second (FEV_1), 54% (16–128); orced vital capacity (FVC), 56% (17–128); and forced expiratory flow 25-75% ($FEF_{25–75}$), 66% (9–132). Thirteen patients underwent DLCO measurement, with a median DLCO of 60% (25–113).

BAL cultures revealed the following microorganisms: *Pseudomonas aeruginosa* (n = 6), *Streptococcus pneumoniae* (n = 1), *Enterobacter* species (n = 1), *Haemophilus influenzae* (n = 3), *Staphylococcus aureus* (n = 1), *Klebsiella* species (n = 2), *Actinomyces* species (n = 1), and a mixed culture of Aspergillus niger and *Stenotrophomonas maltophilia* (n = 1). Fungal isolates included Candida albicans (n = 2), Candida dubliniensis (n = 1), and Candida kefyr (n = 1). Cytomegalovirus was detected in two patients.

When evaluating diagnostic methods for chILD, HRCT was the most frequently performed test, conducted in 111 patients (97.4%). Genetic analysis was performed in 43 patients (37.7%), with only one patient diagnosed with pulmonary alveolar microlithiasis (PAM) via this method. Of the 14 patients (12.3%) who underwent lung biopsy, 10 belonged to the PID group and 4 to the SID group. All patients who underwent lung biopsy or genetic analysis had HRCT imaging available.

During follow-up, four patients were lost to follow-up. At the end of the observation period, 20 patients (17.5%) showed improvement, 45 (39.5%) remained stable, 21 (18.4%) experienced disease progression, and 14 (12.3%) died. The demographic, clinical, spirometric, and diagnostic characteristics of all patients are summarized in Table 1.

The etiologies of immunodeficiency were evaluated among the patients: PID was identified in 77 patients (67.6%), and SID in 37 patients (32.4%). The most common PID etiologies were hypogammaglobulinemia (14, 12.3%), severe combined immunodeficiency (SCID) (11, 9.6%), chronic granulomatous disease (CGD) (8, 7%), dedicator of cytokinesis 8 (DOCK8) deficiency (6, 5.3%), and LPS-responsive beige-like anchor protein (LRBA) deficiency (6, 5.3%). The most frequent SID etiologies included malignancies (24, 21%), thalassemia major with HSCT (8, 7%), and drug-related causes (anakinra, rituximab, blinatumomab) (3, 2.6%). All etiological causes for PID and SID are summarized in Table 2.

The most common chILD diagnosis was BO, observed in 59 patients (51.8%), of whom six (5.3%) had PIBO. Six patients were diagnosed with pleuroparenchymal fibroelastosis, and two patients had hypersensitivity pneumonitis. Other diagnoses included drug-induced ILD (3), pulmonary hemosiderosis (2), PAM (1), CGD-associated pulmonary fibrosis (1), LRBA-associated granulomatous lung disease (1), non-specific interstitial pneumonia (NSIP) (1), granulomatous lymphocytic ILD (GLILD) (1), and pulmonary alveolar proteinosis (PAP) (1). Thirty-five patients had chILD without a specific diagnosis. The chILD diagnoses are presented in Table 3.

TABLE 1. Demographic, Clinical and Diagnostic Data of All Patients.

Total n (%)	114 (100)
Female n (%)	53 (47)
Male n (%)	61 (53)
Current age (months)‡	156 (23-357)
Age at first complaint initiation (months)‡	60 (0-215)
Age at chILD diagnosis (months)‡	85 (2-217)
Time between first complaint-age at chILD diagnosis (months)‡	3 (0-185)
Follow-up time of chILD‡	47 (3-204)
Symptoms	
Cough	83 (72.8)
Dyspnea	47 (41.2)
Tachypnea	44 (38.6)
Cyanosis	40 (35.1)
Nutritional disturbance	14 (12.3)
Fever	13 (11.4)
Gastrointestinal complaints	13 (11.4)
Chest pain	5 (4.4)
Hemoptysis	1 (0.9)
Physical examination	
Crackles	55 (48.2)
Rhonchi	31 (27.2)
Clubbing	22 (19.3)
Decreased breath sounds	20 (17.5)
Retraction	18 (15.8)
Hepatosplenomegaly	16 (14)
Chest deformity	14 (12.3)
Wheezing	13 (11.4)
Nasal flaring	11 (9.6)
Lymphadenopathy	8 (7)
Stridor	3 (2.6)
Cardiac murmur	3 (2.6)
Advanced diagnostic tests	
Bronchoscopy	60 (52.6)
Genetic analyse	43 (37.7)
Lung biopsy	14 (12.3)
Diagnose method of chILD	
Clinical findings and chest X-ray	3 (2.6)
Clinical findings and HRCT	96 (84.2)
Clinical findings and HRCT and genetic analyse	1 (0.9)
Clinical findings and HRCT and lung biopsy	14 (12.3)
Lost to follow-up	4 (3.5)
Outcome of lung disease at the end of follow-up	
Clinical improvement	20 (17.5)
No clinical change/stable condition	45 (39.5)
Clinical deterioration	21 (18.4)
Deceased patients	14 (12.3)

chILD, childhood ınterstitial lung disease; HRCT, high resolution computed tomography.
‡: median (minimum-maximum).

TABLE 2. Etiological Causes in Immun Deficiency.

PID	77 (67.6%)
Hypogammaglobulinemia	14 (12.3)
SCID	11 (9.6)
CGD	8 (7)
DOCK8 deficiency	6 (5.3)
LRBA deficiency	6 (5.3)
Myelodysplastic syndrome	4 (3.5)
STAT3 deficiency	3 (2.6)
CVID	3 (2.6)
Ataxia-telangiectasia	3 (2.6)
Fanconi aplastic anemia	3 (2.6)
Congenital neutropenia	2 (1.7)
ADA deficiency	2 (1.7)
Artemis deficiency	1 (0.9)
Bruton agammaglobulinemia	1(0.9)
NK deficiency	1 (0.9)
APDS	1 (0.9)
MHC class II deficiency	1 (0.9)
DiGeorge syndrome	1 (0.9)
LAD	1 (0.9)
Shwachman-diamond syndrome	1 (0.9)
Undefined immunodeficiency	1 (0.9)
SLE releated immun disregulasyon	1 (0.9)
ZNFX1 deficiency	1 (0.9)
Prolidase deficiency	1 (0.9)
SID	37 (32.4%)
Malignencies	24 (21)
AML	14 (12.3)
ALL	7 (6.1)
Lymphoma	2 (1.7)
JMML	1 (0.9)
Thalassemia major + HSCT	8 (7)
Drug releated (anakinra, rituximab, blinotumomab)	3 (2.6)
Kidney transplant-associated immunodeficiency	1 (0.9)
Hemophagocytic lymphohistiocytosis + HSCT	1 (0.9)

PID, primary immunodeficiency; CGD, chronic granulomatous disease; SCID, severe combined immunodeficiency; DOCK8, dedicator of cytokinesis 8; LRBA, lipopolysaccharide-responsive beige-like anchor protein; STAT3, signal transducer and activator of transcription 3; CVID, common variable immunodeficiency; ADA, adenosine deaminase; APDS, activated PI3K delta syndrome; AML, acute myeloid leukemia; LAD, leukocyte adhesion deficiency; SLE, systemic lupus erythematosus; ZNFX1, zinc finger nuclease 1; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplantation, JMML, juvenile myelomonocytic leukemia.

TABLE 3. Diagnoses of the chILD.

PID	77	SID	37
Bronchiolitis obliterans	34	Bronchiolitis obliterans	25
After HSCT	28	After HSCT	24
PIBO	6	After kidney transplantation	1
Pleuro-parenchymal fibroelastosis	3	Pleuropulmonary fibroelastosis	3
Hypersensitivity pneumonitis	1	Hypersensitivity pneumonitis	1
Pulmonary hemosiderosis	2	Drug-induced ILD (Blinotumomab)	1
Granulomatous lymphocytic ILD	2	Drug-induced ILD (Rituximab)	1
Pulmonary alveolar microlithiasis	1	Drug-induced ILD (Anakinra)	1
NSIP	1	Without any specific diagnosis	5
CGD-associated pulmonary fibrosis	1		
LRBA-associated granulomatous lung disease	1		
PAP	1		
Without any specific diagnosis	30		

ChILD, childhood interstitial lung disease; CGD, chronic granulomatous disease; LRBA, LPS-responsive beige-like anchor protein; NSIP, non-specific interstitial pneumonia; PAP, pulmonary alveolar proteinosis; PIBO, post-infectious bronchiolitis obliterans; PID, primary immunodeficiencies; SID, secondary immunodeficiencies; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease.

In the PID group, 34 patients (44.2%) were female and 43 (55.8%) were male, whereas in the SID group, 19 (51.4%) were female and 18 (48.6%) were male ($p = 0.471$). The median current age was 136 months (range: 23–357) in the PID group and 185 months (51–334) in the SID group ($p = 0.018$). The median age at first chILD-related symptom onset was 35 months (0–214) in the PID group and 102 months (9–215) in the SID group ($p < 0.001$). The median age at chILD diagnosis was significantly lower in the PID group (72 months, range 2–215) compared to the SID group (127 months, range 22–217) ($p < 0.001$). The median interval between first symptom and chILD diagnosis was 2 months (0–185) in the PID group and 3 months (0–123) in the SID group ($p = 0.726$). Median follow-up duration for chILD was 46 months (3–204) in the PID group and 48 months (3–175) in the SID group ($p = 0.623$).

Anthropometric evaluation showed median weight z-scores of −1.20 (−7.25 to 2.39) in the PID group and −1.24 (−4.12 to 3.23) in the SID group; median height z-scores were −0.75 (−9.41 to 1.80) and −1.00 (−3.90 to 2.60), respectively. Median body mass index z-scores were −0.67 (−8.30 to 3.37) in the PID group and −0.77 (−4.87 to 2.76) in the SID group ($p = 0.189$, 0.646, and 0.714, respectively).

Pulmonary function testing revealed median FEV_1 values of 56% (24–109) in the PID group and 53% (16–128) in the SID group; median FVC values were 57% (22–106) and 55% (17–128), respectively; median $FEF_{25–75}$ values were 66% (14–118) and 69% (9–132); and median DLCO values were 60% (35–113) in the PID group and 60% (25–104) in the SID group ($p = 0.597$, 0.882, 0.871, and 0.568, respectively).

The median Fan score was 2 (range, 1–5) in both the PID and SID groups ($p = 0.510$). Oxygen support was required in 20 patients (26%) in the PID group and 6 patients (16.2%) in the SID group ($p = 0.245$). MV support was needed in 3 patients (3.9%) in the PID group and 3 patients (8.1%) in the SID group ($p = 0.327$). A history of MV during the neonatal period was present in 12 patients (15.6%) in the PID group, whereas none was reported in the SID group.

Pulmonary hypertension was observed in 7 patients (9%) in the PID group and 3 patients (8.1%) in the SID group ($p = 0.985$). HSCT had been performed in 31 patients (40.3%) in the PID group and 27 patients (73%) in the SID group ($p = 0.001$). In the SID group, HSCT was performed for malignancy in 18 patients (15.7%), thalassemia major in 8 patients (7%), and hemophagocytic lymphohistiocytosis in 1 patient (0.9%).

BO was diagnosed in 34 patients (44.2%) in the PID group, including 6 with PIBO and 28 post-HSCT, and in 25 patients (67.6%) in the SID group ($p = 0.019$). Parental consanguinity was reported in 55 patients (48.2%) overall—42 (54.5%) in the PID group and 13 (35.1%) in the SID group, without a statistically significant difference ($p = 0.52$). A family history of chronic lung disease was present in 11 patients (14.3%) in the PID group and one patient (2.7%) in the SID group ($p = 0.017$). A family history of chILD was reported in 3 patients (3.9%) in the PID group and none in the SID group. Sibling death occurred in 14 patients (18.2%) in the PID group and 1 patient (2.7%) in the SID group ($p = 0.006$). Overall, 14 patients died during follow-up: 9 (7.9%) in the PID group and 5 (4.4%) in the SID group (Table 4).

In patients with PID, the most common HRCT findings were ground-glass opacities (GGO), observed in 45 patients (58.4%), with a diffuse pattern in 24 (31.1 %) and a patchy pattern in 21 (27.2 %). Other frequent findings included mosaic perfusion in 34 patients (44.2%), nodules or nodular opacities in 28 (36.3 %), bronchial wall thickening in 27 (35.0 %), and linear or reticular opacities in 22 (28.5 %). Representative radiological patterns in PID patients are shown in Figures 2 and 3.

TABLE 4. Comparison of the Primary and Secondary Immunodeficiency Group.

	PID n (%)	SID n (%)	*p*
Female Male	34 (44.2) 43 (55.8)	19 (51.4) 18 (48.69	0.471
Current age‡	136 (23-357)	185 (51-334)	**0.018**
Age at first complaint initiation related chILD‡ (months)	35 (0-214)	102 (9-215)	**< 0.001**
Age at chILD diagnosis‡ (months)	72 (2-215)	127 (22-217)	**< 0.001**
Time between first complaint related to chILD-chILD diagnosis‡ (months)	2 (0-185)	3 (0-123)	0.726
Follow-up time of chILD‡	46 (3-204)	48 (3-175)	0.623
Consanguinity	42 (54.5)	13 (35.1)	0.52
Family history of chronic lung disease	11 (14.3)	1 (2.7)	**0.017**
Family history of chILD	3 (3.9)	-	-
History of sibling death	14 (18.2)	1 (2.7)	**0.006**
Weigth z score‡	-1.20 (-7.25-2.39)	-1.24 (-4.12-3.23)	0.189
Height z score‡	-0.75 (-9.41-1.80)	-1 (-3.90-2.60)	0.646
BMI z score‡	-0.67 (-8.30-3.37)	-0.77 (-4.87-2.76)	0.714
FEV_1 %‡	56 (24-109)	53 (16-128)	0.597
FVC %‡	57 (22-106)	55 (17-128)	0.882
FEF_{25-75} ‡	66 (14-118)	69 (9-132)	0.871
DLCO %‡	60 (35-113)	60 (25-104)	0.568
Fan score	2 (1-5)	2 (1-5)	0.510
Oxygene support n (%)	20 (26)	6 (16.2)	0.245
MV support n (%)	3 (3.9)	3 (8.1)	0.327
History of MV in newborn period	12 (15.6)	-	-
Pulmonary HT	7 (9)	3 (8.1)	0.985
History of HSCT	31 (40.3)	27 (73)	**0.001**
Diagnose of BO	34 (44.2)	25 (67.6)	**0.019**
Deceased patients	9 (11.7)	5 (13.5)	0.840
	SCID + HSCT + BO (1) MDS + HSCT + BO (1) DOCK8 + HSCT + BO (1) CVID + HSCT + BO (1) ADA 2 deficiency + HSCT + BO (1) Di-George (1) LRBA deficiency (1) CVID (Coffin-Siris syndrome) (1) Undefined immunodeficiency (1)	ALL + blinotumomab-related chILD (1) Hodgkin lymphoma rituximab-related chILD (1) ALL + HSCT + NSIP (1) ALL + HSCT (1) Talasemia Major + HSCT + BO (1)	

ADA, adenosine deaminase; ALL, acute lymphoblastic leukemia; BMI, body mass index; BO, bronchiolitis obliterans; CVID, common variable immunodeficiency; chILD, childhood interstitial lung disease; DOCK8, dedicator of cytokinesis 8; HSCT, hematopoietic stem cell transplantation; HT, hypersention; LRBA, lipopolysaccharide-responsive beige-like anchor protein; MDS, myelodysplastic syndrome; MV, mechanical ventilation; PID, primary immunodeficiencies; SCID, severe combined immunodeficiency; SID, secondary immunodeficiencies; FEV_1, forced expiratory volume in 1 second; FEF_{25-75}, forced expiratory flow 25-75%; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide.
‡: median (minimum-maximum).

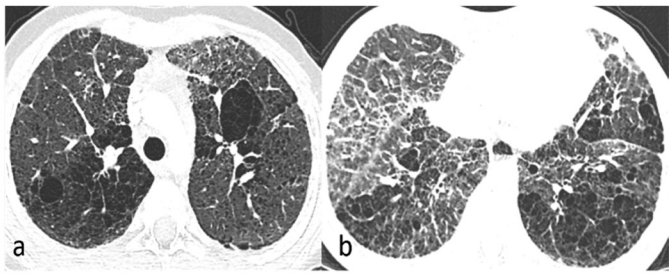

FIG. 2. A 13-year-old boy with primary immunodeficiency (severe combined immunodeficiency). Chest computed tomography images (a, b) show linear and reticular opacities, ground-glass opacities, interlobular septal thickenings, emphysematous changes, and multiple cysts resulting in a honeycomb appearance in both lungs. Childhood interstitial lung disease findings are compatible with lung fibrosis.

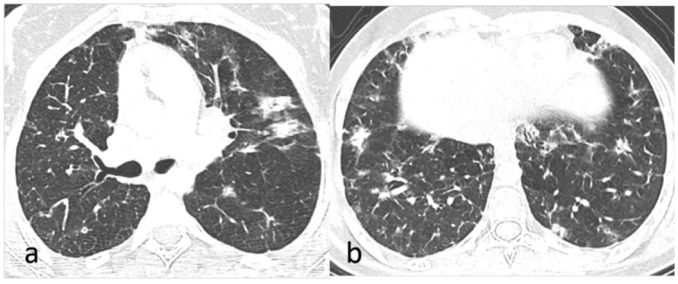

FIG. 3. 15-year-old girl with primary immunodeficiency (LPS-responsive beige-like anchor protein deficiency). Chest computed tomography images (a, b) show multiple irregular nodular opacities, ground-glass opacities, interseptal thickenings, and focal hyperaeration areas.

In the SID group, the most common HRCT findings were mosaic perfusion in 25 patients (67.6%), GGO in 17 (45.9%) [diffuse 9 (24.3%) and patchy 8 (21.6%)], nodules or nodular opacities in 15 (40.5%), bronchial wall thickening in 14 (37.8%), and linear or reticular opacities in 14 (37.8%).

Comparison between PID and SID groups revealed that mosaic perfusion was significantly more frequent in the SID group (25, 67.6%) than in the PID group (34, 44.2%; $p = 0.019$). Mediastinal lymphadenopathy was observed in 19 patients (25.7%) in the PID group and 3 patients (7.7%) in the SID group ($p = 0.035$). HRCT findings in the PID and SID groups are summarized in Table 5.

Bronchoscopy was performed in 60 patients: 46 (76.7%) in the PID group and 14 (23.3%) in the SID group. BAL cultures were positive in 14 patients (18.2%) in the PID group and 2 patients (5.4%) in the SID group.

Among patients with chILD, the most commonly used medications were fluticasone, azithromycin, and montelukast (FAM protocol) in 52 patients (45.6%), oral corticosteroids in 33 (29.4%), and inhaled corticosteroids in 29 (25.4%). All patients receiving the FAM protocol had HSCT-related BO. For the management of immunodeficiency, intravenous immunoglobulin was the most frequently administered therapy, while trimethoprim-sulfamethoxazole was the most commonly used prophylactic agent. Regarding pulmonary hypertension, four patients were receiving therapy, including sildenafil, bosentan, or tadalafil.

TABLE 5. Comparison of the HRCT finding in Primary and Secondary Immunodeficiency.

	PID n = 77 (67.5%)	SID n = 37 (32.4 %)	*p*
GGO	45 (58.4%)	17 (45.9%)	0.084
Mosaic perfusion	34 (44.2)	25 (67.6)	**0.019**
Nodules or nodular opacities	28 (36.3%)	15 (40.5%)	0.783
Bronchial wall thickening	27 (35.0 %)	14 (37.8%)	0.631
Focal consolidation	24 (31.1%)	10 (27%)	0.422
Bronchiectasis	22 (28.6%)	7 (18.9%)	0.122
Linear or reticular opacities	22 (28.6%)	14 (37.8%)	0.589
Interseptal thickening	20 (25.9 %)	11 (29.7%)	0.696
Mediastinal lymphadenopathy	19 (24.6%)	3 (8.1%)	**0.035**
Emphysema	19 (24.6%)	6 (16.2%)	0.986
Increased aeration	16 (20.7%)	12 (32.4%)	0.296
Cystic lesions	13 (16.8 %)	2 (5.4%)	0.089
Fibrosis	9 (11.7 %)	6 (16.2%)	0.478
Traction bronchiectasis	6 (7.8%)	2 (5.4%)	0.771
Honeycomb appearance	5 (6.5%)	5 (13.5%)	0.184
Pectus excavatum	5 (6.5%)	2 (5.4%)	0.986
Pleural effusion	3 (3.9 %)	1 (2.7%)	0.778

GGO, ground glass opacities; HRCT, high resolution computed tomography; PID, primary immunodeficiencies; SID, secondary immunodeficiencies.

DISCUSSION

This study represents the largest national cohort from the chILD-TR registry to date, investigating chILD in the context of immunodeficiency. Our findings demonstrate a diverse range of immunodeficiencies and a broad spectrum of chILD, including numerous rare disorders. By focusing on both PID and SID associated with chILD, we conducted a comparative analysis of their clinical, radiological, and outcome features.

BO emerged as the most significant form of chILD in both PID and SID patients, primarily associated with post-HSCT complications and post-infectious etiologies, which substantially influence mortality. Children with PID typically presented at younger ages and received earlier diagnoses, reflecting the strong genetic and familial contributions to disease burden. In contrast, SID patients generally manifested symptoms later, often in the setting of malignancy or post-transplantation.

Distinct radiological patterns were observed between the two groups. GGO and mediastinal lymphadenopathy were more frequently noted in PID patients, whereas mosaic perfusion was more prominent in SID, highlighting underlying differences in pulmonary radiological findings. Long-term follow-up revealed a high mortality rate, emphasizing the clinical severity of chILD in the context of immunodeficiency. Collectively, these findings provide a comprehensive understanding of how immune status shapes the clinical presentation, imaging features, and outcomes of chILD in children.

Recent studies in Türkiye have reported consanguinity rates of 22.4% in urban areas and 28.8% in rural regions, with most marriages occurring between first- and second-degree cousins.[16] In our cohort, the consanguinity rate was markedly higher at 48.2%, exceeding previously reported national estimates. Furthermore, the frequent occurrence of chronic lung disease among family members and a history of sibling deaths highlight the complex familial backgrounds of these patients. These findings emphasize the importance of comprehensive family history assessments and suggest that genetic analysis should be considered when appropriate, particularly in populations with a high prevalence of hereditary disorders and consanguineous marriages.

Immunodeficiencies and chILD are rare clinical entities that can sometimes be difficult to distinguish. Therefore, recognizing chILD manifestations within different immunodeficiency syndromes is essential. Gao et al.[17] evaluated 90 children with chILD who had an underlying primary or SID. Their study reported a median age at lung disease onset of 2.9 years and a median follow-up of 4.9 years. Among these patients, 44% had PIDs, while 39% had SIDs. The PIDs included phagocytic defects, combined immunodeficiencies, and autoinflammatory syndromes, whereas SIDs were primarily associated with malignancies such as ALL, myelodysplastic syndrome, AML, and other cancers.

Our findings are consistent with this study, underscoring the variability of chILD presentations in immunodeficient patients. The spectrum of diagnoses in our cohort was diverse, encompassing not only BO but also rarer conditions such as pleuroparenchymal fibroelastosis, hypersensitivity pneumonitis, and PAP. This diversity illustrates the complexity of diagnosing and managing chILD in the context of immunodeficiencies, as these patients may present with a wide range of clinical and radiological features. Thus, early recognition and accurate differential diagnosis are critical. Importantly, while Gao et al.[17] focused on chILD in immunodeficient patients, our study approached the issue from the pediatric pulmonology perspective, analyzing immunodeficiency-related features within a chILD registry.

In recent years, significant advancements have been made in HSCT protocols and supportive care. HSCT has become a cornerstone in the treatment of PIDs, particularly in conditions such as DOCK8 deficiency, GATA2 mutation, and CGD, where severe complications and life-threatening events frequently occur within the first two decades of life. Beyond PIDs, HSCT is also the preferred therapeutic approach for various hematological disorders, including AML, ALL, and thalassemia major.[18]

Complications arising early or late after HSCT are associated with substantial morbidity and mortality in children. Among late complications, BO is the most common non-infectious pulmonary sequela.[12,13] In our cohort, BO was the most frequently identified diagnosis, affecting 51.8% of patients, with an especially high prevalence (98.1%) among those who had undergone HSCT. BO can develop both as a complication of HSCT, performed to treat the underlying primary disease, and as a consequence of recurrent lower respiratory tract infections. Its pathophysiology is complex, involving immune dysregulation and airway injury.

This study underscores the critical need to raise awareness of BO in immunodeficiency-associated chILD patients. Given its high prevalence in this population, BO—together with other HSCT-related complications—contributes significantly to mortality. Pre-transplant PFT and DLCO abnormalities, along with frequent recurrent respiratory infections, further increase the risk of post-transplant BO. Current HSCT Guidelines recommend pre-transplant screening for BO risk, including PFTs, lung volumes, and DLCO, as well as inspiratory and expiratory chest computed tomograpgy (CT) imaging for all children. Post-transplant monitoring should include PFTs every three months during the first year and every 3–6 months in the second year. Chest CT imaging is strongly advised if BO is suspected after transplantation.[19] Patients with recurrent lung infections or a history of HSCT should be closely monitored for early signs of BO, as prompt recognition and initiation of appropriate treatment may reduce mortality.

In addition to BO, other distinct diagnoses were identified, including pleuroparenchymal fibroelastosis, GLILD, NSIP, PAM, PAP, hypersensitivity pneumonitis, and drug-induced chILD. These findings highlight the broad spectrum of chILD that may occur in patients with primary and SIDs. The rarity of these conditions in the general population further emphasizes the need for heightened clinical suspicion in this patient group. Such uncommon and diverse diagnoses not only illustrate the extensive range of pulmonary involvement in immunodeficiencies but also underscore the diagnostic challenges clinicians face when distinguishing them from more common chILD entities.

The high proportion of undiagnosed cases (39%) within the PID group likely reflects multiple challenges inherent to the diagnostic process. The coexistence of PID and chILD creates a complex clinical scenario, as each condition individually can present significant diagnostic difficulties. When occurring together, overlapping symptoms further complicate diagnosis and may delay identification of the underlying immunodeficiency. Contributing factors to this diagnostic gap include diverse clinical presentations, limited access to advanced immunological and genetic testing, variability in diagnostic practices across centers, and infections or treatment-related complications that can mimic or obscure PID. These findings underscore the importance of standardized diagnostic pathways, early suspicion of PID in children with unexplained respiratory symptoms, and improved access to comprehensive immunological and genetic testing across centers.[20]

Radiological imaging, particularly HRCT, plays a pivotal role in diagnosing chILD by detecting parenchymal abnormalities such as GGO, mosaic perfusion, interstitial infiltrates and thickening, air trapping, nodules, and fibrotic changes.[2] When clinical suspicion exists, HRCT is often employed as an initial diagnostic modality. In our cohort, the most frequent findings were GGO, mosaic attenuation, nodules or nodular infiltrates, and bronchial wall thickening. GGO were more prevalent in the PID group, suggesting diffuse alveolar involvement or inflammation. In contrast, mosaic perfusion was more commonly observed in the SID group, potentially reflecting small-airway or vascular pathology. These distinct radiological patterns may aid in differentiating underlying immune dysfunctions and, when integrated with clinical data, can enhance diagnostic accuracy and guide management in immunodeficient children with chILD.

In our cohort, a descriptive analysis of the 14 deceased patients revealed distinct mortality patterns between PID- and SID-related chILD. The majority of deaths occurred in the PID group (n = 9), with affected patients predominantly exhibiting severe immunological phenotypes, including SCID, DOCK8 deficiency, LRBA deficiency, ADA2 deficiency, and common variable immunodeficiency. These disorders are characterized by profound immune dysregulation and a high burden of recurrent or severe pulmonary infections, predisposing children to progressive lung injury and respiratory complications. Notably, several deceased PID patients had undergone HSCT and subsequently developed BO, suggesting that transplant-related lung injury and chronic airway disease substantially contributed to mortality.

In contrast, deaths in the SID group (n = 5) were primarily associated with therapy-induced immunosuppression rather than intrinsic immune defects. This included patients receiving chemotherapy for ALL or HSCT, as well as cases of drug-induced chILD following agents such as blinatumomab and rituximab. Collectively, these findings indicate that mortality in PID is largely driven by the severity of the underlying immune disorder and transplant-related pulmonary complications, whereas in SID, mortality appears to result primarily from treatment-related immunosuppression and its pulmonary consequences.[12,17,18]

The reported mortality rate in immunocompetent children with chILD was 6% in the study by Clement[21] and 7% in a multicenter study conducted in Australia and New Zealand.[22] In contrast, the mortality rate in our cohort of immunocompromised children was substantially higher at 12.3%, suggesting that immunocompromised children with chILD may experience a more severe clinical course and an increased risk of adverse outcomes. This finding highlights the significant impact of underlying immunodeficiency on the severity and progression of chILD. Immunocompromised children often have altered immune responses, rendering them more susceptible to infections, disease exacerbations, and progressive pulmonary injury, all of which contribute to higher mortality. A thorough understanding of how immunocompromised status influences chILD outcomes is essential for optimizing management strategies and improving patient prognosis.

This study has several limitations. First, its retrospective design and the absence of comprehensive genetic data for each patient restrict the generalizability of our findings. Second, the number of patients who underwent lung biopsies was small. Spirometry and DLCO measurements were missing for many patients, primarily due to age-related testing limitations in younger children and the lack of routine DLCO availability at some participating centers. Consequently, lung function results should be interpreted with caution. To assess whether missing lung function data could introduce bias, we compared patients with and without available spirometry and DLCO measurements. Aside from expected age-related differences related to test feasibility, no clinically meaningful differences were observed between groups, supporting the assumption that missing data were largely non-informative. Patients with a history of HSCT typically undergo more structured pulmonary monitoring, which may increase the likelihood of lung function testing compared to other patients. Detailed comparisons are provided in Supplementary Tables 1 and 2.

HRCT evaluations in this study were based on non-standardized routine clinical reports without blinded review, which may have introduced subjectivity and interobserver variability in the radiological comparisons. The limited number of deaths (n = 14) and the unequal distribution of outcomes between the PID and SID groups precluded the use of multivariable regression analyses to identify independent predictors of mortality or disease progression. Performing such analyses could have resulted in model instability and overfitting, thereby reducing the reliability of the results.

This descriptive study involved multiple unadjusted comparisons across clinical and radiological variables, and no formal correction for multiple testing was applied due to small sample sizes in specific subgroups. Consequently, the risk of inflated type I error and coincidental findings cannot be excluded. Only four patients were lost to follow-up, rendering the group too small for meaningful statistical comparison, and no subgroup analyses were performed for these individuals. Therefore, statistically significant findings should be interpreted with caution, and the outcome comparisons presented should be considered descriptive and exploratory rather than causal. Future studies with larger multicenter cohorts and

prospective registry designs will be essential to develop adequately powered predictive models.

In conclusion, this study provides valuable insights into immunodeficiency-associated chILD, a field in which data remain limited. Our findings underscore the diverse etiologies and elevated mortality rates associated with these conditions. Immunodeficiency contributes to the complexity of chILD, resulting in more severe disease and greater management challenges. Both PID and SID play significant roles in chILD development, yet they exhibit distinct clinical courses and radiological patterns, highlighting the heterogeneity of disease expression.

The high rate of consanguinity, frequent sibling deaths, and family history of chronic lung disease in the PID group further reflect the hereditary burden. Long-term follow-up demonstrated a mortality rate nearly twice that reported in immunocompetent chILD cohorts, emphasizing the clinical severity of immunodeficiency-associated disease. These findings underscore the urgent need for earlier recognition, tailored diagnostic strategies, and more effective therapies. Future research should focus on optimizing treatment approaches and establishing structured long-term follow-up protocols to improve outcomes in this vulnerable population.

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Informed Consent: Written informed consent was obtained from all parents, guardians, or legal representatives for minor participants. Adult participants provided written informed consent for their own participation.

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

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