Arch Bronconeumol. 2010;46(4):165-175

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Original Article

Validation of the Spanish Version of the Revised Cystic Fibrosis Quality of Life Questionnaire in Adolescents and Adults (CFQR 14+ Spain)

Gabriel Olveira,[a,b] Casilda Olveira,[c,*] Inmaculada Gaspar,[d] Ivette Cruz,[e] Antonio Dorado,[c] Estela Pérez-Ruiz,[f] Nuria Porras,[a] and Federico Soriguer[a,b]

[a] *Unidad de Fibrosis Quística, Servicio de Endocrinología y Nutrición, Hospital Regional Universitario Carlos Haya, Málaga, Spain*
[b] *CIBER de Diabetes y Enfermedades Metabólicas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Unidad de Fibrosis Quística, Servicio de Neumología, Hospital Regional Universitario Carlos Haya, Málaga, Spain*
[d] *Servicio de Neumología, Hospital Costa del Sol, Marbella, Málaga, Spain*
[e] *Departments of Psychology and Pediatrics, University of Miami, United States*
[f] *Unidad de Fibrosis Quística, Servicio de Pediatría, Hospital Regional Universitario Carlos Haya, Málaga, Spain*

ARTICLE INFO

Article history:
Received September 18, 2009
Accepted January 22, 2010
Available online March 20, 2010

Keywords:
Cystic fibrosis
Cystic fibrosis quality of life questionnaire
CFQR 14+ Spain
Lung function
Pulmonary exacerbations
6-minute walk test
Computerized tomography of the chest
Body mass index
Fat-free mass index
Diabetes

ABSTRACT

Background: The aim of this study was to assess the validity and reliability of the Spanish version of the revised disease-specific health related quality of life questionnaire for adolescents and adults with cystic fibrosis (CFQR 14+ Spain).
Patients and methods: A total of 43 cystic fibrosis (CF) patients completed the CFQR 14+ Spain. Forced expiratory volume in 1 second, in percentage of predicted - FEV_1 (%) -, number of respiratory exacerbations, 6-minute walk test, Bhalla score (based on computerized tomography of the chest), fat-free mass index, body mass index (BMI), faecal fat and St George's Respiratory Questionnaire were included as measurements of health status.
Results: Ten out of the twelve scales had alpha coefficients above 0.70. Test–retest correlations (Spearman) ranged from 0.49 to 0.95 and they were significant in all scales. Intraclass correlations ranged from 0.47 to 0.95 (ten out of the twelve scales were >0.70) forty out of the fifty items have correlations between items and scale above 0.70. All the CFQR 14+ scales, except the digestive symptoms scale, discriminated significantly between patients with mild, moderate and severe disease (according to FEV_1 [%]). Other respiratory parameters also discriminated significantly between patients with mild-moderate and severe disease. Only some scales discriminated significantly between nourished and malnourished patients. All of the scales met standards for floor effects (<15% of the responders with the lowest score) but not for ceiling effects (only five out of the twelve).
Conclusion: The Spanish CFQR 14+ (Spain) is a reliable and valid instrument for measuring the health-related quality of life in Spanish adolescents and adults with CF, though with the exception of a few of its subscales.

Validación de la versión española del cuestionario revisado de calidad de vida para fibrosis quística en adolescentes y adultos (CFQR 14+ Spain)

Palabras clave:
Calidad de vida
CFQR 14+
Fibrosis quística
Función pulmonar
Reagudizaciones
Tomografía computerizada de alta resolución
Prueba de la marcha de 6 minutos
Índice de masa corporal
Índice de masa magra
Diabetes

RESUMEN

Objetivos: Estudiar la validez y fiabilidad de la versión española del cuestionario revisado de calidad de vida para fibrosis quística (FQ) en adolescentes y adultos (CFQR 14+ Spain).
Pacientes y métodos: Se estudiaron 43 adolescentes y adultos con FQ, clínicamente estables. Se utilizaron como medidas del estado de salud parámetros radiológicos, espirométricos, número de reagudizaciones, prueba de la marcha de 6 min, antropométricos (índice de masa corporal, desnutrición de masa magra), grasa en heces y el cuestionario respiratorio de St. George (SGRQ).
Resultados: El alfa de Cronbach fue ≥0,70 para todas las escalas, excepto para «síntomas digestivos» y «carga de tratamiento». Cuarenta ítems (de 50) presentaron correlaciones ítems-escala mayores a 0,70 y el 98% mayores a 0,40. La reproductibilidad test-retest (coeficiente de Spearman) osciló entre 0,49–0,95 y el coefi-

* Corresponding author.
E-mail address: casi1547@separ.es (C. Olveira).

0300-2896/$ - see front matter

ciente de correlación intraclase alcanzó puntuaciones mayores de 0,70 en 10 de 12 escalas. Todas las dimensiones correlacionaron significativamente con las puntuaciones del SGRQ. Se observaron correlaciones significativas entre las dimensiones del cuestionario y las variables respiratorias y nutricionales que pretendían medir y permitió diferenciar adecuadamente los distintos grados de gravedad en función de los parámetros respiratorios evaluados. La desnutrición y la malabsorción condicionaron significativamente peores puntuaciones sólo en algunos dominios relacionados (como problemas con el peso). El efecto suelo fue menor al 15% en todas las dimensiones y el efecto techo fue elevado en 7 dimensiones.
Conclusiones: El cuestionario CFQR 14+ Spain es válido y fiable para su aplicación en España, aunque podría ser mejorado en algunas de las subescalas.

Introduction

Cystic fibrosis (CF) is a disease caused by mutation of a gene on the long arm of chromosome 7 that encodes a membrane protein called CFTR (CF transmembrane conductance regulator). This protein behaves as a chloride channel, so that mutations in this gene lead to a defect in chloride transport in epithelial cells of the respiratory, hepatobiliary, gastrointestinal, reproductive, pancreas and sweat glands. Due to the multiple organs and systems affected and its chronic and progressive nature, CF is complex, consumes many resources, and requires a comprehensive approach. In the last few decades, survival of people with CF has greatly increased, changing CF from being a "fatal childhood disease" into a "chronic multisystemic disease" of people who, in the majority of cases, reach adulthood and who wish not only to live longer but also to have good quality of life.[1]

The measurement of health-related quality of life (HRQOL) in CF allows the assessment of the disease from the patients' perspective, which provides valuable clinical and research information.[2] Therefore, although some parameters such as forced expiratory volume (FEV 1) or body mass index (BMI) have prognostic value regarding morbidity and mortality, they are poor predictors of feelings of well-being. To quantify well-being, there is a need for a valid and reliable measurement tool.[2,3] HRQOL is measured by questionnaires. The generic questionnaires (e.g. the SF-36) are not sensitive enough to discriminate specific aspects of the disease (such as the potential benefits of new treatments, the impact of exacerbations or progression markers of the disease) because they have less robust psychometric characteristics than that of the data from questionnaires specifically designed for people with CF.[2-4] Our group validated the St. George Respiratory Questionnaire for use in adults with CF, noting that it discriminated well between different severities of pulmonary function. However, it did not include other specific aspects of the disease such as gastrointestinal involvement or nutritional status.[3] The CFQ is an HRQL questionnaire designed specifically for patients with CF, which was initially developed in France (and translated into several languages including Spanish)[5,6] and includes versions specifically for children (6-13 years), parents of children aged 6-13 years and adolescents and adults (over 14) with CF (CFQ14+). It was translated and validated in its English version[7] and has undergone several modifications, resulting in a revised version (CFQR) that also has been translated and validated into various languages.[4,8-11] This revised version has also been translated into Spanish for use with the Spanish-speaking population of the U.S.[12] and our group has adapted it, making minor modifications to make it more suitable for the Spanish population (CFQR 14+ Spain). Transcultural validation of an HRQL questionnaire already available in a particular language, has the advantage of avoiding the long and tedious development of a new one.[9] In the CFQR 14+ validations in other countries by other authors, basic parameters were used (spirometry, age or BMI).[4,8-11] However, other variables were not used such as classification of severity according to radiology, the number of exacerbations, evidence of 6 min progress (6mP), body composition and laboratory parameters such as measurement of fat in faeces, which would improve validation.

Therefore, the objective of this study was to assess the validity and reliability of the CFQR 14+ Spain questionnaire in a group of adolescents and adults in Spain with CF.

Patients and Methods

Patients

The study included patients over 14 years of age who presented with diagnostic criteria for CF[13] and who are periodically monitored in the adult CF unit of the Hospital Universitario Carlos Haya (Carlos Haya University Hospital, Malaga). Patients were selected (sequentially and prospectively) during an inclusion period of 7 months, and included those who attended the CF unit for routine annual review. If at this time they had a respiratory exacerbation (see criteria below) or acute digestive symptoms (emergency visit) or a recent hospital admission, their inclusion was postponed at least 30 days until completion of treatment of the acute process. We excluded patients who had problems understanding the questionnaire, transplant patients or transplant waiting list patients. The questionnaire was completed before the performance of additional annual tests in order to avoid affecting responses. In a subgroup of patients (clinically stable at both times), the questionnaire was administered in duplicate over the course of 10-15 days. The study was approved by the Research Ethics Committee of Carlos Haya Hospital and all participants gave written informed consent.

CFQR 14+ (Spain) Test

The CFQR 14+ consists of 50 items structured in 12 domains that are divided, in turn, into 6 that assess general aspects of HRQL-capacity (8 items), role limitations (4 items), vitality (4 items), perception of health (3 items), emotional state (5 items) and social isolation (6 items) - and 6 domains that address specific aspects of CF- body image (3 items), feeding problems (3 items), burden of treatment (3 items), weight problems (1 item), respiratory symptoms (7 items) and digestive symptoms (3 items). Completing the questionnaire takes about 10-15min. The ratings vary from 0-100, and the higher scores correspond to a better HRQL. The scores for each round are calculated if at least 2/3 of the questions are answered. There is no total score of the questionnaire that integrates all domains. The questionnaire that, in its original version, was translated into Spanish and validated cross-culturally[6] was validated by Quittner et al.[12] in the United States for use in the Spanish-speaking population

in that country (the CFQR). Our group has adapted the wording of some items of the CFQR for the Spanish population, making small changes without changing the basic concept of the questions. The final version was evaluated by other members of the CF Unit as well as by 8 volunteer patients who determined the suitability of the wording.

Pulmonology Variables

A simple spirometry test was performed. The forced vital capacity (FVC) and FEV 1 were expressed in absolute terms (in ml) and as a percentage of the theoretical value expected for the sex, age, weight and height of a reference population.[14] Structural damage was assessed with the Bhalla scoring system, based on high-resolution computed tomography (HRCT) of the chest, (the lower the final score, the worse the radiological state), and was performed in the context of the annual exam.[15] There was also a test to assess the presence of desaturation during exercise.[16] Following the indications of the European CF Consensus,[17] at each visit to the Unit (every 2 or 3 months) spirometry was performed and a sample of sputum was collected for microbiological study, including general and selective plating for common CF pathogens and bacterial counts. We analysed initial colonisation by common CF organisms, considering the first appearance in sputum (at least 3 positive sputum samples), regardless of their persistence at the time of the study. Respiratory exacerbations were recorded systematically and prospectively in the Unit[18] based on the following criteria: 1) Mild-moderate: increased volume or purulence of sputum and/or increase in dyspnoea not due to other causes, possibly accompanied or not by other symptoms (cough, fever, asthenia, malaise, anorexia, weight loss, pleuritic chest pain, changes in respiratory examination, changes in chest X-ray suggesting infection or an increase in markers of systemic inflammation - C-reactive protein or ESR) and treated with oral antibiotics. 2) Severe: if, in addition, there was significant clinical deterioration (fever > 38° C, tachypnoea, significant decrease in oxygen saturation or respiratory function, hypercapnia or the appearance of complications such as pneumonia, acute respiratory failure, haemoptysis, haemodynamic instability and/or worsening of cognitive status) and treatment with intravenous antibiotics.[18] Exacerbations experienced by patients in the year prior to this evaluation were taken into account.

Nutritional Assessment

The following anthropometric parameters were measured: height and weight (and from these we calculated BMI), skinfolds (triceps, abdominal, biceps and subscapular) using a constant pressure Holtain caliper. Anthropometric measurements were made by the same researcher, in triplicate, in the dominant limb and were averaged. The percentage of lean mass and fat mass were estimated according to the formulas of Durnin[19] and Siri.[20] We calculated the index of malnutrition in lean mass (IMM)[21] expressed in kg of lean mass/height^2 (the lower values corresponded to increased malnutrition). During the routine annual exam, 72h faeces were collected for determination of fat and nitrogen by the (FENIR)® spectrophotometric technique.[22] Exocrine pancreatic insufficiency (EPI) was defined as a history of use of pancreatic enzymes with levels of elastase lower than 50mcg/g. Similarly, a 4-day prospective dietary record was kept (including at least one Saturday or Sunday), according to a previously described protocol,[23] detailing the caloric intake from dietary supplements and/or tube feeding. With both types of data, we estimated the percentage of fat absorption from the diet.[23]

Statistical Analysis

The data analysis was performed with SPPS for Windows, version 15 (SPSS Inc, Chicago, IL). The results are expressed as mean and standard deviation and in percentages. The normality of the distribution of quantitative variables was examined using the Shapiro-Wilks test. Statistical significance was achieved with $p < 0.05$ for 2 tailed-tests.

Consistency

The correlation (Spearman coefficient) was analysed between each item and scale to which it belongs (acceptable correlations were considered to be ≥ 0.40). The Cronbach alpha coefficient of each of the scales was calculated (acceptable ≥ 0.70).[24]

Concurrent Validity

Concurrent validity was tested using the Spearman correlation coefficients of each scale of the questionnaire with those clinical variables that are expected to be measured (spirometry, exacerbations, Bhalla, anthropometric variables, absorption of fat in faeces) and with the comparison with the St. George questionnaire validated by our group in CF[3] (convergent validity).

Predictive Validity

Predictive validity was performed by analyzing its ability to discriminate between different degrees of severity of illness according to FEV 1 (> 80%, 40-80% or < 40%), the number of exacerbations in the previous year (< 3 vs. $\geq$ 3), the presence or absence of desaturation with exertion,[16] Bahlla score 15 (< 16 vs. $\geq$ 16), malnutrition[1] (BMI < 20kg/m^2 vs. $\geq$ 20), according to the IMM (< 15kg/m^2 vs. $\geq$ 15), age (< 25 vs. $\geq$ 25), the percentage of fat absorption[1] (< 90% vs. $\geq$ 90), history of distal bowel obstruction syndrome, intestinal resection or alterations in carbohydrate metabolism.[1] For comparison of the scores of the domains in terms of dichotomous variables (e.g. malnourished vs. normal) non-parametric Mann-Whitney or T tests were used, based on the normality of the sample. When scores were compared between the domains as a function of 3 or more groups (depending on FEV 1 [%]), ANOVA or the Kruskal-Wallis test was used in case of non-normality of the variables compared.

Reproducibility

In the subgroup in which the questionnaire was repeated (16 patients), Spearman correlations were performed between the dimensions of the questionnaire at each of the two times, as well as the intraclass coefficient of variation (adequate > 0.70).[24]

Results

Forty-three patients completed the CFQR 14+ Spain. Six patients were excluded: 3 lung transplants, 1 patient who had problems understanding the questionnaire and 2 subjects who refused to complete it. The average age of subjects was 25.1 years (range 15.4-64.8) with 46.5% males and 53.5% females. Sixty-nine point eight percent of participants had EPI and 44.2% had some alteration in carbohydrate metabolism (ACM). The Bhalla score showed a mean of 14.9 and an FEV 1 that ranged between 20-102% and an average of 57.9 ± 25.3. There were no significant differences between men and women in terms of Bhalla, FEV 1 (%), FVC (%), number of exacerbations, age, genetics (depending on F508del), BMI, the percentage of EPI, ACM or use of supplements or enteral nutrition. Table 1 summarizes the clinical, spirometric, microbiological,

radiological anthropomorphic variables most relevant to our sample, and Table 2 provides the mean scores in our sample of the 12 scales composing the questionnaire, separated by gender. Females had lower scores on all scales except for "weight problems", although only the "physical capacity" scale reached statistical significance. Table 3 shows the general description of the questionnaire, internal consistency and reproducibility. The ground effect (proportion of individuals with the minimum score of 0) was < 15% in all dimensions. The ceiling effect (percentage of subjects who had the maximum score of 100) was elevated in the dimensions of vitality, body image, role constraints, emotional state, feeding problems, gastrointestinal symptoms and weight problems.

Internal Consistency

Ninety-eight percent of the items had an item-scale correlation > 0.40, as shown in Table 4. The Cronbach's alpha coefficient was > 0.70 in all dimensions of the questionnaire, except two (burden of treatment and gastrointestinal symptoms), with a range of 0.31-0.96, as shown in Table 3.

Concurrent Validity

Table 5 details the correlations found between the scores of the CFQR 14+ Spain domains and various clinical, spirometric, radiological, anthropometric and laboratory variables. We found significant negative correlations between scores on the questionnaire between the scales of physical ability, emotional state, social isolation and perceived health with age (the younger the age, the better the HRQOL). There were positive, significant correlations between the scores on physical ability, role limitations, respiratory symptoms, body image and weight problems, with FEV 1 (%) and FVC (%) and Bhalla score, and negative associations between physical fitness scores, role constraints and respiratory symptoms and the number of exacerbations. The FEV 1 (%) and FVC (%) also showed positive correlations with the dimensions of feeding problems, vitality, emotional state and perception of health. Regarding nutritional parameters, BMI and fat mass (kg) correlated significantly and positively with dimensions of weight problems and the IMM with the scales on physical fitness, vitality, body image and feeding problems. The amount of fat in faeces and the percentage of fat absorption only correlated significantly (r = –0.38 p = 0.012 and r = 0.353 p = 0.038, respectively) with the dimension of weight problems. Table 6 shows the correlations between the scores of the domains of the CFQR14+ Spain and St George's respiratory questionnaire.

Discriminative Validity

Figures 1-6 show the results of the CFQR Spain 14+ questionnaire depending on various clinical, lung function, radiological and anthropometric parameters. Figure 1 shows the scores of the dimensions of the questionnaire (averages) as a function of the predicted percentage of FEV 1: FEV 1 < 40% (n = 15); FEV 1 40-80% (n = 19); FEV 1 > 80% (n = 9). All scores showed statistically significant differences (worse quality of life with greater severity) except in the case of digestive symptoms. Figure 3 shows the results of the questionnaire based on the Bhalla score (greater or less than 16) and Figure 4 the presence (n = 9) or absence (n = 34) of desaturation in the 6mP. Patients with 3 or more exacerbations in the previous 12 months (n = 11) had worse scores in all dimensions of the questionnaire with respect to the group that had less than 3 exacerbations (n = 32) and reached statistical significance in the domains of physical capacity (46.4 ± 27.5 vs. 71.6 ± 28.6) and respiratory symptoms 51.5 ± 17.9 vs. 66.2 ± 19.8 (p < 0.05). Figure 5 details the questionnaire scores based on the presence or absence of malnutrition (BMI < 20kg/m^2, n = 17) and Figure 6 as a function of having an IMM < 15kg/m^2 (n = 14) or greater or equal. There were no significant differences in any of the scales based on the presence in the history of

Table 1
Clinical characteristics of patients with CF

General Parameters	(n = 43)
Age in years (M ± SD)	25.1 ± 8.4
Age at diagnosis in years (M ± SD)	6.5 ± 9.9
Patients diagnosed in adulthood (> 14 years) n (%)	7 (16.3)
Males n (%)	20 (46.5)
Genetics according to F508del	
Homozygotes F508del n (%)	11 (25.6)
Heterozygotes F508del n (%)	17 (39.5)
Remaining n (%)	12 (27.9)
Distal bowel obstruction syndrome n (%)	8 (18.6)
Previous intestinal resection n (%)	6 (14%)
Pancreatic insufficiency, n (%)	30 (69.8)
Altered carbohydrate metabolism n (%)	18 (41.9)
CF-related diabetes without fasting hyperglycaemia n (%)	4 (9.3)
Carbohydrate intolerance n (%)	8 (18.6)
Stress hyperglycaemia n (%)	1 (2.3)
CF-related diabetes with fasting hyperglycaemia n (%)	5 (11.6)
Respiratory parameters	
Sinusitis n (%)	34 (79.1)
Daily bronchorrhoea in stable phase (cc) (M ± SD)	29.8 ± 17.2
"Bhalla" score (M ± SD)	14.9 ± 3.9
FEV1% predicted (M ± SD)	57.9 ± 25.1
FVC% predicted (M ± SD)	68.3 ± 22.5
Desaturation with exertion n (%)	9 (20.9)
Bacterial colonisation	
Staphylococcus aureus n (%)	37 (86.0)
Haemophilus influenzae n (%)	23 (53.5)
Pseudomonas aeruginosa n (%)	38 (88.4)
Burkholderia cepacia n (%)	2 (4.7)
Exacerbations in the past year	1.79 ± 1.4
Mild exacerbations (M ± SD)	1.5 ± 1.1
Severe exacerbations (M ± SD)	0.4 ± 0.7
Days revenue in the past year for respiratory exacerbation (M ± SD)	3.3 ± 8.0
Total days taking antibiotics (M ± SD)	29.3 ± 21.7
Anthropometric and nutritional parameters	
BMI (kg/m^2) (M ± SD)	21.3 ± 3.6
% Ideal BMI (M ± SD)	99.3 ± 16.9
BMI < 20kg/m^2 n (%)	17 (39.5%)
Lean mass in kg (M ± SD)	44.6 ± 8.7
% lean mass (M ± SD)	78.3 ± 8.8
Fat mass in kg (M ± SD)	12.7 ± 6.4
% Fat mass (M ± SD)	21.7 ± 8.8
Malnutrition rate of lean mass (kg lean mass/height^2) (M ± SD)	16.5 ± 2.3
Faecal fat (g) (M ± SD)	9.6 ± 5.2
Percentage of fat absorption (%) (M ± SD)	91.1 ± 5.3
Patients with lower fat absorption rate of 90% n (%)	8 (18.6%)
Tube feeding gastrostomy n (%)	2 (4.7)
Dietary supplements n (%)	10 (23.3)

FEV_1: Forced expiratory volume in first second; FVC: forced vital capacity; CF: cystic fibrosis; BMI: body mass index; M±SD: mean ± standard deviation, n: Number of patients.

Bhalla scoring system: based on high-resolution computed tomography of the chest (the lower the final score, the worse radiological status).

Table 2
Average scores on the dimensions of the questionnaire CFQR 14+ Spain (total group and by gender)

Dimension	Total (n = 43)	Males (n = 20)	Women (n = 23)
Physical capacity	65.3 ± 30.1	76.0 ± 29.1*	56.0 ± 28.3
Role limitations	83.1 ± 22.8	85.4 ± 23.1	81.2 ± 22.9
Vitality	70.3 ± 25.1	77.5 ± 24.6	64.1 ± 24.3
Emotional state	76.9 ± 23.5	81.0 ± 25.0	73.3 ± 22.0
Social isolation	67.8 ± 20.1	69.2 ± 20.4	66.7 ± 20.2
Body image	70.0 ± 23.8	70.5 ± 28	69.7 ± 20.1
Feeding problems	81.6 ± 21.9	85.5 ± 23.1	78.3 ± 20.8
Treatment burden	60.5 ± 20.8	62.8 ± 19.2	58.4 ± 22.3
Health perception	66.7 ± 24.7	71.1 ± 23.7	62.8 ± 25.4
Weight problems	72.9 ± 36.5	65.0 ± 35.0	79.7 ± 37.2
Respiratory symptoms	62.4 ± 20.2	67.5 ± 20.9	58.0 ± 18.9
Digestive symptoms	80.9 ± 15.2	81.1 ± 15.3	80.7 ± 15.4

All values are expressed as mean ± standard deviation.
* $p < 0.05$ men vs. women (Student's t test or Mann-Whitney).

Table 3
Overview, internal consistency and reproducibility of CFQR 14+ Spain

Dimension	No. of items	Cronbach α	Test re-test (Spearman) r	P	ICC	Ground effect	Ceiling effect
Physical capacity	8	0.96	0.95	0.000	0.95	2.3	11.6
Role limitations	4	0.81	0.87	0.000	0.78	0	39.5
Vitality	4	0.89	0.90	0.000	0.88	0	18.6
Emotional state	5	0.87	0.77	0.000	0.72	0	25.6
Social isolation	6	0.75	0.80	0.000	0.77	0	0
Body image	3	0.70	0.53	0.034	0.54	2.3	18.6
Feeding Problems	3	0.87	0.78	0.000	0.75	0	46.5
Burden of treatment	3	0.57	0.79	0.000	0.77	2.3	4.7
Health perception	3	0.79	0.86	0.000	0.86	2.3	9.3
Weight problems	1	–	0.74	0.001	0.73	14	55.8
Respiratory symptoms	7	0.78	0.79	0.000	0.78	0	0
Digestive symptoms	3	0.31	0.49	0.057	0.47	0	20.9

ICC: intraclass correlation coefficient.

intestinal resections, distal intestine obstruction syndrome or a percentage of fat absorption < 90% (n = 8) vs. greater than this figure. Patients with EPI had lower scores on all scales, but significant differences were only reached in the weight problems dimension: 65.5 ± 39.6 vs. 89.7 ± 21.2 ($p < 0.05$). The 11 patients taking dietary supplements and/or tube feeding had significantly worse scores in body image dimensions 57.6 ± 23.2 vs. 74.3 ± 22.8 ($p < 0.05$) and feeding problems 71.7 ± 17.4 vs. 85.1 ± 22.5 ($p < 0.05$) and these differences were nearly significant in the dimension weight problems 57.5 ± 36.7 vs. 78.1 ± 35.5 ($p = 0.07$). Patients with an ACM or diabetes did not differ significantly in any of the dimensions of the questionnaire in comparison to those without.

Reproducibility

Two weeks after the administration of the CFQR 14+, the questionnaire was administered again to 16 subjects (in the same state of clinical stability), 8 men and 8 women, mean age 22.3 ± 5.2 years and FEV 1 of 57 ± 27% (no significant differences compared to the other group). The intraclass correlation coefficient (ICC) was above 0.70 in 10 of the 12 scales (Table 3) and only fell short of the cut-off in the dimensions of body image and gastrointestinal symptoms. The Spearman r coefficient was > 0.70 for all dimensions except body image and gastrointestinal symptoms (Table 3).

Discussion

Our study shows that the Spanish version of the revised CF quality of life questionnaire for adolescents and adults (CFQR 14+ Spain) is valid and reliable for use in a Spanish population. Regarding internal consistency, 2 domains were found to have lower values of the Cronbach alpha cut-off point: burden of treatment (0.57) and digestive problems (0.31). However, these values were similar to those reported by other authors in other populations. Therefore, Quittner et al[4] in the validation of the American version of the CFQR 14+, found coefficients $\alpha < 0.70$ in dimensions of burden of treatment (0.18) and digestive problems (0.67) and 0.71 in body image. Wenninger et al[11] found similar values for the scale of digestive ($\alpha = 0.66$) in the version of the CFQR 14+ in German. Bregnballe et al[8] also reported similar alpha values for body image (0.67) and slightly better values for digestive problems (0.64), treatment burden (0.72) and adding the scale of social isolation (0.54), for the Danish version of the CFQR 14+. The Klijn group[9] found alpha values less than 0.70 in the dimensions of emotional state (0.69), social isolation (0.64), body image (0.45), feeding problems (0.66), treatment burden (0.53), shame (0.53) and digestive problems (0.69). The floor effect in our population was < 15% in all domains and better than that found by Quittner et al.[4] A ceiling effect of > 15% was observed in 7 of the 12 scales, with notable percentages in the scales of role limitations, feeding problems and weight problems. Quittner et al[4] also found a high ceiling effect in 5 scales of the English version of the CFQR 14+:

Table 4
Item-scale correlations of the questionnaire CFQR 14+ Spain (n = 43)

Items	Physical	Role	Vitality	Emotion	Social	Body	Feeding	Treatment	Health	Weight	Respiratory	Digestive
Physical[1]	0.878*	0.664*	0.716*	0.559*	0.437*	0.453*	0.487*	0.290	0.584*	0.307**	0.654*	0.139
Physical[2]	0.902*	0.753*	0.722*	0.739*	0.619*	0.641*	0.550*	0.319**	0.591*	0,405**	0.609**	0.174
Physical[3]	0.838*	0.829*	0.734*	0.638*	0.651*	0.505*	0.435*	0.315**	0.728*	0.282	0.723*	0.273
Physical[4]	0.946*	0.719*	0.799*	0.710*	0.611*	0.584*	0.559*	0.466*	0.699*	0.275	0.728*	0.210
Physical[5]	0.943*	0.711*	0.793*	0.720*	0.495*	0.591*	0.535*	0.416*	0.659*	0.290	0.718*	0.237
Physical[13]	0.859*	0.697*	0.635*	0.556*	0.510*	0.486*	0.481*	0.149	0.632*	0.293	0.746*	0.245
Physical[19]	0.838*	0.589*	0.671*	0.669*	0.615*	0.567*	0.482*	0.390*	0.649*	0.241	0.662*	0.123
Physical[20]	0.905*	0.650*	0.710*	0.666*	0.545*	0.501*	0.525*	0.390*	0.644*	0.229	0.660*	0.249
Role[35]	0.607*	0.798*	0.578*	0.455*	0.242	0.422*	0.340**	0.172	0.372**	0.376*	0.563*	0.185
Role[36]	0.580**	0.891*	0.612*	0.569*	0.435*	0.457*	0.428*	0.148	0.606*	0.219	0.644*	0.155
Role[37]	0.641**	0.803*	0.695*	0.692*	0.696*	0.619*	0.510*	0.225	0.775*	0.330**	0.621*	0.456*
Role[38]	0.780*	0.741*	0.720*	0.697*	0.705*	0.517*	0.515*	0.319**	0.794*	0.272	0.704*	0.284
Vitality[6]	0.766*	0.768*	0.928*	0.761*	0.579*	0.568*	0.552*	0.433*	0.726*	0.365**	0.722*	0.377**
Vitality[9]	0.859*	0.789*	0.867*	0.648**	0.519*	0.560*	0.524*	0.327**	0.699*	0.268	0.725*	0.276
Vitality[10]	0.586*	0.614*	0.864*	0.633*	0.501*	0.458*	0.501*	0.318**	0.645*	0.297	0.511*	0.166
Vitality[11]	0.695*	0.625*	0.851*	0.625*	0.525*	0.437*	0.482*	0.539*	0.618*	0.293	0.626*	0.298
Emotion[7]	0.608*	0.625*	0.712*	0.820*	0.533*	0.479*	0.497*	0.203	0.833*	0.103	0.569*	0.233
Emotion[8]	0.668*	0.645*	0.711*	0.806*	0.666*	0.640*	0.619*	0.332**	0.624*	0.405*	0.630*	0.074
Emotion[12]	0.523*	0.556*	0.564*	0.817*	0.560*	0.402*	0.458*	0.210	0.693*	0.097	0.530*	0.051
Emotion[31]	0.567*	0.546*	0.527*	0.821*	0.517*	0.751*	0.601*	0.417*	0.604*	0.506*	0.446*	0.197
Emotion[33]	0.717*	0.657*	0.681*	0.882*	0.727*	0.688*	0.603*	0.471*	0.710*	0.364**	0.573*	–0.013
Social[22]	0.782*	0.770*	0.724*	0.785*	0.736*	0.618*	0.678*	0.285	0.797*	0.308**	0.626*	0.139
Social[23]	0.193	0.256	0.184	0.266	0.617*	0.233	0.254	0.241	0.309**	0.234	0.197	0.114
Social[27]	0.339**	0.180	0.363**	0.358**	0.613*	0.337**	0.383**	0.277	0.350**	0.152	0.204	0.071
Social[28]	0.165	0.276	0.247	0.317**	0.531**	0.146	0.253	0.150	0.346**	0.118	0.200	0.085
Social[29]	0.438*	0.342**	0.392*	0.546*	0.638	0.447*	0.338**	0.359**	0.435*	0.215	0.321**	–0.012
Social[30]	0.563*	0.545*	0.495*	0.586*	0.853*	0.414*	0.415*	0.364**	0.694*	0.128	0.471*	0.235
Body[24]	0.377**	0.318**	0.254	0.304**	0.171	0.728*	0.505*	0.157	0.212	0.605*	0.299	–0.030
Body[25]	0.579*	0.593*	0.610*	0.755*	0.535*	0.839*	0.659*	0.432*	0.720*	0.365**	0.572*	0.194
Body[26]	0.478*	0.552*	0.498*	0.669*	0.650*	0.783*	0.737*	0.297	0.673*	0.435*	0.419*	0.166
Feeding[14]	0.445*	0.423*	0.512*	0.537*	0.525*	0.690*	0.910*	0.151	0.474*	0.494*	0.392*	0.090
Feeding[21]	0.542*	0.539*	0.512*	0.686*	0.635*	0.769*	0.934*	0.169	0.647*	0.448*	0.497*	0.041
Feeding[50]	0.547*	0.477*	0.571*	0.558*	0.386**	0.686*	0.867*	0.266	0.565*	0.510*	0.510*	0.191
Treatment[15]	0.329**	0.156	0.338**	0.362**	0.354**	0.295	0.129	0.844*	0.275	0.103	0.183	0.153
Treatment[16]	0.204	0.169	0.253	0.102	0.096	0.129	0.105	0.496*	0.133	0.169	0.376**	0.252
Treatment[17]	0.319**	0.231	0.400*	0.400*	0.434*	0.378**	0.230	0.826*	0.398*	0.061	0.344**	0.140
Health[18]	0.663*	0.630*	0.787*	0.713*	0.516*	0.568*	0.575*	0.359**	0.804*	0.257	0.689*	0.140
Health[32]	0.523*	0.548*	0.553*	0.623*	0.622*	0.485*	0.455*	0.356**	0.846*	0.160	0.540*	0.271
Health[34]	0.663*	0.739*	0.616*	0.779*	0.728*	0.636*	0.586*	0.237	0.870*	0.160	0.653*	0.091
Weight[39]	0.327**	0.374**	0.350**	0.362**	0.290	0.603*	0.530*	0.145	0.224	1,000*	0.269	0.155
Respiratory[40]	0.612*	0.473*	0.532*	0.525*	0.443*	0.396*	0.466*	0.391*	0.518*	0.144	0.655*	0.126
Respiratory[41]	0.369*	0.471*	0.433*	0.303**	0.150	0.222	0.232	0.119	0.511*	0.010	0.709*	0.127
Respiratory[42]	0.423*	0.397*	0.331**	0.326**	0.314**	0.272	0.278	0.403*	0.353**	0.175	0.721*	0.151
Respiratory[43]	0.114	0.241	0.199	0.186	–0.069	0.113	0.096	0.103	0.170	0.204	0.299	0.048
Respiratory[44]	0.474*	0.571*	0.398*	0.334**	0.302**	0.392*	0.323**	0.063*	0.329**	0.315**	0.558*	0.379**
Respiratory[45]	0.797*	0.734*	0.716*	0.603*	0.613*	0.570*	0.596*	0.283	0.755*	0.326**	0.812*	0.294
Respiratory[46]	0.541*	0.604*	0.608*	0.595*	0.323**	0.457*	0.297	0.353**	0.591*	0.199	0.734*	0.231
Digestive[47]	0.101	0.132	0.134	–0.063	0.000	0.042	0.055	0.161	0.080	0.048	0.161	0.833*
Digestive[48]	0.247	0.312**	0.268	0.218	–0.004	0.046	–0.142	0.267	0.115	0.066	0.183	0.510*
Digestive[49]	0.165	0.282	0.278	0.207	0.353**	0.193	0.268	0.084	0.339**	0.216	0.274	0.563*

*$p < 0.05$ (bilateral).
**The correlation (Spearman) is significant $p < 0.01$ (bilateral).

role limitations (42.8%), weight problems (42.8%), feeding problems (60.6 %), body image (28.8%) and physical capacity (19.7%). In the Danish version of CFQR 14+ a ceiling effect was reported in the domains of physical capacity (23.2%), role limitations (19.8%), body image (27.7%), feeding problems (62.8%) and weight (62.5%).[8] It therefore seems clear in all the versions that the dimensions of body image, feeding problems and weight problems may have little sensitivity to change, so improvements could be made in terms of discriminative power. In this regard it is worth noting that the weight scale is represented by a single item, which means this domain has less variability in responses and therefore, floor and ceiling effects greater than in the other dimensions. Unsurprisingly and in line with publications by other authors,[4,9,11] we have found excellent correlations between respiratory parameters (especially with spirometric and radiological-Bhalla, and less often with flare-ups), and virtually all dimensions of the questionnaire, especially those that are influenced by the respiratory status of subjects. In this sense it is logical that the gastrointestinal symptoms scale did not correlate with these parameters; however, it is surprising that as observed by others,[4,9,11] the burden of treatment dimension did not correlate with it either. Like other authors,[4,8,9] we observed that the questionnaire scores discriminated well according to the degrees of severity classified according to percentage of FEV 1 (which is the best prognostic marker in these patients).[25] Once again, the worse the spirometry, the worse the quality of life, except for the gastrointestinal symptoms and burden of treatment scales. Applying other criteria not explored by other authors, we observed that the Bhalla score, based on HRCT (cut-off point 16) and desaturation in the 6mP, discriminated

Table 5
Correlations between the scales of the CFQR 14+ Spain and various clinical, spirometric, radiological and physical development variables

	Dimension	Predicted FEV1%	Predicted FVC%	Punt. Bhalla *	Number exacerbations	BMI	Fat mass (kg)	Lean mass index malnutrition
Physical capacity	−0.31 *	0.51 **	0.55 **	0.43 **	−0.42 **	0.16	−0.20	0.49 **
Role limitations	−0.18	0.50 **	0.49 **	0.40 **	−0.30 *	0.17	−0.05	0.31
Vitality	−0.29	0.48 **	0.50 **	0.28	−0.29	0.19	−0.08	0.41 *
Emotional state	−0.42 **	0.34 *	0.37 *	0.21	−0.19	−0.03	−0.16	0.19
Social isolation	−0.41 **	0.24	0.08	0.003	0.04	−0.07	−0.17	0.10
Body image	−0.07	0.44 **	0.48 **	0.34 *	−0.27	0.24	0.08	0.32 *
Feeding problems	−0.23	0.44 **	0.41 **	0.29	−0.25	0.20	−0.05	0.37 *
Treatment burden	−0.09	0.10	0.13	0.10	−0.11	0.02	0.08	0.12
Health perception	−0.32 *	0.43 **	0.39 **	0.26	−0.25	−0.02	−0.19	0.17
Problems with weight	−0.12	0.37 *	0.36 *	0.36 *	−0.06	0.37 *	0.46 **	0.13
Respiratory Symptoms	−0.24	0.37 *	0.46 **	0.43 **	−0.44 **	0.09	−0.11	0.29
Digestive symptoms	−0.20	0.28	0.28	0.41 **	−0.20	0.12	0.10	0.11

FEV 1: forced expiratory volume in one second, FVC: forced vital capacity, BMI: body mass index.
Bhalla scoring system*: based on high-resolution computed tomography of the chest (the lower the final score, the worse the radiological state).
* $p < 0.05$ (bilateral).
** Significant Spearman correlation $p < 0.01$ (bilateral).

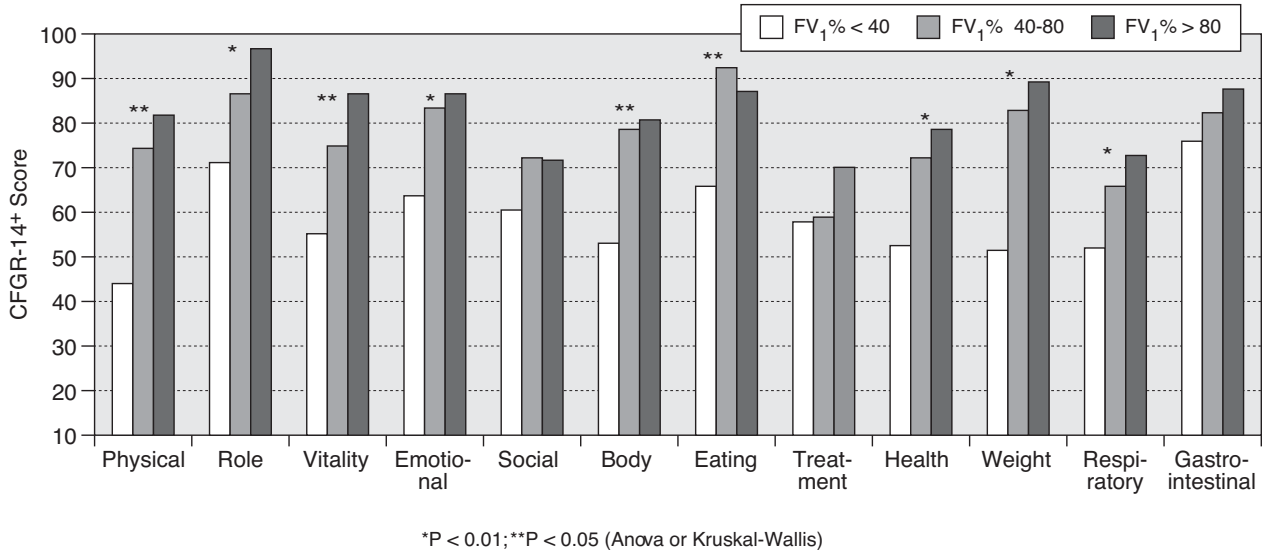


Figure 1. Questionnaire scores for CFQR 14+ Spain in terms of forced expiratory volume in one second as a percentage of predicted (FEV 1%). * P < 0.05, ** p < 0.01 (ANOVA or Kruskal-Wallis).

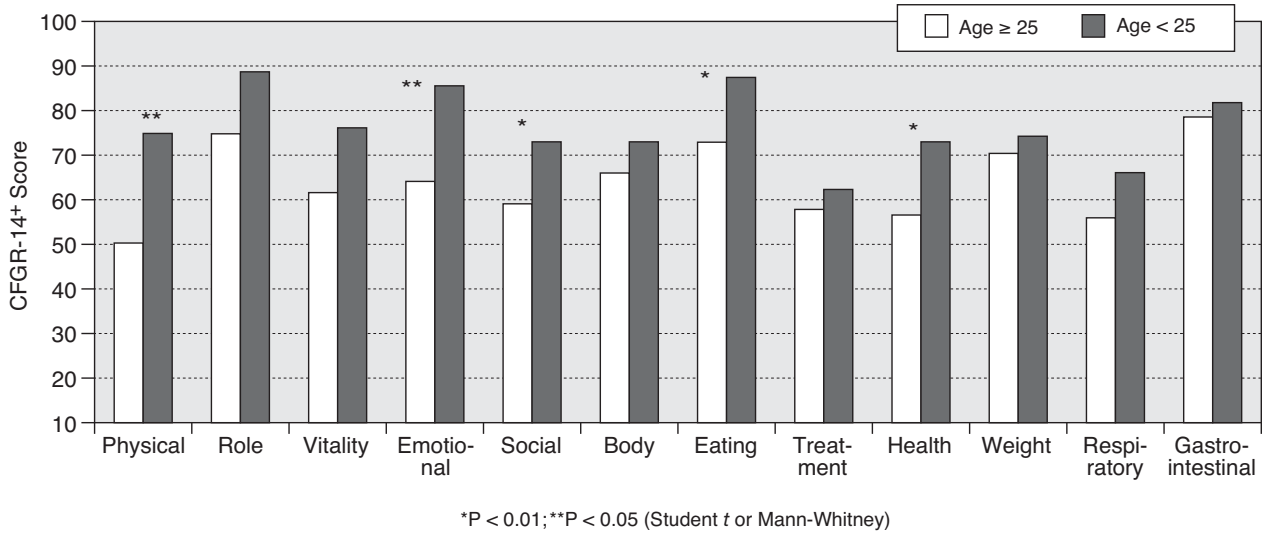


Figure 2. Questionnaire scores for CFQR 14+ Spain on the basis of age.

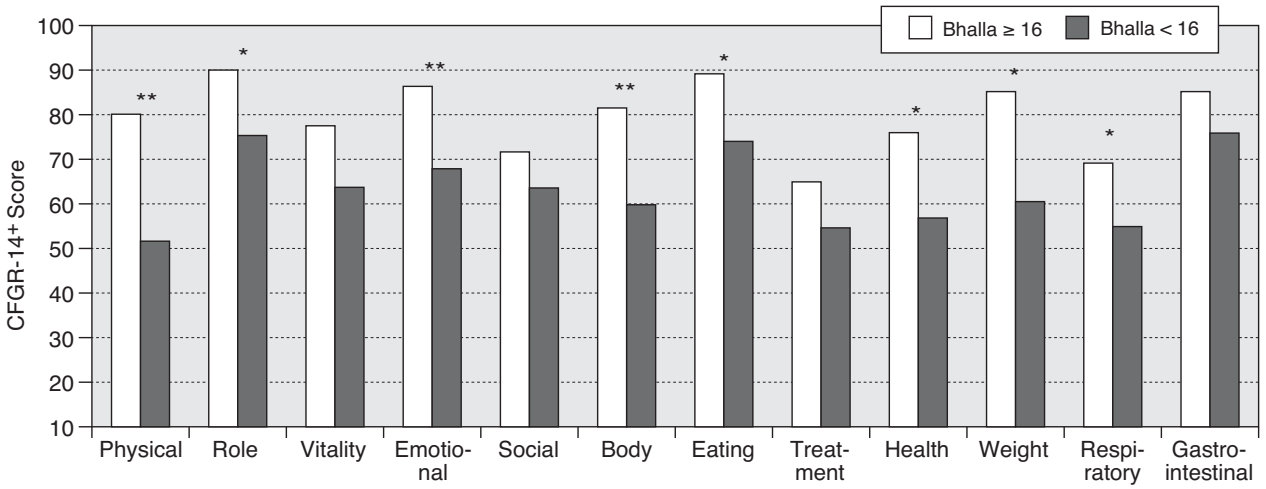


Figure 3. Questionnaire scores for CFQR 14+ Spain in terms of the Bhalla scale (scoring system based on chest computed tomography).

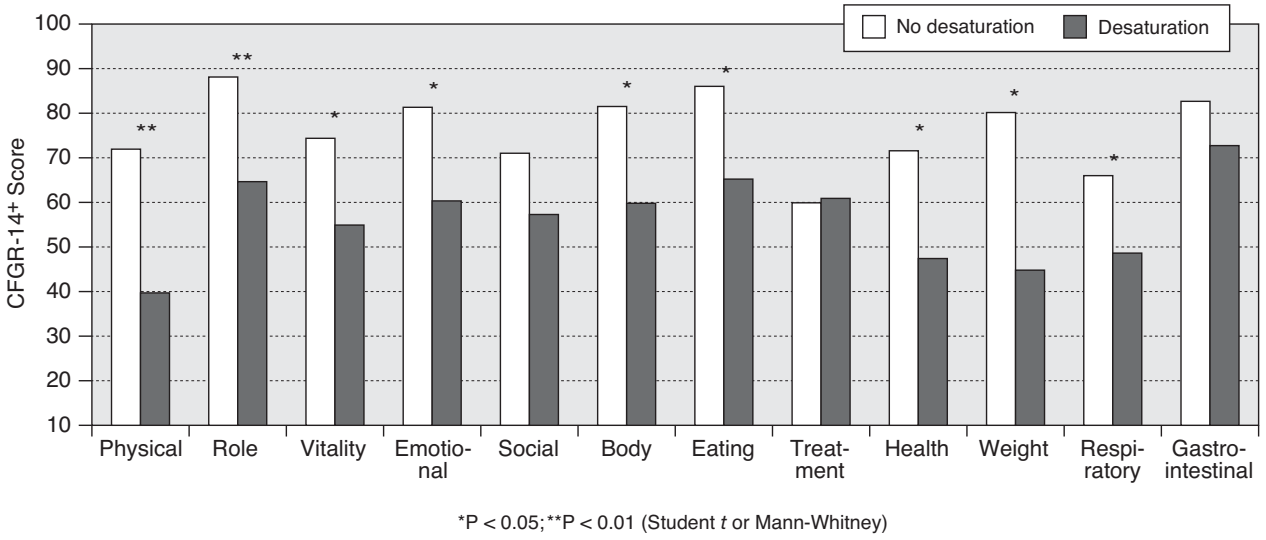
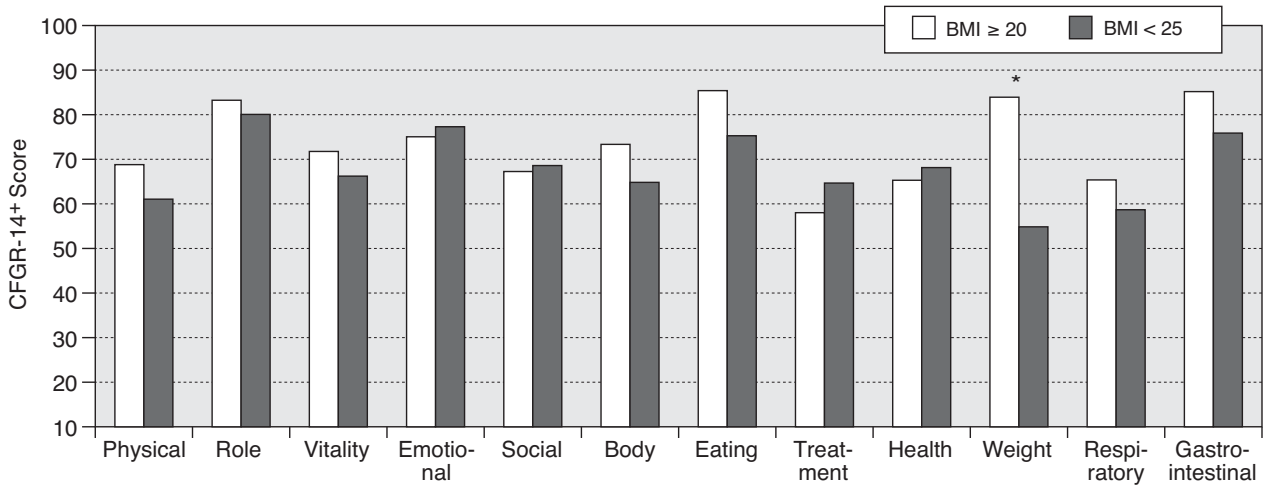


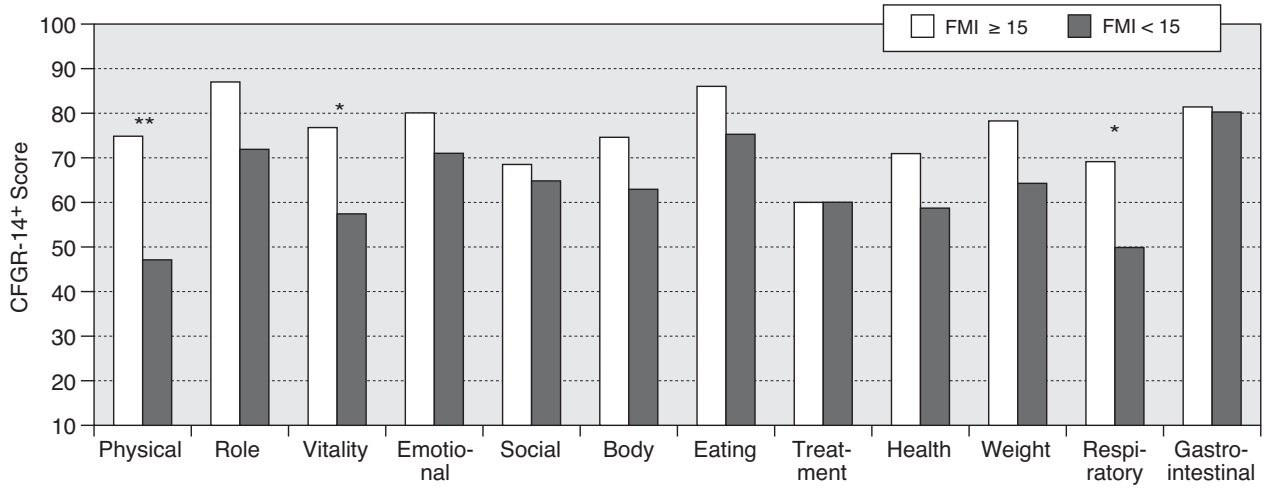
Figure 4. Questionnaire scores for CFQR 14+ Spain in terms of desaturation with exertion, as measured by the 6-minute walk test. * P < 0.05, ** p < 0.01 (Student's t test or Mann-Whitney).

adequately for most dimensions of HRQL. Also, patients who had suffered more than 3 relapses in the previous year had lower scores in the respiratory symptoms and physical capacity scales. Martínez-García et al[26,27] also published similar results in patients with non-CF bronchiectasis (BC) with respect to HRCT and the number of exacerbations. Unlike other non-specific questionnaires, CFQR 14+ Spain includes domains that explore other aspects of the disease not directly related to respiratory symptoms, such as digestive symptoms and other problems such as weight and feeding or body image. As other groups, in this work we have included, in addition to weight or BMI, other anthropometric variables that might have greater clinical significance regarding the prognosis of patients[1] and on their impact on HRQL (such as the measurement of lean mass and its associated indexes). Therefore, we observed a good correlation between the dimensions of problems with weight and BMI and fat mass (as markers of nutritional status). However, perhaps more interesting is the significant correlations between the rate of malnutrition in lean mass and dimensions such as physical capacity, vitality, body image or feeding problems. In this regard, although patients who were malnourished according to BMI had lower scores than well nourished, the differences only reached statistical significance in the dimension of weight problems. Other authors have found similar differences in this scale and other related scales such as body image and feeding problems[9] and even with 10 of the 12 dimensions.[8] In contrast, malnourished patients according to the IMM achieved significantly different scores on the scales of physical capacity, vitality and respiratory symptoms. Both patients with CF and those with CF and non-CF BC and chronic obstructive pulmonary disease associations



*P < 0.05; **P < 0.01 (Student *t* or Mann-Whitney)

Figure 5. Questionnaire scores for CFQR 14+ Spain on the basis of body mass index (BMI).



*P < 0.05; **P < 0.01 (Student *t* or Mann-Whitney)
Index of malnutrition of fat mass (FM); the lower the value, the worse the malnutrition

Figure 6. Questionnaire scores for CFQR 14+ Spain based on the index of malnutrition in lean mass (IMM).

were found (even in clinically stable patients, as in our group) between weight reduction and increased lean muscle proteolysis with increased respiratory exacerbations, poorer lung function and higher levels of proinflammatory mediators.[28,29] Similarly, patients with CF and more severe affectation have less lean body mass, lower maximal inspiratory pressure and decreased thickness of the diaphragm.[30] The fact that patients with feeding tubes and/or oral supplements (n = 11) had worse scores in the dimensions of body image and feeding problems, issues not assessed by other authors for CFQR, also corroborates the appropriateness of including aspects related to food and nutrition in HRQL questionnaires specific to CF. Similarly, patients with EPI showed lower scores in all dimensions, although only significant differences were found in weight problem scale, which is logical since the EPI condition increases the risk of malnutrition.[31-33] In contrast, there were no significant correlations between digestive symptoms (including diarrhoea, presence of gas and abdominal pain) and the amount of fat in faeces 72 h or the percentage of fat absorption. Nor did we observe significant differences in the gastrointestinal symptoms scale depending on the previous presence of reflux, bowel obstruction syndrome or previous history of distal intestinal resection. Unlike other studies,[2] the presence of diabetes or ACM did not affect quality of life, perhaps because of the ease in clinical management and because it is not necessary to significantly change dietary habits.[1] To assess test retest reproducibility, we used measures of agreement (intraclass coefficient of variation) that provided values greater than 0.70 in all scales except for body image (0.54) and digestive symptoms (0.47). The values were similar or slightly lower than those reported for the German version,[9] the Portuguese version[10] and others, or better than those of the English version[4] in which 5 levels (including digestive symptoms) did not achieve coefficients greater than 0.70. The results evaluated using the Spearman coefficient were also similar to or

better than those published by the Danish group[8] in which the digestive symptoms (0.61) and body image (0.45) scales did not reach values higher than 0.70 (in addition to physical capacity [0.68], role limitations [0.52], vitality [0.53] and social isolation [0.42]). The reproducibility is especially important in diseases such as CF, in which the progression of the disease over time is evaluated. If the scale is not stable, it may be difficult to assess whether the observed changes are real or rely on the vagueness of the questionnaire. Although the results may be affected by the sample size or by slight variations in the physical state of patients (highly unlikely since they were evaluated on 2 occasions), given that this finding is repeated in all publications, it may be necessary to improve at least the digestive symptoms scale. With respect to gender, we found lower scores on all scales (except for weight problems) in women, but the differences only reached significance in the physical capacity scale. Other authors have also documented a tendency for women to accept as desirable a lower weight than normal.[3,4,8,9] Although the literature has not always observed the same,[2] since there were no significant differences in the severity of the disease (Bhalla, FEV 1 [%] relapses, age, BMI) between sexes, it is logical that we found no major differences in the HRQL.

Like other authors,[4,9] we found significantly lower scores in older patients and negative correlations (better health) in the dimensions of physical ability, emotional state, social isolation and perceived health. All scales correlated significantly with the dimensions of the St. George questionnaire, reaching very high r-values in the dimensions intended to measure similar parameters (related to respiratory disease). Although still significant, the strength of the correlations were lower with other scales (such as gastrointestinal symptoms or problems with weight), which supports both questionnaires as appropriate to assess perceptions related to respiratory disease, but not other aspects of the disease.[2,3]

As a limitation of the study, it is noteworthy that the sample tested was not large; however, it was sufficient to find similar results (and in some cases better) than those reported by other authors for the English, Danish, Portuguese or German[4,8-11] versions, which had larger study populations. In addition, the inclusion of previously evaluated parameters (clinical, radiological, body composition, analytical) in the validation has strengthened its usefulness and, in turn, identifies areas for improvement in the questionnaire (such as gastrointestinal symptoms and weight problems.)

To conclude, the Spanish version of the revised CF quality of life for adolescents and adults (CFQR 14+ Spain) is valid and reliable for use in the Spanish population, although it could be improved in some of its subscales.

Table 6
Correlations between the scales of CFQR 14+ Spain and scores of St. George's Respiratory Questionnaire

	Symptoms	Activity	Impact	Total
Physical capacity	−0.67*	−0.86*	−0.73*	−0.84*
Role limitations	−0.71*	−0.63*	−0.68*	−0.76*
Vitality	−0.68*	−0.72*	−0.75*	−0.79*
Emotional state	−0.56*	−0.60*	−0.74*	−0.73*
Social isolation	−0.46*	−0.44*	−0.55*	−0.55*
Body image	−0.60*	−0.50*	−0.58*	−0.61*
Feeding problems	−0.58*	−0.46*	−0.40*	−0.48*
Treatment burden	−0.38**	−0.44*	−0.66*	−0.57*
Health perception	−0.61*	−0.61*	−0.75*	−0.75*
Problems with weight	−0.41*	−0.22	−0.33**	−0.36**
Respiratory Symptoms	−0.60*	−0.66*	−0.65*	−0.67*
Digestive symptoms	−0.37**	−0.24	−0.31**	

*$p < 0.05$ (bilateral).
**Significant Spearman correlation $p < 0.01$ (bilateral).

Conflict of Interest

The authors affirm that they have no conflicts of interest.

Funding

This study was supported in part by a grant from Neumosur (Andalusian Society of Pneumology and Thoracic Surgery) and CIBERDEM (CIBER of Diabetes and Associated Metabolic Diseases).

References

1. Olveira G, Olveira C. Nutrición, fibrosis quística y aparato digestivo. Nutr Hosp. 2008;23(Supl. 2):71-86.
2. Abbott J. Health-related quality of life measurement in cystic fibrosis: advances and limitations. Chron Respir Dis. 2009;6:31-41.
3. Padilla A, Olveira G, Olveira C, Dorado A, Plata AJ, Gaspar I, et al. Utilidad del Cuestionario Respiratorio de St. George en población adulta con Fibrosis Quística. Arch Bronconeumol. 2007;43:205-11.
4. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest. 2005;128:2347-54.
5. Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. Qual Life Res. 2003;12:63-76.
6. Henry B, Staab D, Prados C, Aussge P, de Ponth-brune S, Grosskoptf C, et al. How to measure quality of life in cystic fibrosis (CF) patients across countries and cultures: The Cystic Fibrosis Questionnaire (CFQ) [abstract]. Pediatr Pulmonol. 1998; 17(Suppl):392-3.
7. Quittner AL, Sweeny S, Watrous M, Munzenberger P, Bearss K, Gibson Nitza A, et al. Translation and linguistic validation of a disease-specific quality of life measure for cystic fibrosis. J Pediatr Psychol. 2000;25:403-14.
8. Bregnballe V, Thastum M, Lund LD, Hansen CR, Preissler T, Schiøtz PO. Validation of the Danish version of the revised cystic fibrosis quality of life questionnaire in adolescents and adults (CFQR 14+). J Cyst Fibros. 2008;7:531-6.
9. Klijn PH, Van Stel HF, Quittner AL, Van der Net J, Doeleman W, Van der Schans CP, et al. Validation of the Dutch cystic fibrosis questionnaire (CFQ) in adolescents and adults. J Cyst Fibros. 2004;3:29-36.
10. Rozov T, Cunha MT, Nascimento O, Quittner AL, Jardim JR. Linguistic validation of cystic fibrosis quality of life questionnaires. J Pediatr (Rio J). 2006;82:151-6.
11. Wenninger K, Aussage P, Wahn U, Staab D, German Cystic Fibrosis Questionnaire study group. The revised German Cystic Fibrosis Quiestionnaire: Validation of a disease-specific health-related quality of life instrument. Quality of Life Research. 2003;12:77-85.
12. Quittner AL, Zapata C, Landon C. Spanish translation of the Cystic Fibrosis Questionnaire: preliminary results of the cognitive testing phase [abstract]. Pediatr Pulmonol. 2002;24:350.
13. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr. 1998;132:589-95.
14. Roca J, Sanchis J, Agustí Vidal A, Segarra F, Navajas D, Rodriguez-Roisin R, et al. Spirometric reference values for a Mediterranean population. Bull Eur Physiopathol Respir. 1986;18:101-2.
15. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic Fibrosis: Scoring System with thin-section CT. Radiology. 1991;179:783-8.
16. Vilaró J. Prueba de marcha de 6min. In: Burgos F, Casan P, editores. Procedimientos de evaluación de la función pulmonar II. Manual SEPAR de Procedimientos no 4. Madrid: Luzán 5; 2004. Pag:100–114. Available from: http://www.separ.es/publicaciones/procedimientos. Aspx.
17. Kerem E, Conway S, Elborn S, Heijerman H. Consensus Committee. Standards of care for patients with cystic fibrosis: a European consensus. J Cystic Fibros. 2005; 4:7-26.
18. Vendrell M, De Gracia J, Olveira C, Martinez MA, Girón R, Máiz L, et al. Normativa SEPAR: diagnóstico y tratamiento de las bronquiectasias. Arch Bronconeumol. 2008;44:629-40.
19. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr. 1974;32:77-97.
20. Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozeck J y Henschel A, eds. Techniques for measuring body composition. Washington DC. National Academy of Sciences, 1961;223–244.
21. Creutzberg EC, Wouters EFM, Mostert R, Weling-Scheepers CAPM, Schols AMWJ. Efficacy of Nutritional Supplementation Therapy in Depleted Patients With Chronic Obstructive Pulmonary Disease. Nutrition. 2003;19:120-7.
22. Picarelli A, Greco M, Di Giovambattista F, Ramazzotti A, Cedrone C, Corazziari E, et al. Quantitative determination of faecal fat, nitrogen and water by means of a spectrophotometric technique: near infrared reflectance analysis (NIRA). Assessment of its accuracy and reproducibility compared with chemical methods. Clin Chim Acta. 1995;234:147-56.
23. Olveira G, Olveira C, Casado-Miranda E, Padilla A, Dorado A, Rojo G, et al. Markers for the validation of reported dietary intake in adults with cystic fibrosis. J Am Diet Assoc. 2009;109:1704-11.
24. Valderas JM, Ferrer M, Alonso J. Health-related quality of life instruments and other patient-reported outcomes. Med Clin (Barc). 2005;125(Suppl 1):56-60.

25. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. N Engl J Med. 1992;326:1187-91.
26. Martínez-García MA, Perpiñá Tordera M, Román Sánchez P, Soler Cataluña JJ. Internal consistency and validity of the Spanish version of the St. George's respiratory questionnaire for use in patients with clinically stable bronchiectasis. Arch Bronconeumol. 2005;41:110-7.
27. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. Chest. 2005;128:739-45.
28. Ionescu AA, Nixon LS, Luzio S, Lewis-Jenkins V, Evans WD, Stone MD, et al. Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis. Am J Respir Crit Care Med. 2002;165:495-500.
29. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ, Carratalá A, Yago M, et al. The association between bronchiectasis, sistemic inflammation and Tumor Necrosis Factor alpha. Arch Bronconeumol. 2008;44: 8-14.
30. Enrigth S, Chatham K, Ionescu AA, Unnithan VB, Shale DJ. The influence of body composition on respiratory muscle, lung function and diaphragm thickness in adults with cystic fibrosis. J Cyst Fibros. 2007;6:384-90.
31. Olveira-Fuster C, Olveira-Fuster G, Dorado-Galindo A, Padilla-Galo A, Merino-Berdugo J, Miralles-Lozano F. Gasto energético en sujetos adultos con Fibrosis Quística (FQ): concordancia entre la calorimetría indirecta y diferentes fórmulas estimativas. Arch Bronconeumol. 2007;43:366-72.
32. Ramsey BW, Farrel PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. Am J Clin Nutr. 1992;55:108–106
33. Olveira G, Dorado A, Olveira C, Padilla A, Rojo-Martínez G, García-Escobar E, et al. Serum phospholipid fatty acid profile and dietary intake in an adult Mediterranean population with cystic fibrosis. Br J Nutr. 2006;96:343-9.
34. Quittner A, Buu A, Davis M, Modi A. Application of factor analysis and random effects modeling to examine gender differences in HRQOL. Qual Life Res. 2002; 11:661.