RESEARCH PAPER

Health Related Quality of Life in Indian Children with Cystic Fibrosis

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Objective: This study was devised to translate Cystic Fibrosis Questionnaire-Revised to Hindi and administer it to Indian children and adolescents diagnosed with cystic fibrosis.

Design: Cross-sectional study**.**

Setting: This study was carried out in cystic fibrosis patients attending Pediatric Chest Clinic of a tertiary-care hospital in Northern India from July 2012 to December 2012.

Participants: 45 children (6-13 years) and their parents, and 14 adolescents. Patients with unstable health in the past two weeks were excluded.

Intervention: Cystic Fibrosis Questionnaire- Revised translated in Hindi was administered. Clinical evaluation and scoring, throat swab cultures and spirometry were also done during the same visit.

Main Outcome Measures: Health Related Quality of Life scores were the primary measures, and clinical scores, swab cultures and spirometry were secondary measures.

Results: Cronbach's alpha ranged from 0.020-0.863.The Factor analysis indicated that most test-items correlated more with competing scales than the intended scales. Convergence between self and proxy-rating was found to be dependent on the domain. The Cystic Fibrosis Questionnaire- Revised scores correlated well with clinical scores (r=0.65,*P*=0.011), *Pseudomonas spp* culture data and pulmonary function tests. There was an inverse relation between Health Related Quality of Life scores and age at diagnosis (r=-0.339, *P*=0.02).

Conclusions: Hindi versions of Cystic Fibrosis Questionnaire-Revised: Child, Adolescent and Parents' instruments will act as an important step towards data on Health Related Quality of Life of Indian patients with cystic fibrosis.

Keywords: *HRQoL, Outcome, Severity, Validation*.

Cystic fibrosis (CF), a chronic pulmonary disorder is increasingly being recognized in India [1-3]. To measure the quality of life of children with CF various methods have been used, common being: pulmonary function testing, growth parameters, clinical scoring, radiological scoring etc. However, these may not correlate directly with quality of life [4,5]. More recently Patient-reported outcomes such as the generic ones like 36-Item Short Form Health Survey (SF-36), and the Quality of Well-Being scale, and more specific ones like CFQ, CFQoL, Cystic Fibrosis Questionnaire Revised (CFQ-R) have been developed and have been validated to assess psychological wellbeing of the children with CF through various life stages [6-8]. A Patient-reported outcome instrument is defined as any measure of a patient's health status that is directly elicited from the patient and assesses how the patient ''survives, functions or feels'' in relation to his or her health condition [9,10]. CFQ was the first CF-specific patient-reported outcome that gained the form of CFQ-R after few revisions, following psychometric testing [10-16]. The CFQ-R is the only patient-reported outcome instrument with versions for both children and the caregivers. It has been translated into 34 languages all over the world [17-21]. Our objective was to use CFQ-R to assess Quality of Life (QoL) in Indian children with CF.

METHODS

This cross-sectional study was carried out in children with CF attending Pediatric Chest Clinic of a tertiary care hospital in Northern India from July 2012 to December 2012. Subjects included children 6 years and above diagnosed as CF based on compatible clinical features with sweat chloride values of >60 mEq/L on two occasions or with two known identified mutations. Consenting families with children with their parents, and adolescents with ability to read and write in Hindi, were included in the study. Subjects were excluded from the study if they had an unstable health or missed school due to an exacerbation in the past two weeks.

Disease severity was quantitated in three domains *viz*., general activity of the child, findings on physical examination, and nutrition of the child. Clinical scores were generated out of 25 for each domain where maximum score was 100 and minimum score was 0. A scaled clinical CF score [2,22] was calculated as

previously described. Other assessments done included throat swab cultures and spirometry evaluation.

Health Related Quality of Life (HRQoL) was assessed using the English version of CFQ-R. The English CFQ-R has three formats; Child version (6-13) is a self-rating questionnaire comprising of 35 test items and 8 domains, Adolescents version (14 and above) containing 50 test items and 12 domains, while the Parents' version is a proxy rating consisting of 44 test items and 11 domains applicable only for children 6-13 years of age. Adolescent's version does not require any proxy rating. The questions had to be answered keeping in mind the physical and psychological health status over the two weeks preceding the day of administration of the questionnaire. The questionnaire was culturally adapted and translated in Hindi for use in Indian population. It was translated from English to Hindi and back-translated by the two translators independently. The words found misfit after back- translation were substituted and agreed upon by both the translators. Children aged 6-11 years were questioned by the interviewer and were presented with options on flash cards. The chosen option was pointed out by the child to the interviewer. The questionnaires were administered to the patients and the parents in separate rooms, to avoid parents influencing patients' answers or vice-versa. All the other formats were self-administered with an initial introductory brief by the investigator. After completion by the patient/ parent, any missing answers were searched for by the investigator and the participant was informed, eliminating most missing answers. It took about 10-15 min to complete the questionnaire. Scaled scores for each domain were calculated as described in the English CFQ-R.

The present study was approved by the Ethics Committee of All India Institute of Medical Sciences. In all cases, informed consent was obtained from at least one parent, and assent from the child. Permission to use and translate English CFQ-R was obtained from the authors.

Statistical analysis was conducted using the SPPS 20.0. Characteristics of study subjects including demographic profile, clinical characteristics, PFT results, and *Pseudomonas spp.* on culture results were analyzed. For reliability, internal consistency was calculated using Cronbach's alpha [23] for each domain in all three questionnaire categories, *viz.*, 6-13 years,14 and above and parents' version with a cutoff of 0.6 for reliability, before and after deletion of the unreliable items.

Construct validity was evaluated by Factor analysis (Principal Component Analysis, PCA) [24,25] and the Scree plot is presented to test the given structure of the English CFQ-R. The Rotated Component Matrix shows the domains in which the each individual test items should be placed according to Factor analysis. The point at which the plot dips down in the Scree plot marks the maximum number of factors (domains) suggested by the analysis.

The difference in the mean HRQoL score was tested between sex, spirometry findings and *Pseudomonas spp* culture results using student's t-test for independent samples. The subjects were divided into four groups based on FEV1 percent predicted, FVC percent predicted, PEF percent predicted: less than 40, 40-59, 60-79 and ≥80. In case of more than two groups, one way ANOVA was used for comparison for parametric data and Kruskal-Wallis H for non-parametric data. We used Bonferroni post-hoc test with alpha set at 0.05.Correlation between clinical scores, age, and age at diagnosis, with HRQoL scores were calculated by Pearson's/Spearman's correlation coefficient. The convergent validity of the Child and Parent versions were calculated by Intra Class Correlation. *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 59 (planned sample size was 60 but 1 patient was included twice) patients with CF were studied with 76% (45) belonging to age group 6-13. The mean age (SD) of our study population was 11.5 years (4.5), and 61% of the participants were boys. The mean age (SD) of diagnosis was 5.7 years (4.5) (range 6 mo- 19 y). 28.8 % (17) of all subjects were positive for *Pseudomonas spp.* on culturing throat swab samples, out of which 16 belonged to the age group 6-13 and only 1 to the adolescent group. The average scaled clinical scores were 78.5 (out of 100), children aged 6-13 scored an average of 80 percent (13.8 and adolescents aged 14 and above scored a mean of 73.8 percent (24.6). The maximum average (95% C.I.) was in General Activity (21.5/25) (20.60-22.40) and the minimum in Nutrition (20/25) (18.95-21.05), Physical examination scored an average of (20.7/25) (19.6-21.6).

The spirometry findings were as follows: mean FEV1% predicted (S.D.) was 62.7% (24.7%), mean FVC% predicted (S.D.) was at 64.2% (24.3%) and mean PEF % predicted (S.D.) was 61.6% (26.6%). The mean CFQ-R scores in different domains across the different versions are shown in ***Table* I**. The mean HRQoL score (95% C.I.) was 71.5/100 (68.51-74.63) for the Child version, 65.8/100 (54.64-77.07) for the Adolescents and was 63 (59.24-66.81) according to the proxy rating by parents.

TABLE I HRQOL SCORES DOMAIN WISE {6-13 YEARS (N=45), 14 YEARS AND ABOVE (N=14) AND PARENTS (N=45)}

Domains/ age group	*No. of items*	*Mean scores (95% CI)*	*Cronbach's alpha*
Physical			
6-13	6	65.7(57.37-73.96)	0.863
≥ 14	8	56.4(41.77-70.94)	0.722
Parents	9	54.2 (47.73-60.56)	0.786
Vitality			
6-13	–	–	–
≥ 14	4	64.3 (50.8-77.8)	0.657
Parents	5	63.7 (57.6-69.8)	0.734
Emotion			
6-13	8	78.8 (75.59-82.06)	0.704
≥ 14	5	78.9 (65.72-92.14)	0.817
Parents	5	79.9 (74.95-84.78)	0.441
Eat			
6-13	3	79.3 (72.75-85.79)	0.440
≥ 14	2	77.4 (62.46-92.40)	0.738
Parents	2	73.3 (62.46-92.40)	0.208
Treatment Burden			
6-13	3	62.1 (56.05-68.17)	0.020
≥ 14	3	62.9 (53.95-71.91)	0.026
Parents	3	58.2 (51.23-65.06)	0.347
Health Perceptions			
6-13	–	–	–
≥14	3	73.1 (59.77-86.37)	0.391
Parents	3	61.4 (56.18-66.54)	0.415
Social/ School			
6-13	7	63.7 (58.62-68.84)	0.510
≥14	6	69.1 (56.00-82.29)	0.362
Parents	3	69.9 (63.33-76.42)	0.119
Body			
6-13	3	65.3 (57.11-73.51)	0.632
≥ 14	3	43.6 (22.02-65.27)	0.797
Parents	3	50.2 (43.59-56.82)	0.559
Role			
6-13	–	–	–
≥ 14	4	69.6 (55.53-83.61)	0.766
Parents	–	–	–
Weight			
6-13	–	–	–
≥14	1	47.6 (21.71-73.43)	–
Parents	1	29.6 (19.12-40.14)	–
Respiratory			
6-13	4	73.5 (68.86-78.12)	0.487
≥14	6	69.7 (53.39-86.04)	0.857
Parents	6	68.7 (64.61-72.70)	0.620
Digestion			
6-13	1	84.6 (79.60-89.60)	–
≥14	3	77.9 (63.37-92.35)	0.672
Parents	3	84.5 (80.65-88.24)	0.148
HRQoL score (%)			
6-13	35	71.6 (68.51-74.63)	–
≥14	50	65.9 (54.64-77.07)	–
Parents	44	63.0 (59.24-66.81)	–

Reliability: For the child version, the Cronbach's alpha values were calculated for 7 domains (Digestion excluded because of only 1 test item), the domains Physical (0.86), Emotional (0.70), Body Image (0.63) were acceptable. Social domain was intermediate (0.532). The domains Eating, Treatment Burden and Respiration were unacceptable. Deleting question 33 from the Respiration domain would elevate the alpha value to 0.58 making it acceptable. For Adolescent version, reliability analysis showed that among 11 domains tested (Weight excluded because of single test item), all domains showed good reliability; Physical (0.722), Vitality (0.65), Emotion (0.8), Eat (0.73), Body (0.79), Role (0.76), Respiration (0.85), Digestion (0.67), except for Treatment Burden, Health Perceptions and Social domains. Reliability analysis of proxy rating by parents showed mixed results with Physical (0.78), Vitality (0.73) and Respiration (0.62) faring well; Body (0.56) barely acceptable and Emotional, Eat, Treatment Burden, Health Perceptions, School, Digestion performing poorly. Deleting question 31 may make Treatment Burden reliable.

Construct validity: For the 6-13 questionnaire format, all the items of the Physical factor are assigned to the Physical factor according to Factor analysis but the rest differ. The English CFQ-R has 8 domains but the Factor analysis of our study recommends a maximum of 5 factors (***Web Fig*. 1a**). For the Adolescent's format**,** the English CFQ-R has 12 domains but Factor analysis suggests a maximum of 7 factors (***Web Fig* 1b**). None of the items are allocated to a single factor. In the Parents' format most of the items of the Physical factor are assigned to the Physical factor according to Factor analysis but the rest differ. The English CFQ-R has 11 domains but Factor analysis recommends a maximum of 2 factors (***Web Fig* 1c**).

Known-group validity: We did not find any difference in self-rated HRQoL scores in any domain between girls and boys for all age groups. However, a statistically significant difference was found with girls scoring higher than boys in proxy-rated HRQoL scores for Physical (P= 0.03) and Treatment burden (P=0.02) domains. A higher self-rated mean (SD) HRQoL scores in Respiratory domain for *Pseudomonas spp* negative [76.9 (14.8)] as compared to *Pseudomonas spp* positive for subjects in the age group 6-13 years [67.2 (15.1)] (P=0.042). No such statistically significant difference was found in HRQoL scores between culture negative and culture positive subjects aged 14 and above and for proxy rating. We found better mean (SD) self-rated HRQoL scores in Respiration domain for groups with higher FEV1 values, *i.e.*, FEV1% pred≥80% [82.5 (9.7)] compared to 40-59% [63.6 (19.1)]

in subjects of ages 6-13 years (P=0.01). Similar analysis of HRQol scores obtained by proxy rating by parents showed higher scores in Health perceptions (P=0.006) and Respiration (P=0.005) domains and for the FEV1% predicted >80% compared to <40% (P=<0.05). Similar differences were found with higher scores in PEFR percent predicted group >80% compared to <40% in proxy rated HRQoL scores in domain respiration. No difference were found in self rated HRQoL scores for any of spirometric parameters for age group 14 and above.

Correlation: There was a statistically significant correlation between self-rated HRQoL scores and Clinical scores for subjects aged 14 and above (r=0.65, P=0.011) (***Fig* 1a**). No such correlation was found for age 6-13 proxy rating by parents. There was a statistically significant inverse correlation between self-rated HRQoL scores and age at diagnosis for ages 6-13; (r=-0.339, P=0.02) (***Fig.* 1b**). No such correlation was found for age 14 and above, proxy rating by parents.

Convergent validity: Reliability analysis showed statistically significant correlation between self and proxy rating for 4 out of 8 domains; Physical (ICC=0.36, P= 0.008), Eat (ICC=0.42, P=0.002), Respiration (ICC=0.58, P=0.0001), Digestion (ICC=0.37, P= 0.006). The other domains did not show any statistically significant correlation.

DISCUSSION

This is the first study looking at HRQoL of patients diagnosed with cystic fibrosis in a *Hindi*-speaking population. Our study demonstrated good internal consistency in most domains, especially in the adolescent version. We also noted a pattern of domains with less number of items (viz. Treatment Burden, Eating, Digestion, Health Perceptions, School) having poor internal consistency across all versions.

Our study trends the quality of life through the different life stages. It also combines the self–rating with an independent proxy rating by the parents. The low to moderate correlation observed in many studies establishes the importance of both the ratings to get a holistic picture of the quality of life of children with CF [27]. Moreover, the observed correlations with objective health parameters renders a new clinical dimension to the questionnaire, proving that it is sensitive enough to detect clinically significant changes. Our study has a few limitations too. Firstly, in a cross-sectional study, design-causation cannot be proved; and secondly, this being a single-center study, the sample size was not sufficient to gain adequate power for the factor analysis.

The Principal Factor Analysis did not allocate most of the items to the respective domains in the questionnaire, only items belonging to the domain Physical had factor loadings >0.4 for the child and the parents' version. This may be due to the sample size, considering inclusion of at least 10 subjects per item is recommended to increase the power for Factor analysis [17]. The Factor analysis also suggested reducing the number of domains across all the versions, especially the parents' version. This contrast with the good Cronbach salpha values becomes difficult, especially in light of the questionable importance of factor loadings for validation of a psychometric tool involving causal items [24,25]. The mean scores were greater for the self-rating in most domains, except for Emotion and Social fshowing that the parents overestimated the emotional and social quality of life of their children.

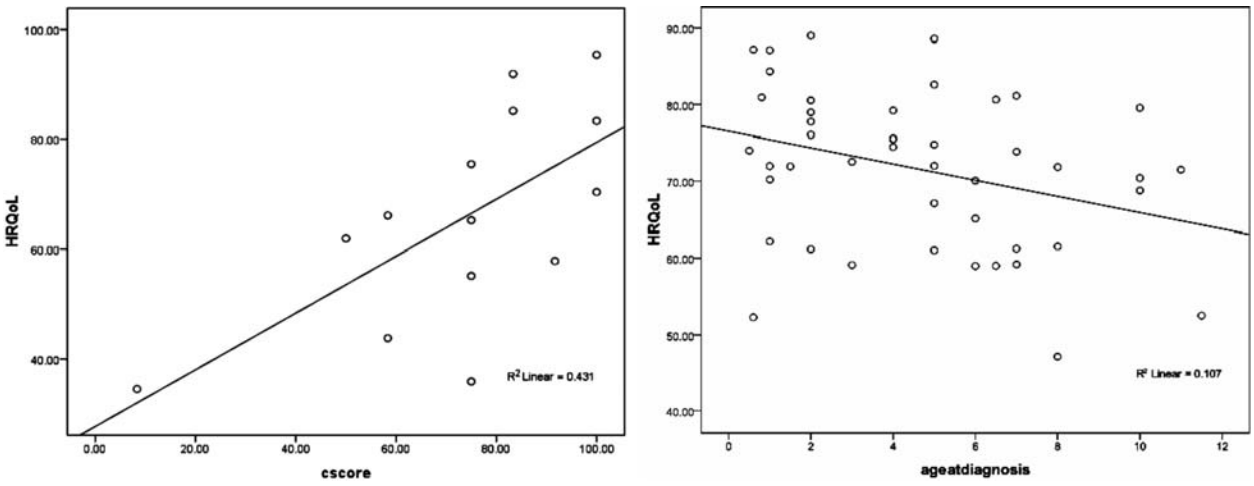

FIG. 1 *A correlation between HRQoL scores (Adolescent's format) and Clinical scores, r= 0.65, P= 0.01; (b) Correlation between HRQoL scores (Child format) and age at diagnosis, r= -0.3, P= 0.02.*

WHAT IS ALREADY KNOWN?

- Cystic fibrosis specific English version of CFQ-R is a valid psychometric instrument with profound clinical impact.

WHAT THIS STUDY ADDS?

- Cystic fibrosis specific Hindi version of CFQ-R is a valid psychometric instrument.

The delayed diagnosis reported in this study is possibly due to less awareness, and non-availability of sweat testing. This contrasts with the statistics in areas where newborn screening is in place [3]. This, however, has been found in earlier studies on cystic fibrosis in India, attributed to lack of newborn screening and low awareness of the existence of cystic fibrosis. We also found an inverse correlation between age at diagnosis and the HRQoL scores for children aged 6-13 years. To address the clinical relevance of the HRQoL scores, we used objective clinical parameters and found significant associations.

Our study replicated the low Cronbach's alpha values for domains Treatment Burden and Social, found in previous studies of CFQ-R (17,18,21). The low correlation between the and proxy-rating in this study has also been reported previously for Physical and Emotion domains [17,18]. The domains Emotion, Treatment Burden, Social, Body Image also showed no correlation, as seen in the Spanish study and the study by Havermans, *et al*. [20,26]. The positive association between scores in Respiration domain and spirometry [16] have also been previously reported [16,26], thereby validating CFQ-14+ showing correlation between pulmonary function and Respiration domain. Similar to our study, an Italian study also found lower Respiration scores for Pseudomonas positive, compared to negative patients [19].

We conclude that the Hindi version of CFQ-R is a valid psychometric instrument. With a few changes in its present structure and by addressing the present statistical shortcomings, it may be possible to integrate CFQ-R Hindi in the clinics for monitoring the QoL of cystic fibrosis patients.

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Contributors: DK: Developed protocol, collected data, analyzed data and wrote manuscript; SG: involved in data collection and manuscript writing; GPJ involved in data collection; MK: involved in data analysis and manuscript writing; RL: involved in protocol development, and manuscript writing; SKK: Involved in protocol development, data collection, data analysis and manuscript writing, will act as guarantor for the paper.
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