Variation in lung function and clinical aspects in adults with cystic fibrosis

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TO THE EDITOR:

An important marker for monitoring disease progression is FEV_1, which is considered the single most important predictor of life expectancy in individuals with cystic fibrosis (CF).[1,2] The coefficient of variation (CoV) for FEV_1 has been studied in individuals with CF to investigate its relationship with treatment adherence, clinical outcomes, exacerbations, and hospitalizations, as well as a predictor of future decline in FEV_1 and of future reduction of functional capacity.[3-5] One study[5] reported that patients who had a variation in $FEV_1 \geq 10\%$ in one year had a worse rate of decline in FEV_1 in the next two years.

The present study aimed to assess the relationship between CoV for FEV_1 and the number of days of hospitalization for adult individuals with CF. Secondarily, the relationship of CoV for FEV_1 with the number of pulmonary exacerbations and performance in the six-minute walk test (6MWT) was also assessed.

This was a retrospective cohort study, conducted under the auspices of the Adult CF Program at the *Hospital de Clínicas de Porto Alegre* (HCPA), in the city of Porto Alegre, Brazil, over a period of one year (from January to December of 2019). Inclusion criteria were individuals ≥ 18 years of age with a confirmed diagnosis of CF, being regularly monitored at the adult CF outpatient clinic at least three times a year and having undergone at least three spirometry tests at three-month intervals.

Clinical and demographic data were extracted from electronic medical records from HCPA. Data on the following variables were recorded at the entry date in the study: BMI, sputum bacteriology, number of exacerbations in the last year, number of hospitalizations in the last year, length of hospital stay (days), 6MWT results, and spirometric parameters. The number of respiratory exacerbations was recorded by determining the number of hospital admissions due to exacerbations and the frequency of oral antibiotic use.

Spirometry was performed in accordance with Brazilian guidelines.[6] The variables compiled were FEV_1, FVC and FEV_1/FVC expressed in liters and percentages of predicted values.[6] The highest and lowest FEV_1 values obtained within the study period were extracted, and CoV was calculated as the ratio of standard deviation to the mean for each subject individually and expressed as a proportion.

The 6MWT was performed at the HCPA Pulmonary Physiology Unit in accordance with international guidelines.[7] The distance walked on the 6MWT (6MWD) was expressed in meters and in percentage of predicted values.[8] The presence of chronic infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Burkholderia cepacia* was recorded. Chronic bacterial infection was defined as three or more positive bacterial isolates during the previous 12 months.

For analysis purposes, subjects were classified into two groups according to CoV for FEV_1: CoV for $FEV_1 < 10\%$ and CoV for $FEV_1 \geq 10\%$. The correlations between CoV for FEV_1 and other variables were analyzed using Spearman's correlation coefficient. Categorical variables were compared between the groups using the chi-square test, and data were expressed as number of cases.

The electronic medical records of 58 patients who attended the HCPA Adult CF Program during the study period were evaluated, and 47 were considered eligible and included in the study. The remaining 11 patients were excluded because of incomplete records. In the final sample, 20 and 27 patients were male and female, respectively, with a median age of 27 years and a mean BMI of 21.3 kg/m^2. Mean FEV_1 was 47% of the predicted value, and mean 6MWD was 81% of the predicted value. The median numbers for exacerbations and hospitalizations within a year were 2 and 1, respectively. Regarding the CoV groups, 28 (59.5%) and 19 (40.5%) of the subjects were allocated to the $FEV_1 \geq 10\%$ and $FEV_1 < 10\%$ groups, respectively. The comparisons between the two groups are shown in Table 1.

There were no statistically significant correlations of CoV for FEV_1 with age at diagnosis and sputum bacteriology. There were statistically significant correlations of CoV for FEV_1 with age ($\rho = -0.358$; $p = 0.013$); BMI ($\rho = -0.423$; $p = 0.003$); total number of exacerbations within a year ($\rho = 0.345$; $p = 0.018$); number of days of oral antibiotic use within a year ($\rho = 0.356$; $p = 0.014$); length of hospital stay in days within a year ($\rho = 0.386$; $p = 0.007$); 6MWD in % of the predicted value ($\rho = -0.359$; $p = 0.013$); and SpO_2 at the end of the 6MWT ($\rho = -0.330$; $p = 0.024$).

In this study, CoV for $FEV_1 \geq 10\%$, in comparison with CoV for $FEV_1 < 10\%$, was related to a greater number of hospitalizations; that is, a greater number of pulmonary exacerbations and a greater number of

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Table 1. General characteristics of adult subjects with cystic fibrosis according to the coefficient of variation for FEV_1.[a,b]

Variable	Overall sample (n = 47)	Group		p
		CoV for FEV_1 ≥ 10% (n = 28)	CoV for FEV_1 < 10% (n = 19)	
Sex, n (%)				0.514
Male	20 (42,5)	13 (46.4)	7 (36.8)	
Female	27 (57.5)	15 (53.5)	12 (63.1)	
Age, years	27 (10)	25 (10)	27.5 (12)	0.185
Age at diagnosis, years	3 (10.8)	3 (8.5)	2 (10.8)	0.752
BMI, kg/m^2	21.3 ± 3	20.4 ± 2.7	22.0 ± 3.1	0.068
Exacerbations/year	2 (3)	4 (3)	2 (3)	0.007
Oral antibiotics, cycles/year	2 (3)	4 (4)	2 (3)	0.003
Oral antibiotics, days/year	35 (37)	42 (51)	21 (28)	0.026
Hospitalizations/year	1 (2)	2 (2)	0 (2)	0.003
Hospitalizations, days/year	15 (38)	27 (30)	0 (24)	0.002
6MWD, m	525 (111)	475 (83)	536 (87)	0.009
6MWD, % predicted	81.2 (15.1)	76.4 (15.3)	84.1 (14.2)	0.018
SpO_2 at the end of the 6MWT, %	94 (4)	93 (10)	95 (5)	0.031
Best spirometric results within a year				
FEV_1, L	1.78 (1.0)	1.47 (0.9)	1.91 (1.5)	0.135
FEV_1, % predicted	46.90 (2.9)	45 (30.2)	48 (33.6)	0.274
FVC, L	2.69 (1.84)	2.05 (1.6)	2.97 (1.7)	0.031
FVC, % predicted	68.6 ± 24.7	63.7 ± 29.6	72.8 ± 20.4	0.220
FEV_1/FVC	68.3 + 12.2	68.7+ 10.6	65.1 + 13.1	0.220
FEV_1/FVC, % predicted	78 ± 14.6	80.3 ± 11.8	75.5 ± 16.2	0.256
Bacteriology, n (%)				
MSSA	32 (68)	13 (46.4)	19 (100)	0.968
MRSA	7 (14.9)	3 (10.7)	4 (21)	0.887
Pseudomonas aeruginosa	32 (68)	15 (53.7)	17 (89.5)	0.188
Burkholderia cepacia	12 (25.5)	5 (17.8)	7 (36.8)	0.919

CoV: coefficient of variation; 6MWD: six-minute walk distance; 6MWT: six-minute walk test; MSSA: methicillin-sensitive *Staphylococcus aureus*; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Values expressed as mean ± SD (normal distribution) or median (IQR) for non-normal distribution, except where otherwise indicated. [b]Only the best spirometric results were used in the calculations.

days of oral or intravenous antibiotic use throughout the year. The findings are in agreement with those of Heinzmman-Filho et al.,[5] who identified a significant relationship between variations in pulmonary function and the number of hospitalizations. Also, there was a relationship between that variation in one year and a higher number of hospitalizations in the two subsequent years.

In general, regular monitoring of pulmonary function in individuals with CF during outpatient visits is essential for establishing early and aggressive treatment of pulmonary exacerbations, seeking to avoid huge variations over time and ensuring greater disease stability.[9] In this context, CoV for FEV_1 presents itself as a valid tool for monitoring the abrupt decline of lung function and progression of the disease in individuals with CF.

The retrospective nature of the present study, the small number of participants, the lack of assessment of adherence to treatment, and the unavailability of other, more sophisticated, tests, such as imaging tests and the lung clearance index, are some of the limitations of the study. Another important limitation is that only FEV_1 was used for the prognostic evaluation of hospitalizations and pulmonary exacerbations.

In conclusion, our findings suggest that a CoV for FEV_1 ≥ 10% over a year is associated with a greater number of exacerbations and hospitalizations in adult individuals with CF. The use of CoV for FEV_1 can benefit the screening and monitoring of disease progression in this population.

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AUTHOR CONTRIBUTIONS

EAS: data collection. DR: study design. PTRD: study design, data analysis, and review of the manuscript. BZ: data collection, study design, data analysis, and review of the manuscript. All authors participated in the literature search, drafting of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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