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Evaluation of the Modified Medical Research Council Dyspnea Scale for Predicting Hospitalization and Exacerbation in Japanese Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective The modified Medical Research Council (mMRC) scale is recommended for conducting assessments of dyspnea and disability and functions as an indicator of exacerbation. The aim of this study was to investigate whether the mMRC scale can be used to predict hospitalization and exacerbation in Japanese patients with chronic obstructive pulmonary disease (COPD).

Methods In a previous 52-week prospective study, 123 patients with COPD were classified into five groups (grades 0 to 4) according to the mMRC scale and four groups (stages I to IV) according to the spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. The frequency and period until the first event of hospitalization and exacerbation were compared among the groups.

Results The population of patients who experienced hospitalization and exacerbation during the 52-week study period, with an mMRC scale grade of 4, 3, 2, 1 and 0 was 50.0 and 100, 55.6 and 88.9, 21.1 and 73.7, 2.6 and 48.7, and 4.0 and 22.0%, respectively. A multivariate analysis adjusted for the GOLD stage and age showed that the patients with an mMRC scale grade of ≥3 had higher frequencies of hospitalization and exacerbation than those with lower grades. Meanwhile, the patients with an mMRC scale grade of ≥2 showed a significantly earlier time until the first exacerbation, but not hospitalization, in comparison with those with grade 0.

Conclusion The present results indicate that, among Japanese patients with COPD, those with an mMRC scale grade of ≥3 have a significantly poorer prognosis and that the mMRC scale can be used to predict hospitalization and exacerbation.

Key words: COPD, dyspnea, hospitalization, exacerbation

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Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document 2014 is a useful guideline for physicians who are currently following patients with chronic obstructive pulmonary disease (COPD) (1). Exacerbation is an important life-threatening event in patients with COPD and can result in hospitalization and death (2-4). The modified British Medical Research Council (mMRC) scale employing a self-reported questionnaire is useful for assessing dyspnea and disability, and it's reliability has been confirmed (1, 5, 6). However, evidence of the relationship between the findings of dyspnea and disability and the incidence of hospitalization and exacerbation is limited, although dyspnea is known to be associated with mortality in COPD patients as a whole (7-9). In the present study, we evaluated the utility of the mMRC scale for predicting mor-

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tality, hospitalization and exacerbation as a consequence of the level of dyspnea (mMRC scale) and airflow obstruction (spirometric GOLD classification) in Japanese patients with COPD. For this purpose, we used the data obtained from our previous 52-week prospective observational trial involving 123 Japanese patients with COPD (10).

Materials and Methods

Data collection

Baseline mMRC scale data, including age, gender, body mass index, smoking habits, smoking index, comorbidities, duration of disease, lung function and medications, were collected based on our 52-week prospective observational trial involving 123 Japanese COPD patients conducted in accordance with the Good Clinical Practice (GCP) guidelines and approved by the Ethics Committee of Kurume University and Chikugo City Hospital (GCP no. 11127, September 2011) (10). Information regarding comorbidities in this study was obtained via interviews with the patients and the diagnoses of disease were confirmed by physicians. Hypertension, hyperlipidemia and diabetes were evaluated as comorbidities. The duration of COPD was defined as the period of time (yr) since the patient had been diagnosed by a physician as having COPD, emphysema and/or chronic bronchitis (10, 11). All patients received influenza virus vaccinations annually.

Assessment of the mMRC scale

The mMRC scale was assessed only once based on a self-report completed by each patient before observation.

Diagnosis and spirometric GOLD classification stage of COPD

The diagnosis of COPD was based on the findings of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7 after bronchodilator administration and the spirometric GOLD classification (GOLD stage), i.e. stage I (%FEV_1 predicted ≥80%), II (≤50%FEV_1 predicted <80%), III (≤30%FEV_1 predicted <50%) and IV (%FEV_1 predicted <30%), according to the GOLD documents (1). In order to exclude patients with asthma, only patients with a classification of FEV_1 <200 mL and/or <12% after bronchodilation were enrolled (10).

Frequency and dates of mortality, hospitalization and exacerbation

COPD-related and other causes of death were followed for 52 weeks. COPD-related death and hospitalization were considered as markers of severe exacerbation, whereas other causes of events were excluded from this analysis.

Exacerbation was classified as moderate or severe, excluding mild events from the medical records created by physicians and the daily journals of the patients covering a period of 52 weeks (10). Moderate exacerbation requiring a prescription for antibiotics and/or systemic corticosteroids was defined according to the symptom-based diagnosis, such as symptoms of increased cough and sputum production, changes in sputum color and worsening of dyspnea from a stable state beyond normal day-to-day variations, i.e. showing acute onset and necessitating a change in regular medications, in accordance with previous reports (12, 13). The need for hospitalization was determined by each examining physician when the patient exhibited hypoxemia requiring additional or intensive oxygen and/or assisted ventilation therapy, a performance status of ≥3 and unconsciousness occurring in association with COPD exacerbation (10, 11, 14).

Statistical analysis

An intention to treat analysis was performed, and the patients were divided into groups in accordance with the two different classifications, namely, an mMRC scale of 0 to 4 (5 grades) and a GOLD stage of I to IV (4 stages). The data are expressed as the mean ± standard deviation (SD) and number (percent) of patients. The subjects' characteristics were compared using an analysis of variance (ANOVA) and the χ^2 test. All pairs of characteristics and the frequency of hospitalization and exacerbation were compared between the groups using the Tukey-Kramer honestly significant difference test. The risk ratios [95% confidence interval (CI)] of the mMRC scale for the frequency of death, hospitalization and exacerbation and the time (survival) until the first death, hospitalization and exacerbation after obtaining informed consent were analyzed using logistic multivariate regression tests adjusted for the spirometric GOLD classification, an age of >65 years and a history of previous exacerbation. The risk ratios for the group with an mMRC scale of grade 1-2 and grade 3-4 were also analyzed as the reference to grade 0. Differences at p values of <0.05 were considered to be statistically significant. Kaplan-Meier analyses were performed using the statistical software package JMP version 9.0® (SAS Institute Japan, Tokyo, Japan).

Results

Study subjects

The mMRC scale and spirometric GOLD classification were applied in 123 patients with COPD (Fig. 1). During the 52-week observation period, one patient with an mMRC scale of grade 1 and one patient with grade 2 dropped out due to the development of *de novo* renal cell and hepatocellular carcinoma, respectively. One patient with an mMRC scale of grade 3 and two patients with grade 4 died due to cerebral infarction and severe exacerbation, respectively. Two patients with GOLD stage II dropped out due to the onset of *de novo* renal cell and hepatocellular carcinoma, and one patient with stage III died due to cerebral infarction. One patient with GOLD stage III and one patient with stage IV both died due to severe COPD exacerbation.

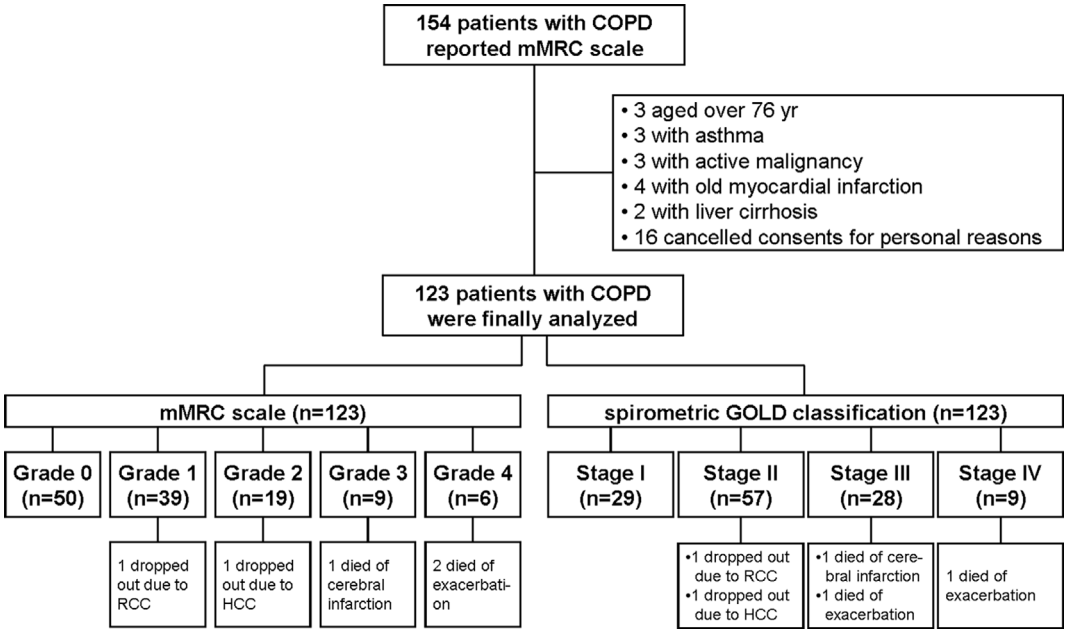

Figure 1. **Study design. One hundred and fifty-four patients with reported mMRC scale scores were studied. Sixteen patients were excluded because of age (n=3), asthma (n=3), active malignancy (n=3), history of myocardial infarction (n=4) and liver cirrhosis (n=2). Sixteen other patients withdrew their consent within 52 weeks. A total of 123 patients with COPD completed the study. mMRC: modified Medical Research Council, COPD: chronic obstructive pulmonary disease, GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease**

Table 1. **Contingency Table for the MMRC Scale and Spirometric GOLD Classification in Patients with COPD at the Baseline.**

Spirometric GOLD classification / mMRC scale	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total no.
Stage I	21 (72.4%)	8 (27.6%)	0 (0%)	0 (0%)	0 (0%)	29 (23.6)
Stage II	25 (43.9%)	22 (38.6%)	7 (12.3%)	2 (3.5%)	1 (1.8%)	57 (46.3)
Stage III	4 (14.3%)	8 (28.6%)	7 (25.0%)	5 (17.9%)	4 (14.3%)	28 (22.8)
Stage IV	0 (0%)	1 (11.1%)	5 (55.6%)	2 (22.2%)	1 (11.1%)	9 (7.3)
Total no.	50 (40.7)	39 (31.7)	19 (15.4)	9 (7.3)	6 (4.9)	123

Each percentage value shows the row percent.
GOLD: Global Initiative for Obstructive Lung Disease, mMRC: modified Medical Research Council

Baseline characteristics

The contingency table (Table 1) at baseline showed that eight of the 29 (27.6%) patients with GOLD stage I suffered from dyspnea (mMRC ≥1), with the following ratios (total number of patients with an mMRC scale grade from 1 to 4 to the total number in each GOLD stage) at stages II, III and IV: 56.1% (32 of 57), 85.7% (24 of 28) and 100% (9 of 9), respectively.

The baseline characteristics of the patients with COPD are shown in Table 2. The number of patients with an mMRC scale of grade 0, 1, 2, 3 and 4 was 50, 39, 19 and 9, respectively, whereas that of patients with GOLD stage I, II, III and IV was 29, 57, 28 and 9, respectively. Patient age and the duration of COPD were positively correlated with a more severe mMRC scale grade (age, r=0.23, p=0.010; duration, r=0.27, p=0.0022) and GOLD stage (age, r=0.27, p=0.0023; duration, r=0.28, p=0.0017), whereas BMI had negative correlations with both of these factors (mMRC scale, r=-0.40, p<0.0001; GOLD stage, r=-0.32, p=0.0003). In addition, a more severe mMRC scale grade showed a significant negative correlation with %FVC (r=-0.33, p=0.0001), %FEV_1 predicted (r=-0.63, p<0.0001) and the FEV_1/FVC ratio (r=-0.57, p<0.0001), as determined using spirometry after bronchodilation. It is noteworthy that the prevalence of use of any respiratory medicine or long-acting muscarinic antagonist increased with the GOLD stage, but not the mMRC scale grade. Seventeen (13.8%) patients were receiving ICS/LABA. In contrast, the prevalence of use of long-acting β_2 agonists and previous pneumococcal vaccination increased as the mMRC scale grade and GOLD stage became more severe.

Comparison of the mMRC scale and spirometric GOLD classification in terms of the frequency of hospitalization and exacerbation

Fifteen (12.2%) and 58 (47.2%) of all patients experienced at least one hospitalization and episode of exacerba-

Table 2. Baseline Characteristics of COPD Patients Enrolled in the Study.

Characteristics	mMRC scale (n=123)						Spirometric GOLD classification (n=123)				
	Grade 0 (n=50)	Grade 1 (n=39)	Grade 2 (n=19)	Grade 3 (n=9)	Grade 4 (n=6)	p value	Stage I (n=29)	Stage II (n=57)	Stage III (n=28)	Stage IV (n=9)	p value
Age, yr	64.7 ± 0.8	68.6 ± 0.9*	69.8 ± 1.3*	69.3 ± 1.9	69.3 ± 2.4	0.0025a	64.3 ± 1.1	67.8 ± 0.8	68.5 ± 1.1*	70.4 ± 2.0*	0.0118a
Male gender, n (%)	44 (88.0)	36 (92.3)	17 (89.5)	6 (66.7)	4 (66.7)	0.16b	23 (79.3)	51 (89.5)	24 (85.7)	9 (100)	0.36b
Body mass index, kg/m^2	23.2 ± 0.5	22.0 ± 0.5	21.5 ± 0.7	19.5 ± 1.1*	18.6 ± 1.3*	0.0009a	23.8 ± 0.6	22.0 ± 0.4	21.4 ± 0.6*	19.3 ± 1.1*	0.0018a
Current smoker, n (%)	17 (34.0)	11 (28.2)	7 (36.8)	3 (33.3)	2 (33.3)	0.97b	8 (27.6)	21 (36.8)	11 (39.3)	0 (0)	0.13b
Smoking index, pack*yr	58.6 ± 3.8	55.3 ± 4.3	55.9 ± 6.2	53.1 ± 9.0	49.0 ± 11.1	0.91a	53.6 ± 5.0	59.0 ± 3.6	54.7 ± 5.1	52.9 ± 9.0	0.78b
Hypertension, n (%)	5 (10.0)	8 (20.5)	2 (10.5)	1 (11.1)	2 (33.3)	0.41b	3 (10.3)	7 (12.3)	7 (25.0)	1 (11.1)	0.37b
Hyperlipidemia, n (%)	3 (6.0)	2 (5.1)	0 (0)	0 (0)	1 (16.7)	0.50b	3 (10.3)	2 (3.5)	1 (3.6)	0 (0)	0.45b
Diabetes, n (%)	12 (24.0)	7 (18.0)	8 (42.1)	3 (33.3)	3 (50.0)	0.29b	3 (10.3)	11 (19.3)	16 (57.1)	3 (33.3)	0.0003b
Duration of COPD, yr	4.1 ± 0.6	6.5 ± 0.6*	6.0 ± 0.9	8.6 ± 1.3*	7.7 ± 1.6	0.0039a	5.0 ± 0.7	4.7 ± 0.5	7.0 ± 0.7	9.2 ± 1.3*†	0.0034a
FVC, L	4.0 ± 0.1	3.6 ± 0.1	3.1 ± 0.2**	2.8 ± 0.2**†	2.8 ± 0.3*	<0.0001a	4.2 ± 0.1	3.6 ± 0.1*	3.0 ± 0.1***†	2.8 ± 0.2***†	<0.0001a
%FVC predicted, %	104.3 ± 2.5	100.4 ± 2.9	90.5 ± 4.1*	87.9 ± 6.0**†	84.7 ± 7.3*	0.0043a	114.6 ± 2.9	99.6 ± 2.1***	87.6 ± 2.9***†	78.0 ± 5.2***†	<0.0001a
FEV_1, L	2.3 ± 0.1	1.8 ± 0.1*	1.2 ± 0.1***††	0.9 ± 0.2***†††	1.0 ± 0.2***†	<0.0001a	2.6 ± 0.1	1.9 ± 0.0***	1.1 ± 0.1***†††	0.6 ± 0.1***†††§	<0.0001a
%FEV_1 predicted, %	76.9 ± 2.5	64.8 ± 2.8*	44.2 ± 4.0***††	39.1 ± 5.8***†	39.8 ± 7.1***†	<0.0001a	92.0 ± 1.6	65.9 ± 1.1***	41.6 ± 1.6***†††	23.3 ± 2.5***†††¶	<0.0001a
FEV_1 / FVC, %	56.9 ± 1.6	50.7 ± 1.8*	38.3 ± 2.6***††	33.2 ± 3.7***†	37.3 ± 4.6***†	<0.0001a	63.3 ± 1.4	52.4 ± 1.0***	37.2 ± 1.4***†††	23.1 ± 2.5***†††¶	<0.0001a
Use of respiratory medicine, n (%)											
Any	38 (76.0)	36 (92.3)	17 (89.5)	9 (100)	5 (83.3)	0.14b	19 (65.5)	50 (87.7)	27 (96.4)	9 (100)	0.0034b
Long-acting beta agonists	6 (12.0)	7 (18.0)	11 (57.9)	4 (44.4)	2 (33.3)	0.0008b	2 (6.9)	14 (24.6)	9 (32.1)	5 (55.6)	0.015b
Long-acting muscarinic agonists	35 (70.0)	34 (87.2)	15 (79.0)	9 (100)	5 (83.3)	0.16b	18 (62.1)	45 (79.0)	26 (92.9)	9 (100)	0.0125b
Inhaled corticosteroids	5 (10.0)	5 (12.8)	5 (26.3)	1 (11.1)	2 (33.3)	0.31b	1 (3.5)	9 (15.8)	7 (25.0)	1 (11.1)	0.14b
Previous pneumococcal vaccination within 5 yr, n (%)	1 (2.0)	8 (20.5)	2 (10.5)	3 (33.3)	4 (66.7)	0.0001b	3 (10.3)	3 (5.3)	7 (25.0)	5 (55.6)	0.0003b

All spirometry data are those after bronchodilation. All data were expressed as mean ± standard deviation and compared between two groups using ANOVA test and χ^2 test. The p values obtained using ANOVA and χ^2 tests were expressed as numerals with a and b in the columns, respectively.

*p<0.05, **p<0.001, and ***p<0.0001 vs. grade 0; †p<0.05, ††p<0.001, and †††p<0.0001 vs. grade 1 in mMRC scale, and *p<0.05, **p<0.01, and ***p<0.0001 vs. stage I;†p<0.05, and †††p<0.0001 vs. stage II; and §p<0.05, and ¶p<0.0001 vs. stage III in GOLD classification for comparison of all pairs by Tukey-Kramer honestly significant difference test.

FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, GOLD: the Global initiative for chronic obstructive lung disease

tion during the 52 weeks. According to the mMRC scale, the proportion of patients who experienced hospitalization and exacerbation with grade 4, 3, 2, 1 and 0 was 50.0% and 100%, 55.6% and 88.9%, 21.1% and 73.7%, 2.6% and 48.7%, and 4.0% and 22.0%, respectively. Based on the spirometric GOLD classification, the proportion of patients who experienced hospitalization and exacerbation with stage IV, III, II and I was 10.3% and 88.9%, 17.2% and 67.9%, 24.1% and 50.9%, 0% and 6.9%, respectively.

Association of the mMRC scale and spirometric GOLD classification with the annual frequency of exacerbation and hospitalization

The annual frequency (events per patient per year) of hospitalization among the patients with an mMRC scale of grade 4 (0.5±0.1, p=0.0002 vs. 0 and 1), 3 (0.6±0.1, p< 0.0001 vs. 0 and 1) and 2 (0.2±0.1, p=0.0267 vs. 0 and p= 0.0205 vs. 1) was significantly higher than that observed in the patients with grade 0 (0.0±0.0) and 1 (0.0±0.1), respectively (grade 0-4, p=0.0002 by ANOVA).

The annual frequency of exacerbation in the patients with grade 3 (1.8±1.4, p=0.0002 vs. grade 0 and p=0.0371 vs. grade 1) and 4 (2.2±1.3, p=0.0004 vs. grade 0 and p=0.0167 vs. grade 1) was significantly higher than that noted in the subjects with grade 0 (0.5±1.1) and 1 (0.8±0.9), respectively. The patients with grade 1 (p=0.0126) and 2 (1.4±1.1) (p=0.0002) had a significantly higher frequency of exacerbation than the grade 0 patients (grade 0-4, p=0.0002 by ANOVA) (Fig. 2a).

The annual frequency of hospitalization among the GOLD stage IV patients (0.3±0.1, p=0.0016) was significantly higher than that seen in the stage I patients (0.0±0.1), but

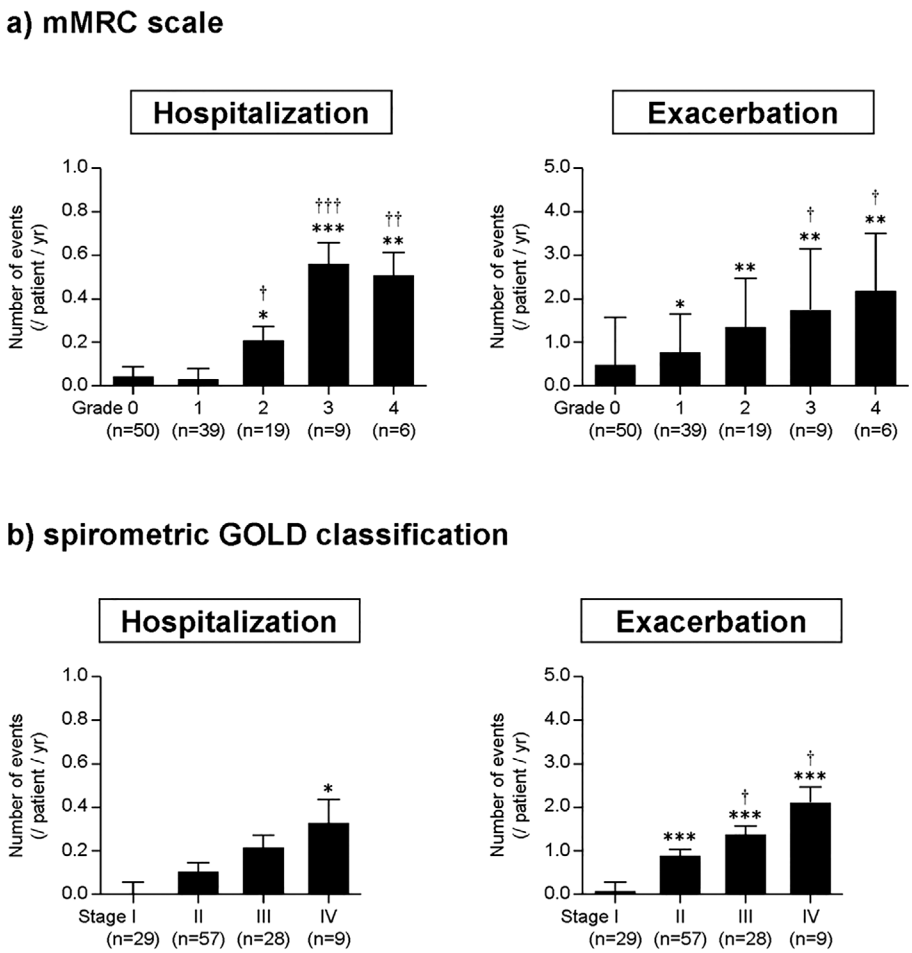

Figure 2. Annual frequency of hospitalization and exacerbation. All data are expressed as the frequency (events/patient/yr) of hospitalization and moderate or severe exacerbation (error bars=standard deviation). a) mMRC scale: *p<0.05, **p<0.001, ***p<0.0001 vs. grade 0, and †p<0.05, ††p<0.001, †††p<0.0001 vs. grade 1, respectively. b) spirometric GOLD classification *p<0.05, ***p<0.0001 vs. stage I, and †p<0.05 vs. stage II, respectively. mMRC: modified Medical Research Council, GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease

not stage II (0.1±0.0, p>0.05) or III (0.2±0.1, p>0.05) patients (stage I-IV, p>0.05 by ANOVA).

The annual frequency of exacerbation in the patients with stage IV (2.1±0.4, p<0.0001 vs. I and p=0.0059 vs. II) and III (1.4±0.2, p<0.0001 vs. I and p=0.0302 vs. II) was significantly higher than that seen in the patients with stage I (0.1±0.2) and II (0.9±0.1), respectively, whereas the stage II patients (p<0.0001) had a significantly higher rate of exacerbation than the stage I patients (stage I-IV, p<0.0001 by ANOVA) (Fig. 2b).

Kaplan-Meier analysis of the time until the first hospitalization and moderate or severe exacerbation

As shown in Fig. 3a, the period (mean ± SD, days) until the first hospitalization in the patients with grade 4, 3, 2, 1 and 0 was 257±68, 235±51, 347±12, 361±4 and 360±4 days (log-rank test, p<0.0001), respectively, while that until the first exacerbation was 143±42, 162±42, 252±28, 270±19 and 319±14 days (log-rank test, p<0.0001), respectively.

As demonstrated in Fig. 3b, the period until the first hospitalization in the patients with stage IV, III, II and I was 302±40, 324±19, 353±5 and 365±0 days (log-rank test, p=0.0219), respectively, while that until the first exacerbation was 220±43, 236±25, 258±17 and 357±8 days (log-rank test, p<0.0001), respectively.

Frequency of annual hospitalization and exacerbation and Kaplan-Meier analysis of the period until the first moderate or severe exacerbation and hospitalization according to the mMRC scale (grade 0, grades 1-2 and grades 3-4)

The annual frequency (events per patient per year) of hospitalization in the patients with an mMRC scale of grades 3-4 (0.5±0.5, p<0.0001) was significantly higher than that observed in the patients with grade 0 (0.0±0.2) or grades 1-2 (0.1±0.3), respectively. The annual frequency of exacerbation in the patients with grades 3-4 (2.0±1.3, p<0.0001 vs. grade 0 and p=0.0085 vs. grades 1-2) was significantly higher than that seen in the patients with grade 0 (0.5±1.1) and grades 1-2 (1.0±1.0), respectively (Fig. 4a). As pre-

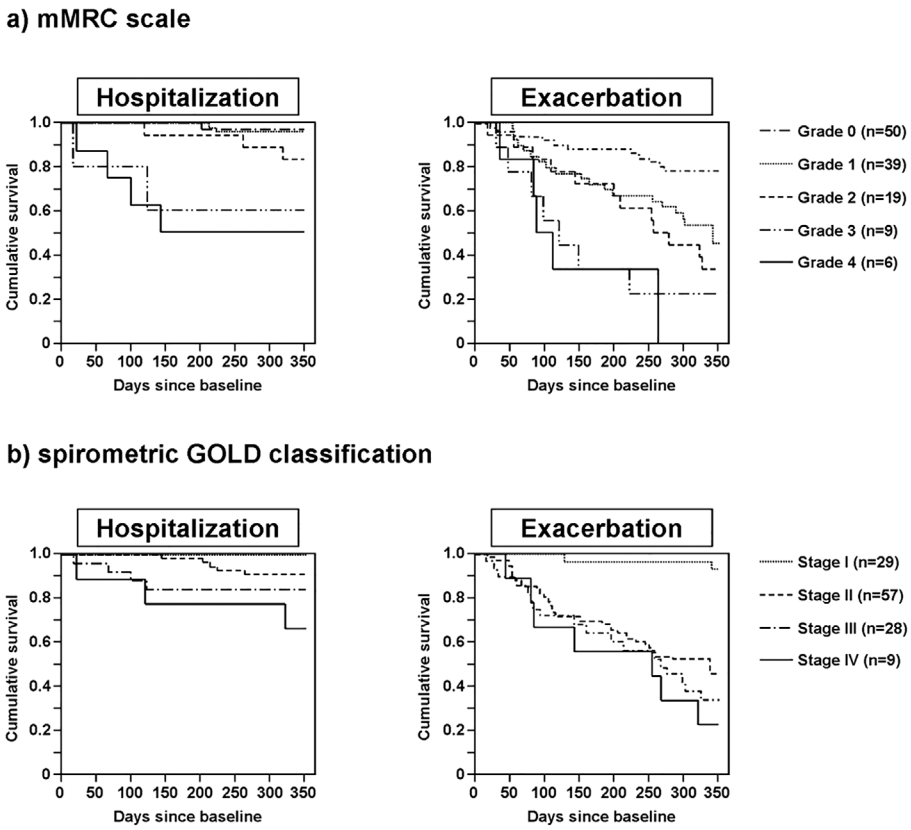

Figure 3. **Cumulative survival curves for the patients with first hospitalization and exacerbation. Cumulative survival curves for the patients with first hospitalization and moderate or severe exacerbation during the 52-week period. a) mMRC scale. b) spirometric GOLD classification. mMRC: modified Medical Research Council, GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease**

sented in Fig. 4b, the period (mean ± SD, days) until the first hospitalization in the patients with grades 3-4, 1-2 and 0 was 249±36, 353±6 and 360±4 days (log-rank test, $p< 0.0001$), respectively, while that until the first exacerbation was 168±31, 258±16 and 319±14 days (log-rank test, $p< 0.0001$), respectively.

Risk ratios of the mMRC scale and spirometric GOLD classification for exacerbation and hospitalization

The logistic univariate regression analysis showed that the mMRC scale, spirometric GOLD classification, an age of >65 years and history of previous exacerbation were predictors of hospitalization and exacerbation (Table 3). The logistic multivariate regression analysis adjusted for the spirometric GOLD classification, age and history of previous exacerbation showed that the patients with an mMRC scale of grades 3 and 4 had significantly higher risk ratios for the frequency of hospitalization, but not exacerbation, when compared to the grade 0 patients (Table 4). The risk ratios in the patients with GOLD stages II, III and IV adjusted for the mMRC scale, age and history of previous exacerbation were significantly higher for the frequency of exacerbation, but not hospitalization, than that observed in the stage I patients (Table 4).

Discussion

The current prospective observational study demonstrated that the mMRC scale can be used as a predictor of hospitalization and exacerbation in Japanese COPD patients with GOLD stage I to IV. Approximately one-third (8 of 29) of the COPD patients with GOLD stage I in this study suffered from some type of disability due to dyspnea, and an increased percentage of patients exhibited dyspnea as the GOLD stage progressed. The mMRC scale was positively associated with an increased annual frequency of hospitalization and exacerbation. It is well known that the QOL worsens after exacerbation (15, 16). In the current study, the proportion of patients who had experienced previous exacerbation with an mMRC scale of grade 0, 1, 2, 3 and 4 was 18.4%, 23.7%, 45.0%, 100% and 85.7%, respectively. Hence, previous exacerbation may have affected the levels of dyspnea and disability. An adjusted logistic multivariate regression analysis was performed including the spirometric GOLD stage, history of previous exacerbation and age, as the patients with GOLD stages II, III, and IV showed similar findings in terms of exacerbation and hospitalization (Fig. 3b). The patients with an mMRC scale of grades 4 and 3 suffered from 12.2-, and 20.1-fold higher hospitalization

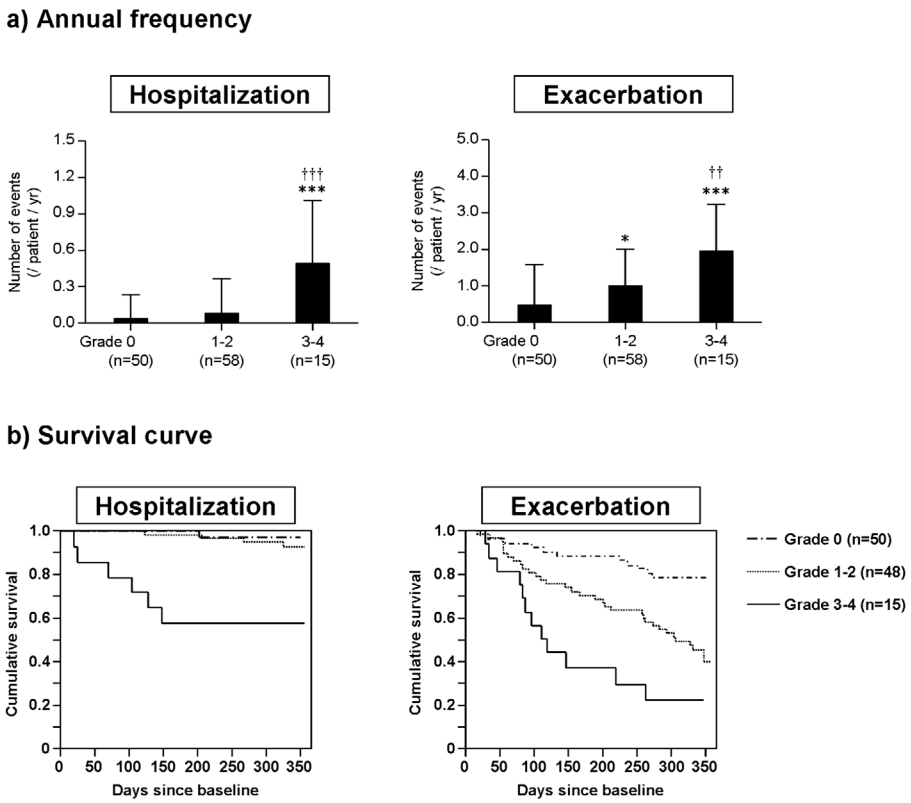

Figure 4. Annual frequency of hospitalization and exacerbation and cumulative survival curves for the patients with first hospitalization and exacerbation. a) All data are expressed as the frequency (events/patient/yr) of hospitalization and moderate or severe exacerbation (error bars=standard deviation). *p<0.05, ***p<0.0001 vs. grade 0, and ††p<0.001, †††p<0.0001 vs. grade 1-2, respectively. b) Cumulative survival curves for the patients with first hospitalization and moderate or severe exacerbation during the 52-week period. mMRC: modified Medical Research Council

rates and 9.91- and 6.81-fold higher exacerbation rates when compared with the grade 0 patients. Additionally, the patients with grades 3-4 had a poorer prognosis than those with grade 0 and grades 1-2 (Table 3, 4, Fig. 4). Taken together, the present study showed that an mMRC scale of grade 3 is an important cut-off point for the future risk of hospitalization and exacerbation in Japanese patients with COPD. Therefore, dyspnea and disability may reflect current symptoms as well as future risk factors, such as hospitalization and exacerbation.

We also investigated mortality during the 52-week observation period. Two patients having an mMRC scale of grade 4 at baseline died due to COPD exacerbation. One COPD patient with MRC grade 3 died due to cerebral infarction without exacerbation. Moreover, the patients with a higher mMRC scale score tended to have a higher risk of mortality, although the sample size did not reach a statistically significant level. Mortality associated with exacerbation and dyspnea is likely a predictor of future exacerbation, hospitalization and death.

Previous studies have demonstrated that the frequency of annual moderate or severe exacerbation per patient among Japanese individuals may be lower than that noted in the United States and Europe (17-20). In the current study, nine (7.3%) and 43 (35.0%) of the 123 patients had experienced at least one previous hospitalization and episode of moderate to severe exacerbation during the previous 52 weeks, and the number (range) of annual hospitalizations and exacerbations per patient was 0.07 (0 to 1) and 0.73 (0 to 6), respectively. Fifteen (12.2%) and 58 (47.2%) of the patients experienced at least one hospitalization and exacerbation during the 52 weeks, and the mean number (range) of annual hospitalizations and exacerbations per patient was 0.12 (0 to 1) and 0.88 (0 to 6), respectively. Both the proportion of patients who experienced hospitalization and exacerbation and the number of annual hospitalizations and exacerbations per patient increased after informed consent was provided. These increases may be associated with the physicians and patients being better informed about both the study and use of daily journals. We recorded comorbidities based only on interviews with the patients and the physicians' diagnoses, without employing further examinations or questionnaires. Previous studies have demonstrated that several comorbidities, such as depression (21), asthma-COPD overlap syndrome (ACOS) (22) and gastroesophageal reflux disease (GERD) (18, 23), are strongly associated with exacerbation and hospitalization in patients with COPD. In the present study, information about comorbidities was obtained via in-

Table 3. Risk Ratios for Hospitalization and Exacerbation Revealed by Logistic Univariate Regression Analysis.

	Frequency of events				Time until first event			
	Hospitalization		Exacerbation		Hospitalization		Exacerbation	
mMRC scale	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
Grade 1	0.64 (0.03 to 6.88)	0.71	3.45 (1.39 to 8.95)	0.0072	0.93 (0.60 to 1.43)	0.76	1.47 (0.95 to 2.25)	0.09
Grade 2	5.87 (1.05 to 45.4)	0.0444	8.06 (2.62 to 27.7)	0.0002	1.12 (0.65 to 1.88)	0.70	2.10 (1.20 to 3.53)	0.0103
Grade 3	29.4 (4.81 to 262)	0.0002	27.6 (4.41 to 542)	0.0001	2.10 (0.87 to 4.33)	0.10	5.13 (2.16 to10.9)	0.0006
Grade 4	17.6 (2.32 to 170)	0.0064	20.7 (3.10 to 414)	0.0010	1.53 (0.53 to 3.48)	0.39	4.45 (1.49 to 10.8)	0.0104
Grade 1-2	2.22 (0.45 to16.0)	0.3347	4.56 (2.00 to 11.0)	0.0002	0.99 (0.68 to 1.46)	0.97	1.63 (1.11 to 2.42)	0.0132
Grade 3-4	23.5 (4.88 to 176)	<0.0001	24.2 (5.68 to 170)	<0.0001	1.82 (0.92 to 3.30)	0.08	4.79 (2.36 to 9.22)	<0.0001
Spirometric GOLD classification								
Stage II	0.95×10^6 (1.44 to infinity)	0.0231	13.0 (3.46 to 85.6)	<0.0001	1.05 (0.65 to 1.67)	0.83	1.74 (1.12 to 2.78)	0.0140
Stage III	2.19×10^6 (3.38 to infinity)	0.0023	33.8 (7.75 to 243)	<0.0001	1.18 (0.69 to 2.01)	0.55	2.38 (1.38 to 4.07)	0.0019
Stage IV	4.02×10^6 (4.73 to infinity)	0.0020	108 (12.3 to 2,694)	<0.0001	1.53 (0.65 to 3.18)	0.31	3.02 (1.27 to 6.42)	0.0144
Age								
>65 yrs	2.86 (0.85 to 13.1)	0.0930	2.96 (1.40 to 6.47)	0.0043	1.03 (0.72 to 1.51)	0.86	1.48 (1.02 to 2.16)	0.0371
Previous exacerbations*								
Yes	6.83 (2.16 to 26.2)	0.0009	4.73 (2.15 to 11.0)	<0.0001	1.23 (0.82 to 1.80)	0.31	2.16 (1.43 to 3.19)	0.0003

The grade 0, stage I, <65 yrs, and no exacerbation were used as a reference of mMRC scale, spirometric GOLD classification, age, and previous exacerbations, respectively.
* Patients who had experienced at least one previous moderate to severe exacerbation were identified as yes within one year after providing informed consent.
CI: confidence interval

Table 4. Risk Ratios of the MMRC Scale and Spirometric GOLD Stage for Hospitalization and Exacerbation Revealed by Logistic Multivariate Regression Analysis.

	Frequency of events				Time until first event			
	Hospitalization		Exacerbation		Hospitalization		Exacerbation	
mMRC scale	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value	Risk ratio (95% CI)	p value
Grade 1	0.37 (0.02 to 4.23)	0.42	2.13 (0.74 to 6.30)	0.16	0.90 (0.56 to 1.44)	0.67	1.34 (0.84 to 2.10)	0.21
Grade 2	3.03 (0.43 to 27.5)	0.27	2.36 (0.60 to 9.87)	0.22	1.05 (0.54 to 1.97)	0.89	1.50 (0.78 to 2.80)	0.22
Grade 3	14.6 (1.50 to 202)	0.0200	6.56 (0.76 to 146)	0.09	1.93 (0.72 to 4.66)	0.18	3.09 (1.20 to 7.32)	0.0213
Grade 4	10.8 (0.93 to 158)	0.06	5.21 (0.57 to 118)	0.15	1.41 (0.45 to 3.57)	0.52	3.06 (0.95 to 8.36)	0.06
Grade 1-2	1.13 (0.20 to 8.92)	0.89	2.19 (0.80 to 6.11)	0.13	0.93 (0.60 to 1.46)	0.77	1.37 (0.89 to 2.11)	0.15
Grade 3-4	8.88 (1.19 to 93.9)	0.0328	5.74 (0.98 to 48.2)	0.052	1.60 (0.73 to 3.33)	0.23	2.99 (1.35 to 6.39)	0.0077
Spirometric GOLD classification								
Stage II	3.55×10^6 (0.40 to infinity)	0.16	8.06 (1.97 to 55.0)	0.0024	1.00 (0.62 to 1.65)	0.99	1.45 (0.90 to 2.36)	0.13
Stage III	2.14×10^6 (0.17 to infinity)	0.28	11.7 (2.15 to 95.2)	0.0037	1.05 (0.54 to 1.99)	0.89	1.53 (0.81 to 2.83)	0.18
Stage IV	2.32×10^6 (0.13 to infinity)	0.29	23.3 (1.83 to 700)	0.0137	1.07 (0.37 to 2.91)	0.89	1.29 (0.47 to 3.34)	0.61

All data for risk ratios on the mMRC scale were adjusted for spirometric GOLD stage, age and previous exacerbation, whereas those for the spirometric GOLD classification were adjusted for mMRC scale, age and previous exacerbation. The grade 0 and stage I were used as a reference of mMRC scale and spirometric GOLD classification, respectively.
CI: confidence interval

terviews with the patients and the diagnoses made by the physicians; therefore, some comorbidities may have been missed.

The present study is associated with a number of limitations. First, although we carefully excluded patients with asthma, individuals with asthma and ACOS may have been included because we did not investigate changes in the pulmonary function or determine the sputum and blood eosino-

phil counts or serum total IgE levels. Second, the assessments of comorbidities associated with exacerbation, such as depression and GERD, were not complete.

Spirometry is considered to be the gold standard for diagnosing COPD and assessing its severity. However, spirometry continues to show low worldwide dissemination and use, although it is an important tool for the detection and management of chronic respiratory diseases (24-26). The present findings demonstrated that the spirometric GOLD classification is an independent factor predicting the future risk of hospitalization and exacerbation. We believe that assessments conducted using the mMRC scale provides an easy, safe and useful tool for examining current symptoms as well as future risks in patients with COPD. However, longer trials are needed to clarify whether the mMRC scale can be used as a predictor of lung function decline and mortality in such patients. In addition, investigations of future risks using the ABCD category classification should be conducted in Japanese patients with COPD.

Conclusion

The present results indicate that Japanese patients with COPD showing a high mMRC scale grade have a poor prognosis. Assessments of COPD patients obtained using the mMRC scale can be employed to predict exacerbation and hospitalization.

Author's disclosure of potential Conflicts of Interest (COI).
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