Journal of Cystic Fibrosis 20 (2021) 648–654

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

The modified shuttle test as a predictor of risk for hospitalization in youths with cystic fibrosis: A two-year follow-up study

Márcio Vinícius Fagundes Donadio[a,#,*], Fernanda Maria Vendrusculo[a,#], Natália Evangelista Campos[a], Nicolas Acosta Becker[a], Ingrid Silveira de Almeida[a], Karen Caroline Vasconcelos Queiroz[b], Luanna Rodrigues Leite[b], Evanirso Silva Aquino[b]

[a] *Laboratory of Pediatric Physical Activity, Centro Infant, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil*

[b] *Pontifícia Universidade Católica de Minas Gerais (PUCMG), Campus Betim and Hospital Infantil João Paulo II, FHEMIG, Brazil*

ARTICLE INFO

Article history:
Received 30 September 2020
Revised 17 December 2020
Accepted 18 December 2020
Available online 7 January 2021

Keywords:
Exercise tolerance
Field tests
Exacerbation
Hospitalization

ABSTRACT

Background: Patients with cystic fibrosis (CF) present exercise intolerance and episodes of pulmonary exacerbations. This study aimed to evaluate the association of the distance covered on the modified shuttle test (MST), as well as other clinical variables (anthropometry, chronic colonization by *Pseudomonas aeruginosa*, lung function), with the risk of hospitalization for pulmonary exacerbation.

Methods: Cohort study including CF patients older than 6 years, from two specialized CF centers. All patients underwent a MST and a lung function test at the time of inclusion. Demographic, anthropometric and clinical data were collected. Free time until the first hospitalization, total days of hospitalization and use of antibiotics during the two years of follow-up were recorded.

Results: Sixty-seven patients with a mean (SD) age of 12.4 (5.2) years and forced expiratory volume in the first second (FEV_1) of 78.7% (22.4) were included. The mean distance covered (m) in the MST was 775.6 (255.7) (73.4 ± 19.5% of predicted). The distance achieved (MST) was considered as the main independent variable to predict the risk of hospitalization (Cox HR 0.97, $p = 0.029$). Patients who walked a distance of less than 80% of predicted in the MST showed an increase of 3.9 (95%CI 1.0–15.3) in the relative risk for hospitalization and significantly higher total number of days of hospitalization ($p = 0.022$).

Conclusion: There is an association between the distance covered in the MST and the risk of hospitalization in youths with CF. Patients with reduced exercise capacity presented a 3.9 times increase in the relative risk for hospitalization due to pulmonary exacerbation.

1. Introduction

Cystic fibrosis (CF) is a multisystemic disease characterized by progressive decline in lung function and exercise tolerance, with episodes of acute worsening of respiratory symptoms, named pulmonary exacerbations [1]. Although there is no consensus for a single definition, the clinical characteristics of exacerbations include increased cough and sputum production, fever, weight loss, dyspnea, decreased lung function and decreased exercise tolerance [2,3]. Milder events are commonly treated with oral antibiotics (ATB) on an outpatient basis, but hospitalization with the use of intravenous antibiotics is often necessary in several cases [4].

Studies have shown that frequent exacerbations negatively influence quality of life, prognosis and accelerate the decline in lung function, in addition to being associated with increased morbidity and mortality in these patients [5,6]. Recent evidence has shown that functional capacity, as assessed by the six-minute walk test (6MWT), is an independent predictor of the risk for hospitalization due to exacerbation, as patients with CF who walked the shortest distance on the test had a higher risk of hospitalization in the following years [7].

However, despite the fact that the 6MWT is widely used in clinical practice, it is considered a submaximal test and may not

* Corresponding author at: Laboratory of Pediatric Physical Activity, Centro Infant, Av. Ipiranga, 6690, 2° andar, Porto Alegre, Rio Grande do Sul, CEP 90610-000, Brazil.
E-mail address: mdonadio@pucrs.br (M.V.F. Donadio).

# Both authors contributed equally to the manuscript.

https://doi.org/10.1016/j.jcf.2020.12.014
1569-1993/

be sensitive to detect changes in patients with low severity [8]. Thus, the gold standard test for assessing exercise capacity in patients with CF is the cardiopulmonary exercise test (CPET). Studies have shown an association between maximum oxygen consumption (VO_2peak) and both hospitalization due to acute respiratory exacerbations in children with mild to moderately severe CF [9] as well as with the risk of mortality [10], considering that CPET provides additional prognostic information to established predictors of death/lung transplantation [11]. However, CPET is not yet available in many CF centers due to the need for high-cost equipment and highly trained staff. Thus, the modified shuttle test (MST) consists of an alternative, considering that it was previously validated for CF [12,13], presents an incremental load protocol [12] and its main outcome (distance achieved on the test) is strongly correlated with oxygen consumption, as measured through CPET [14].

Therefore, considering the importance of pulmonary exacerbations and hospitalization in patients with CF and the need for low-cost and easy-to-use monitoring alternatives, the objective of this study was to assess the association of exercise capacity, assessed through the distance achieved in the MST, as well as other clinical variables (anthropometry, chronic colonization *Pseudomonas aeruginosa* [PA], lung function), with the risk of hospitalization for pulmonary exacerbation in youths with CF. Our working hypothesis was that a shorter distance achieved in the MST would be associated with a greater risk of hospitalization due to pulmonary exacerbation. Additionally, we have also evaluated if the association of exercise performance and the risk for hospitalization would be distinct between boys and girls.

2. Methods

A prospective cohort study was carried out in patients with CF of both sexes. Inclusion criteria were: (i) diagnosis of CF confirmed by genetic testing, (ii) age above six years old, and (iii) regular follow-up at two specialized CF centers between the years 2016 and 2019. Patients were excluded if signs of hemodynamic instability (altered blood pressure or heart rate responses), exacerbation of respiratory symptoms in the past 30 days (increased cough and expectorated sputum, change in secretion, decreased pulmonary function by more than 10%) and/or osteo-articular or musculoskeletal changes that would interfere in the performance of the tests were found. The study was approved by the Research Ethics Committee of both reference centers, under the numbers 52583416.5.0000.5336 and 54142716.8.3001.5119. All legal guardians and patients over 18 years of age signed an informed consent form and children and adolescents up to 18 years of age signed an assent form.

All patients were submitted to a lung function test and a MST at the time of inclusion (regular clinic visit). In addition, demographic (age and sex) anthropometric (weight, height, body mass index), clinical (chronic colonization by PA) and genetic (genotyping) data were collected. Chronic colonization by PA was defined as the persistent presence of the bacterium in the oropharynx swab or sputum culture for at least six months or in 3 consecutive collections [15]. The patients were followed for a period of two years from the inclusion in the study. At the end of the second year, anthropometric and lung function data were again collected.

The total number of days of hospitalization and use of antibiotics was recorded over the two years of follow-up of the study. Only hospitalizations for acute pulmonary exacerbations were considered. Pulmonary exacerbations were determined according to criteria previously defined by Bilton et al. [16] Free time (days) for the first hospitalization for treatment of pulmonary exacerbation was defined as the average time between the date of inclusion of the patient in the study and the date of the first hospitalization.

Anthropometric data were measured in triplicate. Weight measurement was performed in orthostasis, using a digital scale (G-tech, Glass 1 FW, Rio de Janeiro, Brazil) previously calibrated with an accuracy of 100 gs. Height was obtained with a portable stadiometer (AlturaExata, TBW, São Paulo, Brazil), accurate to 1 mm, and the participants were barefoot [17]. The body mass index (BMI) was calculated and expressed in kg/m^2.

The evaluation of lung function was performed through spirometry using a KOKO spirometer (Louisville, CO, USA), following the criteria established by the American Thoracic Society - European Respiratory Society ATS/ERS [18]. The parameters evaluated were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio and forced expiratory flow between 25 and 75% of FVC ($FEF_{25-75\%}$). The data were presented in absolute values and percentage of predicted based on an international reference equation [19].

The MST used in this study was the one described by Bradley et al. [12], which has 15 levels and patients must walk or run, with increasing speed, in a 10 meter course delimited by two cones. An audio signal, representing the change in level, as well as the increase in the speed, is an integral part of the test. During the first minute of testing, patients were accompanied by a physical therapist to adapt to the rhythm of the audio signal. The test started with an average speed of 0.5 $m{\cdot}sec^{-1}$ (level 1), followed by an increase of 0.17 $m{\cdot}sec^{-1}$ in each next level. The test was concluded when participants reported inability to continue due to exhaustion, failed to reach the cone in the rhythm of the audio signal for 2 consecutive times, reached the maximum distance of 1500 m or presented an oxygen saturation (SpO_2) below 75%. Before the start of the test and immediately at the end, heart rate (HR), SpO_2 (Nonin®, Minneapolis, USA), blood pressure (BIC sphygmomanometer, Itupeva, Brazil) and the modified BORG scale score for dyspnea were measured. In addition, HR and SpO_2 were monitored throughout the test. The distance achieved in the test was calculated by counting the total number of shuttles and expressed in meters and percent of predicted [20]. The VO_2 peak was estimated using the formula VO_2 ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) = 20.301 + 0.019 x MST distance (meters) [14].

2.1. Statistical analysis

The normality of the data was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IR), according to normality. Categorical variables were presented in absolute and relative frequencies. Comparisons of variables between the beginning of the study and after two years were performed with the Student t-test for paired samples. The comparison between patients who covered a distance in the MST $<$80% and $\geq$80% of the predicted was performed using the Mann-Whitney U test. A receiver operating characteristic (ROC) curve was also used and the area under its curve calculated. For the univariate analysis of Cox proportional hazards regression, the dependent variable was the time (days) required for the first hospitalization, measured from the inclusion of patients in the study. The independent variables included in the model were age, BMI, sex (male), chronic colonization by PA, genotyping (F508del homozygous), FEV_1 (%), FVC (%), $FEF_{25-75\%}$ (%) and the distance achieved in the MST (% of predicted). Subsequently, a multivariate analysis of Cox proportional hazards regression was performed, with the time required for the first hospitalization as a dependent variable and including as independent variables those significantly ($p<0.05$) associated with the dependent variable in the univariate model. In addition, age and BMI were also entered in the model, as they are variables considered to be important risk factors in CF. Cox hazard ratio of each variable was determined for free time (days) until the first hos-

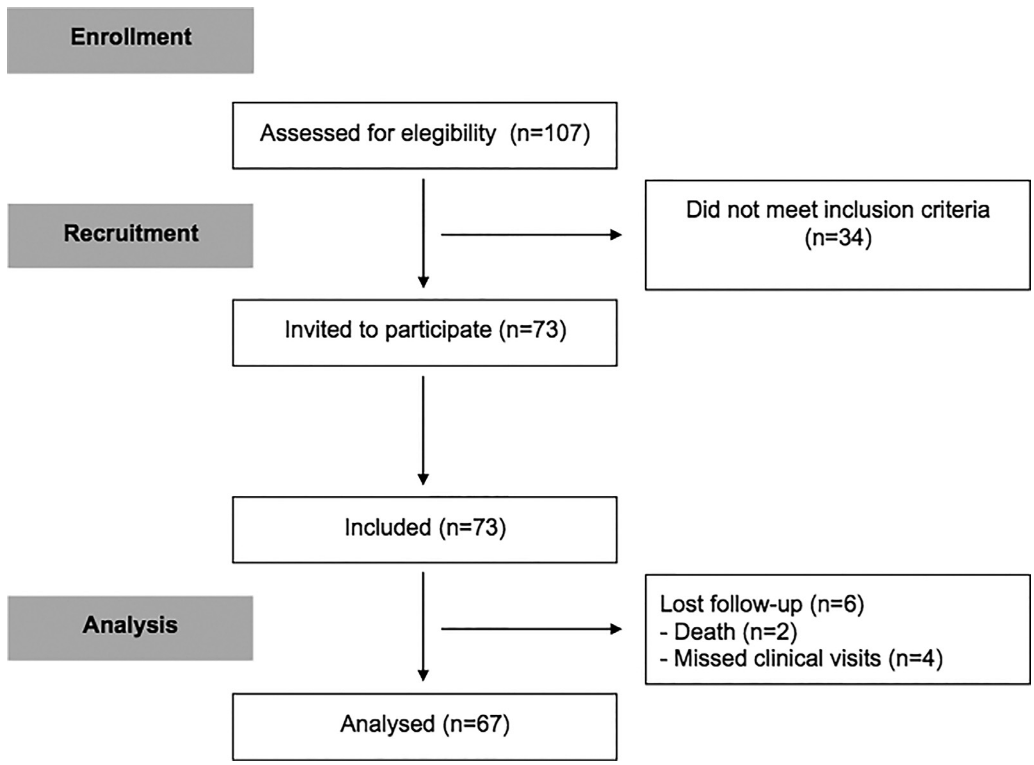

Fig. 1. Flow diagram of study selection.

pitalization. All analyses and data processing were performed in the SPSS version 18.0 (SPSS Inc., USA) and the level of significance adopted was $p<0.05$.

3. Results

Of a total of 107 patients with CF available in both centers, 73 met the eligibility criteria for recruitment and were included in the study. However, 2 (2.7%) patients died during the two-year follow-up and 4 (5.5%) did not attend outpatient consultations during that period. Thus, the analyzes are presented for a total of 67 patients. Fig. 1 shows the study flowchart.

The mean (SD) age at the time of inclusion in the study was 12.4 (5.2) years, 65.7% were male and 58.2% presented a F508del heterozygous mutation. Table 1 shows the characteristics of the sample regarding demographic, anthropometric and clinical information at inclusion in the study and after two years of follow-up. Significant differences were found in the anthropometric and lung function variables.

Regarding exercise capacity evaluated by the MST, the mean (SD) level reached was 10.6 (2.0) and the mean (SD) distance reached was 775.6 (255.7) meters, corresponding to 73.4 (19.5)% of the predicted. In addition, the mean estimated VO_2peak was 35.0 (4.8) $mL \cdot kg^{-1} \cdot min^{-1}$ and the HR at the end of the test was 178.0 (16.5) $beats \cdot min^{-1}$. The physiological variables assessed at rest and at the end of the MST are shown in Table 2.

Of the 67 patients, 58 used antibiotics during the two-year follow-up and 19 required hospitalization during the same period. The median (IR) time to first hospitalization was 232 (53–410) days. Table 3 shows the results of the univariate and multivariate analysis of Cox proportional hazards regression. The variables associated with the risk of a first hospitalization in the univariate analysis were chronic colonization by PA (Cox HR 0.32; $p = 0.022$), FEV_1 in % of predicted (Cox HR 0.95; $p<0.001$), FVC in % of predicted (Cox HR 0.95; $p<0.001$), $FEF_{25-75\%}$ in % of predicted (Cox HR 0.97; $p<0.001$) and the distance achieved in the MST in % of predicted (Cox HR 0.95; $p = 0.001$). As for the multivariate regression model, the only independent variable associated with a greatest risk for the first hospitalization was the distance achieved in the MST in % of predicted (Cox HR 0.97; $p = 0.029$), indicating that patients with worse exercise capacity had higher risk of hospitalization in the follow-up period. In addition, patients who walked a distance in the MST of less than 80% of predicted, had a higher risk of hospitalization during the two years of follow-up (relative risk 3.9; 95%CI 1.0–15.3). In addition, Cox proportional hazards regression was also performed separately for boys and girls (Supplemental File 1). Although significance was not reached, boys with a reduced exercise capacity presented a relative risk for hospitalization of 4.5 (95%CI 0.7 - 31.9) and girls of 3.2 (95%CI 0.4 −23.2).

Fig. 2 shows the comparison of the total days of hospitalization and days of use of ATB according to the percentage of the predicted distance achieved in the MST. Patients who covered a distance of less than 80% in the MST had a significantly higher total days of hospitalization ($p = 0.022$) compared to individuals with a distance ≥80%. A ROC curve was also generated in order to evaluate the performance of the distance achieved (% of the predicted) in the MST on predicting hospitalization (Fig. 3). The results have shown an area under the curve of 0.755 (95%CI 0.627 – 0.884) with a p-value of 0.001.

4. Discussion

The results of the present study showed that there is an association between the distance achieved in the MST and the risk of hospitalization for pulmonary exacerbation in youths with CF. Patients who walked less than 80% of the distance presented 3.9 times more risk of hospitalization during the two-year follow-up period.

The periods of pulmonary exacerbations are frequent in patients with CF and are associated with progression to end-stage

Table 1
Clinical characteristics of the study sample in the follow-up period.

Variables	n = 67		
	Year 1	Year 2	p-value
Demographics			
Age (years)	12.4 ± 5.2		–
Male, n (%)	44 (65.7)		–
Anthropometrics			
Weight (kg)	40.6 ± 16.0	45.3 ± 14.8	**<0.001**
Weight (z-score)	−0.4 ± 1.2	−0.6 ± 1.4	**0.002**
Height (cm)	146.2 ± 17.9	153.9 ± 15.0	**<0.001**
Height (z-score)	−0.3 ± 1.2	−0.4 ± 1.2	0.063
BMI (kg/m^2)	18.2 ± 3.5	18.6 ± 3.2	**0.010**
BMI (z-score)	−0.2 ± 1.1	−0.4 ± 1.2	**0.007**
Airway Colonization			
Chronic Pseudomonas aeruginosa, n (%)	11 (16.2)		–
Staphylococcus aureus, n (%)	48 (70.6)		–
Haemophilus influenzae	6 (8.8)		–
Burkholderia cepacea	3 (4.4)		–
Diabetes			
Yes, n (%)	8 (11.9)		–
Genotyping			
F508del Homozygous, n (%)	16 (23.9)		–
F508del Heterozygous, n (%)	39 (58.2)		–
Other mutations, n (%)	12 (17.9)		–
Pulmonary function			
FEV_1 (% predicted)	78.7 ± 22.4	73.7 ± 25.2	**0.006**
FEV_1 (z-score)	−1.8 ± 1.8	−2.2 ± 2.1	**0.006**
FVC (% predicted)	85.5 ± 19.4	81.6 ± 23.1	**0.023**
FVC (z-score)	−1.3 ± 1.7	−1.6 ± 2.0	**0.018**
FEV_1/FVC (% predicted)	90.8 ± 12.9	88.2 ± 13.1	**0.030**
FEV_1/FVC (z-score)	−1.0 ± 1.5	−1.3 ± 1.4	**0.034**
$FEF_{25-75\%}$ (% predicted)	66.0 ± 31.0	59.0 ± 32.0	**0.008**
$FEF_{25-75\%}$ (z-score)	−1.8 ± 1.7	−2.3 ± 1.9	**0.001**

Results presented as mean and standard deviation, except for gender, chronic airway colonization and genotyping – n (%). p-value refers to the Student t-test for paired samples. BMI: body mass index. FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, $FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity.

Table 2
Physiological responses to the modified shuttle test (MST).

Variables evaluated	n = 67
Resting	
Heart rate (beats·min^{-1})	93.1 ± 14.7
Systolic blood pressure (mmHg)	99.6 ± 14.9
Diastolic blood pressure (mmHg)	62.9 ± 9.5
SpO_2 (%)	96.7 ± 1.9
Breathing frequency (cpm)	20.9 ± 4.3
Borg for dyspnea	0.1 ± 0.3
Peak exercise	
MST level	10.6 ± 2.0
MST distance (m)	775.6 ± 255.7
MST distance (% predicted)	73.4 ± 19.5
VO_2 estimated (mL·kg^{-1}·min^{-1})	35.0 ± 4.8
Heart rate (beats·min^{-1})	178.0 ± 16.5
Systolic blood pressure (mmHg)	119.8 ± 24.9
Diastolic blood pressure (mmHg)	69.0 ± 9.7
SpO_2 (%)	93.7 ± 3.6
Breathing frequency (cpm)	35.8 ± 6.8
Borg for dyspnea	5.7 ± 2.8

MST: modified shuttle test; VO_2: oxygen consumption; SpO_2: peripheral oxygen saturation. cpm: cycles per minute; m: meters; kg: kilograms; mL: milliliters. Values expressed as mean ± standard deviation.

Table 3
Cox regression analysis of factors related to hospitalization.

Variables	Cox hazard ratio	95%CI	p-value
Univariate Cox regression			
Clinical information			
Age	1.04	0.96 - 1.12	0.374
Sex, male	0.87	0.33 - 2.29	0.776
BMI	0.99	0.87 - 1.13	0.935
Chronic Pseudomonas	0.32	0.12 - 0.85	**0.022**
Genotype, F508del homozygous	1.29	0.43 - 3.88	0.654
Pulmonary function,% of predicted			
FEV_1	0.95	0.93 - 0.97	**<0.001**
FVC	0.95	0.92 - 0.97	**<0.001**
$FEF_{25-75\%}$	0.97	0.95 - 0.98	**<0.001**
Modified Shuttle Test,% of predicted			
Distance achieved	0.95	0.92 - 0.98	**0.001**
Multivariate Cox regression			
Age	0.93	0.80 - 1.07	0.296
BMI	1.19	0.95 - 1.49	0.140
Chronic Pseudomonas	0.36	0.12 - 1.10	0.074
FEV_1 (%)	0.97	0.88 - 1.08	0.580
FVC (%)	0.99	0.91 - 1.07	0.750
$FEF_{25-75\%}$ (%)	0.99	0.95 - 1.04	0.649
Distance achieved (%)	0.97	0.94 - 0.99	**0.029**

BMI: body index mass; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of forced vital capacity; CI: confidence interval. Significant hazard ratios appear in bold.

lung disease and increased mortality [21]. The treatment of exacerbations usually consists of increasing the intensity of respiratory physiotherapy, as well as the use of oral or intravenous antibiotics, often requiring hospitalization [22]. Hospitalization leads to school absenteeism and interferes with social and sports activities, causing a negative impact on quality of life and increased costs related to health care [6]. According to data from the CF Foundation registry, in 2019, exacerbations requiring intravenous ATB occurred in 22% of pediatric patients and 41% of adults [23]. Studies that evaluated risk factors for exacerbation have already identified different variables, including low baseline FEV_1, chronic colonization by PA, CF-related *diabetes mellitus*, advanced age, a greater number of ex-

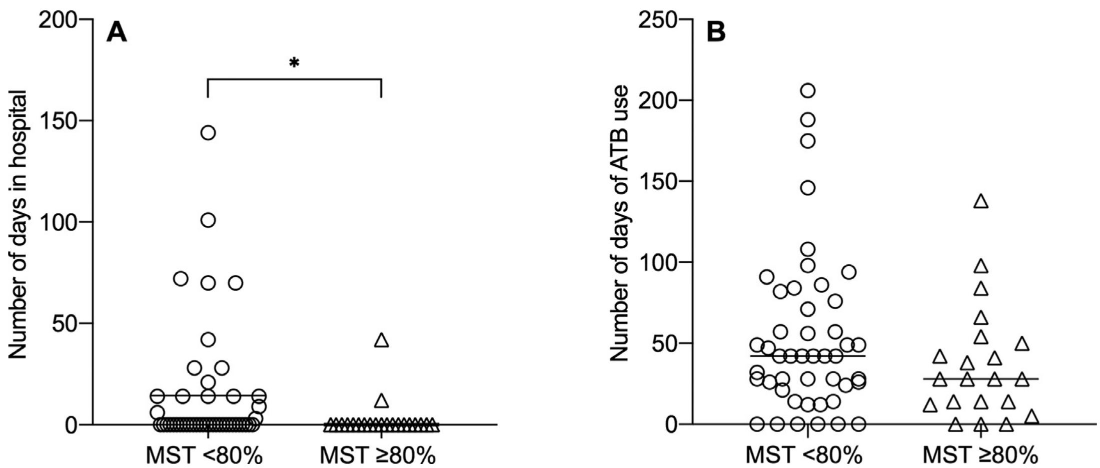

Fig. 2. Comparison of the total number of days in hospital (A) and the total number of days of antibiotics (ATB) use (B) during the two-year follow-up period between patients with the distance achieved in the modified shuttle test (MST) of less than 80% or greater/equal to 80% of predicted values. Each dot/triangle represent a patient. Straight line represents the median. *indicates a significant difference between groups as compared by the Mann-Whitney U test.

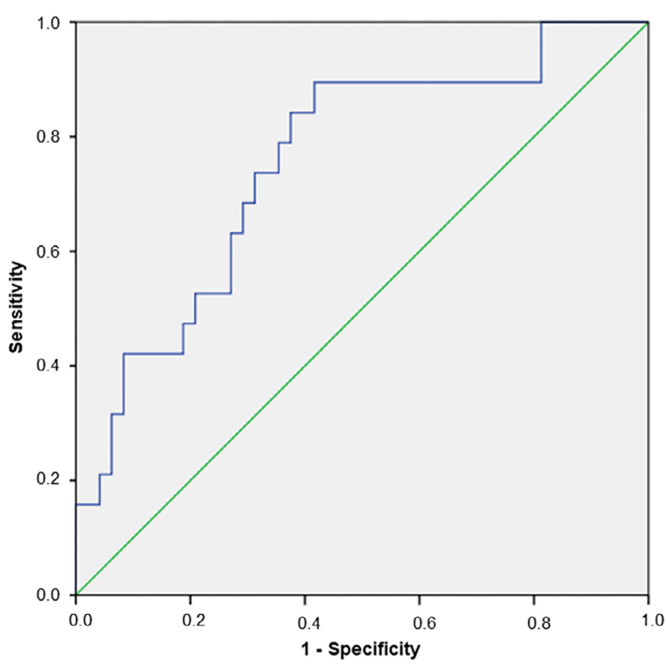

Fig. 3. Receiver operating characteristic (ROC) curve evaluating the performance of the distance achieved (% of the predicted) in the modified shuttle test (MST) on predicting hospitalization.

acerbations in the previous year, among others [24–26]. Our results showed that patients with less exercise capacity, that is, those who achieved a distance of less than 80% in the MST, had a significantly longer total of hospitalization days compared to patients with normal exercise capacity, although no differences in the total days of ATB use were found.

Evidence has already shown that exercise capacity can be an important predictor of morbidity [7,9] and mortality [10] in CF, considering that CPET provides additional prognostic information for death or lung transplantation [11], reinforcing the importance of its periodic assessment in this population. The results of the present study corroborate these findings, considering that the main variables associated with the risk of hospitalization in a univariate analysis were chronic colonization by PA, lung function and the distance achieved in the MST. However, in the multivariate regression model, the distance covered in the MST proved to be the main independent variable to predict the risk of hospitalization for pulmonary exacerbation, supporting the important role of exercise capacity. According to the recommendations for the management of patients with CF, the assessment of exercise capacity must be performed annually, contributing to the identification of possible factors responsible for exercise intolerance and allowing an individualized prescription for the practice of physical exercise [8]. In spite of the association of oxygen consumption levels with survival [10], physical exercise has several benefits for patients with CF, including an improvement in the exercise capacity and quality of life, in addition to a reduction in the number of days of intravenous ATB use [27,28].

Previous studies had already demonstrated an association of both performance in the 6MWT [7] and the VO_2peak [9], measured through CPET, with the risk of hospitalization in children and adolescents with CF. These results are in agreement with those obtained in the present study. However, the 6MWT is a submaximal test and CPET requires high-cost equipment and highly trained staff, reason why it is not yet available in many CF centers. To the best of our knowledge, this is the first study evaluating the MST as a predictor of hospitalization. The MST is a field test, easily-to-perform and considered as maximum test, since an incremental protocol with increasing speed is used, similar to the most common CPET protocols, which takes subjects to levels close to exhaustion [12]. In addition, the use of the MST has already been validated in CF [12,13] and studies have shown a strong correlation of the distance achieved in the MST with the VO_2peak measured through CPET [12–14], making it an alternative for evaluation of exercise capacity in cases where performing CPET is not possible.

Our results have also shown a higher relative risk for hospitalization in boys (4.5) than in girls (3.2) with reduced distance achieved in the MST, although the multivariate analysis showed no association between exercise capacity and hospitalization, when separated by sex. Differences between sexes have been shown in previous CF studies. Kulich et al. [29] demonstrated that the relative risk for survival is significantly lower for females compared to males for all ages from 2 to 20 years and that this gender gap does not narrow over time. In addition, the onset of the progressive decline in lung function tends to occur earlier in girls [30,31], in an effect that may also be related to puberty. The effects of puberty on the influence of exercise capacity on morbidity and mortality should be considered in future studies. Cohort studies have evaluated the rate of fall in FEV_1 in children and adolescents, showing a decrease of 1.0% [32] to 2.4% [33,34] per year. In the present study, patients were followed for a period of two years and showed a decrease in all lung function values, with significant differences between values of year one and year two, showing an annualized FEV_1 drop of 2.5%, despite the recommendation of the best treatment available. Determining the rate of decline in FEV_1 allows a better understanding of the progression of lung disease and allows the identification of factors that can delay, modify or accelerate the trajectory of lung function over time [35].

This study also presents limitations, including the mild impairment of lung function and nutritional status in the population studied, which may have interfered with the need for hospitalization. In addition, the lack of evaluation of habitual activity levels and pubertal status may be considered as a limitations.

5. Conclusion

Our results demonstrate an association of the distance achieved in the MST with the risk of hospitalization in youths with CF. Patients with reduced exercise capacity presented a 3.9 times increase in the relative risk for hospitalization. Considering the importance of hospitalizations in the prognosis of CF and the low cost and ease of application of the MST, the present data support the importance of regular assessment of exercise capacity in the management of patients with CF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors have no conflict of interests to declare.

CRediT authorship contribution statement

Márcio Vinícius Fagundes Donadio: Conceptualization, Formal analysis, Investigation, Supervision, Resources, Funding acquisition, Writing - review & editing. **Fernanda Maria Vendrusculo:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft. **Natália Evangelista Campos:** Methodology, Investigation, Data curation, Writing - review & editing. **Nicolas Acosta Becker:** Methodology, Investigation, Data curation, Writing - review & editing. **Ingrid Silveira de Almeida:** Methodology, Investigation, Data curation, Writing - review & editing. **Karen Caroline Vasconcelos Queiroz:** Methodology, Investigation, Data curation, Writing - review & editing. **Luanna Rodrigues Leite:** Methodology, Investigation, Data curation, Writing - review & editing. **Evanirso Silva Aquino:** Investigation, Resources, Data curation, Supervision, Funding acquisition, Writing - review & editing.

Acknowledgments

The researchers would like to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES – finance code 001), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo à Pesquisa da PUC Minas (FIP 11009-S2) for financial support. ESA would also like to thank Fundação Hospitalar do Estado de Minas Gerais (FHEMIG).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2020.12.014.

References

[1] Waters V, Ratjen F. Pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc 2015;12:S200–6. doi:10.1513/AnnalsATS.201502-098AW.

[2] Rosenfeld M, Emerson J, Williams-Warren J, Pepe M, Smith A, Montgomery AB, et al. Defining a pulmonary exacerbation in cystic fibrosis. J Pediatr 2001;139:359–65. doi:10.1067/mpd.2001.117288.

[3] Heltshe SL, Goss CH, Thompson V, Sagel SD, Sanders DB, Marshall BC, et al. Short-term and long-term response to pulmonary exacerbation treatment in cystic fibrosis. Thorax 2016;71:223–9. doi:10.1136/thoraxjnl-2014-206750.

[4] Goss CH, Burns JL. Exacerbations in cystic fibrosis. 1: epidemiology and pathogenesis. Thorax 2007;62:360–7. doi:10.1136/thx.2006.060889.

[5] Sanders DB, Bittner RCL, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. Am J Respir Crit Care Med 2010;182:627–32. doi:10.1164/rccm.200909-1421OC.

[6] Britto MT, Kotagal UR, Hornung RW, Atherton HD, Tsevat J, Wilmott RW. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest 2002;121:64–72. doi:10.1378/chest.121.1.64.

[7] 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.

[8] Hebestreit H, Arets HGM, Aurora P, Boas S, Cerny F, Hulzebos EHJ, et al. Statement on exercise testing in cystic fibrosis. Respiration 2015;90:332–51. doi:10.1159/000439057.

[9] Pérez M, Groeneveld IF, Santana-Sosa E, Fiuza-Luces C, Gonzalez-Saiz L, Villa-Asensi JR, et al. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. Pediatr Pulmonol 2014;49:641–9. doi:10.1002/ppul.22878.

[10] Vendrusculo FM, Heinzmann-Filho JP, da Silva JS, Perez Ruiz M, Donadio MVF. Peak oxygen uptake and mortality in cystic fibrosis: systematic review and meta-analysis. Respir Care 2019:64. doi:10.4187/respcare.06185.

[11] Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, et al. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. Am J Respir Crit Care Med 2019;199:987–95. doi:10.1164/rccm.201806-1110OC.

[12] Bradley J, Howard J, Wallace E, Elborn S. Validity of a modified shuttle test in adult cystic fibrosis. Thorax 1999;54:437–9. doi:10.1136/thx.54.5.437.

[13] Selvadurai HC, Cooper PJ, Meyers N, Blimkie CJ, Smith L, Mellis CM, et al. Validation of shuttle tests in children with cystic fibrosis. Pediatr Pulmonol 2003;35:133–8. doi:10.1002/ppul.10197.

[14] Vendrusculo FM, Heinzmann-Filho JP, Campos NE, Gheller MF, de Almeida IS, Donadio MVF. Prediction of peak oxygen uptake using the modified shuttle test in children and adolescents with cystic fibrosis. Pediatr Pulmonol 2019;54:386–92. doi:10.1002/ppul.24237.

[15] Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa infection in cystic fibrosis patients. J Cyst Fibros 2003;2:29–34. doi:10.1016/S1569-1993(02)00141-8.

[16] Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. J Cyst Fibros 2011;10(Suppl 2):S79–81. doi:10.1016/S1569-1993(11)60012-X.

[17] Borman H, Ozgür F. A simple instrument to define the Frankfurt horizontal plane for soft-tissue measurements of the face. Plast Reconstr Surg 1998;102:580–1. doi:10.1097/00006534-199808000-00057.

[18] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38. doi:10.1183/09031936.05.00034805.

[19] Quanjer PH, Hall GL, Stanojevic S, Cole TJ, Stocks J. Age- and height-based prediction bias in spirometry reference equations. Eur Respir J 2012;40:190–7. doi:10.1183/09031936.00161011.

[20] Lanza F de C, Zagatto E do P, Silva JC, Selman JPR, Imperatori TBG, Zanatta DJM, et al. Reference Equation for the Incremental Shuttle Walk Test in Children and Adolescents. J Pediatr 2015;167:1057–61. doi:10.1016/j.jpeds.2015.07.068.

[21] Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol 2001;153:345–52. doi:10.1093/aje/153.4.345.

[22] Bhatt JM. Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev 2013;22:205–16. doi:10.1183/09059180.00006512.

[23] 2019 Cystic Fibrosis Foundation Patient Registry Highlights. Bethesda, Maryland. Available from: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/Cystic-Fibrosis-Foundation-Patient-Registry-Highlights.pdf (accessed August 28, 2020).

[24] Jarad NA, Giles K. Risk factors for increased need for intravenous antibiotics for pulmonary exacerbations in adult patients with cystic fibrosis. Chron Respir Dis 2008;5:29–33. doi:10.1177/1479972307085635.

[25] Sequeiros IM, Jarad N. Factors associated with a shorter time until the next pulmonary exacerbation in adult patients with cystic fibrosis. Chron Respir Dis 2012;9:9–16. doi:10.1177/1479972311433575.

[26] VanDevanter DR, Pasta DJ, Konstan MW. Treatment and demographic factors affecting time to next pulmonary exacerbation in cystic fibrosis. J Cyst Fibros 2015;14:763–9. doi:10.1016/j.jcf.2015.02.007.

[27] Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database Syst Rev 2017;2017;. doi:10.1002/14651858.CD002768.pub4.

[28] Urquhart D, Sell Z, Dhouieb E, Bell G, Oliver S, Black R, et al. Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis. Pediatr Pulmonol 2012;47:1235–41. doi:10.1002/ppul.22587.

[29] Kulich M, Rosenfeld M, Goss CH, Wilmott R. Improved survival among young patients with cystic fibrosis. J Pediatr 2003;142:631–6. doi:10.1067/mpd.2003.197.

[30] Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. J Pediatr 1997;131 809–14. doi:10.1016/s0022-3476(97)70025-8.

[31] Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. Am J Epidemiol 1997;145:794–803. doi:10.1093/oxfordjournals.aje.a009172.

[32] Cogen J, Emerson J, Sanders DB, Ren C, Schechter MS, Gibson RL, et al. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. Pediatr Pulmonol 2015;50:763–70. doi:10.1002/ppul.23217.

[33] Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. J Pediatr 2007;151:134–9 139.e1. doi:10.1016/j.jpeds.2007.03.006.

[34] Liou TG, Elkin EP, Pasta DJ, Jacobs JR, Konstan MW, Morgan WJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. J Cyst Fibros 2010;9:250–6. doi:10.1016/J.JCF.2010.04.002.

[35] Harun SN, Hennig S, Wainwright C, Klein K. A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. Paediatr Respir Rev 2016;20:55–66. doi:10.1016/j.prrv.2016.03.002.