Evaluation of the Quality of Life and associated factors of Children and Adolescents with Cystic Fibrosis in the northern region of Portugal

Avaliação da Qualidade de Vida e fatores associados de Crianças e Adolescentes com Fibrose Quística da região Norte de Portugal

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Abstract

Introduction: Children/adolescents (C/A) 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 C/A aged 4-17 years was included in a cross-sectional observational study. 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). To identify associations between HRQoL domains and determinants, Spearman's Correlations and Mann-Whitney Test were performed. Spearman's Correlations were calculated to analyze the agreement between children's and parents' reports.

Results: The scores of CFQ-R domains were in general high, with the lowest value of median being 66.67 for all ages. The main factors associated with HRQoL were current age, age at diagnosis, physical activity and seric iron levels. It was found positive moderate associations between HRQoL reports of children and their parents in 3 domains: Eating disturbances, Body image and Respiratory symptoms. The median scores were similar in the Eating disturbances (about 80.00) and the Respiratory symptoms domains (83.33). However, there is a consistent difference of 14.07 in the Body image domain.

Conclusion: The findings of this study reinforce the need to evaluate HRQoL during childhood and adolescence in order to adapt the clinical treatment and to improve the quality of life of C/A.

Keywords: Cystic Fibrosis, Cystic Fibrosis Questionnaire-Revised, Health-Related Quality of Life, Pediatric Age

Resumo

Introdução: Crianças e adolescentes (C/A) com Fibrose Quística (FC) experienciam dificuldades psicológicas e físicas que afetam a sua qualidade de vida relacionada com a saúde (QVRS).

Objetivos: Avaliar o impacto da FC na QVRS numa amostra de idade pediátrica, identificando os seus principais determinantes e comparando as respostas das crianças com as dos respetivos pais.

Métodos: Inclui-se uma amostra de 27 C/A entre os 4 e os 17 anos num estudo observacional transversal. Aplicou-se um questionário para avaliar dados sociodemográficos e o estado nutricional. A QVRS foi avaliada através da versão do Questionário da FC validada para língua portuguesa. Para identificar associações entre os domínios da QVRS e os determinantes, realizaram-se correlações de Spearman e o teste Mann-Whitney. A comparação entre as respostas das crianças e dos pais foi realizada através de correlações de Spearman.

Resultados: As pontuações dos domínios da QVRS foram, em geral, elevadas, sendo 66,67 o menor valor da mediana para todas as idades. Os principais fatores associados à QVRS foram: idade atual, idade ao diagnóstico, atividade física e níveis de ferro. Foram encontradas associações positivas e moderadas entre as respostas das crianças e dos pais em 3 domínios: Alimentação, Imagem corporal e Respiratório. A mediana da pontuação foi semelhante nos domínios “Alimentação” (cerca de 80,00) e “Respiratório” (83,33). Contudo, há uma diferença consistente de 14.07 no domínio “Imagem corporal”.

Conclusão: Os resultados reforçam a necessidade de avaliar a QVRS em C/A na infância e adolescência, de forma a adequar o tratamento clínico e melhorar a qualidade de vida das C/A.

Palavras-chave: Fibrose Quística, Questionário de Fibrose Quística, Qualidade de Vida Relacionada com a Saúde, Idade Pediátrica

Abbreviations

BMI – Body Mass Index

CF - Cystic Fibrosis

CFTR - Cystic Fibrosis Transmembrane Conductance Regulator

CFQ - Cystic Fibrosis Questionnaire

CFQ-R - Cystic Fibrosis Questionnaire-Revised

CHUSJ – Centro Hospitalar Universitário de São João

CESCHUSJ - Ethics Committee of the Centro Hospitalar Universitário de São João

C/A – Children and Adolescents

ENaC - Epithelial Sodium Channel

GOLD - Global Initiative for Chronic Obstructive Lung Disease

HDL-C - High-Density Lipoprotein Cholesterol

HRQoL - Health-Related Quality of Life

LDL-C – Low-Density Lipoprotein Cholesterol

SPSS - Statistical Package for the Social Sciences

TG - Triglycerides

Table of contents

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/A)[3]. CF is caused by a mutation in a gene of chromosome 7 that encodes a glycoprotein called CF Transmembrane Conductance Regulator (CFTR)[4-6].

CFTR, located in epithelial cells, is responsible for producing mucus, sweat, saliva and digestive enzymes, and actively transports chloride ion[7]. CFTR also produces bicarbonate, which influences the pH of airway surface liquid[8] and indirectly regulates epithelial sodium channel (ENaC) by stopping the influx of sodium into the cell[9]. The absence or lack of adequately functioning CFTR protein increases the absorption of sodium and fluid mediated by ENac, causing dehydration, acidification of the mucosa and thickened mucus secretions in the lung airways, pancreas, intestine and sweat glands[10].

Although CF is a monogenetic disease, it covers a myriad of phenotypic manifestations[11, 12], 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[13-15].

In the recent decades, advances in the treatment and management of this illness have been made[16-18]. The implementation of neonatal screening in some countries, as in Portugal, is allowing an early diagnosis and treatment[19]. As a result, the estimated median age of survival nowadays is close to 50 years and is expected to continue to rise[20, 21]. However, living with CF imposes psychological

and physical difficulties that have a severe impact on patients' health-related quality of life (HRQoL)[22].

HRQoL is a multidimensional concept that includes multiple domains related to patients' health, namely physical, social, functional and emotional wellbeing[23, 24], as reported by them. Awareness of the importance of patient-reported outcomes (PROs) in those with CF[25, 26] has led to the development of a CF-specific instrument to measure HRQoL, the Cystic Fibrosis Questionnaire (CFQ)[27]. The CFQ has a revised version called CFQ-R, that has been translated into several languages, including American English[28, 29], German[30], Dutch[31] and Portuguese[32], and is being used in countless investigations recently[33-35].

HRQoL in adolescents seems to be more affected by the percentage of predicted forced expiratory volume in one second (FEV_1%) and pulmonary exacerbations[36]. Low socioeconomic and minority status are correlated with lower HRQoL scores[37], as well as female gender[38, 39].

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/A with CF.

Aim

Thus, this study aimed to evaluate the impact of CF on HRQoL in a pediatric age sample. The specific objectives are: I) to characterize the HRQoL of C/A with CF; II) to compare the HRQoL reports of children with CF with the reports of the respective parent; III) to identify determinants associated with HRQoL.

Methodology

1. 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. Inclusion criteria were an age between 4 and 18 years, diagnosis of CF according to the national guidelines[19] and the attendance of a caregiver in patients under 14 years old. From the 28 C/A followed in pulmonology consultation of CHSJ, 27 (96,4%) were included in this study. One C/A refused to participate.

2. 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/A were asked to read and sign an informed consent form.

3. 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[29, 40] in people with CF.

A questionnaire was developed by the hospitaller team and was applied by interview, including demographic information of the patients and their parents, lifestyle information, clinical data, and anthropometric measures of the child.

Demographic data included sex and patient's age, in years. Regarding the parents, it was asked their age, in years, and their education level. 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). Lifestyle information was related to the physical activity of the patients. It was asked if 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" (in hours) that corresponds to the sum of physical activity in school (in hours) and out of school (in hours).

Anthropometric measurements were collected following standard procedures[41]. 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 (BIA) Tanita: TBF-300A with a 0.1 kg resolution. In children under 7 years old, was only measured body weight (in kg) 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)[42], and the respective percentile and *z-score* were established using the *softwares* WHO Anthro®[43] and WHO AnthroPlus®[44]. Nutritional status was classified using the *z-score* of BMI. C/A were grouped into underweight (*z-score* <-1), normal weight (-1 ≤ *z-score* < 1) and overweight (*z-score* ≥ 1)[45]. According to the fat mass percentiles, obtained from body fat reference curves for children, C/A were categorized into underfat (<2nd), normal fat (2nd to 85th), overfat (85th to 95th) and obese (>95th)[46].

Clinical data was 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 (HDL-C), low-density lipoprotein (LDL-C), triglycerides (TG), vitamin D, and iron were collected, and it was used the reference values established in *The Harriet Lane Handbook*[47]. Finally, it was extracted the FEV_1% values, to assess the lung function. FEV_1% were classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification into four groups (mild: $FEV_1 \geq 80\%$; moderate: $50\% \leq FEV_1 < 80\%$; severe: $30\% \leq FEV_1 < 50\%$; very severe: $FEV_1 < 30\%$)[48].

The Portuguese version of the CFQ-R was administered to evaluate both patient's and parent's perspectives[32]. 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) - 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. Teenagers/Adults and Parent versions also include Vitality, Health perceptions, and Weight domains. Children and Teenagers/Adults versions also include a Social domain, while the Parents' version includes a School domain. The Teenagers/Adults version also includes a role domain. CFQ-R uses a 4-point Likert scale, with 4 points representing the answer suggesting greater HRQoL for each question. 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[49]. Even though there is not a version for children under 6 years old, we used the Respiratory, Physical and Eating disturbances domains of the parent-proxy CFQ-R to assess HRQoL in preschool children, due to its strong reliability demonstrated in previous studies[35, 50, 51].

4. 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 results were described as median (25th and 75th percentiles), considering that variables presented non-normal distribution.

Spearman's correlation between patients and their parent scores was 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, TG, glucose, iron, and vitamin D. The strength of each correlation was considered and rated from very weak to very strong[50]. Mann-Whitney test was performed to evaluate the associations between CFQ-R domains with sex, and with FEV1%. Since there are no patients in the "very severe" category of FEV1% and only one patient in the "severe" category, this patient was included in the "moderate" group to execute this test. So, to do this test, participants were grouped according to FEV1% into two categories: "FEV_1 ≥80%" and "FEV_1<80%".

Results were considered significant when $p \leq 0.05$. 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 described in Attachment A. In the current study, 27 patients were evaluated, ranging from 4 to 17 years old, with a median age of 10 years. Of the total, 59.3% were female, 44.4% did physical activity out of school and 88.9% had

pancreatic insufficiency and received enzyme therapy. Concerning the nutritional status, 18.5% were underweight, 70.4% had normal weight, and 11.1% were overweight. Lastly, regarding pulmonary function, the sample revealed a low-to-severe disease, highlighting the fact that 72.7% has a $FEV_1\%$ > 80%.

Table 1 characterized the HRQoL scores for CFQ-R versions. In preschool children (<6 years), their parents gave very high median scores (higher than 90) to the Respiratory and Physical domains, except for the Eating disturbances domain, which had a median punctuation of 66.67, with a minimum score of 0. Children (6-13 years) median scores ranged from 66.67 (Social and Digestion symptoms domains) to 88.89 (Eating disturbances, Treatment burden and Body image domains). Adolescents (> 14 years) rated their HRQoL regarding Eating disturbances and weight domains with the highest scores (median of 100.00), while the lowest score was attributed to the Vitality domain (median of 66.67).

Results of the comparison between child self-report and parent-proxy report of HRQoL concerning CFQ-R common domains are shown in Table 1. While 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). It was found positive moderate associations 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 appears 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).

Table 1. Characterization of HRQoL of children/adolescents, according to the CFQ-R domain scores.

Legend – Min: minimum; P25: 25th percentile; P50: 50th percentile; P75: 75th percentile; Max: maximum

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

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Table 2. Agreement between child (6-13 years) self-report and parent-proxy report scores for CFQ-R common domains.

Legend – CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; P25: 25th percentile; P75: 75th percentile; SD: standard deviation.

CFQ-R domain (n=15)	Spearman Correlation (95% CI)	P-value	Children's Median Score (P25;P75)	Parents' Median Score (P25;P75)	Mean of difference (SD)
Physical	0.481 (-0.066;0.839)	0.069	83.33 (61.11;94.44)	79.17 (58.33;95.83)	-3.88 (20.35)
Emotion	0.295 (-0.269;0.697)	0.285	75.00 (62.50;91.67)	86.67 (66.67;93.33)	3.33 (20.03)
Eating disturbances	0.660 (0.156;0.946)	**0.007**	88.89 (33.33;100.00)	83.33 (33.33; 100.00)	-6.30 (30.34)
Treatment burden	0.348 (-0.234;0.778)	0.204	88.89 (55.56;100.00)	77.78 (55.56;100.00)	-5.93 (28.13)
Body image	0.603 (0.122;0.879)	**0.017**	88.89 (66.67;100.00)	66.67 (44.44;100.00)	-14.07 (28.32)
Respiratory symptoms	0.692 (0.184;0.971)	**0.004**	83.33 (58.33;100.00)	83.33 (72.22;94.44)	5.56 (14.51)
Digestion symptoms	0.422 (-0.141;0.792)	0.117	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 $p<0.05$.

The results of the Spearman Correlations and the Mann-Whitney Test between HRQoL domains and the different factors are displayed in Attachment B. For this analysis, it was included the CFQ-R domains of patients ≥ 6 years old. It was also included in this analysis parent-proxy CFQ-R domains that showed previously to be statistically significant correlated with children CFQ-R domains.

No association was found between sex and the 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.

Regarding FEV_1%, in this study, the group of patients with FEV_1% < 80% appeared to have a better child-rated CFQ-R Body image domain in relation to the group of patients with FEV_1% ≥ 80% (median of 100 vs 72.23). Concerning the nutritional variables, BMI *z-score* and fat mass were not statistically associated with HRQoL domains. In relation to the clinical variables, it was found a moderate negative association between TG and child-rated CFQ-R Social domain. Iron was positively associated with child-rated CFQ-R Respiratory and Digestion symptoms domains. No statistically significant associations were found between CFQ-R domains and total cholesterol, glucose, and vitamin D.

Discussion

In this study, HRQoL values concerning the CFQ-R domains were, in general, high, which corroborates the increasing life expectancy for people diagnosed with CF[21]. 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 < 6 years, for children between 6 and 13 years and for adolescents above 14 years, respectively. For C/A ≥ 6 years, current age was positively associated with Emotion, Eating disturbances, Role and Digestion symptoms CFQ-R domains. The total hours of physical activity was 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 in this study.

Consistent with Driscoll *et al*. study that found concerns of the parents towards their children's eating (2-6 years old) due to a low score (62.10) on the Eating disturbances domain[50], in our study parents also gave the lowest score to

the Eating disturbances domain (66.67). It has been shown that children under 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[52]. Furthermore, the lower score may reflect parents' own worries towards their child 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[53].

Additionally, in this work, parents of preschool (<6 years) children reported high scores in Physical and Respiratory domains, which was expected considering that even though lung disease may occur, it develops usually in the absence of symptoms or signs[54]. Therefore, the lack of impact of symptoms in their life result in higher CFQ-R scores, according to parents.

For children between 6 and 13 years old 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 is necessary to adjust the dosage of the enzyme therapy. The low score given to the Social 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[34, 55]. In fact, C/A with CF frequently face emotional problems such as social exclusion, frequent hospitalizations, separation from family and friends and fear of death[56], which reflects as a higher prevalence of anxiety disorders and depression in CF patients in comparison to a control group[57], with consequences in their social life. On the other hand, the Treatment burden domain was one of the highest scored. This domain focuses on questions related to the difficulties in performing the treatments. Therefore, it appears that children may deny the life

impact of the strict treatment regimen as a coping mechanism by not admitting the difficulty in performing it and by having a positive attitude towards it. Besides, in some of these patients, the disease is still at an early stage and they do not need to spend much time doing the treatment comparing with older patients.

Adolescents (≥14 years) reported, in this investigation, no concerns towards 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. Vitality includes questions concerned with their mood. Because they are in adolescence, it's important to consider that this phase is associated with behavioral and cognitive changes, along with mood swings that might reflect as a lower score in the Vitality domain[58].

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, and Respiratory symptoms domains[35, 59, 60]. Our results correspond to the expected agreement on objective domains (correlation found in the Respiratory and Eating disturbances 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[61]. 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 may indicate that with increasing age, they feel better and less pushed to eat. Also, with the years passing by, it appears that the disease interferes less with their attendance at school and other activities and that they have less diarrhea, intestinal gas and stomach hurt, since the questions that correspond to these domains are in line with this reflection. This might be explained by an increasingly early diagnosis that translates into monitoring by multidisciplinary teams that include psychologists, nutritionists, pediatricians, pulmonologists, among others, who work together for promoting the patient's well-being[19].

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 and knowing the characteristics of their disease and its treatment, namely the hypercatabolic nature and the need to do high-calorie meals[62].

This study also analyzed variables that, according to our knowledge, have not been studied before such as fat mass, total cholesterol, TG, 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/A had low seric iron levels. Literature has been demonstrating that iron deficiency occurs frequently in

patients with CF[63]. Consequently, iron deficiency is a major cause for anemia in patients with CF, leading to poor lung function and overall deficit of health[64, 65]. Although the prevalence of anemia was not study 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 association in patients with CF, further studies are needed and recommended.

According to literature, in adolescents and adults, FEV_1% is associated with all domains of the CFQ-R teenagers/adults version, except with the Digestion symptoms domain[36]. 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[35]. In this study, contrary to what was expected, FEV_1% was only associated with CFQ-R Body image domain in children > 6 years, and the group of patients with FEV_1% < 80% appeared to have a better child-rated CFQ-R Body image domain in relation to the group of patients with FEV_1% ≥ 80%. This could have happened due to the small sample size and because was analyzed as a categorical variable instead of a numerical variable, automatically losing its statistical power. Additionally, 72.5% of this sample has a FEV1% ≥ 80%.

The results of the current study should be interpreted considering its limitations. Firstly, 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 CF patients. Secondly, 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. Thirdly, it is difficult to clearly interpret the results of the

HRQoL scores because there are no cut-offs that define what is a poor, good and an excellent quality of life. Fourthly, the CFQ-R does not provide an overall score to assess HRQoL. Lastly, due to the cross-sectional nature of the 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 was not self-reported but measured by a trained researcher. The participation rate was very high (96.4%). 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 in this public health theme, once they reflect both the patients' own perception of their quality of life and the parents' perception, allowing the medical team to adapt their intervention in order to improve their quality of life.

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 and Eating disturbances CFQ-R domains and a poor agreement was found for Body Image CFQ-R domain. The main factors associated with HRQoL were the following ones: current age, age at diagnosis, physical activity and seric iron.

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Attachments

Attachments Index

Attachment A

Characterization of the sample of children and adolescentes.	
Age, years, median (P25, P75)	10 (7, 15)
n=27	
Sex, n (%)	
n=27	
Female	16 (59.3)
Male	11 (40.7)
Age at diagnostic, years, median (P25, P75)	1 (0, 3)
n=27	
Associated pathologies, n (%)	
n=27	
Pancreatic insufficiency	24 (88.9)
Without pathologies	3 (11.1)
Physical activity at school, n (%)	
n=27	
No	7 (25.9)
Yes	20 (74.1)
Physical activity out of school, n (%)	
n=27	
No	15 (55.6)
Yes	12 (44.4)
Total of physical activity, hours per week, median (P25, P75)	3 (0, 4)
n=27	
Education level, n (%)	
n=27	
Preschool	4 (14.8)
Primary (1st-6th grade)	13 (48.2)
Secondary (7th-12th grade)	10 (37)
Average age of parents, years, median (P25, P75)	41 (37.75, 44.88)
n=26	
Maximum parental education, n (%)	
n=27	
Primary (1st-6th grade)	4 (14.8)
Secondary (7th-12th grade)	11 (40.7)
Higher education	12 (44.4)
Enteral nutrition, n (%)	
n=27	
No	18 (66.7)
Yes	9 (33.3)
Parenteral nutrition, n (%)	
n=27	
No	27 (100)
Yes	0 (0)
Nutritional supplementation, n (%)	
n=27	
No	18 (66.7)
Yes	9 (33.3)

Vitamin and mineral supplementation, n (%)	
n=27	
No	1 (3.7)
Yes	26 (96.3)
Pancreatic enzyme replacement, n (%)	
n=27	
No	3 (11.1)
Yes	24 (88.9)
Disease severity defined by FEV_1%, n (%)	
n=22	
Mild ($FEV_1 \geq 80\%$)	16 (72.7)
Moderate ($50 \leq FEV_1 < 80\%$)	5 (22.7)
Severe ($30 \leq FEV_1 < 50\%$)	1 (4.5)
Very Severe ($FEV_1 < 30\%$)	0 (0)
BMI *z-score*, median (P25, P75)	-0.19 (-0.93, 0.25)
n=27	
Nutritional status, n (%)	
n=27	
Underweight (z-score<-1)	5 (18.5)
Normal (-1≤z-score<1)	19 (70.4)
Overweight *(z-score≥1)*	3 (11.1)
Fat mass, n (%)	
n=20	
Underfat (<P2)	9 (45)
Normal (P2-P85)	7 (35)
Overfat (P85-P95)	4 (20)
Obese (>P95)	0 (0)
Glucose, n (%)[1]	
n=20	
Low	0 (0)
Adequate	18 (90)
High	2 (10)
Total cholesterol, n (%)[2]	
n=16	
Adequate	15 (93.8)
Borderline	0 (0)
High	1 (6.3)
HDL-C, n (%)[3]	
n=16	
Low	3 (18.8)
Adequate	13 (81.3)
LDL-C, n (%)[4]	
n=16	
Adequate	15 (93.8)
Borderline	0 (0)
High	1 (6.3)
TG, n (%)[5]	
n=17	
Low	0 (0)
Adequate	16 (94.1)
High	1 (5.9)

Vitamin D, n (%)[6]	
n=21	
Very low	0 (0)
Low	4 (19)
Adequate	17 (81)
Iron, n (%)[7]	
n=23	
Low	5 (21.7)
Adequate	15 (55.6)
High	3 (11.1)

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

[1]Reference values of glucose*
<16 years: **low** < 60mg/dL; **adequate** [60-100[mg/dL; **high** ≥100mg/dL
≥16 years: **low** < 70mg/dL; **adequate** [70-105[mg/dL; **high** ≥105mg/dL
[2]Reference values of total cholesterol*
adequate < 170mg/dL; **borderline** [170;200[mg/dL; **high** ≥ 200mg/dL
[3]Reference values of HDL-cholesterol*
low ≤ 35mg/dL; **adequate** >35mg/dL
[4]Reference values of LDL-cholesterol*
adequate < 110mg/dL; **borderline** [110; 130[mg/dL; **high** ≥ 130mg/dL
[5]Reference values of triglycerides*
female: **low** < 37mg/dL; **adequate** [37-140[mg/dL; **high** ≥140 mg/dL
male: **low** < 24mg/dL; **adequate** [24-145[mg/dL; **high** ≥145 mg/dL
[6]Reference values of vitamin D*
very low <12 ng/mL; **low** [12-20[ng/dL; **adequate** ≥ 20 ng/mL
[7]Reference values of iron*
low < 50ug/dL; **adequate** [50-120[ug/dL; **high** ≥120 ug/dL

*According to *The Harriet Lane Handbook*[(47)].

Attachment B

Table 1B – Spearman correlations between CFQ-R domains and age, age at diagnosis, total of physical activity, BMI z-score and fat mass.

Patient domains	Age		Age at diagnosis		Physical Activity		BMI *z-score*		Fat mass	
	Correlation	p-value	Correlation	p-value	Correlation	p-value	Correlation	p-value	Correlation	p-value
Physical	0.111	0.614	0.084	0.702	0.669	**<0.001**	-0.088	0.690	-0.129	0.588
Number of observations	27		27		27		27		20	
Vitality	0.673	0.067	-0.405	0.319	0.323	0.435	-0.099	0.861	-0.037	0.938
Number of observations	8		8		8		8		7	
Emotion	0.421	**0.046**	0.128	0.561	-0.036	0.872	0.313	0.146	0.297	0.204
Number of observations	23		23		23		23		20	
Eating disturbances	0,520	**0.011**	0.163	0.457	0.188	0.390	-0.067	0.762	-0.188	0.427
Number of observations	23		23		23		23		20	
Treatment burden	-0.050	0.821	-0.164	0.455	0.004	0.984	0.181	0.409	-0.071	0.767
Number of observations	23		23		23		23		20	
Health perceptions	0.654	0.079	-0.519	0.187	-0.050	0.907	0.148	0.726	0.302	0.511
Number of observations	8		8		8		8		7	
Social	0.326	0.129	0.129	0.559	0.269	0.215	-0.361	0.090	-0.141	0.553
Number of observations	23		23		23		23		20	
Body image	0.117	0.596	-0.363	0.089	-0.325	0.130	0.331	0.123	0.311	0.182
Number of observations	23		23		23		23		20	
Role	0.711	**0.048**	0.091	0.830	0.223	0.595	-0.254	0.544	-0.371	0.413
Number of observations	8		8		8		8		7	
Weight	0.153	0.718	-0.803	**0.016**	0.228	0.587	0.536	0.171	0.490	0.264
Number of observations	8		8		8		8		7	
Respiratory symptoms	-0.003	0.988	-0.098	0.665	0.239	0.273	-0.076	0.732	-0.326	0.161
Number of observations	23		23		23		23		20	

Digestion symptoms	0.449	**0.031**	0.148	0.501	0.010	0.965	0.186	0.398	0.208	0.378
Number of observations	23		23		23		23		20	
Parent Domains										
Eating disturbances	0.347	0.145	-0.010	0.967	0.322	0.179	0.293	0.325	0.052	0.865
Number of observations	19		19		19		19		13	
Body image	0.030	0.914	-0.220	0.431	-0.090	0.749	0.455	0.089	0.397	0.180
Number of observations	15		15		15		15		13	
Respiratory symptoms	-0.412	0.080	-0.174	0.477	-0.238	0.327	-0.091	0.710	-0.327	0.276
Number of observations	19		19		19		19		13	

Legend – BMI: body mass index.

The values in bold represent statistically significant correlations, with $p<0.05$.

Table 2B. Spearman correlations between CFQ-R domains and total cholesterol, triglycerides, glucose, iron and vitamin D.

Patient domains	**Total cholesterol**		**TG**		**Glucose**		**Iron**		**Vitamin D**	
	Correlation	p-value	Correlation	p-value	Correlation	p-value	Correlation	p-value	Correlation	p-value
Physical	-0.136	0.644	0.107	0.704	0.420	0.105	0.225	0.354	-0.049	0.846
Number of observations	16		17		20		23		21	
Vitality	-0.316	0.604	-0.136	0.797	-0.265	0.612	0.353	0.492	-0.313	0.545
Number of observations	5		6		6		6		6	
Emotion	-0.254	0.382	0.341	0.214	0.187	0.487	-0.098	0.689	-0.374	0.127
Number of observations	14		15		16		19		18	
Eating disturbances	0.139	0.636	0.764	0.085	0.158	0.559	0.397	0.092	-0.216	0.390
Number of observations	14		15		16		19		18	
Treatment burden	0.269	0.352	0.330	0.229	0.081	0.765	0.044	0.857	0.025	0.921
Number of observations	14		15		16		19		18	
Health perceptions	0.158	0.800	0.246	0.638	-0.239	0.648	0.359	0.485	-0.061	0.909
Number of observations	5		6		6		6		6	
Social	-0.211	0.469	-0.523	**0.045**	-0.274	0.305	0.150	0.541	-0.066	0.794
Number of observations	14		15		16		19		18	
Body image	-0.215	0.460	0.248	0.373	0.010	0.970	-0.089	0.716	0.009	0.973
Number of observations	14		15		16		19		18	
Role	0.224	0.718	0.174	0.742	0.169	0.749	-0.101	0.848	-0.189	0.720
Number of observations	5		6		6		6		6	
Weight	-0.316	0.604	-0.016	0.976	-0.339	0.510	0.679	0.138	-0.078	0.883
Number of observations	5		6		6		6		6	
Respiratory symptoms	0.440	0.116	-0.272	0.327	-0.057	0.833	0.577	**0.010**	-0.057	0.821
Number of observations	14		15		16		19		18	

Digestion symptoms	-0.330	0.249	-0.012	0.967	0.148	0.584	0.468	**0.043**	-0.110	0.665
Number of observations	14		15		16		19		18	
Parent Domains										
Eating disturbances	0.087	0.799	0.072	0.833	0.550	**0.042**	0.002	0.094	-0.110	0.697
Number of observations	11		11		14		17		15	
Body image	-0.142	0.716	0.532	0.140	0.339	0.338	0.166	0.588	0.258	0.418
Number of observations	9		9		10		13		12	
Respiratory	0.086	0.801	-0.119	0.728	0.258	0.373	0.358	0.159	0.408	0.131
Number of observations	11		11		14		17		15	

Legend – TG: triglycerides.

The values in bold represent statistically significant correlations, with $p<0.05$.

Table 3B. Association between CFQ-R domains and sex and FEV_1%.

Patient domains	**Sex, median (P25-P75)**			**FEV_1%, median (P25-P75)**		
	Feminine	Masculine	p-value*	<80%	≥80%	p-value*
Physical	83.33 (67.01-100.00)	79.17 (66.67-91.67)	0.829	73.61 (50.00-87.50)	83.33 (71.18-98.61)	0.329
Number of observations	23			22		
Vitality	66.67 (64.59-87.50)	79.17 (58.33-100.00)	0.999	66.67 (66.67-75.00)	66.67 (58.33-100.00)	0.999
Number of observations	8			8		
Emotion	83.33 (75.00-92.09)	73.33 (60.42-91.25)	0.305	89.17 (82.50-95.00)	75.00 (63.54-86.67)	0.059
Number of observations	23			22		
Eating disturbances	100.00 (88.89-100.00)	55.56 (27.78-100.00)	0.224	94.45 (66.67-100.00)	100.00 (38.89-100.00)	0.802
Number of observations	23			22		
Treatment burden	77.78 (63.89-88.89)	88.89 (66.67-100.00)	0.159	83.34 (52.78-91.67)	83.34 (66.67-88.89)	0.914
Number of observations	23			22		
Health perceptions	77.78 (66.67-100.00)	66.67 (55.56-77.78)	0.429	77.78 (77.78-88.89)	66.67 (61.12-88.89)	0.250
Number of observations	8			8		
Social	66.67 (61.90-86.51)	61.00 (53.97-76.19)	0.250	71.43 (54.77-90.28)	66.67 (61.90-79.76)	0.999
Number of observations	23			22		

Body image	94.45 (66.67-100.00)	77.78 (44.45-100.00)	0.250	100.00 (97.22-100.00)	72.23 (66.67-97.22)	**0.013**
Number of observations		23			22	
Role	95.84 (72.92-100.00)	79.17 (58.33-100.00)	0.643	100.00 (66.67-100.00)	91.67 (66.67-100.00)	0.786
Number of observations		8			8	
Weight	83.34 (33.33-100.00)	100.00 (100.00-100.00)	0.429	100 (66.67-100.00)	100.00 (50.00-100.00)	0.999
Number of observations		8			8	
Respiratory symptoms	72.22 (52.78-100.00)	83.33 (75.00-90.28)	0.439	65.28 (33.33-91.67)	83.33 (59.03-97.92)	0.261
Number of observations		23			22	
Digestion symptoms	66.67 (66.67-100.00)	66.67 (66.67-100.00)	0.926	83.34 (25.00-100.00)	66.67 (66.67-100.00)	0.914
Number of observations		23			22	
Parent domains						
Eating disturbances	83.33 (25.00-100.00)	66.67 (25.00-100.00)	0.720	33.33 (16.67-66.67)	83.33 (33.33-100.00)	0.456
Number of observations		19			14	
Body image	72.23 (58.34-77.78)	44.44 (33.33-100.00)	0.779	66.67 (61.12-83.34)	66.67 (33.33-77.78)	0.555
Number of observations		15			14	
Respiratory symptoms	86.11 (66.67-100.00)	88.89 (80.56-94.44)	0.780	83.33 (50.00-91.67)	83.33 (72.22-94.44)	0.885
Number of observations		19			14	

Legend - P25: 25th percentile; P75: 75th percentile; FEV_1%: percentage of predicted forced expiratory volume in one second.
The values in bold represent statistically significant correlations, with $p<0.05$.
*Mann-Whitney test.

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