Factors associated with malnutrition in adolescent and adult patients with cystic fibrosis

Gabriela Cristofoli Barni[1], Gabriele Carra Forte[1], Luis Felipe Forgiarini[1,2], Claudine Lacerda de Oliveira Abrahão[3], Paulo de Tarso Roth Dalcin[1,4]

1. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Laboratório de Vias Aéreas e Pulmão, Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
3. Serviço de Nutrição, Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
4. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

Submitted: 27 October 2016.
Accepted: 26 February 2017.

Study carried out at the Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To determine the prevalence of malnutrition in patients attending an adult cystic fibrosis (CF) program and to investigate the associations of malnutrition with the clinical characteristics of those patients. **Methods:** This was a cross-sectional study involving patients with clinically stable CF patients (16 years of age or older). The patients underwent clinical assessment, nutritional assessments, pulmonary function tests, and pancreatic function assessment. They also completed a questionnaire regarding diet compliance. On the basis of their nutritional status, the patients were classified divided into three groups: adequate nutrition; at nutritional risk; and malnutrition. **Results:** The study has included 73 patients (mean age, 25.6 ± 7.3 years), 40 of whom (54.8%) were female. The mean body mass index was 21.0 ± 3.0 kg/m^2 and the mean FEV_1 was 59.7 ± 30.6% of predicted. In this sample of patients, 32 (43.8%), 23 (31.5%), and 18 (24.7%) of the patients were allocated to the adequate nutrition, nutritional risk, and malnutrition groups, respectively. The logistic regression analysis identified three independent factors associated with the risk of malnutrition: Shwachman-Kulczycki score, percent predicted FEV_1; and age. **Conclusions:** Malnutrition remains a common complication in adolescents and adults with CF, despite dietary advice. Malnutrition is associated with age, clinical severity, and lung function impairment.

Keywords: Cystic fibrosis; Malnutrition; Exocrine pancreatic insufficiency; Respiratory function tests.

INTRODUCTION

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease in caucasians, and it is caused by the absence or dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Mutations in the *CFTR* gene are known to alter the airway and the intestinal microenvironment.[1,2] This protein is expressed as a chloride channel in the apical membrane of airway cells, as well as in intestine, liver, and reproductive tissues; it affects exocrine pancreatic function and sweat ducts. The CFTR protein regulates and participates in the electrolyte transport across the membranes of those cells. Thus, its absence or partial functioning is related to the pathophysiology of CF.[3,4]

The clinical manifestations of the disease result from an increased viscosity of secretions, which leads to the obstruction of ductal epithelial cells. The classic phenotype of the CF, or mucoviscidosis, is characterized by pulmonary infections, pancreatic insufficiency, malabsorption of nutrients, liver disease, male infertility, and loss of sweat electrolytes.[5]

In recent years, medical and technological advances have increased the mean survival rates worldwide, primarily through the early diagnosis of CF, input of experts, better treatments, and organ transplantations. Nearly half of the CF population is ≥ 18 years of age.[5]

The clinical course of CF and the quality of life of the patients are directly affected by their nutritional status, and malnutrition is one of the most serious and difficult challenges in CF treatment.[6] Malnutrition results from a discrepancy between energy/nutrient requirements and food intake, which can be caused by malabsorption.[7]

Malnutrition and lung disease are inextricably woven together in CF. Studies have shown that lung function decline and malnutrition are related and are dependent factors. The occurrence of malnutrition is associated with reductions in lung function and survival. Chronic pulmonary infections and decreased lung function result in increased calorie needs and reduced appetite, which worsen the nutritional status of CF patients.[8,9] There is a growing body of literature looking at malnutrition and CF; however, those studies are mostly related to pediatric patients.[10,11]

The aims of the present study were to determine the prevalence of malnutrition in patients attending an adult CF program and to investigate the associations of malnutrition with the clinical characteristics of those patients.

METHODS

Study design

This was a single-center, cross-sectional study of prospectively collected data, and it was approved by the Research Ethics Committee of the *Hospital de Clínicas* de Porto Alegre, located in the city of Porto Alegre, Brazil. All of the subjects gave written informed consent.

Population

The study included patients with CF who were 16 years of age or older. We included only CF patients who had been diagnosed on the basis of consensus criteria.[12] All patients had to be clinically stable in order to be included in the study, clinical stability being defined as no current changes in medications and no use of i.v. or p.o. antibiotics due to pulmonary exacerbations in the last 30 days. Patients were excluded if they declined to participate in the study, did not meet the inclusion criteria, or were pregnant.

Clinical variables

The following data were recorded: age, gender, ethnicity, presence of the F508del mutation (homozygous, heterozygous, or other mutations), presence of diabetes mellitus, and a liver score (normal or abnormal).[13]

Nutritional evaluation

Nutritional status was assessed using the body mass index (BMI) and its percentile. BMI was calculated from the ratio weight/height^2 (kg/m^2). Patients younger than 20 years of age had their BMI percentile calculated. On the basis of their nutritional status, the patients were divided into three groups: adequate nutrition (AN): BMI > 22 kg/m^2 for women and BMI > 23 kg/m^2 for men (for patients ≥ 20 years of age) or BMI percentile > 25 (for patients < 20 years of age); at nutritional risk (NR): BMI = 19-22 kg/m^2 for women and 19-23 kg/m^2 for men (for patients ≥ 20 years of age) or BMI percentile = 10-25 (for patients < 20 years of age); and malnutrition (MN): BMI < 19 kg/m^2 (for patients ≥ 20 years of age) or BMI percentile < 10 (for patients < 20 years of age).[6,14]

Bacteriological status

Bacterial isolates from sputum cultures of the participants were assessed in the Microbiology Department of the *Hospital de Clínicas* de Porto Alegre. The presence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia* was registered. The presence of any of the aforementioned pathogens was confirmed by their isolation from routine sputum samples in the laboratory on at least two occasions, at least 12 months apart.

Clinical score

The clinical score used was the Shwachman-Kulczycki (S-K) score,[15] assessed by the physician of the CF team at an outpatient setting.

Pulmonary function tests

Pulmonary function tests were performed with a computerized spirometer (MasterScreen v4.31; Jaeger, Würzburg, Germany). At least three curves were obtained, the best ones being selected, for the determination of FVC and FEV_1, both in L and percentage of predicted values for age, stature, and gender.[16]

Assessment of pancreatic function

The fecal elastase-1 test was performed using monoclonal ELISA. Stool samples were collected and stored at a temperature of −22°C until being tested. The cut-off point of 200 μg/g was used in order to classify the exocrine pancreatic function of the patients (≥ 200 μg/g: sufficiency; < 200 μg/g: insufficiency). Patients whose results were ≥ 100 μg/g but < 200 μg/g were classified as having moderate exocrine pancreatic insufficiency. Patients with elastase-1 levels < 100 μg/g were classified as having severe exocrine pancreatic insufficiency.[17]

Compliance with dietary treatment

Patients were asked to complete a questionnaire (adapted from another study)[18] with three questions about their compliance with pancreatic enzyme replacement therapy, multivitamin supplement (vitamins A, D, E, and K) intake, and a hypercaloric diet (a diet high in energy, protein, and fat, based on a nutritional care plan and tailored to meet the nutritional requirements of each individual). Each question was to be answered on the basis of their weekly frequency of intake, as follows: a) every day or almost every day; b) 3-5 days a week; c) less than 3 days a week or never; and d) not applicable.

Statistical analysis

All data were processed and analyzed using the *Statistical Package for the Social Sciences*, version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative results were expressed as means and standard deviations or as medians and interquartile ranges, whereas qualitative variables were expressed as numbers of cases and proportions. Quantitative data with normal distribution were subjected to one-way ANOVA with Tukey's post hoc test. For continuous data with non-normal distribution, the Kruskal-Wallis test and the post hoc Z test were used. The chi-square test was applied to all qualitative data, as was Yates' correction or Fisher's exact test, as required. Multivariate analyses were generated through logistic regression analysis using the enter method. On this basis, the odds ratio was the odds ratio for malnutrition. Selected variables with p < 0.10 were introduced in the binary logistic regression controlled by gender and age. ROC curves were then created for each predictor variable identified in the logistic regression analysis and used to calculate the sensitivity, specificity, and predictive values of the clinical variables related to malnutrition. All statistical tests used were two-tailed. The level of significance was set at p < 0.05.

RESULTS

In the period between May of 2013 and May of 2014, 104 patients were invited to participate in the study. Of these, 6 patients died before all the tests were completed, 1 moved to another country, 6 declined to participate, and 18 patients did not perform the fecal elastase-1 test; therefore, the total sample comprised 73 patients who completed the study. The result of the fecal elastase-1 test was inconclusive for 7 patients (of 66 patients), although the test was run twice. The mean age of the subjects was 25.6 ± 7.3 years (19 adolescents and 54 adults), 40 (54.8%) of whom were females and 33 (45.2%) of whom were males. All subjects were White. The mean BMI was 21.0 ± 3.0 kg/m², and the mean FEV_1 was 59.7 ± 30.6% of the predicted value. Groups were formed on the basis of the nutritional status of the patients: AN group (n = 32; 43.8%); NR group (n = 23; 31.5%); and MN group (n = 18; 24.7%; Table 1).

Table 2 presents a comparison of the clinical characteristics among the aforementioned groups. There were no significant differences among the groups regarding gender, age, presence of F508del mutation, and liver score. The proportion of patients with diabetes mellitus was significantly higher in the NR group than in the AN and MN groups (p = 0.014). The S-K score was significantly lower in the NR and MN groups than in the AN group (p < 0.001). Percent predicted FVC and FEV1 were significantly lower in the MN group than in the AN and NR groups (p < 0.001 for both). Fecal elastase-1 levels were significantly lower in the NR group than in the AN and MN groups (p < 0.001 for both). Fifty-six patients were on pancreatic enzyme replacement therapy, and the number of enzyme units/kg/meal was significantly higher in the MN group than in the AN group (p < 0.001) and in the NR group (p = 0.001).

Table 3 shows the self-reported compliance with the high calorie diet, pancreatic enzyme replacement therapy, and vitamin supplementation intake in the three nutritional groups. No significant differences were found among the groups regarding those variables.

The logistic regression analysis identified three independent factors associated with malnutrition: age (OR = 0.78; p = 0.013), S-K score (OR = 0.90; p = 0.015), and FEV_1 in % of the predicted value (OR = 0.95; p = 0.046; Table 4).

The ROC curve analyses showed that the area under the curve for the S-K score was 0.85. Using a cut-off value of ≤ 65 points as a predictor of malnutrition, we found a sensitivity of 78.8%, a specificity of 67.3%, a positive predictive value of 43.8%, and a negative predictive value of 90.2%. The area under the curve for FEV_1 in % of the predicted value was 0.83. Using a cut-off value of ≤ 40% as a predictor of malnutrition, we found a sensitivity of 67.7%, a specificity of 81.8%, a positive predictive value of 54.5%, and a negative predictive value of 88.2%. As for age, the area under the curve was 0.57. Using a cut-off value of ≤ 22 years of age as a predictor of malnutrition, we found a sensitivity of 50.0%, a specificity of 58.2%, a positive predictive value of 28.1%, and a negative predictive value of 78.1%.

Table 1. Clinical characteristics of the patients included in the study (N = 73).[a]

Variable	Result
Gender	
Male	33 (45.2)
Female	40 (54.8)
Age, years	25.6 ± 7.3
BMI, kg/m²	21.0 ± 3.0
Nutritional classification	
Adequate nutrition	32 (43.8)
Nutritional risk	23 (31.5)
Malnutrition	18 (24.7)
CFRD	10 (13.7)
Type of mutation	
Homozygous for F508del	13 (17.8)
Heterozygous for F508del	33 (45.2)
Other/unidentified mutations	27 (37.0)
Age at diagnosis, years[b]	8 (16)
S-K score	70.41 ± 16.4
Lung function	
FVC, L	3.0 ± 1.24
FVC, % predicted	71.3 ± 31.5
FEV_1, L	2.1 ± 1.1
FEV_1, % predicted	59.7 ± 30.6
Fecal elastase-1, µg/g	92.3 ± 36.8
Bacterial colonization	
Pseudomonas aeruginosa	48 (65.8)
Staphylococcus aureus	50 (68.5)
MRSA	8 (11.0)
Burkholderia cepacia	15 (20.5)

BMI: body mass index; S-K: Shwachman-Kulczycki; CFRD: cystic fibrosis-related diabetes; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Values expressed as n (%) or mean ± SD, except where otherwise indicated. [b]Value expressed as median (interquartile range).

DISCUSSION

The current cross-sectional study provided relevant information about the prevalence of malnutrition and the clinical characteristics associated with malnutrition in CF patients attending an adult program at a large tertiary care center in southern Brazil. First, half of the patients presented adequate nutrition, and one-fourth was malnourished. Second, we identified some independent factors associated with the risk of malnutrition: S-K score, FEV_1 in % of the predicted value, and age. Therefore, our findings contribute to raising the awareness of the multifactorial aspects of malnutrition in adolescent and adult patients with CF. In an attempt to improve nutrition in clinical practice, the CF multidisciplinary team should take into account patients at a younger age, with low clinical scores and with impaired pulmonary function.

Table 2. Comparison of clinical characteristics among the study groups.[a]

Variable	Group			p
	Adequate nutrition (n = 32)	Nutritional risk (n = 23)	Malnutrition (n = 18)	
Gender				
Male	11(34.4)	12 (52.2)	10 (55.6)	0.254
Female	21 (65.6)	11 (47.8)	8 (44.4)	
Age, years	25.8 ± 8.8	26.7 ± 6.2	23.8 ± 5.5	0.454
Age at diagnosis, years[b]	12.0 (18.0)	4.0 (8.0)	9.5 (18.0)	0.043
S-K score	79.5 ± 12.1[A]	70.6 ± 10[B]	53.9 ± 17.0[C]	< 0.001
Type of mutation				
Homozygous for F508del	5 (15.6)	3 (13.0)	5 (27.8)	0.326
Heterozygous for F508del	13 (40.6)	10 (43.5)	10 (55.6)	
Other/unidentified mutations	14 (43.8)	10 (43.5)	3 (16.7)	
Liver score				
Normal	24 (75.0)	17 (73.9)	12 (66.7)	0.806
Abnormal	8 (25.0)	6 (26.1)	6 (33.3)	
CFRD	1 (3.1)	7 (30.4)	2 (11.1)	0.014
Lung function				
FVC, L	3.4 ± 1.2[A]	3.0 ± 1.1[AB]	2.2 ± 1.1[B]	0.002
FVC, % predicted	83.9±32.3[A]	73.1±25.5[A]	46.7± 23.0[B]	< 0.001
FEV_1, L	2.5 ± 1.0[A]	2.1 ± 1.0[A]	1.3 ± 0.7[B]	< 0.001
FEV_1, % predicted	74.2 ± 30.8[A]	58.9 ± 25.9[A]	35.0 ± 18.1[B]	< 0.001
Fecal elastase-1 test classification[c]				
Moderate pancreatic insufficiency (100-200 µg/g)	17 (56.7)	6 (28.6)*	13 (86.7)*	0.002
Severe pancreatic insufficiency (< 100 µg/g)	13 (43.3)	15 (71.4)*	2 (13.3)*	
Fecal elastase-1, µg/g	94.0 ± 32.6[A]	70.8 ± 35.4[B]	119.2 ± 28.9[C]	< 0.001
Bacterial colonization				
Pseudomonas aeruginosa	20 (62.5)	16 (69.6)	12 (66.7)	0.858
Staphylococcus aureus	22 (68.8)	14 (60.9)	14 (77.8)	0.512
MRSA	1 (3.1)	4 (17.4)	3 (16.7)	0.166
Burkholderia cepacia	6 (18.8)	6 (26.1)	3 (16.7)	0.718
Enzyme units of lipase/kg/meal	725.0 ± 476.4[A]	830.2 ± 456.9[A]	1423.9 ± 404.3[B]	<0.001

S-K: Shwachman-Kulczycki; CFRD: cystic fibrosis-related diabetes; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Values expressed as n (%) or mean ± SD, except where otherwise indicated. [b]Values expressed as median (interquartile range). [c]n = 66. *Adjusted standard residual > 1.96 or < -1.96 implies significantly different percentages. One-way ANOVA with Tukey's post hoc test and Kruskal-Wallis with post-hoc Z test: the means or medians were significantly different when subscript letters (A, B, and C) are different (chi-square test for categorical variables).

To discuss nutritional status is challenging, since authors use different parameters to assess it. Moreover, the definition of malnutrition varies in the literature. Although guidelines recommend BMI as a simple anthropometric indicator to classify nutritional status with the purpose of improving nutritional care for CF patients, the use of multiple and appropriate nutritional indicators could be of great importance to improve care for individual patients in CF health care practices.[7,14,19,20]

The proportion of CF patients with malnutrition in the present study (24.7%) is similar to findings reported in other studies.[21-24] A cross-sectional study conducted in Greece[21] and using the same methodology and the same cut-off points in order to classify nutritional status showed that 23% of 68 patients with CF were malnourished. However, that study involved 37 children and adolescents.[21] In contrast, a study carried out in an adult tertiary CF center in France with 163 patients showed that 49.7% of the patients suffered from malnutrition.[22] That study also used the same methodology and the same cut-off points for classifying malnutrition.[22] A retrospective cross-sectional study conducted in São Paulo, Brazil, and involving 30 adolescents (in the 10.1- to 19.8-year age bracket), using a different methodology (BMI for age) to evaluate their nutritional status.[23] The cut-off points were the following: ≥ z-score −3 and < z-score −2 (thinness); z-score −2 and ≤ z-score +1 (normal weight); and > z-score +1 (overweight or obesity). The median (minimum; maximum) BMI-for-age z-score was −0.6 (−3.7; +2.6), which corresponds to adequate nutritional status in accordance with the World Health Organization parameters.[23] In 2007, a previous study conducted in our hospital included 41 CF patients (16-47 years of age), used the same methodology and the same cut-off

Table 3. Self-reported adherence to a high-calorie diet, pancreatic enzyme replacement therapy, and vitamin supplementation intake, by group.

Variable	Group			p
	Adequate nutrition	Nutritional risk	Malnutrition	
High-calorie diet				
High	25 (78.1)	15 (65.2)	10 (55.6)	0.49
Moderate	4 (12.5)	6 (26.1)	5 (27.8)	
Low	3 (9.4)	2 (8.7)	3 (16.7)	
Pancreatic enzyme replacement therapy[a]				
High	15 (93.8)	20 (87.0)	15 (88.2)	0.33
Moderate	0 (0.0)	3 (13.0)	2 (11.8)	
Low	1 (6,3)	0 (0.0)	0 (0.0)	
Vitamin supplementation[b]				
High	17 (89.5)	20 (87.0)	16 (94.1)	0.816
Moderate	1 (5.3)	1 (4.3)	1 (5.9)	
Low	1 (5.3)	2 (8.7)	0 (0.0)	

[a]n = 56; pancreatic enzyme replacement therapy not indicated in 17 patients. [b]n = 59: vitamin supplementation not indicated in 14 patients.

Table 4. Logistic regression analysis (enter method) for malnutrition.

Variable	Beta	p	OR	95% CI for OR
Male gender	−0.41	0.961	0.96	0.19-4.95
Age	−0.24	0.013	0.78	0.65-0.95
S-K score	−0.11	0.015	0.90	0.82-0.98
FEV_1, % predicted	−0.05	0.046	0.95	0.90-0.99
Constant	14.65	0.002	2,312,450.04	-

S-K: Shwachman-Kulczycki.

point for malnutrition, and identified 9 malnourished patients (22%).[24] These remarkable discrepancies in the prevalence of malnutrition in CF patients can be attributed to the heterogeneity of the disease, the survival effect observed in cohorts of adult subjects, interpopulation variations, and differences in quality of health care or in study design (sample selection, age groups included, indicators of malnutrition, and cut-off values).

The association between nutritional status and lung function has been long recognized. Numerous studies have noted the negative effect of malnutrition on respiratory function and prognosis.[25,26] The results of the present study confirm that nutrition and lung function are codependent variables in CF patients, poor lung function being predictive of malnutrition. In a recent study, Hulzebos et al.[27] showed that the use of BMI combined with FEV_1 could accurately predict mortality in CF patients. Another recent study with 14,732 patients (≥ 6 years of age) from the European Cystic Fibrosis Society Patient Registry confirmed that poor BMI was significantly associated with poor lung function.[28] The authors emphasized that BMI is a preventable or potentially treatable factor; however, despite the available guidelines for the prevention and correction of nutritional deficiencies in CF, 9.5% of the patients with CF in Europe still suffer from chronic severe malnutrition.[28]

Exocrine pancreatic insufficiency has been found to be a prognostic factor for malnutrition. Couper et al.,[29] in a longitudinal study, showed that patients with pancreatic sufficiency developed pancreatic insufficiency at an older age. In the current study, the fecal elastase-1 test was used in order to quantify the severity of pancreatic insufficiency and to predict malnutrition. All of the patients in our sample had levels of fecal elastase-1 < 200 μg/g. Surprisingly, fecal elastase-1 levels were higher in the MN group than in the AN group, as well as being higher in the AN group than in the NR group. One possible explanation for this finding is that the differences in mean levels of fecal elastase-1 among the groups, although statistically significant, were of low magnitude and did not impact on the nutritional outcome.

Another finding in the present study was that the malnourished patients were treated with significantly higher pancreatic enzyme replacement dosing than were those in the other groups. This finding contrasts with a recent retrospective analysis by Haupt et al.,[30] who suggested that pancreatic enzyme replacement dosing is associated with better nutritional status; however, that study included children only. The mean enzyme replacement dosing in our patients was in agreement with recommendations of the guidelines[7]: not greater than 2,500 lipase units/kg/meal.

The S-K score[15] is a general clinical severity score with four domains: general activity, physical examination, nutrition, and radiological findings. Each domain ranges from 0 to 25 points, and the domain scores are added to give the overall score (up to 100). Higher scores

reflect better clinical status. In the current study, low clinical scores were predictive of malnutrition. The S-K score was not used in three previous studies of the nutritional status in CF patients.[21-23] In contrast, there was no significant association between malnutrition and the S-K score in the study by Ziegler et al.[24]

Longitudinal studies have demonstrated that malnutrition can be expected to increase with aging.[31,32] However, it is interesting that our results showed that young age was a predictor of malnutrition only in the multivariable analysis. Nevertheless, it is likely that age and the preservation of nutritional status are related to milder disease, and that a later onset of the disease has a positive impact on the nutritional status of the patients. One hypothesis for this finding is the survival bias in the present CF population. Patients with poor lung function and malnutrition did not reach the age range under consideration in the present study.

In our study, the self-reported compliance with a high calorie diet, pancreatic enzyme replacement therapy, and vitamin supplementation intake was high and was not associated with the nutritional status. In a previous study,[33] 65.8%, 96.3%, and 79.4% of the patients, respectively, self-reported good compliance with a high-calorie diet, pancreatic enzyme replacement therapy, and vitamin supplementation intake. Arias Llorente et al.[34] suggested that patients would be more compliant with their treatment if they believed it to be beneficial and to improve their quality of life. Moreover, previous studies demonstrated that patients who understand the importance of following medical instructions and trust their physicians are probably more compliant. The fact that treatment adherence tends to diminish with age has also been mentioned.[18,35]

The present study has potential limitations. Because it was a cross-sectional study, it was impossible to establish the temporal sequence of the factors studied and malnutrition. In addition, our sample of patients was also small.

In conclusion, the present study has demonstrated that malnutrition remains a common complication in adolescents and adults with CF, despite dietary advice. Malnutrition is associated with age, clinical severity, and lung function impairment.

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