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Clinical Outcomes and Prognostic Factors in a Cohort of Adults With Cystic Fibrosis: A 7-Year Follow-Up Study

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BACKGROUND: Due to the heterogeneity of cystic fibrosis (CF), the longer survival observed in cohorts of adult subjects, and inter-population variations, there is a clear need to seek further information about clinical outcomes and prognostic factors in different cohorts of subjects with CF. Our objectives were to evaluate clinical outcomes and prognostic factors in a cohort of adult subjects with CF after a 7-y follow-up period and investigate longitudinal changes in clinical scores, spirometry, 6-min walk test performance, and pulmonary artery systolic pressure as assessed by Doppler echocardiography. METHODS: A cohort of clinically stable subjects (≥16 y old) who were enrolled in an adult CF program in 2004–2005 underwent clinical evaluation. Outcome was classified as good (survival) or poor (survival with lung transplantation or death). In 2011–2012, survivors were re-examined. RESULTS: Of 40 subjects with CF evaluated in 2004–2005, 32 (80%) survived, 2 (5%) survived with lung transplantation, and 6 (15%) died. Logistic regression analysis showed that a low percent-of-predicted FEV_1 was associated with poor outcome. An FEV_1 cut-off value of ≤30% and pulmonary artery systolic pressure of ≥42 mm Hg predicted poor outcome with high sensitivity, specificity, and positive and negative predictive values. Deterioration was observed in clinical scores ($P = .03$), FVC ($P = .02$), FEV_1 ($P < .001$), distance walked in the 6-min walk test ($P = .002$), baseline S_{pO_2} ($P < .001$), and final S_{pO_2} ($P < .001$). CONCLUSIONS: After 7 y of follow-up, 20% of subjects with CF had a poor outcome. Pulmonary artery systolic pressure of ≥42 mm Hg and FEV_1 of ≤30% were the most significant prognostic predictors of poor outcome. Clinical and functional deterioration was observed in survivors. *Key words: cystic fibrosis; prognosis; cohort studies; lung function; pulmonary hypertension.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) is a progressive, autosomal recessive hereditary disease that primarily affects the white population.[1] The prognosis of people with CF has improved considerably over the past 4 decades. Data from a United States registry of adult CF patients show that the mean predicted survival in CF is currently 38.3 y of age and 43% of individuals with CF are age 18 y or older.[2] This increased survival has led to an increased prevalence of medical conditions related to age and disease progression, changing the health-care needs of these patients. The

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growing demand for non-pediatric specialists has become particularly evident in this population.[3]

Lung disease is the strongest predictor of death in CF, and FEV_1 is the main parameter used to assess the severity of lung disease in subjects with CF.[4] However, due to the heterogeneity of the disease, the longer survival observed in cohorts of adult subjects, and inter-population variations, there is a clear need to seek further information about clinical outcomes and prognostic factors in different cohorts of subjects with CF.[3-5]

Two cross-sectional studies of participants attending an adult CF program at Hospital de Clínicas de Porto Alegre (HCPA), southern Brazil, assessed 40 of 41 subjects enrolled in the program between September 2004 and December 2005.[6,7] We hypothesized that a longitudinal study of this patient cohort would provide more relevant prognostic information for the treatment of this condition than a cross-sectional approach.

The current study was therefore designed (1) to evaluate clinical outcomes and prognostic factors in a cohort of adult subjects with CF after a 7-y follow-up period and (2) to investigate longitudinal changes in clinical scores, lung function, 6-min walk test (6MWT) performance, and pulmonary circulation as assessed by Doppler echocardiography in survivors.

QUICK LOOK

Current knowledge

The prognosis of people with CF has improved considerably over the past 4 decades. The mean predicted survival in CF is currently to 38.3 y of age. Lung disease is the strongest predictor of death in CF, and FEV_1 is the main parameter used to assess the severity of lung disease in subjects with CF.

What this paper contributes to our knowledge

After 7 y of follow-up, 20% of adult CF subjects had poor outcome (survival with lung transplantation or death). Pulmonary artery systolic pressure of $\geq$42 mm Hg and FEV_1 of $\leq$30% were the most significant prognostic predictors of poor outcome. Clinical and functional deterioration was observed in survivors.

Method

Study Design and Population

This was a prospective cohort study with a prognostic approach. Participants were selected for the current study from the sample of 41 patients with CF enrolled in the adult CF program at the Serviço de Pneumologia of HCPA who had been previously assessed in 2004 and 2005.[6,7] HCPA is a tertiary care teaching hospital located in Porto Alegre, the capital of the state of Rio Grande do Sul, in southern Brazil. Briefly, subjects of either sex were included in the 2004–2005 assessment if they were $\geq$16 y old at the time of assessment, had a diagnosis of CF according to consensus criteria,[8] were clinically stable, had not been hospitalized, and had no changes in their treatment regimen for at least 30 d before assessment. Exclusion criteria were the presence of cardiac, orthopedic, and trauma conditions or any other impairment that could prevent patient assessment. In the current study, we examined longitudinal changes in clinical scores, spirometry, 6MWT performance, and pulmonary artery systolic pressure as assessed by Doppler echocardiography in survivors after a 7-y follow-up period (2011–2012).

The initial project was approved by the HCPA Research Ethics Committee under protocol number 04182, and the current study was conducted under protocol number 100293. Written informed consent was obtained from all individual participants included in both phases of the study.

Study Procedures

Clinical variables were assessed using questionnaires designed specifically for this purpose. Data on the following variables were recorded: age, gender, ethnicity, presence of the F508del mutation (homozygous or heterozygous), body mass index, presence of exocrine pancreatic insufficiency, presence of diabetes mellitus, and liver score,[9] which was classified as normal (3 points) or abnormal (>3 points). Disease severity was assessed using the Shwachman–Kulczycki score.[10] Scores were assigned by the most experienced member of the research team (PTRD).

As part of the 2004–2005 assessment, all subjects had undergone at least 3 bacteriological examinations of CF sputum in the previous year for the presence of *Pseudomonas aeruginosa* and members of the *Burkholderia cepacia* complex. All bacteriological examinations were conducted at the Microbiology Department of HCPA, and subjects were considered carriers of *B. cepacia* or *P. aeruginosa* if at least 2 sputum samples examined in the previous year were positive for one of these bacteria.

Spirometry was performed using a computerized spirometer (Jaeger 4.31, Jaeger, Würzburg, Germany). The best of 3 acceptable measurements was recorded, and the following parameters were evaluated: FEV_1, FVC, and FEV_1/FVC. All parameters were expressed as a percentage of the expected value for age, height, and sex.[11]

All 6MWTs were conducted by the same physiotherapist and performed in a 30-m-long hallway according to

the American Thoracic Society standard protocol for the 6MWT.[12] S_{pO_2} was recorded at rest (baseline) and immediately after the 6MWT (final) using a pulse oximeter (NPB-40, Nellcor Puritan Bennett, Pleasanton, California).

All participants underwent transthoracic Doppler echocardiography (ATL HDI 5000, Philips Medical Systems, Bothell, Washington). With subjects at rest in a semi-supine left lateral position, M-mode 2-dimensional scanning was performed, and images were obtained from the parasternal, apical, and subcostal windows. All echocardiographic examinations were performed by the same examiner (AFFP), who was blinded to the subjects' clinical status. All measurements were obtained according to the recommendations of the American Society of Echocardiography.[13] Tricuspid regurgitation was assessed by measuring the backflow of blood across the tricuspid valve at each contraction of the right ventricle from the apical parasternal 4-chamber view. At least 5 consecutive complexes were measured in each case. The peak velocity of the regurgitant jet was used to calculate the systolic pressure gradient by the modified Bernoulli equation (dP = 4v2, where dP is the difference between the peak pressure in the right ventricle and atrium, and v is the peak velocity of the regurgitant jet). Subjects with no trace of tricuspid regurgitation were considered normal. The right ventricle-pulmonary artery systolic acceleration time (normal value is ≥120 m/s) was calculated based on the antegrade pulmonary blood flow as the time from onset of flow in the pulmonary artery to peak blood flow velocity.

In the current study, the subjects' medical records were reviewed for outcome data, and, if necessary, the participants were contacted via telephone for additional information. Outcome was classified as good (survival without lung transplantation) or poor (survival with transplantation or death). Subjects with good outcome were called for clinical re-evaluation, spirometry, 6MWT, and echocardiography after 7 y of follow-up. Echocardiographic examinations were performed by the same examiner (AFFP) and following the same protocol in both phases of the study.

Statistical Analysis

Data analysis was performed using the SPSS 18.0 (SPSS, Chicago, Illinois). Quantitative data were expressed as mean ± SD or median (interquartile range), and qualitative data were expressed as *n* (%). Paired-samples *t* tests (for normally distributed continuous variables) and paired-samples Wilcoxon test (for ordinal variables) were used to compare the results of the initial (2004–2005) and final (2011–2012) assessments. Statistical significance was set at $P < .05$ (2-tailed tests).

Univariate logistic regression analysis was performed to investigate the association between clinical variables and poor outcome. In order to avoid collinearity, variables with a *P* value of <.05 in the univariate analysis were entered in a multivariate binary logistic regression model using the forward conditional method to identify predictors of poor outcome. Receiver operating characteristic curves were then generated for each predictor identified in the multivariate analysis and used to calculate the sensitivity, specificity, and predictive values of clinical variables for poor outcome.

Table 1. Subjects' Characteristics at the Time of the First Assessment (2004–2005)

Variables	N = 40
Sex, *n* (%)	
Female	22 (55.0)
Male	18 (45.0)
Age, mean ± SD y	23.7 ± 6.3
Age at diagnosis, median (IQR) y	9 (15.0)
Mutation, *n* (%)	
F508del homozygous	9 (22.5)
F508del heterozygous	14 (35.0)
Other unidentified mutations	17 (42.5)
Pancreatic insufficiency, *n* (%)	31 (77.5)
CFRD, *n* (%)	2 (5.0)
Liver score, *n* (%)	
Normal (3 points)	32 (80.0)
Abnormal (>3 points)	8 (20.0)
BMI, mean ± SD kg/m^2	20.4 ± 2.4
Shwachman-Kulczycki score, median (IQR)	75 (20.0)
% predicted FEV_1, mean ± SD	55.3 ± 27.3
% predicted FVC, mean ± SD	67 ± 22.7
Bacterial colonies, *n* (%)	
B. cepacia	10 (25.0)
P. aeruginosa	23 (57.5)
Pulmonary artery systolic pressure, mean ± SD mm Hg	36.0 ± 6.9
6MWT, mean ± SD	
Baseline S_{pO_2}	96.8 ± 1.8
Final S_{pO_2}	93.8 ± 6.2
Desaturation	3.17 ± 5.3
Baseline heart rate, beats/min	86.5 ± 13.5
Final heart rate, beats/min	125.3 ± 22.3
Distance walked, m	558.6 ± 76.5
Distance walked, %	73.9 ± 10.6

IQR = interquartile range
CFRD = cystic fibrosis-related diabetes
BMI = body mass index
6MWT = 6-min walk test

Results

Subjects

Between September 2004 and December 2005, 41 subjects attended the adult CF program at HCPA. Of these, 1 refused to participate in the study, and 40 were enrolled.

Table 2. Univariate Logistic Regression Analysis for Poor Outcome (Survival With Transplantation or Death)

Variable	β	OR	95% CI	*P*
Sex	0.25	1.29	0.27–6.07	.75
Age, y	0.08	1.09	0.97–1.22	.17
Age at diagnosis, y	0.005	1.01	0.93–1.08	.90
BMI, kg/m^2	0.07	1.07	0.78–1.47	.66
S-K score, points	−0.07	0.93	0.86–1.01	.07
% predicted FVC	−0.13	0.88	0.79–0.98	.02
% predicted FEV_1	−0.19	0.83	0.71–0.98	.02
B. cepacia	2.20	9.00	1.61–50.27	.01
P. aeruginosa	0.26	1.30	0.26–6.37	.75
F508del homozygous	0.96	2.60	0.48–14.01	.27
CFRD	−22.88	0.00	0.00	.99
Pancreatic insufficiency	0.17	1.19	0.20–7.25	.85
Abnormal liver score (>3 points)	1.18	3.24	0.58–18.10	.18
Pulmonary artery systolic pressure, mm Hg	0.36	1.43	1.11–1.85	.01
TRJV	7.99	2963.85	8.55–1,028,073.75	.01
Baseline S_{pO_2}, %	−1.14	0.32	0.15–0.67	.002
Final S_{pO_2}, %	−0.45	0.64	0.46–0.88	.01
Desaturation, %	0.32	1.37	1.03–1.83	.03
Distance walked, m	−0.006	0.99	0.98–1.01	.31
Distance walked, % predicted	−0.02	0.98	0.91–1.06	.58

OR = odds ratio
BMI = body mass index
S-K score = Shwachman-Kulczycki score
CFRD = cystic fibrosis-related diabetes
TRJV = tricuspid regurgitant jet velocity

Between September 2011 and December 2012, the clinical outcome of all 40 subjects with CF was assessed. Also, in this second phase of the study, of 32 subjects with CF who survived without transplantation, 27 agreed to participate and were reassessed with clinical and spirometric evaluation, 6MWT, and Doppler echocardiography.

Characteristics At Inclusion

Table 1 shows the characteristics of the study sample at the initial assessment. These subjects had a mean age of 23.7 ± 6.3 y (range 16–47 y), and 22 (55%) were women. Nine subjects (22.5%) were F508del homozygous, and 14 (35%) were F508del heterozygous. The median baseline Shwachman–Kulczycki score was 75 points, and the mean baseline FEV_1 was 55.3% of the predicted value. The mean baseline pulmonary artery systolic pressure was 36 mm Hg, and the mean distance walked in 6MWT was 558.6 m.

Clinical Outcomes and Prognostic Factors

Between September 2011 and December 2012, the clinical outcome of all 40 subjects with CF was assessed. Of these, 6 had died, 2 survived with lung transplantation, and 32 survived without transplantation. Of the 6 deaths, 4 were due to chronic respiratory failure, 1 was due to immediate post-transplant complications, and 1 was caused by chronic rejection and sepsis in the third year following lung transplantation.

Table 2 shows the results of univariate logistic regression analysis for poor outcome (survival with transplantation or death). The following variables were significantly associated with poor outcome: percent-of-predicted FVC (odds ratio [OR] = .88, P = .02), percent-of-predicted FEV_1 (OR = .83, P = .02), presence of *B. cepacia* in sputum cultures (OR = 9.0, P = .01), pulmonary artery systolic pressure (OR = 1.4, P = .01), baseline S_{pO_2} (OR = .32, P = .002), S_{pO_2} after the 6MWT (OR = .64, P = .01), and desaturation during the 6MWT (OR = 1.37, P = .03).

Table 3 shows the results of the multivariate analysis using variables in a forward conditional regression model for poor outcome. Pulmonary artery systolic pressure, percent-of-predicted FEV_1, baseline S_{pO_2}, and presence of *B. cepacia* in sputum were significant in the univariate analysis and then included in the multivariate regression model. However, only pulmonary artery systolic pressure (OR = 1.43, P = .038) and percent-of-predicted predicted FEV_1 (OR = .83, P = .09) could reliably predict poor outcome.

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Table 3. Multivariate Logistic Regression Analysis Using the Forward Conditional Method

Variable	β	OR	95% CI	P
% predicted FEV_1	−0.185	0.831	0.671–1.030	.09
Pulmonary artery systolic pressure	0.359	1.432	1.019–2.013	.038

The following variables were included in the model: percent-of-predicted FEV_1, pulmonary artery systolic pressure, baseline S_{pO_2}, and positive cultures for *B. cepacia*.
OR = odds ratio

The area under the curve for pulmonary artery systolic pressure was 0.91. The sensitivity of a pulmonary artery systolic pressure cut-off value of ≥42 mm Hg for the prediction of poor outcome was 62.5%, with a specificity of 93.1%, positive predictive value of 71.4%, and negative predictive value of 90.0%. For percent-of-predicted FEV_1, the area under the curve was 0.10, and the sensitivity of a cut-off value of ≤30% for the prediction of poor outcome was 50%, with a specificity of 93.8%, positive predictive value of 66.7%, and negative predictive value of 88.2%.

Longitudinal Changes in Clinical Scores, Lung Function, 6MWT Performance, and Doppler Echocardiography

Between 2011 and 2012, of 32 subjects with CF who survived without transplantation, 27 agreed to participate and were reassessed. Figure 1 shows a comparison between the results of clinical evaluation and spirometry obtained in the initial assessment (2004–2005) and after 7 y of follow-up (2011–2012). Over the follow-up period, clinical scores decreased by 7.8 points ($P = .03$), percent-of-predicted FVC decreased by 8.2% ($P = .02$), percent-of-predicted predicted FEV_1 decreased by 14.4% ($P < .001$), and FEV_1/FVC decreased by 8.7% ($P < .01$). The distance walked in 6MWT decreased by 50.8 m ($P = .002$), baseline S_{pO_2} decreased by 2.5 points ($P < .001$), and final S_{pO_2} decreased by 5.4 points ($P < .001$), whereas desaturation increased by 2.66 points ($P = .01$) (Fig. 2). Although echocardiographic examinations were performed by the same investigator in both phases of the study, pulmonary artery systolic pressure calculation was technically possible only in 16 subjects at reassessment. Therefore, these results were not longitudinally analyzed in the present study.

Correlations Between FEV_1 and Clinical Score, Pulmonary Artery Systolic Pressure, S_{pO_2} at Rest, and Distance Walked in 6MWT

Figure 3 shows correlations between FEV_1 and Shwachman–Kulczycki score ($R = 0.77$, $P < .001$), pulmonary artery systolic pressure ($R = 0.60$, $P < .001$), S_{pO_2} at rest ($R = 0.56$, $P < .001$), and distance walked in 6MWT ($R = 0.34$, $P = .031$) at the initial assessment (2004–2005).

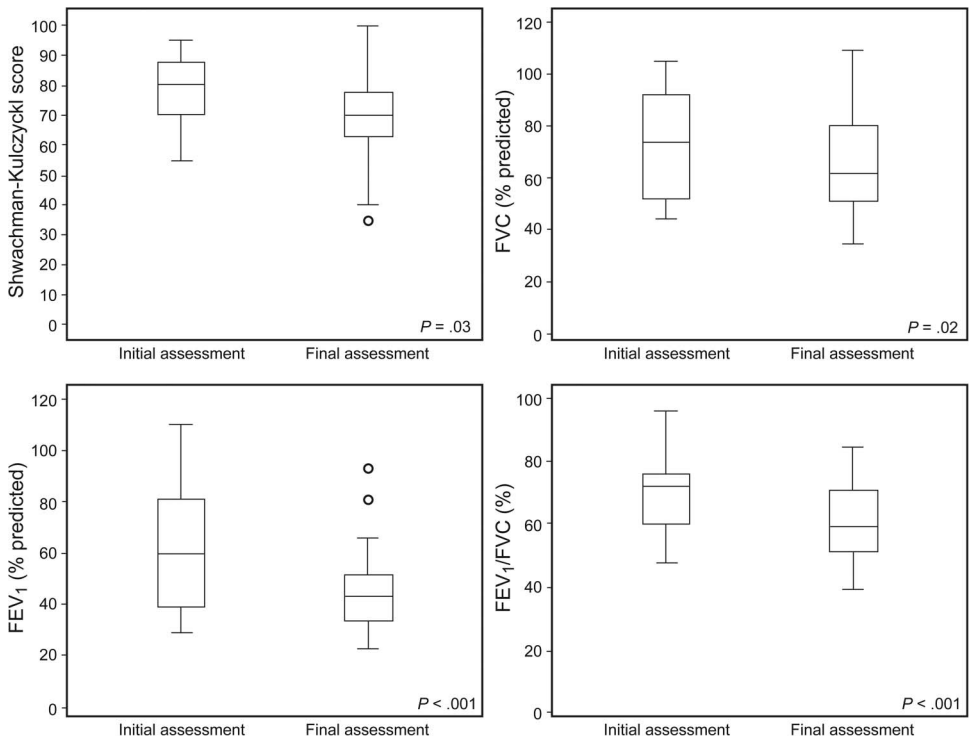

Fig. 1. Clinical scores, FEV_1, FVC, and FEV_1/FVC of 27 surviving subjects with cystic fibrosis at initial assessment (2004–2005) and after 7 y of follow-up (2011–2012).

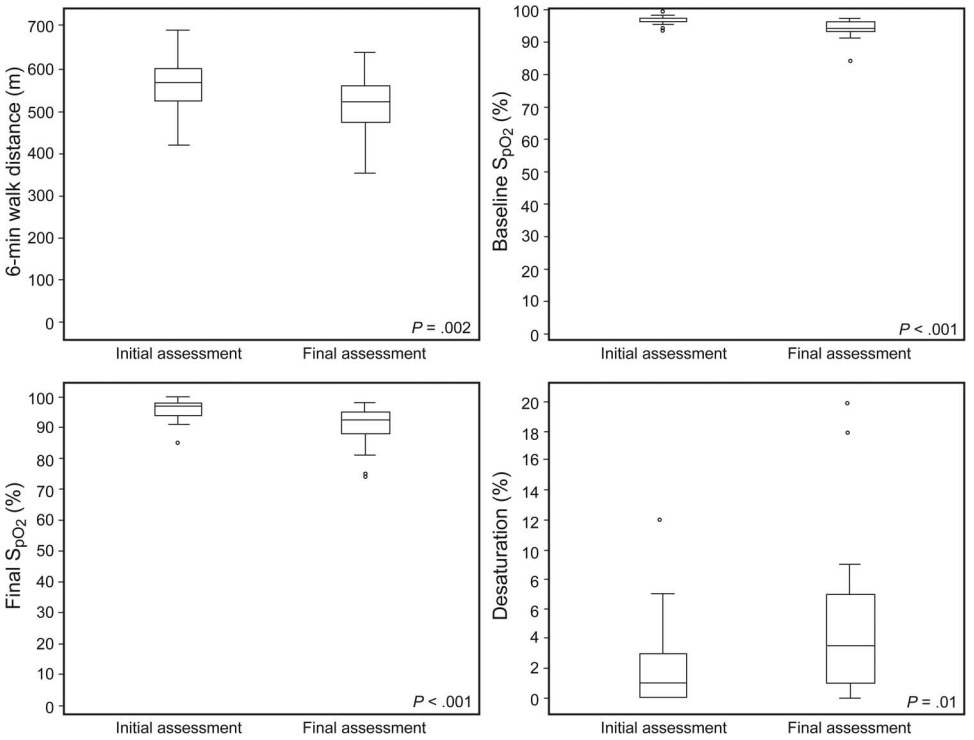

Fig. 2. 6-min walk test (6MWT) performance (distance walked, baseline S_{pO_2}, final S_{pO_2}, and desaturation) of 27 surviving subjects with cystic fibrosis at initial assessment (2004–2005) and after 7 y of follow-up (2011–2012).

Discussion

The current study analyzed clinical outcomes in a cohort of 40 adult subjects with CF after a 7-y follow-up. FEV_1 is the main parameter used to assess the severity of lung disease in CF,[4] and the present results support the prognostic importance of assessing this variable in clinical practice as well as monitoring pulmonary artery systolic pressure values in adult patients with CF. In CF, the expression of lung disease severity varies widely, and early identification of decreased FEV_1 or changes in pulmonary artery systolic pressure values indicate the need for a more comprehensive approach to disease management.

A previous study[5], conducted in the same Brazilian center of the current study, retrospectively analyzed a cohort of 94 subjects attending the adult CF program between October 1998 and October 2008. Data on the demographic and clinical characteristics, nutritional status, lung function, laboratory parameters, and sputum cultures of these individuals were collected, and the following outcomes were assessed: survival, survival with lung transplantation, and death. Of the subjects, 77 were found to have survived, 6 survived with transplantation, and 11 died. Logistic regression analysis showed that FEV_1 and clinical scores were reliable predictors of poor outcome (death and lung transplantation). The cause of death in most cases was chronic respiratory failure exacerbated by acute respiratory infections. Although the study involved a larger number of subjects and a longer follow-up period than those in the current study, the retrospective nature of the investigation (data were obtained from medical records and databases used in previous studies employing significantly different methodologies) was an important limitation of the study. Missing data prevented the analysis of important variables, such as pulmonary artery systolic pressure and 6MWT performance. Therefore, the current study, despite the smaller sample size, provided more reliable results, obtained by using a carefully standardized method.

Right heart catheterization is the accepted standard for the diagnosis of pulmonary arterial hypertension. Noninvasive assessment of right heart function using Doppler echocardiography is a reliable indirect method of diagnosis of pulmonary arterial hypertension.[13] However, the variable efficacy of Doppler ultrasonography in assessing pulmonary artery systolic pressure in subjects with chronic lung disease has been extensively documented, which may lead to both over- and underestimation of pulmonary artery systolic pressure values compared with a direct measurement of this variable. Furthermore, Doppler ultrasonography can be performed in only a minority of patients with chronic lung disease, leading to progressively less accurate pulmonary artery systolic pressure estimates as pulmonary hypertension or chronic lung disease progresses, resulting in the hypertrophy and dilation of the right heart chambers.[14-16]

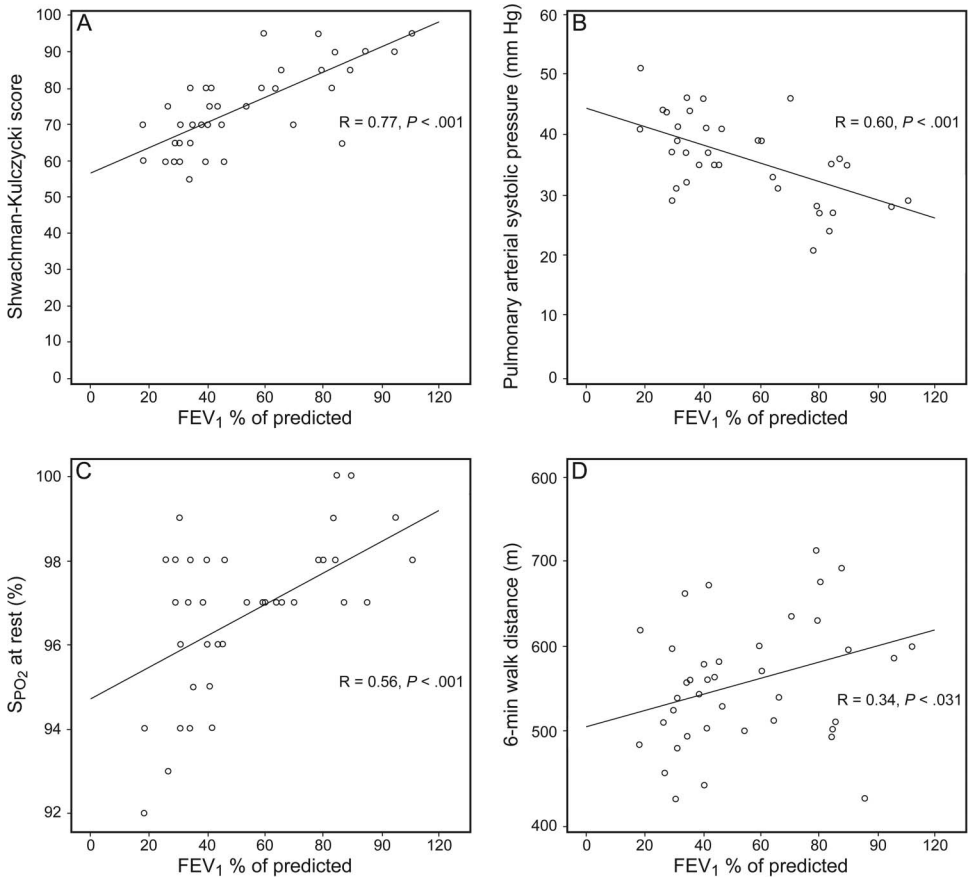

Fig. 3. Correlations between clinical scores, pulmonary arterial systolic pressure, and distance walked in 6-min walk test with FEV_1 at the initial assessment.

In the present study, subjects had a mean age of 23.7 y at the time of the first assessment and were younger than most of the cohorts assessed in similar studies.[4] Whereas only 6 (15%) of our participants were age 30 y or older, this age group accounts for approximately 35% of subjects included in United States cohorts.[2] In addition, our participants appear to have more severe lung disease than individuals evaluated in Canadian cohorts, since the mean percent-of-predicted FEV_1 of subjects in the current study was 55.3%, whereas subjects age 18 y or older in the Canadian CF registry had a mean percent-of-predicted FEV_1 of 63.1%.[17] These differences may be explained by the fact that the pediatric department of HCPA started treating CF only in the 1980s, whereas most CF centers in developed countries began their activities in the 1960s. Thus, in our CF center, the impact on survival and lung disease rates has not yet reached the same level as that of similar centers in developed countries.

The present study has some limitations. First, because of the small sample size, only a limited number of variables could be included in the multivariate regression model. Second, technical difficulties associated with pulmonary artery systolic pressure estimation in older subjects with more severe lung disease reduced the prognostic impact of this variable. Finally, intra- and inter-observer variability associated with pulmonary artery systolic pressure estimation using Doppler ultrasonography may have had an impact on the accuracy of this procedure,[18] and, although all measurements were performed by the same experienced echocardiographer, this may be considered a possible source of bias. Despite these limitations, the clinical relevance of the present findings should be highlighted. This is one of the first studies to investigate longitudinal changes in a cohort of subjects with CF in Brazil. The study described the development of lung disease in adulthood, and the findings support the prognostic importance of assessing FEV_1 and pulmonary artery systolic pressure in adult patients with CF.

Conclusions

Of our initial cohort of 40 subjects with CF assessed in 2004–2005, 6 (15%) died after a 7-y follow-up period, and 2 (5%) survived with lung transplantation, and pulmonary artery systolic pressure of ≥42 mm Hg and percent-of-

predicted FEV_1 of ≤30% were factors associated with this poor outcome. Furthermore, the 32 non-transplant subjects (80%), when reassessed after 7 y, showed a significant decrease in clinical scores, spirometric parameters, and 6MWT performance.

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