Childhood interstitial lung disease survivors in adulthood: a European collaborative study

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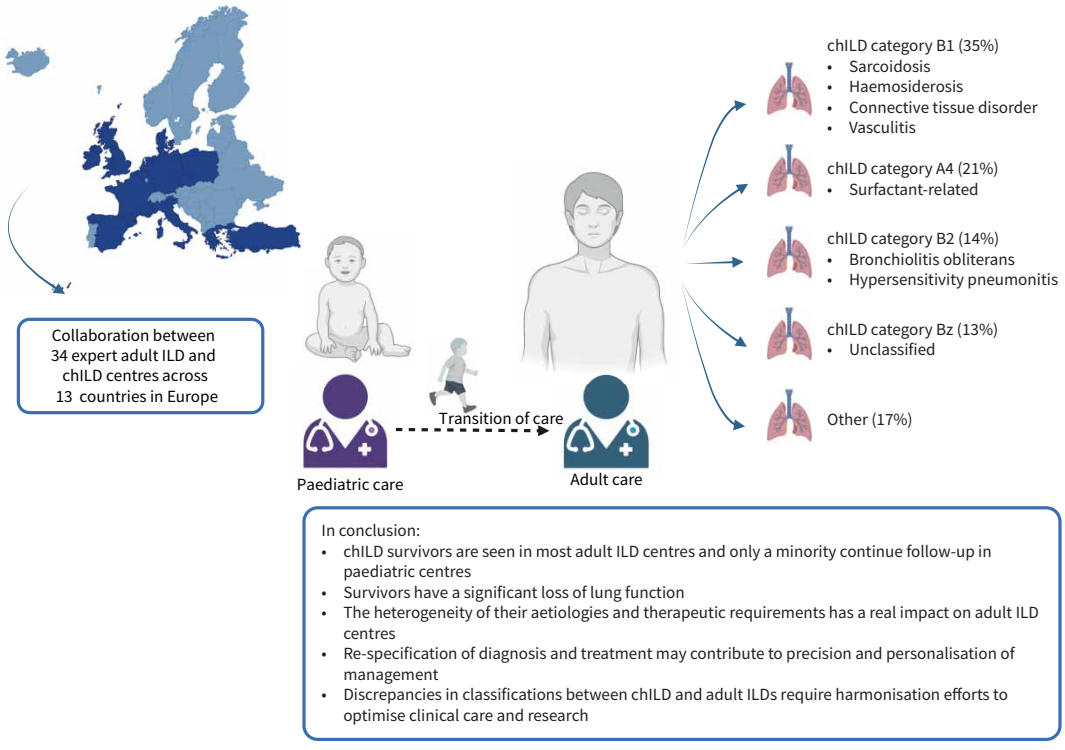

GRAPHICAL ABSTRACT Overview of the study findings. Increasing numbers of children diagnosed with interstitial lung disease (ILD) now survive into adulthood. Commonest diagnoses (82%) of childhood interstitial lung disease (chILD) survivors encompass chILD category B1 (sarcoidosis, hemosiderosis, connective tissue disorders, vasculitis) (35%), A4 (surfactant-related) (21%), B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) (14%) and Bz (unclassified ILD) (13%).

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Shareable abstract (@ERSpublications)
Increasing numbers of children diagnosed with ILD now survive into adulthood. Many have substantial functional impairment and/or are at risk of late relapse or complications. They need individualised care in adult ILD clinics. https://bit.ly/3UDSxsM

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Abstract

Background Interstitial lung disease is rarer in children than adults, but, with increasing diagnostic awareness, more cases are being discovered. The prognosis of childhood interstitial lung disease is often poor, but increasing numbers are now surviving into adulthood.

Aim To characterise childhood interstitial lung disease survivors and identify their impact on adult interstitial lung disease centres.

Methods This was a European study (34 adult and childhood interstitial lung disease centres) reporting incident/prevalent cases of childhood interstitial lung disease survivors from January to July 2023. Epidemiological, clinical, physiological and genetic data were collected.

Results 244 patients were identified with a median (interquartile range) age at diagnosis of 12.5 years (6–16 years) and age at study inclusion of 25 years (22–33 years), with 51% male, 86% nonsmokers and a median (interquartile range) % predicted forced vital capacity of 70% (47–89%) and diffusing capacity of the lungs for carbon monoxide of 48% (32–75%). 32% were prescribed long-term oxygen and 227 (93%) were followed up in adult centres whereas 17 (7%) never transitioned. The commonest diagnoses (82%) were childhood interstitial lung disease category B1 (sarcoidosis, hemosiderosis, connective tissue disorders, vasculitis) at 35%, A4 (surfactant-related) at 21%, B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) at 14% and Bz (unclassified interstitial lung disease) at 13%. Bz patients had the worst functional status. 60% of all patients were still being prescribed corticosteroids. Re-specification of diagnosis and treatment were made after transition for 9.8% and 16% of patients, respectively. Not all childhood interstitial lung disease diagnoses were recognised in adult interstitial lung disease classifications.

Conclusion Childhood interstitial lung disease survivors are seen in most adult interstitial lung disease centres and only a minority continue follow-up in paediatric centres. Survivors have a significant loss of lung function. The heterogeneity of their aetiologies and therapeutic requirements has a real impact on adult interstitial lung disease centres. Re-specification of diagnosis and treatment may contribute to precision and personalisation of management.

Introduction

Interstitial lung diseases (ILDs) in adults refer to a very large and heterogeneous group of diffuse parenchymal lung disorders, not necessarily all strictly interstitial, sharing overlapping clinical, imaging and functional characteristics [1]. They encompass a spectrum of diseases from ultra-rare single organ, to more common and multisystem conditions. Some have a clear underlying genetic cause [1]. A minority of ILDs may improve or even apparently resolve completely. However, most progressively deteriorate. This is especially true for the chronic fibrotic ILDs [2]. Childhood ILDs (chILD), although much rarer, are increasingly recognised [3–6]. Some chILD classifications include conditions that are also not strictly "interstitial" according to adult classifications (*e.g.* bronchiolitis obliterans (BO) and conditions related to pulmonary hypoplasia, such as bronchopulmonary dysplasia) and may have a different clinical course and prognosis compared to adult ILDs [7]. There is significant concordance between adult and paediatric classifications but not complete agreement, because some ILDs are specific to children or adults. Genetic causes are more common in chILD, especially in those occurring in infancy. An unknown proportion survive and reach adulthood [8, 9], but the diversity and nature of chILD survivors into adulthood, and

hence the burden on adult clinics, is unknown. Uninterrupted provision of specialist care is necessary across the entire developmental course. To ensure optimal care of chILD survivors after transition, bespoke programmes should be widely available but none have been reported to the European Respiratory Society (ERS) clinical research collaboration (CRC) or yet published [10]. The aim of this study was to characterise chILD survivors in adulthood and identify their impact on adult ILD centres to determine whether the needs of survivors are being met [11].

Methods

This was a multicentre, observational, retrospective, European collaborative study including incident and prevalent cases of chILD survivors from childhood into adulthood followed up in 34 European adult ILD and chILD paediatric expert centres from January to July 2023. Initially, 43 centres from the ERS CRC for chILD, ERN-Lung, European Management Platform of the chILD-EU register, RespiFIL, Orphalung and already established collaborations were invited to participate in the study. Nine centres declined owing to very time-consuming data transfer agreement rules, busy schedules or no interest. All adult patients (>18 years old) with chILD diagnosed in childhood in paediatric centres who had survived into adulthood and were followed up in adult ILD centres or continued to be followed up in paediatric centres were eligible for the study. chILD diagnosis was by the referring clinician based on the chILD-EU classification (figure 1, supplementary table S1) [7]. Correlation of chILD diagnoses with adult ILD taxonomy was based on the 2022 adult classification (supplementary table S2) [1].

Anonymised questionnaires were used for the collection of clinical, radiological, physiological and genetic data after written informed consent. Age of transition was defined as the age at which the patient had the first outpatient clinic consultation in an adult expert centre. Data for chILD survivors were provided by adult ILD centres unless the patient had not been transitioned and continued to be followed up in their paediatric centre, in which case all information was provided by the paediatric centre. Only patients diagnosed in paediatric centres were included in this study. Lung disease secondary to malignancy or infection, as well as diseases that could be misdiagnosed as chILD, such as veno-occlusive disease or pulmonary oedema related to cardiac dysfunction, were excluded. In accordance with current chILD classifications, obliterative bronchiolitis, although primarily an airway disease, was included. A review of the categories of chILD provided in the study questionnaires by the participating centres was performed by the principal investigators of the study (EDM, MG, NN, AB, SAP) and led to the exclusion of seven patients who did not fulfil the criteria of chILD and to the re-allocation to the appropriate category of five patients after initial incorrect allocation. Hence, 244 patients were analysed [7]. All participating centres retrieved data from electronic and paper files. The study was approved by all the medical ethics

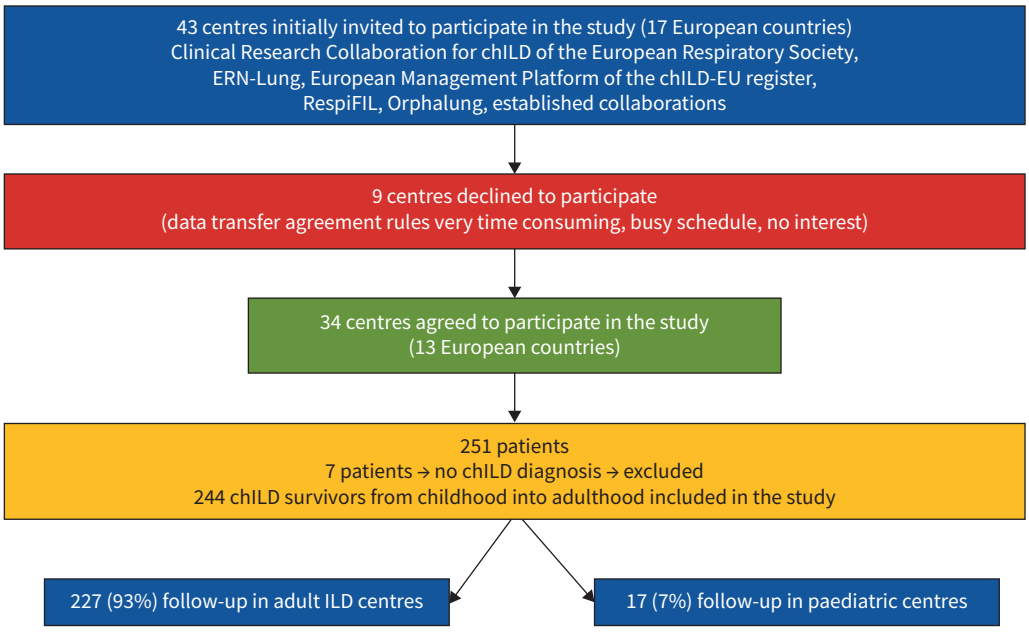

FIGURE 1 Flow diagram showing the number of centres and patients participating in the study. chILD: childhood interstitial lung disease; ILD: interstitial lung disease.

committees of the participating centres, with the General University Hospital "Attikon", Athens, Greece, being the lead centre (ΒΠΝΕΥΜ, ΕΒΔ784/30–12–2022).

Statistical analysis

Categorical variables are presented as n (%) and numerical variables are presented as median (interquartile range (IQR)). Comparisons between groups were performed using chi-square tests for categorical data and Mann–Whitney U test or Kruskal–Wallis test for numerical data. *Post hoc* analysis was performed using Dunn's tests for numerical data. Data were analysed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA); p-values <0.05 were considered statistically significant. In table 1, where "%" is quoted, the ratio of valid to missing values is provided to enable the reader to better understand the number impacted and the number for whom data were available.

Results

Baseline characteristics of the whole cohort

We analysed 244 chILD survivors into adulthood in multiple diagnostic groups based on the chILD-EU register classification (figure 2). Median age (IQR) was 13 years (6–16 years) at diagnosis and 25 years (22–33 years) at inclusion in the study. Patients were followed for a median (IQR) of 62 months (19–120 months). 51% were male and 86% were nonsmokers. Data on employment at last follow-up were only available for 67 patients (27%): 41 (61%) were employed in manual labour, nine (13%) in intellectual labour (desk jobs), five (7.5%) were students and five (7.5%) were unable to work due to their health status. The most common diagnoses, encompassing 201 out of 244 of the study group (82%) were chILD B1 (sarcoidosis, hemosiderosis, connective tissue disorders, vasculitis) (n=85, 35%); A4 (surfactant-related) (n=51, 21%); B2 (BO, hypersensitivity pneumonia) (n=34, 14%) and Bz (unclassified ILD) (n=31, 13%). Importantly, some chILD diagnoses (BO, developmental and structural abnormalities and neuroendocrine cell hyperplasia of infancy (NEHI), here considered synonymous with persistent tachypnoea of infancy) [12] are not identified in adult ILD classifications (table 1). Almost all groups of the chILD-EU register classification were represented (table 2 and figure 2).

Of 244 patients, 227 (93%) were followed up in adult centres and 17 (7.0%) never transitioned and continued to be followed up in paediatric centres (table 1). When focusing on chILD survivors who transitioned to adult care, median (IQR) age at diagnosis was 13 years (6–16 years) at diagnosis, 18 years (18–20 years) at transition and 26 years (22–34 years) at inclusion in the study. Patients were followed for a median (IQR) of 61 months (19–120 months). 50% were male and 85% were nonsmokers. High-resolution computerised tomography (HRCT) of the chest at last follow-up in the adult ILD clinic showed the following patterns based on the American Thoracic Society/ERS/Japanese Respiratory Society/Latin American Thoracic Association official guidelines 2022 [2]: usual interstitial pneumonia (UIP) (n=36, 16%), probable UIP (n=7, 3.1%), indeterminate for UIP (n=9, 4.0%) and alternative (compatible with a diagnosis other than UIP/IPF) (n=105, 46%); no information was available for 70 patients (31%) from the study questionnaires. A history of bronchoscopy with bronchoalveolar lavage, lung biopsy and genetic analysis for a diagnosis of chILD in childhood was reported in 123 (54%), 121 (53%) and 9 (41%) of 227 patients, respectively (tables 1 and 3).

At inclusion in the study, median (IQR) values for lung parameters were as follows: forced expiratory volume in 1 s (FEV_1) 61% (39–81%) predicted, forced vital capacity (FVC) 69% (47–88%) predicted, FEV_1/FVC ratio 83% (70–90%), total lung capacity 76% (56–96%) predicted and diffusing capacity of the lungs for carbon monoxide (D_{LCO}) 48% (32–75%) predicted. Pulmonary hypertension diagnosed by echocardiography was reported in 35 out of 227 patients (15%) and 76 out of 227 patients (33%) were prescribed long-term oxygen therapy (LTOT) (table 1).

Treatment at last follow-up in the adult ILD clinic consisted of systemic corticosteroids (n=138, 61%), macrolides (n=14, 6.2%), hydroxychloroquine (n=8, 3.5%), antifibrotics (n=4, 1.8%) and combinations of the above (n=14, 6.2%) of 227 patients. 47 of 227 patients (21%) received other treatments related to specific diagnoses such as whole lung lavage for pulmonary alveolar proteinosis (PAP); immunosuppressive treatments such as rituximab, azathioprine and mycophenolate mofetil for systemic autoinflammatory diseases; and methotrexate for sarcoidosis. During follow-up in adulthood, 146 of 227 patients (64%) were reported to be stable, 30 (13%) were in remission and 36 (16%) were deteriorating; for 15 of 227 patients (6.6%) no information was available. Pre-lung transplantation evaluation was reported in 53 of 227 patients (23%) (table 1).

Follow-up in paediatric chILD centres in adulthood

The vast majority of chILD survivors (n=227, 93%) were followed up in adult ILD centres and only 17 (7%) continued to be followed up in paediatric centres after the age of 18 years in three centres, one each

TABLE 1 Demographic, clinical, functional, radiological and genetic characteristics of the entire study population of chILD survivors (n=244) and of subcategories based on transition and follow-up in adult or paediatric ILD centres

Parameter	Valid values	Missing values	Entire study population of chILD survivors	Follow-up in adult ILD centres	Follow-up in paediatric centres	p-value[#]
Patients, n			244	227	17	
Gender	244	0				0.494
Male			124 (51)	114 (50)	10 (59)	
Female			120 (49)	113 (50)	7 (41)	
Age (years)						
At diagnosis	244	0	13 (6–16)	13 (6–16)	11 (4–15)	0.670
At transition	220	24	18 (18–20)	18 (18–20)	NA	
At inclusion in the study	244	0	25 (22–33)	26 (22–34)	23 (18–29)	**0.033**
Follow-up (months)	145	99	62 (19–120)	61 (19–120)	67 (6–120)	0.803
Last follow-up findings						
FEV_1 % pred	198	46	63 (40–83)	61 (39–81)	84 (64–90)	**0.025**
FVC % pred	209	35	70 (47–89)	68.7 (47–88)	86 (70–91)	0.10
FEV_1/FVC	198	46	84 (70–91)	83 (70–90)	95 (89–104)	**0.002**
TLC % pred	95	149	76 (56–96)	76 (56–96)	74 (32–106)	0.719
D_{LCO} % pred	135	109	48 (32–75)	48 (32–75)	55 (22–81)	0.785
Bronchoscopy at chILD diagnosis	244	0	133 (55)	123 (54)	10 (59)	0.711
Biopsy at chILD diagnosis	244	0	131 (54)	121 (53)	10 (59)	0.660
Genetic analysis at chILD diagnosis	244	0	99 (40)	93 (41)	6 (35)	0.646
Positive molecular diagnosis	244	0	57 (23)	52 (23)	5 (29)	0.188
Transition to adult care	244	0	227 (93)	227 (100)	0	
Smoking status	244	0				0.477
Nonsmoker			209 (86)	193 (85)	16 (94)	
Current smoker			17 (7.0)	17 (7.5)	0 (0)	
Ex-smoker			18 (7.4)	17 (7.5)	1 (5.9)	
Vaping	244	0	4 (1.6)	4 (1.8)	0	0.581
LTOT	233	11	78 (32)	76 (33)	2 (12)	**0.049**
HRCT pattern	174	70				0.477
UIP			38 (16)	36 (16)	2 (12)	
Probable UIP			9 (3.7)	7 (3.1)	2 (12)	
Indeterminate			10 (4.1)	9 (4.0)	1 (5.9)	
Alternative			117 (48)	105 (46)	12 (71)	
Pulmonary hypertension	243	1	36 (15)	35 (15)	1 (5.9)	0.536
Pharmacological treatment	242	2				0.094
Corticosteroids			146 (60)	138 (61)	8 (47)	
Macrolides			14 (5.7)	14 (6.2)	0 (0)	
Hydroxychloroquine			8 (3.3)	8 (3.5)	0 (0)	
Antifibrotics			4 (1.6)	4 (1.8)	0 (0)	
Combination of the above			18 (7.4)	14 (6.2)	4 (24)	
Other			52 (21)	47 (21)	5 (29)	
Diagnosis re-specification	243	1	24 (9.8)	23 (10)	1 (5.9)	0.57
Treatment re-specification	241	3	40 (16)	38 (17)	2 (12)	0.59
Progression	229	15				**0.002**
Stable			154 (63)	146 (64)	8 (47)	
Improving			38 (16)	30 (13)	8 (47)	
Worsening			37 (15)	36 (16)	1 (6.9)	
Pre-lung Tx evaluation	244	0	54 (22)	53 (23.3)	1 (5.9)	0.095
Correspondence of chILD to adult ILD based on international classifications [7]	244	0				0.782
No=0[¶]			51 (21)	47 (21)	4 (24)	
Yes=1			193 (79)	180 (79)	13 (76)	
Categories	244	0				0.965
A1			0 (0)	0 (0)	0 (0)	
A2			2 (0.8)	2 (0.9)	0 (0)	
A3			6 (2.5)	5 (2.2)	1 (5.9)	
A4[+]			51 (21)	46 (20)	5 (29)	

Continued

TABLE 1 Continued

Parameter	Valid values	Missing values	Entire study population of chILD survivors	Follow-up in adult ILD centres	Follow-up in paediatric centres	p-value[#]
Ax			0 (0)	0 (0)	0 (0)	
Ay			0 (0)	0 (0)	0 (0)	
B1[§]			85 (35)	81 (36)	4 (24)	
B2[f]			34 (14)	30 (13)	4 (24)	
B3			9 (3.7)	9 (4)	0 (0)	
B4			6 (2.5)	6 (2.6)	0 (0)	
B5			1 (0.4)	1 (0.4)	0 (0)	
Bx			1 (0.4)	1 (0.4)	0 (0)	
By			4 (1.6)	4 (1.8)	0 (0)	
Bz[##]			31 (13)	29 (13)	2 (12)	
C1			11 (4.5)	10 (4.4)	1 (5.9)	
C2			1 (0.4)	1 (0.4)	0 (0)	
D			2 (0.8)	2 (0.9)	0 (0)	

Categorical variables are presented as n (%) and numerical variables are presented as median (interquartile range). Values in bold show statistical significance. chILD: childhood interstitial lung disease; ILD: interstitial lung disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; LTOT: long-term oxygen therapy; HRCT: high-resolution computed tomography; Tx: transplantation. [#]: for patients followed up at adult centres compared to those followed up in paediatric centres (comparison between groups was performed with Mann–Whitney U test for numerical values and chi-square test for categorical values); [¶]: not included as such in the most recent classification of adult ILD [1]; [+]: surfactant-related; [§]: sarcoidosis, hemosiderosis, connective tissue disorders, vasculitis; [f]: bronchiolitis obliterans, hypersensitivity pneumonitis; [##]: unclassified ILD.

in Greece, Turkey and Italy. These patients were diagnosed with haemosiderosis (n=2), hereditary PAP (colony-stimulating factor 2 receptor subunit β (*CSF2RB*) and solute carrier family 7 member 7 (*SLC7A7*) gene variants; n=2), lung damage due to chemotherapy (n=1), granulomatosis with polyangiitis (n=1), chronic exogenous lipoid pneumonia (n=1), pulmonary lymphangiectasia (n=1), BO (n=1), nonspecific interstitial pneumonia (NSIP) (n=1), non-Langerhans cell lymphohistiocytic proliferation (n=1), cellular interstitial pneumonia (n=1), NEHI (n=1), surfactant protein C-related ILD (n=1), unclassifiable pulmonary fibrosis (n=2) and PAP (n=1). Differences observed between the two groups were younger age at inclusion in the study (23 years (18–29 years) *versus* 26 years (22–34 years), p=0.033) and higher rate of disease amelioration (47% *versus* 13%, p=0.002) for those continuing to be followed up in paediatric centres and worse functional status as reflected by a lower value of FEV_1 % predicted (61% (39–81%) *versus* 84% (64–90%), p=0.025), and a higher rate of oxygen requirement (33% *versus* 12%, p=0.049) for those transferred to adult care (table 1).

Genetic and environmental factors

A molecular diagnosis (presence of likely pathogenic or pathogenic variants) was found in 57 out of 244 (23%) of the entire study population, 52 out of 227 (23%) in those followed up in adult centres and five out of 17 (30%) in those who continued to be followed up in paediatric centres (p=0.188). The genes involved are detailed in tables 2 and 3. Bi-allelic variants of the ATP-binding cassette subfamily A member 3 gene (*ABCA3*) were the most common (13 out of 55, 24%) followed by variants in the surfactant protein C gene (*SFPC*) (eight out of 55, 14%) (table 3). Environmental and occupational exposures were identified or suspected in 43 (18%), not identified in 53 out of 244 (22%) and no information was provided for 148 (61%) out of 244 patients. Exposure to organic particulate matter (moulds/yeasts, avian feathers) was the most common (69%) followed by exposure to inorganic particulate matter (chemicals, metals) (27%); one patient was diagnosed with drug-induced chILD (nitrofurantoin). For other reported exposures at work or at home, whether the exposure was related to the ILD was unclear, although seemed highly likely.

Re-specification of diagnosis of chILD in chILD survivors

Re-evaluation leading to re-specification of diagnosis was reported in 24 out of 244 patients (9.8%) in the entire cohort: 23 out of 227 (10%) in those followed up in adult ILD centres and one out of 17 (5.9%) in those who continued to be followed up in paediatric centres. Re-specification of diagnosis resulted from a more precise molecular or histological/radiological diagnosis (table 4). Re-specification of treatment was reported in 40 out of 244 patients (16%) in the entire cohort: 38 out of 227 (17%) in those followed up in adult ILD centres and two out of 17 (12%) in those who continued to be followed up in paediatric centres.

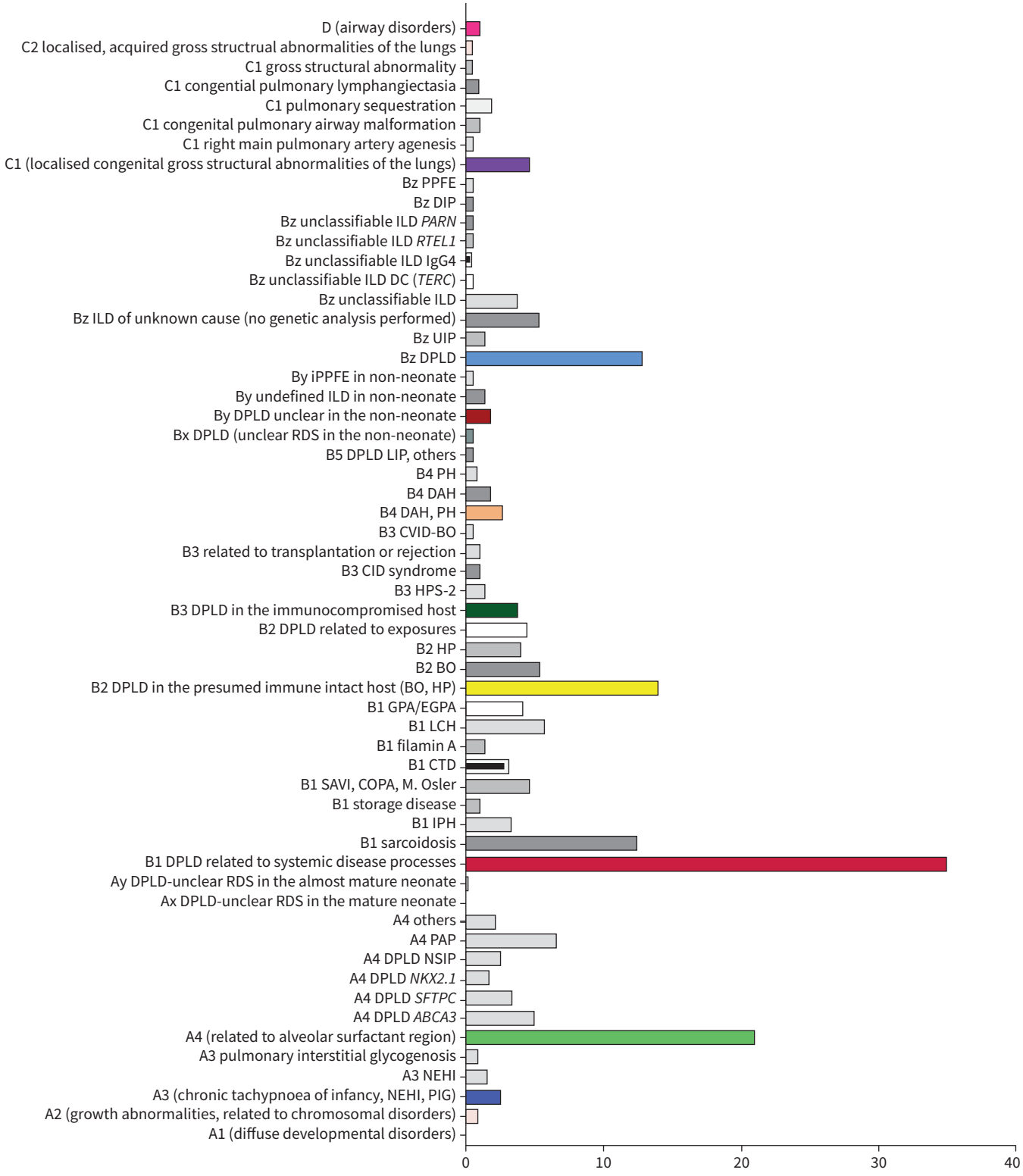

FIGURE 2 Frequency (%) distribution of categories and subcategories of childhood interstitial lung disease (chILD) survivors into adulthood (n=244) based on chILD-EU classification. PPFE: pleuroparenchymal fibroelastosis; DIP: desquamative interstitial pneumonia; ILD: interstitial lung disease; PARN: poly(A)-specific ribonuclease; *RTEL1*: regulator of telomere elongation helicase 1; *TERC*: telomerase RNA component; IgG4: immunoglobulin G4; UIP: usual interstitial pneumonia; DPLD: diffuse parenchymal lung disease; iPPFE: idiopathic pleuroparenchymal fibroelastosis; RDS: respiratory distress syndrome; PH: pulmonary hypertension; DAH: diffuse alveolar haemorrhage; CVID-BO: common variable immunodeficiency-bronchiolitis obliterans; CID: combined immunodeficiency; HPS-2: Hermansky–Pudlack syndrome-2 caused by a mutation in adaptor related protein complex 3 subunit β1 (*AP3B1*); HP: hypersensitivity pneumonitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis;

CTD: connective tissue disease; SAVI: STING-associated vasculopathy with onset in infancy; COPA: coatomer protein complex subunit α; IPH: idiopathic pulmonary haemosiderosis; PAP: pulmonary alveolar proteinosis; NSIP: nonspecific interstitial pneumonia; *NKX2.1*: NK2 homeobox 1; *SFTPC*: surfactant protein C; NEHI: neuroendocrine cell hyperplasia of infancy; PIG: pulmonary interstitial glycogenosis.

Re-specification of treatment consisted of modulating the dose of existing therapies in six out of 40 patients (15%) or introducing specific treatments in the majority of patients (32 out of 40, 80%).

The four main chILD groups: B1 (sarcoidosis, hemosiderosis, connective tissue disorders, vasculitis), A4 (surfactant-related), B2 (BO, hypersensitivity pneumonitis) and Bz (unclassified ILD)

The four main chILD categories, *i.e.* B1 (n=85), A4 (n=51), B2 (n=34) and Bz (n=31), accounted for 201 out of 244 of the study population (82%) (figure 2). Disease categories differed significantly in terms of gender balance, age at transition and inclusion in the study, functional status, diagnostic procedures including biopsy and genetic testing, requirement for LTOT, corticosteroid treatment, likelihood of deterioration of clinical status and evaluation for lung transplantation. These differences were noted both in the analysis of the entire cohort and in the analysis of the survivors that were followed up in adult centres (tables 5 and 6). ChILD category Bz survivors followed up in adult ILD centres had the worst % predicted FVC and D_{LCO} values (p=0.004 and p=0.017, respectively), LTOT (p=0.004) and deterioration (p<0.001) and the highest rate of pre-lung transplantation assessment (p=0.005). chILD category A4 survivors were most likely to have had a genetic analysis leading to the detection of pathogenic variations (p<0.001) and chILD category B2 survivors were most likely to receive systemic corticosteroid treatment (p=0.028) (tables 5 and 6, figures 3 and 4).

Discussion

This European collaborative study documented for the first time that chILD survivors, although rare, are consistently part of the workload of adult ILD expert centres. Very few adults with chILD continue to be seen in paediatric clinics. Patients often have substantial physiological impairment mandating ongoing monitoring and treatment. Most diagnoses in child survivors corresponded to similar ILD categories in the adult classification, facilitating uninterrupted transition of specialist care.

chILDs often have a poor prognosis, but a growing number of patients survive into adulthood. However, these patients may be forgotten or subsumed into inappropriate diagnostic categories and to date are not regularly identified as part of the estimated relative distribution of specific ILDs followed up in adult ILD centres [13, 14]. In our study cohort, four out of 17 categories accounted for the vast majority of survivors followed up into adulthood. ChILD category B1 (sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis) was the commonest (35%) followed by category A4 (surfactant-related), B2 (BO, hypersensitivity pneumonitis) and Bz (unclassified ILD). chILD category Bz was shown to be one of the most challenging groups, having the worst functional status, higher requirements of LTOT and the highest rates of disease progression compared to the other chILD categories. Although Bz chILD is by definition any diffuse parenchymal lung disease not further characterised and as such is “unclassified”, the present study showed that the chILD Bz category included diverse entities corresponding to several adult idiopathic interstitial pneumonias with known poor prognosis, such as UIP, pleuroparenchymal fibroelastosis or telomere-related gene (*TRG*) variation-associated pulmonary fibrosis [7, 15, 16]. This observation mandates a re-evaluation of management and treatment, which had previously been mostly based on corticosteroids (more than half of the patients in the study). We speculate that these patients might benefit from the knowledge gained and new medications licensed in adult fibrotic and familial ILDs [2, 17, 18]; unfortunately, these are not yet approved in children. Making these medications available for children is a high priority.

Many of the commonest entities in the remaining major chILD survivors’ categories are related to pathogenic variants in a wide range of genes [4]. NEHI, which is an umbrella term based on pattern recognition on HRCT, includes specific endotypes associated with mutations in NK2 homeobox 1 (*NKX2.1*) and forkhead box P1 (*FOXP1*) [9, 12, 19]. Based on this observation and the new documentation of a genetic background later in life in patients transitioned to adult ILD centres, we highlight the importance of regularly re-evaluating undiagnosed chILD patients using new advances in gene panels [1, 20–25]. Fewer than half of the study population had undergone genetic testing on diagnosis, partly because a genetic diagnosis was not systematically sought in every centre and partly because genetic analysis is not universally available even when indicated. This again is a priority area to be addressed.

TABLE 2 Categories and subcategories of chILD survivors into adulthood based on chILD-EU classification [7]

Categories and subcategories of chILD survivors	Patients[#]
A1 (Diffuse developmental disorders)	0 (0)
A2 (Growth abnormalities, related to chromosomal disorders)[¶] (unclassifiable ILD in patient with trisomy 21)	2 (0.8)
A3 (Chronic tachypnoea of infancy, NEHI, pulmonary interstitial glycogenosis)[¶]	6 (2.5)
A3 NEHI	4 (1.6)
A3 Pulmonary interstitial glycogenosis	2 (0.8)
A4 (Related to alveolar surfactant region: *ABCA3, SFTPC, NKX2-1* variation, NSIP[¶], PAP)	51 (21)
A4 DPLD *ABCA3* variations	12 (4.9)
A4 DPLD *SFTPC* variations	8 (3.3)
A4 DPLD *NKX2-1* variations	4 (1.6)
A4 DPLD NSIP	6 (2.5)
A4 PAP	16 (6.6)
A4 Others (microlithiasis, eosinophilic pneumonia)	5 (2.0)
Ax DPLD – unclear RDS in the mature neonate	0 (0)
Ay DPLD – unclear RDS in the almost mature neonate	0 (0)
B1 DPLD related to systemic disease processes (sarcoidosis, pulmonary haemosiderosis, collagen vascular diseases, GPA)	85 (35)
B1 Sarcoidosis	30 (12)
B1 Idiopathic pulmonary haemosiderosis	8 (3.3)
B1 Storage disease (Niemann–Pick)	2 (0.8)
B1 Collagen vascular diseases	7 (2.9)
B1 Immune-mediated diseases (SAVI, COPA, M. Osler)	11 (4.5)
B1 Filamin A variation	3 (1.2)
B1 Langerhans cell histiocytosis	14 (5.7)
B1 GPA/EGPA	10 (4.0)
B2 DPLD in the presumed immune intact host (BO, hypersensitivity pneumonitis)	34 (14)
B2 BO	13 (5.3)
B2 Hypersensitivity pneumonitis	10 (4.1)
B2 DPLD related to exposures (infectious/noninfectious)	11 (4.5)
B3 DPLD in the immunocompromised host (NSIP, related to transplantation or rejection)	9 (3.7)
B3 Hermansky–Pudlak syndrome 2	3 (1.2)
B3 Combined immunodeficiency syndrome	2 (0.8)
B3 Related to transplantation or rejection	2 (0.8)
B3 Common variable immunodeficiency-BO	1 (0.4)
B4 (Pulmonary haemorrhage, pulmonary hypertension)[¶]	6 (2.5)
B4 Pulmonary capillaritis	4 (1.6)
B4 Pulmonary hypertension	2 (0.8)
B5 DPLD related to reactive lymphoid lesions (lymphocytic interstitial pneumonia, others)	1 (0.4)
Bx DPLD (unclear RDS in the non-neonate)	1 (0.4)
By DPLD unclear in the non-neonate	4 (1.6)
By Undefined ILD in non-neonate	3 (1.2)
By Idiopathic pleuroparenchymal fibroelastosis in non-neonate	1 (0.4)
Bz DPLD	31 (13)
Bz Usual interstitial pneumonia	3 (1.2)
Bz ILD of unknown cause (no genetic analysis performed)	13 (5.3)
Bz Unclassifiable ILD no pathogenic variation found (genetic analysis performed including whole-exome sequencing in one patient)	9 (3.7)
Bz Unclassifiable ILD dyskeratosis congenita (*TERC*)	1 (0.4)
Bz Unclassifiable ILD IgG4-related disease	1 (0.4)
Bz Unclassifiable ILD *RTEL1*	1 (0.4)
Bz Unclassifiable ILD *PARN*	
Bz Desquamative interstitial pneumonia	1 (0.4)
Bz Pleuroparenchymal fibroelastosis	1 (0.4)
C1 (Localised congenital gross structural abnormalities of the lungs)[¶]	11 (4.5)
C1 Right main pulmonary artery agenesis	1 (0.4)
C1 Congenital pulmonary airway malformation	2 (0.8)
C1 Pulmonary sequestration	5 (2.0)

Continued

TABLE 2 Continued

Categories and subcategories of chILD survivors	Patients[#]
C1 Congenital pulmonary lymphangiectasia	2 (0.8)
C1 Gross structural abnormality	1 (0.4)
C2 (Localised, acquired gross structural abnormalities of the lungs)	1 (0.4)
D (Airway disorders)[¶]	2 (0.8)

chILD: childhood interstitial disease; ILD: interstitial lung disease; NEHI: neuroendocrine cell hyperplasia of infancy; *ABCA3*: ATP binding cassette subfamily A member 3; *SFTPC*: surfactant protein C; *NKX2-1*: NK2 homeobox 1; NSIP: nonspecific interstitial pneumonia; PAP: pulmonary alveolar proteinosis; DPLD: diffuse parenchymal lung diseases; RDS: respiratory distress syndrome; GPA: granulomatosis with polyangiitis; SAVI: STING-associated vasculopathy with onset in infancy; COPA: coatomer protein complex subunit α; EGPA: eosinophilic granulomatosis with polyangiitis; *TERC*; telomerase RNA component; BO: bronchiolitis obliterans; *RTEL1*: regulator of telomere elongation helicase 1; *PARN*: poly(A)-specific ribonuclease. [#]: n=244; [¶]: not included as such at the most recent classification of adult ILD.

Another common subcategory of the study was BO. Some paediatric chILD classifications include BO in diffuse parenchymal lung diseases because, in addition to airway injury, the adjacent interstitial tissue is also affected and these patients are often under-recognised in asthma-focused services. Positioning BO and conditions related to pulmonary hypoplasia at different developmental stages into a harmonised classification

TABLE 3 Genes with pathogenic variants in chILD survivors by chILD categories and specific ILD conditions

	Genes involved
ChILD category	
A2	*NKX2.1* (1/55, 1.8%)
A4[#]	*ABCA3* (13/55, 24%), *SFTPC* (6/55, 11%), *NKX2.1* (4/55, 7.3%), *CSF2RA* (3/55, 5.5%), *SLC34A2* (3/55, 5.5%), *CSF2RB* (1/55, 1.8%), *SLC7A7* (1/55, 1.8%)
B1[¶]	*COPA* (4/55, 7.3%), *STING1* (3/55, 5.5%), *BRAF* (2/55, 3.6%), *FLNA* (2/55, 3.6%), *NLRP3* (1/55, 1.8%), *NPC1* (1/55, 1.8%), *FARSA* (1/55, 1.8%)
B2[+]	*SFTPC* (2/55, 3.6%)
B3	*HPS2* (2/55, 3.6%), *TTC37* (1/55, 1.8%), *TGFBR1* (1/55, 1.8%)
Bz[§]	*TERC* (1/55, 1.8%), *PARN* (1/55, 1.8%), *RTEL1* (1/55, 1.8%)
chILD-specific ILD conditions	
ILD	*ABCA3* (13/55, 24%), *SFTPC* (8/55, 15%), *NKX2.1* (4/55, 7.3%), *PARN* (1/55, 1.8%), *RTEL1* (1/55, 1.8%)
PPFE and dyskeratosis congenita	*TERC* (1/55, 1.8%)
NEHI	*NKX2.1* (1/55, 1.8%)
Langerhans cell histiocytosis	*BRAF* (2/55, 3.6%)
Systemic diseases	*COPA* (4/55, 7.3%), *STING1* (3/55, 5.5%), *NPC1* (1/55, 1.8%), *NLPR3* (1/55, 1.8%), *HPS2* (AP3B1) (2/55, 3.6%), *FARSA* (1/55, 1.8%), *FLNA* (2/55, 3.6%)
PAP	*CSF2RB* (1/55, 1.8%), *CSF2RA* (3/55, 5.5%), *SLC7A7* (1/55, 1.8%)
CID syndrome	*TTC37* (1/55, 1.8%), *TGFBR1* (1/55, 1.8%)
Microlithiasis	*SLC34A2* (3/55, 5.5%)

ChILD: childhood interstitial lung disease; ILD: interstitial lung disease; PPFE: pleuroparenchymal fibroelastosis; NEHI: neuroendocrine hyperplasia of infancy; PAP: pulmonary alveolar proteinosis; CID: combined immunodeficiency; *NKX2-1*: NK2 homeobox 1; *ABCA3*: ATP binding cassette subfamily A member 3; *SFTPC*: surfactant protein C; *CSF2RA/B*: colony-stimulating factor 2 receptor subunit α/β; *SLC34A2*: solute carrier family 34 member 2; *SLC7A7*: solute carrier family 7 member 7; *COPA*: coatomer protein complex subunit α; *STING1*: stimulator of interferon response cGAMP interactor 1; *BRAF*: proto-oncogene B-Raf: *FLNA*: filamin A; *NLRP3*: NLR family pyrin domain containing 3; *NPC1*: NPC intracellular cholesterol transporter 1; *FARSA*: phenylalanyl-tRNA synthetase subunit α; *HPS2-AP3B1*: adaptor-related protein complex 3 subunit β1; *TTC37*: tetratricopeptide repeat domain 37; *TGFBR1*: transforming growth factor β receptor 1; *TERC*: telomerase RNA component; *PARN*: poly(A)-specific ribonuclease; *RTEL1*: regulator of telomere elongation helicase 1. [#]: surfactant-related; [¶]: sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis; [+]: bronchiolitis obliterans, hypersensitivity pneumonitis; [§]: unclassified ILD.

TABLE 4 Re-specification of chILD diagnosis in adult ILD centre

Initial chILD diagnosis (presented for each consecutive patient of the study cohort[#])	Diagnosis post re-evaluation at adult ILD centre
ILD of unknown cause	Chronic hypersensitivity pneumonitis
ILD of unknown cause	Pulmonary alveolar proteinosis
ILD of unknown cause	Chronic hypersensitivity pneumonitis
Chylothorax, ILD	Lymphangioleiomyomatosis
ILD of unknown cause	Chronic hypersensitivity pneumonitis
ILD of unknown cause	Lymphangioleiomyomatosis
B1[¶] category DPLD	A2[+] category DPLD
DPLD	Lung fibrosis and emphysema[§]
DPLD	Familial hypersensitivity pneumonitis
DPLD	Familial ILD
Post infectious ILD (measles)	*SFTPC*-related ILD[f]
Idiopathic NSIP	*SFTPC*-related ILD[f]
DPLD	Drug-induced ILD (nitrofurantoin)
Diffuse bullae	Unclassifiable ILD
Sarcoidosis	Unclassifiable ILD
Sarcoidosis	Niemann–Pick ILD[f]
DPLD	Systemic lupus erythematosus and Sjögren's ILD
Tuberculosis – sarcoidosis	Sarcoidosis
Idiopathic pulmonary hemosiderosis	MPO-associated ILD
Unclassifiable ILD	IgG4- related ILD
Hemosiderosis	Pulmonary alveolar proteinosis
Familial ILD-PH	Granulomatosis with polyangiitis
Granulomatosis with polyangiitis	Sarcoidosis
NKX2.1-ILD	Desquamative interstitial pneumonia[§]

chILD: children interstitial lung disease; ILD: interstitial lung disease; DPLD: diffuse parenchymal lung disease; NSIP: nonspecific interstitial pneumonia; *SFTPC*: surfactant protein C; MPO: myeloperoxidase; PH: pulmonary hypertension; *NKX2-1*: NK2 homeobox 1. [#]: n=24; [¶]: sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis; [+]: surfactant-related; [§]: for certain patients the new diagnosis corresponds to a more precise molecular or histological/radiological diagnosis; [f]: molecular diagnosis later in life.

will be discussed in the future [26–29]. Very few data exist in the literature on the natural history of these entities from childhood to adulthood and further studies are needed [9, 30–32]. Most chILDs are diagnosed before the age of 2 years [3]. The median age of diagnosis for those surviving into adulthood and transferred to adult care was much older (13 years (6–16 years)). Many early onset chILD entities are rapidly fatal [33]; however, others, especially NEHI, have a favourable prognosis with a high rate of remission and in many cohorts are the most common category of chILD. The scarcity of NEHI patients in our study suggests that most are not transitioned [12, 34]. Indeed, only a small minority of patients (1.6%) were NEHI survivors who had a good clinical status. These data in combination with the observation that a minority of chILD survivors continued to be followed up in paediatric centres suggests that there might be a loss to follow-up of chILD patients within paediatric services or at the point of transition to adult services, meaning they are only reviewed in primary care or not at all. Indeed, an informal questionnaire study showed that this is true for many patients (C. Gilbert, personal communication). This may be due to the refusal of children and parents to transition due to uncertainties regarding a new healthcare system and reluctance to leave their paediatric clinicians with whom they have long-lasting bonds and/or to the inadequate preparation and coordination for the transition process [35, 36]. Based on our results, disease severity could also play a role, so that a patient with a chILD with better functional status and treatment burden and a better prognosis could be less likely to transfer to adult care. It is arguable that this is a mistake, because we will only determine whether there are any long-term complications by continuing to review these patients. It is also important to study the impact of suboptimal transition to adult centres on the future respiratory health of chILD patients. By so doing, we would learn more about the lung function trajectories of chILD patients reaching adulthood as well as morbidity and mortality in adulthood.

Re-assessment should be performed in every chILD patient at transition [36]. However, re-specification of diagnosis was reported only in a minority of patients; these were mainly for previously unclassifiable chILDs for which a more precise molecular or histological/radiological diagnosis could be reached. These included genetically determined ILD, exposure-related ILD (hypersensitivity pneumonitis), documentation of collagen tissue disease-related ILD or vasculitis, or rare diseases such as PAP and IgG4-related disease.

TABLE 5 Comparisons of demographic, epidemiological, clinical, functional, radiological and genetic characteristics between the four major chILD categories in chILD survivors

Parameter	Total cohort	A4	B1	B2	Bz	p-value[#]
Patients (n)	244	51	85	34	31	
Gender						**0.020**
Male	124 (51)	24 (47)	39 (46)	25 (74)	20 (65)	
Female	120 (49)	27 (53)	46 (54)	9 (27)	11 (35)	
Age (years)						
At diagnosis	13 (6–16)	10 (2–15)	13 (8.25–16)	10 (5–16)	14 (11–16)	**0.025**
At transition	18 (18–20)	18 (18–19)[+]	18 (18–20)[§]	18 (18–20)	20 (18–34)[+§]	**<0.001**
At inclusion in the study	25 (22–33)	24 (22–29)[+]	26 (21–35)	25 (22–29)	33 (21–45)[+]	0.053
Follow-up (months)	62 (19–120)	55 (21–115)	90 (22–150)	67 (49–95)	40 (12–73)	0.154
Last follow-up findings						
FEV_1 % pred	63 (40–83)	68 (38–86)[+§]	69 (48–88)	54 (39–64)	48 (29–62)[+§]	**0.007**
FVC % pred	70 (47–89)	72 (61–83)	72.5 (55–91)[+]	57 (47–90)	48 (37–71)[+]	**0.014**
FEV_1/FVC	84 (70–91)	86 (78–95)[+]	84 (73–90)	72 (56–86)[+]	83.4 (73–90)	**0.027**
TLC % pred	76 (56–97)	74 (50–85)	76 (64–97)	96 (54–108)	59 (43–98)	0.286
D_{LCO} % pred	48 (32–75)	43 (31–72)	55 (40–70)	46 (24–96)	35 (21–58)	0.2
Bronchoscopy at chILD diagnosis	133 (55)	23 (45)	56 (66)	20 (59)	14 (45)	0.06
Biopsy at chILD diagnosis	131 (54)	25 (49)	58 (68)	10 (30)	15 (48)	**0.001**
Genetic analysis at chILD diagnosis	99 (40)	35 (69)	26 (30)	8 (23)	12 (39)	**<0.001**
Positive molecular diagnosis	57 (23)	31 (61)	15 (18)	3 (8.8)	4 (13)	**<0.001**
Transition to adult care	227 (93)	46 (90)	81 (95)	30 (88)	29 (93)	0.513
Smoking status						0.203
Nonsmoker	209 (86)	44 (86)	68 (80)	33 (97)	26 (84)	
Current smoker	17 (7.0)	2 (3.9)	11 (13)	1 (2.9)	3 (9.7)	
Ex-smoker	18 (7.4)	5 (9.8)	6 (7.1)	0 (0)	2 (6.5)	
Vaping	4 (1.6)	0	3 (3.5)	1 (2.9)	0	0.414
LTOT	78 (32)	**11 (22)**	**21 (25)**	**11 (32)**	**16 (52)**	**0.003**
HRCT pattern						0.209
UIP	38 (16)	10 (20)	12 (14)	4 (12)	9 (29)	
Probable UIP	9 (3.7)	4 (7.8)	1 (1.2)	0 (0)	3 (9.7)	
Indeterminate	10 (4.1)	2 (3.9)	5 (5.9)	0 (0)	3 (9.7)	
Alternative	117 (48)	24 (47)	39 (46)	19 (56)	14 (45)	
Pulmonary hypertension	36 (15)	5 (9.8)	10 (12)	6 (18)	12 (39)	**0.018**
Pharmacological treatment						**0.024**
Corticosteroids	146 (60)	23 (45)	52 (61)	27 (79)	16 (52)	
Macrolides	14 (5.7)	6 (12)	3 (3.5)	0 (0)	1 (3.2)	
Hydroxychloroquine	8 (3.3)	3 (5.9)	4 (4.7)	0 (0)	1 (3.2)	
Antifibrotics	4 (1.6)	2 (3.9)	5 (5.9)	0 (0)	2 (6.5)	
Combination of the above	18 (7.4)	3 (5.9)	20 (24)	5 (15)	4 (13)	
Other	52 (21)	13 (26)	0 (0)	2 (5.9)	7 (23)	
Progression						**<0.001**
Stable	154 (63)	30 (59)	55 (65)	25 (74)	9 (29)	
Improving	38 (16)	8 (16)	23 (27)	3 (8.8)	2 (6.5)	
Worsening	37 (15)	7 (14)	7 (8.2)	5 (15)	15 (48)	
Pre-lung Tx evaluation	54 (22)	14 (28)	13 (15)	4 (12)	15 (48)	0.002
Correspondence of chILD to adult ILD based on international classifications [7]						**<0.001**
No=0[¶]	51 (21)	0 (0)	4 (4.7)	19 (56)	0 (0)	
Yes=1	193 (79)	51 (100)	81 (95)	15 (44)	31 (100)	

The four major chILD categories in chILD survivors, A4 (surfactant-related), B1 (sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis), B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) and Bz (unclassified ILD), represented 82.4% of the study population (n=201/244). Categorical variables are presented as n (%) and numerical variables are presented as median (interquartile range). Values in bold show statistical significance. chILD: childhood interstitial lung disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; LTOT: long-term oxygen therapy; HRCT: high-resolution computed tomography; Tx: transplantation. [#]: comparison between groups was performed with Kruskal–Wallis test; [¶]: not included as such at the most recent classification of adult-ILD [1]; [+,§]: p<0.05, significant difference between the groups; *post hoc* analysis for numerical data was performed with Dunn's multiple comparisons test, categorical data were compared using chi-square test.

TABLE 6 Comparisons of demographic, epidemiological, clinical, functional, radiological and genetic characteristics between the four major chILD categories in chILD survivors who were transferred and followed up in adult centres

Parameter	Total cohort	A4	B1	B2	Bz	p-value[#]
Patients (n)	227	46	81	30	29	
Gender						**0.017**
Male	114 (50)	20 (44)	37 (46)	22 (73)	19 (66)	
Female	113 (50)	26 (56)	44 (54)	8 (27)	10 (34)	
Age (years)						
At diagnosis	13 (6–16)	9 (2–14)	13 (8.7–16)	12 (5.8–16)	13 (10/16)	**0.020**
At transition	18 (18–20)	18 (17–19)$^{+}$	18 (18–20)§	18 (18–20)^{f}	21 (18–34)$^{+\S f}$	**<0.001**
At inclusion in the study	26 (22–34)	24 (22–29)$^{+}$	27 (22–35)	26 (22–30)	37 (22–45)$^{+}$	**0.020**
Follow-up (months)	61 (19–120)	43 (20–97)	94 (23–151)	60 (48–84)	49 (12–80)	0.143
Last follow-up findings						
FEV_1 % pred	61 (39–81)	68 (38–88)$^{+f}$	67 (47–87)	53 (38–61)$^{+}$	42 (27–61)^{f}	**0.003**
FVC % pred	69 (47–88)	73 (60–83)$^{+}$	72 (55–91)^{f}	57 (45–89)	47 (36–64)$^{+f}$	**0.004**
FEV_1/FVC	83 (70–90)	86 (77–94)$^{+}$	84 (73–90)^{f}	68 (53–85)$^{+f}$	83 (74–90)	**0.021**
TLC % pred	76 (56–96)	76 (55–86)	76 (64–97)	82 (52–108)	59 (42–98)	0.387
D_{LCO} % pred	48 (32–73)	49 (31–72)	55 (40–70)$^{+}$	54 (24–97)	31 (20–47)$^{+}$	**0.017**
Bronchoscopy at chILD diagnosis	123 (54)	19 (41)	54 (7)	17 (57)	13 (45)	**0.027**
Biopsy at chILD diagnosis	121 (53)	22 (48)	57 (70)	7 (23)	14 (48)	**<0.001**
Genetic analysis at chILD diagnosis	93 (41)	33 (72)	25 (31)	6 (20)	11 (38)	**<0.001**
Positive molecular diagnosis	52 (23)	29 (63)	15 (18)	1 (3.3)	3 (10.)	**<0.001**
Transition to adult care	227 (100)	46 (100)	81 (100)	30 (100)	20 (100)	
Smoking status						0.291
Nonsmoker	193 (85)	40 (87)	64 (79)	29 (96)	24 (83)	
Current smoker	17 (7.5)	2 (4.3)	11 (14)	1 (3.3)	3 (10)	
Ex-smoker	17 (7.5)	4 (8.7)	6 (7.4)	0 (0)	2 (6.9)	
Vaping	4 (1.8)	0	3 (3.7)	1 (3.3)	0	0.427
LTOT	76 (33)	10 (21.7)	21 (26)	11 (37)	15 (52)	**0.004**
HRCT pattern						0.287
UIP	36 (16)	10 (22)	10 (12)	4 (13)	9 (31)	
Probable UIP	7 (3.1)	3 (6.5)	1 (1.2)	0 (0)	2 (6.9)	
Indeterminate	9 (4)	1 (2.2)	5 (6.2)	0 (0)	3 (10)	
Alternative	105 (46)	21 (46)	37 (46)	15 (63)	13 (45)	
Pulmonary hypertension	35 (15)	5 (11)	10 (12)	5 (17)	12 (41)	**0.016**
Pharmacological treatment						**0.028**
Corticosteroids	138 (61)	20 (44)	51 (63)	24 (80)	15 (52)	
Macrolides	14 (6.2)	6 (13)	3 (3.7)	0 (0)	1 (3.4)	
Hydroxychloroquine	8 (3.5)	3 (6.5)	4 (4.9)	0 (0)	1 (3.4)	
Antifibrotics	4 (1.8)	2 (4.3)	0 (0)	0 (0)	2 (6.9)	
Combination of the above	14 (6.2)	2 (4.3)	4 (4.9)	4 (13)	3 (10)	
Other	47 (21)	12 (26)	18 (22)	2 (6.7)	7 (24)	
Progression						**<0.001**
Stable	146 (64)	27 (59)	54 (67)	22 (73)	9 (31)	
Improving	30 (13)	6 (13)	20 (25)	2 (6.7)	1 (3.4)	
Worsening	36 (16)	7 (15)	7 (8.6)	5 (17)	14 (48)	
Pre-lung Tx evaluation	53 (23)	14 (30)	13 (16)	4 (13)	14 (48)	**0.005**
Correspondence of chILD to adult ILD based on international classifications [7]						**<0.001**
No=0[¶]	47 (21)	46 (100)	81 (100)	13 (43)	29 (100)	
Yes=1	180 (79)					

The four major chILD categories in chILD survivors, A4 (surfactant-related), B1 (sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis), B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) and Bz (unclassified ILD), represented 81.9% of the study population (n=186/227). Categorical variables are presented as n (%) and numerical variables are presented as median (interquartile range). Values in bold show statistical significance. chILD: childhood interstitial lung disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; LTOT: long-term oxygen therapy; HRCT: high-resolution computed tomography; Tx: transplantation. [#]: comparison between groups was performed with Kruskal–Wallis test; [¶]: not included as such at the most recent classification of adult-ILD [1]; $^{+,\S,f}$: p<0.05, significant difference between the groups; *post hoc* analysis for numerical data was performed with Dunn's multiple comparisons test, categorical data were compared using chi-square test.

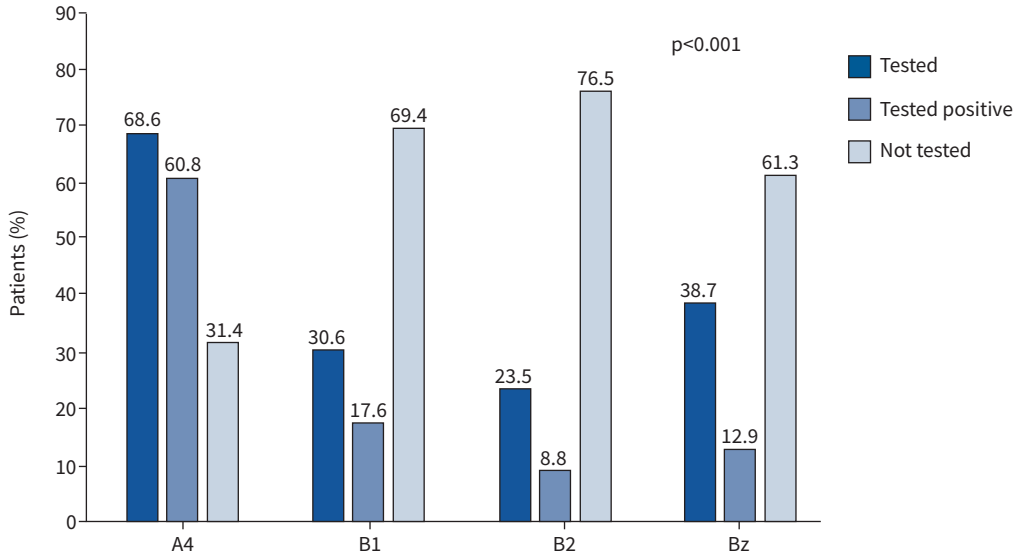

FIGURE 3 Differences between the four main childhood interstitial lung disease (chILD) categories A4 (surfactant-related), B1 (sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis), B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) and Bz (unclassified ILD) regarding genetic analysis for documentation of molecular diagnosis. p<0.05 was considered statistically significant.

These changes may relate to the evolution of the disease and/or the increase in diagnostic possibilities (especially genetic) and knowledge in the time period between the original diagnosis and the transition to adult care. The differences in paediatric and adult ILD classifications may also contribute to change in diagnosis. Re-assessment of treatment at transition to adult centres mostly led to the introduction of new treatment modalities (antifibrotics, not licensed in children) as well as modification of immunomodulatory treatment [37–41].

Employment and career development in rare diseases is influenced by many parameters including educational attainment and limited expectations as well as the severity of the illness and personal and

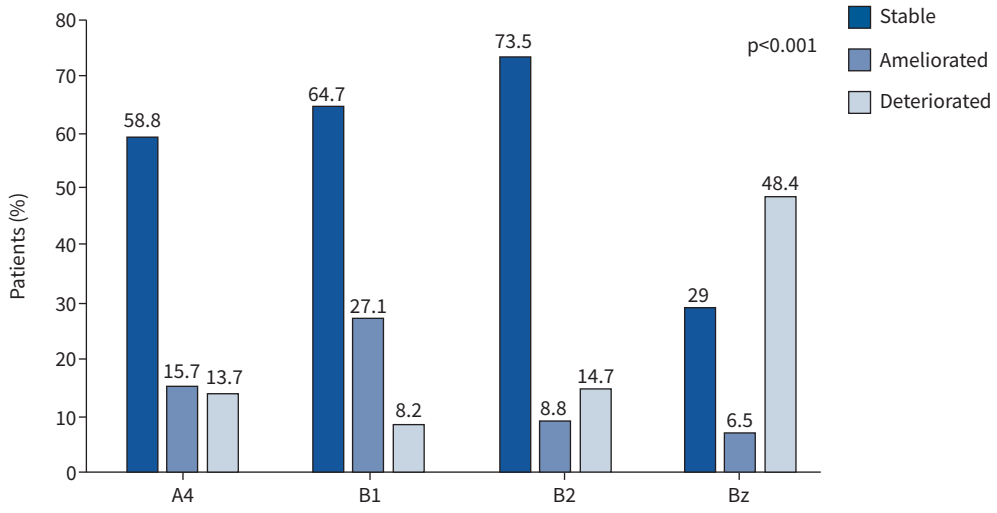

FIGURE 4 Differences between the four main childhood interstitial lung disease (chILD) categories A4 (surfactant-related), B1 (sarcoidosis, haemosiderosis, connective tissue disorders, vasculitis), B2 (bronchiolitis obliterans, hypersensitivity pneumonitis) and Bz (unclassified ILD) regarding disease progression. p<0.05 was considered statistically significant.

social characteristics. Unfortunately, our data were available only for one quarter of the study population. These data are therefore limited and should be interpreted with caution. chILD survivors were employed in occupations demanding both manual and intellectual labour. The high rate of missing data regarding employment in our study cohort might further reflect the fact that employment seems to be an under-recognised and under-researched aspect in many rare diseases [42, 43].

Limitations of our study include the fact that our figures are likely an underestimate influenced by variation in referral patterns between regions and countries as well as the retrospective nature of data collection and the limited number of many disease entities. However, the present study is the first attempt to provide an overall evaluation of this rare but newly recognised young-adult patient population that needs ongoing specialist care and represents numerous participating centres and clinical practices [13, 14, 44, 45]. In the future, increased diagnostic awareness of chILD and optimisation of care should increase the number of patients being transferred to adult care [46].

In conclusion, chILD survivors do exist and are widely geographically distributed, at least as shown by this multicentre European study. Owing to the significant loss of lung function, as well as the heterogeneity of their aetiologies and therapeutic requirements, these patients have a significant impact on adult ILD referral centres. Only a minority continues to be followed up in paediatric centres. It is important to study the impact of suboptimal transition to adult ILD centres on the future respiratory health of chILD patients. Re-specification of diagnosis and treatment may contribute to precision and personalisation of management. Discrepancies in classifications between chILD and adult ILDs requires harmonisation efforts to optimise clinical care and research.

Ethics approval: This multicentre retrospective cohort study had ethics committee approval for the handling and analysis of personal data (clinical, functional, radiological and genetic) regarding the patients included in the study.

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