DOI: 10.1590/1809-2950/20006927042020

Respiratory muscle strength and quality of life in children and adolescent with cystic fibrosis

Força muscular respiratória e qualidade de vida em crianças e adolescentes com fibrose cística

Fuerza muscular respiratoria y calidad de vida en niños y adolescentes con fibrosis quística

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ABSTRACT | Cystic fibrosis (CF) is a multisystemic genetic disease characterized by chronic obstruction that, associated with other pulmonary changes, can compromise respiratory muscle strength (RMS) and, consequently, interfere with the performance of typical childhood activities, changing the quality of life(QOL) of this population. The aim of the study was to evaluate the relationship between RMS and QOL of children and adolescents with CF. This is a cross-sectional study, which included patients without acute pulmonary exacerbation, aged between 6 and 14 years, from a reference center in Brazil. Anthropometric and RMS assessments were performed, using maximum inspiratory (MIP) and expiratory (MEP) pressures using digital manovacuometry (Globalmed® MVD300). The Cystic Fibrosis Questionnaire was applied, a specific questionnaire to assess QOL in this disease, in versions for children (QOL-C) and for parents or guardians (QOL-P). The severity of the disease was classified according to the Schwachman Doeurshuk score (ESD). Data on colonization and genotype were consulted through the analysis of medical records. The data was analyzed using the SPSS version 20.0 for Windows software. After the Shapiro-Wilkt test, Pearson's or Spearman's correlation test was applied. Throughout the analysis, a significance level of 5% was adopted. Twenty-eight children (15 boys) participated in the study, with a mean age of 10.10 ± 1.79 years, who had a near-predicted RMS and QOL scores indicating good QOL. The ESD was negatively related to the digestive domain (p=0.03; rho=-0.400). MEP showed a negative correlation with the QOL-P body domain (p=0.002; rho=-0.426) and with the QOL-C treatment domain (p=0.01; rho=-0.453). MIP showed a positive correlation with the physical (p=0.03; rho=0.410), emotional (p=≤0.001; rho=0.573) and treatment (p=≤0.01; rho=-0.605) domains of the QOL-C. MIP also showed a positive correlation with the respiratory domain (p=0.01; rho=0.572) of the QOL-P. In conclusion, an association was identified between QOL and RMS domains, as well as with ESD and nutritional aspects. This sample showed higher than expected RMS values and good QOL.

Keywords | Cystic Fibrosis; Muscle Strength; Quality of Life.

RESUMO | A fibrose cística (FC) é uma doença genética multissistêmica caracterizada por obstrução crônica que, associada a outras alterações pulmonares, pode comprometer a força muscular respiratória (FMR) e, em consequência, interferir no desempenho de atividades típicas da infância, alterando a qualidade de vida (QV) dessa população. O objetivo do estudo foi avaliar a relação entre FMR e QV de crianças e adolescentes com FC. Trata-se de um estudo transversal, que incluiu pacientes com idades entre 6 e 14 anos, provenientes de um centro de referência no Brasil. Realizou-se avaliação antropométrica e da FMR, esta utilizando as pressões inspiratória (PImáx) e expiratória máximas (PEmáx) por meio da manovacuômetria digital (Globalmed® MVD300). Aplicou-se o *Cystic Fibrosis Questionnaire* (QFC), questionário específico para a avaliar a QV nessa doença, nas versões para crianças (QFC-C)

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Financing Source: Contract Term Fapesc nº 2017TR645 – Conflict of interest: nothing to declare – Presentation: Apr. 1st, 2020 – Accepted for publication: May. 15th, 2020.

e para os pais ou responsáveis (QFC-R). A gravidade da doença foi classificada segundo o escore de Schwachman Doeurshuk (ESD). Dados sobre a colonização de bactérias e o genótipo da doença foram consultados por meio da análise dos prontuários. Analisou-se os dados por meio do software SPSS version 20.0 for Windows. Após o teste Shapiro-Wilk, aplicou-se o teste de correlação de Pearson ou Spearman. Em toda a análise foi adotado nível de significância de 5%. Participaram do estudo 28 crianças (15 meninos) com média de idade de 10,10±1,79 anos, as quais apresentaram FMR próxima ao predito e pontuações do QFC indicando boa QV. O ESD relacionou-se negativamente com domínio digestivo (p=0,03; rho=-0,400). A PEmáx apresentou correlação negativa com domínio corpo do QFC-R (p=0,002; rho=-0,426) e com domínio tratamento do QFC-C (p=0,01; rho=-0,453). A PImáx apresentou correlação positiva com os domínios físico (p=0,03; rho=0,410), emocional (p=≤0,001; rho=0,573) e tratamento (p=≤0,01; rho=-0,605) do QFC-C. A PImáx também mostrou correlação positiva com o domínio respiratório (p=0,01; rho=0,572) do QFC-R. Em conclusão, identificou-se associação entre domínios da QV e FMR, bem como com o ESD e aspectos nutricionais. Essa amostra apresentou valores de FMR acima do esperado e boa QV.
Descritores | Fibrose Cística; Força Muscular; Qualidade de Vida.

RESUMEN | La fibrosis quística (FQ) es una enfermedad genética multisistémica caracterizada por una obstrucción crónica que, asociada a otras alteraciones pulmonares, puede comprometer la fuerza de los músculos respiratorios (FMR), lo que en consecuencia interfiere en el desempeño de las actividades típicas de la infancia alterando la calidad de vida (CV) de esta población. El objetivo de este estudio fue evaluar la relación entre la FMR y la CV de niños y adolescentes con FQ. Este es un estudio transversal, en el cual participaron pacientes de entre 6 y 14 años de un centro de referencia en Brasil. Se realizaron evaluaciones antropométricas y de FMR, para esta se utilizó presión inspiratoria máxima (PImáx.) y presión espiratoria máxima (PEmáx.) mediante manovacuometría digital (Globalmed MVD300). Se aplicó el Cuestionario de fibrosis quística (CFC) específico para evaluar la CV en esta enfermedad, en versiones para niños (CFC-N) y para padres o tutores (CFC-T). La clasificación de la gravedad de la enfermedad siguió el puntaje de Schwachman Doeurshuk (ESD). Se consultaron datos sobre la colonización bacteriana y el genotipo de la enfermedad mediante el análisis de historias clínicas. Para el análisis de datos se utilizó el software SPSS versión 20.0 para Windows. Tras la prueba de Shapiro-Wilk, se aplicó la prueba de correlación de Pearson o Spearman. El nivel de significancia que se adoptó fue del 5%. En el estudio participaron 28 niños (15 varones), con promedio de edad de 10,10±1,79 años, que presentaron puntuaciones de FMR cerca al predicho y el puntaje de CFC que indicaba una buena CV. El ESD se relacionó negativamente con el dominio digestivo (p=0,03; rho=-0,400). La PEmáx. presentó una correlación negativa con el dominio cuerpo de CFC-T (p=0,002; rho=-0,426) y con el dominio de tratamiento de CFC-N (p=0,01; rho=-0,453). La PImáx. mostró una correlación positiva con los dominios físico (p=0,03; rho=0,410), emocional (p=≤0,001; rho=0,573) y tratamiento (p=≤0,01; rho=-0,605) del CFC-N. La PImáx. también presentó una correlación positiva con el dominio respiratorio (p=0,01; rho=0,572) del CFC-T. En conclusión, se identificó una asociación entre los dominios CV y FMR, así como el ESD y los aspectos nutricionales. Esta muestra presentó valores de FMR superiores a los esperados y una buena CV.
Palabras clave | Fibrosis Quística; Fuerza Muscular; Calidad de Vida.

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic genetic autosomal recessive disease caused by a mutation in the gene *Cystic Fibrosis Transmembrane Regulator* (CFTR), which compromises the regulator protein of transmembrane conductance, resulting in imbalanced concentrations of chlorine and sodium in the exocrine glands. This is a recessive genetic disorder more common and life-limiting in Caucasian populations. It is characterized mainly by chronic obstructive pulmonary alteration, pancreatic insufficiency and malnutrition[1,2]. Currently, chronic obstructive pulmonary disease is the main cause of morbidity[3]. According to the Brazilian record of cystic fibrosis, in the year 2017, 86% of deaths were caused by respiratory alterations[4].

Obstruction of the airways is caused by excessive production of secretion, increasing chances of chronic inflammation and recurrent infections. As a result, increased resistance of the airways and work of breathing, lung hyperinflation, nutritional deficit, alteration of lung compliance and loss of chest-abdominal balance are

some of the factors which may determine alterations in respiratory muscle strength (RMS)[5,6].

Some studies indicate loss of respiratory pressure[6,7] in CF, attributing this decrease in RMS to compromised ventilatory capacity, possibility of fatigue, intolerance to exercise and daily life activities (DLA)[8,9]. Such physical inactivity, combined with progressive decrease of physical fitness, initiates a vicious cycle in which worsening shortness of breath combines with decreasing physical activity, which eventually reflects in DLA and typical childhood activities, compromising this populations' quality of life (QOL)[10].

Hence, the measuring of QOL and monitoring of RMS are relevant in the evaluation routine of individuals with CF, and essential in monitoring the development of children. Yet, few studies are conducted in the pediatric age range specifically on the association between QOL and RMS. The objective of this study, therefore, was to analyze the relation between RMS and QOL in children and adolescents with CF, and the working hypothesis was that this relation exists in the population studied.

METHODOLOGY

This research consists in an analytic, observational, cross-sectional study including children and adolescents aged between 6 and 14 years with a confirmed diagnosis of CF through the sweat test of genetic testing[11]. It is a convenience sample made up of patients monitored in the CF ambulatory in Joana de Gusmão Children's Hospital, in Florianópolis SC, Brazil, and children and adolescents enrolled in the Santa Catarina State University outreach program "Brincando de Respirar". The project was approved by the Research Ethics Committee of the aforementioned hospital under CAAE record 36493314.8.00005361. All the principles of ethics in research with human beings in resolution 466/122 of the National Health Council were complied with, as well as ethical confidentiality and privacy.

For the sample calculation, the maximal inspiratory pressure (PImáx) and maximal expiratory pressure (PEmáx) data obtained in a pilot study with 10 individuals were analyzed. For this calculation, these data were compared to the values presented in the literature and, considering a difference of 3cmH2O to be detected, a standard deviation of 8cmH2O, a statistical power of 95% with a significance level of 5%, it was estimated that 28 individuals would be sufficient to make up the final sample.

In the study were included children and adolescents with collaborative CF, without musculoskeletal, rheumatic, neurological, visual or hearing disorders, and with no acute respiratory disease at the moment of data collection. Clinical stability[12] was ensured by the low scores in the application of the *Cystic Fibrosis Clinical Score*[13] and *Cystic Fibrosis Foundation Score*[14] at the moment of data collection, which identify the presence of acute lung exacerbation. There were also recorded data on colonization, and the genotypes were consulted through analysis of medical records; as well as the severity of the disease determined by the multidisciplinary team based on the Schwachman Doeurshuk (ESD)[15] score. Individuals would be excluded who could not understand the execution of the test or who showed inability to adequately undertake the proposed evaluation, which did not occur in this study.

Once the participants were selected, initially an anthropometric evaluation was performed using mass measures (Veta SlimWiso model W904i), stature (mounted stadiometer by manufacturer Sanny®) and the calculation of body mass index (BMI)[16]. For evaluation of QOL, the *Cystic Fibrosis Questionnaire* was used, a questionnaire of quality of life in cystic fibrosis (QCF) translated and validated for use in Brazil by Rozov, Cunha, Nascimento, Quittner, Jardim[17]. There are four versions of the QCF: (1) developed for children (QCF-C) with CF aged 6 to 11 years; (2) children aged 12 to 13; (3) individuals aged 14 or older; and (4) for parents or guardians (QCF-G) of patients aged 6 to 13[17]. The questionnaire was applied by age, with the same one being applied by the evaluator to children aged 6 to 11. For participants aged 12 or older, the questionnaire was self-applied[17]. The four versions of the QCF comprise nine domains of QOL, three symptom scales and one item related to health perception: physical, body image, emotional, social/school, social roles, vitality, eating, digestive tract, respiratory, weight and health. The score ranges from 0 to – 100, the highest score representing a better state of QOL[10,17].

Finally, RMS evaluation was done by measuring PImáx and PEmáx with a digital manometer (MDV300, G-MED®, Brazil) in compliance with *American Thoracic Society* and *European Respiratory Society*[18,19] rules. To obtain the PImáx, each child was instructed to exhale to the

residual volume (RV) and to perform a full inhalation up to approximately total lung capacity (TLC). PEmáx was measured from a full inhalation close of TLC followed by a full exhalation close to RV. Both measures were considered acceptable (without air leaks and sustained for 2 seconds) and reproductible when the maximum value varied less than 10% between itself. The highest measurement was recorded[20].

Three to seven maneuvers were performed for each of the PImáx and PEmáx measures, and the values obtained were compared to the ones proposed in the reference equations of the literature. The proposal by Rosa et al.[20] was considered for children aged 6 to 10, and the equations by Domènech-Clar et al.[21] for patients aged 11 or older.

All the data were analyzed using the SSPSS software, version 20.0 for Windows. Data distribution was checked with the Shapiro-Wilk test, then the Wilcoxon test was used to compare the collected RMS values with the ones predicted in the literature. Spearman's (rho) and Pearson's (r) correlation tests were used to check the relation between the variables, considering the magnitude of the correlation as low (r<0.49), moderate (r=0.50 a 0.69), high (r=0.70 a 0.89) or excellent (r>0.90)[22]. Significance of 5% was adopted in all the statistical analysis.

RESULTS

A total of 28 patients participated in the study, of whom 15 were boys. The descriptive characteristics of the sample are shown in Table 1.

Table 1. Characteristics of sample by: age, mass, height, BMI, severity of disease, PImax and PEmax parameters

Variables	Mean±SD or Median (IQ_{25-75})
Age (years)	10.10±1.79
Mass (Kg)	29.55 (25.60 – 31.30)
Height (cm)	137.12±10.74
BMI (Kg/m²)	15.84±1.76
ESD (ponints)	85.00 (80.00 – 90.00)
PImáx (cmH_2O)	-57.50 (-88.75 – -45.25)
Predicted PImáx (cmH_2O)	-61.90±27.46
PEmáx(cmH_2O)	78.29±25.30
Predicted PEmáx (cmH_2O)	82.50±24.06

Kg: Kilograms, cm: centimeters, BMI: Body Mass Index, ESD: Schwachman Doeurshuk Score, PImáx: Maximal Respiratory Pressure, cmH2O: Centimeters of Water, PEmáx: Maximal Expiratory Pressure. The values are shown in mean±SD for the parametric data and median (IQ_{25-75}) for the non-parametric data.

The sample was comprised mostly of eutrophic children (71.43%) and boys (53.57%). Colonization solely by *Pseudomonas aeruginosa* amounted to 26.5% of the sample, as well as by *Staphylococcus aureus*. Combinations of 2 or more pathogens were identified in 17.8% of patients and 25% did not show any colonization. As for genotype, 53.6% of the sample showed mutation ΔF508 heterozygote, 28.6% ΔF508 homozygote, and 17.9% of patients showed other mutations.

The descriptive variables of the QCF-C are shown on Table 2. This group showed scores compatible with good QOL.

Table 2. Descriptive variable scores of Cystic Fibrosis Questionnaire answered by children (QFC-C)

Domains	Mean±SD or Median (IQ_{25-75})
Physical	60.18±24.30
Emotional	70.10±14.40
Social	61.90 (52.38 – 71.42)
Body	66.66 (44.44 – 100.00)
Eating	65.50±25.46
Treatment	88.88 (66.66 – 97.22)
Respiratory	75.00 (50.00 – 91.66)
Digestion	100.00 (66.66 – 100.00)

The values are shown in mean±SD for the parametric data and median (IQ_{25-75}) for the non-parametric data.

The scores of the descriptive values of QCF-C are expressed on Table 3. Scores compatible with good QOL were observed.

Table 3. Descriptive variable scores of Cystic Fibrosis Questionnaire answered by guardians (QFC-G)

Domains	Mean±SD or Median (IQ_{25-75})
Physical	81.48 (68.51 – 95.55)
Schooling	77.77 (66.66 – 88.89)
Vitality	73.33 (66.66 – 80.00)
Emotional	86.66 (61.66 – 93.33)
Bodily	88.88 (66.66 – 100.00)
Eating	64.55±25.32
Treatment	66.66 (58.33 – 88.88)
Health	77.77 (66.66 – 86.10)
Weight	66.66 (33.33 – 66.66)
Respiratory	79.25±17.44
Digestive	72.22 (58.33 – 88.88)

The values are shown in mean±SD for the parametric data and median (IQ_{25-75}) for the non-parametric data.

The Wilcoxon test did not detect differences in the obtained RMS values to those predicted by the literature, for both PImáx (Z=-0.11; p=0.90) and PEmáx (Z=-0.56; p=0.56).

The result of the correlations of QCF-C between RMS is shown in Figure 1. Still regarding the QCF-C, the BMI showed low positive correlation with the domain eating (p=0.02; r=0.434) according to Pearson's test. The domain treatment showed negative correlation with the genotype (p=0.02; rho=-0.418).

The correlations of the QCF-G with RMS and the ESD are shown in Figure 2. In addition, a positive correlation was found of BMI with the physical domain (p=0.04; rho=0.387), and weight (p=≤0.01; rho=0.588) of the QCF-G.

There was low positive correlation between the respiratory domain of the QCF-G and the emotional domain of the QCF-C (p=0.04 and r=0.380) according to Pearson's test.

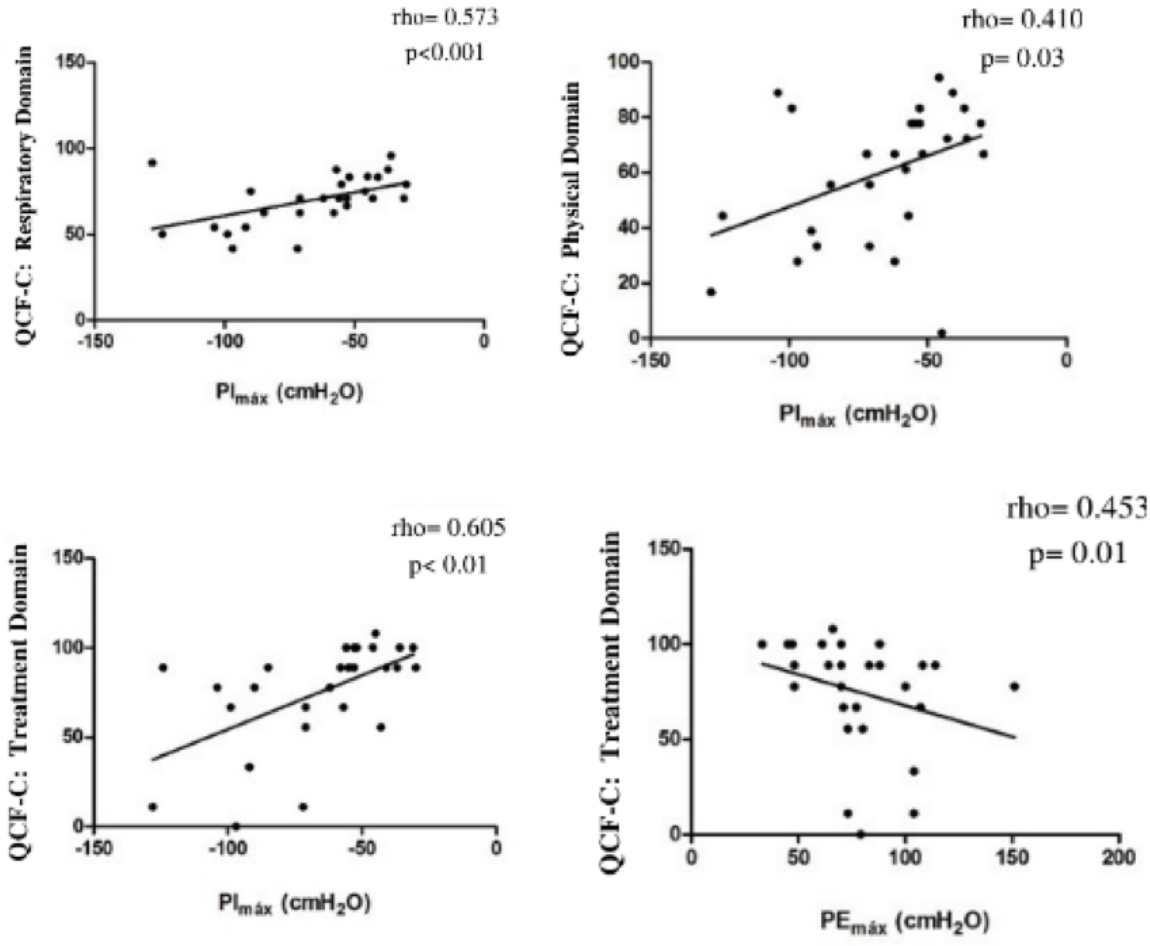

Figure 1. QCF-C dispersion graph with PImáx and PEmáx parameters

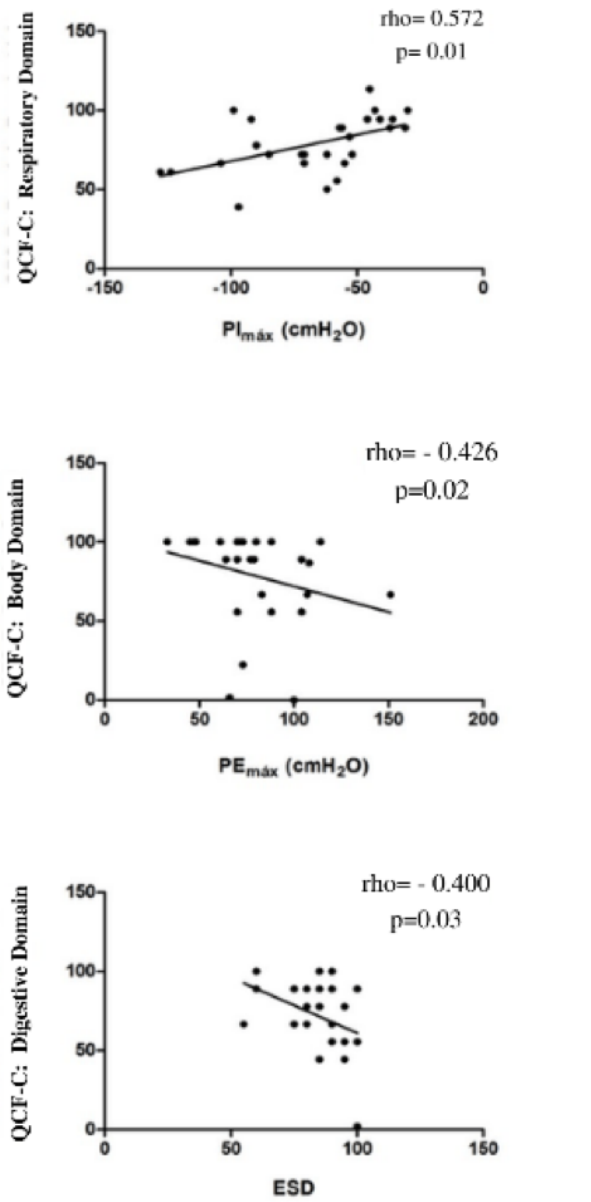

Figure 2. QCF-C dispersion graph with PImáx e PEmáx parameters and ESD

DISCUSSION

The studied sample evaluated exclusively children and adolescents with CF and showed results matching the initial hypothesis, in which the compromising of QOL was associated with RMS. It was found that some QCF domains showed positive correlation with PImáx and other domains showed negative correlation with PEmáx. The participants showed good scores for QOL and RMS values close to the ones established by the literature.

The participants were distributed uniformly by sex and showed good clinical conditions, with ESD scores regarded as excellent and BMI within or close to normal values. The presence of colonization by *Pseudomonas aeruginosa* was identified in only 28.6% of the sample. Such characteristics may have influenced the positive results shown for both QOL and RMS. Similar data were found in a study by Vendrusculo et al.[9], in which children with CF without colonization by *Pseudomonas aeruginosa* showed a higher value of inspiratory muscle strength when compared to healthy children.

The values obtained for PEmáx and PImáx proved close to the ones established by the literature[14,15]. The cohort study by Donadio et al.[4] showed that patients with CF, followed for a period of five years, presented a slight decline in lung function and increased PImáx while functional capacity and PEmáx remained stable[4]. The authors attribute those findings to the increase in the work of breathing caused by the infection and obstruction of airways, which could cause a conditioning effect of respiratory muscles, reflecting in stable or even increased RMS. This analysis, associated to the fact that the sample showed good clinical conditions, could explain the findings of the current research, in which patients presented adequate PImáx and PEmáx values when compared to the predictions.

However, there was no longitudinal following, which may be regarded as a limitation. Nevertheless, the literature indicates diverging results concerning the effects that infections by pathogens may show in RMS. While some studies show that the presence of infection by *Pseudomonas aeruginosa* leads to an increase in the load of the work of breathing, thus exerting a conditioning effect of RMS[6,23,24], other studies[25,26] suggest that the characteristics of the chronic disease, such as malnutrition, recurrent infection and lung hyperinflation, end up limiting and decreasing RMS.

As regards QOL, in the QCF-G there was a good mean of the general score for the evaluated domains, with the exception the domain weight, a result also reported by Vandeleur et al.[27] The good scores found in the QCF-G may be a reflection of the good clinical conditions shown by the evaluated children. This result may also be accounted for by the guardians' perception and acceptance of the disease and the children's physical state, as was reported in the study by Santos et al.[28] The

authors report that the family enters a gradual process of accepting and living with the chronic disease, and in many cases they fail to have a realistic outlook toward the disease and its future consequences[28].

It is known that progressive respiratory disease results in an increased load imposed on the airways, which may compromise efficiency and RMS, contributing to respiratory muscle fatigue and even respiratory failure[25]. The fact that appropriate RMS strength values are obtained may impact on better ventilatory capacity during DLA and physical activity[8,9], which may have positive repercussions on typical childhood activities. With this assumption, the good QOL scores found in this study, particularly in the respiratory and body domains, may indicate how comfortable a patient feels from a respiratory point of view, which creates a sensation of wellness and health. This perception may enable children to better perform their activities, which may reflect on the parents' perception of a child's health.

An inverse relationship was identified between the QOL scores and the PEmáx values, so that the worse the QOL is, larger values are obtained by manovacuometry. This relationship may show those patients' ventilatory demand[6]. Other researchers found similar results[6,9] and suggest that the increase in RMS is due to larger work of breathing previously imposed by the disease, and that this is caused by the obstruction of the airways.

The same inverse relationship was observed between QOL and disease severity detected through the ESD score, so that a more severe disease may reflect in worse QOL. Bodnár et al.[29] evaluated 59 patients and found a moderate correlation between QOL and ESD. According to the authors, ESD may be a useful tool in supplying information not only related to clinical severity of CF, but also as a QOL indicator[29].

This study highlights an interesting association between the emotional domain of the QCF-C and the respiratory domain of the QCF-G, which may indicate that the emotional state of CF patients has an influence on their health condition. Recent studies [25,29,30] found high prevalence of depression and low adhesion to treatment among populations with CF. Knudsen et al.[31] identified a frequency of 32.8% in CF patients with some symptom of depression. Besides, 74.2% showed low adhesion to treatment. Depression symptoms are also associated with poor QOL and higher health costs[31]. Therefore, evaluation and monitoring of QOL in CF patients and their families is relevant. This knowledge enables optimization of therapeutic interventions and signals physical, psychic and social aspects which ought to be continually monitored in those patients.

Another important finding in this study was the presence of positive correlations of PImáx with QOL, showing that, for the population of children studied, adequate respiratory muscle strength has a positive influence on QOL. A recent study by Magnet et al.[23], evaluating adults with chronic infection by *Pseudomonas aeruginosa* found that the reduced efficacy of RMS was associated with a reduction in QOL. The authors then discuss the fact that, in the more advanced stage of the disease, RMS shows interference in QOL and, in this case, of a negative kind.

A limiting factor in this study is due to the low severity of the disease in the individuals evaluated, which may have influenced the results found. Future studies with more severe populations should be conducted in order to analyze the relationship between RMS and QOL in such conditions. In addition, the questionnaires may have been little sensitive in evaluating the QOL of those patients, considering the complexity of the questions and the choice of answers, which may render comprehension difficult for evaluated individuals, particularly children aged 6 to 13.

CONCLUSION

This study has shown that RMS is associated with QOL of children and adolescents with CF. The PImáx values indicate a positive association with QOL, suggesting that: the higher their values, more QOL is shown. Differently, the PEmáx values show an inverse relationship with QOL. A relationship between disease severity and nutritional aspects was also found. In addition, in the studied sample participants showed RMS values above expected and good QOL.

REFERENCES

1. Reyna SL, Holbrook J, Griffiths HHJ, Peckham D, Mcdermott MF. Dysregulated signalling pathways in innate immune cells with cystic fibrosis mutations. Cell Mol Life Sci. 2020;77:4485-503. doi: 10.1007/s00018-020-03540-9
2. Fiorotto R, Strazzabosco M. Cystic fibrosis-related liver diseases: new paradigm for treatment based on pathophysiology. Clin Liver Dis. 2016;8(5):113-6. doi: 10.1002/cld.583

3. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015;16(1):45-56. doi: 10.1038/nrg3849
4. Grupo brasileiro de estudos de fibrose cística. Registro Brasileiro de Fibrose Cística [Internet]. São Paulo: GBEFC, 2017 [cited 2021 Mar 10]. Available from: http://portalgbefc.org.br/ckfinder/userfiles/files/REBRAFC_2017.pdf
5. Leroy S, Perez T, Neviere R, Aguilaniu B, Wallaert B. Determinants of dyspnea and alveolar hypoventilation during exercise in cystic fibrosis: impact of inspiratory muscle endurance. J Cyst Fibros. 2011;10(3):159-65. doi: 10.1016/j.jcf.2010.12.006
6. Donadio MVF, Heinzmann-Filho JP, Vendrusculo FM, Frasson PXH, Marostica PJC. Six-Minute walk test results predict risk of hospitalization for youths with cystic fibrosis: a 5-year follow-up study. J Pediatr. 2017;182:204-9. doi: 10.1016/j.jpeds.2016.11.071
7. Saglam M, Vardar-Yagli N, Savci S. Six minute walk test versus incremental shuttle walk test in cystic fibrosis. Pediatr Int. 2016;58(9):887-93. doi: 10.1111/ped.12919
8. Dassios T, Katelari A, Doudounakis S, Dimitriou G. Aerobic exercise and respiratory muscle strength in patients with cystic fibrosis. Respir Med. 2013;107(5):684-90. doi: 10.1016/j.rmed.2013.01.016
9. Vendrusculo FM, Heinzmann-Filho JP, Piva TC, Marostica PJC, Donadio MVF. Inspiratory muscle strength and endurance in children and adolescents with cystic fibrosis. Respir Care. 2016;61(2):184-91. doi: 10.4187/respcare.04231
10. Cohen MA, Ribeiro MÂGO, Ribeiro AF, Ribeiro JD, Morcillo AM. Avaliação da qualidade de vida de pacientes com fibrose cística por meio do Cystic Fibrosis Questionnaire. J Bras Pneumol. 2011;37(2):184-92. doi: 10.1590/S1806-37132011000200008
11. Athanazio RA, Vicente L, Ferreira R, Ribeiro AF, Riedi CA, Procianoy EFA, et al. Diretrizes brasileiras de diagnóstico e tratamento da fibrose cística. J Bras Pneumol. 2017;43(3):219-45. doi: 10.1590/S1806-37562017000000065
12. Santos CIS, Ribeiro JD, Ribeiro AF, Hessel G. Análise crítica dos escores de avaliação de gravidade da fibrose cística: estado da arte. J Bras Pneumol. 2004;30(3):286-98. doi: 10.1590/S1806-37132004000300016
13. Ramsey B, Boat T. Outcome measures for clinical trials in cystic fibrosis Summary of a Cystic Fibrosis Foundation Consensus Conference. J Pediatr. 1994;124(2):177-92. doi: 10.1016/S0022-3476(94)70301-9
14. Kanga J, Kuhn R, Craigmyle L, Haverstock D, Church D. Cystic fibrosis clinical score: a new scoring system to evaluate acute pulmonary exacerbation. Clin Ther. 1999;21(8):1343-56. doi: 10.1016/S0149-2918(99)80035-6
15. Doershuk CF, Matthews LRW, Tucker AS, Nudelman H, Eddy G, Wise M, et al. A 5 year clinical evaluation of a therapeutic program for patients with cystic fibrosis. J Pediatr. 1964;65(5):677-93. doi: 10.1016/S0022-3476(64)80152-9
16. Biblioteca virtual em saúde. Programa Telessaúde Brasil. Calculadora IMC infantil [Internet]. Brasília (DF): Ministério da Saúde; [modified 2009 Jul 7; cited 2021, Mar 10]. Available from: http://www.telessaudebrasil.org.br/apps/calculadoras
17. Rozov T, Cunha MT, Nascimento O, Quittner AL, Jardim JR. Linguistic validation of cystic fibrosis quality of life questionnaires. J Pediatr. 2006;82(2):151-6. doi: 10.2223/JPED.1463
18. Gibson GJ, Whitelaw W, Siafakas N. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624. doi: 10.1164/rccm.166.4.518
19. Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M, et al. ERS statement on respiratory muscle testing at rest and during exercise. Eur Respir J. 2019;53(6):1801214. doi: 10.1183/13993003.01214-2018
20. Rosa GJ, Morcillo AM, de Assumpção MS, Schivinski CIS. Predictive equations for maximal respiratory pressures of children aged 7-10. Brazilian J Phys Ther. 2017;21(1):30-6. doi: 10.1016/j.bjpt.2016.04.002
21. Domènech-Clar R, López-Andreu JA, Compte-Torrero L, Diego-Damiá D, Macián-Gisbert V, Perpiña-Tordera M, et al. Maximal static respiratory pressures in children and adolescents. Pediatr Pulmonol. 2003;35(2):126-32. doi: 10.1002/ppul.10217
22. Munro BH. Statistical methods for health care research. Philadelphia: Lippincott; 2005.
23. Magnet FS, Callegari J, Dieninghoff D, Spielmanns M, Storre JH, Schmoor C, et al. Impact of *Pseudomonas aeruginosa* infection on respiratory muscle function in adult cystic fibrosis patients. Respiration. 2016;93(1):42-50. doi: 10.1159/000452893
24. Dunnink MA, Doeleman WR, Trappenburg JCA, de Vries WR. Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis. J Cyst Fibros. 2009;8(1):31-6. doi: 10.1016/j.jcf.2008.07.006
25. Dassios TG, Katelari A, Doudounakis S, Dimitriou G. Chronic *Pseudomonas aeruginosa* infection and respiratory muscle impairment in cystic fibros. Respir Care. 2014;59(3):363-70. doi: 10.4187/respcare.02549
26. Hahn A, Ankermann T, Claass A, Mann M, Lindemann H, Neubauer BA. Non-invasive tension time index in relation to severity of disease in children with cystic fibrosis. Pediatr Pulmonol. 2008;43(10):973-81. doi: 10.1002/ppul.20887
27. Vandeleur M, Walter LM, Armstrong DS, Robinson P, Nixon GM, Horne RSC. Quality of life and mood in children with cystic fibrosis: associations with sleep quality. J Cyst Fibros. 2018;17(6):811-20. doi: 10.1016/j.jcf.2017.11.021
28. Santos SMR, Duarte TR, Barroso MD, Jesus MCP. Vivências dos familiares frente à criança com fibrose cística. J Heal Sci. 2017;19(2):89-94. doi: 10.17921/2447-8938.2017v19n2p89-94
29. Bodnár R, Kádár L, Szabó L, Hernádi M, Mikóczi M, Mészáros Á. Health related quality of life of children with chronic respiratory conditions. Adv Clin Exp Med. 2015;24(3):487-95. doi: 10.17219/acem/24991
30. Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of the international depression epidemiological study across nine countries. Thorax. 2014;69(12):1090-7. doi: 10.1136/thoraxjnl-2014-205983
31. Knudsen KB, Pressler T, Mortensen LH, Jarden M, Skov M, Quittner AL, et al. Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis. Springerplus. 2016;5(1). doi: 10.1186/s40064-016-2862-5