






Routine spirometry in cystic fibrosis patients: impact on pulmonary exacerbation diagnosis and FEV₁ decline

Carolina Silva Barboza de Aquino¹ , Joaquim Carlos Rodrigues¹ ,
Luiz Vicente Ribeiro Ferreira da Silva-Filho^{1,2} 

1. Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Centro de Pesquisa Experimental, Instituto de Ensino e Pesquisa, Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.

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ABSTRACT

Objective: Pulmonary disease in cystic fibrosis (CF) is characterised by recurrent episodes of pulmonary exacerbations (PEXs), with acute and long-term declines in lung function (FEV₁). The study sought to determine whether routine spirometry increases the frequency of PEX diagnosis, resulting in benefits to long-term pulmonary function. **Methods:** CF patients in the 5- to 18-year age bracket were followed for 1 year, during which they underwent spirometry before every medical visit. The main variables were the frequency of PEX diagnosis and use of antibiotics; the use of spirometry as a criterion for PEX diagnosis (a decline $\geq 10\%$ in baseline FEV₁); and median percent predicted FEV₁ over time. The data were compared with those for the previous 24-month period, when spirometry was performed electively every 6 months. **Results:** The study included 80 CF patients. PEXs were diagnosed in 27.5% of the visits, with a mean frequency of 1.44 PEXs per patient/year in 2014 vs. 0.88 PEXs per patient/year in 2012 ($p = 0.0001$) and 1.15 PEXs per patient/year in 2013 ($p = 0.05$). FEV₁ was used as a diagnostic feature in 83.5% of PEXs. In 21.9% of PEXs, the decision to initiate antibiotics was solely based on an acute decline in FEV₁. The median percent predicted FEV₁ during the follow-up year was 85.7%, being 78.5% in 2013 and 76.8% in 2012 ($p > 0.05$). The median percent predicted FEV₁ remained above 80% during the two years after the study. **Conclusions:** Routine spirometry is associated with higher rates of diagnosis and treatment of PEXs, possibly impacting long-term pulmonary function.

Keywords: Cystic fibrosis; Respiratory function tests; Respiratory tract infections; Spirometry.

INTRODUCTION

Pulmonary disease is the main cause of morbidity and mortality for patients with cystic fibrosis (CF), which is characterised by recurrent episodes of acute worsening of pulmonary symptoms, known as pulmonary exacerbations (PEXs).⁽¹⁻³⁾ The severity of lung disease is assessed by FEV₁, which is a well-documented predictor of mortality^(4,5) and which is used as an outcome in clinical trials^(6,7) and as a parameter to indicate and monitor therapeutic responses,⁽⁸⁾ as well as to refer patients for lung transplantation.⁽⁹⁾ The annual rate of decline in FEV₁ has been used as a predictor of survival and is a robust outcome measure in clinical trials, although it is still underused because of the individual variability of FEV₁ over time.⁽¹⁰⁻¹²⁾

FEV₁ is also routinely used as one of the parameters for diagnosing PEXs, which are established by a combination of clinical features and spirometry results.⁽⁶⁾ PEXs have a major impact on long-term survival, quality of life, and deterioration of lung function.⁽¹³⁾ Roughly a quarter of patients do not recover their baseline lung function after intravenous or oral antibiotic treatment.^(14,15) Despite

their significant role in the progression of lung disease, PEXs are still not fully understood, and a clear definition and well-established criteria for their diagnosis are lacking. This results in discrepancies in the treatment approach to PEXs between many CF centres, increasing the risk of significant pulmonary function decline for the patients.⁽¹⁶⁾ In recent years, some authors have recommended antibiotic therapy for an acute decline in FEV₁ (a decline $\geq 10\%$ in percent predicted FEV₁ at baseline), even in the absence of clinical signs and symptoms.^(17,18) They argue that this approach is associated with a greater likelihood of recovering lung function and has long-term benefits.^(17,18)

Several international CF guidelines recommend routine FEV₁ measurements at all medical encounters,⁽¹⁹⁻²¹⁾ but this practice is not universally adopted for several reasons. In developing countries such as Brazil, there are centres with limited technical and financial resources, which limit the availability of pulmonary function tests. In our CF centre, patients usually undergo medical consultations every 2 months, and spirometry used to be performed every 6 months. The objective of the present study was

Correspondence to:

Carolina Silva Barboza de Aquino. Serviço de Pneumologia Pediátrica, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Avenida Dr. Enéas de Carvalho Aguiar, 647, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-8500 or 55 71 99978-2681. E-mail: aquinocarolina04@yahoo.com.br
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to evaluate the impact that performing spirometry at every encounter has on the frequency of diagnosis of PExs, as well as on long-term pulmonary function.

METHODS

This was a prospective study including CF patients in the 5- to 18-year age bracket followed at the outpatient clinic of our institution. The diagnosis of CF was based on newborn screening or clinical manifestations, in combination with two positive sweat chloride tests (> 60 mmol/L) and/or identification of two pathogenic variants in the *CFTR* gene. The study was approved by the local research ethics committee (CAAE: 28176614.7.0000.0068), and parents or caregivers gave written informed consent. A modified written informed consent was obtained from all of the patients over 7 years of age.

Beginning in January of 2014, all of the CF patients visiting our outpatient clinic underwent spirometry, with the results being immediately available to the attending physician during the consultation. Spirometry was performed with a previously calibrated Koko[®] spirometer (nSpire Health, Inc., Longmont, CO, USA), in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society. Percent predicted FEV₁ values were calculated with the Global Lung Initiative equation.⁽²²⁾ All included patients were followed for 12 consecutive months from the date of entry, and encounters were usually scheduled 2-3 months apart, with unscheduled, urgent visits when necessary. At the end of each encounter, the attending physician completed a questionnaire about whether or not a PEx was diagnosed at the time, whether or not antibiotic therapy was prescribed, and whether or not the pre-consultation spirometry had contributed to the treatment decision. Only the PExs diagnosed during patient encounters were considered for the analyses of frequency, but many patients were seen at unscheduled encounters. The choice of antibiotics was guided by culture, in accordance with the Brazilian guidelines for the diagnosis and treatment of CF.⁽²³⁾

Data collected during the 12-month follow-up period were compared with data for the 24 months prior to the study, during which spirometry was performed at 6-month intervals. To facilitate the description of the outcomes, the 24 months prior to the study were referred to as the years 2012 and 2013, and the follow-up year was referred to as 2014. The data for the 24 months prior to the study were collected from patient medical records. Additionally, FEV₁ values for the years 2015 and 2016 were obtained from the Brazilian CF Patient Registry. The registry contains the best FEV₁ (in L) in a given year and the anthropometric data collected on the same day, allowing the calculation of percent predicted FEV₁ values.

The primary outcome analysed was a diagnosis of PEx, defined as a new prescription of antibiotic therapy for a clinical worsening of respiratory symptoms. A

secondary outcome was the utility of the spirometry results for the diagnosis of PEx, established by the attending physician using as a criterion an FEV₁ decline $\geq 10\%$ with or without worsening pulmonary symptoms indicative of PEx. A tertiary outcome was percent predicted FEV₁ at baseline, defined as the best percent predicted FEV₁ in a given year. Qualitative data are described as absolute and relative frequencies (proportions), whereas quantitative data are summarised as means and standard deviations or medians and interquartile ranges, depending on the pattern of distribution of each variable. A paired t-test and the Wilcoxon signed-rank test were performed to evaluate the contribution of spirometry to the clinical decisions, as well as to compare mean FEV₁ values before and after the intervention. For the comparative analysis of data in the three periods, only patients with historical data were included. Analysis of the three periods was performed in pairs, 95% CIs being included. The probability of making a type I error was set at $p < 0.05$. All analyses were performed with the IBM SPSS statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The study included a total of 80 patients. The mean age was 12.1 years (Figure 1). The characteristics of the patients are displayed in Table 1. During the follow-up, there were 418 encounters and an average of 5.2 consultations per patient/year. PExs were diagnosed in 27.5% of the encounters (115 occasions), at an average frequency of 1.44 PExs per patient/year (Figure 2). This was a significantly higher frequency than that observed in the year 2012 (0.88 PExs/patient/year), but there was a marginal difference in the year 2013 (1.15 PExs/patient/year).

The vast majority of PExs were treated on an outpatient basis with oral antibiotics in 85% of the occasions and inhaled antibiotics in 5% of the cases (with or without oral antibiotics). Hospitalisation for intravenous antibiotics was indicated in 10.4% of the cases. Pulmonary function (FEV₁) was cited by the attending physician as a criterion for the diagnosis of PEx in 83.5% of the cases. In 21.9% of the cases diagnosed with a PEx, the decision to initiate antibiotic therapy was exclusively defined by the acute decline in FEV₁ (Figure 3). Furthermore, in approximately 9% of the occasions, physicians reported that spirometry contributed to excluding an episode of PEx.

The median percent predicted FEV₁ was 85.7% (IQR: 54.7-102.7) during the follow-up period. The value was considerably higher than that for the 24 months prior to the study (76.9% [IQR: 57.6-95.2] for 2012 and 78.5% [IQR: 54.0-101.2] for 2013), but the difference was not statistically significant (Figure 4). When the data from the years 2015 and 2016 were included in the analysis, we observed a steady linear decline of approximately 2% per year in median percent predicted FEV₁ values during the

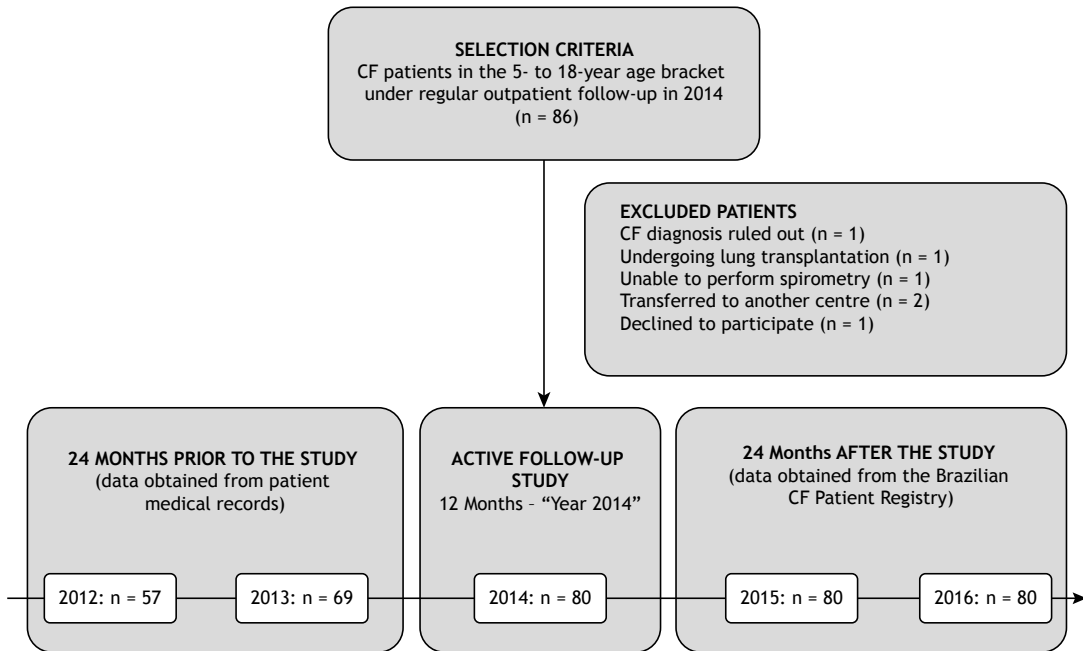


Figure 1. Study design. The study was completed in October of 2015, at which time the last patient to be included in the analysis completed 12 months of follow-up. CF: cystic fibrosis.

Table 1. Baseline characteristics of the study population (N = 80).^a

Characteristic	Result
Sex	
Female	31 (38.7)
Male	49 (61.3)
Age, years	12.13 ± 3.43
Age at diagnosis, years	2.60 ± 3.71
Genotype	
F508del heterozygote	30 (40.5)
F508del homozygote	32 (43.3)
Other	12 (16.2)
Pancreatic insufficiency	80 (100)
BMI, kg/m ²	17.38 ± 3.64
Shwachman-Kulczycki score	73.4 ± 14.7
Microbiology	
<i>Staphylococcus aureus</i>	67 (84.8)
MRSA	16 (20.2)
<i>Pseudomonas aeruginosa</i>	37 (46.8)
Chronic medication use	
Dornase alfa	71 (89.9)
Inhaled tobramycin	33 (41.8)
Hypertonic saline	29 (36.7)
Azithromycin	30 (39.2)
CFTR modulators	0
FEV ₁ , % predicted	
≥ 90 (normal)	32 (40)
70-89 (normal/mild)	21 (26.3)
40-69 (moderate)	18 (22.5)
< 40 (severe)	9 (11.2)

MRSA: methicillin-resistant *Staphylococcus aureus*; and CFTR: cystic fibrosis transmembrane conductance regulator. ^aValues expressed as n (%) or mean ± SD.

follow-up period. However, they remained above 80% in the years following the study (Figure 4).

DISCUSSION

This study shows that performing spirometry at each encounter has a significant impact on the diagnosis of PExs during the outpatient management of CF patients. Spirometry was also associated with a meaningful increase in lung function. These findings reinforce the recommendations of several guidelines that spirometry be performed at each patient encounter and also indicate that recognising and treating PExs more often results in better lung function for CF patients.

An FEV₁ decline ≥ 10% was identified in 83.5% of PExs, and this finding was frequently used for the clinical decision to start antibiotics. Hence, a tendency was observed to diagnose more PExs and thus to prescribe more courses of antibiotics in comparison with the years prior to the study. Although there is still no clear definition of a PEx, the most used criterion⁽⁶⁾ requires that a decline ≥ 10% in baseline FEV₁ be associated with another 3 out of 11 clinical features to establish a PEx diagnosis.⁽⁶⁾ Currently, there is still much controversy regarding the definition of PEx.⁽¹⁶⁾ Most definitions usually involve a medical decision to start a new course of antibiotics guided by worsening of the respiratory disease, as evidenced by intensification or new pulmonary signs and symptoms. Nevertheless, it is clear that FEV₁ measurements are very important.^(16,23)

Frequent measurement of FEV₁ is vital to monitor its variations and to assess the severity of pulmonary disease in CF. Morgan et al.⁽²⁴⁾ showed that baseline FEV₁ variability is a predictor of subsequent declines in lung function at all stages of the disease. They concluded that quantification of FEV₁ changes is

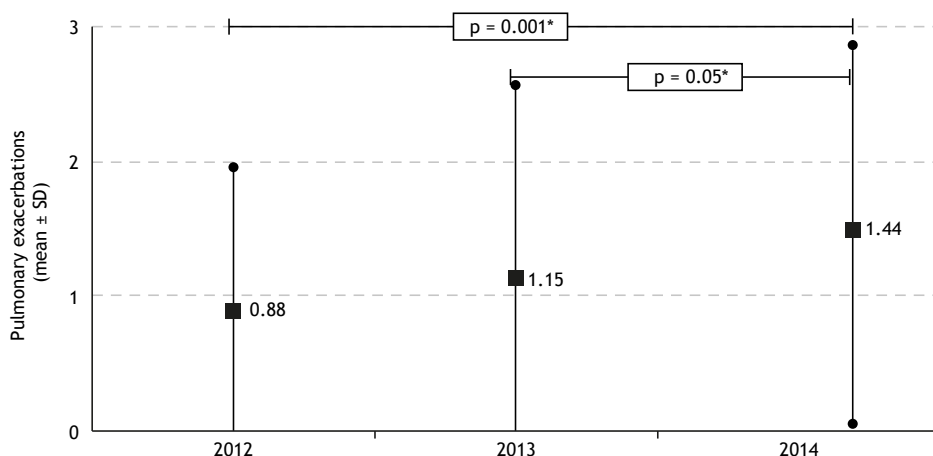


Figure 2. Frequency of pulmonary exacerbations in the study population (N = 80), expressed as the mean ± SD of pulmonary exacerbations per patient/year during the follow-up period and the two previous years. *Wilcoxon signed-rank test.

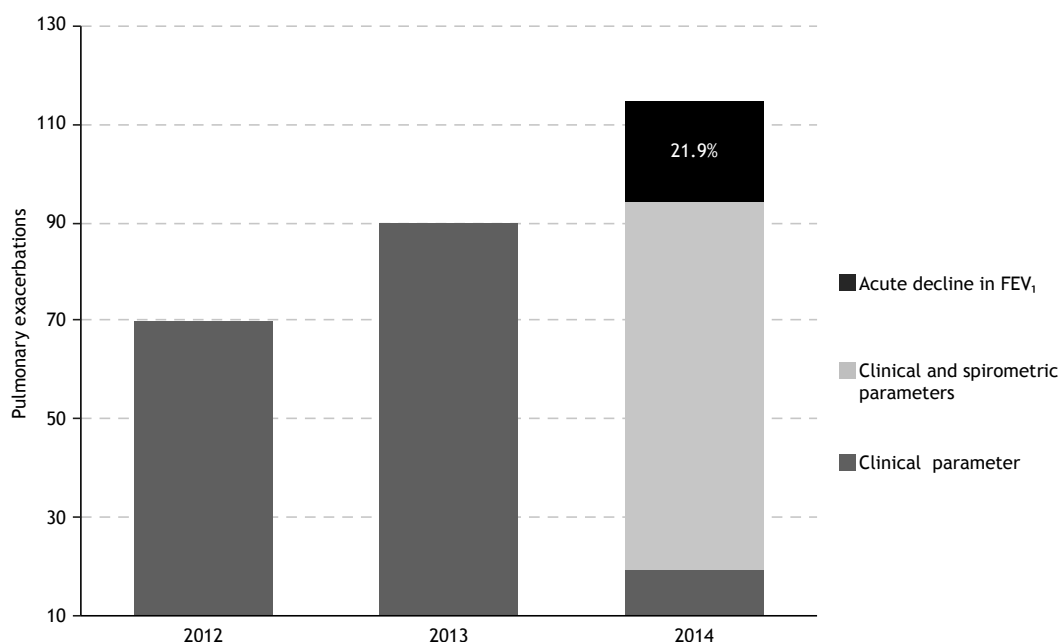


Figure 3. Absolute frequency of pulmonary exacerbation diagnosis in the study population (N = 80) in the years 2012, 2013, and 2014. The year 2014 displays the criteria used in order to diagnose pulmonary exacerbations.

important for identifying patients with a greater risk of decline in lung function.⁽²⁴⁾ Additionally, there are data suggesting that patients with higher baseline FEV₁ have a higher risk of FEV₁ decline over time,⁽¹⁷⁾ which may be due to the fact that they receive fewer therapeutic interventions when facing a decline in their FEV₁ (such as antibiotics and hospitalisations).⁽²⁵⁾ The current study showed that 21.9% of PEx diagnoses were recognised exclusively by the acute decline in FEV₁ in the absence of other signs and symptoms of worsening pulmonary disease.

A significant increase in the diagnosis of PEx was observed in the current study as a result of frequent FEV₁ measurements. However, other studies have shown that doctors do not treat all episodes of FEV₁

decline, even when they occur at a rate $\geq 10\%$.⁽²³⁾ In a retrospective analysis of data from an epidemiologic study of CF,⁽²⁶⁾ Wagener et al.⁽²³⁾ showed that 29.3% of patients with an acute decline in FEV₁ $\geq 10\%$ were not treated with antibiotics, particularly if they had not been admitted for intravenous treatment for PEx in the previous year. This may result in a significant decline in lung function over time because half of the functional declines seen in CF patients are associated with the occurrence of PExs.⁽¹⁶⁾ A higher frequency of PExs and a shorter interval between them are associated with a greater decline in FEV₁, especially if the interval between PExs is less than 6 months.⁽¹³⁾

Most of the PExs identified in the present study had a mild to moderate presentation characterised by a

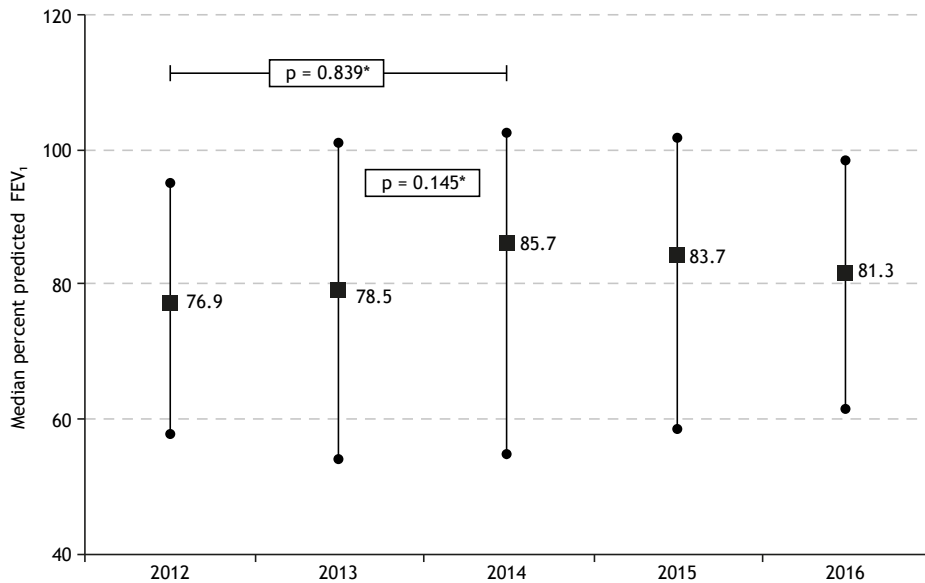


Figure 4. Median percent predicted FEV₁ values (IQR) during the study period. Data for the years 2015 and 2016 were obtained from the Brazilian Cystic Fibrosis Patient Registry. *Wilcoxon signed-rank test.

higher proportion of oral antibiotic use (85%), with only 10% of patients requiring hospitalisation for intravenous antibiotics. Although these events appeared to have a minor impact, most of the orally treated patients with PExs exhibited a decline in FEV₁. This could indicate a slow or long-term decline and a lack of perception. Recent data indicate that even orally treated PExs may have a significant impact on lung function decline, even in patients without a significant decline in FEV₁ at the time of the PEx diagnosis.⁽¹⁵⁾ There are still controversies in establishing a patient's baseline FEV₁ and defining how much recovery is expected following the treatment of a PEx. Nevertheless, it is reasonable to suggest that it is more detrimental to fail to diagnose and treat a PEx than to overtreat patients for an incorrect diagnosis.⁽¹⁶⁾

This study has several limitations. The study was not randomised, and we did not assess FEV₁ variations over time as an outcome measure or other aspects that could impact lung function decline, such as microbiological colonisation and adherence to treatment. Patients who had more advanced lung disease and who experienced frequent and prolonged hospitalisations were not included, because they had few outpatient consultations. The FEV₁ data for the years 2015 and 2016 were not obtained during regular consultations, being instead obtained from the Brazilian CF Patient Registry. In addition, a longer follow-up would be necessary to determine the annual rate of decline in FEV₁ and to identify additional risk factors. A possible bias is a change in behaviour of attending physicians facing more frequent lung function data. On the other hand, this was a real-life study, and the results were so impressive for our practice that spirometry was definitely incorporated into the

routine of CF outpatient consultations, providing data for future studies.

The hypothesis that earlier diagnosis and more frequent treatment of PExs are associated with improved lung function in CF patients seems to be very likely. The median percent predicted FEV₁ increased from 78.5% to 85.7% during the follow-up period. Although this difference was not statistically significant, the improvement was sustained in the following years in which the pre-consultation spirometry protocol was maintained, with a median percent predicted FEV₁ above 80%.

New data stemming from the use of technological resources such as electronic home monitoring suggest that serial measurements of FEV₁ can improve the ability to detect a PEx at home, with high sensitivity and specificity.⁽²⁷⁾ Furthermore, in a recent study, Schechter et al. reported the promising results of a standardised approach to recognising and treating PExs as early as possible.⁽²⁸⁾ The approach emphasised frequent measurements of FEV₁, being very sensitive and consistent with regard to intervention, which is triggered by changes as small as 5% in percent predicted FEV₁. They reported a significant and marked improvement in lung function, with mean percent predicted FEV₁ values increasing from 87% to 98% in 5 years.⁽²⁸⁾

In conclusion, the present study demonstrated that performing spirometry in CF patients during routine visits resulted in a significant increase in the frequency of PEx diagnosis and treatment. The impact of such a simple initiative can be substantial and even more relevant in countries such as Brazil, with reduced treatment resources and financial constraints. Further

studies could be of value to identify other aspects that impact lung function in CF patients in Brazil.

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AUTHOR CONTRIBUTIONS

CSBA, JCR, and LVRFSF: conception and planning of the study. CSBA and LVRFSF: drafting and revision of the manuscript. LVRFSF: approval of the final version.

CONFLICT OF INTEREST

None declared.

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