

Understanding Pulmonary Fibrosis in Pediatric Interstitial Lung Disease

A Comprehensive Analysis

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BACKGROUND: Childhood interstitial lung diseases (chILDs) encompass a wide range of rare, chronic respiratory disorders, with pulmonary fibrosis (PF) being the clinical entity closely associated with mortality and morbidity.

RESEARCH QUESTION: What is the prevalence and radiologic spectrum of PF in children with chILD, and how is it associated with pulmonary function and clinical characteristics?

STUDY DESIGN AND METHODS: This multicenter, retrospective observational cohort study used data from the Turkish Childhood Interstitial Lung Disease Registry as of January 2024. An experienced radiologist reviewed the chest CT scans for PF findings. Patients were divided into 2 groups based on the presence or absence of PF findings, and their clinical and demographic data were analyzed.

RESULTS: A total of 404 patients (47.5% female) from 25 centers were included. The median age was 137 months (interquartile range [IQR], 24-376 months). The median z score for weight was -1.02 (IQR, -8.8 to 6.88), and the median z score for height was -0.59 (IQR, -7 to 6.45). The median FEV₁ was 68% (IQR, 16%-127%), and the median diffusion capacity of the lungs for carbon monoxide (DLCO) was 66% (IQR, 21%-132%). The PF findings were as follows: reticular abnormalities, 34.9% of patients; cystic abnormalities, 21% of patients; traction bronchiectasis, 19.8% of patients; architectural distortion, 14.4% of patients; and honeycombing, 2.5% of patients. Two groups were compared based on the presence (n = 183) or absence (n = 221) of PF findings; the group with fibrotic findings showed a higher age and lower z score for weight ($P < .05$). Although no differences were found in PFT parameters between groups ($P > .05$), DLCO was lower in the fibrotic group ($P = .015$). The prevalence of PF was higher in patients with diffuse parenchymal lung disease (DPLD) group A disorders than in those with DPLD group B ($P = .014$).

INTERPRETATION: Our results show that PF is a common complication in chILD and becomes more pronounced with age, underscoring the importance of early detection. The higher rate of PF findings in patients with DPLD-A disorders suggests that children with surfactant dysfunction or alveolar developmental abnormalities may be at an increased risk of PF developing. PF may be more common in children with a lower DLCO score, with a DPLD-A disorder, or of an older age.

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KEY WORDS: chILD; diffuse parenchymal lung disease; pulmonary fibrosis

Take-Home Points

Research Question: What is the prevalence and radiologic spectrum of pulmonary fibrosis (PF) in children with childhood interstitial lung disease (chILD), and how is it associated with pulmonary function and clinical characteristics?

Results: PF was detected in 45% of children with chILD, was more frequent in group A diffuse parenchymal lung disease disorders, and was associated with older age and lower diffusion capacity of the lungs for carbon monoxide values.

Interpretation: Our results indicate that PF is a common radiologic finding in pediatric chILD, and early, systematic evaluation of key fibrotic CT imaging patterns—such as reticulation density, cystic abnormalities, traction bronchiectasis, architectural distortion, and honeycombing—can help to identify children at risk of fibrotic progression and can support planning for closer clinical management follow-up.

Childhood interstitial lung diseases (chILDs) encompass a broad spectrum of rare, chronic respiratory conditions primarily affecting infants and young children. These conditions often present with diffuse parenchymal abnormalities and comprise > 200 distinct clinical entities, many of which share similar clinical, radiologic, and histopathologic

features.¹ Although grouped under a single term, chILD disorders exhibit significant differences in their causes and clinical behavior. Diffuse parenchymal lung disease (DPLD) initially was defined and classified according to the histopathologic scheme proposed by Deutsch et al² in 2007. To address the variability and heterogeneity observed in chILD and to support a more systematic and standardized diagnostic approach, the chILD-European network, led by Griese et al³ in 2015, refined this framework and developed the comprehensive, dynamic DPLD classification system that is currently used for children. Under this system, childhood DPLDs are categorized into 2 main groups: group A DPLD (DPLD-A) and group B DPLD (DPLD-B). DPLD-A includes disorders that primarily present in infancy, such as developmental lung disorders, growth impairments with impaired alveolarization, surfactant dysfunction disorders, and early-onset chILD of unknown cause. Conversely, DPLD-B comprises conditions that can occur at any age during childhood and covers a wider, more diverse range of diseases, including chILDs associated with systemic or rheumatologic conditions, environmental or infectious exposures, primary or secondary immunodeficiencies, after transplant immune issues, and vascular abnormalities. Within this diverse group of disorders, pulmonary fibrosis (PF) development is a key factor affecting morbidity and mortality in various chILDs.²⁻⁴

ABBREVIATIONS: chILD = childhood interstitial lung disease; chILD-TR = Turkish Childhood Interstitial Lung Disease Registry; DLCO = diffusion capacity of the lungs for carbon monoxide; DPLD = diffuse parenchymal lung disease; DPLD-A = group A diffuse parenchymal lung disease; DPLD-B = group B diffuse parenchymal lung disease; ILD = interstitial lung disease; HSCT = hematopoietic stem cell transplantation; HRCT = high-resolution CT; IQR = interquartile range; MV = mechanical ventilation; NIV = noninvasive ventilation; PF = pulmonary fibrosis; PFT = pulmonary function testing; PH = pulmonary hypertension

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The challenge is performing pulmonary function testing (PFT) reliably to assess clinical severity in children younger than 6 years. This difficulty is compounded by the challenge of interpreting fibrotic changes in children, because their alveolar and vascular development is ongoing, which affects histopathologic and radiologic evaluations. Although PF is a well-defined end-stage feature and a strong prognostic marker in adult interstitial lung diseases (ILDs), its significance in children remains

uncertain.^{1,5-8} As a result, PF is still undercharacterized and likely underdiagnosed in chILD, highlighting a critical knowledge gap in pediatric respiratory medicine that requires further research and pediatric-specific criteria. This study aimed to investigate the prevalence of PF in chILD, its findings on high-resolution CT (HRCT) imaging of the lung, and its impact on disease severity using data from the Turkish Childhood Interstitial Lung Disease Registry (chILD-TR).

Study Design and Methods

This multicenter, retrospective cohort study is based on data from the chILD-TR as of January 2024. The chILD-TR was established in November 2021.⁹ All research procedures involving human participants followed the ethical principles set forth by the institutional ethics committee and received approval from the University Ethics Board. They were consistent with the tenets of the Declaration of Helsinki and its subsequent revisions or equivalent ethical guidelines. All individual participants gave written informed consent to participate. For participants younger than 18 years, permission was obtained from their parents or legal guardians. Written informed consent to publish clinical details and images was obtained from the patients or their legal guardians whose data or images are included in this article, or both.

Patients with a confirmed diagnosis of chILD, available HRCT imaging, and essential clinical data necessary for evaluating the diagnostic classification were included in the analysis. Patients were excluded if HRCT imaging or key clinical information needed for PF assessment or diagnostic classification were missing.

Each patient's clinical and demographic variables were collected, including sex, current age, age at symptom onset, age at diagnosis of chILD, duration of follow-up, neonatal history, parental consanguinity, presenting symptoms, growth z scores, physical examination findings, and radiologic assessments. The functional respiratory parameters included PFT results and, when available, diffusion capacity of the lungs for carbon monoxide (DLCO). Additional data included results from genetic analyses, use of supplemental oxygen, a history of mechanical ventilation (MV), hematopoietic stem cell transplantation (HSCT), and the patients' vital status (alive or deceased). According to the patients' medical records, video-assisted thoracoscopic surgery

was used to perform lung biopsies when histopathologic confirmation was necessary. All patients were divided into 2 groups based on the presence or absence of PF, and the demographic, clinical, and radiologic data were compared between the groups.

Ethics Approval

All research procedures involving human participants adhered to the ethical principles established by the institutional ethics committee (Gazi University Ethics Board, December 10, 2024, meeting 20; Identifier: 2025-14). They were consistent with the tenets of the Declaration of Helsinki and its subsequent revisions or equivalent ethical guidelines.

Classification of chILD

All patients with a confirmed diagnosis of chILD who meet the established criteria, as defined by the internationally recognized definition, are registered in the chILD-TR. On registration, patients are categorized systematically into 2 main diagnostic groups. The chILD-TR diagnostic categorization was based on the DPLD classification system developed by the multicenter chILD-European network. According to this framework, childhood DPLDs are categorized as DPLD-A and DPLD-B groups. In the chILD-TR, similar to the chILD-European network, the current subcategories of group A DPLD disorders, primarily appearing in infancy, include A1-DPLD, diffuse developmental disorders; A2-DPLD, growth abnormalities deficient alveolarization; A3-DPLD, infant conditions of undefined etiology; A4-DPLD, related to alveolar surfactant region; Ax-DPLD, unclear respiratory distress syndrome in mature neonate; and Ay-DPLD, unclear respiratory distress syndrome in the almost (30-36 weeks) mature neonate. The subcategories of group B DPLD disorders, which can occur at any age, include B1-DPLD, related to systemic disease processes; B2-DPLD, in the presumed immune intact host, related

to exposures (infectious or noninfectious); B3-DPLD, in the immunocompromised host or transplanted; B4-DPLD, related to the lung vessels' structural processes; B5-DPLD, related to reactive lymphoid lesions; and Bx-DPLD, unclear respiratory distress syndrome in the nonneonate.³

Pulmonary Function Testing

PFT was conducted in accordance with the standardized acceptability criteria outlined by the American Thoracic Society and European Respiratory Society for pediatric populations. The DLCO was measured using the single-breath method. Values between the fifth and 95th percentiles were considered to fall within the normal reference range.¹⁰ All spirometry and DLCO measurements were performed at the time of the chILD diagnosis.

Pulmonary Hypertension Evaluation

As part of routine clinical practice in Turkey, children with a diagnosis of chILD undergo annual transthoracic echocardiographic screening for pulmonary hypertension (PH) by pediatric cardiology specialists. In patients with echocardiographic findings suggestive of PH, confirmatory pulmonary artery pressure measurement is performed via cardiac catheterization.

Radiologic Evaluation

All patients' HRCT scans were transferred to the reporting workstation, where they were reviewed independently by an experienced pediatric radiologist masked to the patients' clinical data. Each scan was assessed systematically for radiologic features potentially indicative of PF; the presence or absence of reticular abnormalities, cystic changes, traction bronchiectasis, architectural distortion, and honeycombing was documented using a standardized binary (present or absent) reporting format. Honeycombing is defined as a distinct fibrotic pattern characterized by clustered, well-defined cystic airspaces mainly located in the subpleural and basal regions. These cystic spaces can be single or arranged in multiple stacked layers, with varying diameters and wall

thicknesses. Their presence indicates complete destruction of normal lung structure and signifies advanced fibrotic remodeling. Traction bronchiectasis is the dilatation of the bronchial lumen accompanied by thickened and irregular bronchial walls secondary to fibrosis. Cystic changes were characterized by air-filled lesions with central low attenuation, surrounded by walls of varying thickness and regularity, and occurring either within lung tissue or in subpleural regions. The cysts varied in size, reflecting the spectrum of cystic remodeling seen in fibrotic lung disease. In the context of fibrosis, cystic changes were evaluated alongside other fibrotic features. Architectural distortion is identified by the displacement of pulmonary vessels, airways, fissures, and septa. Reticular opacities, often located subpleurally, are defined as a collection of intersecting linear opacities that create a meshlike or netlike appearance. Many of these features, particularly reticular opacities, may appear either in isolation or alongside ground-glass opacities. Ground-glass opacity describes a region of increased attenuation in which the underlying bronchial and vascular structures remain visible. A focal or diffuse increase in pleural thickness or irregularity, commonly resulting from fibrosis, appears on a CT scan as a curvilinear soft tissue stripe located internal to the ribs and innermost intercostal muscles (Fig 1).^{6,11}

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 22.0 software (IBM Corp.). Descriptive statistics were reported as frequencies and percentages for categorical variables and as mean (SD) or median (interquartile range [IQR]) for continuous variables. Associations between categorical variables were examined using Pearson χ^2 test or Fisher exact test as appropriate. For comparisons between 2 independent groups, the Mann-Whitney *U* test was used for nonnormally distributed data, whereas the independent samples *t* test was applied for normally distributed variables. A *P* value of $< .05$ was considered indicative of statistical significance.

Results

A total of 667 patients with chILD were recorded in the chILD-TR in 2024; however, 263 patients were excluded because of missing HRCT imaging data, insufficient clinical information, diagnostic classification issues, or a combination thereof. Ultimately, 404 patients with

complete clinical data and available HRCT scans were included in the study. The study's flow diagram is presented in Figure 2.

The study group comprised 192 female patients (47.5%) and 212 male patients (52.5%). The median current age was 137 months (range, 24-376 months), the age at

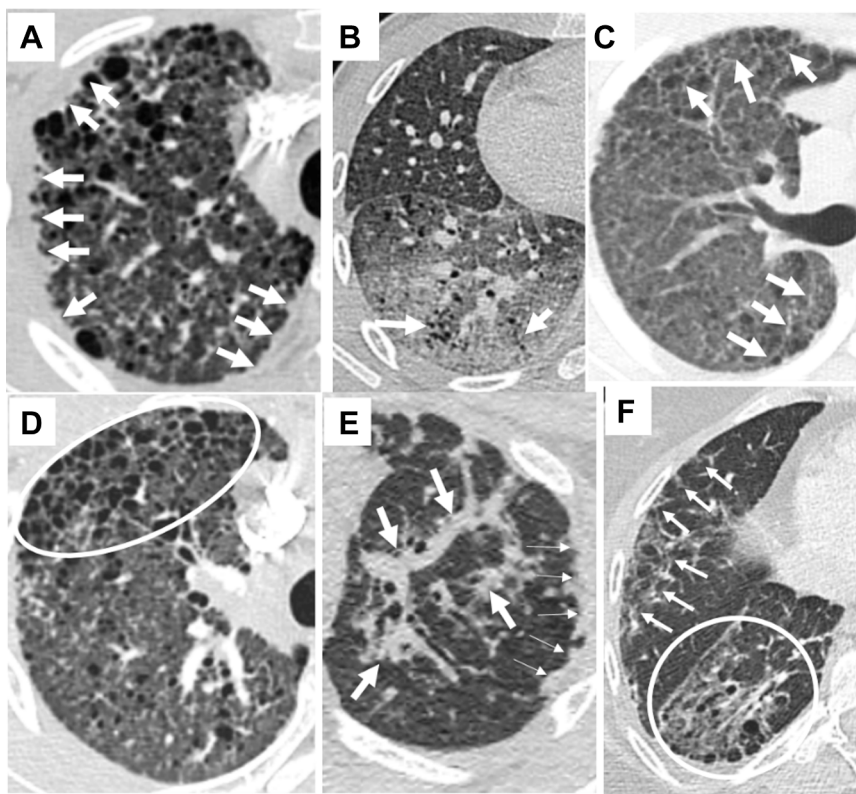


Figure 1 – A-F, Axial CT images obtained from different patients showing radiologic patterns potentially indicative of pulmonary fibrosis; irregular pleural thickening (arrows) with cystic changes (A), patchy ground-glass opacities in the right lower lobe with cystic changes (arrows) (B), diffuse ground glass with linear reticular opacities that create a meshlike or netlike appearance in subpleural region (arrows) (C), honeycombing pattern (within oval) (D), architectural distortion (thick arrows) and irregular pleural thickening (thin arrows) (E), traction bronchiectasis (within circle) in the right lower lobe with volume loss and linear reticular opacities creates a meshlike appearance in the subpleural region in the right middle lobe (arrows) (F).

symptom onset was 61 months (range, 14-267 months), and the age at chILD diagnosis was 78 months (range, 15-349 months). The median z score for weight was -1.02 (IQR, -8.80 to 6.88), and the median z score for height was -0.59 (IQR, -7 to 6.45). The most common presenting symptoms included cough ($n = 231$ [57.2%]) and dyspnea ($n = 148$ [36.6%]). Seventy-nine patients (19.6%) needed oxygen support, and 23 patients (5.7%) required MV support. A history of parental

consanguinity was noted in 148 patients (36.6%). The median FEV_1 was 68% (IQR, 16%-127%), the median FVC was 64% (IQR, 17%-136%), and the median $DLCO$ was 66% (IQR, 21%-132%). A history of HSCT was noted in 51 patients (12.6%). The median duration of oxygen requirement was 4 months (IQR, 0.5-172 months). Regarding ventilatory support, 18 patients required noninvasive ventilation (NIV), and 5 patients needed invasive MV. The median duration of MV was 3 months (IQR, 0.2-172 months). A total of 18 patients (4.5%) died. [Table 1](#) presents the demographic, clinical, PFT data, and lung biopsy results for all patients.

Forty-three patients underwent pulmonary biopsy: 16 patients from the group without PF and 27 patients from the group with PF. In the group without PF (16 patients), no findings of PF were noted in the pathology report. In the group with PF findings on HRCT imaging, the pathology reports indicate that 3 patients showed usual interstitial pneumonia with fibrotic findings, 3 patients showed pulmonary alveolar proteinosis, 2 patients showed pulmonary alveolar microlithiasis, 2 patients showed nonspecific interstitial pneumonia, 1 patient showed hypersensitivity pneumonia, and 1 patient showed pulmonary interstitial glycogenosis. One patient showed Langerhans cell histiocytosis, 1 patient

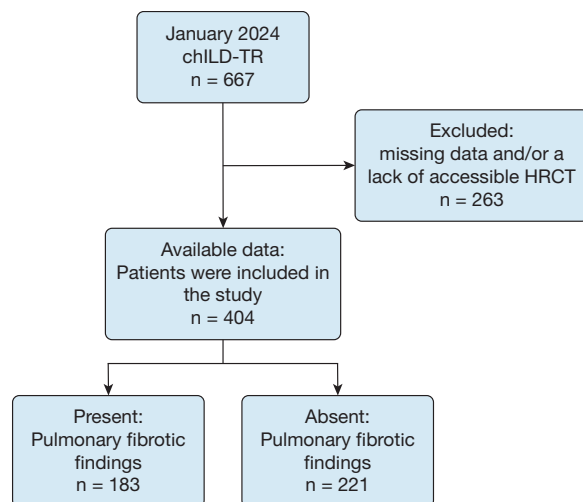


Figure 2 – Flow diagram of the study. chILD = childhood interstitial lung disease; HRCT = high-resolution CT.

TABLE 1] Demographic, Clinical, and PFT Data of All Patients (N = 404)

Variable	Data
Sex	
Female	192 (47.5)
Male	212 (52.5)
Current age, mo	137 (24 to 376)
Age at symptom onset, mo	61 (14 to 267)
Age at diagnosis of chILD, mo	78 (15 to 349)
z Score	
Weight	-1.02 (-8.80 to 6.88)
Height	-0.59 (-7 to 6.45)
BMI	-0.60 (-11.4 to 5)
Parents consanguinity	148 (36.6)
Symptoms	
Cough	231 (57.2)
Dyspnea	148 (36.6)
Feeding impairment	39 (9.7)
Cyanosis	26 (6.4)
Chest pain	23 (5.7)
Hemoptysis	17 (4.2)
Physical examination findings	
Crackles	150 (37.1)
Wheezing	138 (34.2)
Rhonchi	114 (28.2)
Retractions	71 (17.6)
Reduced breath sounds	62 (15.3)
Clubbing	58 (14.4)
Chest deformities	47 (11.6)
Hepatosplenomegaly	36 (8.9)
Murmurs	28 (6.9)
Stridor	4 (1)
Oxygen support	79 (19.6)
Time of oxygen requirement, mo	4 (0.5 to 172)
MV support	23 (5.7)
NIV	18 (4.4)
Invasive MV	5 (1.2)
Time of MV requirement, mo	3 (0.2 to 172)
Pulmonary hypertension	29 (7.2)
No. of exitus	18 (4.5)
History of HSCT	51 (12.6)
PFT findings	
FEV ₁ , % ^a	68 (16 to 127)
FVC, % ^a	64 (17 to 136)
FEF _{25%-75%} , % ^a	75 (11 to 68)

(Continued)

TABLE 1] (Continued)

Variable	Data
Dlco, % ^b	66 (21 to 132)
Lung biopsy	43 (10.6)

Data are presented as No. (%) or median (interquartile range). chILD = childhood interstitial lung disease; Dlco = diffusion capacity of lung for carbon monoxide; FEF_{25%-75%} = forced expiratory flow between 25% and 75% of forced vital capacity; HSCT = hematopoietic stem cell transplantation; MV = mechanical ventilation; NIV = noninvasive ventilation; PFT = pulmonary function testing.

^an = 81.^bn = 46.

showed pleuroparenchymal fibroelastosis, 1 patient showed granulomatous-lymphocytic ILD, 1 patient showed bronchiolitis obliterans organizing pneumonia, 1 patient showed granulomatous formation, and 1 patient showed organizing pneumonia. The pathology reports for the remaining 6 patients noted chronic fibrotic findings, chronic inflammation, and nonspecific findings, including intralobular septal thickening. For the 4 patients, the pathology report includes nonspecific findings, such as multicentric cells, inflammation, bronchial metaplasia, as well as any specific diagnostic findings. When evaluating the radiologic findings of PF, the most common finding was reticular abnormality in 141 patients (34.9%), followed by cystic changes in 85 patients (21%), traction bronchiectasis in 80 patients (19.8%), architectural distortion in 58 patients (14.4%), and honeycombing in 10 patients (2.5%). HRCT imaging findings of all patients with chILD are shown in [Table 2](#).

The comparison of groups based on PF findings showed no difference in sex ($P = .111$). The median current age, age at symptom onset, and age at diagnosis of chILD were lower in the group without PF findings ($P = .002$, $P = .011$, and $P < .001$, respectively). The median z score for weight was lower in the PF group ($P = .038$). A total of 14 patients (7.6%) required MV in the PF group, compared with 9 patients in the non-PF group ($P = .367$). Oxygen support was required in 51 patients (27.8%) in the PF group and in 28 patients (12.2%) in the nonfibrotic group, with a significantly higher need observed in the PF group ($P = 0.009$). The median Dlco value was 61% (IQR, 21%-113%) for the group with PF findings and 89% (IQR, 45%-132%) for the group without PF findings ($P = .015$). Comparison of the groups (the presence or absence of PF findings) is shown in [Table 3](#).

TABLE 2] HRCT Imaging Findings of All Patients With chILD

Variable	No. (%)
Pulmonary fibrosis findings	
Reticular abnormality	141 (34.9)
Cystic changes	85 (21)
Traction bronchiectasis	80 (19.8)
Architectural distortion	58 (14.4)
Honeycombing	10 (2.5)
Other findings	
Ground-glass opacities	205 (50.7)
Diffuse	91 (44.4)
Patchy	114 (55.6)
Mosaic perfusion	169 (41.8)
Nodule or nodular opacities	111 (27.5)
Pleural thickening or irregularity	77 (19)
Mediastinal lymphadenopathy	61 (15.1)
Emphysema	34 (8.4)
Pleural effusion	14 (3.5)

chILD = childhood interstitial lung disease; HRCT = high-resolution CT.

Although no statistically significant differences were detected between the groups based on the presence or absence of PF findings, the diagnoses of A4-DPLD (surfactant dysfunction disorders) were more prevalent in the group with PF findings present. Table 4 shows the comparison of groups based on the chILD-European classification. Different radiologic patterns of chILD are shown in Figures 3 and 4.

Discussion

PF plays an important role in the clinical progression of chILD; however, its prevalence, radiologic features, and clinical associations in children still are not well understood. This study, based on data from the chILD-TR, shows that PF is a significant clinical finding in children with chILD, present in 45.2% of the group, highlighting its notable frequency. Patients with PF tend to be older, to experience later symptom onset, and to receive a chILD diagnosis at an older age. They also have lower *z* scores for weight and reduced DLCO values compared with those without PF. This study offers a thorough overview of PF prevalence and associated HRCT imaging findings, improving understanding of the clinical profile of pediatric patients with PF within chILD.

The observed prevalence of PF in this cohort was higher than that reported in previous pediatric chILD studies. Although the reported prevalence of PF in pediatric

chILD varies widely, from 2% to 26% across studies, the higher prevalence in this cohort may be the result of several factors. First, the relatively advanced age at diagnosis suggests a potential delay in diagnosis, allowing more time for fibrotic changes to develop. Additionally, the high rate of parental consanguinity may indicate a genetic predisposition to fibrotic phenotypes, warranting further genetic analysis to identify underlying risk factors.¹²⁻¹⁴

In children with chILD, PF was linked to significantly lower weight and BMI *z* scores, indicating a poorer nutritional profile in this group. These patients may be more vulnerable to growth challenges because of increased respiratory workload and the overall burden of chronic respiratory disease. Therefore, early and comprehensive nutritional assessment, along with personalized dietary support, remain essential parts of clinical care. PF also was associated with older age at presentation and longer symptom duration before diagnosis, emphasizing the subtle and progressive nature of fibrotic changes in children. The observed PFT impairment further reflects disease severity in patients with PF. Incorporating regular nutritional monitoring and PFT into multidisciplinary follow-up plans can help to detect deterioration earlier and improve long-term management.^{5,15,16}

That fibrotic ILDs, particularly in advanced stages, impact pulmonary vascular structures negatively, thereby elevating the risk of right ventricular dysfunction, is well established. Although no significant differences in PH prevalence were noted between PF and non-PF groups in this cohort, the potential for cardiovascular complications linked to fibrotic patterns should not be disregarded, especially in the context of chronic hypoxemia and respiratory compromise. A systematic review of chILD PH indicated that pulmonary PH prevalence in pediatric chILD varies significantly, ranging from 1% to 64%, with PH markedly increasing mortality risk, up to 7-fold in some studies. Although pediatric data remain sparse, the effect of fibrotic remodeling on cardiac function highlights the need for careful monitoring for early signs of right ventricular dysfunction in children with fibrotic ILD. Therefore, incorporating routine cardiac assessments into clinical follow-up protocols and adopting early intervention strategies are essential in reducing cardiovascular morbidity in this high-risk group.¹⁷

Interestingly, the significant reduction in DLCO values observed in the PF group underscores the impact of

TABLE 3] Comparison of Groups Based on the Presence of PF Findings

Variable	Patients With PF Findings (n = 183)	Patients Without PF Findings (n = 221)	P Value
Sex			.111
Female	79 (43.2)	113 (51.1)	
Male	104 (56.8)	108 (48.9)	
Current age, mo	147 (24 to 376)	128 (25 to 334)	.002
Age at symptom onset, mo	67 (14 to 267)	55 (14 to 228)	.011
Age at diagnose of chILD, mo	90 (16 to 349)	70 (15 to 323)	< .001
Delay in diagnosis of chILD, mo	4 (0 to 272)	3 (0 to 173)	.040
z Score			
Weight	-1.24 (-7.25 to 6.88)	-0.87 (-8.8 to 2.56)	.038
Height	-0.72 (-7 to 5.94)	-0.53 (-6.67 to 6.45)	.088
BMI	-0.8 (-8.9 to 5)	-0.51 (-11.4 to 2.76)	.086
No. of hospital admissions last year	3 (1-25)	4 (0-39)	.653
Pulmonary hypertension	12 (6.6)	17 (7.7)	.660
MV support	14 (7.6)	9 (4)	.367
Oxygen support	51 (27.8)	28 (12.6)	.009
PFT findings			
No. of patients	36	45	
FEV ₁ , %	66 (16 to 113)	69 (18 to 127)	.374
FVC, %	63 (17 to 109)	66 (25 to 136)	.460
FEF _{25%-75%}	66 (11 to 168)	82 (13 to 148)	.509
DLCO			
No. of patients	24	22	
DLCO, %	61 (21 to 113)	89 (45 to 132)	.015
DPLD group			.014
A	46 (25.1)	36 (16.3)	
B	137 (74.9)	180 (81.4)	

Data are presented as No. (%) or median (interquartile range) unless otherwise indicated. Boldface indicate statistically significant results ($P < .05$). chILD = childhood interstitial lung disease; DLCO = diffusion capacity of the lungs for carbon monoxide; DPLD = diffuse parenchymal lung disease; FEF_{25%-75%} = forced expiratory flow between 25% and 75% of forced vital capacity; PF = pulmonary fibrosis; PFT = pulmonary function testing.

fibrosis on gas exchange, aligning with previous reports that identify DLCO as a sensitive marker of fibrotic alterations in chILD. Despite the overall stability in FVC values, the decline in DLCO suggests ongoing fibrotic remodeling, emphasizing its prognostic value in detecting subclinical fibrotic changes across the broader chILD population. Given the limited availability of DLCO data in younger children, further studies are warranted to validate its usefulness as an indicator of fibrotic transformation, potentially facilitating timely intervention in high-risk pediatric patients.^{1,18,19}

In our study, HRCT imaging findings revealed that the most common radiologic pattern of PF was reticular abnormality (34.9%), followed by cystic changes (21%), traction bronchiectasis (19.8%), architectural distortion (14.4%), and honeycombing (2.5%). These findings

align with previous studies indicating that reticular patterns, traction bronchiectasis, and cystic changes are early and common fibrotic markers in pediatric chILD, particularly in surfactant dysfunction-associated ILD. Simultaneously, the relatively high prevalence of cystic changes underscores the potential for surfactant dysfunction disorders to present with advanced fibrotic patterns. The high prevalence of cystic changes in our study may indicate a more advanced or progressive fibrotic process driven by underlying genetic conditions or surfactant dysfunction disorders. Cystic lesions potentially represent transitional stages preceding honeycombing, especially in children with risk factors. The low prevalence of honeycombing (2.5%) in this cohort is consistent with existing literature, because honeycombing is typically a more advanced fibrotic manifestation, more frequently reported in adult

TABLE 4] Comparison of Groups Based on chILD-European Classification

Classification	PF Finding		P Value
	With (n = 183)	Without (n = 221)	
A1, Diffuse developmental disorders	1 (0.5)	— ^a	
A2, Alveolarization deficiencies	14 (7.7)	14 (6.3)	
A3, Specific conditions of undefined cause	4 (2.2)	8 (3.6)	
A4, Surfactant dysfunction disorders	24 (13.1)	11 (5)	
Ax, Unclear RDS in the mature neonate	2 (1.1)	3 (1.4)	
Ay, Unclear RDS in the almost (30-36 wk) mature neonate	1 (0.5)	1 (0.5)	
B1, DPLD related to systemic disease processes	35 (19.1)	43 (19.5)	.050 ^b
B2, DPLD in the presumed immune-intact host, related to exposures (infectious or noninfectious)	67 (36.6)	88 (39.8)	
B3, DPLD in the immunocompromised or transplanted host	30 (16.4)	31 (14)	
B4, DPLD related to lung vessels structural processes	5 (2.7)	15 (6.8)	
B5, DPLD related to reactive lymphoid lesions	— ^a	3 (1.4)	
Bx, Unclear RDS in the nonneonate	— ^a	— ^a	
NA, Not available	— ^a	4 (1.8)	

Data are presented as No. (%) unless otherwise indicated. chILD = childhood interstitial lung disease; DPLD = diffuse parenchymal lung disease; PF = pulmonary fibrosis; RDS = respiratory distress syndrome.

^a— indicates that data are not available or not applicable.

^bP value represents the overall comparison between groups.

populations with idiopathic pulmonary fibrosis. The presence of cystic lesions may indicate an ongoing fibrotic transformation, underscoring the need for close radiologic and functional monitoring in genetically predisposed populations.^{1,18,20-22}

Among the pathophysiologic characteristics of chILD, injury mechanisms within the developing lung

significantly influence progression toward PF. Genetic factors, fetal or neonatal events, infections, drugs, toxins, and systemic diseases can damage the immature alveolar epithelium and capillary endothelium. When these injuries recur, the normal repair process is disrupted, leading to ongoing inflammation, fibroblast activation, excess extracellular matrix accumulation, and collagen deposition, ultimately causing fibrotic

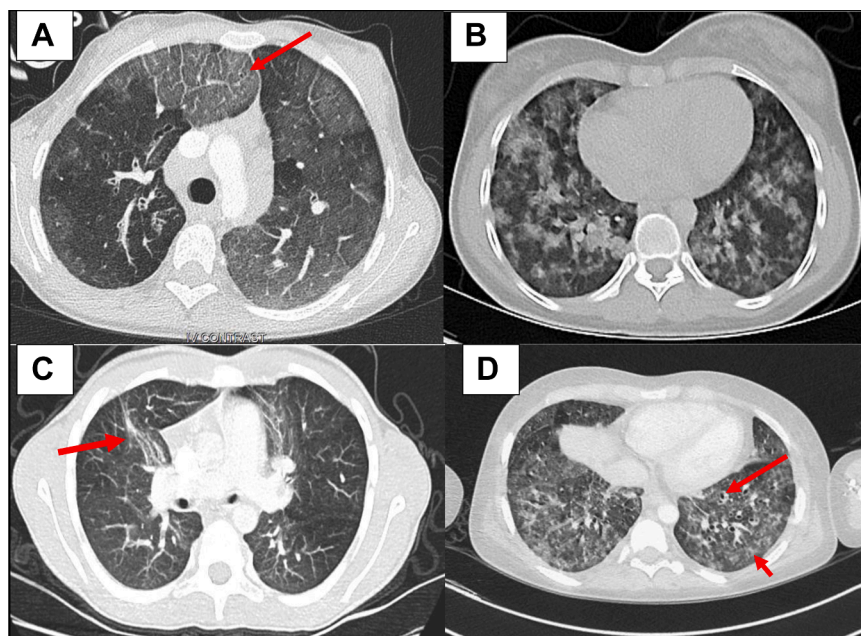
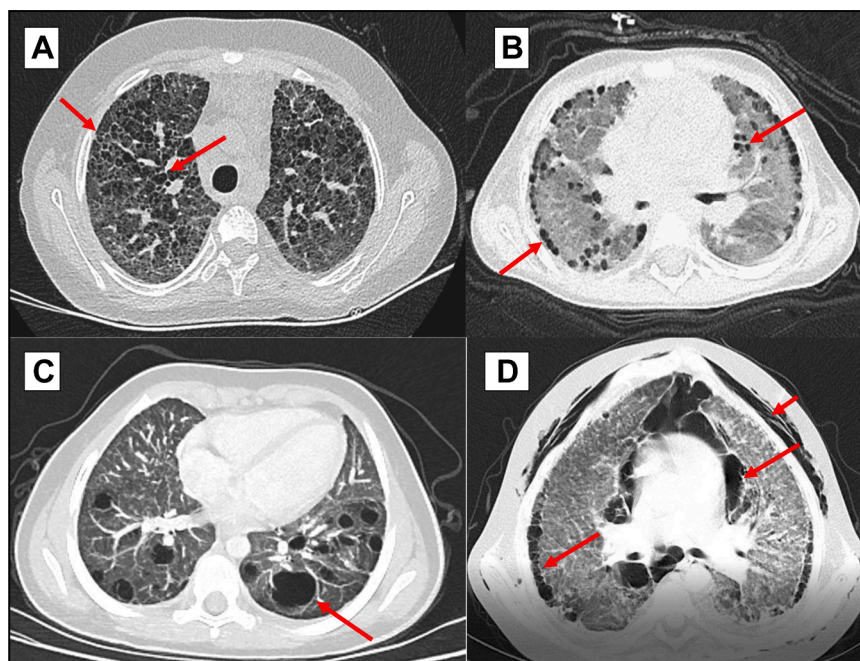


Figure 3 – A-D, Axial CT images showing different radiologic patterns of pulmonary fibrosis in patients with childhood interstitial lung disease: 17-year-old female patient with postinfectious bronchiolitis obliterans demonstrating mosaic perfusion and ground-glass opacities with superimposed interlobular septal thickening referring to a crazy paving pattern (arrow) (A), 20-year-old female patient with a diagnosis of pulmonary hemosiderosis demonstrating reticular opacities and patchy ground-glass opacities in both lungs' parenchyma (B), 13-year-old male patient with surfactant protein C deficiency demonstrating architectural distortion (arrow) (C), and 15-year-old female patient with a MUC5 mutation demonstrating ground-glass opacities, reticular densities (short arrow), and bronchiectasis (arrow) in both lungs suggesting a progressive fibrosis course (D).

Figure 4 – A-D, Axial CT images showing different cystic presentations of the patients with childhood interstitial lung disease: 12-year-old female patient with stimulator of interferon genes-associated vasculopathy with onset in infancy demonstrating multiple intraparenchymal cystic lesions with also honeycombing pattern (arrows) (A), 8-year-old female patient with a Down syndrome-associated alveolarization defect demonstrating subpleural and intraparenchymal multiple cysts (arrows) on diffuse ground-glass density (B), 8-year-old male patient with Langerhans cell histiocytosis demonstrating large cystic lesions (arrow) located in the parenchyma of both lungs (C), 9-year-old female patient with immunodeficiency (ZFX1 mutation) and postinfectious bronchiolitis obliterans resulting from recurrent lower respiratory tract infections demonstrating subpleural (arrows) and intraparenchymal multiple cysts on diffuse ground-glass density, pneumothorax, pneumomediastinum, subcutaneous emphysema (short arrow), and increased anteroposterior chest diameter (D).



remodeling. These disorders are linked to early epithelial vulnerability and impaired parenchymal growth, making these conditions more prone to fibrosis.²³ Consequently, it is suggested that the higher prevalence of increased need for supplemental oxygen observed in children with DPLD-A and PF in our study reflects earlier symptoms, longer diagnostic delays, and more severe growth impairment, indicating prolonged, unnoticed parenchymal injury during critical stages of lung development.

Regarding the classification of chILD subtypes, our findings showed a higher prevalence of PF in patients with DPLD-A than in those with DPLD-B. This distribution is noteworthy because it suggests that children with surfactant dysfunction or alveolar developmental abnormalities may be at a heightened risk of PF developing. Surfactant dysfunction mutations may indicate early alveolar damage, supporting the hypothesis that surfactant dysfunction could be an early indicator of progressive fibrosis. The proposed pathophysiologic mechanisms suggest that dysfunctional surfactant proteins contribute to alveolar collapse, chronic inflammation, and subsequent fibrotic remodeling. Specifically, mutations in *ABCA3* and *SFTPC* have been associated with early-onset fibrotic changes, characterized by structural lung damage that manifests as reticular patterns and cystic lesions. When evaluating the subcategories of DPLD-A and DPLD-B, although the difference was not

statistically significant in this cohort, the number of patients with A4-coded surfactant protein dysfunctions was significantly higher in the group with fibrotic changes than in those without fibrotic changes. Observing more pronounced fibrotic changes in patients carrying these mutations aligns with these findings and supports the existing literature. These findings support the concept that early-onset developmental disorders, particularly in infants with DPLD-A, carry a greater risk of progressive fibrosis and oxygen dependence, consistent with the current understanding of the mechanisms underlying chILD. Therefore, close monitoring of PF development is essential in these populations. Furthermore, B2-DPLD in presumed immune-intact hosts with infectious and noninfectious exposures, and B3-DPLD in patients who are immunocompromised or have undergone organ transplantation, are significant risk factors for PF. Additionally, the high rate of consanguinity observed in this cohort emphasizes the critical need for genetic screening to identify at-risk populations. This can enable earlier detection of children at risk of progressive fibrosis, allowing for timely intervention. This finding underscores the importance of diagnostic imaging and functional assessments for effective disease progression monitoring.^{6,18-20,24}

This study has several limitations. A total of 263 patients were excluded because of missing HRCT imaging or incomplete clinical data, which may have

introduced variability into the analyses and reduced the consistency of specific subgroup evaluations. Although our research highlights radiologic markers of PF, the lack of histopathologic correlation limits our ability to identify fibrotic patterns definitively. Although PF development often shows similar radiologic and clinical features across different chILD types, chILD remains a diverse group of disorders with various underlying causes, limiting direct comparisons between subgroups. Spirometry and DLCO measurements were available for only some patients because of age-related feasibility challenges and limited access, potentially limiting the depth of functional assessment. The single-country design could restrict the generalizability of the findings, although the cohort includes patients across all major chILD diagnostic subgroups. These factors might influence the applicability of our results; however, a careful inclusion process was necessary to ensure diagnostic accuracy and to minimize bias from misclassification.

Interpretation

Information about PF in children is quite limited and not yet defined clearly. PF seems to be an important and common part of pediatric chILD, significantly affecting respiratory function and overall prognosis. Our findings highlight the crucial role of early radiologic and

functional assessments in identifying high-risk patients. Delayed diagnosis, older age at diagnosis, and longer symptom duration are linked to worsening fibrotic changes, stressing the need for prompt intervention. Notably, the higher prevalence of fibrotic patterns seen in patients with DPLD-A emphasizes the importance of closer monitoring and earlier treatment in this group, because they might face an increased risk of progressive fibrosis. This also demonstrates the usefulness of HRCT imaging in detecting early fibrotic changes. Based on our findings, this patient group is among the largest studied in PF and will provide valuable insights into the literature. Further international, multicenter studies are needed to confirm these results across larger, more diverse populations. Future longitudinal studies that include genetic analyses and targeted treatments are vital for understanding better the natural course of PF in pediatric chILD and for improving clinical outcomes.

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Data availability: The data supporting the findings of this study can be obtained from the corresponding author on reasonable request.

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