Original Article

PORTO BIOMEDICAL JOURNAL
WHERE SCIENCE MEETS KNOWLEDGE

OPEN

Evaluation of the quality of life and associated factors of a group of children and adolescents with cystic fibrosis in the northern region of Portugal: a cross-sectional pilot study

Olívia Pita, BSc Honor[a,*], Beatriz Teixeira, Master[a,b,c], Cláudia Camila Dias, PhD[d,e], Paulo Almeida, PhD[f,g], Inês Azevedo, PhD[a,d,h], Diana e Silva, PhD[a,e,h,i]

Abstract

Introduction: Children/adolescents with cystic fibrosis (CF) have psychological and physical difficulties that have a severe impact on their health-related quality of life (HRQoL).

Aim: To evaluate the impact of CF on HRQoL in a pediatric age sample by identifying major determinants and comparing the HRQoL reports of children and their parents.

Methods: A sample of 27 children/adolescents was included in a cross-sectional observational study. Inclusion criteria were age between 4 and 18 years, diagnosis of CF, and the attendance of a caregiver in patients younger than 14 years. A questionnaire was applied to assess sociodemographic data and nutritional status. HRQoL was evaluated using the Portuguese revised version of the CF questionnaire (CFQ-R). Spearman correlations were calculated to analyze the agreement between children's and parents' reports. Spearman correlations and Mann–Whitney *U* tests were performed to identify associations between HRQoL domains and determinants.

Results: The scores of CFQ-R domains were high, with the lowest median value being 66.67. It was found positive moderate associations between children's and parents' reports in 3 domains ($P < .05$): eating disturbances, body image, and respiratory symptoms. The median scores were similar in the eating disturbances (approximately 80.00) and in the respiratory symptoms (83.33). However, there is a consistent difference of 14.07 in the body image domain. Current age, physical activity, and iron were positively associated with HRQoL, whereas age at diagnosis was negatively associated.

Conclusion: These findings reinforce the importance to evaluate HRQoL during childhood and adolescence and to invest in this public health theme.

Keywords: cystic fibrosis, cystic fibrosis questionnaire-revised, health-related quality of life, pediatric age

Introduction

Cystic fibrosis (CF), a life-limiting autosomal recessive disease,[1] has an estimated prevalence of 0.737 per 10,000 people in European Union.[2] In Portugal, there are 370 patients with CF and 52% correspond to children and adolescents (C/As).[3]

CF is caused by a mutation in a gene on chromosome 7 that encodes a glycoprotein called CF Transmembrane Conductance Regulator.[4] Although CF is a monogenetic disease, it covers a myriad of phenotypic manifestations,[5] such as obstructive lung disease with chronic bacterial infection, pancreatic insufficiency associated with poor nutrient absorption, diabetes, gastrointestinal disorders with subsequent malnutrition, liver disease, impaired growth, and male infertility.[6]

In the recent decades, advances in the treatment and management of this illness have been made.[7] The implementation of neonatal screening in some countries, as in Portugal, is allowing an early diagnosis and treatment.[8] As a result, the estimated median age of survival nowadays is close to 50 years and is expected to continue to rise.[9] However, living with CF imposes psychological and physical difficulties that have a severe impact on patients' health-related quality of life (HRQoL).[10]

HRQoL is a multidimensional concept that includes multiple domains related to patients' health, namely physical, social, functional, and emotional well-being,[11] as reported by them. Awareness of the importance of patient-reported outcomes in those with CF[12] has led to the development of a CF-specific instrument to measure HRQoL, the Cystic Fibrosis Questionnaire (CFQ).[13] The CFQ has a revised version called CFQ-R that has been translated into Portuguese.[14]

[a] Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Porto, Portugal, [b] EPIUnit—Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal, [c] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal, [d] Faculdade de Medicina da Universidade do Porto, Porto, Portugal, [e] Center for Health Technology and Services Research—CINTESIS, Porto, Portugal, [f] Serviço de Psicologia—Centro Hospitalar Universitário São João (CHUSJ), Porto, Portugal, [g] ISMAI—Universidade da Maia, Porto, Portugal, [h] Serviço de Pediatria—UAG da Mulher e da Criança/Centro Hospitalar Universitário São João (CHUSJ), Porto, Portugal, [i] Serviço de Nutrição/CHUSJ, Porto, Portugal

* Corresponding author: Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto, Rua do Campo Alegre, 823/4150-180 Porto, Portugal. E-mail address: olivia_coelho_pita@hotmail.com (Olívia Pita).

This is a cross-sectional observational study conducted at the Cystic Fibrosis Reference Center of Centro Hospitalar Universitário de São João (CHUSJ).

Porto Biomed. J. (2022) 7:5(e194)

Received: 27 February 2022 / Received in final form: 8 July 2022 / Accepted: 12 July 2022

http://dx.doi.org/10.1097/j.pbj.0000000000000194

In Portugal, CF has been poorly studied in the pediatric age, and the research team is not aware of any Portuguese study that measures HRQoL in C/As with CF. According to the literature, it is known that there are factors associated with HRQoL in C/As with CF, such as mealtime problem behaviors and psychological issues, such as anxiety, stress, and depression.[15-17] Thus, we hypothesized that the HRQoL of Portuguese C/As diagnosed with CF is affected. The specific objectives of this study are (1) to characterize the HRQoL of C/As with CF, (2) to compare the HRQoL reports of children with CF with the reports of the respective parent, and (3) to identify determinants associated with HRQoL.

Materials and methods

Study design and sampling

This is a cross-sectional observational study conducted at the CF Reference Center of Centro Hospitalar Universitário de São João (CHUSJ) between May 2019 and July 2021. This CF Reference Central was chosen for convenience, and all the patients with CF were invited to participate. Inclusion criteria were age between 4 and 18 years, diagnosis of CF according to the national guidelines,[8] and the attendance of a caregiver in patients younger than 14 years. From the 28 C/As followed in this CF Reference Central, 27 (96%) were included in this study. One C/A refused to participate.

Ethics

This research was conducted according to the ethical principles established by the Declaration of Helsinki, the Portuguese Law and the Good Clinical Practice Guidelines. The study protocol was approved by the Ethics Committee of the CHUSJ (CESCHUSJ-122/2019). All legal representatives of C/As were asked to read and sign an informed consent form.

Data collection

The study protocol contained two structured questionnaires: a sociodemographic data and nutritional status assessment questionnaire and the CFQ-R, a valid and reliable measure of HRQoL[18,19] in people with CF.

A questionnaire was developed by the team to collect demographic information of the patients and their parents, physical activity information, clinical data, and anthropometric measures of the child. This questionnaire was used in the interview.

Demographic data included sex and patient's age, in years. For parents, their age, in years, and their education level were requested for. The educational level was categorized in agreement with *the Portuguese educational system* into 4 categories: preschool (0 years of schooling), primary (first and second cycle), secondary (third cycle and high school), and higher education (>12 years of schooling). Regarding physical activity, it was asked whether they performed exercise in and out of school and its duration. With this information, it was created a new variable named "total of physical activity" that corresponds to the sum of physical activity in school and out of school (in hours).

Anthropometric measurements were collected following standard procedures.[20] Standing height (in cm) was obtained with a calibrated stadiometer (Seca 206) with 0.1-cm resolution. Body weight (in kg) and fat mass (in %) were measured using bioelectrical impedance analysis Tanita: TBF-300A with a 0.1 kg resolution. In children younger than 7 years, only body weight (in kg) was measured with a calibrated scale (Seca 799) with 0.1 kg resolution. The body mass index (BMI) was calculated using the formula BMI = weight/height^2 (kg/m^2), and the respective percentile and *z-score* were established using the software WHO Anthro and WHO AnthroPlus. Nutritional status was classified using the *z-score* of BMI. C/As were grouped into underweight (*z-score* <-1), normal weight ($-1 \leq$ *z-score* < 1), and overweight (*z-score* ≥ 1).[21] According to the fat mass percentiles, obtained from body fat reference curves for children, C/As were categorized into underfat (<2nd), normal fat (2nd to 85th), overfat (85th to 95th), and obese (>95th).[22]

Clinical data were mainly obtained through medical records. It was collected the age at diagnosis (in years) and the survey of associated pathologies. Enteral nutrition, parenteral nutrition, nutritional supplementation, vitamin and mineral supplementation, and pancreatic enzyme replacement were categorized into "no" and "yes" for each patient. Biochemical parameters such as glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein, vitamin D, and iron were collected, and it was used the reference values established in *The Harriet Lane Handbook*.[23] These nutritional variables were included because it is known that children's nutritional status affects their HRQoL. For example, iron deficiencies have associated with a lower HRQoL in C/As with CF.[24] As so, hypothetically, other blood variables related to food and nutrition could also be related. Finally, it was extracted the values of the percentage of predicted forced expiratory volume in one second (FEV_1%) to assess the lung function. FEV_1% was classified according to the Global Initiative for Chronic Obstructive Lung Disease classification into four groups (mild: $FEV_1 \geq 80\%$, moderate: $50\% \leq FEV_1 < 80\%$, severe: $30\% \leq FEV_1 < 50\%$, and very severe: $FEV_1 < 30\%$).[25]

The Portuguese version of the CFQ-R was administered to evaluate both patient's and parent's perspectives.[14] CFQ-R is based on a 2-week recall and has 4 versions for young children (6–11 years) applied by an interview format, older children (12–13 years), teenagers/adults (14 years or older)—both self-administered—and parents, a proxy-report version. All versions include seven common domains of HRQoL: physical, emotion, body image, eating disturbances, treatment burden, respiratory, and digestion symptoms. Teenager/adult and parent versions also include vitality (that concerns the energy and well-being of the teenager), health perceptions, and weight domains. Children and teenager/adult versions also include a social domain, while the parents' version includes a school domain. The teenager/adult version also includes a role domain. CFQ-R uses a 4-point Likert scale, with 4 points representing the answer suggesting greater HRQoL. Each item is summed to generate a domain score. Each domain score range from 0 to 100, with higher scores indicating better HRQoL. For this study, it was used an electronic application to do the CFQ-R scoring.[26] Although there is not a version for children younger than 6 years, we used the respiratory, physical, and eating disturbance domains of the parent-proxy CFQ-R to assess HRQoL in preschool children because of its strong reliability demonstrated in previous studies.[15,27]

Statistical analysis

Categorical variables were reported as absolute and relative frequencies. Regarding quantitative variables, the normality of the distribution was evaluated through the Shapiro–Wilk test and the results were described as median (25th and 75th percentiles), considering that variables presented non-normal distribution.

Table 1

Characterization of the sample of children and adolescents (n = 27)

Age, years, median (P25, P75)	10 (7, 15)
Sex, n (%)	
Female	16 (59)
Male	11 (41)
Age at diagnostic, years, median (P25, P75)	1 (0, 3)
Associated pathologies, n (%)	
Pancreatic insufficiency	24 (89)
Without pathologies	3 (11)
Physical activity at school, n (%)	
No	7 (26)
Yes	20 (74)
Physical activity out of school, n (%)	
No	15 (56)
Yes	12 (44)
Total of physical activity, hours per week, median (P25, P75)	3 (0, 4)
Education level, n (%)	
Preschool	4 (15)
Primary (1st-6th grade)	13 (48)
Secondary (7th-12th grade)	10 (37)
Average age of parents, years, median (P25, P75) (n = 26)	41 (37.75, 44.88)
Maximum parental education, n (%)	
Primary (1st-6th grade)	4 (15)
Secondary (7th-12th grade)	11 (41)
Higher education	12 (44)
Enteral nutrition, n (%)	
No	18 (67)
Yes	9 (33)
Parenteral nutrition, n (%)	
No	27 (100)
Yes	0 (0)
Nutritional supplementation, n (%)	
No	18 (67)
Yes	9 (33)
Vitamin and mineral supplementation, n (%)	
No	1 (4)
Yes	26 (96)
Pancreatic enzyme replacement, n (%)	
No	3 (11)
Yes	24 (89)
Disease severity defined by FEV_1% (n = 22), n (%)	
Mild (FEV_1 ≥80%)	16 (73)
Moderate (50≤ FEV_1 <80%)	5 (22)
Severe (30≤ FEV_1 <50%)	1 (5)
Very Severe (FEV_1 <30%)	0 (0)
BMI *z-score*, median (P25, P75)	−0.19 (−0.93, 0.25)
Nutritional status, n (%)	
Underweight (*z*score<−1)	5 (19)
Normal (−1≤ *z*score <1)	19 (70)
Overweight (*z*score ≥1)	3 (11)
Fat mass (n = 20), n (%)	
Underfat (<P2)	9 (45)
Normal (P2-P85)	7 (35)
Overfat (P85-P95)	4 (20)
Obese (>P95)	0 (0)
Glucose (n = 20), n (%)*	
Low	0 (0)
Adequate	18 (90)
High	2 (10)
Total cholesterol (n = 16), n (%)†	
Adequate	15 (94)
Borderline	0 (0)
High	1 (6)
HDL-C (n = 16), n (%)‡	
Low	3 (19)
Adequate	13 (81)
LDL-C (n = 16), n (%)§	
Adequate	15 (94)
Borderline	0 (0)
High	1 (6)
Vitamin D (n = 21), n (%)‖	
Very low	0 (0)
Low	4 (19)
Adequate	17 (81)
Iron (n = 23), n (%)¶	
Low	5 (22)
Adequate	15 (56)
High	3 (11)

BMI, body mass index; FEV_1%, percentage of predicted forced expiratory volume in one second; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P2, 2nd percentile; P25, 25th percentile; P75, 75th percentile; P85, 85th percentile; P95, 95th percentile; TG, triglycerides.

* Reference values of glucose#

<16 years: low < 60 mg/dL; adequate [60–100 mg/dL]; high ≥100 mg/dL.

≥16 years: low < 70 mg/dL; adequate [70–105 mg/dL]; high ≥105 mg/dL.

† Reference values of total cholesterol#

Adequate < 170 mg/dL; borderline [170; 200 mg/dL]; high ≥ 200 mg/dL.

‡ Reference values of HDL cholesterol#

Low ≤ 35 mg/dL; adequate >35 mg/dL.

§ Reference values of LDL cholesterol#

Adequate < 110 mg/dL; borderline [110; 130 mg/dL]; high ≥ 130 mg/dL.

‖ Reference values of vitamin D#

Very low <12 ng/mL; low [12–20 ng/dL]; adequate ≥ 20 ng/mL.

¶ Reference values of iron#

Low < 50 ug/dL; adequate [50–120 ug/dL]; high ≥120 ug/dL.

According to *The Harriet Lane Handbook*.[23]

Spearman correlations between patients and their parent scores were calculated for common domains to measure the strength and direction of the association among their reports.

The same approach was used to identify the associations between CFQ-R domains with age, age at diagnosis, total of physical activity, BMI *z-score*, fat mass, total cholesterol, glucose, iron, and vitamin D. The strength of each correlation was considered and rated from very weak to very strong. The Mann–Whitney *U* test was performed to evaluate the associations between CFQ-R domains with sex and with FEV_1%. Because there are no patients in the "very severe" category of FEV_1% and only one patient in the "severe" category, this patient was included in the "moderate" group to execute this test. Hence, to do this test, participants were grouped according to FEV_1% into two categories: "FEV_1 ≥80%" and "FEV_1 <80%".

The results were considered statistically significant when $P \leq .05$. Statistical Package for the Social Sciences (SPSS) version 27 was used to perform the statistical analyses.

Results

The demographic, clinical, and nutrition-related characteristics of the participants are presented in Table 1. In this study, 27 patients were evaluated, ranging from age 4 to 17 years, with a median age of 10 years. Of the total, 59% were female and 41% were male, 44% did physical activity out of school and 89% had pancreatic insufficiency and received enzyme therapy. Concerning the nutritional status, 70% had normal weight. Finally, regarding pulmonary function, the sample revealed a low-to-severe disease, highlighting the fact that 73% has a FEV_1% > 80%. In this sample, it was observed that most had normal weight and consequently also decent lung function.

Table 2 presents the HRQoL scores for CFQ-R versions. In preschool children (younger than 6 years), their parents gave very

Table 2

Characterization of HRQoL of children/adolescents, according to the CFQ-R domain scores

Domains	Preschool children version, 4–5 years (n = 4, 15%)					Children version, 6–13 years (n = 15, 55%)					Teenager version, ≥14 years (n = 8, 30%)				
	Min	P25	P50	P75	Max	Min	P25	P50	P75	Max	Min	P25	P50	P75	Max
Physical	83.33	84.37	91.67	98.96	100.00	44.44	61.11	83.33	94.44	100.00	33.33	71.87	81.25	100.00	100.00
Vitality	—	—	—	—	—	—	—	—	—	—	58.33	60.42	66.67	95.83	100.00
Emotion	—	—	—	—	—	45.83	62.50	75.00	91.67	100.00	66.67	75.00	86.67	91.67	100.00
Eating disturbances	0.00	16.67	66.67	91.67	100.00	0.00	33.33	88.89	100.00	100.00	22.22	91.67	100.00	100.00	100.00
Treatment burden	—	—	—	—	—	33.33	55.56	88.89	100.00	100.00	44.44	69.45	77.78	88.89	88.89
Health perceptions	—	—	—	—	—	—	—	—	—	—	55.56	66.67	77.78	94.45	100.00
Social	—	—	—	—	—	47.62	57.14	66.67	76.19	85.71	55.56	58.34	77.78	98.61	100.00
Body image	—	—	—	—	—	22.22	66.67	88.89	100.00	100.00	66.67	69.45	88.99	100.00	100.00
Role	—	—	—	—	—	—	—	—	—	—	58.33	68.75	95.84	100.00	100.00
Weight symptoms	—	—	—	—	—	—	—	—	—	—	33.33	41.67	100.00	100.00	100.00
Respiratory symptoms	88.89	90.28	97.22	100.00	100.00	0.00	58.33	83.33	100.00	100.00	44.44	55.56	75.00	88.89	100.00
Digestion symptoms	—	—	—	—	—	0.00	66.67	66.67	100.00	100.00	66.67	66.67	83.34	100.00	100.00

Max, maximum; Min, minimum; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile.

high median scores (higher than 90) to the respiratory and physical domains, except for the eating disturbance domain, which had a median value of 66.67, with a minimum score of 0. Children (age 6–13 years) median scores ranged from 66.67 (social and digestion symptom domains) to 88.89 (eating disturbances, treatment burden, and body image domains). Adolescents (older than 14 years) rated their HRQoL regarding eating disturbances and weight domains with the highest scores (median of 100.00), whereas the lowest score was attributed to the vitality domain (median of 66.67).

The results of the comparison between child self-report and parent-proxy report of HRQoL concerning CFQ-R common domains are presented in Table 3. Although evaluating the HRQoL of their children, parents gave the lowest median score to the body image domain (66.67) and the highest median score to the emotion domain (86.67). Positive moderate associations were found in three domains: eating disturbances, body image, and respiratory symptoms. Analyzing the medians of each of these domains for the children and the respective parent, it seems that the medians between parents and children are similar in the eating disturbances domain (88.89 vs 83.33) and in the respiratory symptoms domain (83.33). On the other hand, there is a consistent mean difference of 14.07 between the median of the body image domain of the children (88.89) and the respective parent (66.67).

The results of the Spearman correlations and the Mann–Whitney *U* test between HRQoL domains and the different factors are presented in Tables 4–6. For this analysis, the CFQ-R domains of patients 6 years or older and the parent-proxy CFQ-R domains that showed previously to be statistically significantly correlated with children CFQ-R domains were included.

No association was found between sex and HRQoL domains. Current age was positively and moderately associated with child-rated CFQ-R emotion, eating disturbances, and digestion symptoms CRQ-R domains. Current age was also associated with the role domain, with this association being positive and strong. Weight domain was negatively and strongly associated with age at diagnosis. There was a moderate positive association between child-rated CFQ-R physical domain and total of hours doing physical activity (Table 4).

Concerning the nutritional variables, BMI *z-score* and fat mass were not statistically associated with HRQoL domains (Table 4). Iron was positively associated with child-rated CFQ-R respiratory symptom and digestion symptom domains. No statistically significant associations were found between CFQ-R domains and total cholesterol, glucose, and vitamin D (Table 5). Regarding $FEV_1\%$, in this study, the group of patients with $FEV_1\% < 80\%$ seemed to have a better child-rated CFQ-R body image domain in relation to the group of patients with $FEV_1\% \geq 80\%$ (median of 100 vs 72.23) (Table 6).

Discussion

In this study, HRQoL values concerning the CFQ-R domains were generally high. These data can be attributed to better early life CF care and better general health, speculating a possible agreement with the increasing life expectancy for people diagnosed with CF.[9]

Table 3

Correlation between child (6–13 years) self-report and parent-proxy report scores for CFQ-R common domains

CFQ-R domain (n = 15)	Spearman correlation (95% CI)	*P*	Children's median score (P25; P75)	Parents' median score (P25; P75)	Mean of difference (SD)
Physical	0.481 (−0.066 to 0.839)	.069	83.33 (61.11; 94.44)	79.17 (58.33; 95.83)	−3.88 (20.35)
Emotion	0.295 (−0.269 to 0.697)	.285	75.00 (62.50; 91.67)	86.67 (66.67; 93.33)	3.33 (20.03)
Eating disturbances	0.660 (0.156 to 0.946)	**.007**	88.89 (33.33; 100.00)	83.33 (33.33; 100.00)	−6.30 (30.34)
Treatment burden	0.348 (−0.234 to 0.778)	.204	88.89 (55.56; 100.00)	77.78 (55.56; 100.00)	−5.93 (28.13)
Body image	0.603 (0.122 to 0.879)	**.017**	88.89 (66.67; 100.00)	66.67 (44.44; 100.00)	−14.07 (28.32)
Respiratory symptoms	0.692 (0.184 to 0.971)	**.004**	83.33 (58.33; 100.00)	83.33 (72.22; 94.44)	5.56 (14.51)
Digestion symptoms	0.422 (−0.141 to 0.792)	.117	66.67 (66.67; 100.00)	77.78 (55.56; 100.00)	5.93 (29.95)

The values in bold represent statistically significant correlations, with $P < .05$.
CFQ-R, Cystic Fibrosis Questionnaire-Revised; CI, confidence interval; P25, 25th percentile; P75, 75th percentile; SD, standard deviation.

Table 4

Spearman correlations between CFQ-R domains and age, age at diagnosis, total of physical activity, BMI z-score and fat mass

	Age			Age at diagnosis			Physical activity			BMI *z-score*			Fat mass		
	n	Correlation	*P*	n	Correlation	*P*	n	Correlation	*P*	n	Correlation	*P*	n	Correlation	*P*
Patient domains															
Physical	27	0.111	.614	27	0.084	.702	27	0.669	**<.001**	27	−0.088	.690	20	−0.129	.588
Vitality	8	0.673	.067	8	−0.405	.319	8	0.323	.435	8	−0.099	.861	7	−0.037	.938
Emotion	23	0.421	**.046**	23	0.128	.561	23	−0.036	.872	23	0.313	.146	20	0.297	.204
Eating disturbances	23	0.520	**.011**	23	0.163	.457	23	0.188	.390	23	−0.067	.762	20	−0.188	.427
Treatment burden	23	−0.050	.821	23	−0.164	.455	23	0.004	.984	23	0.181	.409	20	−0.071	.767
Health perceptions	8	0.654	.079	8	−0.519	.187	8	−0.050	.907	8	0.148	.726	7	0.302	.511
Social	23	0.326	.129	23	0.129	.559	23	0.269	.215	23	−0.361	.090	20	−0.141	.553
Body image	23	0.117	.596	23	−0.363	.089	23	−0.325	.130	23	0.331	.123	20	0.311	.182
Role	8	0.711	.048	8	0.091	.830	8	0.223	.595	8	−0.254	.544	7	−0.371	.413
Weight	8	0.153	.718	8	−0.803	**.016**	8	0.228	.587	8	0.536	.171	7	0.490	.264
Respiratory symptoms	23	−0.003	.988	23	−0.098	.665	23	0.239	.273	23	−0.076	.732	20	−0.326	.161
Digestion symptoms	23	0.449	**.031**	23	0.148	.501	23	0.010	.965	23	0.186	.398	20	0.208	.378
Parent domains															
Eating disturbances	19	0.347	.145	19	−0.010	.967	19	0.322	.179	19	0.293	.325	13	0.052	.865
Body image	15	0.030	.914	15	−0.220	.431	15	−0.090	.749	15	0.455	.089	13	0.397	.180
Respiratory symptoms	19	−0.412	.080	19	−0.174	.477	19	−0.238	.327	19	−0.091	.710	13	−0.327	.276

The values in bold represent statistically significant correlations, with $P < .05$.
BMI, body mass index.

The minimum median value presented in the CFQ-R domains for all ages was 66.67. On the other hand, the maximum median value in the CFQ-R domains was 97.22, 88.89, and 100.00 for children younger than 6 years, children between 6 and 13 years, and adolescents 14 years or older, respectively. For C/As 6 years or older, current age was positively associated with emotion, eating disturbances, role, and digestion symptoms CFQ-R domains. The total hours of physical activity were positively associated with the physical domain. The eating disturbances, body image, and respiratory CFQ-R domains reported by patients and their parents were the ones that were found to be positively correlated.

Consistent with Driscoll et al[15] study that found concerns of the parents toward their children's eating (2–6 years) because of a low score (62.10) on the eating disturbances domain, in this study, parents also gave the lowest score to the eating disturbances domain (66.67). It has been shown that children younger than 6 years with CF have a higher prevalence of eating problem behaviors compared with healthy children, being twice as likely to experience more mealtime problem behaviors.[16] Furthermore, the lower score may reflect parents' own worries toward their child's dietary intake. In a UK case–controlled study, 70% of the parents reported that CF made them more anxious about food intake and 28% felt unhappy with their child's growth.[28]

In addition, in this work, parents of preschool children (younger than 6 years) reported high scores in physical and respiratory domains, which were expected considering that although lung disease may occur, it develops usually in the absence of symptoms or signs. Therefore, the lack of symptoms' impact in their life results in higher CFQ-R scores, according to parents.

For children age between 6 and 13 years, the lowest scores reported were related to the digestive condition and social aspect. The digestion CFQ-R domain includes only one question related to stomach hurt, which could indicate that it is necessary to adjust the dosage of the enzyme therapy. The low score given to the social

Table 5

Spearman correlations between CFQ-R domains and total cholesterol, glucose, iron and vitamin D

	Total cholesterol			Glucose			Iron			Vitamin D		
	n	Correlation	*P*	n	Correlation	*P*	n	Correlation	*P*	n	Correlation	*P*
Patient domains												
Physical	16	−0.136	.644	20	0.420	.105	23	0.225	.354	21	−0.049	.846
Vitality	5	−0.316	.604	6	−0.265	.612	6	0.353	.492	6	−0.313	.545
Emotion	14	−0.254	.382	16	0.187	.487	19	−0.098	.689	18	−0.374	.127
Eating disturbances	14	0.139	.636	16	0.158	.559	19	0.397	.092	18	−0.216	.390
Treatment burden	14	0.269	.352	26	0.081	.765	19	0.044	.857	18	0.025	.921
Health perceptions	5	0.158	.800	6	−0.239	.648	6	0.359	.485	6	−0.061	.909
Social	14	−0.211	.469	16	−0.274	.305	19	0.150	.541	18	−0.066	.794
Body image	14	−0.215	.460	16	0.010	.970	19	−0.089	.716	18	0.009	.973
Role	5	0.224	.718	6	0.169	.749	6	−0.101	.848	6	−0.189	.720
Weight	5	−0.316	.604	6	−0.339	.510	6	0.679	.138	6	−0.078	.883
Respiratory symptoms	14	0.440	.116	16	−0.057	.833	19	0.577	**.010**	18	−0.057	.821
Digestion symptoms	14	−0.330	.249	16	0.148	.584	19	0.468	**.043**	18	−0.110	.665
Parent domains												
Eating disturbances	11	0.087	.799	14	0.550	**.042**	17	0.002	.094	15	−0.110	.697
Body image	9	−0.142	.716	10	0.339	.338	13	0.166	.588	12	0.258	.418
Respiratory symptoms	11	0.086	.801	14	0.258	.373	17	0.358	.159	15	0.408	.131

Table 6

Association between CFQ-R domains and sex and FEV_1%

	Sex, median (P25-P75)				FEV_1%, median (P25-P75)			
	n	Feminine	Masculine	*P**	n	<80%	≥80%	*P**
Patient domains								
Physical	23	83.33 (67.01–100.00)	79.17 (66.67–91.67)	.829	22	73.61 (50.00–87.50)	83.33 (71.18–98.61)	.329
Vitality	8	66.67 (64.59–87.50)	79.17 (58.33–100.00)	.999	8	66.67 (66.67–75.00)	66.67 (58.33–100.00)	.999
Emotion	23	83.33 (75.00–92.09)	73.33 (60.42–91.25)	.305	22	89.17 (82.50–95.00)	75.00 (63.54–86.67)	.059
Eating disturbances	23	100.00 (88.89–100.00)	55.56 (27.78–100.00)	.224	22	94.45 (66.67–100.00)	100.00 (38.89–100.00)	.802
Treatment burden	23	77.78 (63.89–88.89)	88.89 (66.67–100.00)	.159	22	83.34 (52.78–91.67)	83.34 (66.67–88.89)	.914
Health perceptions	8	77.78 (66.67–100.00)	66.67 (55.56–77.78)	.429	8	77.78 (77.78–88.89)	66.67 (61.12–88.89)	.250
Social	23	66.67 (61.90–86.51)	61.00 (53.97–76.19)	.250	22	71.43 (54.77–90.28)	66.67 (61.90–79.76)	.999
Body image	23	94.45 (66.67–100.00)	77.78 (44.45–100.00)	.250	22	100.00 (97.22–100.00)	72.23 (66.67–97.22)	**.013**
Role	8	95.84 (72.92–100.00)	79.17 (58.33–100.00)	.643	8	100.00 (66.67–100.00)	91.67 (66.67–100.00)	.786
Weight	8	83.34 (33.33–100.00)	100.00 (100.00–100.00)	.429	8	100 (66.67–100.00)	100.00 (50.00–100.00)	.999
Respiratory symptoms	23	72.22 (52.78–100.00)	83.33 (75.00–90.28)	.439	22	65.28 (33.33–91.67)	83.33 (59.03–97.92)	.261
Digestion symptoms	23	66.67 (66.67–100.00)	66.67 (66.67–100.00)	.926	22	83.34 (25.00–100.00)	66.67 (66.67–100.00)	.914
Parent domains								
Eating disturbances	19	83.33 (25.00–100.00)	66.67 (25.00–100.00)	.720	14	33.33 (16.67–66.67)	83.33 (33.33–100.00)	.456
Body image	15	72.23 (58.34–77.78)	44.44 (33.33–100.00)	.779	14	66.67 (61.12–83.34)	66.67 (33.33–77.78)	.555
Respiratory symptoms	19	86.11 (66.67–100.00)	88.89 (80.56–94.44)	.780	14	83.33 (50.00–91.67)	83.33 (72.22–94.44)	.885

The values in bold represent statistically significant correlations, with $P < .05$.
FEV_1%, percentage of predicted forced expiratory volume in one second; P25, 25th percentile; P75, 75th percentile.
* Mann–Whitney *U* test.

CFQ-R domain reflects the impact of this disease on the performance of the daily social activities. These findings are in concordance with the results of similar studies.[29,30] In fact, C/As with CF frequently face emotional problems such as social exclusion, frequent hospitalizations, separation from family and friends, and fear of death,[17] which reflects as a higher prevalence of anxiety disorders and depression in patients with CF in comparison with a control group,[31] with consequences in their social life.

Adolescents (14 years or older) reported, in this investigation, no concerns toward HRQoL in relation to gaining weight and their food habits. This may result from an early education about the need to do a high-energy diet and frequent medical monitoring. Some of these patients take oral energy supplements, which may be responsible for the easier weight gain. On the other hand, in this age group, the domain that was scored lowest was vitality. This domain is not usually analyzed in the literature because normally only CFQ-R domains common to parents' and children's versions are studied. The lower score in this domain reflects the impact of this disease on their physical shape, specifically declining energy levels.

As to the second study goal, previous studies have shown a pattern regarding the agreement between children's and parents' reports. This pattern is characterized by a poorer agreement for non-observable functioning, such as emotion, treatment burden, and body image domains, and a greater agreement for observable functioning, such as physical, digestion symptom, and respiratory symptom domains.[27,32] Our results correspond to the expected agreement on objective domains (correlation found in the respiratory disturbance and eating disturbance domains) and the expected disagreement on subjective domains (body image domain).

Physical activity is associated with physiological benefits common to healthy individuals, but particularly in CF, slows the rate of decline of FEV_1% and improves survival.[33] In this study, physical activity was only positively correlated with the physical CFQ-R domain, which may be a consequence of the small sample size and the low statistical power associated. Age was the variable that was related to a greater number of CFQ-R domains: the older the patient, the higher the score of the emotion, eating disturbances, role, and digestion domains. This might be explained by an increasingly early diagnosis that translates into monitoring by multidisciplinary teams that include psychologists, nutritionists, pediatricians, and pulmonologists, among others, who work together for promoting the patient's well-being.[8]

Furthermore, weight domain was negatively and strongly associated with age at diagnosis. These findings show that an early diagnosis is associated with a higher weight CFQ-R domain score, which is explained by the fact that being diagnosed early in life enables the children to grow up being accompanied by a nutritionist.

This study also analyzed variables that, according to our knowledge, have not been studied before such as fat mass, total cholesterol, glucose, iron, and vitamin D. Iron was positively associated with respiratory CFQ-R domain, meaning that lower seric iron levels are associated with lower score in this domain, and indeed, these study results revealed that five C/As had low seric iron levels. The literature has been demonstrating that iron deficiency occurs frequently in patients with CF.[24] Consequently, iron deficiency is a major cause for anemia in patients with CF, leading to poor lung function and overall deficit of health.[34] Although the prevalence of anemia was not studied in this sample, this is a possible justification. It was also found positive and moderate associations between seric iron and digestion symptoms CFQ-R domain and between total cholesterol and social CFQ-R domain. Once there is no study until data investigating these associations in patients with CF, further studies are needed and recommended.

According to the literature, FEV_1% is associated with all domains of the CFQ-R teenagers/adults version, except with the digestion symptoms domain.[35] In preschool children, a recent study that evaluated HRQoL found that higher FEV_1% was associated with higher parents' scores on HRQoL domains, corroborating the results found in older patients.[27] In this study, contrary to what was expected, FEV_1% was only associated with CFQ-R body image domain in children older than 6 years and the group of patients with $FEV_1\% < 80\%$ seemed to have a better child-rated CFQ-R body image domain in relation to the group of patients with $FEV_1\% \geq 80\%$. This could have happened because of the small sample size and because 72.5% of this sample has a $FEV_1\% \geq 80\%$. In addition, FEV_1 is an insensitive marker of

underlying lung disease helping to explain the lack of relationship with HRQoL domains.

The results of this study should be interpreted considering its limitations. First, the sample size was small to do statistical treatment because CF is a rare disease, so it is not possible to extrapolate the findings to all patients with CF. Second, the amount of missing data for some variables (for example, fat mass and total cholesterol) was substantial, which may compromise some of the results obtained. Third, it is difficult to clearly interpret the results of the HRQoL scores because there are no cutoffs that define the poor, good, and excellent quality of life. Fourth, the CFQ-R does not provide an overall score to assess HRQoL. Finally, owing to the cross-sectional nature of this study, it is not possible to establish cause–effect relationships.

One the other hand, there are several strengths in this study. It was applied a questionnaire validated for the Portuguese language that was specially developed for this pathology with different versions adapted for pediatric age. Anthropometric data were not self-reported but measured by a trained researcher. The participation rate was very high (96%). Finally, according to our knowledge, this is the first study conducted in Portugal that evaluates HRQoL in pediatric age through a specific CF instrument.

The findings of this work are crucial to reinforce the importance of investing this public health topic, once it reflects both patients' own perception of their quality of life and parents' perception, allowing the medical team to adapt their intervention to improve the life quality of C/As with CF. In addition, this study opens a new path for future investigations to study associations between biochemical parameters and HRQoL.

In conclusion, this Portuguese pediatric sample presented high scores of HRQoL concerning CFQ-R domains, with all the median scores above 66.67. Comparing the CFQ-R reports of patients and their parents, a good agreement was found for the respiratory disturbance and eating disturbance CFQ-R domains and a poor agreement was found for body image CFQ-R domain. The main factors associated with HRQoL were the following: current age, age at diagnosis, physical activity, and seric iron.

Acknowledgements

The research team would like to thank all children and adolescents with cystic fibrosis and their families for voluntarily participating in this study.

Conflicts of interest

The authors report no conflicts of interest.

References

[1] Elborn JS. Cystic fibrosis. Lancet. 2016;388:2519–2531.
[2] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibrosis. 2008;7:450–453.
[3] Associação Nacional de Fibrose Quística. O que é a Fibrose Quística?; 2021. Available from: http://www.anfq.pt/o-que-e-a-fibrose-quistica/. Accessed September 13, 2021.
[4] Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989;245:1066.
[5] Cutting GR. Modifier genes in Mendelian disorders: the example of cystic fibrosis. Ann N Y Acad Sci. 2010;1214:57–69.
[6] Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nat Rev Dis Primers. 2015;1:15010.
[7] Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med. 2020;8:65–124.
[8] Ratchford TL, Teckman JH, Patel DR. Gastrointestinal pathophysiology and nutrition in cystic fibrosis. Expert Rev Gastroenterol Hepatol. 2018;12:853–862.
[9] Scotet V, L'Hostis C, Férec C. The changing epidemiology of cystic fibrosis: incidence, survival and impact of the CFTR gene discovery. Genes (Basel). 2020;11:589.
[10] de Jong W, Kaptein AA, van der Schans CP, et al. Quality of life in patients with cystic fibrosis. Pediatr Pulmonol. 1997;23:95–100.
[11] Abbott J, Webb K, Dodd M. Quality of life in cystic fibrosis. J R Soc Med. 1997;90(suppl 31):37–42.
[12] Goss CH, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:378–386.
[13] 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.
[14] Rozov T, Cunha M, Nascimento O, Quittner A, Jardim J. Linguistic validation of cystic fibrosis quality of life questionnaires. J Pediatr (Rio J). 2006;82:151–156.
[15] Driscoll KA, Modi AC, Filigno SS, et al. Quality of life in children with CF: psychometrics and relations with stress and mealtime behaviors. Pediatr Pulmonol. 2015;50:560–567.
[16] Ward C, Massie J, Glazner J, et al. Problem behaviours and parenting in preschool children with cystic fibrosis. Arch Dis Child. 2009;94:341.
[17] Withers AL. Management issues for adolescents with cystic fibrosis. Pulm Med. 2012;2012:134132.
[18] 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;128:2347–2354.
[19] Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28:535–545.
[20] Stewart A, Marfell-Jones M, Olds T, De Ridder J. International Standards for Anthropometric Assessment. International Society for the Advancement of Kinanthropometry. 2011.
[21] de Onis M, Lobstein T. Defining obesity risk status in the general childhood population: which cut-offs should we use? Int J Pediatr Obes. 2010;5:458–460.
[22] McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes. 20052006;30:598–602.
[23] Hughes HK, Lauren K. Harriet Lane Handbook. 21st ed. Elsevier; 2018. Kahl. "TABLE 28.1: reference values. Available from: www.unboundmedicine.com/harrietlane/view/Harriet_Lane_Handbook/309269/all/TABLE_28_1:_Reference_Values. Accessed October 23, 2021.
[24] Uijterschout L, Nuijsink M, Hendriks D, Vos R, Brus F. Iron deficiency occurs frequently in children with cystic fibrosis. Pediatr Pulmonology. 2014;49:458–462.
[25] (GOLD) GIfCOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD; 2011. Available from: https://goldcopd.org. Accessed November 20, 2021.
[26] Ronit A, Gelpi M, Argentiero J, et al. Electronic applications for the CFQ-R scoring. Respir Res. 2017;18:108.
[27] Cheney J, Vidmar S, Gailer N, Wainwright C, Douglas TA. Health-related quality-of-life in children with cystic fibrosis aged 5-years and associations with health outcomes. J Cyst Fibros. 2020;19:483–491.
[28] Duff AJA, Wolfe SP, Dickson C, Conway SP, Brownlee KG. Feeding behavior problems in children with cystic fibrosis in the UK: prevalence and comparison with healthy controls. J Pediatr Gastroenterol Nutr. 2003;36:443–447.
[29] Schmidt A, Wenninger K, Niemann N, Wahn U, Staab D. Health-related quality of life in children with cystic fibrosis: validation of the German CFQ-R. Health Qual Life Outcomes. 2009;7:97.
[30] Nakov ZN, Fushtikj SN, Tonikj-Ribarska J, Jolevska ST. Health-related quality of life of Macedonian families experiencing cystic fibrosis in pediatric practice. Folia Med (Plovdiv). 2019;61:213–222.
[31] Gundogdu U, Fis NP, Eralp EE, Karadag BT. Major depression and psychiatric comorbidity in Turkish children and adolescents with cystic fibrosis. Pediatr Pulmonology. 2019;54:1927–1935.
[32] Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res. 2001;10:347–357.
[33] Wilkes DL, Schneiderman JE, Nguyen T, et al. Exercise and physical activity in children with cystic fibrosis. Paediatric Respir Rev. 2009;10:105–109.
[34] Gifford AH, Miller SD, Jackson BP, et al. Iron and CF-related anemia: expanding clinical and biochemical relationships. Pediatr Pulmonol. 2011;46:160–165.
[35] Habib A-RR, Manji J, Wilcox PG, Javer AR, Buxton JA, Quon BS. A systematic review of factors associated with health-related quality of life in adolescents and adults with cystic fibrosis. Ann Am Thorac Soc. 2015;12:420–428.