European Journal of Pediatrics
https://doi.org/10.1007/s00431-023-05290-9

RESEARCH

Childhood interstitial lung disease in Turkey: first data from the national registry

Halime Nayır-Büyükşahin[1,2] · Nagehan Emiralioğlu[1] · Ayşe Ayzıt Kılınç[3] · Saniye Girit[4] · Ebru Yalçın[1] · Tuğba Şişmanlar Eyüboğlu[5] · Nazan Çobanoğlu[6] · Güzin Cinel[7] · Sevgi Pekcan[8] · Yasemin Gökdemir[9] · Berna Oğuz[10] · Diclehan Orhan[11] · Deniz Doğru[1] · Uğur Özçelik[1] · Azer Kılıç Başkan[3] · Hüseyin Arslan[3] · Haluk Çokuğraş[3] · Zeynep Reyhan Onay[4] · Sinem Can Oksay[4] · Deniz Mavi Tortop[4] · Ayşe Tana Aslan[5] · Handan Kekeç[5] · Fazılcan Zirek[6] · Merve Nur Tekin[6] · Figen Gülen[12] · Bahar Girgin Dindar[12] · Sanem Eryılmaz Polat[7] · Salih Uytun[7] · Aslı İmran Yılmaz[8] · Gökçen Ünal[8] · Ela Erdem Eralp[9] · Bülent Karadağ[9] · Melih Hangül[13] · Mehmet Köse[14] · Beste Özsezen[15] · Erkan Çakır[16] · Ayşen Bingöl[17] · Mina Hızal[18] · Gökçen Kartal Öztürk[19] · Zeynep Seda Uyan[20] · Tuğba Ramaslı Gürsoy[21] · Mahir Serbes[22] · Nural Kiper[1]

Received: 23 August 2023 / Revised: 9 October 2023 / Accepted: 14 October 2023

Abstract

The childhood interstitial lung diseases (chILD) Turkey registry (chILD-TR) was established in November 2021 to increase awareness of disease, and in collaboration with the centers to improve the diagnostic and treatment standards. Here, the first results of the chILD registry system were presented. In this prospective cohort study, data were collected using a data-entry software system. The demographic characteristics, clinical, laboratory, radiologic findings, diagnoses, and treatment characteristics of the patients were evaluated. Clinical characteristics were compared between two main chILD groups ((A) diffuse parenchymal lung diseases (DPLD) disorders manifesting primarily in infancy [group1] and (B) DPLD disorders occurring at all ages [group 2]). There were 416 patients registered from 19 centers. Forty-six patients were excluded due to missing information. The median age of diagnosis of the patients was 6.05 (1.3–11.6) years. Across the study population ($n=370$), 81 (21.8%) were in group 1, and 289 (78.1%) were in group 2. The median weight z-score was significantly lower in group 1 (-2.0 [-3.36 to -0.81]) than in group 2 (-0.80 [-1.7 to 0.20]) ($p<0.001$). When we compared the groups according to chest CT findings, ground-glass opacities were significantly more common in group 1, and nodular opacities, bronchiectasis, mosaic perfusion, and mediastinal lymphadenopathy were significantly more common in group 2. Out of the overall study population, 67.8% were undergoing some form of treatment. The use of oral steroids was significantly higher in group 2 than in group 1 (40.6% vs. 23.3%, respectively; $p=0.040$).

Conclusion: This study showed that national registry allowed to obtain information about the frequency, types, and treatment methods of chILD in Turkey and helped to see the difficulties in the diagnosis and management of these patients.

What is Known:

• *Childhood interstitial lung diseases comprise many diverse entities which are challenging to diagnose and manage.*

What is New:

• *This study showed that national registry allowed to obtain information about the frequency, types and treatment methods of chILD in Turkey and helped to see the difficulties in the diagnosis and management of these patients. Also, our findings reveal that nutrition should be considered in all patients with chILD, especially in A-DPLD disorders manifesting primarily in infancy.*

Keywords Interstitial lung disease · Childhood · Registry

Abbreviations

BAL	Bronchoalveolar lavage
ChILD	Childhood interstitial lung diseases
ChILD-TR	ChILD registry system in Turkey
CT	Computed tomography

Communicated by Peter de Winter

Extended author information available on the last page of the article

Published online: 25 October 2023

DLCOadj	Adjusted diffusion capacity for carbon monoxide
DPLD	Diffuse parenchymal lung disease
GERD	Gastroesophageal reflux disease
FVC	Forced vital capacity
FEV1	Forced expiratory volume in 1 s
NEHI	Neuroendocrine cell hyperplasia of infancy
TLC	Total lung capacity
WLL	Whole-lung lavage

Introduction

Children's interstitial lung disease (chILD) is a heterogeneous group of diseases that diffusely affects the lungs, the incidence of which is growing with the increasing awareness of physicians [1]. ChILD refers to diffuse parenchymal lung disease (DPLD) in children because it may involve the interstitium, alveoli, distal small airways, and/or terminal bronchioles [2, 3]. ChILD is divided into two main groups based on the etiology and pathology; A-DPLD disorders manifest primarily in infancy and B-DPLD disorders occurring at all ages [4–6]. Although early diagnosis provides better management of patients with chILD, the highly variable clinical manifestations lead to challenging and often delayed diagnosis and treatment [7].

Patient registries allow for examining data on trends and clinical outcomes among patients and investigating the natural history of a disease [8]. The national chILD registry system in Turkey (chILD-TR) was established by Hacettepe University to increase disease awareness and diagnostic and treatment standards in collaboration with specialist centers in the follow-up of patients with chILD to help create a profile of the clinical and demographic characteristics of the patients in our country.

The primary aim of this report was to present the establishment of the chILD-TR and demonstrate the characteristics of patients who registered in the first year. Our secondary aim is to evaluate the differences between the two main groups regarding clinical findings, diagnostic examination tools, and treatment modalities.

Methods

Study design

This was a prospective cohort study, and data were collected using a data-entry software system from the chILD-Turkey registry. Patients registered between November 2021 to January 2023 were included in the study. All patents with suspected chILD, according to Kurland et al.'s [5] definition, were included in the registry.

The chILD-Turkey registry was established in November 2021. In the national registry, diseases were grouped according to the chILD-EU study group classification [9]. The category of the A-DPLD disorders manifesting primarily in infancy group were A1 (diffuse developmental disorders), A2 (alveolarization deficiencies), A3 (specific conditions of undefined etiology), A4 (surfactant dysfunction disorders), Ax (unclear respiratory distress syndrome in the mature neonate), and Ay (unclear respiratory distress syndrome in the almost mature neonate). The category of the B-DPLD disorders occurring at all ages group were B1 (DPLD related to systemic disease processes), B2 (DPLD in the presumed immune-intact host, related to exposures [infectious/non-infectious]), B3 (DPLD in the immunocompromised or transplanted host), B4 (DPLD related to lung vessels structural processes), B5 (DPLD related to reactive lymphoid lesions), and Bx (unclear respiratory distress syndrome in the non-neonate).

The Registry's software was specially developed for chILD. Every participating center can only access their patients' data via personal usernames and passwords. Data consist of demographic, examination, and laboratory information at first admission, epicrisis with detailed information including diagnostic examinations and treatment, and annual follow-up information. The patients' names are not entered into the registry. Each patient is allocated a unique code. Each patient gave age-appropriate consent, and their caregiver gave written informed consent before any data were entered.

Patients and procedures

Demographic data; clinical features; personal/family history, including parent consanguinity and history of child death in the family; pulmonary function as measured using forced vital capacity (FVC); forced expiratory volume in 1 s (FEV1); adjusted diffusion capacity for carbon monoxide (DLCOadj) and total lung capacity (TLC); six-minute walking test; bronchoscopy findings; chest computed tomography (CT) findings; lung biopsy results; and treatments were obtained from the registry software.

DPLD disorders manifesting primarily in infancy (group 1) and DPLD disorders occurring at all ages (group 2) constituted the two main groups. The demographic characteristics; clinical, laboratory, and chest CT findings; diagnoses; and treatment characteristics of the patients were compared between the main groups.

Statistical analysis

Statistical analyses were performed using the SPSS 22 software package (IBM Corp.). Normally distributed continuous variables were analyzed using Student's *t*-test and expressed as mean ± standard deviation (SD). Nonnormally distributed

continuous variables were analyzed using the Mann–Whitney *U* test and expressed as median (1st–3rd quartiles). Variables suitable for normal distribution were assessed using Shapiro–Wilk tests. Categorical variables are presented as percentages (%) and were analyzed using the Chi-square (χ [2]) test (with or without continuity correction) or Fisher's exact test. Values of $p < 0.05$ were considered statistically significant.

Results

Clinical presentation and characteristics of the study population

From November 2021, when the registration system was established, to January 2023, 416 patients (53.5% male) from 19 centers were enrolled in the database. Forty-six patients were excluded from the study due to missing information. The flowchart of inclusion and the diagnosis group in the study is shown in Fig. 1. The most common subdiagnosis among A-DPLD disorders manifesting primarily in infancy was A3 (including surfactant metabolism disorders), whereas it was B2 (related to exposures, including an immune-intact host) among B-DPLD disorders occurring at all ages. The distribution of percentages of subgroup diagnoses of chILD in the study is shown in Fig. 2. The median age at diagnosis of the patients was 6.05 (range, 1.3–11.6) years. The demographic, clinical, and examination findings of the study population are given in Table 1.

The median age at diagnosis of the patients was 1.01 (range, 0.3–4.2) years in group 1 and 7.7 (3.0–12.1) years in group 2. The onset of symptoms was similar between the two main groups. Tachypnea (49.3%) was significantly higher in group 1, and cough (61.2%) was the most common symptom in group 2. Neonatal intensive care history was significantly higher in group 1 than in group 2 (49.4% vs. 17.3%, respectively; $p < 0.001$). Weight *z*-scores and height *z*-scores were significantly lower in group 1 than in group 2 [median weight *z*-scores − 2.0 vs. − 0.80, respectively ($p < 0.001$), and median height *z*-scores: − 0.9 vs. − 0.54, respectively ($p = 0.045$)]. The rate of gastroesophageal reflux disease (GERD) was 10% among the study population. And 2.1% ($n = 8$) of the study population had gastrostomy.

Pulmonary function tests

Eighty-nine (22.8%) patients had spirometry. There was no statistical difference between group 1 and group 2 in terms of FVC% ($p = 0.165$) and FEV1% ($p = 0.606$). The mean DLCOadj was significantly lower in group 1 than in group 2 (42 ± 9 vs. 74 ± 26, $p = 0.007$). The distribution of spirometry results by subcategories among DPLD disorders occurring at all ages is given in Fig. 3.

Chest CT scan

Three hundred forty-two (92.4%) of 370 patients had at least one chest CT. In terms of chest CT findings, and ground-glass opacities were significantly higher in group 1 than in group 2 (79.1% vs. 52.9%, $p < 0.001$; 13.8% vs. 3.3%, $p = 0.004$, respectively), and nodules or nodular opacities, bronchiectasis, mosaic perfusion, and mediastinal lymphadenopathy

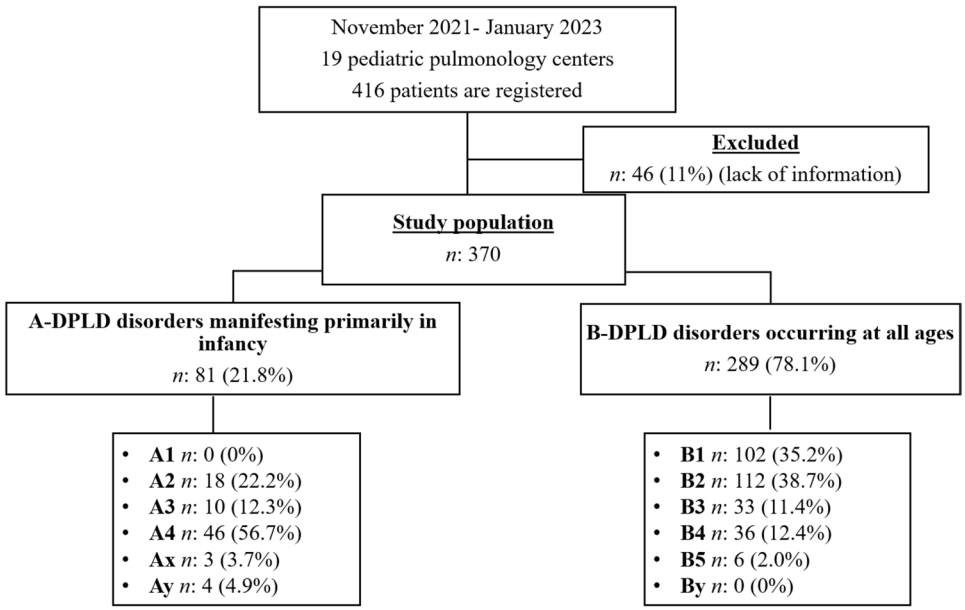

Fig. 1 Flow chart of inclusion and the diagnosis group in the study

Abbreviations: DPLD: Diffuse parenchymal lung diseases.

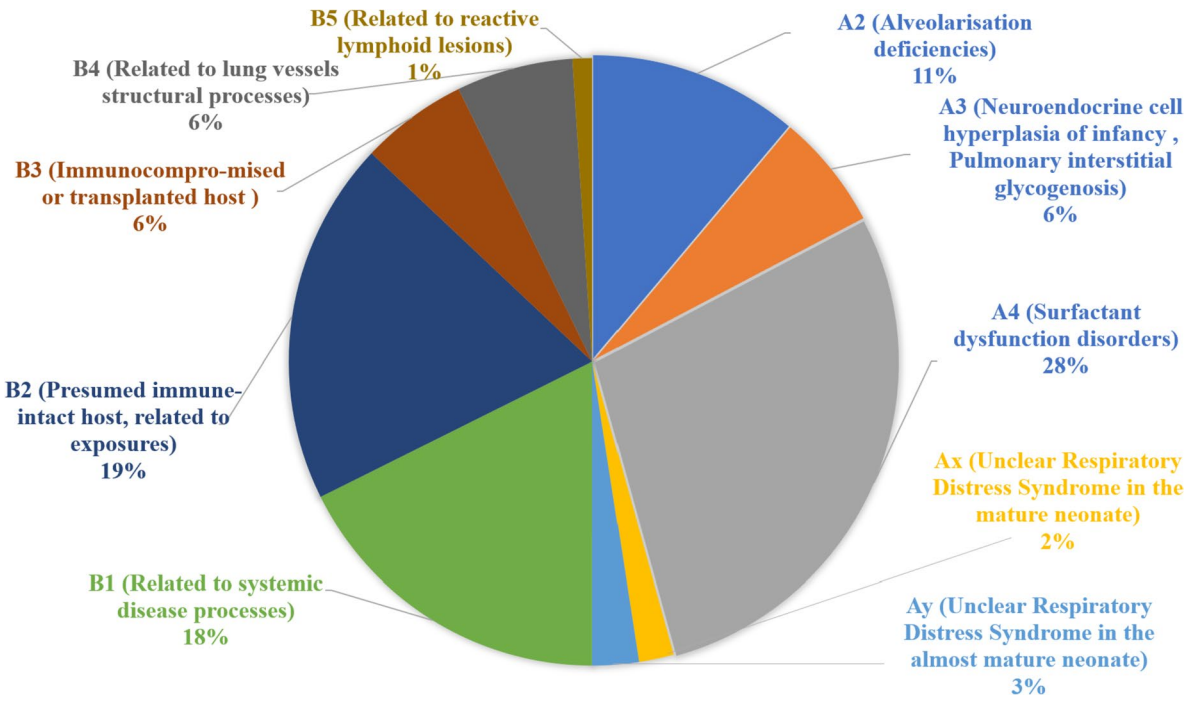

Fig. 2 Distribution of percentage of subgroups diagnoses of chILD among study population

were significantly lower in group 1 than in group 2 (20.8% vs. 31.8%, $p=0.049$; 18.1% vs. 2.7%, $p<0.001$; 15.2% vs. 45.1%, $p<0.001$; 2.7% vs. 20%, $p<0.001$; respectively). A comparison of clinical features and chest CT between group 1 and group 2 is given in Table 2.

Bronchoalveolar lavage

Bronchoscopy was performed in 141 (39.2%) patients; 17 (12.1%) had bacterial growth in the bronchoalveolar lavage (BAL). No congenital anomalies that could mimic chILD were detected in the bronchoscopies of any patients.

Genetic tests

Genetic examinations were performed on 122 (30.9%) patients. Positive findings among genetic tests were as follows: 15 patients had surfactant metabolism-related mutations (six were *ABCA3*, five were *SFTPC*, two were *NKX2-1*, one was *CSF2RB*, one was *SFTPB*), three patients had telomere-related mutations, three patients had sodium phosphate co-transporter gene *SLC34A2* mutations, two patients had *STAT3* mutations, one patient had a *FARSB* mutation, and one patient had a *MARS* mutation.

Lung biopsy

Lung biopsy was performed on 53 (14.3%) patients. Nine of the 53 patients had fibrosis in their lung biopsies. There was no significant difference between the groups in terms of fibrosis in lung biopsies.

Treatments

Out of the overall study population, 67.8% were undergoing some form of treatment. The use of oral steroids was significantly higher in group 2 than in group 1 (40.6% vs. 23.3%, respectively; $p=0.040$). There was no significant difference between the groups in terms of inhaled steroid, pulse steroid, and hydroxychloroquine treatment. The treatments used apart from steroid and hydroxychloroquine treatments were immunosuppressive therapy (9%) and other treatments (14.5%) such as whole-lung lavage (WLL), etidronate, atorvastatin, and endobronchial fresh frozen plasma. A comparison of treatments between group 1 and group 2 is given in Table 3.

Table 1 Demographic, clinical, and examination findings of the study population

	Overall study population ($n=370$)	DPLD disorders manifesting primarily in infancy ($n=81$)	DPLD disorders occurring at all ages ($n=289$)
Demographic and clinical findings, *n* (%)			
• Male	198 (53.5)	46 (56.7)	152 (53.5)
• Parent consanguinity	148 (40)	38 (46.9)	110 (38.0)
• History of child death in the family	32 (8.6)	11 (13.5)	21 (7.2)
• Family history of chronic disease	33 (8.9)	12 (14.8)	21 (7.2)
• Referral for lung transplant	15 (4.1)	1 (1.2)	14 (4.8)
• Exitus	20 (5.4)	8 (9.8)	12 (4.1)
Respiratory system examination findings			
• Saturation, median (Q1–Q3)	96 (93–98)	95 (86–98)	96 (95–98)
• Clubbing, *n* (%)	51 (13.8)	13 (16)	38 (13.1)
• Chest deformity, *n* (%)			
Pectus carinatum	25 (6.7)	5 (6.1)	20 (6.9)
Pectus excavatum	22 (5.9)	8 (9.8)	14 (4.8)
• Auscultation findings, *n* (%)			
Decreased breath sounds	58 (15.7)	10 (12.3)	48 (16.6)
Fine rales	119 (32.2)	30 (37.0)	89 (30.7)
Roncus	76 (20.5)	12 (14.8)	64 (22.1)
Wheezing	47 (12.7)	9 (11.1)	38 (13.1)
Extrapulmonary examination findings, *n* (%)			
• Murmur	27 (7.3)	9 (11.1)	18 (6.2)
• Hepatosplenomegaly	43(11.6)	6 (7.4)	37 (12.8)
• Lymphadenopathy	19 (5.1)	1 (1.2)	18 (6.2)
• Abnormal finding in neurologic examination	28 (7.6)	6 (7.4)	22 (7.6)
Pulmonary function test findings, mean (SD)			
• Forced expiratory volume in 1 s % ($n=89$)	78 (25)	75 (17), $n=9$	78 (26), $n=80$
• Forced vital capacity % ($n=89$)	75 (24)	69 (12), $n=9$	76 (25), $n=80$
• Diffusing lung capacity for carbon monoxide (Adj) ($n=56$)	72 (26)	42 (9), $n=3$	74 (26), $n=53$
• Total lung capacity ($n=9$)	96 (13)	70, $n=1$	99 (9), $n=9$
• Six-minute walk test (m) ($n=56$)	447 (103)	435 (129), $n=8$	448 (100), $n=48$

DPLD diffuse parenchymal lung disease

Discussion

This study showed that national registry allowed to obtain information about the frequency, types, and treatment methods of chILD in Turkey and helped to see the difficulties in the diagnosis and management of these patients. According to our results, the frequency of B-DPLD disorders occurring at all ages was higher. Second, A-DPLD disorders manifesting primarily in the infancy group had worse nutritional status. Finally, prominent chest CT findings changed with advancing age; ground-glass opacities were more common in early ages; and nodular opacities, bronchiectasis, mosaic perfusion, and mediastinal lymphadenopathy were more common in older ages.

For chILD, both national and international registry systems (chILD EU in Europe, chILD Research Network (chILDRN) in the USA, and the chILDRANZ in Australia and New Zealand) have been developed by bringing patient data together from specialist centers. These registries provide a better understanding of the disease. For instance, ChILD-EU published studies on many special topics such as diagnosis, treatment, describing pulmonary exacerbations, a randomized controlled trial of hydroxychloroquine, the cost of the disease, and much more [10–13]. Therefore, ChILD-EU collaboration has made a great contribution to the diagnosis, management, and treatment of the chILD. Casey et al. [14] summarized the crucial contribution of chILDRN from the first thought of chILD being different from adult ILD to the recently published first clinical trial, which was about nintedanib for fibrotic diffuse lung disease in chILD. Apart from research, this process also involved many multidisciplinary team meetings for patient care and education for both physicians and families. McKnight et al. [15] reported on the establishment of chILDRANZ, from its background to

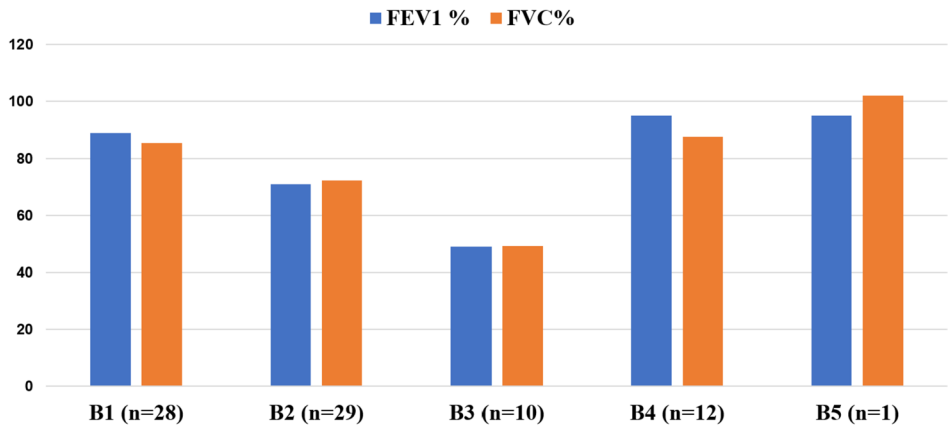

Fig. 3 Distribution of spirometry results by subcategories among diffuse parenchymal lung disease disorders occurring at all ages

Abbreviations: FEV1%: Forced expiratory volume in 1 second %; FVC: Forced vital capacity %.

date. They stated that in the past, only one physician was dealing with this issue, and all patients in the country had to go to one center, so they started to train other physicians in the country on chILD, later establishing chILDRANZ, and now physicians are included in chILDRN's meetings. In light of these reports about the benefits of registries and the high number of patients who entered the chILD-TR registry in the first year, we expect that chILD-TR will help improve the diagnosis and treatment of patients in our country.

Nevel et al. [16] reported the initial enrolment cohort in chILDRN in which neuroendocrine cell hyperplasia of infancy (NEHI) accounted for 23% of their 683 patients. By contrast, NEHI made up 1.8% of our cohort. In the ChILD-EU report of 346 patients, the largest proportion of the DPLD disorders manifesting primarily in the infancy group was subgroup A4 (22.3%), whereas it was B1 (15.6%) in the all-ages group. In our cohort, A4 was the most common subgroup among DPLD disorders manifesting primarily in the infancy group, likewise the chILD-EU report; however, B2 was the most common DPLD disorder occurring in the all-ages group.

Children need more calories when they work harder to breathe, so proper nutrition is especially emphasized for patients with chILD by the chILD-EU [17]. In our cohort, weight *z*-scores and height *z*-scores were significantly lower in group 1 than in group 2. Neonatal intensive care history, which means breathing started with difficulty from the first moment of life, was significantly higher in group 1 than in group 2. We wanted to draw attention to the fact that group 1 had worse nutrition status than group 2 because DPLD disorders manifesting primarily in infancy group progress more severely. Nevertheless, the median weight *z*-score (−2.0) was also lower in group 2.

It is well known that poor nutrition status has a negative impact on chronic lung diseases. Although there are no studies in this regard in chILD, studies on adult ILD have shown that poor nutritional status and even weight loss (≥2 kg within 1 year) are factors that independently shorten life expectancy [18, 19]. Another reason for low weight for patients with chILD can be insufficient feeding due to hypoxemic events interrupting nutrition [20]. Stubbs et al. [21] showed that this problem could be managed via a multidisciplinary feeding treatment approach. In this report, the team worked successfully with families to develop a safety plan for hypoxemic events during mealtimes for 3-year-old patients. Another important point that should be highlighted is gastroesophageal reflux disease (GERD), one of the factors suggested to be associated with the etiopathogenesis of chILD due to repeated episodes of microaspiration of gastric contents into the respiratory tract, which leads to alveolar inflammation and fibrotic remodeling [22]. Dziekiewicz et al. [23] prospectively determined the frequency and characteristics of GERD in children with chILD. They enrolled 62 patients, and all underwent 24-h multichannel intraluminal pH-impedance monitoring, and GERD was diagnosed in 32.3% of the study population. In our cohort, 10% of the study population had GERD. When these studies are combined, it is worth noting that when patients are diagnosed as having chILD, nutrition and the associated conditions and the necessary steps to improve nutrition such as multidisciplinary feeding treatment should be among the main treatment goals.

Pulmonary function tests (PFT) are one of the main tests in the practice of evaluating respiratory tract diseases, and it is recommended to be among the diagnostic examinations in chILD [5, 10, 24]. Furthermore, Matties et al. [25] used FEV1 and FVC as anchors to predict minimal important difference, which is defined as the smallest change in a parameter that is perceived as important and that would prompt a physician to change the treatment in chILD. However, there is a large gap in the knowledge about PFT in chILD. Accordingly, Ring et al. [26] aimed to analyze the literature regarding PFT among patients with chILD. They showed

Table 2 Comparison of clinical features and chest computed tomography

	DPLD disorders manifesting primarily in infancy (*n* = 81)	**DPLD disorders occurring at all ages (*n* = 289)**	***p* Value**
Age at diagnosis, median (Q1–Q3)	1.01 (0.3–4.2)	7.7 (3.0–12.1)	**< 0.001**
Time between the onset of symptoms and the time of admission to the hospital (months), median (Q1–Q3)	4.21 (0.95–12.98)	4.27 (0.76–31.7)	0.595
How to start symptoms? (*n, %*)	63 (77.7)	230 (79.5)	
• Suddenly	24 (38.0)	64 (27.8)	0.220
• Insidiously	28 (44.4)	104 (35.9)	
• Suddenly with respiratory infection	11 (13.5)	62 (21.4)	
Findings at presentation (*n, %*)			
• Chest pain	2 (2.4)	23 (7.95)	0.219
• Dyspnea	28 (34.5)	94 (32.5)	0.223
• Cough	30 (37.0)	177 (61.2)	**< 0.001**
• Fever	3 (3.7)	23 (8.6)	0.414
• Tachypnea	40 (49.3)	90 (31.1)	**0.003**
• Wheezing	16 (19.7)	81 (28.0)	0.321
• Hemoptysis	0 (0)	20 (6.9)	0.052
• Recurrent infection	29 (35.8)	101 (34.9)	0.926
Neonatal intensive care history (*n, %*)	40 (49.4)	50 (17.3)	**< 0.001**
Feeding issues and nutrition status			
• Gastroesophageal reflux disease (*n, %*)	8 (9.8)	29 (10.0)	0.967
• Gastrostomy (*n, %*)	4 (4.93)	4 (1.38)	0.073
• Weight *z*-score**,** median (Q1–Q3)	− 2.0 (− 3.36 to − 0.81)	− 0.80 (− 1.7 to 0.20)	**< 0.001**
• Height *z*-score**,** median (Q1–Q3)	− 0.9 (− 1.95 to − 0.10)	− 0.54 (− 1.52 to 0.24)	**0.045**
Chest computed tomography findings (*n, %*)	72 (88.8)	270 (93.4)	
• Linear or reticular opacities	20 (27.7)	61 (22.5)	0.449
• Nodules or nodular opacities	15 (20.8)	86 (31.8)	**0.049**
• Ground-glass opacities	57 (79.1)	143 (52.9)	**< 0.001**
• Focal consolidation	17 (23.6)	55 (20.3)	0.754
• Cystic lesions	12 (16.6)	30 (11.1)	0.250
• Honeycombing	7 (9.7)	14 (5.1)	0.188
• Emphysema	9 (12.5)	23 (8.5)	0.412
• Bronchial wall thickening	16 (22.2)	85 (31.4)	0.076
• Bronchiectasis	2 (2.7)	49 (18.1)	**< 0.001**
• Mosaic perfusion	11 (15.2)	96 (35.5)	**< 0.001**
• Hyperaeration	18 (25)	46 (17.0)	0.141
• Pleural effusion	3 (4.1)	12 (4.4)	0.880
• Fibrosis	9 (12.5)	33 (12.2)	0.908
• Interseptal thickening	29 (40.2)	83 (30.7)	0.187
• Mediastinal lymphadenopathy	2 (2.7)	54 (20)	**< 0.001**
Underwent bronchoscopy (*n, %*)	30 (37.0)	111 (38.4)	0.951
Genetic examination (*n, %*)	42 (51.8)	70 (2.4)	**< 0.001**
Lung biopsy-histopathology findings (*n, %*)			
• Lymphocytic interstitial pneumonia	0 (0)	2 (0.69)	NA
• Nonspecific interstitial pneumonia	1 (1.2)	0 (0)	NA
• Usual interstitial pneumonia	2 (2.4)	0 (0)	NA
• Fibrosis	2/18 (11.1)	7/35 (20.0)	0.701

Bold values are statistically significant values

DPLD diffuse parenchymal lung disease, *NA* not available

Table 3 Comparison of treatments

	DPLD-disorders manifesting primarily in infancy ($n=81$)	DPLD-disorders occurring at all ages ($n=289$)	p Value
	n (%)	*n* (%)	
Received any treatment	42 (51.8)	209 (72.3)	**< 0.001**
Steroids			
• Oral steroid	10 (23.8)	85 (40.6)	**0.040**
• Pulse steroid	12 (28.5)	44 (21.0)	0.286
• Inhaled steroid	10 (23.8)	51 (24.4)	0.935
Hydroxychloroquine	2 (4.6)	4 (1.9)	0.270
Immunosuppressive therapy	0 (0)	19 (9.0)	NA
Whole-lung lavage	3 (7.1)	0 (0)	NA
Others			
• Etidronate	2 (4.6)	0 (0)	NA
• Atorvastatin	1 (2.3)	0 (0)	NA
• Endobronchial fresh frozen plasma	0 (0)	1 (0.4)	NA

DPLD diffuse parenchymal lung disease

that most studies included older children and findings were not diagnostic of a specific chILD, but restrictive changes in spirometry might be a helpful pointer to chILD. They suggested that larger studies based on registries should be conducted to better elucidate this issue. Similarly, our cohort includes very low PFTs. In our cohort, 22.8% of the study population had spirometry, and 15.1% had DLCO, which measures the lungs' ability to transfer gas from exhaled air to red blood cells in the pulmonary capillaries. DLCO was significantly lower in the DPLD disorders manifesting primarily in infancy group; again, this may be due to the rapid progression of this group.

Chest CT is the cornerstone of chILD diagnoses in combination with the clinical findings [1, 10, 24, 27]. It allows us to know the extent and distribution of parenchymal abnormalities. Although chest CT usually describes findings suggestive of ILD, it may rarely lead to a direct diagnosis such as NEHI [28, 29]. Besides, radiologists can contribute to narrowing the differential diagnosis and guide the site of biopsy owing to chest CT. In our cohort, 92.4% of the study population had at least one chest CT. Nathan et al. [24] stated that CT findings vary according to age in a review on the diagnosis of chILD. Likewise, in the present study, ground-glass opacities were more common in early ages, and nodular opacities, bronchiectasis, mosaic perfusion, and mediastinal lymphadenopathy were more common in older ages.

ChILD management mostly consists of supportive treatment. The ChILD-EU treatment protocol, in terms of medical treatment, suggests steroids, hydroxychloroquine, and azithromycin, and adjusting the days and doses according to the patient's condition [10]. However, specific therapies can be used according to the type of chILD, such as Janus kinase inhibitors in interferonopathy-associated ILD, whole-lung lavage for pulmonary alveolar proteinosis, and disodium etidronate for pulmonary alveolar microlithiasis [30–32]. In our cohort, steroids were the most commonly used treatment, but other specific treatments were also used.

Our study has several limitations. First, there was a high rate of missing data. However, despite the remarkable missing data, this report's strength lies in it being at the beginning for our country with a high number of registered patients in the first year. Another limitation is the low rate of genetic tests because a genetic cause can identify one-fifth of patients with chILD [9]. Finally, patients' diagnoses were not re-evaluated by a peer review team. The ChILD-EU collaboration showed that the diagnoses of 13% of their cohort changed from the initial diagnosis after a peer review team evaluation (consisting of a respiratory pediatrician, pediatric radiologist, and pathologist; also, a geneticist if needed) [9]. Taking this real-world experience into account, one of our registry goals is to peer review patients in the registry by a multidisciplinary team.

In conclusion, the high number of patients who entered the registry in first year of chILD-TR showed that physicians need collaboration and a multidisciplinary team approach in diagnosing and treating these challenging patients.

Acknowledgements We thank all the families and patients for their participation. We thank all the chILD-TR collaborators.

Authors' contributions H.N.B., N.E., and N.K. wrote the main manuscript text. All authors contributed data and reviewed the manuscript.

Funding This project was funded by Hacettepe University Scientific Research Project Coordination Department (Project number: TOA-2021–19075).

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

Declarations

Ethics approval The establishment of the national registry and data input was approved by the local ethics committee (Hacettepe University Ethics Board, reference numbers: GO 20/604), in addition to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Competing interests The authors declare no competing interests.

References

1. Nayir Buyuksahin H, Kiper N (2023) Childhood interstitial lung disease. Pediatr Allergy Immunol Pulmonol 36:5–15
2. Griese M (2022) Etiologic classification of diffuse parenchymal (interstitial) lung diseases. J Clin Med 11
3. Cinel G, Kiper N, Orhan D, Emiralioglu N, Yalcin E, Dogru D, Ozcelik U, Oguz B, Haliloglu M (2020) Childhood diffuse parenchymal lung diseases: we need a new classification. Clin Respir J 14:102–108
4. Rice A, Tran-Dang MA, Bush A, Nicholson AG (2013) Diffuse lung disease in infancy and childhood: expanding the chILD classification. Histopathology 63:743–755
5. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, Dell S, Fan LL, Hamvas A, Hilman BC, Langston C, Nogee LM, Redding GJ (2013) An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med 188:376–394
6. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H (2010) Interstitial lung diseases in children. Orphanet J Rare Dis 5:22
7. Ferraro VA, Zanconato S, Zamunaro A, Carraro S (2020) Children's interstitial and diffuse lung diseases (ChILD) in 2020. Children (Basel) 7
8. (2014) AHRQ Methods for Effective Health Care. In: Gliklich RE, Dreyer NA, Leavy MB (eds) Registries for evaluating patient outcomes: a user's guide. Agency for Healthcare Research and Quality (US), Rockville (MD)
9. Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, Kiper N et al (2018) International management platform for children's interstitial lung disease (chILD-EU). Thorax 73:231–239
10. Bush A, Cunningham S, de Blic J, Barbato A, Clement A, Epaud R, Hengst M, Kiper N, Nicholson AG, Wetzke M, Snijders D, Schwerk N, Griese M (2015) European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax 70:1078–1084
11. Clement A, de Blic J, Epaud R, Galeron L, Nathan N, Hadchouel A, Barbato A, Snijders D, Kiper N, Cunningham S, Griese M, Bush A, Schwerk N (2016) Management of children with interstitial lung diseases: the difficult issue of acute exacerbations. Eur Respir J 48:1559–1563
12. Seidl E, Schwerk N, Carlens J, Wetzke M, Cunningham S, Emiralioğlu N, Kiper N, Lange J, Krenke K, Ullmann N, Krikovszky D, Maqhuzu P, Griese CA, Schwarzkopf L, Griese M (2022) Healthcare resource utilisation and medical costs for children with interstitial lung diseases (chILD) in Europe. Thorax 77:781–789
13. Griese M, Kappler M, Stehling F, Schulze J, Baden W, Koerner-Rettberg C, Carlens J, Prenzel F, Nährlich L, Thalmeier A, Sebah D, Kronfeld K, Rock H, Ruckes C, Wetzke M, Seidl E, Schwerk N (2022) Randomized controlled phase 2 trial of hydroxychloroquine in childhood interstitial lung disease. Orphanet J Rare Dis 17:289
14. Casey AM, Deterding RR, Young LR, Fishman MP, Fiorino EK, Liptzin DR (2020) Overview of the ChILD Research Network: a roadmap for progress and success in defining rare diseases. Pediatr Pulmonol 55:1819–1827
15. McKnight L, Schultz A, Vidic N, Palmer EE, Jaffe A (2023) Learning to make a difference for chILD: value creation through network collaboration and team science. Pediatr Pulmonol
16. Nevel RJ, Deutsch GH, Craven D, Deterding R, Fishman MP, Wambach JA, Casey A et al (2023) The US national registry for childhood interstitial and diffuse lung disease: report of study design and initial enrollment cohort. Pediatr Pulmonol
17. Kiper N, Emiralioglu N. Nutrition booklet for families of patients with chILD. Available from: www.klinikum.uni-muenchen.de/Child-EU. [Last accessed: January 6, 2020]
18. Comes A, Wong AW, Fisher JH, Morisset J, Johannson KA, Farrand E, Fell CD, Kolb M, Manganas H, Cox G, Gershon AS, Halayko AJ, Hambly N, Khalil N, Sadatsafavi M, Shapera S, To T, Wilcox PG, Collard HR, Ryerson CJ (2022) Association of BMI and change in weight with mortality in patients with fibrotic interstitial lung disease. Chest 161:1320–1329
19. Rinaldi S, Gilliland J, O'Connor C, Seabrook JA, Mura M, Madill J (2021) Fat-free mass index controlled for age and sex and malnutrition are predictors of survival in interstitial lung disease. Respiration 100:379–386
20. Gilbert C, Bush A, Cunningham S (2015) Childhood interstitial lung disease: family experiences. Pediatr Pulmonol 50:1301–1303
21. Stubbs KH, McMahon MXH, Popler J, Berry RC, Sharp WG (2022) Multidisciplinary feeding treatment for a patient with interstitial lung disease. Pediatr Pulmonol 57:3183–3185
22. Ghisa M, Marinelli C, Savarino V, Savarino E (2019) Idiopathic pulmonary fibrosis and GERD: links and risks. Ther Clin Risk Manag 15:1081–1093
23. Dziekiewicz M, Marczak H, Banasiuk M, Aksionchyk M, Krenke K, Banaszkiewicz A (2023) Characteristics of gastroesophageal reflux disease in children with interstitial lung disease. Pediatr Pulmonol 58:171–177
24. Nathan N, Griese M, Michel K, Carlens J, Gilbert C, Emiralioglu N, Torrent-Vernetta A, Marczak H, Willemse B, Delestrain C, Epaud R (2023) Diagnostic workup of childhood interstitial lung disease. Eur Respir Rev 32
25. Griese M, Schwerk N, Carlens J, Wetzke M, Emiralioğlu N, Kiper N, Lange J, Krenke K, Seidl E (2023) Minimal important difference in childhood interstitial lung diseases. Thorax 78:476–483
26. Ring AM, Carlens J, Bush A, Castillo-Corullón S, Fasola S, Gaboli MP, Griese M, Koucky V, La Grutta S, Lombardi E, Proesmans M, Schwerk N, Snijders D, Nielsen KG, Buchvald F (2020) Pulmonary function testing in children's interstitial lung disease. Eur Respir Rev 29
27. Spagnolo P, Bush A (2016) Interstitial lung disease in children younger than 2 years. Pediatr 137
28. Verma N, Altmayer S, Hochhegger B, Barros MC, Rajderkar D, Mohammed TL (2021) ChILD: a pictorial review of pulmonary imaging findings in childhood interstitial lung diseases. Curr Probl Diagn Radiol 50:95–103
29. Liang TI, Lee EY (2020) Interstitial lung diseases in children, adolescents, and young adults: different from infants and older adults. Radiol Clin North Am 58:487–502
30. Nayir Buyuksahin H, Basaran O, Balık Z, Bilginer Y, Ozen S, Dogru D (2023) Interstitial lung disease in autoinflammatory disease in childhood: a systematic review of the literature. Pediatr Pulmonol 58:367–373
31. Doğru D, Yalçin E, Aslan AT, Ocal T, Ozçelik U, Güçer S, Kale G, Haliloglu M, Kiper N (2009) Successful unilateral partial lung lavage in a child with pulmonary alveolar proteinosis. J Clin Anesth 21:127–130

32. Emiralioglu N, Beken B, Ozcan HN, Yalcin E, Dogru D, Ozcelik U, Haliloglu M, Kiper N (2016) Diagnosis and treatment of pulmonary alveolar microlithiasis. Pediatr Int 58:805–807

Authors and Affiliations

Halime Nayır-Büyükşahin[1,2] · Nagehan Emiralioğlu[1] · Ayşe Ayzıt Kılınç[3] · Saniye Girit[4] · Ebru Yalçın[1] · Tuğba Şişmanlar Eyüboğlu[5] · Nazan Çobanoğlu[6] · Güzin Cinel[7] · Sevgi Pekcan[8] · Yasemin Gökdemir[9] · Berna Oğuz[10] · Diclehan Orhan[11] · Deniz Doğru[1] · Uğur Özçelik[1] · Azer Kılıç Başkan[3] · Hüseyin Arslan[3] · Haluk Çokuğraş[3] · Zeynep Reyhan Onay[4] · Sinem Can Oksay[4] · Deniz Mavi Tortop[4] · Ayşe Tana Aslan[5] · Handan Kekeç[5] · Fazılcan Zirek[6] · Merve Nur Tekin[6] · Figen Gülen[12] · Bahar Girgin Dindar[12] · Sanem Eryılmaz Polat[7] · Salih Uytun[7] · Aslı İmran Yılmaz[8] · Gökçen Ünal[8] · Ela Erdem Eralp[9] · Bülent Karadağ[9] · Melih Hangül[13] · Mehmet Köse[14] · Beste Özsezen[15] · Erkan Çakır[16] · Ayşen Bingöl[17] · Mina Hızal[18] · Gökçen Kartal Öztürk[19] · Zeynep Seda Uyan[20] · Tuğba Ramaslı Gürsoy[21] · Mahir Serbes[22] · Nural Kiper[1]

✉ Halime Nayır-Büyükşahin
hnayirbuyuksahin@gmail.com

[1] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[2] Department of Pediatric Pulmonology, School of Medicine, Hacettepe University, Ihsan Dogramaci Children's Hospital, Ankara, Turkey

[3] Division of Pulmonology, Department of Pediatrics, Cerrahpaşa Faculty of Medicine Faculty of Medicine, İstanbul University-Cerrahpaşa, Istanbul, Turkey

[4] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey

[5] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Gazi University, Ankara, Turkey

[6] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Ankara University, Ankara, Turkey

[7] Division of Pulmonology, Department of Pediatrics, Ankara City Hospital, Ankara, Turkey

[8] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

[9] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Marmara University, Istanbul, Turkey

[10] Division of Pediatric Radiology, Department of Radiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[11] Department of Pathology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[12] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Ege University, İzmir, Turkey

[13] Division of Pediatric Pulmonology, Gaziantep Cengiz Gökçek Maternity and Children Hospital, Gaziantep, Turkey

[14] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, Erciyes University, Kayseri, Turkey

[15] Division of Pediatric Pulmonology, Şanlıurfa Children Hospital, Şanıurfa, Turkey

[16] Division of Pulmonology, Department of Pediatrics, Faculty of Medicine, İstinye University, Istanbul, Turkey

[17] Department of Pediatric Pulmonology, Allergy and Immunology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

[18] Department of Pediatric Pulmonology, Ankara Training and Research Hospital, University of Health Science, Ankara, Turkey

[19] Division of Pulmonology, Department of Pediatrics, University of Health Sciences Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, İzmir, Turkey

[20] Division of Pediatric Pulmonology, Faculty of Medicine, Koc University, Istanbul, Turkey

[21] Division of Pediatric Pulmonology, Dr Sami Ulus Maternity and Children Training and Research Hospital, Ankara, Turkey

[22] Division of Pediatric Allergy and Immunology, Department of Pediatrics, Faculty of Medicine, Çukurova University, Adana, Turkey