Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis

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Author's Role

Ryo Kozu is responsible for the design of this study, collection of the data, the analysis and interpretation of the data and preparation of the manuscript.

Sue Jenkins provided intellectual input to the design of this study, the analysis and interpretation of the data and to preparation of the manuscript.

Hideaki Senjyu contributed to the design of this study, provided intellectual input to the interpretation of the data and contributed to the preparation of the manuscript.

SUMMARY AT A GLANCE

This study investigated response to pulmonary rehabilitation in subjects with IPF grouped according to the Medical Research Council (MRC) dyspnea scale. Compared to those with severe disability (MRC grades 4 and 5) who showed little or no benefit following rehabilitation, greater benefits occurred in MRC grade 2 and 3 subjects.

ABSTRACT

Background and objective: It is unclear whether the severity of functional limitation resulting from IPF affects the response to pulmonary rehabilitation. The aim of this study was to compare the outcomes of rehabilitation in patients with IPF grouped according to the Medical Research Council (MRC) dyspnea scale.

Methods: Sixty-five subjects (46, 71% males) with stable IPF enrolled in an 8-week pulmonary rehabilitation program. Subjects in MRC grades 2, 3 and 4 undertook a supervised out-patient program, and MRC grade 5 subjects participated in an unsupervised, home-based program with review every 2 weeks. Outcome measures included functional exercise capacity (6MWD), health status (SF-36) and dyspnea (Transition Dyspnea Index, TDI) measured at baseline and immediately post-program. Hospitalizations for respiratory exacerbations were compared for the 12 months pre- and post-program.

Results: The number of subjects in MRC grades 2, 3, 4 and 5 was 16 (25%), 17 (26%), 17 (26%) and 15 (23%), respectively. There were differences between groups in the magnitude of change in 6MWD, SF-36 and TDI (all $P<0.05$). Specifically, subjects in MRC grades 2 and 3 demonstrated clinically and statistically significant (all $P<0.05$) improvements in 6MWD and SF-36 following rehabilitation. In contrast, for all measures, MRC grade 4 and 5 subjects showed little or no improvement, or deteriorated following rehabilitation. Hospitalizations were reduced in MRC grade 2, 3 and 4 subjects only following rehabilitation ($P<0.05$).

Conclusions: The response to pulmonary rehabilitation in subjects with IPF varies depending on MRC grade, with little benefit occurring in those with severe functional limitation.

INTRODUCTION

Patients with IPF commonly report exertional dyspnea that leads to a decrease in exercise tolerance, limits their ability to perform activities of daily living (ADL) and results in impaired health-related quality of life (HRQoL).[1] Pulmonary rehabilitation, has been shown to improve dyspnea, exercise tolerance and HRQoL in patients with a variety of interstitial lung diseases (ILD), including IPF.[2, 3]

However, in patients with IPF, the magnitude of improvement following rehabilitation tends to be more modest than that observed in individuals with other types of ILD,[4] and significantly less when compared to the benefits reported in patients with chronic obstructive pulmonary disease (COPD).[5] Further, any improvements seen in patients with IPF appear to be short-lived.[2, 5]

Idiopathic pulmonary fibrosis is a heterogeneous disorder in terms of disease progression, response to therapy and prognosis.[6] Therefore, the optimal timing for pulmonary rehabilitation in the disease trajectory requires consideration. It is unclear whether the severity of IPF and the associated disability that arises due to exertional dyspnea affects the response to rehabilitation. We hypothesized that the baseline level of disability would influence the magnitude of response to pulmonary rehabilitation.

The aim of this study was to investigate whether there was a difference in the response to pulmonary rehabilitation in subjects with IPF grouped according to their disability level categorized using the Medical Research Council (MRC) (1 to 5) dyspnea scale.[7]

METHODS

Subjects

A prospective non-randomized, non-controlled study was undertaken. We recruited consecutive patients with a diagnosis of IPF based on the International Consensus Statement[6] who were referred to the pulmonary rehabilitation program (PRP) at Nagasaki University Hospital. Individuals were eligible to participate if they were under the care of a respiratory physician, ambulant, reported dyspnea on exertion and were clinically stable with no changes in medication for at least 4 weeks prior to recruitment. Data from some subjects have contributed to previous work.[5, 8] Exclusion criteria were MRC grade 1, severe orthopedic or neurological disorders limiting exercise performance, unstable cardiac disease, active cancer, inability to complete questionnaires and previous participation in a PRP.

The Human Ethics Review Committee of Nagasaki University Graduate School of Biomedical Sciences approved this study. Subjects gave written, informed consent prior to data collection.

Measurements

The following variables were recorded at the time of recruitment to the study; BMI, time since diagnosis, use of long term oxygen therapy (LTOT) and oral corticosteroids, presence of cough, and right ventricular systolic pressure measured by transthoracic echocardiogram. Measures were obtained of spirometry and DL_{CO}, [9, 10] and MRC grade was recorded during patient interview. Subjects in grades 2, 3 and 4 underwent an incremental cycle ergometry test (ICET) using methodology previously described. [8] The purpose of this test was to measure peak power to enable prescription of the initial

intensity for lower limb endurance training.

Outcome Measures

The following measurements were completed at baseline and immediately following the 8-week PRP. The primary outcome measures were functional exercise capacity (6MWD) and health status (Medical Outcomes Study Short Form 36, [SF-36], Version 2[11]). The 6-minute walk test was performed twice, separated by 24 hours.[12] The best 6MWD was used in the analysis. Subjects who were receiving LTOT performed the test breathing oxygen supplied at their prescribed flow rate for daily activities. Oxygen saturation (SpO_2, Konica Minolta Pulsox Me Oximeter and finger probe, Osaka, Japan) was monitored continuously throughout the test and the test was terminated if SpO_2 reached below 80%.[13] The lowest SpO_2 measured during or immediately post-test was recorded. The Borg category ratio scale [14] was used to measure dyspnea prior to and upon test completion. Heart rate was monitored continuously throughout the test using telemetry (Polar A1, Polar Electro, Oy, Finland).

Secondary outcome measures comprised dyspnea (Baseline and Transition Dyspnea Indices, BDI/TDI [15]), peripheral muscle force (quadriceps force, QF) and limitations in ADL. Quadriceps force was assessed during a maximum isometric quadriceps contraction using a hand-held dynamometer with fixing-belt (μTas F-1, Anima Corporation, Tokyo, Japan). Measurements were made on the dominant side and the highest value of three technically correct attempts was used in the analyses. Subjects rated their limitations in ADL using a standard scale.[16] This scale evaluates six activities (i.e. feeding, transfers, dressing, bathing, shopping, and transportation) and assigns a score of 1 (independent) or 0 (dependent) for each activity. The total score was used in

the analysis.

Hospitalization

The number of hospital admissions and total bed-days (sum of bed-days from all admissions) in the 12-month period before and following the PRP were recorded. These data were collected by self report and verified by searching hospital databases.

Pulmonary Rehabilitation Program

Subjects in MRC grades 2, 3, and 4 attended an 8-week outpatient program comprising two sessions each week (90 minutes duration) during which they were individually supervised for the exercise training and, together with other subjects with IPF, participated in the education component of the program. This program has been described in detail elsewhere.[5] In brief, each session included exercise training, relaxation, breathing retraining (breathing control techniques aimed at reducing respiratory frequency) and education. The exercise component comprised endurance and strength training of the upper and lower limbs. Lower limb endurance training was performed using a cycle ergometer with the initial workload prescribed at 50% of the peak power achieved on the baseline ICET. Once subjects could achieve 20 min of continuous cycling, the workload was increased within symptom tolerance.[5] Subjects were instructed to undertake a home exercise program on 4 or 5 days each week that included walking training and strength training. Progression of the intensity and/or duration of each exercise occurred each week within symptom tolerance provided that SpO_2 was maintained above 85%. Patients received education regarding the benefits and importance of exercise, energy conservation techniques and self-management of exacerbations.

Subjects in MRC grade 5 underwent an unsupervised, 8-week home-based program. The decision to provide a home-based program was made because of severe symptoms that restricted their ability to travel to the hospital to attend classes, and evidence of a high attrition from center-based PRP among patients with severe disability.[17] Exercise training comprised endurance and strength training similar to that prescribed for subjects in MRC grades 2, 3, and 4 with the exception that lower limb endurance exercise was confined to walking. Subjects were prescribed interval training (walk for 1 minute at 100% of the average walking speed achieved on the 6-minute walk test alternating with 1 minute of walking at 50% of this speed). A physiotherapist (RK) provided instruction in exercise and breathing retraining (breathing control techniques). An education booklet was provided at the baseline assessment that covered the topics included in the out-patient program. In addition, the physiotherapist reviewed subjects every 2 weeks when they attended the hospital for consultation with their respiratory physician. At this time, subjects performed their exercise program in the presence of the physiotherapist and, where necessary, the exercise prescription and flow rate of supplemental oxygen were modified to ensure symptoms were tolerable and SpO_2 was maintained above 85%. During the 8 weeks, subjects were encouraged to undertake daily exercise and a physiotherapist made contact by phone twice each week to provide motivation and support, and to resolve any problems with the program.

For all subjects, adherence with the home exercise program was recorded using a diary card and medical therapy was unchanged during the PRP.

Data Management and Statistical Analysis

The Shapiro-Wilks test was used to examine the extent to which data approached a

normal distribution. Data that did not conform to a normal distribution were transformed or were analyzed using non-parametric tests. Missing data were replaced by the last observation carried forward method.[18]

Within group changes in the outcome measures following the PRP were compared using paired *t* tests or Wilcoxon signed rank test. Differences between groups (i.e. MRC grades) at baseline and the magnitude of change in outcome measures following rehabilitation were compared using a one-way analysis of variance (ANOVA) or Kruskal-Wallis test, and Chi-square test. For those variables showing a significant difference, Bonferroni adjustments were applied to post-hoc tests to account for multiple comparisons. Hospitalization data for the 12 months pre- and post-rehabilitation were compared using were compared using Chi-square test (number of subjects admitted to hospital and total number of admissions) and paired t-tests (total bed days) and Wilcoxon signed rank test (average length of stay). Data from individuals who did not survive the 12 months following the PRP were excluded from this analysis.

Data are expressed as means ± SD or 95% confidence intervals unless otherwise stated. The significance level was set at $P<0.05$. All analyses were performed using SPSS software Version 17 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Subject Characteristics and Baseline Measures

The baseline characteristics of the subjects grouped by MRC grade are shown in Table 1. Six-minute walk distance, QF, ADL score and all subscales of the SF-36, with the exception of bodily pain, decreased with increasing MRC grade (all $P<0.05$).

Effects of the Rehabilitation Program

No adverse events were recorded during exercise training. Table 2 provides data on adherence with the PRP and the outcome measures following rehabilitation. Subjects in MRC grades 2 and 3 improved in all outcomes with the exception of the SF-36 subscale for bodily pain (all $P<0.05$). There were differences between groups in the magnitude of change in 6MWD, TDI, QF, ADL and SF-36 scores with the exception of bodily pain and social function (all $P<0.05$). Specifically, subjects in MRC grades 2 and 3 achieved a greater improvement in all outcome measures except ADL score, compared with those in grades 4 or 5. The magnitude of increase in 6MWD in subjects in grade 2 was within the range (29 to 34m) considered to be clinically important.[19] Subjects in MRC grades 2 and 3 demonstrated improvements in all subscales of the SF-36 that exceeded the minimum important difference, with the exception of bodily pain in grade 2 subjects.[20]

Hospitalization

During the follow-up period, two subjects in grade 5 died. Table 3 shows the number of admissions and total bed-days for the remaining 63 subjects in the 12 months before and following rehabilitation. Subjects in MRC grades 2, 3 and 4 had less admissions following rehabilitation (all $P<0.05$).

DISCUSSION

In this study, we compared the response to pulmonary rehabilitation in IPF subjects grouped according to their severity of disability using the MRC dyspnea scale. While adherence with the PRP was similar irrespective of MRC grade, attrition tended to be greater in MRC grade 4 and 5 subjects, however, this difference was not significant possibly due to the small sample size. Most notably, the magnitude of benefit following rehabilitation varied depending on the baseline level of disability. In MRC grade 2 and 3 subjects, there were significant improvements in 6MWD, SF-36, QF and ADL score after the PRP. The magnitude of improvement in 6MWD in MRC grade 2 subjects and health status, in both MRC grade 2 and 3 subjects reached the thresholds for clinical significance.[19,20] In contrast, subjects in grades 4 and 5 showed little or no improvement, or deteriorated. We also evaluated the effect of rehabilitation on hospitalization, and found that hospitalizations were reduced in the 12 months following rehabilitation for subjects in MRC grades 2, 3 and 4. To our knowledge, this is the first study investigating the effects of a PRP on outcomes that include hospitalizations in subjects with IPF.

The finding that subjects in MRC grade 5 show little benefit from rehabilitation is consistent with some [21, 22] but not all studies [23] in COPD subjects with severe disability. However, in contrast to our findings, these studies [21-23] all reported improvements in MRC grade 4 subjects. There are several factors that may contribute to the lack of improvement following rehabilitation in IPF subjects in grades 4 and 5. The clinical course of patients with IPF is variable [24, 25] and the median survival is approximately 3 years from the time of diagnosis.[26-28] The MRC dyspnea grade is both a good indicator of disease severity and survival in IPF.[29] It is possible that rapid disease progression

limited the capacity for benefits to be gained from rehabilitation in MRC grade 4 and 5 subjects. The increase in the length of stay for hospital admissions in the 12 months following rehabilitation in grade 5 subjects provides support for this contention and suggests that the clinical status of these patients was deteriorating rapidly. The problem of attempting to control severe dyspnea, cough and profound hypoxemia during exercise training may have resulted in a training intensity that was insufficient to achieve a physiologic effect. A high proportion of subjects in grades 4 (76%) and 5 (87%) were taking oral corticosteroids and it is possible that the effects of the training regimen were diluted by steroid-induced muscle abnormalities.[30, 31] Further, the program may have been too short to overcome the very poor physical fitness and muscle deconditioning that had occurred after a long period of reduced activity.[22] Although possible, we consider it unlikely that the home-based setting and lower number of exercise sessions per week account for the lack of benefit in subjects in grade 5 given those in grade 4 also failed to show significant improvements in 6MWD, health status or quadriceps strength despite undergoing an out-patient program that demonstrated benefit in subjects with less severe disability (i.e. grades 2 and 3).

Ferreira et al[32] in a retrospective study, examined the effects of rehabilitation in 99 patients with ILD (50 with IPF). These authors reported an association between a lower baseline 6MWD and a greater magnitude of increase following rehabilitation. Our findings contrast with these observations. However, these authors did not state whether the patients were in a stable condition at the time of commencing the PRP. Therefore, deconditioning resulting from physical inactivity during a recent exacerbation may have contributed to this observation.

Pulmonary rehabilitation has been shown to reduce hospitalization in patients with COPD,[33-35] and it may be the result of improved muscle function, increased physical activity or changes in behavior or attitudes to disease management.[36-38] In grade 4 subjects, a decrease in hospitalization occurred in the absence of significant improvements in other outcome measures. The education sessions may have contributed to the reduction in hospitalization as a result of improved adherence with treatments and earlier recognition and management of exacerbations.[39]

Limitations

This study has several limitations that include the small sample size. We did not include a control group and thus are unable to account for confounding factors that may have affected both the outcomes measured immediately following the PRP and the hospitalization data. Further, due to the lack of a control group we are both unable to comment on whether a rapid rate of disease progression in MRC grade 4 and 5 subjects impacted on outcomes or whether the PRP had any effect on the rate of decline. We used the SF-36 because there are no disease-specific instruments to measure HRQoL in subjects with IPF. However, the SF-36 may lack sensitivity to demonstrate improvements in subjects with severe disability. Finally, we did not measure physical activity and therefore it is unknown whether changes in physical activity occurred following the PRP, and if such changes contributed to the reduction in hospitalization following rehabilitation.

Implications

The present findings suggest that patients with IPF should be referred for pulmonary rehabilitation at an early stage in their disease trajectory. It would appear that patients

with IPF in MRC grades 2 and 3 can undertake an exercise training program that is similar to that provided to COPD patients. However, a different approach to exercise training should be considered for grade 4 and 5 patients with IPF who are likely to require high flow of supplementary oxygen during exercise.[40] Future studies are required to examine training approaches that may benefit those with severe disability, such as neuromuscular electrical stimulation of the quadriceps.[41]

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Table 1. Baseline characteristics of the subjects

	Grade 2 (n=16)	Grade 3 (n=17)	Grade 4 (n=17)	Grade 5 (n=15)
Age, yr	65.4 ± 7.7	67.8 ± 7.4	68.1 ± 7.6	68.7 ± 7.5
Gender, M/F	13/3	13/4	11/6	9/6
BMI, kg/m^2	22.2 ± 1.7	22 ± 3.9	20.1 ± 3.5	19.8 ± 2.2
Time since diagnosis, months	15 ± 10	27 ± 16	38 ± 19*	42 ± 21*
LTOT	2 (13%)	11 (65%)*	15 (88%)*	15 (100)*
Oral corticosteroids	1 (6%)	7 (41%)	13 (76%)*	13 (87%)*†
Cough	6 (38%)	10 (59%)	12 (71%)	13 (87%)*
RVSP, mm Hg	27 ± 14	42 ± 11	62 ± 20*†	69 ± 17*†
Pulmonary function				
FEV_1, L	1.8 ± 0.5	1.7 ± 0.4	1.6 ± 0.5	1.3 ± 0.4
FEV_1, % predicted	88 ± 12	78 ± 13	73 ± 19	65 ± 15*
FVC, L	2.2 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	1.5 ± 0.5*
FVC, % predicted	83 ± 11	67 ± 13*	60 ± 16*	51 ± 11*†
DL_{CO}, mL/min/mmHg	8.4 ± 2.5	5.8 ± 1.4*	4.4 ± 1.9*	3.5 ± 1.5*†
DL_{CO}, % predicted	58 ± 20	35 ± 10*	28 ± 12*†	21 ± 8*†
Exercise capacity				
6MWD, m	439 ± 52	330 ± 60*	201 ± 50*†	157 ± 43*†
Nadir SpO_2 during or post- test, %	87 ± 7	83 ± 7	80 ± 6*	78 ± 4*
Peak-exercise dyspnea	4.3 ± 1.1	5.3 ± 1.3	5.4 ± 1.2	5.9 ± 0.7*
Peak-exercise HR, bpm	120 ± 11	124 ± 12	122 ± 18	123 ± 16
Health status				
SF-36				
Physical functioning	55.3 ± 7.2	34.1 ± 18.4*	20.3 ± 7.0*	16.0 ± 9.1*†‡
Role physical	55.9 ± 15.9	22.4 ± 17.3*	23.2 ± 13.4*	19.6 ± 10.3*
Bodily pain	66.5 ± 25.1	57.2 ± 29.0	65.6 ± 29.1	65.6 ± 28.4
General health	50.9 ± 11.0	35.8 ± 18.9	24.1 ± 16.8*	19.1 ± 10.7*
Vitality	54.7 ± 11.7	37.9 ± 21.5*	26.5 ± 18.0*	19.6 ± 15.3*
Social function	62.5 ± 18.8	42.6 ± 27.6	36.0 ± 15.2*	30.0 ± 14.8*
Role emotional	66.7 ± 15.2	47.1 ± 28.2	30.9 ± 21.4*	19.4 ± 15.3*†
Mental health	61.6 ± 14.3	42.9 ± 20.8*	41.8 ± 17.2*	35.0 ± 12.0*
Dyspnea				
BDI focal score	8.8 ± 1.3	4.7 ± 1.6*	3.1 ± 0.8*†	2.3 ± 0.5*†
Muscle force				
QF, kg	27 ± 10	19 ± 8	14 ± 9*	10 ± 4*†
QF, % body weight	49 ± 14	32 ± 10*	28 ± 13*	22 ± 9*
ADL				
ADL score	5.8 ± 0.4	4.9 ± 1.0*	4.0 ± 1.0*†	2.1 ± 0.9*†‡

Values are mean ± SD or numbers (%) of subjects. ADL = activities of daily living; BDI = baseline dyspnea index; BMI = body mass index; LTOT = long term oxygen therapy; QF = quadriceps force; RVSP = right ventricular systolic pressure; SF-36 = Medical Outcomes Study Short Form 36; SpO_2 = percutaneous oxygen saturation; RVSP data MRC grade 2 n=13, grade 3 n=16, grade 4 n=16, grade 5 n=14.

Post-hoc: * P<0.05 versus grade 2; † versus grade 3; ‡ versus grade 4.

Table 2. Program adherence and changes in outcome measures following rehabilitation

	Grade 2 (n=16)	Grade 3 (n=17)	Grade 4 (n=17)	Grade 5 (n=15)
Attrition	2 (13%)	2 (12%)	5 (29%)	6 (40%)
Exacerbation	1	0	2	3
Declined	1	1	1	1
Other	0	1	2	0
Deceased	0	0	0	2
Supervised sessions	14.9 ± 1.0	14.9 ± 0.8	15.4 ± 1.0	NA
Home exercise, sessions per week	4.2 ± 0.9	4.4 ± 0.9	3.9 ± 1.6	3.9 ± 1.5
6MWD, m	31 (19, 44)¶	19 (4, 33)§	9 (-1, 20)*	0 (-8, 8)*†
% change	7 (4, 10)	5 (1, 10)	3 (-2, 8)	-1 (-6, 4)*†
SF-36				
Physical functioning	6.6 (1.5, 11.6)§	11.2 (6.2, 16.2)¶	0.3 (-1.8, 2.4)†	-1.0 (-3.6, 1.6)*†
Role physical	12.5 (4.6, 20.4)¶	9.2 (0.8, 17.6)§	0.2 (-4.6, 4.8)*†	-0.8 (-2.6, 1.0)*†
Bodily pain	2.3 (-4.3, 6.5)	4.9 (-6.9, 16.7)	-3.7 (-10.6, 3.2)	-0.9 (-13.9, 12.2)
General health	10.3 (3.4, 17.1)¶	7.9 (1.4, 14.4)§	-1.8 (-4.5, 1.0)*†	-0.7 (-3.0, 1.6)*
Vitality	8.2 (2.4, 14.0)¶	9.6 (2.7, 16.4)¶	0.4 (-3.1, 3.9)	-2.9 (-10.0, 4.2)*†
Social function	8.6 (1.0, 16.2)§	4.4 (-4.0, 12.9)	-0.7 (-4.3, 2.8)	-0.8 (-4.9, 3.3)
Role emotional	7.3 (2.2, 12.4)¶	7.4 (2.3, 12.3)¶	-1.0 (-6.0, 4.0)†	-1.4 (-3.5, 0.7)*†
Mental health	6.9 (2.3, 11.4)¶	8.5 (-1.4, 18.4)	2.4 (-2.9, 7.6)	-2.7 (-8.2, 2.9)*
TDI focal score	1.6 (1.0, 2.3)	0.8 (0.1, 1.6)	-0.2 (-0.8, 0.3)*	-0.6 (-1.2, -0.1)*†
QF, kg	4.4 (2.3, 6.4)¶	2.7 (0.4, 5.0)§	0.02 (-0.4, 0.5)*	0.2 (-0.6, 0.9)*
QF, % body weight	8.3 (4.7, 11.9)¶	5.5 (0.7, 10.2)§	-0.1 (-1.0, 0.8)*	0.3 (-1.2, 1.9)*
ADL score	0.7 (0.3, 1.1)§	1.1 (0.7, 1.6)¶	0.7 (0.3, 1.1)¶	0.2 (-0.03, 0.4)†

Values are mean ± SD, numbers (%) of subjects and mean difference (95% confidence intervals) between baseline and immediately following the pulmonary rehabilitation program. Data for number of supervised sessions relates only to subjects who completed the program. ADL = activities of daily living; NA = not applicable; QF = quadriceps force; SF-36 = Medical Outcomes Study Short Form 36; TDI = Transition Dyspnea Index.

§ $P<0.05$, ¶ $P<0.01$ for comparison of pre- and post-rehabilitation data

Post-hoc: * $P<0.05$ versus grade 2; † versus grade 3.

Table 3. Hospitalization data for the 12 months before and immediately following pulmonary rehabilitation excluding deceased patients

	Grade 2 (n=16)		Grade 3 (n=17)		Grade 4 (n=17)		Grade 5 (n=13)	
	Pre PR	Post PR	Pre PR	Post PR	Pre PR	Post PR	Pre PR	Post PR
Subjects admitted	7 (44%)	4 (25%)	13 (76%)	5 (29%)	14 (82%)	9 (53%)	12 (92%)	12 (92%)
Total number admissions	10	4*	18	7*	25	11*	19	18
Total bed-days	227	75*	408	172*	733	360*	520	811*
Median LOS per admission, days	23 (18 – 47)	17 (15 – 23)*	28 (18 – 35)	26 (19 – 46)*	50 (27 – 68)	36 (24 – 42)*	35 (18 – 48)	63 (39 – 87)*

Data from the two subjects in grade 5 who died during the pulmonary rehabilitation program are not included.

Values are means or numbers (%) of subjects, or median (interquartile range). LOS = length of stay; PR = pulmonary rehabilitation.

* $P<0.05$ versus Pre PR.