Title: Evaluation of Activity Limitation in Patients with Idiopathic Pulmonary Fibrosis Grouped According to Medical Research Council Dyspnea Grade

Running head: Activity Limitation in Idiopathic Pulmonary Fibrosis

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ABSTRACT

Objective: To investigate relationships between Medical Research Council (MRC) dyspnea grade and peripheral muscle force, activities of daily living (ADL) performance, health status, lung function and exercise capacity in subjects with idiopathic pulmonary fibrosis (IPF).

Design: Prospective cross-sectional observational study.

Setting: University hospital

Participants: Subjects with IPF (n=65, 46 men) in a stable clinical state with mean age 68 ± 7 years.

Interventions: Not applicable.

Main Outcome Measures: Right ventricular systolic pressure (RVSP) via transthoracic echocardiography, pulmonary function, isometric quadriceps force (QF) and handgrip force (HF), 6-minute walk distance (6MWD), ADL score, and health status (SF-36) were assessed, and compared between subjects grouped according to MRC grade.

Results: Sixteen, 17, 17 and 15 subjects were in MRC grade 2, 3, 4, and 5 respectively. RVSP, pulmonary function, QF, HF, 6MWD, ADL and SF-36 scores decreased with increasing MRC grade (all $p<0.001$). All measures were lower ($p<0.05$) in grade 4 and 5 compared to grade 2 and 3 subjects. Strong associations were found between MRC grade and 6MWD (rho=-0.89, p=0.001) and ADL score (rho=-0.82, p=0.001). MRC grade was also associated with RVSP, pulmonary function, QF and HF (all rho≥0.56, p=0.001).

Conclusions: The MRC dyspnea scale provides a simple and useful method of categorizing individuals with IPF with respect to their activity limitation and may assist in understanding the impact of IPF on an individual.

KEYWORDS

Dyspnea; Medical Research Council dyspnea scale; Activity limitation; Idiopathic pulmonary fibrosis.

LIST OF ABBREVIATIONS

ADL: activities of daily living; ANOVA: one-way analysis of variance; COPD: chronic obstructive pulmonary disease; DL_{CO}: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HF: handgrip force; IPF: idiopathic pulmonary fibrosis; LTOT: long term oxygen therapy; MRC: Medical Research Council; PRP: pulmonary rehabilitation program; QF: quadriceps force; RVSP: right ventricular systolic pressure; 6MWD: 6-minute walk distance; 6MWT: 6-minute walk test; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; SpO_2: oxygen saturation; TLC: total lung capacity.

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease that results in severe activity limitation. The activity limitation arises as a result of exertional dyspnea that limits the ability to undertake activities of daily living (ADL) and leads to impairment in health status.[1]

Quantification of activity limitation is an important component of the assessment of patients with IPF in order to determine the impact of the disease on an individual and as an outcome measure of treatment. The Medical Research Council (MRC) dyspnea scale is commonly used to grade the severity of activity limitation due to dyspnea in patients with chronic obstructive pulmonary disease (COPD).[2, 3] This scale has the advantage of being simple to use, and, in patients with COPD has demonstrated validity and reliability, and provides information regarding survival.[2-6] Further, the MRC dyspnea scale has been proposed as a method for selecting individuals who are likely to benefit from pulmonary rehabilitation.[7]

In patients with IPF, several studies have demonstrated an association between MRC dyspnea grade and radiographic features, pulmonary function, exercise capacity and prognosis.[8-12] However, there are no studies that have compared the extent of activity limitation due to dyspnea, as assessed using the MRC dyspnea scale, and impairments in peripheral muscle force, ADL performance and health status; impairments that may be amenable to pulmonary rehabilitation.[7] We hypothesized that strong relationships would exist between MRC dyspnea grade and measures that reflect physiologic impairments impacting on exercise tolerance such as quadriceps strength and ADL performance, measures that are not routinely collected in patients undergoing pulmonary rehabilitation. In this study, we examined relationships between MRC dyspnea grade and peripheral muscle force, ADL performance, health status, lung function and exercise capacity in subjects with IPF grouped according to MRC dyspnea grade.

METHODS

Study Design

A prospective cross-sectional study design was utilized. During a 2-week period, all subjects completed measurements of body anthropometrics, right ventricular systolic pressure (RVSP) via transthoracic echocardiography, pulmonary function, arterial blood gas tensions, peripheral muscle force, functional exercise capacity and assessment of ADL and health status.

Subjects

A convenience sample of 65 consecutive subjects with IPF, who were referred to the pulmonary rehabilitation program (PRP) at Nagasaki University Hospital, Japan, was included in this study. The diagnosis of IPF was made in accordance with published guidelines.[1] Subjects were included if they were under the care of a respiratory physician, ambulant, reported dyspnea during normal daily physical activities (MRC grades 2-5) 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.[13, 14] The study was confined to patients with MRC dyspnea grades 2 or higher as individuals who report dyspnea only on strenuous activity (i.e. MRC dyspnea grade 1) were not referred to the PRP. Other exclusion criteria comprised severe orthopedic or neurological impairments limiting exercise performance, unstable cardiac disease, active cancer, inability to complete questionnaires or perform the 6-minute walk test (6MWT), and any previous participation in a PRP.

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

MRC dyspnea scale

Subjects read the descriptive phrases for each of the five grades (numbered 1-5) of the MRC dyspnea scale [2] and then selected the number that best corresponded to their severity of activity limitation due to dyspnea during daily living.

Pulmonary Function and Arterial Blood Gas Tensions

Pulmonary function (spirometry, lung volumes and diffusing capacity for carbon monoxide) and arterial blood gas tensions were measured in accordance with a standard protocol [15, 16] and referenced to predicted values.[17]

Peripheral Muscle Force

Quadriceps force (QF) was measured as the peak force (kilograms, kg) developed during a maximum isometric quadriceps contraction using a hand-held dynamometer with fixing-belt [a] in accordance with a standard protocol.[18] The measurement was made with the subject seated with their hip and knee in 90 degrees flexion. Handgrip force (HF, kg) was measured with a hand dynamometer [b]. Measurements were made on the dominant side and the highest value of three technically correct attempts was used in the analyses. Quadriceps force was expressed as a percentage of body weight.

Functional Exercise Capacity

The 6MWT was performed twice, separated by 24 hours, in accordance with published guidelines.[19] The best distance was used in the analysis. Subjects who were receiving long term oxygen therapy (LTOT) performed the 6MWT breathing oxygen supplied at their prescribed flow rate for normal daily activities. Oxygen saturation (SpO_2) measured by pulse oximetry [c] was monitored continuously throughout the test and the test was terminated if SpO_2 fell below 80%. The Borg category ratio scale [20] was used to measure dyspnea before and upon test completion.

Activities of Daily Living

Limitations in ADL were assessed using a standard scale.[21] The scale evaluates six fundamental daily activities (feeding, ability to transfer, dressing, bathing, shopping and transportation). For each of the six activities, a score of 0 (dependent) or 1 (independent) is assigned and the scores of the six activities are summed to provide a measure of ADL performance. The total score was used in the analysis.[22]

Health Status

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36, Version 2) was used to assess health status.[23] The SF-36 consists of eight subscales that assess components of physical and mental health and includes an additional health transition item that is not scored. Scores for each subscale range from 0 to 100, with a lower score indicating a greater level of impairment. Measurement of health status using the SF-36 has been shown to be valid and reliable in subjects with IPF.[24]

Data Management and Statistical Analyses

We used the Shapiro-Wilks test 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.

All analyses were performed using SPSS Statistics v. 17[d]. Comparison of variables between subjects grouped according to MRC dyspnea grade were performed using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, and Chi-squared test. Bonferroni adjustments were applied to account for multiple comparisons. Specifically, to minimize the risk of a Type I error, we set the significance level (p value) for the ANOVA and Kruskall-Wallis tests at 0.05 divided by the number of comparisons performed (i.e. 0.05 / 29 where 29 was the number of comparisons performed). Spearman's rank correlation coefficients were used to examine relationships between MRC dyspnea grade and RVSP, pulmonary function [% predicted forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DL_{CO})][1], muscle force, 6MWD and ADL performance. The significance level was adjusted (i.e. significance = $p<0.006$) to account for multiple tests being performed.

RESULTS

The number of subjects in MRC dyspnea grade 2, 3, 4 and 5 was 16 (25%), 17 (26%), 17 (26%) and 15 (23%), respectively. Data for demographic variables, RVSP, pulmonary function, arterial blood gas tensions, 6MWD and SF-36 subscale scores are shown in Table 1. Significant differences were observed between MRC dyspnea grade and time since diagnosis of IPF, use of LTOT and oral corticosteroids, RSVP and pulmonary function (% predicted). Post-hoc analyses revealed that the significant differences mostly were found between subjects in dyspnea grade 2 and those in grades 3, 4 and 5 (Table 1).

Six-minute walk distance showed a progressive and significant decline with increasing MRC grade (Table 1). A total of 43 subjects (2, 11, 15 and 15 in MRC grades 2, 3, 4 and 5 respectively) performed the 6MWT breathing supplemental oxygen at flow rates ranging from 1 to 5 L/min. The 6MWT was terminated prematurely when SpO_2 fell below 80% in three (19%), three (18%), seven (41%) and six (40%) subjects in MRC dyspnea grades 2, 3, 4 and 5 respectively. The number of subjects who rested during the 6MWT due to intolerable dyspnea was one (6%), three (18%), eight (47%) and nine (60%) in grades 2, 3, 4 and 5 respectively. Mean scores for dyspnea on completion of the 6MWT were 4.3 ± 1.1, 5.3 ± 1.3, 5.4 ± 1.2 and 5.9 ± 0.7 for subjects in grade 2, 3, 4 and 5 respectively ($p<0.05$ grade 5 *vs.* grade 2 subjects). The mean difference in 6MWD between subjects in MRC dyspnea grades 3, 4 and 5, compared to grade 2 subjects, was -109 m, (95% confidence intervals 69 to 149 m), -238 m (201 to 273 m), and -282 m (247 to 316 m) respectively.

Scores for all subscales of the SF-36, with the exception of bodily pain, were lower as the MRC dyspnea grade increased (all $p<0.001$, Table 1). Post-hoc analyses revealed significant differences between grade 2 *vs.* 3 for Physical functioning, Role physical, Vitality, and Mental health subscales; grade 2 *vs.* 4 and 5 for all subscales except bodily pain; grade 3 *vs.* 4 and 5 for Physical functioning and Role emotional, and, grade 4 *vs.* 5 for Physical functioning (Table 1).

Figure 1 shows data for muscle force, 6MWD, and ADL scores. All measures were significantly lower in grade 4 and 5 subjects compared to subjects in grades 2 and 3 ($p<0.01$).

The associations between MRC grade and other measures are shown in Table 2. Strong associations were found between MRC grade and 6MWD (rho=-0.89, p=0.001) and ADL score (rho=-0.82, p=0.001). MRC grade was also associated with RVSP, FVC, TLC, DL_{CO}, QF and HF(all $p<0.001$).

DISCUSSION

The main findings of this study are that, in subjects with IPF, (i) pulmonary function, peripheral muscle force, 6MWD, ability to perform ADL and health status all deteriorated with increasing MRC dyspnea grade, (ii) subjects in grades 4 and 5 had significantly greater impairments than those in grades 2 and 3, and, (iii) the associations between MRC dyspnea grade and impairment in exercise capacity and ADL performance were stronger than with the magnitude of pulmonary function impairment. These findings support the use of the MRC dyspnea scale as a simple and valid method of categorizing individuals with IPF in terms of their activity limitation due to dyspnea.

To our knowledge, this is the first study to compare peripheral muscle force in subjects with IPF grouped according to the MRC dyspnea scale. Factors that may contribute to the greater impairment in muscle force with increasing MRC dyspnea grade in our sample include more pronounced deconditioning due to the longer duration of the disease and an increase in the proportion of subjects who were taking oral corticosteroids.[25, 26] The greater impairment in QF observed with increasing MRC dyspnea grade may be a factor contributing to the lower 6MWD.[27]

We found marked differences in measures of lung function, that reflect the extent of lung fibrosis and gas exchange abnormalities, between MRC dyspnea grades. In subjects with IPF, an association between MRC dyspnea grade and impairment in pulmonary function has been reported,[8, 9] and is consistent with data in COPD populations.[28]

The lower 6MWD with increasing MRC dyspnea grade suggests that functional exercise capacity is strongly related to the severity of dyspnea experienced in daily life. The mean difference in 6MWD between subjects in MRC dyspnea grades 3, 4 and 5, compared to grade 2 subjects exceeded the threshold of 28 m reported to be the minimum important difference in this population.[29] Although there are few data pertaining to the relationship between MRC dyspnea grade and 6MWD in subjects with IPF, our findings are consistent with previous research.[10]

Differences in ADL score and health status were found between subjects across the MRC dyspnea grades with the exception of the SF-36 subscale for bodily pain. Specifically, subjects in grades 4 and 5 were markedly limited in their ability to perform ADL and had severely impaired health status. This is not surprising given the progressive and debilitating nature of the disease. We used the SF-36 as our measure of health status because the only disease specific health-related quality of life measure for the IPF population has not been translated into Japanese.[30] Dyspnea has been shown to be the most important determinant of health status in people with IPF,[24, 31] and the severity of dyspnea has been shown to be associated with the duration of the disease.[32]

Study Limitations

Although the sample size in our study was greater than in other studies that have examined the utility of the MRC dyspnea scale in subjects with IPF,[8-11] it was still relatively modest. Measurement of daily physical activity or participation in an exercise regimen, and identification of the presence of pulmonary hypertension via right heart catheterization, would have been useful to evaluate their contribution to activity limitation in our subjects,[33] but was beyond the scope of the study.

Large differences were observed in most variables when comparing subjects in dyspnea grades 3, 4 and 5 with those in grade 2. However often little difference was observed in these same measures between subjects in grades 4 and 5. This is likely to reflect a limitation in the ability of the MRC dyspnea scale to discriminate between subjects with more severe activity limitation.[34]

Clinical Implications

In subjects with IPF, the MRC dyspnea scale not only reflects the severity of activity limitation but also impairment in pulmonary function and health status. This information may aid in the understanding of disease severity and progression, and the impact of IPF on the individual. In situations where it is not possible to measure peripheral muscle force, functional exercise capacity or ADL performance, the MRC dyspnea scale may provide useful information. We conclude that the MRC dyspnea scale is useful as a measure of activity limitation in the comprehensive assessment of patients with IPF.

CONCLUSIONS

In conclusion, our findings show that the MRC dyspnea scale provides a simple and useful method of categorizing individuals with IPF with respect to their activity limitation.

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SUPPLIERS' LIST

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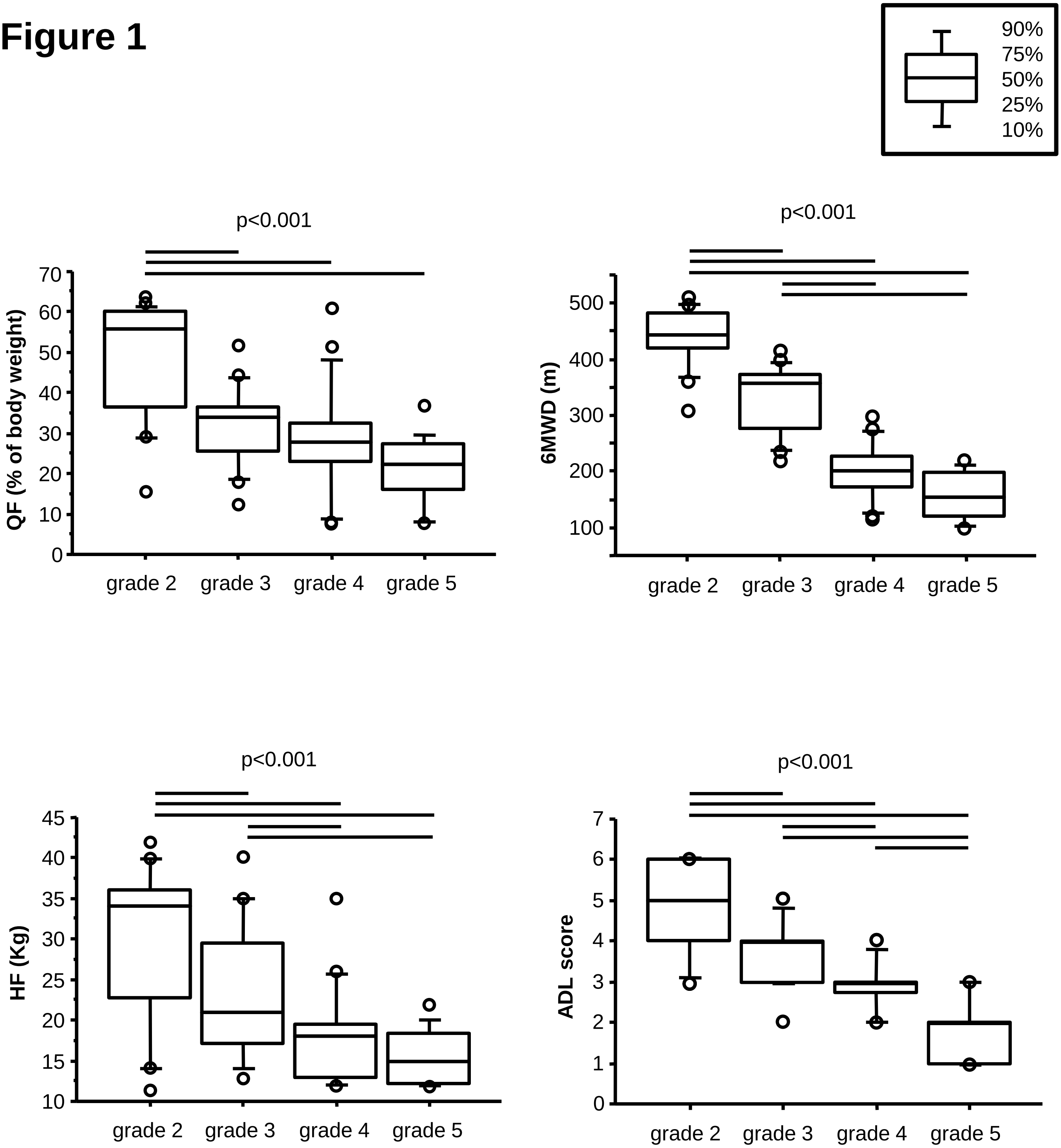
FIGURE LEGENDS

Figure 1. QF, HF, 6MWD, and ADL score for subjects grouped according to MRC dyspnea grade.

Significant differences ($p<0.001$) were found between the grades for all measures (ANOVA or Kruskal-Wallis test). The median line overlaps the line identify the 75th percentile for the ADL scores for subjects in grades 3, 4 and 5.

Figure 1



90%
75%
50%
25%
10%
p<0.001
QF (% of body weight)
0
10
20
30
40
50
60
70
grade 2
grade 3
grade 4
grade 5
p<0.001
6MWD (m)
100
200
300
400
500
grade 2
grade 3
grade 4
grade 5
p<0.001
HF (Kg)
10
15
20
25
30
35
40
45
grade 2
grade 3
grade 4
grade 5
p<0.001
ADL score
0
1
2
3
4
5
6
7
grade 2
grade 3
grade 4
grade 5

Table 1. Demographic, pulmonary function, 6MWD and health status data of the 65 subjects grouped according to MRC dyspnea grade

	Grade 2 (n=16)	Grade 3 (n=17)	Grade 4 (n=17)	Grade 5 (n=15)	p Value
Age, yr	65.4 ± 7.7	67.8 ± 7.4	68.1 ± 7.6	68.7 ± 7.5	0.611
Gender, M/F	13/3	13/4	11/6	9/6	0.520
BMI, kg/m^2	22.2 ± 1.7	22.0 ± 3.9	20.1 ± 3.5	19.8 ± 2.2	0.055
Smokers/ex smokers	3/9	0/12	0/13	0/10	0.122
Time since diagnosis, months	15 ± 10	27 ± 16	38 ± 19*	42 ± 21*	< 0.001
LTOT	2 (13%)	11 (65%)*	15 (88%)*	15 (100)*	< 0.001
Oral corticosteroids	1 (6%)	7 (41%)	13 (76%)*	13 (87%)*†	< 0.001
RVSP, mm Hg	27 ± 14	42 ± 11	62 ± 20*†	69 ± 17*†	< 0.001
Pulmonary function					
FEV_1, L	1.8 ± 0.5	1.7 ± 0.4	1.6 ± 0.5	1.3 ± 0.4	0.050
FEV_1, % predicted	88 ± 12	78 ± 13	73 ± 19	65 ± 15*	< 0.001
FVC, L	2.2 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	1.5 ± 0.5	0.016
FVC, % predicted	83 ± 11	67 ± 13*	60 ± 16*	51 ± 11*†	< 0.001
FRC, L	1.8 ± 0.4	1.7 ± 0.4	1.5 ± 0.6	1.3 ± 0.4	0.075
FRC, % predicted	73 ± 14	68 ± 11	58 ± 14*	55 ± 11*†	< 0.001
TLC, L	3.6 ± 0.6	2.8 ± 0.7*	2.7 ± 0.8*	2.4 ± 0.6*	< 0.001
TLC, % predicted	78 ± 11	61 ± 11*	54 ± 12*	49 ± 9*†	< 0.001
DL_{CO}, mL/min/mmHg	8.4 ± 2.5	5.8 ± 1.4*	4.4 ± 1.9*	3.5 ± 1.5*†	< 0.001
DL_{CO}, % predicted	58 ± 20	35 ± 10*	28 ± 12*†	21 ± 8*†	< 0.001
PaO_2 at rest, mmHg	79.4 ± 8.2	72.3 ± 6.5	70.7 ± 10.2	64.9 ± 17.2	0.006
$PaCO_2$ at rest, mmHg	40.1 ± 1.0	41.0 ± 4.6	40.9 ± 5.1	43.9 ± 3.2	0.084
6MWD, m	439 ± 52	330 ± 60*	201 ± 50*†	157 ± 43*†‡	< 0.001
Health status					
Physical functioning	55.3 ± 7.2	34.1 ± 18.4*	20.3 ± 7.0*	16.0 ± 9.1*†‡	< 0.001
Role physical	55.9 ± 15.9	22.4 ± 17.3*	23.2 ± 13.4*	19.6 ± 10.3*	< 0.001
Bodily pain	66.5 ± 25.1	57.2 ± 29.0	65.6 ± 29.1	65.6 ± 28.4	0.679

General health	50.9 ± 11.0	35.8 ± 18.9	24.1 ± 16.8*	19.1 ± 10.7*	< 0.001
Vitality	54.7 ± 11.7	37.9 ± 21.5*	26.5 ± 18.0*	19.6 ± 15.3*	< 0.001
Social function	62.5 ± 18.8	42.6 ± 27.6	36.0 ± 15.2*	30.0 ± 14.8*	< 0.001
Role emotional	66.7 ± 15.2	47.1 ± 28.2	30.9 ± 21.4*	19.4 ± 15.3*†	< 0.001
Mental health	61.6 ± 14.3	42.9 ± 20.8*	41.8 ± 17.2*	35.0 ± 12.0*	< 0.001

Data are presented as means ± SD or number (n) and percentage (%) of subjects. BMI = body mass index; DL_{CO} = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; LTOT = long term oxygen therapy; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; RVSP = right ventricular systolic pressure; 6MWD = 6-minute walk distance; TLC = total lung capacity; RVSP data missing for 3 subjects in Grade 2 and 1 subject in each of grades 3, 4 and 5. Arterial blood gas tensions measured breathing oxygen in subjects in LTOT or breathing room air.

p values within the table refer to differences in group means or proportion of subjects. Significance level for undertaking post-hoc analyses as set at p<0.0017 [i.e. = 0.05/29 (where 29 = number of comparisons)]. Post-hoc analyses: *p<0.05 versus grade 2; † versus grade 3; ‡ versus grade 4.

Table 2. Spearman's correlation coefficients for the relationship between MRC grade and other variables

Variable	MRC grade	
	Spearman's rho value	p value
RVSP, mm Hg	0.73	0.001
Pulmonary function		
FVC, % predicted	-0.67	0.001
TLC, % predicted	-0.65	0.001
DL_{CO}, % predicted	-0.74	0.001
Peripheral muscle force		
QF, % of body weight	-0.62	0.001
HF, kg	-0.56	0.001
6MWD, m	-0.89	0.001
ADL score	-0.82	0.001

ADL = activities of daily living; DL_{CO} = diffusing capacity for carbon monoxide; FVC = forced vital capacity; HF = handgrip force; QF = quadriceps force; RVSP = right ventricular systolic pressure; 6MWD = 6 minute walk distance; TLC = total lung capacity.