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Financial support and sponsorship

Our work on chILD is support by grants from the Institut National de la Santé et la Recherche Médicale (INSERM), the European Union's Seventh Framework Program (FP7-ChILD-EU 2007-2013) under grant agreement n°305653, as well as funding from the patient organizations Respirer c'est Grandir and Belleherbe Association. However, this study did not receive any specific funding.

Key words: Interstitial lung disease, children, quality of life, scale, chILD

Running Title: Quality of life in kids' interstitial lung disease

Word count: 3137/3500

Abstract word count: 224/250

Tables and figures: 5/6

References: 36/40

Title: 86/100 characters including spaces

Running title: 50/50 characters including spaces

Abstract

Introduction: Interstitial lung disease in children (chILD) is a highly heterogeneous group of rare and severe respiratory disorders. The disease by itself, the burden of the treatments (oxygen therapy, corticosteroid pulses, nutritional support) and recurrent hospitalisations may impair the quality of life (QoL) of these children. The aim of the study was to compare the health-related QoL (HR-QoL) in chILD compared to a healthy population and to find out the predictive factors of an altered QoL.

Methods: Patients aged 1 month to 18 years with ILD of known or unknown aetiology were prospectively included. Parents and children over 8 years old were asked to fill the PedsQL^{TM} 4.0 Generic Core Scale ranging from 0 to 100 points.

Results: A total of 78 children were recruited in 13 French paediatric centres. Total scores were 11.94 points ($p=0.0003$) less for child self-report and 14.08 points ($p<0.0001$) less for parent proxy-report with respect to the healthy population. The clinical factors associated with a lower total score were: extra-pulmonary expression of the disease, higher Fan severity score, long-term oxygen therapy, nutritional support and number of oral treatments.

Conclusion: Using a validated QoL scale, we showed that HR-QoL is significantly impaired in chILD compared to a healthy population. Factors altering QoL score are easy to recognize and could help identify children at a heightened risk of low QoL.

1. INTRODUCTION

Interstitial lung disease (ILD) in infants and children (chILD) is a highly heterogeneous group of rare respiratory disorders, characterized by inflammatory and/or fibrotic changes that affect alveolar walls and interstitium [1]. The four main aetiologies are surfactant disorders, pulmonary alveolar proteinosis, pulmonary haemosiderosis and sarcoidosis [2,3]. Other chILD can be related to various aetiologies such as environmental or toxic exposure-related ILD (hypersensitivity pneumonitis, medication), autoimmune diseases (connective tissue disease, or pulmonary vasculitis), metabolic disorders and developmental disorders [4–7]. However, depending on the recruitment strategy, 8 to 27% of chILD remain of unknown aetiology [8–11]. Nearly 16% of cases appear to be familial [12]. The chILD incidence is difficult to evaluate but the estimations provided by European studies are under 1 per 100 000 children [3,12–14].

ILD is usually a chronic and severe disease that is associated with substantial morbidity and around 15% mortality [3]. Children suffering from severe ILD, may develop hypoxemia and growth issues, requiring long-term treatments such as oxygen therapy, corticosteroids and nutritional support. Systematic follow-up and acute exacerbations lead to recurrent hospitalizations and visits [15]. The disease by itself and the burden of the treatments may affect children's quality of life (QoL) in different ways.

Health-related (HR)-QoL measurement is a crucial tool used as a health outcome in clinical trials [16–18]. It is also a key feature to estimate the clinical, socio-familial and psychological impacts of the disease [19]. Generic QoL using validated questionnaires is a necessary step to assess a specific paediatric population's HR-QoL and to provide insights to create or improve a chILD specific QoL questionnaire such as the one recently proposed by the German group [20]. This strategy has already been used to validate specific paediatric QoL questionnaires for other chronic lung diseases such as cystic fibrosis and asthma [21–25].

The aim of this study was (i) to assess HR-QoL in a large cohort of infants and children with ILD using validated questionnaires; (ii) to identify the clinical factors that were associated with lower HR-QoL scores and (iii) to compare the child and his parents' QoL scores.

2. METHODS

2.1. Study subjects

In France, in 2008, the National Reference Centre for Rare Lung Diseases (RespiRare) created a national database for paediatric interstitial lung diseases [2]. Over 400 cases of chILD have been collected. Among these patients, 200 are currently followed. Patients aged 1 month to 18 years diagnosed with ILD of known or unknown aetiology and followed in a French paediatric clinical centre of RespiRare were included. As legally recommended, the patient and his parents or legal representative received a written and an oral information and declared their non-opposition to the study participation. The study obtained all legal authorizations and the research protocol was approved by the French Paediatric Society ethics committee (CERSFP_2017_062).

2.2. Study design

The study was prospective and multicentric in France. The parents were contacted by phone before receiving the survey by email. In case of non-response, a second email was sent after one month. The clinical data of the included patients were retrieved from the national internet-linked based database for paediatric interstitial lung diseases (e-RespiRare) [2] and from the medical files for the missing data. The clinical data were collected either at the date of the questionnaire, or at the nearest visit, spaced less than 2 months from the date of the questionnaire. They included clinicals characteristics such as the gender, age, date of diagnosis, aetiology of the ILD, family medical history of ILD, extra-pulmonary localisations, Fan

severity score (**Supplemental material 1)** [26], lung function tests, treatments and truancy. The main outcome measure was the mean difference between the QoL scores of chILD and published scores in an aged-matched healthy population [21]. The secondary outcomes were (i) the correlations between clinical characteristics and PedsQL scores; (ii) the correlations between child self-report and his parents' proxy-report and (iii) the correlations between the mother's and the father's reports.

2.3. Questionnaire

We used a validated generic paediatric QoL questionnaire, the PedsQL™ 4.0 Generic Core Scales (PedsQL™, Copyright © 1998 JW Varni, Ph.D, all rights reserved). It is a non-specific disease questionnaire, composed of child self-reports for children over 8 years old (8-12 years for children and 13-18 years for teenagers) [27] and parent proxy-report for all ages (1-12 months, 13-24 months, 2-4 years, 5-7 years, 8-12 years, 13-18 years) [21]. The patients and parents were asked to consider the past month condition. A five-point response scale was used (0 = never a problem; 1= almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Each answer was then reverse-scored to a 0-100 scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0). A total score was obtained ranging from 0 to 100, a higher score indicating better HR-QoL. The total score reflects different dimensions: a physical score and a psychosocial score (split into different functioning scores: emotional, social and school or cognitive for infants under 1 year of age). The PedsQL™ 4.0 Generic Core Scales author suggested that a 4.4 points change in the total scale score for child self-report and a 4.5 points change for parent proxy-report reflects a clinically meaningful difference [21]. Following the survey, the parents were freely invited to propose improvements for their children's QoL.

2.4. Statistical analysis

Differences by 0.5 standard deviation (SD) in mean QoL scores are considered as relevant for the patient [28]. This corresponds to approximately 8 points in total score. At least 50 patients were necessary to have 80% power to evidence such a difference, assuming a SD by 20 points in patients' response, slightly larger than the healthy population. We used the participants of the validation study of the PedsQL™ 4.0 Generic Core Scales [21] as the healthy population reference. Scores of chILD patients were compared to this reference using one sample *t-tests.* Effect sizes, computed as the difference between the mean score in the reference group and the chILD group divided by the healthy group SD, were used to summarize differences between healthy children and children with ILD. Effect size were described as small (0.20), medium (0.50) and large (0.80) [29]. Concordance between child self-report and parent proxy-report was determined with the intraclass correlation coefficient (ICC) accounting for both correlation and level. ICC ranges from 0 (low concordance) to 1 (high concordance) [30,31], and described as small (0.10), medium (0.30) and large (0.50) [32]. Factors predictive of HR-QoL scores were determined by linear regression. For multivariable analysis, we adjusted on sex, and used backward selection for other variables, starting with all variables with $p<0.2$ in the univariable analysis and removing stepwise until all remaining variables had $p<0.05$.

3. RESULTS

3.1 Study population

Between June 2016 and January 2018, 112 families were contacted. A total of 78 patients were included in 13 French paediatric centres, reaching a 70% response rate. **Table 1** shows the main characteristics of the study population. The sex ratio (male/female) was 1.1. The mean age at diagnosis was 2.3 years old (SD = 3.4). The mean age at inclusion was 7.2 years old (SD = 5.0) with a range of 0.2-17.6 years. The chILD aetiologies of the included patients were representative of the heterogeneity of chILD diagnoses. As expected, the main conditions were surfactant disorders including alveolar proteinosis, haemosiderosis, neuroendocrine cell

hyperplasia of infancy, sarcoidosis and systemic disease with vasculitis. The aetiology of chILD remained unknown for n=25, 32% of the patients. The mean duration of the disease was 4.2 years at the time of the study (SD = 4.2). A family history of ILD was found in 18% of the cases. Almost a third of the children (n=24, 31%) were asymptomatic (Fan score = 1) and another third (n=23, 29%) presented a severe ILD (Fan score 3-5) **(Supplemental material 1)**. At least one extra-pulmonary organ was involve in n=29, 37% of the patients (central nervous system (n=11), liver (n=8), thyroid (n=8), spleen (n=5), skin (n=4), joints (n=2), kidney (n=2), digestive system (n=1), haematologic system (n=1), muscular (n=1), eyes (n=1), ENT (n=1)). Two patients presented a chILD associated to a Down Syndrome [33]. At the time of the study, 50 (64%) patients were currently under treatment: 35% received corticosteroid pulses (70% intravenous), 29% required long-term oxygen therapy and 18% were under nutritional support.

3.2 chILD HR-QoL scores

Among the families, 68 mothers (87%) and 44 fathers (56%) completed the parent-proxy report. At inclusion, 44 children were older than 8 years, 88% of them (n=29) answered to the child's self-report. Both parents answered for 44% of the children (n=35). At least one parent answered for 77 (99%) children. **Table 2** presents mean and SD of the PedsQL 4.0 scores for child self-report and parent proxy-report compared to a healthy control population [21]. Mean differences of 11.94 points for child self-report and 14.08 points for parent proxy-report were found, in favour of the healthy population. The effect sizes for the total score were respectively 0.96 and 0.91 for child self-report and parent proxy-report, revealing a large magnitude in the difference with the healthy population's means. The PedsQL mean scores in chILD were significantly lower than those observed in a healthy population (*p-value*=0.0003 for the total score of child self-report and *p-value*<0.0001 for parent-proxy report).

3.3 Predictive factors impairing HR-QoL

Factors impairing HR-QoL were studied with univariate and multivariable analysis **(Table 3)**. An extra-pulmonary localisation (*p-value*<0.0001), a higher Fan score (*p value*<0.0001), long-term oxygen therapy (*p-value*=0.02), nutritional support (*p-value*<0.0001) and the number of oral treatments (*p-value*=0.03) were significantly associated with a lower total score in univariate analysis. Each additional oral medication lowered the total score by 3.3 points (for 3 oral treatments -9.9 points). The absence of a characterized aetiology for the chILD was not associated with a lower HR-QoL (+7.44 points, non-significative). A longer duration of the disease and a family history of ILD had little impact on the HR-QoL score. In multivariable analysis, an extra-pulmonary localisation (*p-value*=0.04), nutritional support (*p-value*<0.0001) and a higher Fan score (*p-value*<0.0001) were still associated with a lower total score and the included variables had similar impact in children with or without extra-pulmonary localisation (**Supplemental material 3**).

The Fan score was associated with an altered HR-QoL score. However, the reverse linear relationship between the total score at PedsQL and the Fan severity score did not reach significance, probably due to the small number of included patients. The small number of lung function tests collected didn't enable to study their correlation with the QoL scores. Almost half of the included patients (n=35, 45%) were under 6 years of age and only a small number of the others had full lung function testing in the past month.

3.4 Concordance between child and parent reports

Table 4 analyses the differences between means PedsQL scores of child self-report and parent proxy-report for 28 of the 29 children over 8 years old who completed the child report. The ICC for the total score between the child and his parents was 0.76, showing large concordance in

their responses. The ICC for the emotional score was only medium (0.48), essentially due to more severe feeling of the disease by the parents.

3.5 Concordance between mother and father reports

Table 5 compares the means PedsQL scores of the mother's and the father's report for the 35 children for whom both parents answered the questionnaire. The ICC for the total score between the mother and the father (0.75) was also in favour of a large concordance. For the emotional, social and school scores, the concordance was lower (respectively 0.63 – 0.66 – 0.60). The ICC couldn't be calculated for the cognitive score, due to the small number of concerned patients (n=9).

3.6 Parents proposals

The parents suggested several ideas to improve their children's QoL. The main proposals were a technical improvement of oxygen therapy devices, a better nutritional and orality disorders management, more psychological support, a wider medical information about the disease for the family but also for the children's teachers and school friends, and a better care organization at hospital and at home.

4. DISCUSSION

HR-QoL evaluation is important in all diseases, but still not widely used in rare diseases. The targeted population is by definition restricted and, in chILD, heterogeneous. Patient self-reporting gives back to the patient, here the child, a central role in his own management. In this study, the high response rate (88%) of children over 8 years old confirmed their great interest in taking part in the assessment of their condition. The overall response rate (70%) is comparable with others QoL studies [20,24,25]. The main finding of this study is the confirmation

that HR-QoL is significantly impaired in chILD. The mean total score in chILD is comparable to the published scores in other chronic respiratory diseases such as asthma and cystic fibrosis [24,25].

QoL was altered by specific predictive factors. Some of them were intuitively expected: a higher Fan score, corresponding to more severe disease, was correlated with a lower QoL score; the deleterious impact of extra-pulmonary localisations, oxygen therapy, and nutritional support had similar impact. Other predictive factors of reduced QoL were more surprising. Each additional oral medication lowered the total score by 3.3 points (for 3 oral treatments -9.9 points). This was not expected, since other treatments considered as more burdensome (such as intravenous corticosteroid pulses) were not found to significantly alter the QoL score. Patients may associate the latter with better efficacy, or value shorter treatment duration (3 days) compared to long-term oral daily treatments [34]. This finding may also reflect the real or feared side effects of each additional treatment and should encourage the clinicians to discuss carefully the indication of each medication, and to re-evaluate regularly the need to pursue them. Better information on the treatments (purpose, expected results, side effects) may enhance his feeling about it and its involvement in his own care. ~~The HR-QoL was also degraded in the absence of treatment. This may be explained by the own impact of the disease and the generated anxiety, the risk of a pejorative evolution, or having to (re)-need medication again in the future.~~ It is also important to note that parents had thoughts on how to improve medical devices, especially for oxygen therapy that remains bulky, heavy and ill adapted to the daily-life of the children (school, sport).

A family history of ILD, which could exacerbate the daily-life burden of these families, had no impact on the QoL score nor on psychosocial/emotional functioning scores (data not shown). One may assume that already affected parents may better understand and endure their child's problems. Disease duration did not affect the QoL score. Interestingly, the absence of a characterised aetiology impacted positively the QoL, although the difference was non-

significant. The reason for such a result is unknown but it is tempting to speculate that an unknown diagnosis does not preclude hope of a less severe illness.

~~Finally, 41% of the study population required non-pharmacological treatments (oxygen therapy, nutritional support, ventilation) with equipment dependency. The small number of lung function tests collected didn't enable to study their correlation with the QoL scores. Almost half of the included patients (n=35, 45%) were under 6 years of age and only a small number of the others had full lung function testing in the past month.~~

We found large concordance between the parents and their child. However, even if non-significant, we observed that parents generally assessed their children's QoL more pejoratively than the children themselves. ~~When parents reported a lower score than their child (n=15, 54%), the difference was important (-11 points in average). When they reported a higher score (n=13, 46%), the difference was smaller (+6 points in average).~~ This was also noticed in previous paediatric QoL studies and it has been suggested that parents' feeling is more related to the disease and the burden of the treatments and that parents' and children's judgments rely on different information, both perspectives being interesting [35] [36]. We also found large concordance between the mother and the father. This interchangeability of parent in reporting children's HR-QoL was noticed by Doostfatemeh et al. for total score. As in our study, he however described a higher emotional functioning score for the father [37]. The emotional dimension relies more on the subjectivity and the fantasies of each individual (parent's age and health status ~~(beside ILD history)~~, culture, beliefs, trauma and fears) ~~that are highly dependent on personal characteristics~~ that were not collected in this study. Finally, as already reported in other studies, more mothers than fathers (87% versus 56%) participated to the study [25]. Even if no relationship could be done with the father's implication in the disease, this is damaging as it has been suggested that the father's implication in his child's care could be associated with a better treatment compliance and also a better QoL [38].

~~Individually, the parents' and the children's feelings are not always in line with the severity of the disease observed by the clinician.~~ QoL longitudinal evaluation ~~remains a subjective asset, specific to each person, but with a~~ is of valuable long-term interest for the patients. Over time, the repetition of a specific and simple HR-QoL could help the clinician to personalise the management of his patient~~, considering both drugs and medical supplies~~. To reach this objective, as it was done with great efficacy in other chronic lung diseases such as asthma, the HR-QoL questionnaire needs to be short and easy to fulfil~~. In, the Childhood Asthma Control Test (C-ACT) is a HR-QoL tool largely used in the follow up of the patients that has proven its efficacy in assessing the control of the disease~~ [39]. HR-QoL questionnaires should also be more widely used as health outcome in clinical trials. For chILD, Niemitz et al recently proposed a modified QoL questionnaire based on the Generic PedsQL with more disease specific items. ~~This QoL questionnaire was composed of~~ (5 to 11 questions according to the age of the child) [20]. This first chILD-specific HR-QoL demonstrated moderate to high correlations with the generic PedsQL, depending on the dimensions and the ages. With the collaboration of patient associations, efforts need to be pursued in creating and validating new specific chILD QoL questionnaire that could reach high correlations in all the dimensions with validated paediatric questionnaires. ~~To this end,~~ A dedicated working group of the European Network for Translational research in children and adult ILD (ENTeR-chILD) (European Cooperation in Science and Technology (COST) action CA16125) has recently been dedicated to these crucial issues [40]. Already, regarding the patient's information on the disease, a booklet for chILD has ~~already~~ been set up in English and is now available in 5 other languages (http://www.klinikum.uni-muenchen.de/Child-EU/en/child-eu-register/services/booklet/index.html) [41].

CONCLUSION

This study confirms that HR-QoL is highly impaired in chILD compared to a control population. The factors associated with a lower total score are: an extra-pulmonary localisation, a higher

Fan score, a long-term oxygen therapy, a nutritional support and the number of oral treatments. These predictive factors are easily recognisable by the clinician and could help to identify the patients at-risk of a severely impaired QoL. ~~A disease-specific has been recently validated and international collaborative efforts are being pursue to improve its correlation with validates scales.~~ More efforts are needed to improve a disease-specific QoL questionnaire, to study longitudinal evolution of chILD QoL and finally to improve the patients QoL. Finally, an evaluation of the parents' QoL would be necessary, since they are at the centre of their child's management.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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~~**Legends to Figure**~~

~~**Figure 1: Relationship between PedsQL total score distribution and Fan severity score**~~

~~The total PedsQL score of the patients were segregated per Fan severity score. A linear regression was assessed and highlights a trend to a reverse linear relationship between PedsQL total score and Fan score. However, due to the small number of patients, the correlation did not reach significance.~~

Acknowledgements

The authors would like to thank the patients and their families for their participation to the study and their interest in reading the results. We thank the French patient associations for rare lung diseases and for chILD: Respirer c'est Grandir, Belleherbe Association, Association Française des Pneumopathies Interstitielles de l'Enfant (AFPIE). We also thank the participating clinicians of the 13 French paediatric centres for their help to include patients. We thank the Assistance Publique Hôpitaux de Paris, Sorbonne Université, Paris, France, and the national network for rare lung diseases: Centre de référence des maladies respiratoires rares (RespiRare). The ILD cohort is developed in collaboration with the Rare Cohort Disease (RaDiCo)-PID project (ANR-10-COHO-0003), the FP7-305653-child-EU project and the COST Action European network for translational research in children's and adult interstitial lung disease, COST ENTeR-chILD project (CA16125). We thank Dr James W Varni, Texas A&M University, College Station, TX, USA and Mapi Research Trust for providing the questionnaire. PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org and www.pedsql.org.

Table 1: Characteristics of the 78 included patients

Clinical characteristics	n	%
Gender		
Male	40	51
Female	38	49
Age		
0-12 months	9	12
13-24 months	8	10
2-4 years	14	18
5-7 years	13	17
8-12 years	25	32
13-18 years	9	12
Aetiology		
Surfactant disorders	25	32
Haemosiderosis	7	9
Neuroendocrine cell hyperplasia of infancy	5	6
Sarcoidosis	4	5
Systemic disease wih vasculitis	4	5
Histiocytosis	2	3
Connective tissue diseases	2	3
Metabolic disorders	1	1
Eosinophilic lung diseases	1	1
Other ILD	2	3
ILD of unknown aetiology	25	32
Family history of ILD	14	18
Severity Fan score		
Fan = 1	24	31
Fan = 2	31	40
Fan = 3	10	13
Fan = 4	10	13
Fan = 5	3	4
Extra-pulmonary localisation	29	37

Treatments	n	%
Pharmaceutical therapies	50	64
Corticosteroid pulses	27	35
Intravenous	19	24
Oral	8	10
Continuous oral corticosteroids	22	28
Azithromycin	19	24
Hydroxychloroquin	9	12
Other specific therapies	16	21
Immunosuppressive therapy	6	8
Immunomodulatory therapy	3	4
Tyrosin kinase inhibitor	4	5
Specific monoclonal antibody	3	4
PH-targeted therapy	1	1
Aspecific adjuvent therapy		
Nebulizer	5	6
Trimethoprim sulfametoxazole	25	32
Non pharmaceutical therapies	32	41
Respiratory		
Oxygen therapy	23	29
Continuous	13	17
Discontinuous	10	13
Whole lung lavage	1	1
Non invasive ventilation	3	4
Invasive ventilation	1	1
Lung transplantation	1	1
Nutritional		
Nutritional support	14	18
Other		
Haematopoietic stem cells graft	1	1

ILD, Interstitial Lung Disease

PH, Pulmonary Hypertension

Table 2: PedsQL scores of chILD: child self-report (n=29) and parent proxy-report (112 parents of 77 children) compared to a healthy population

	Healthy population*		chILD					
	Mean	**SD**	**Mean**	**SD**	**Difference**	**ES**	**IC 95%**	***p-value***
Child report (n=29)								
Total score	**83.91**	**12.47**	**71.97**	**15.41**	**11.94**	**0.96**	**0.51 - 1.41**	**0.0003**
Physical score	87.77	13.12	75.21	19.70	12.56	0.96	0.41 - 1.50	0.0037
Psychosocial score	81.83	13.97	70.45	16.35	11.38	0.81	0.39 - 1.24	0.0016
Emotional functioning	79.21	18.02	67.41	21.16	11.80	0.65	0.13 - 1.18	0.0335
Social functioning	84.97	16.71	78.10	22.38	6.87	0.41	-0.18 - 1.01	0.6577
School functioning	81.31	16.09	65.86	18.18	15.45	0.96	0.46 - 1.46	0.0005
Parent's report (n=77)								
Total score	**82.29**	**15.55**	**68.21**	**17.54**	**14.08**	**0.91**	**0.49 - 1.32**	**<0.0001**
Physical score	84.08	19.70	68.90	22.71	15.18	0.77	0.35 - 1.19	<0.0001
Psychosocial score	81.24	15.34	67.96	17.14	13.28	0.87	0.46 - 1.27	<0.0001
Emotional functioning	81.20	16.40	64.92	18.24	16.28	0.99	0.50 - 1.49	<0.0001
Social functioning	83.05	19.66	74.69	22.23	8.36	0.42	-0.08 - 0.93	0.0089
School functioning	78.27	19.64	62.59	22.35	15.68	0.80	0.29 - 1.30	<0.0001

SD, Standard Deviation

ES, Effect Size (small 0.20, medium 0.50, large 0.80)

IC 95%, Confidence Interval 95%

*, (17)

Table 3: Predictive factors of a PedsQL total score variation in univariate and multivariable analysis

	Total Score discrepancy	SD	*p-value*
Univariate analysis			
Clinical characteristics			
Male gender (versus female)	-7.99	4.42	0.07
Unknown aetiology (versus known aetiology)	7.44	4.21	0.08
Duration of the disease	-0.12	0.48	0.81
Z-score of the BMI	-0.34	1.19	0.78
Family history of ILD	-3.14	5.20	0.55
Extra-pulmonary localisation	-11.65	3.96	<0.0001
Fan score (2 versus 1)	-19.40	4.00	<0.0001
Fan score (≥3 versus 1)	-22.30	4.30	<0.0001
Treatments			
Treatment (versus no treatment)	-3.76	4.16	0.37
Pharmaceutical therapies			
Intravenous corticosteroids pulses	-6.78	4.60	0.14
Oral corticosteroids pulses	-6.60	4.15	0.12
Azithromycin	0.00	4.67	1.00
Hydroxychloroquin	-8.86	6.18	0.16
Other specific therapies	-8.40	4.65	0.08
Number of oral therapies	-3.30	1.51	0.03
Non pharmaceutical therapies			
Oxygen support	-10.35	4.23	0.02
Enteral nutritional support	-14.80	4.93	<0.0001
Other			
Truancy	-0.94	0.71	0.19
Multivariable analysis			
Male gender (versus female)	-5.76	3.60	0.11
Extra-pulmonary localisation	-7.26	3.40	0.04
Fan score (2 versus 1)	-16.46	3.91	<0.0001
Fan score (≥3 versus 1)	-18.94	4.21	<0.0001
Enteral nutritional support	-9.08	4.31	0.04

SD, Standard Deviation

BMI, Body Mass Index

ILD, Interstitial Lung Disease

Table 4: Concordance between the PedsQL scores of child self-report and parent proxy-report (n=28)

	n	Responder	Mean	SD	Difference	ES	ICC	IC 95%
Total score	28	Child	71.61	15.57	3.27	0.21	0.76	0.51 - 0.89
		Parents	68.34	17.20				
Physical score	28	Child	75.00	20.03	2.04	0.10	0.58	0.34 - 0.81
		Parents	72.96	19.35				
Psychosocial score	28	Child	70.04	16.50	4.50	0.27	0.69	0.36 - 0.86
		Parents	65.54	18.50				
Emotional functioning	28	Child	66.61	21.08	5.36	0.25	0.48	0.10 - 0.71
		Parents	61.25	18.94				
Social functioning	28	Child	77.68	22.67	2.66	0.12	0.78	0.53 - 0.91
		Parents	75.02	24.00				
School functioning	28	Child	65.89	18.51	5.36	0.29	0.69	0.47 - 0.83
		Parents	60.54	22.64				

SD, Standard Deviation

ES, Effect Size (small 0.10, medium 0.30, large 0.50)

ICC, Intraclass Correlation Coefficient (0: low concordance - 1: high concordance)

IC 95%, Confidence Interval 95%

Table 5: Concordance between the PedsQL scores of the mother's and the father's report (n=35)

	n	Responder	Mean	SD	Difference	ES	ICC	IC 95%
Total score	35	Mother Father	68.26 68.69	18.02 19.49	0.43	0.02	0.75	0.50 - 0.88
Physical score	35	Mother Father	69.94 69.77	23.54 23.85	0.17	0.01	0.73	0.36 - 0.91
Psychosocial score	35	Mother Father	67.51 68.54	17.44 18.53	1.03	0.06	0.70	0.44 - 0.85
Emotional functioning	35	Mother Father	62.20 63.06	22.43 18.75	0.86	0.04	0.63	0.23 - 0.82
Social functioning	35	Mother Father	74.23 75.85	22.29 23.50	1.62	0.07	0.66	0.44 - 0.83
School functioning	23	Mother Father	68.48 68.17	18.62 25.80	0.30	0.02	0.60	0.25 - 0.80
Cognitive score	9	Mother Father	71.89 74.44	24.92 16.02	2.56	NA	NA	NA

SD, Standard Deviation

ES, Effect Size (small 0.10, medium 0.30, large 0.50)

ICC, Intraclass Correlation Coefficient (0: low concordance - 1: high concordance)

IC 95%, Confidence Interval 95%

NA, Non Applicable

Supplemental Material 1

Fan severity score is provided herein as well as the repartition of the 78 included patients' scores (Fan LL, Deterding RR, Langston C. Pediatric interstitial lung disease revisited. Pediatr Pulmonol. 2004 Nov;38(5):369–78) (Ref 22).

Fan Score	Symptoms	Oxygen saturation <90% at exertion and /or sleep	Oxygen saturation <90% at rest	Pulmonary hypertension	Patients	
					n	%
1	No	No	No	No	24	31
2	Yes	No	No	No	31	40
3	Yes	Yes	No	No	10	13
4	Yes	Yes	Yes	No	10	13
5	Yes	Yes	Yes	Yes	3	4

Supplemental Material 2

Detailed results for the 78 included patients, retrieved by chILD diagnosis

Inclusion number	Sex	Diagnosis	Mutation	Age at inclusion	Age at diagnosis	Fan score	Extra-pulmonary localisation	Total score reported by the mother	Total score reported by the father	Total score reported by the child
2	F	Surfactant disorder	SPC	5.8	1.5	2	No	66	NA	NA
9	M	Surfactant disorder	NKX2.1	2.7	0.1	4	Yes	51	55	NA
11	M	Surfactant disorder	SPC	12.1	0.0	1	No	82	NA	94
12	M	Surfactant disorder	SPC	14.9	3.9	1	No	87	NA	90
19	F	Surfactant disorder	NKX2.1	0.2	0.1	4	Yes	83	NA	NA
21	F	Surfactant disorder	SPC	10.3	1.6	3	No	51	55	57
23	M	Surfactant disorder	SPC	9.6	0.3	1	No	76	84	76
28	M	Surfactant disorder	NKX2.1	4.4	4.1	2	Yes	74	NA	NA
29	F	Surfactant disorder	NKX2.1	11.7	0.2	3	Yes	46	NA	NA
31	F	Surfactant disorder	NKX2.1	3.4	0.2	4	Yes	39	31	NA
33	M	Surfactant disorder	ABCA3	1.0	0.1	3	No	NA	76	NA
37	F	Surfactant disorder	SPC	9.7	0.3	1	No	89	NA	80
38	F	Surfactant disorder	SPC	10.8	0.1	2	No	65	NA	68
39	M	Surfactant disorder	NKX2.1	2.6	0.0	2	Yes	49	NA	NA
40	M	Surfactant disorder	NKX2.1	7.6	0.4	2	Yes	46	NA	NA
41	M	Surfactant disorder	ABCA3	5.9	0.3	1	No	95	NA	NA
49	F	Surfactant disorder	SPC	7.0	0.7	1	No	90	91	NA
47	M	Surfactant disorder	SPC	10.8	0.4	1	No	NA	97	93
54	F	Surfactant disorder		10.9	0.4	3	No	38	48	39
55	M	Surfactant disorder	SPC	10.8	0.3	2	No	45	38	37
62	F	Surfactant disorder	SPC	6.7	0.4	1	Yes	53	NA	NA
73	M	Surfactant disorder	ABCA3	0.7	0.1	4	No	NA	35	NA
6	F	Alveolar proteinosis	MARS	1.5	0.2	5	Yes	42	80	NA
51	F	Alveolar proteinosis	CSF2RA	9.5	0.2	2	No	72	75	75
68	M	Alveolar proteinosis		7.9	0.6	3	Yes	53	NA	NA
1	F	Haemosiderosis		9.8	4.8	2	No	78	66	60
7	M	Haemosiderosis		8.0	6.4	1	No	70	NA	68
13	M	Haemosiderosis		1.5	0.6	2	Yes	67	46	NA
15	F	Haemosiderosis		10.4	4.4	2	No	80	NA	84
25	M	Haemosiderosis		12.6	11.4	2	Yes	59	NA	NA
27	F	Haemosiderosis		13.5	2.6	2	Yes	53	NA	NA
77	F	Haemosiderosis		8.0	4.3	2	No	39	NA	61
4	M	NEHI		3.3	0.8	3	No	NA	79	NA
24	F	NEHI		1.8	0.5	3	No	85	NA	NA
36	M	NEHI		5.1	0.6	3	No	59	64	NA
44	F	NEHI		0.8	0.5	1	No	74	NA	NA
78	M	NEHI		1.5	1.0	2	No	83	54	NA
5	F	Sarcoidosis		16.5	8.2	2	Yes	66	56	67
56	M	Sarcoidosis		17.7	5.6	2	Yes	NA	NA	82
71	F	Sarcoidosis		10.5	5.0	1	Yes	91	85	80
72	F	Sarcoidosis		16.3	12.4	2	Yes	NA	66	66
30	F	Vascularitis		12.9	2.8	4	Yes	57	NA	50
43	M	Vascularitis		0.7	0.4	1	Yes	91	91	NA
46	M	Vascularitis		10.6	0.3	2	Yes	52	NA	NA
48	F	Vascularitis		16.7	11.9	1	Yes	70	62	78
22	F	Histiocytosis		17.6	1.5	2	Yes	87	87	79
61	M	Histiocytosis		15.7	1.0	1	No	98	100	92
32	F	Connective disorder		6.7	5.3	4	Yes	NA	57	NA
45	F	Connective disorder		9.9	8.2	2	Yes	37	NA	75
59	M	Eosinophilic lung disease		7.1	1.5	2	No	48	51	NA
35	M	Metabolic disorder		8.5	1.2	2	Yes	40	NA	NA
17	M	Other ILD		10.8	10.6	2	No	85	65	90
42	M	Other ILD		3.2	1.5	2	No	65	79	NA
3	M	ILD of unknown aetiology		1.0	0.5	4	No	74	58	NA
8	M	ILD of unknown aetiology		11.2	1.0	4	No	NA	51	60
14	M	ILD of unknown aetiology		2.7	0.8	1	No	82	86	NA
10	F	ILD of unknown aetiology		2.4	1.0	5	No	28	13	NA
16	F	ILD of unknown aetiology		6.1	0.0	1	No	63	70	NA
18	F	ILD of unknown aetiology		12.9	12.8	4	No	64	NA	59
20	M	ILD of unknown aetiology		3.4	0.3	3	No	85	NA	NA
26	M	ILD of unknown aetiology		3.9	0.3	1	No	85	NA	NA
34	F	ILD of unknown aetiology		5.2	4.0	2	No	98	NA	NA
50	M	ILD of unknown aetiology		12.6	11.5	2	No	55	88	88
52	F	ILD of unknown aetiology		4.6	3.1	5	No	71	NA	NA
53	F	ILD of unknown aetiology		2.2	0.6	2	Yes	60	76	NA
57	M	ILD of unknown aetiology		4.1	1.7	1	No	NA	79	NA
58	F	ILD of unknown aetiology		0.7	0.3	3	No	58	60	NA
60	M	ILD of unknown aetiology		1.8	0.2	1	No	78	83	NA
63	M	ILD of unknown aetiology		0.9	0.2	1	No	88	NA	NA
64	M	ILD of unknown aetiology		3.1	0.2	1	Yes	82	81	NA
65	M	ILD of unknown aetiology		2.0	0.1	1	No	83	NA	NA
66	F	ILD of unknown aetiology		6.5	0.2	1	No	88	95	NA
67	F	ILD of unknown aetiology		6.2	0.4	2	No	90	84	NA
69	M	ILD of unknown aetiology		1.9	0.3	1	No	78	77	NA
70	F	ILD of unknown aetiology		15.4	0.1	2	No	55	NA	59
74	F	ILD of unknown aetiology		10.8	9.2	2	Yes	64	NA	80
75	M	ILD of unknown aetiology		1.3	0.6	2	Yes	61	70	NA
76	F	ILD of unknown aetiology		0.2	0.1	4	No	NA	89	NA

NEHI, Neuroendocrine cell Hyperplasia of Infancy
ILD, Interstitial Lung Disease

Supplemental material 3: Change in HR-Qol according to children characteristics in those with and without extra-pulmonary localization of the disease.

	No extra-pulmonary localisation (n=49)	**Extra-respiratory localisation (n=29)**
Male gender (versus female)	-7.0 +/-4	-3.60+/-6.8
Fan score (2 versus 1)	-14.5+/-5.0	-18.3+/-7.3
Fan score (≥3 versus 1)	-19.2+/-5.0	-18.5+/-8.3
Enteral nutrition (yes versus. no)	-12.0+/-5.7	-6.7+/-7.6