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WILEY PEDIATRIC PULMONOLOGY

Development and validation of a health-related quality of life questionnaire for pediatric patients with interstitial lung disease

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Abstract

Purpose: Children's interstitial lung disease (chILD) is often associated with multiple burdens and chronic impairment of health-related quality of life. Patient reported outcomes describe the patients' perspective on medical conditions and their treatments. We aimed to develop and evaluate the psychometric properties of a chILD-specific PRO (chILD-QoL) as an instrument for monitoring the patients' health status.

Methods: Items were generated through focus groups with parents, patients, and interviews with pediatric pulmonologists. After a pretest of the German pilot version, the questionnaire was refined and translated into four European languages. Psychometric properties of the questionnaire were analyzed within a multi-center collaborative throughout Europe involving 180 parents of children with an interstitial lung disease and 65 pediatric patients.

Results: The final instrument is available in different developmentally adapted versions from infancy to adolescence, comprising between 5 and 11 items. The scales showed high internal consistency (Cronbachs'α between 0.85 and 0.94). Convergent validity was indicated by moderate to high correlations (r = 0.43-0.91) with the Pediatric Quality of Life Questionnaire (PedsQL™ 4.0 Core module). Lower scores were significantly associated with dyspnoea (t_{proxy} = 3.18, P = 0.002), tachypnoea (t_{proxy} = 2.95, P = 0.002), and with worse clinical course of lung disease (t_{self} = 3.96, P < 0.05) as reported by the physicians.

Conclusions: The results indicate the reliability and validity of the chILD-QoL for pediatric patients with interstitial lung diseases. It can be used for screening and monitoring subjective health status as perceived by the patients and/or their caregivers, as well as for evaluation of health-related quality of life in clinical trials and intervention research.

KEYWORDS
chILD, health-related quality of life, interstitial lung disease, patient-reported outcome

1 | INTRODUCTION

Children's interstitial lung disease (chILD) is an umbrella term used to describe a heterogeneous group of extremely rare pulmonary diseases

[†]Deceased.

Mandy Niemitz and Nicolaus Schwerk contributed equally to this manuscript.

mainly affecting the lung parenchyma.[1] chILD encompasses more than 200 different diseases with varying morbidity and with a prevalence of 0.36 per 100 000 and an incidence of 1.32 per 1 000 000.[2–5] Symptoms are nonspecific but patients typically present with tachypnoea, hypoxemia, failure to thrive, crackles on examination, and diffuse infiltrates on chest radiography.[6,7] Depending on the condition, there is a wide range of disease severity. Overall morbidity and even mortality are high, unfortunately no evaluated treatments are available at the present time. Hence, for pediatric pulmonologists, treating patients with chILD constitutes one of the greatest challenges.[8]

Similarly for the patients and their caregivers, chILD raises many challenges, including uncertainty about the individual clinical course, lack of appropriate therapy, residual symptoms, persisting functional restrictions, late sequelae for psychosocial development, frequent hospitalizations, school absenteeism, and restrictions of activities due to the physical impairment or the medical regimen.[9,10] Patient-reported outcomes (PRO) can provide a more comprehensive description of the impact of the medical condition on the lives of affected families than signs and symptoms alone.[11] HrQoL is a multi-dimensional construct, including physical, emotional, mental and behavioral components of well-being, and function as perceived by the patient and/or by observers.[12] Therefore, assessment of HrQoL in pediatric patients with chronic diseases has become increasingly important in clinical routine care and research.[13–17]

Disease-specific instruments may enhance the measurement sensitivity for health domains pertinent to a particular chronic health condition, may be more comprehensive for a specific complaint, more sensitive to change in condition over time, and better at identifying differences between sub-groups within a disease category.[18,19] In addition, pediatric HrQoL measures must be developmentally adapted and also sensitive to cognitive development.[18]

Pediatric HrQoL instruments include self-reports for children and adolescents and parent proxy-reports.[18] Children's self-reports are more sensitive than parents' reports in detecting minor emotional and behavioral disturbances.[20,21] Parents are more able to judge their child's HrQoL in terms of physical rather than social or emotional domains.[22,23] Therefore, a multi-informant approach including both children's and parent proxy-reports has been suggested for the most comprehensive assessment of pediatric adaptation outcomes.[13,24,25]

To our knowledge, there are no HrQoL studies of pediatric patients with chILD. In the absence of a disease-specific measure, the primary step of this study was to develop a disease-specific instrument that considered developmentally adjusted indicators of HrQoL in this subpopulation. The second step was to investigate the reliability and validity of the instrument in a clinical sample of patients with chILD.

For the newly developed disease-specific HrQoL questionnaire we hypothesized finding (i) sufficient internal consistency; (ii) moderate to high positive correlation coefficients with the self- and parent report of the generic HrQoL instrument Pediatric Quality of Life Questionnaire (PedsQL™ 4.0) to explore convergent validity; and (iii) significant associations with clinical indicators of disease severity to examine criterion validity. (iv) We also investigated the concordance of the patients' self- and parents' proxy reports.

2 | METHODS

2.1 | Study design

The new chILD-QoL scales were developed through a literature review of the relevant research[18,26,27] and focus groups of caregivers and patients with chILD. Children, adolescents aged 8-18 years and parents of children aged 0 month-18 years with chILD and sufficient knowledge of the German language were eligible for inclusion.

The format of the items and response scales of the chILD-QoL were conceptualized as a supplement to the generic HrQol instruments, based on cumulative disease-specific lists of HrQoL topics regarding burdens and restrictions due to the illness. A 5-point rating scale of frequency (from *never* to *almost always*) was used. A pretest regarding comprehensibility and feasibility of the chILD-QoL scales was conducted within a pilot study at two German specialized clinics in Munich and Hannover.

After pretesting these measures were translated into English, French, Italian, and Turkish, forward-backward regarding international guidelines,[28] and implemented on the chILD-EU lung registry. The chILD-EU consortium is conceptualized for clinical scientists and pediatric pulmonologists collaborating to assemble cohorts in which children with well-defined disease entities, verified by international panels of clinicians, radiologists, geneticists, and pathologists, are monitored in a web-based database and biobank compatible with others worldwide to allow common projects. The aim of this project was to develop evidence-based and consensus-agreed clinical guidelines to achieve better care of patients afflicted by chILD and to improve their quality of life (http://www.childeu.net). All forms of the newly developed questionnaire are compiled in the supplement (E1-E-8).

Subsequent continuous data collection for psychometric testing took place in 26 European centers in patients aged between 0 month and 18 years diagnosed with chILD. The questionnaires were completed by patients and their caregivers at the clinics. Children and adolescents with co-morbid medical conditions or developmental delays (eg, trisomy 21) were not excluded from this part of the study. The main steps of the study are shown in supplement E-Figure 9.

The research protocol was approved by the Institutional Review Board at the University of Munich, Germany, which is the coordinating site of the chILD-EU lung registry and by all participating centers. All participating patients, if old enough, gave their informed assent and all caregivers gave their informed consent.

2.2 | Procedures

2.2.1 | Item generation

Information for initial item generation was gathered using two independent focus groups to obtain children' and parents' perceptions of the patients' HrQoL. Participants in the focus groups were recruited at two centers for pediatric pulmonology in Germany on the basis of their availability during a patient information day. The discussion of children's disease-specific HrQoL domains was stimulated by open questions such as "How does chILD affect your/your child's QoL?" Each idea from

children and parents was noted and then discussed. Families who could not participate in focus groups were asked the same questions via e-mail. Candidate items were generated based on cumulative lists of HrQoL topics and domains. Redundant items were eliminated.

2.2.2 | Pretest and item reduction

Preliminary developmentally adapted versions of the questionnaire were created based on the results of the focus groups. Comprehensibility and feasibility were pretested. Item-level analyses on the basis of a total item raw score were performed to minimize floor and ceiling effects, and to determine the frequency of missing values. Floor and ceiling effects were defined as a relative frequency of >65% of respondents selecting a single response at one extreme point of the scale. The content of the items in each of the forms is essentially identical, differing in developmentally appropriate language. For self- and parent proxy-reports, a 5-point response scale was utilized (0 = *never a problem*; 1 = *almost never a problem*; 2 = *sometimes a problem*; 3 = *often a problem*; 4 = *almost always a problem*). Items were reverse-scored and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Higher scores indicate better HrQoL.

2.2.3 | Evaluation of the psychometric properties of the final questionnaire

Generic HRQoL instruments (Core Module and Infant Scales of the PedsQL™ 4.0; self- and parent proxy version) were administered to examine convergent validity. The Core Module of the PedsQL™ 4.0 applies to the age range of 2-18 years, and Infant Scales of the PedsQL™ 4.0 apply to infants and toddlers aged between 0 month and 23 months. Both instruments are developmentally adapted.

2.3 | Additional instruments

The PedsQL™ 4.0 infant scales and generic core scales are established measures of generic HrQoL and are available in different age versions as self- and parent proxy-reports. Parent proxy-reports assess parents' perceptions of their child's generic HrQoL. Detailed description of the used questionnaires can be found in the online supplement (E10) and are briefly named in the following.

2.3.1 | Questionnaire for Measuring HrQoL in infants

The PedsQL™ 4.0 infant scales are questionnaires on HrQoL, applicable to infants between 1 and 24 month.[26] The different age-appropriate versions of this instrument showed moderate to high internal consistencies (Cronbachs' α between 0.65 and 0.98).

2.3.2 | Questionnaire for Measuring HrQoL in toddlers, children, and adolescents

The PedsQL™ 4.0 generic core scales assess HrQoL of toddler, young children, children and adolescents.[27] In the current study Cronbachs' α ranged between 0.81 and 0.98.

2.3.3 | Medical and socio-demographic information

Medical and sociodemographic variables were retrieved from the chILD-EU lung registry data base. Medical information was provided by the responsible physician, based on the patient's medical charts. Furthermore, the physicians assessed the health status of their patients (*inter alia* Fan 5 point severity scale and clinical course of lung disease). On the basis of these assessments, disease severity was determined. The Fan 5 point severity scale displays a classification of the subject status introduced by Fan et al.[29] Due to the heterogeneous group of rare disease entities, initial diagnoses underwent a peer-review process by specialized clinicians within the study and were finally categorized applying the chILD-EU Classification Scheme.[1,3,7,30] Socio-demographic and socio-economic information were provided by the caregivers and the children or adolescents themselves.

2.4 | Statistical analysis

Medical and socio-demographic variables were expressed as absolute and relative frequencies. Chi-square tests were computed to analyze differences regarding medical characteristics between responders and non-responders.

Outcomes of item-level analyses were reported as means (with SD), skewness, and excess. In accordance with the item response theory (IRT) for psychometric analyses of the responsiveness of persons on items, and to check whether all items were appropriate to measure the same latent characteristic, item discriminatory power, item difficulty and homogeneity were analyzed.

All statistical analysis was exploratory and descriptive. No corrections for multiple comparisons were made and a one-sided level of $P < 0.05$ was considered significant.

To determine the internal consistency of the chILD-QoL, Cronbach's α was calculated. Construct validity was assessed using convergent validity and was determined by *Pearson* correlations with the Core Module and Infant Scales of the PedsQL™ 4.0. Criterion validity was substantiated by association with disease severity and prognosis. *t*-tests for independent samples were used for variables with two characteristics. Between group effect sizes (Cohen's d) were computed using the following formula: $d = M_1 - vM_2/SD_{\text{pooled}}$.[31] Univariate ANOVAs were performed for variables with more than two characteristics. The medical variables were used as independent variables and HrQoL total score as a dependent variable. To compare the associations of different indicators of disease severity with HrQoL, these characteristics were dichotomized, and based on sociodemographic and medical information until baseline patients were assigned to the following categories: duration of the disease, pulmonary exacerbation, coughing, dyspnoea, tachypnoea, treatment with medication/drugs, non-medical interventions, general rating of the Fan 5 point severity scale, and clinical course and comorbidities. Categories of disease severity were specified by the physicians. Requirements for *t*-tests for independent samples and univariate ANOVAS were fulfilled with the exception of the variable Fan 5 point severity scale. A non-parametric test (Kruskal-Wallis

TABLE 1 Characteristics of the study sample

	Responders (*n* = 180)		Non-responders (*n* = 171)		
	n	%	*n*	%	*P*
Medical characteristics of patients					
Gender					
Male	91	50.6	89	52.09	0.53
Female	81	45.0	69	40.4	
Not reported	8	4.4	13	7.6	
Age (in years)					
Mean (span 0-18)	5.85		7.50		0.24
SD	5.36		7.11		
Span	0-18		0-17		
Age group (parent-proxy report)[a]					
1-12 months	40	22.2			
13-24 months	17	9.4			
2-4 years	37	20.6			
5-7 years	17	9.4			
8-12 years	38	21.1			
13-18 years	27	15.0			
Age group (self-report)					
8-12 years	36	20.0			
13-18 years	29	16.1			
Fan 5 point severity scale					
Asymptomatic	18	10.0	17	9.9	0.08
Symptomatic, normal room air oxygen saturation under all conditions	34	18.9	48	28.1	
Symptomatic, normal resting room air saturation, but abnormal saturation (< 90%) with sleep or exercise	24	13.3	15	8.8	
Symptomatic, abnormal resting room air saturation (< 90%)	47	26.1	28	16.4	
Symptomatic with pulmonary hypertension	18	10.0	17	9.9	
Not reported	39	21.7	46	26.9	
Clinical course of lung disease (until QoL assessment)					
Healthy	30	16.7	20	11.7	0.14
Sick better	39	21.7	34	19.9	
Sick same	49	27.2	49	28.7	
Sick worse	40	22.2	31	18.1	
Patient died			7	4.1	
Not reported	22	12.3	30	17.5	
Pulmonary exacerbation (until QoL assessment)					
Yes	84	46.7	66	38.6	0.40
No	64	35.6	61	35.7	
Unknown	12	6.7	16	9.4	
Not reported	20	11.1	28	16.5	
Dyspnea (current)					
Yes	63	35.0	69	40.4	0.25
No	63	35.0	53	31.0	
Not reported	54	30.0	49	28.7	

(Continues)

TABLE 1 (Continued)

	Responders (*n* = 180)		Non-responders (*n* = 171)		
	n	%	*n*	%	*P*
Tachypnoe (current)					
Yes	63	35.5	58	33.9	0.84
No	63	35.5	61	35.7	
Not reported	54	29.0	52	30.4	
Treatment with medication/drugs (current)[b]					
Yes	116	64.4	102	59.6	0.35
No	40	22.2	27	15.8	
Not reported	24	13.3	42	24.6	
Non-pharmacological interventions (current)[b]					
Yes	89	49.4	52	30.4	0.002
No	61	33.9	77	45.0	
Not reported	30	16.7	42	24.6	
Comorbidities (current)[b]					
Yes	40	22.2	33	19.3	0.11
Yes, more than 1	56	31.1	40	23.4	
No	55	30.6	58	33.9	
Not reported	29	15.8	40	23.4	
Socio-demographic characteristics					
Participating caregivers					
Mother/partner	128	71.1			
Father/partner	34	18.9			
Legal guardian	1	0.6			
Other	9	5.0			
Not reported	8	4.4			

[a]Two parent-proxy reports (13-18 years), one parent-proxy report (8-12 years), one self-proxy reports (13-18 years), and three self-reports (8-12 years) were not available. Medical information of subjects based on physicians' reports.
[b]For details about group of medication/drugs, type of non-pharmacological intervention current, and type of comorbidity see online supplement (E-Table 3).

TABLE 2 Cronbach's α of the chILD-QoL for all age versions

chILD- QoL	*N*	Number of items	M	SD	Cronbach's α
Parent-reports					
1-12 months	24	5	52.81	31.13	0.88
13-24 months	10	8	55.00	30.38	0.91
2-4 years	22	11	76.69	17.45	0.85
5-7 years	7	11	64.30	32.43	0.95
8-12 years	26	11	62.59	23.63	0.90
13-18 years	17	11	71.08	21.93	0.91
Self-reports					
8-12 years	23	11	71.31	22.02	0.94
13-18 years	24	11	69.22	23.45	0.88

N, number of participants; M, mean; SD, tandard deviation; chILD-QoL, chILD-specific PRO.
Cronbach's α <0.8: low, 0.8 – 0.9: medium, >0.9: high.

TABLE 3 Correlations of the chILD-QoL questionnaire with the PedsQL™ 4.0

	PedsQL™ 4.0 parent reports		
chILD- QoL	**Psychosocial health summary score**	**Physical health summary score**	**Total score**
Parent-reports			
1-12 months	0.39	0.63**	0.56**
13-24 months	0.42	0.36	0.43
2-4 years	0.71*	0.60**	0.68**
5-7 years	0.84**	0.91**	0.91**
8-12 year	0.78**	0.81**	0.85**
13-18 years	0.72**	0.53**	0.69**
	PedsQL™ 4.0 self-reports		
	Psychosocial health summary score	**Physical health summary score**	**Total score**
Self-reports			
8-12 years	0.89**	0.79**	0.90**
13-18 years	0.72**	0.67**	0.75**

PedsQL™ 4.0, Pediatric Quality of Life Questionnaire; chILD-QoL, chILD-specific PRO.
Total score = Psychosocial health summary score + Physical health summary score.
*$P \leq 0.05$ (two-sided).
**$P \leq 0.01$ (two-sided).

test) was calculated to compare the associations of the Fan 5 point severity scale. Concordance of the patients' self- and parents' proxy reports was investigated by *Pearson* correlations. Statistical tests were performed using the software program, Statistical Package, for the Social Sciences (SPSS) for Windows Version 21.0 and Excel for Windows XP.

3 | RESULTS

3.1 | Participants

Altogether 351 patients, who consecutively attended the medical centers and met the inclusion criteria, were approached to participate in this study. Finally, 245 patients who were eligible for inclusion were enrolled. Non-responders were patients with missing PROs in the chILD-EU lung registry. Reasons for missing are unknown. Medical and socio-demographic characteristics of the study group are displayed in Table 1, demonstrating diversity within the study sample. A detailed description of the medical characteristics, especially distribution of different major specific diagnoses, diagnosis categories, medications, and non-pharmacological intervention, and comorbidities is given in the online supplement (E-Table 11).

3.2 | Item-level results

The results of item-level analyses of the preliminary version of the questionnaire are presented in supplement E-Table 12. Seven items had >70% responses on a single response. Item difficulties ranged between 0.38 and 0.95. Discriminatory power coefficients (ritc) varied from 0.38 to 0.88. The item homogeneity coefficient (rii') was between 0.39 and 0.68. Most distributions showed a negative skewness (excess <0) (Table 2).

3.3 | Reliability

The outcomes from analyses of the internal consistencies of Cronbachs α are given in Table 3. Cronbach's α ranged between 0.85 and 0.95 and for self-reports between 0.88 and 0.94.

3.4 | Validity

Correlations (r) of the chILD-QoL scales with the total score of the PedsQL™ 4.0 Infant scales and core module varied between 0.43 and 0.91 (see Table 3). The majority of these correlations were >0.70. Correlations with the subscales psychosocial health summary score and physical health summary ranged between 0.36 and 0.91.

chILD-QoL scores distinguished between different categories of disease severity. For instance, patients without dyspnoea recorded significantly higher chILD-QoL scores than patients with dyspnoea ($P < 0.002$). Similar differences are shown in Table 4 for the other medical characteristics (Fan 5 point severity scale, clinical course of lung disease, pulmonary exacerbation, cough, tachypnoea, and non-pharmacological interventions).

3.5 | Child/parent concordance

Correlations (r) of the patients' self- with their parents' proxy reports were 0.89 for children (8-12 years) and 0.80 for adolescents (13-18 years), as well as separately with mothers' proxy reports 0.85 and fathers' proxy reports 0.93.

TABLE 4 Associations of chILD-QoL with disease severity as indicated by clinicians

	Proxy						Self					
Variable	***n***	**M**	**SD**	**T/F**	***P***	***d***	***n***	**M**	**SD**	**T/F**	***P***	***d***
Fan 5 point severity scale[a]												
Asymptomatic	9	90.77	7.56	3.57	0.006		4	88.64	12.72	7.74	0.098	
Symptomatic, normal room air oxygen saturation under all conditions	25	66.08	25.48				11	74.59	21.77			
Symptomatic, normal resting room air saturation, but abnormal saturation (<90%) with sleep or exercise	17	56.99	34.45				4	59.09	30.77			
Symptomatic, abnormal resting room air saturation (<90%)	30	63.47	24.08				13	66.61	21.00			
Symptomatic with pulmonary hypertension	11	48.65	29.96				7	46.98	35.72			
Clinical course of lung disease												
Healthy	15	79.45	15.74	5.94	0.001		6	71.97	15.46	3.96	0.015	
Sick-better	28	73.19	20.33				10	81.14	16.60			
Sick-same	33	56.68	28.63				12	67.23	22.00			
Sick-worse	23	50.74	31.37				13	48.72	30.15			
Pulmonary exacerbation												
No	38	70.98	24.77	2.19	0.031	.47	15	72.88	16.89	1.72	0.096	0.55
Yes	53	58.31	28.77				21	59.60	29.30			
Cough												
No	55	67.95	27.24	3.01	0.004	.76	23	71.71	22.48	2.23	0.032	0.81
Yes	23	48.06	24.86				13	52.27	28.37			
Dyspnea												
No	35	71.49	26.16	3.18	0.002	.75	19	69.26	25.16	1.07	0.296	0.41
Yes	39	51.45	27.86				12	59.03	27.39			
Tachypnea												
No	35	70.98	22.38	2.95	0.004	.67	17	67.51	24.14	0.39	0.702	0.14
Yes	41	52.86	30.91				14	63.91	27.78			
Treatment with medication/drugs												
No	27	68.24	24.53	1.08	0.280	.25	10	75.68	22.73	1.33	0.193	0.49
Yes	72	61.52	28.39				33	63.62	25.90			
Non-pharmacological interventions												
No	40	72.35	25.30	2.76	0.007	.58	21	70.02	25.89	0.90	0.372	0.29
Yes	56	56.92	28.15				20	62.69	26.05			
Comorbidities												
No	33	68.31	26.55	0.80	0.429	0.23	16	73.30	21.71	0.22	0.828	0.10
Yes	19	62.09	27.93				7	71.01	25.75			
Duration of the disease												
Prevalent cases	77	67.24	26.47	1.04	0.299	0.20	36	71.00	25.45	1.87	0.068	0.60
Incident cases	39	61.77	27.23				13	55.94	23.30			
Age group												
1-12 months	24	52.81	31.13	2.76	0.022							
13-24 months	10	55.00	30.38									
2-4 years	25	76.69	17.45									
5-7 years	10	64.30	32.43									

(Continues)

TABLE 4 (Continued)

	Proxy						Self					
Variable	***n***	**M**	**SD**	**T/F**	***P***	***d***	***n***	**M**	**SD**	**T/F**	***P***	***d***
8-12 years	28	63.93	24.25				26	65.18	27.22	0.53	0.600	0.03
13-18 years	23	71.31	22.02				23	69.07	23.96			

M, mean; SD, standard deviation; T, standard score of the Student's *t*-statistic; *P*, *P* value of the statistical significance test; d, between group effect size Cohen's d (formula: $d = M1-M2/SD_{pooled}$).

Total score = Psychosocial health summary score + Physical health summary score.

[a]A non-parametric test (Kruskal-Wallis test) was calculated.

4 | DISCUSSION

This study presents the development and psychometric properties for the chILD-QoL scales. The results support the reliability and validity of the chILD-QoL self- and parent proxy-reports within a wide age range between infancy and adolescence.

The item homogeneity is slightly higher than the acceptable range (r_{ii} between 0.2 and 0.4) which might indicate some redundancy within the items. With the exception of six items with moderate ($0.30<r_{itc}>0.50$) and six items with low ($r_{itc}<0.30$) discriminatory power, the discriminatory power was high ($r_{itc}>0.50$). Item difficulty is an estimate of the state level needed to pass an item.[32] With the exception of seven items which were in the "easy area" ($P > 0.80$), most items were in the "moderate area" ($0.80<ID>0.20$) indicating a moderate probability to pass the item (answer with "often" or "almost always"). Consequently, most items measure the same latent construct. Items with lower discriminatory power were not excluded because these items seemed to be clinically relevant and can provide a more comprehensive description of the HrQoL of patients with chILD. We found good or excellent internal consistency of the total scale. Hence, HrQoL can be measured robustly with our developed additional chILD-QoL. Convergent validity was substantiated by mainly moderate to high positive correlations with the generic HrQoL instrument PedsQL™ 4.0. To achieve a broader picture of the patients' quality of life, the disease-specific chILD-QoL scales may be combined with the generic PedsQL™ 4.0 or similar generic quality of life scales.

Criterion validity of the chILD-QoL was indicated by significant associations with disease severity indicated by the Fan 5 point severity scale, pulmonary exacerbation, cough, dyspnoea, tachypnoea, non-pharmacological interventions, and clinical course. Lower chILD-QoL scores were associated with greater disease severity and worse clinical course at the measurement time point. Importantly, the ability of the newly developed questionnaire to discriminate between mild, moderate, and severe disease stages was established. Hence, our results do not support discrimination for non-pharmacological treatments and tachypnoe by self-reports measures as well as duration of the disease by self- and parent-proxy reports measure. Sensitivity is given due to a potential to assess higher levels of subjectively perceived impairment and to identify patients at risk with reduced HrQoL.

Correlations of parallel self- and parents' proxy reports were strong, suggesting agreement between patients and parents about the child's/adolescent's HrQoL. This result is in contrast to other QoL studies of chronically ill children and adolescents reporting significant differences[33,34] or only limited correlations between self- and parent proxy-reports.[13,23,24] Children completed the questionnaires in the presence of their parents at the clinics. Although the instructions advised the children and parents to fill in the questionnaires independently, it cannot be ruled out that parents and children might have been aware of each other's answers. This might have caused some convergence of the responses and is in line with earlier findings of Niemitz et al.[14] The strong correlation between the patients' and their parents' estimations might also be due to the close involvement of caregivers in their sick child's daily life.[35]

Limitations of this study are first due to the small sample size, especially on subgroup levels by different age-groups. However, in the case of rare diseases it is extremely difficult to recruit more patients in limited study duration. Second, only a small number of patients participated in the focus group phase that did not represent each age group. Additionally, parents and patients were in the same focus group. Therefore, relevant HrQoL topics were not discussed independently with parents and patients. Third, open-ended interviews in the developmental phase were not conducted. Fourth, it is possible that patients and parents, who participated in the focus group and in phase 2 also completed phase 3. In our study design it was not possible to control for this important point. Sensitivity analysis was not performed to see if this subgroup altered the overall results. Consequently, the interpretability of our outcomes may be limited. Fifth, there are missing data for medical variables such as the Fan scale, clinical course, dyspnoea, and tachypnoea, as well as cough. Sixth, no additional analysis on the convergent validity of the measure could be performed due to the small sample size (especially in sub-groups). As the developed instrument assesses individual additional disease specific treatment burden it might be of a valuable information for the physicians and family. Finally, test-retest reliability of the chILD-QoL was not investigated, neither was its sensitivity to changes in health state over time. As we cannot draw any conclusions on long-term effects or the individual patient's clinical course over time, longitudinal studies with repeated assessments are needed in future.

Despite the limitations mentioned above, it can be concluded that the results of this study indicate the reliability and validity of the specific chILD-QoL. The measure is freely available in several

European languages on the chILD-EU platform (http://www.childeu.net), together with instructions for users. The questionnaire is thought to contribute to the explicit goals of the chILD-EU consortium, namely to improve medical care and, in this context, to include the patients' and their parents' perspective. The use of the measure as an important additional outcome variable in future clinical studies, as recommended for example by the Food and Drug Administration (FDA),[15] will probably extend our knowledge of the effects of interventions on children and adolescents with chILD.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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