Assessing the Liverpool Respiratory Symptom Questionnaire in Children with Cystic Fibrosis

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Abstract
Monitoring respiratory status in cystic fibrosis (CF) is challenging, particularly in young children. We aimed to test whether the Liverpool Respiratory Symptom Questionnaire (LRSQ) could distinguish well, preschool and older children from those similarly aged with stable CF, whether it could distinguish stable and unwell children with CF, and finally, whether LRSQ scores in older children correlated with established measures of disease severity.

Stable preschool children with CF (n=20) had significantly higher total LRSQ scores than preschool controls (n=51), and higher scores in 2/8 domains. Similarly, stable 6-12 yr
children with CF (n=21) had higher total scores than 6-12 yr controls (n=97), and higher scores in 7/8 domains. In older children with CF, LRSQ scores negatively correlated with Shwachman score and FEV1 (r -0.58 p<0.001 [n=31] and r -0.46 p<0.010 [n=34] respectively). Within the CF group, patients who cultured Pseudomonas aeruginosa, who used more ‘back-up’ antibiotics or whose school attendance was lower, also had higher LRSQ scores.

The LRSQ differentiates well children from those with CF in both preschool and 6-12 age groups, even at a point of stability. It also differentiates stable from unwell children with CF, and scores correlate with other measures of respiratory disease, highlighting it’s potential as a clinical monitoring tool in paediatric CF.
Key Words

Cystic Fibrosis
Monitoring
Paediatrics
Patient reported outcome measure
Symptom score
Introduction

Recent improvements in CF survival have been attributed to prevention and timely, active treatment of chest disease. In an increasingly well population, measures to monitor respiratory status, including spirometry and chest radiograph scores[1], lack the required sensitivity to objectively detect deterioration in condition. Novel non-invasive measures, applicable to standard clinical practice, are needed to identify potential windows for early intervention.[2, 3]

Recently, there has been considerable interest in Patient Reported Outcome measures (PRO), with the National Institutes of Health aiming to develop a large test bank of PRO measures useful in the clinical assessment of chronic disease.[4, 5] The two main types of PRO are health related quality of life questionnaires (HRQOL) and symptom scores. In paediatric CF, respiratory symptom score development has been limited, particularly in preschool children, for whom assessment is difficult and reliant on parental reports or direct behavioural observations. To date, there is no CF specific validated tool for this age group. Those tools that have been validated in children focus on the recognition of acute pulmonary exacerbations or short-term trial outcomes, rather than a longer-term reflection of parent reported respiratory condition. The Cystic Fibrosis Questionnaire Revised (CFQ-R) respiratory symptom scale has been well validated in the 6-13 age group but is focussed on a two week recall period and has mainly been used in clinical trial outcomes rather than clinical monitoring. [6-10]

We have previously validated a respiratory symptom questionnaire in non-CF preschool children, one of few studies to attempt respiratory symptom score validation in this age group.[11, 12] The Liverpool Respiratory Symptom Questionnaire (LRSQ), which carefully documents respiratory symptoms across multiple domains, proved to be sensitive at detecting respiratory disease in this young population. It showed strong divergent construct validity,
good internal consistency and short-term reliability of questions, and importantly, was practical and acceptable for parents. The LRSQ is designed to detect symptoms over three months. This longer time period lessens the effect of acute changes in clinical condition, thus making this score more relevant to both healthcare professionals and parents when tracked over time.

In this study, we aimed to assess whether the LRSQ could distinguish between well children and children with stable CF in the preschool age group. We also aimed to assess whether it could further distinguish ‘well’ and ‘unwell’ children within the CF group. In view of the known limitations of current clinical measures of respiratory status in preschool children, we included a school age group (age 6-12 years). This would enable us to assess correlations of LRSQ score with other objective measures of disease status, such as Shwachman score, Northern chest x-ray score (NCXRs) and spirometry, giving an indication of the scale’s sensitivity to disease status within the paediatric CF population.

**Material and Methods**

**Study Subjects**
Parents of children with and without CF completed the LRSQ following consent for inclusion in the study.

All patients were recruited at routine clinic appointments and were included if they had CF and were aged 0-12 years. All were prescribed antibiotic prophylaxis. There is no agreed definition for ‘stability’ in CF, and therefore this definition was agreed locally amongst a group of respiratory paediatricians. Children were deemed ‘stable’ if they had needed no more than one course of back-up oral antibiotics in the preceding three months and this course had not been within the previous two weeks.
Healthy controls without respiratory disease were recruited from local nurseries and schools or were children of members of staff or friends of patients admitted to Alder Hey Children’s Hospital. Exclusion criteria included children with chronic illnesses or needing regular medications.

The Liverpool Local Research Ethical Committee approved the study (02/07/108/A(C)).

**Study Design**

This was a questionnaire based, cross-sectional study.

**Questionnaire (LRSQ) and Outcome Measures**

The LRSQ consists of eight domains each containing between three and five items. The first six domains assess respiratory symptoms and the remaining two assess the impact of symptoms on the child and family (Table 1). Parents were asked to consider symptoms over the last three months with questions being scored on a five point Likert Scale from “not at all” (score 0) to “every day” (score 4). A score for each domain and for the complete questionnaire was calculated (maximum score 128).

Demographic information including age, gender, and number of smokers in the household were recorded. Children with CF had their recent NCXRs, Shwachman score, spirometry results, Pseudomonas carriage, antibiotic usage and school attendance (over the last three months) recorded. A single radiologist scored all chest radiographs.[1] The Shwachman score comprises four domains reflecting respiratory symptoms, activity, nutritional status and CXR appearances.[13] Pseudomonas carriage was recorded in two ways. Firstly, on the clinic specimen at the time of the study, and secondly, on a four point scale of carriage according to the Leeds Criteria.[14] Clinic spirometry results were recorded at the time of questionnaire completion and children were classified by percentage predicted FEV1 according to established cut offs for ‘mild’ (FEV1 > 70%), ‘moderate’ (FEV1 40-69%) or ‘severe’ (<40%) disease.[15]
**Statistical Analysis**

SPSS version 18.0 was used. Data are expressed as median and inter-quartile range [IQR]. The Mann Whitney U test was used for comparison of ages between the CF and healthy control groups. The Chi Squared test was used for comparison of gender and number of smokers per household between groups. Following log transformation of LRSQ scores, multiple linear regression analysis was performed to compare domain and total scores between healthy controls and stable children with CF, taking account of potential confounders between groups such as differences in number of smokers per household. A Bonferroni correction was used to minimise the risk of type 1 error. Spearman’s rank correlation was used to examine the correlation of total LRSQ scores with NCXRs, Shwachman Score, FEV1 and FVC. The Kruskal-Wallis H Test was used to compare total LRSQ scores across multiple categorical groups.

Cronbach's alpha coefficients were calculated to assess internal consistency of items within individual questionnaire domains, indicating the extent to which they measured the same construct. Coefficients of $r=0.70$ were considered acceptable.[16]

Ceiling and floor effects (the percentage of children scoring at scale extremes) within LRSQ total scores were studied. Ceiling or floor effects of $>20\%$ are considered significant.[17, 18]

**Results**

**Demographics and Clinical Details**

64 children with CF were recruited. One questionnaire was incomplete and therefore excluded, leaving 63 children in the CF group ($31 < \text{five years age}$). 41/63 children with CF ($20 < \text{five years age}$) were considered to be ‘stable’ at the time of questionnaire completion.
148 healthy controls were included (51 < five years age). The median age for both controls and children with CF in the five and under group was 3 years (range 3 months-5 years). The median age in the over five age group was 10 (range 6-12) for control children and 9 (range 6-12) for CF patients (p=0.095). There was no significant difference in gender between the CF and control group (56% male vs. 46%, p=0.259). There were significantly more smoking households in the CF group (48% of CF households vs. 21% in the control group p<0.001).

Within the whole CF group (n=63), 20% cultured Pseudomonas persistently from sputum or cough swab at the time of LRSQ completion (n=5 in the five and under group and n=8 in over five age group). All children with CF over five years of age (n=32) completed spirometry. We classified FEV1 results according to established cut offs for ‘mild’ (FEV1 > 70%), ‘moderate’ (FEV1 40-69%) or ‘severe’ (<40%) disease. 19 patients (58%) were within the ‘mild’ category, and 13 patients were within the ‘moderate’ category. No children were classified ‘severe’.

**Discriminant Validity – Five and Under Age Group**

Preschool, ‘stable’ children with CF (n=20) scored significantly higher in total LRSQ score (11.5[8-20] vs. 5[1-11] p<0.020) and 2/8 domain scores (‘Effects on Family’ p<0.010 and ‘Other symptoms’ p<0.050) than healthy controls (Table 2, Figure 1). The difference in total score persisted even if only the 8 children with CF entirely free of supplementary antibiotics for the study period were included in the analysis (10.5[8.3-16.3] vs. 5[1-11] p<0.05).

Examination of cross sectional data for different age categories (under two years, two-four years and four-six years) showed that mean LRSQ scores in preschool children with CF rose with age, and that the difference between CF and controls became more pronounced in older preschool children (Figure 2).

No correlation between LRSQ score and NCXR score or Shwachman score was seen. On assessing the entire group (stable and unstable, n=31), a trend was seen in LRSQ scores
dependent on the number of courses of antibiotics needed during the study period (Figure 3). Despite small study numbers, there was a significant difference in scores between those not needing supplementary antibiotics and those needing two courses (p<0.05).

**Discriminant Validity – Six to Twelve Age Group**

‘Stable’ children with CF aged 6-12 years scored higher in total LRSQ and 7/8 domain scores compared with controls (total score 14[5-33] vs. 3[0-6] p<0.001) (Table 2, Figure 1). Differences in total LRSQ score persisted even if only the 9 children with CF, entirely free of supplementary antibiotics for the study period were included in the analysis (p<0.010).

For all children with CF (stable and unstable, n=32), correlations were examined between total LRSQ score and current NCXR scores, Shwachman score and FEV1. Significant correlations were seen between total LRSQ score and FEV1 (r= -0.45 p<0.010 n=32), FVC (r= -0.37 p<0.050 n=32), Shwachman Score (r= -0.58 p<0.001 n=31). The correlation between total score and NCXR score showed a positive trend but did not reach statistical significance (r=+0.311 p=0.089 n=31). Following classification of CF disease severity by FEV1, we compared total LRSQ scores across the ‘mild’ and ‘moderate’ groups to total scores for control patients (control patients did not complete spirometry). We noted a decline in median scores from those with moderate disease severity to mild disease severity to control patients (p<0.001) (Figure 4).

We compared LRSQ scores with Pseudomonas carriage (Figure 5a). Total median scores were higher in those children who cultured Pseudomonas at the time of LRSQ completion compared to those who were negative (PsA +ve 23[16.8-34.5] (n=12) vs. PsA –ve 10[3.5-24] (n=18) p<0.050). Pseudomonas carriage was classified according to the Leeds Criteria. No statistically significant difference was found in scores across the groups but a rising trend in LRSQ scores was seen (Figure 5b).

Finally, we analysed total LRSQ scores based on school attendance and found that median total LRSQ score was higher in those children with CF needing 1-2 days per month off school.
school compared to those with full attendance (median 47[29-64.5] vs. 15[3-23] p<0.01 (n = 5 and 25 respectively).

**Internal Consistency**

In preschool children with CF, the Cronbach’s alpha coefficients in 6/8 domains ranged between 0.76-0.89, demonstrating acceptable to good internal consistency (Table 3). The ‘Night-time symptoms’ domain had a coefficient of 0.64, which improved to 0.71 if the question regarding snoring was removed. The ‘cold symptoms’ domain had a coefficient of 0.66. Internal consistency was consistently acceptable to good across all domains in the over fives with CF (0.74-0.87)

**Ceiling and Floor Effects**

No ceiling effects or floor effects were observed in CF patient scores (n=64). However, in preschool control children, there were borderline floor effects in total score (19.6%). Floor effects were observed to a greater degree in the older control patients (40.5% floor effect in total score). This further supports the suitability of the LRSQ in detecting respiratory symptoms in the CF population.

**Discussion**

We have shown that the LRSQ total score successfully distinguishes ‘stable’ CF patients from healthy children in the preschool and in the 6-12 age group. These differences persisted when children with CF who needed one course of oral ‘back-up’ antibiotics in the previous three months were excluded. We have also shown that LRSQ score correlates with school attendance and antibiotic usage over a three month period in children with CF. The LRSQ score therefore appears to distinguish children based on general clinical status within the CF cohort over a period of months. Correlations between LRSQ scores and other measures of respiratory status in the 6-12 age group highlight the potential role for this tool in both
clinical and research paediatric CF settings. The LRSQ also allows respiratory symptom comparison across different paediatric diseases (previously validated in a non-CF preschool group).

In the 6-12 year old CF group, children scored higher than controls in 7/8 domains. Domain scores were generally higher in preschool children with CF, although statistical significance was only reached in two domains. In part, this reflects the higher scores seen in the healthy preschool children, which may be due to the frequency of viral respiratory infections seen in this age group. One of the domains where scores were higher in preschool children with CF was ‘Effect on the family’. This is perhaps not surprising given that this domain covers how a child’s respiratory symptoms impact on family life. More interestingly, scores for the ‘Other respiratory symptom’ domain were also higher than the control group. This domain covers noisy breathing not from the chest, fast breathing and noisy breathing from the back of the throat, all symptoms that may relate to increased large airway secretions.

No formal validation of a respiratory symptom questionnaire for preschool children with CF has been successful to date. In adults and adolescents, the CFQ-R and the Cystic Fibrosis Quality of Life Questionnaire (CFQoLQ) are widely used, reliable and valid. The CFQ-R (HRQOL questionnaire) has a fully validated child and parent completed version for children aged 6-13 years, but there is currently no fully validated preschool version.[7-9, 15] Although the CFQ-R respiratory domain has been validated and adopted as an outcome measure in clinical trials, it’s utility in paediatric clinical use (monitoring) may be limited by having only four items in the child version and six in the parent version.[10, 19] The LRSQ has potential advantages, as it has been designed as an instrument for parental completion, is partially validated in the under fives and covers an extensive number of symptoms, whilst maintaining acceptability. Unlike other respiratory conditions such as asthma,[20] much of the focus in the development of respiratory symptom scores for CF has been on creating shorter-term
recall tools, which are capable of identifying pulmonary exacerbations.[2, 6] In contrast, the LRSQ is not designed to be used as a pulmonary exacerbation score. It assesses symptoms over a 3 month period and as such, may have utility as a measure of longer term respiratory status (for example, incorporated into an annual review assessment). In addition, there is potential for the LRSQ to be used as a remote monitoring tool with parents being able to compare with previous values and provide objective data for the CF team to assess condition from afar.

There has been debate within the literature surrounding the reliability of longer term symptom recall[21]. We have demonstrated that the LRSQ score can differentiate children based on number of antibiotic courses and school attendance over a three month period. This supports our assertion that the LRSQ is collecting data which reflects longer term symptomatology. There is also debate within the literature surrounding the reliability of symptom reporting in reflecting disease status. Many studies have examined the relationship between early inflammatory changes and other clinical parameters of disease (including symptomatology) in preschool children. Some studies reported poor correlation between parent reported symptoms and markers of infection and inflammation, lung function or computerised tomography scan (CT) findings. However, these studies either recorded general symptoms without the use of an objective tool or used a tool which was not validated for use in young children with CF. [22-25] In this study, we have demonstrated a cross sectional trend of increasing symptom development over preschool years (in contrast to healthy controls) as well as correlation of symptom scores with other measures of both short and longer term clinical disease status. This suggests that the use of a standardised symptom questionnaire may yield more useful results. The correlation of LRSQ scores with other disease monitoring tools, which we know have limited sensitivity, does not confirm the questionnaire’s value. Shwachman score and NCXRs are known to be insensitive in young
children, which may explain the lack of correlation in the preschool group. Future studies, investigating the correlation of LRSQ scores with early measures of structural, inflammatory or infective processes such as BAL inflammatory markers and CT changes would be extremely useful, and would further assess the potential of this tool in identifying windows of opportunity for early intervention.

A source of bias in our study was the control group, some recruits being children of healthcare staff. The higher incidence of passive household smoking in the CF group highlights the potential for socioeconomic status inequality between groups,[26] but regression analysis did not demonstrate a confounding effect on LRSQ scores. It is of note that this study was conducted in an area with high levels of socioeconomic deprivation. Forty-eight percent of CF patients were exposed to passive smoke within the home. This is highly concerning and highlights the need to enquire about passive smoking and offer smoking cessation support. Data about other possible confounding factors, including the age and gender of the person completing the questionnaire, nursery attendance and number of siblings (affecting exposure to respiratory pathogens), household pets and allergies were unavailable or not assessed.

With regards to LRSQ validity, we have shown acceptable to good internal consistency in 6/8 domains in preschool children and 8/8 domains in older children. The ‘night-time symptoms’ domain could be improved by excluding the question on snoring. The prevalence of snoring in children varies between 3.2-12% depending on age, primarily due to pharyngeal airway size. This physiological variation, the range of possible associated underlying pathologies, together with the potential bias of the arbitrary definition of snoring and reliance on parental reporting (who may not sleep in the same room), could render this item unreliable in assessing night-time respiratory symptoms within a paediatric population. [27, 28] Previous studies have demonstrated moderate to good test-retest repeatability of the LRSQ, further
indicating it’s validity.[11] The acceptability of the questionnaire to parents was also assessed previously and found to be practical and acceptable.[11] This is supported by the high percentage of correctly completed questionnaires (>99%) in this study.

The wide range of total scores from CF patients provides reassurance that the questionnaire is capable of detecting differences, even within a stable CF paediatric population. Further evidence of discriminant validity is provided by the correlation of LRSQ scores with other outcome measures. Future studies will assess children at a time of instability and examine the scores for evidence of a ceiling effect. No floor effects were seen in total scores for CF patients, even at a time of stability. This was in contrast to healthy control patients in whom floor effects were seen. This indicates that the LRSQ is appropriate for detecting mild symptoms in a ‘stable’ CF population.

Some other aspects of questionnaire validation were not assessed in this study, including inter-rater reliability and an assessment of the sensitivity of the LRSQ in detecting longitudinal changes in respiratory condition. Further limitations of the study include the relatively small numbers of patients within some of our sub-group analyses and the question of whether parental completion of a questionnaire is appropriate for older children. There is some conflict within the literature regarding concordance of child and parent reported respiratory symptoms.[29, 30] However, strong convergence of child/parent respiratory symptom reporting was confirmed in the CFQ-R Child validation study (6-13 age group).[7] This supports our use of parental assessment, which is particularly useful in younger children.

A limitation of this study is the absence of longitudinal data in individual patients. We are planning a large longitudinal study to more formally assess the sensitivity of the LRSQ to change in clinical status over time. This future study will also allow some aspects of psychometric validation not possible in this study, to be assessed. We have shown that the LRSQ can distinguish ‘stable’ children with CF from children with CF who are ‘unwell’. The
cross sectional data presented highlights the potential sensitivity of this tool in detecting symptoms in preschool children. We believe this tantalising data highlights the potential of this measure for monitoring respiratory condition through childhood.

Conclusions

This study suggests that the LRSQ is a sensitive tool for detecting respiratory disease in the pre-school and school age CF population. Correlations between LRSQ scores and other measures of CF disease severity in older children suggest that the questionnaire will have a role in the objective monitoring of long term respiratory status. This may be a particularly important tool in preschool children with CF, where other clinical measures are limited.
Acknowledgements

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References


### Table 1: Details of the Components of the LRSQ

<table>
<thead>
<tr>
<th>Questionnaire Domain</th>
<th>Symptoms Assessed</th>
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<tbody>
<tr>
<td>Daytime Symptoms, Symptoms with Colds, Interval Symptoms (between colds), Symptoms with Activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough, wheeze, shortness of breath, ‘rattly’ chest</td>
</tr>
<tr>
<td>Night-time Symptoms</td>
<td>Cough, wheeze, shortness of breath, ‘rattly chest’, snoring</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>Noisy breathing not from chest, noisy breathing from throat, fast breathing</td>
</tr>
<tr>
<td>Effects on child</td>
<td>Feeding, activity levels, sleep disturbance, fatigue</td>
</tr>
<tr>
<td>Effects on family</td>
<td>Family activities, adjustment to family life, disturbed sleep, worry/anxiety</td>
</tr>
</tbody>
</table>

### Table 2: Total and Domain Scores for CF and Control Groups (median [IQR]).

* p<0.050 ** p<0.010

<table>
<thead>
<tr>
<th>Questionnaire Domain</th>
<th>CF patients (5 yrs and under n=20)</th>
<th>Controls (5yrs and under n=51)</th>
<th>CF patients (6-12 yrs n=21)</th>
<th>Controls (6-12 yrs n=97)</th>
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</table>

20
<table>
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<tr>
<th></th>
<th>CF 5 and Under Group</th>
<th>CF 6-12 Group</th>
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<tr>
<td><strong>Domain</strong></td>
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<tr>
<td>Daytime</td>
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</tr>
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<td>Night-time</td>
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<tr>
<td>Symptoms with Colds</td>
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Table 3: Cronbach’s alpha coefficients for LRSQ domains. Coefficients shown for CF patients aged five and under and 6-12 years.
<table>
<thead>
<tr>
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<th>Value 2</th>
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<td>Interval Symptoms</td>
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<td>Activity Symptoms</td>
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<td>0.87</td>
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<tr>
<td>Effects on Family</td>
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<td>0.74</td>
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</table>

Figure 1
Figure 2
Figure 3

Figure 4
Figure 5b

Pseudomonas Status at Time of LRSQ Completion
Pseudomonas Carriage (Leeds Criteria)