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Quality of life in cystic fibrosis patients

Qualidade de vida em pacientes com fibrose cística

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ABSTRACT

Introduction: Cystic Fibrosis (CF) is a rare, hereditary, multisystemic, and potentially lethal disease.Currently,with the advancement of medicine and the emergence of new therapies, CF patients are allowed to reach 40 years of age in developed countries. **Objective:** To assess the quality of life (QoL) ofpatients with CF to optimize their multidisciplinary care, based on criteria that impact their well-being. **Material and Methods:** Cross-sectional, prospective, quantitative, and exploratory study. Forty-seven interviews were collected from patients and their parents or legal guardians at a university referral center for CF in Minas Gerais, Brazil. The evaluation method was the Cystic Fibrosis Questionnaire (CFQ), associated with the analysis of the Shwachman-KulczyckiScore (SKS). **Results:** Our data showed that most of the CFQ domains were satisfactory (mean >50) and the SKS had good/excellent values (score >71 points) in all groups. The group of patients older than 14 years had a worse QoL. Moreover, there was a divergence between the response of the 6 to 11 and 12 to 13-year group in comparison with the response of their legal guardians ($p < 0.05$). **Conclusion:** We found satisfactory means in all groups for the weight, digestive, and respiratory domains. However, the social role, vitality, emotional, and social domains had lower and decreasing means according to advancing age, then it would beparamount a multidisciplinary approach focused on these domains that most impact theirQoL. A limitation of research on rare diseases is the small sample, therefore not being possible to generalize the results. However, the analysis is still significant and relevant, demonstrating areas of impact that need to be improved.

Key-words: Cystic Fibrosis; Quality of Life; Psychosocial Impact.

RESUMO

Introdução: A fibrose cística (FC) é uma doença rara, hereditária, multissistêmica e potencialmente letal. Atualmente, com o avanço da medicina e o surgimento de novas terapias, os pacientes com FC podem chegar aos 40 anos de idade em países desenvolvidos. **Objetivo:** Estudar a qualidade de vida dos pacientes com fibrose cística com o intuito de otimizar o atendimento multidisciplinar, baseando-se nos critérios que impactam seu bem-estar geral. **Material e Métodos:** Estudo do tipo transversal, prospectivo, quantitativo e exploratório. Foram coletadas 47 entrevistas de pacientes e de seus responsáveis no centro de referência ao tratamento de fibrose cística de uma instituição pública de nível terciário. O método de avaliação foi o *Cystic Fibrosis Questionnaire* (CFQ), associado à análise do escore de Shwachman (SKS). **Resultados:** Nossos dados evidenciaram a maioria dos domínios do CFQ satisfatórios (média >50) e o SKS com valores bom/excelente (escore >71 pontos) em todos os grupos. O grupo de pacientes com mais de 14 anos apresentou pior QV, e houve uma divergência entre a resposta do grupo de 6 a 11 e 12 a 13 anos em relação à resposta dos seus pais e responsáveis ($p<0,05$). **Conclusão:** Encontramos médias satisfatórias em todos os grupos para os domínios peso, digestivo e respiratório. Porém, os domínios papel social, vitalidade, emocional e social apresentaram médias mais baixas e decrescentes com o avançar da idade, sendo essencial uma abordagem multidisciplinar focada nos domínios que mais impactam a qualidade de vida (QV). Uma limitação de pesquisas sobre doenças raras é a pequena amostra, não podendo, assim, generalizar os resultados. No entanto, a análise é significativa e relevante, demonstrando áreas de impacto e que devem ser aprimoradas.

Palavras-chave: Fibrose Cística; Qualidade de Vida; Impacto Psicossocial.

INTRODUCTION

Cystic Fibrosis (CF) is a rare, hereditary, autosomal recessive, multisystemic, and potentially lethal disease that mainly affects people descended from Caucasianand has no predilection for gender.[1] In the past, most cystic fibrosis patients died in the first year of life.[2] However, with the advancement of medicine and the emergence of new therapies, this perspective has changed. Currently, patients are allowedto reach 40 years of age in developed countries.[3]

Regarding its pathophysiology, CF is characterized by mutations in gene that encodes an iontransport regulatory protein, the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), so that the mucous secretions become thick and viscous, favoring the obstruction of ducts.[2] Thus, alterations are multisystemic and lead to an important limitation,especiallyin the respiratory tract, whosemanifestationsarethe main cause of morbidity and mortality. [4] In this context, patients have moderate or severe pulmonary obstruction, with higher parameter in advancing agegroups.[5]

According to the World Health Organization (WHO), the quality of life (QoL) is the individual's perception of the cultural context in which he/she is inserted, in relation to his/her goals, expectations, standards, and concerns. Therefore, a balance between social, psychological, and physical aspects is necessary, to achieve well-being and utterly physical and mental health.[3]In this sense, Lopes-Pacheco refers that although thelife expectancy of these patients has been increasing, their QoL seems limited, as they are subject to clinical, psychosocial, and economic issues.[6]

With the purpose of reducing the impact of CF symptoms on QoL, cystic fibrosis patients undergo multidisciplinary follow-up, receiving intensive symptomatic treatment through nutritional supplementation, pancreatic enzyme replacement, daily respiratory physiotherapy, and recurrent use of antibiotics and anti-inflammatory drugs, in addition to drugs that contain the rheological characteristics of mucus.[7,8] It is noteworthy that, currently, modulating gene therapies, despite their high cost, have emerged as an effective option for achieving well-being.[9]

Despite the increase in life expectancy of patients with CF over the last decades, QoL measurement in these patients has an utmost importance in order to optimize their multidisciplinary approach, guiding implementation of protocols that approach this condition entirely. Thereby, as a parameter to be used, the Cystic Fibrosis Questionnaire (CFQ) reveals the impact of the disease in the social, psychological, and physical spheres.[11] Furthermore, the Shwachman-Kulczycki Score (SKS) assesses the severity of CF through its clinical, social, nutritional, and radiological conditions.[12]

The current study aims to assess the QoL of patients with CF followed at a university referral center for CF in Minas Gerais, Brazil (RCCF) in a tertiary-level public institution, by means of the CFQ and the SKS analyze as a parameter of severity.

MATERIAL AND METHODS

This study was approved by the Human Ethics Committee of the *Hospital Universitário* of the *Universidade Federal de Juiz de Fora* (UFJF) on June 10, 2020, under approval number 4.080.543 and CAAE registration 31687820.30000.5133.

This is an original study, with a cross-sectional and quantitative design, conducted ata referral center for CF in *Hospital Universitário* of the *Universidade Federal de Juiz de Fora*, Minas Gerais, Brazil. The patients were referred for care at the CF Outpatient Clinic through neonatal screening from either SUS or accredited network.

The (n) sample was defined by intentional non-probabilistic sampling, selecting 28 patients in current attendance at that center. Among the inclusion criteria, patients from 6 years of age, with confirmed diagnosis of CF, literate, and with self-reported ability to answer the data collection instrument, as well as the parents or caregivers of the children from 6 to 13 years of age were invited to participate in the study. Moreover, all of them were under regular follow-up for a period equal to or greater than one year, stable from a respiratory point of view in the last 15 days, with no worsening of cough and secretion, and without using of systemic antibiotic therapy during this period.

The individuals were approached in a standardized manner by a trained researcher and informed in detail about the study, about the guarantee of anonymity, the voluntary nature of the research, and the right to withdraw at any time, in accordance with Resolution n. 466/12 of the National Health Council. Thus, those who voluntarily consented to participate in the study by signing the Informed Consent Forms [*Termo de Consentimento Livre e Esclarecido* (TCLE) or *Termo de Assentimento Livre e Esclarecido* (TALE)]were included. Participants under the age of 18 years received authorization from their parents through *TCLE* or *TALE*. The only exclusion criterion was patients, parents, or legal guardians who were not able to understand the questions or who did not answer the entire questionnaire.

The assessment instrument used was the CFQ, developed and validated in Brazil by Rozovet al[13], and it was applied in a single moment, while the routine medical care was being provided at the Outpatient Clinic. The CFQis structured as follows:

1. Questionnaire for patients aged 6 to 11 years: 5 questions about demography and 35 about QoL.
2. Questionnaire for patients aged 12 to 13

years: 5 questions about demography and 35 about QoL.

3. Questionnaire for patients aged 14 and over: 7 questions about demography, 34 about QoL, 4 about school, work, and activities of daily living, and 12 about difficulties and symptoms.

4. Questionnaire for parents/legal guardians of patients aged 6 to 13: 8 questions about demography, 32 about QoL, and 12 about difficulties and symptoms.

The CFC must be answered according to a Likert-type scale with five points. For each age group there is a specific number of items: 35 items (6 to 11 years old; 6 to 13 years old; and 12 to 13) and 50 items (over 14 years old). Eventually, the answers will be transformed into 12 clinical domains: physical, social role, vitality, emotional, social, image, nutrition, treatment, health, weight, respiratory and digestive, which will be representative of patient's quality of life (QoL) standard. Furthermore, the domain scores are calculated using the simple arithmetic mean, followed by a multiplication between the scores of the facets of the items that make up each domain (the composition of each domain is available in the Supplementary Material). Finally, to facilitate clinical interpretation, the results of the Likert scales will be converted to a scale from 0 to 100 points.[1,14] In this sense, QoL will be considered satisfactory when the domain presents scores above 50 points.[14]

The severity of clinical-radiological condition was also assessed using the Shwachman-Kulczycki Score (SKS), obtained through analysis of patients` electronic medical records, being score ≤40, severe; 41-55, moderate; 56-70, medium; 71-85, good; and 86-100, excellent. [15] For analysis purposes, patients were divided into two groups: excellent/good SKS and medium/moderate/severe SKS. Therefore, the domains were regarded as independent variables and the score calculation as dependent variable. Finally, the variables were described in absolute and relative frequencies and their differences were compared through mean, median, and variability measures (standard deviation, amplitude).

The variables were describedin absolute and relative frequencies and their differences compared by using mean, median and measures of variability (standard deviation and confidence interval).

After transforming the 12 domains that represent QoL into a continuous quantitative metric scale, we assessed the normality of the distribution of each domain using the Kolmogorov-Smirnof test. The goal was to determine which type of statistic should be used, parametric or non-parametric.

For a comparison between measures from 12 domains versus the 4 comparison groups, we used the Kruskal-Wallis H test. The H test is an analogue of the non-parametric analysis of variance used in comparison of three or more independents. It tells us if there is a difference between at least two of them. A test application uses numerical values transformed into ranks and grouped into a single dataset. The level of significance was alpha ≤0.05 for the 95% CI.

The comparison of the correlation between the variables associated with the domains and the SKS was performed using the Spearman Correlation Coefficient (Rho) for variables with asymmetric distribution (not normal), the alpha level was set at $p < 0.05$ for the 95% confidence interval.

Analyzes were performed at STATA 15 (Data Analysis and Statistical Software College Station, Texas, USA).

RESULTS

The population eligible to participate in the study corresponded initially to 50 individuals. The initial sample loss was 2%on account of either not understanding the questionnaire or failing to sign the informed consent form, being automatically excluded. In addition, there was a loss of another 4%. Therefore, 47 interviews were valid, obtained from 28 patients, with a mean age of 9.5±1.9 years in the group from 6 to 11 years (group I); 12.6±0.8 in the group from 12 to 13 years (group II); and 20.2±5.3 in the group over 14 years (group III).

Among patients, most were male, 85.71% (12/14) in group I, 75% (3/4) in group II, and 50% (5/10) in group III. As for parents and legal guardians (group IV), who assessed the QoL of patients aged from 6 to 13 years, 78.95% (15/19) were represented by mothers, 63.16% (12/19) were white, and 57.89% (11/19) were full-time or part-time workers.

The variables transformed into the 12 domains did not show normal distribution in the Kolmogorov-Smirnof test. Table 1 shows the data attribute to the domains of groups I to IV. In group I, the means ranged from 28.4±20.4 for physical domain to 88.9±14.9 for self-image. In group II, they ranged from 26.7±18.6 for physical to 94.2±9.8 for weight. On the other hand, group III had a lower overall QoL, with means ranging from 32.6±8.4 in treatment domain to 64.0±11.3 in nutrition. Finally, in group IV, the means ranged from 34.8±7.5 for vitality to 72.4±10.2 for digestive domain.

It is intriguing that, in 4 domains, vitality, social, image and treatment, parents and guardians reported a qoL divergent and lower than that reported by their children, represented by groups I and II, but it is not possible to affirm between which groups there is a statistically significant difference. We also observed that means of the domains in group IV answers were close to those in group III. Furthermore, when we compared means of the domains between the groups, apart from nutrition, we observed statistically significant differences in all domains ($p<0.05$).

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Regarding SKS, the overall score had a mean of 86.3±20.2. The scores of groups IandIIwere excellent, while group IIIwas classified as good. Table 2 and figure 1 show the correlation between the SKS and the CFC domains.In table 2, weak correlations were observed for Physique (Rho= 0.518), Emotional (Rho= 0.488),Nutrition (Rho= 0.482), Weigth (Rho= 0.476) and Digestive (Rho= 0.434) domains in relation to SKS, which were respectively significant ($p<0.05$).

DISCUSSION

The patients in our sample from the Cystic Fibrosis referral center in *Hospital Universitário* of the *Universidade Federal de Juiz de Fora* presented a good quality of life (QoL) in its clinical-radiological aspect. However, contrary to what was reported by Santana et al[3], the mean age of the oldest group of patients is still low. In our study, the average was 20 years in group III, which is an important fact as it goes against the worldwide trend of increasing life expectancy of patients.[3]

Despite the good overall QoL, group III had the lowest scores in almost all domains, showing a gradual decline in QoL with advancing age. This result has similarities to other research in which the sample population was only comprised of adults with CF.[15,16] This may be due to the progressive worsening of lung function, frequent pulmonary exacerbations, and other clinical complications throughout life, which need to intensify specific treatments.[17,18] However, it is also possible that adult population better understands the questionnaires, or even that the disease perception changes over the years, as each patient is subjected to individual experiences and their current social context.[15]

The same as what is exposed by Cronlyet al[11], respiratory domain was satisfactory in all groups. Thus, effective therapy minimizes symptoms in the airways, as well as reduces bacterial lung infections.[11] Therefore, it can be inferred that controlling the symptoms has a positive impact, since the health self-perception by CF patients is closely related to impairment of respiratory system and lung function, being an important factor for the onset of emotional stress, even stricter treatments, morbidity, and mortality.[1]

However, in relation to treatment domain, the values were lower, being unsatisfactory in group III. In this sense, it is believed that the complexity of therapeutic approaches impacts QoL, since it requires a lot of discipline, dedication, and time from patients and their families, as well as multidisciplinary follow-up.[1] Thus, although the main objective of the treatment is to make the patient live batter and longer, the need of intense daily care has a negative result in general well-being, especially in those who have been living with the disease for a long time.[19]

Furthermore, with age, there is an increase in comorbidities due to CF progression and, consequently, an increase in the treatment burden. Associated with this, the individual goes through a phase of transition from childhood to adulthood, in which new responsibilities and social attributions begin to emerge, which, added to therapeutic commitments, lead to exhaustion to accomplish self-care.[20] Thus, the multidisciplinary team must work to help adolescents in this transition, making it be progressive and natural, so that regular treatment will not have such an impact on QoL.

As the age progresses, there was also lower scores in the social role, emotional, vitality, and self-image domains in our. While life expectancy increases for children and adolescents with CF, worries and apprehension about the future begin to emerge, which can lead to anxiety, anguish, and depression.[11] Therefore, psychic symptoms should be addressed, through increased social support, development of resilience, and cognitive-behavioral therapy interventions.[21] Furthermore, patients should beencouraged to participate in social activities, which will enhance their self-confidence and their sense of vitality.

Hence, our data reaffirm that health self-perception and QoL in CF patients are directly related to age. As children do not have a full understanding of CF seriousness, they tend to be less anxious and more optimistic.[1] Adolescents, nevertheless, suffer from shyness and lack of acceptance of their disease in front of their peers, since they are going through a major psychological and social challenge, in addition to their rapid growth.[12,25] Moreover, the relationship in school environment is sometimes hampered by the lack of coping strategies that help child and their family, oncemisunderstandingofCF is the main cause of distancing from friends and increasing family problems.[22] Adults, on the other hand, also suffer from social changes, especially because of greater independence, entry into the job market and prejudice due to their condition.[11,23] Consequently, it is possible to infer that social and cultural circumstances also reflect on QoLperception among patients throughout life.

Regarding the perception of parents and legal guardians about their children` QoL, our study identified domains with heterogeneous values, in which had unsatisfactory means for social, emotional, treatment, and health domains. In this context, similar to what is suggested by Borawska-Kowalczyk and Sands,[24] the domains that, in short, reflect physical and nutritional patients` conditions had higher averages, while areas related to coping with the disease in the face of individual and family challenges obtained lower averages.[23,24] Thus, it is feasible to conclude that biopsychosocial context of coping, even before the emergence of physical impairments related to the disease, reflects in a worse QoLperception, especially from parents' point of view.[1,11,25-27]

According with CF clinical-radiologicalscore, the

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Table 1: Analysis of domains by groups.

Domains	6 to 11 years (GROUP I)		12 to 13 years (GROUP II)		> 14 years (GROUP III)		Parents or guardians (GROUP IV)		p-value Kruskal-Wallis H test
	Mean ± SD (Median)	CI	Mean ± SD (Median)	CI	Mean ± SD (Median)	CI	Mean ± SD (Median)	CI	
Physique	28.4 ± 20.2 (23.5)	16.7 - 40.8	26.7 ± 18.6 (27.8)	8.0 – 45.5	48.3 ± 11.9 (52.5)	38.7 -56.8	69.6 ± 19.0 (78.4)	60.4 -78.8	0,978
Social role	77.4 ± 14.8 (82.3)	68.8 – 85.9	70,0 ± 9,7 (71,4)	60.1 – 79.8	38.4 ± 6.4 (38.3)	33.8 – 42.9	67.8 ± 15.8 (75.0)	60.2 – 75.4	0,517
Vitality	84.5 ± 15.3 (85.7)	75.6 – 93.3	66,4 ± 25,5 (68,5)	40.6 – 92.1	36.6 ± 4.4 (36.0)	33.4 – 39.8	34.8 ± 7.5 (34.0)	31.2 – 38.4	0,005
Emotional	82.4 ± 11.6 (88.6)	75.7 – 89.1	83,5 ± 17,6 (85,7)	65.8 – 100.3	42.8 ± 7.0 (42.0)	37.7 – 47.8	40.6 ± 6.8 (40.9)	37.3 – 43.9	0,442
Social	74.4 ± 20.3 (75.4)	62.7 – 86.1	75,4 ± 9,7 (78,8)	65.7 – 85.2	42.0 ± 8.2 (44.0)	36.0 – 47.9	37.5 ± 12.2 (40.9)	31.7 – 43.4	0,042
Image	88.9 ± 14.9 (91.4)	80.3 – 97.6	77,1 ± 19,2 (74,3)	57.5 – 96.8	54.6 ± 11.1 (57.0)	46.6 – 62.5	46.9 ± 11.3 (54.5)	41.6 – 52.2	<0,0001
Nutrition	47.0 ± 18.6 (44.6)	36.2 – 57.7	60,0 ± 5,7 (57,1)	54.2 – 65.7	64.0 ± 11.3 (72.0)	55.9 – 72.0	62.4 ± 23.3 (68.2)	51.2 – 73.6	0,021
Treatment	82.4 ± 17.4 (85.7)	72.3 – 92.5	77,1 ± 8,5 (80,0)	59.9 – 94.3	32.6 ± 8.4 (33.6)	26.6 – 38.6	47.4 ± 10.7 (45.4)	42.2 – 52.5	0,002
Health	49.8 ± 19.3 (57.1)	38.6 – 60.9	81,4 ± 9,9 (77,1)	72.8 – 90.0	38.0 ± 7.3 (40.0)	32.7 – 43.3	46.9 ± 11.0 (45.5)	41.6 – 52.2	0,040
Weight	75.9 ± 22.1 (85.7)	63.2 – 88.6	94,2 ± 9,8 (94,2)	84.3 – 100.2	56.0 ± 10.6 (56.0)	38.4 – 63.6	63.5 ± 17.3 (68.2)	55.2 – 71.6	0,005
Respiratory	83.2 ± 19.2 (91.4)	72.1 – 94.4	88,6 ± 14,3 (91,4)	74.1 -100.0	54.2 ± 10.6 (53.1)	44.6 – 61.7	68.3 ± 11.1 (70.4)	62.6 – 73.4	<0,0001
Digestive	84.5 ± 19.5 (85.7)	73.2 – 95.4	85,7 ± 19,7 (85,6)	65.8 – 100.0	61.9 ± 11.6 (64.8)	53.6 –70.42	72.4 ± 10.2 (68.2)	67.5 – 77.4	0,352

Note: SD (standard deviation), CI (95% confidence interval). P: value Kruskal-Wallis H test (alpha value for rank test). It was not possible to make a post roc analysis because of n was <30 in every group.

Table 2: Correlation between domains and the Shwachman-Kulczycki Score (SKS).

Domains	Physique	Social Role	Vitality	Emotional	Social	Image	Nutrition	Treatment	Health	Weight	Respiratory	Digestive
***p-value < 0.05**	*			*			*			*		*
Spearman Rho	0.518	0.243	-0.251	0.488	0.243	0.009	0.482	0.040	0.303	0.476	0.085	0.434
Correlation %	51.8%	24,3%	-25.1%	48.5%		< 0,1%	48.1%	4.0%	30.3%	47.6%	8.5%	43.4%
p-value (CI 95%)	0.0002	0.098	0.087	0.005	0.098	0.639	0.0006	0.788	0.038	0.0007	0.576	0.002

Nota: correlação de Spearman (não aritmética).

mean SKS value was considered good/excellent in our study, influenced by social role andrespiratory domains. Congruently, previous research conducted at Cystic Fibrosis Outpatient Clinic of the *Hospital dasClínicas* from the State University of Campinas (UNICAMP) associates the severity of the disease with reports of QoL in children in social and respiratory domains, but not in adolescents and adults.[1] On the other hand, study carried out by the *Hospital das Clínicas* of the Medical School of the University of São Paulo (USP), with patients aged between 14 and 21 years, has found a significant association between SKS and physical, health, and social role domains.[28] Consequently, we believe that patient's physical condition and lung function, represented by respiratory domain, and perception of their social role represent a bridge between QoL and CF severity, relatively addressed by the SKS.

CONCLUSION

Altogether, we conclude that CF has a direct impact on individual's biopsychosocial context. In this sense, controlling physical symptoms has been crucial for improving QoL, which can be confirmed by satisfactory means in all groups for weight, digestive, and respiratory domains. However, social role, vitality, emotional, and social domains had lower and decreasing means according toolder ages. Therefore, the data reinforce that continuous care must be multidisciplinary, aiming to both clinical stabilization and improvement of patients` mental, psychological, and social well-being, emphasizing the domains that have the greatest impact. Furthermore, interaction between health team and family members can contribute to greater adherence to treatment.

One of the limitations found by researchers was the fact that study development had occurred at the same time as COVID-19 pandemic, as patients with CF are included in the risk group. Another obstacle was the absence of scientific articles which determine the CFQ domains classification for data analysis and interpretation. Therefore, in order to contribute to future national research, we developed supplementary material exposing our way of grouping. Furthermore, the major obstacle in research on rare diseases is the small sample, which makes it impossible for us to generalize the results. However, the analysis is still significant and relevant, demonstrating areas of impact that should be improved, evidencing, for example, the need of a prospective cohort study in this group. Consequently, although the results do not allow generalization, they constitute representative data because this is one of the two Referral Centers for the CF treatment in the interior of Minas Gerais, Brazil.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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