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Evaluation of the Modified Medical Research Council dyspnea scale for prediction of hospitalization and exacerbation in Japanese patients with chronic obstructive pulmonary disease

Short title: Evaluation of mMRC scale for COPD in Japan

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Abstract (244 words)

Background: The modified Medical Research Council (mMRC) scale has been recommended for evaluation of dyspnea and disability, and as an indicator of exacerbations. The aim of this study was to investigate whether the mMRC scale can predict hospitalizations and exacerbations in Japanese patients with chronic obstructive pulmonary disease (COPD).

Methods: In a previous 52-week prospective study 123 patients with COPD were classified into 5 groups (grades 0 to 4) according to the mMRC scale, and into 4 groups (stages I to IV) according to the spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. The frequencies and the period until the first event of hospitalization or exacerbation were compared among the groups.

Results: The frequencies of patients who experienced at least hospitalization and exacerbation for 52 weeks with an mMRC scale grade of 4, 3, 2, 1, and 0 were 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. Multivariate analysis adjusted for GOLD stage and age showed that patients with mMRC scale grade $\geq$3 had higher frequencies of hospitalization and exacerbation than those with lower grades. Patients with mMRC scale grade $\geq$2 showed a significantly earlier time until the first exacerbation, but not hospitalization, in comparison with grade 0.

Conclusion: Our present results indicate that among Japanese patients with COPD, those with an mMRC scale grade $\geq$3 have a significantly poorer prognosis, and that the mMRC scale is able to predict hospitalization and exacerbation.

Trial registration: none

Key words: COPD; dyspnea; hospitalization; exacerbation.

Lists of Abbreviations

BMI	body mass index
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	global initiative for chronic obstructive lung disease
ICS	inhaled corticosteroid
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic receptor antagonist
SD	standard deviation
mMRC	modified Medical Research Council

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document 2014 is a useful guide for physicians who are following patients with chronic obstructive pulmonary disease (COPD) [1]. Exacerbation is an important life-threatening event for patients with COPD, and can lead to 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 its' reliability has been confirmed [1, 5, 6]. However, the evidences of relationship between the assessment of dyspnea and disability, and hospitalization and exacerbation are few, although it is known that dyspnea is associated with mortality in COPD patients as a whole [7-9]. In the present study, we evaluated the utility of the mMRC scale for prediction of mortality, hospitalization and exacerbation as a consequence of dyspnea level (mMRC scale) and airflow obstruction (spirometric GOLD classification) in Japanese patients with COPD. For this we used the data from our previous 52-week prospective observation 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 from our 52-week prospective observation trial involving 123 Japanese COPD patients that had been 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 about comorbidities in our study was obtained by interviews with patients and the diagnoses of disease were confirmed by physicians. Hypertension, hyperlipidemia, and diabetes were accepted as comorbidities. Duration of COPD was defined as the period (yr) since the patient had been diagnosed by a physician as having COPD, emphysema, and/or chronic bronchitis [10, 11]. All patients had received influenza virus vaccinations every year.

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 $FEV_1/FVC<0.7$ after bronchodilator administration, and the spirometric GOLD classification (GOLD stage), i.e. stage I (%FEV_1 predicted $\geq$80%), II ($\leq$50%FEV_1 predicted <80%), III ($\leq$30%FEV_1 predicted <50%), and IV (%FEV_1 predicted <30%) according to the GOLD documents [1]. To

exclude any patients with asthma, only patients with a classification of FEV_1 <200mL and/or <12% after bronchodilation were enrolled [10].

Frequency and date of mortality, hospitalizations, and exacerbations

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

Exacerbations were accepted as moderate and severe, but not mild events from the medical records made by physicians and the daily journals of patients covering a period of 52 weeks [10]. Moderate exacerbations that required a prescription for antibiotics and/or systemic corticosteroids were defined on the basis of symptom-based diagnosis such as increased cough and sputum production, a change in sputum color, and worsening of dyspnea from a stable state and beyond-normal day-to-day variations, i.e. showing acute onset and necessitating a change in regular medication, in accordance with previous reports [12, 13]. Hospitalization was decided by each examining physician, when the conditions with hypoxemia with required additional or intensive oxygen and/or assisted ventilation therapy, performance status $\geq$3, and unconsciousness were occurred with COPD exacerbations [10, 11, 14].

Statistical analysis

Intention to treat analysis was accepted and patients were divided into groups in accordance with the two different classifications; namely the mMRC scale 0 to 4 (5 grades) and GOLD stage I to IV (4 stages). Data were expressed as mean ± standard deviation (SD) and number (percent) of patients. Characteristics were compared using

analysis of variance (ANOVA) and χ^2 test. All pairs of characteristics and the frequency of hospitalization and exacerbation between the groups were compared using the Tukey-Kramer honestly significant difference test. The risk ratios [95% confidence interval (CI)] of the mMRC scale for frequency of death, hospitalization and exacerbation, and time (survival) until the first death, hospitalization and exacerbation since informed consent was analyzed using logistic multivariate regression tests adjusted by spirometric GOLD classification, age >65 yrs, and history of previous exacerbation. The risk ratios of the group of mMRC scale grades 1~2, and grades 3~4, were also analyzed as the reference to grade 0. Differences at $p < 0.05$ were considered statistically significant. Kaplan-Meier analyses were performed using the statistical software package JMP version 9.0® (SAS Institute Japan Inc., Tokyo, Japan).

Results

Study subjects

The mMRC scale and spirometic GOLD classification were assessed in 123 patients with COPD (Figure 1). During the 52-week observation period, one patient with mMRC scale grade 1 and one with grade 2 dropped out due to *de novo* renal cell and hepatocellular carcinoma, respectively. One patient with mMRC scale grade 3 and two patients with grade 4 died due to cerebral infarction and severe exacerbations, respectively. Two patients with GOLD stage II dropped out due to *de novo* renal cell and hepatocellular carcinoma. One patient with stage III died due to cerebral infarction. One patient with GOLD stage III and another with stage IV died due to severe COPD exacerbations.

Baseline characteristics

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

Baseline characteristics of the patients with COPD are shown in Table 2. The numbers of patients with mMRC scale grade 0, 1, 2, 3, and 4 were 50, 39, 19, and 9, respectively, whereas those with GOLD stage I, II, III, and IV were 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 (mMRC scale, $r = -0.40$, $p < 0.0001$; COLD stage, $r = -0.32$, $p = 0.0003$). A more severe mMRC scale grade showed a significant negative correlation with %FVC ($r = -0.33$, $p = 0.0001$) and %FEV_1 predicted ($r = -0.63$, $p < 0.0001$), and with the FEV_1/FVC ratio ($r = -0.57$, $p < 0.0001$) determined by spirometry after bronchodilation. It was 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, and became more severe. 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 mMRC scale and spirometric GOLD classification in frequency of patients who experienced hospitalization and exacerbation

Fifteen (12.2%) and 58 (47.2%) of all patients experienced at least one hospitalization and exacerbation during the 52 weeks. In mMRC scale, the frequencies of patients who experienced hospitalizations and exacerbations with grade 4, 3, 2, 1, and 0 were 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. In spirometric GOLD classification, the frequencies of patients who experienced hospitalizations and exacerbations with stage IV, III, II, and I were 10.3 and 88.9, 17.2 and 67.9, 24.1 and 50.9, 0 and 6.9%, respectively.

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

Annual frequencies (events per patient per year) of hospitalization in patients with mMRC scale 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) were significantly higher than those in 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 frequencies of exacerbations in 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) were significantly higher than in those with grade 0 (0.5 ± 1.1) and 1 (0.8 ± 0.9), respectively. Patients with grade 1 (p=0.0126) and 2 (1.4 ± 1.1) (p=0.0002) had significantly higher frequencies of exacerbation than grade 0 patients (grade 0-4, p=0.0002 by ANOVA tests) (Figure 2a).

Annual frequencies of hospitalization in GOLD stage IV patients (0.3 ± 0.1, p=0.0016) was significantly higher than in stage I patients (0.0 ± 0.1), but not stage II (0.1 ± 0.0, p>0.05) and III (0.2 ± 0.1, p>0.05) patients (stage I-IV, p>0.05 by ANOVA tests).

The annual frequencies of exacerbations in 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) were significantly higher than those in patients with stage I (0.1 ± 0.2) and II (0.9 ± 0.1), respectively, whereas stage II patients (p<0.0001) had significantly higher rates of exacerbation than stage I patients (stage I-IV, p<0.0001 by ANOVA tests) (Figure 2b).

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

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

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

Frequency of annual hospitalizations and exacerbations and Kaplan-Meier analysis of period until the first moderate or severe exacerbation and hospitalization between mMRC scale grade 0, grades 1~2, and grades 3~4

Annual frequencies (events per patient per year) of hospitalization in patients with mMRC scale grades 3~4 (0.5 ± 0.5, $p<0.0001$) were significantly higher than those in patients with grade 0 (0.0 ± 0.2) or grades 1~2 (0.1 ± 0.3), respectively. The annual frequencies of exacerbation in patients with grades 3~4 (2.0 ± 1.3, $p<0.0001$ vs grade 0 and $p=0.0085$ vs grades 1~2) were significantly higher than those in patients with grade 0 (0.5 ± 1.1) and grades 1~2 (1.0 ± 1.0), respectively (Figure 4a). Figure 4b shows that the periods (mean ± SD, days) until the first hospitalization in patients with grades 3~4, 1~2, and 0 were 249 ± 36, 353 ± 6, and 360 ± 4 days (log-rank test, $p<0.0001$), respectively, and that those until the first exacerbation were 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

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

Discussion

Our prospective observation 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 COPD patients with GOLD stage I were suffering from some disability due to dyspnea, although an increased percentage of patients had dyspnea as the GOLD stage progressed. The mMRC scale was positively associated with an increased annual frequency of hospitalizations and exacerbations. It is well known that QOL worsens after exacerbation [15, 16]. The frequency of patients who experienced previous exacerbations with mMRC scale grade 0, 1, 2, 3 and 4 were 18.4%, 23.7%, 45.0%, 100% and 85.7%, respectively. Previous exacerbations may have affected the levels of dyspnea and disability. Adjusted logistic multivariate regression analysis was performed with spirometric GOLD stage, history of previous exacerbation, and age, as patients with GOLD stages II, III, and IV showed similar correlations in terms of exacerbation and hospitalization (Figure 3b). Patients with mMRC scale grades 4 and 3 suffered 12.2-, and 20.1-fold higher hospitalization rates and 9.91- and 6.81-fold higher exacerbation when compared with grade 0. The patients with grades 3~4 had poorer prognosis than those with grade 0, and grades 1~2 (Table 3 and 4, Figure 4). Taken together, our present study showed that mMRC scale grade 3 is an important cut-off point for future risk of hospitalization and exacerbation in Japanese patients with COPD. Dyspnea and disability may reflect not only the current symptoms but also future risk factors such as hospitalization and exacerbation.

We also investigated mortality during the 52-week observation period. Two patients having mMRC scale grade 4 at the baseline died due to COPD exacerbation. One COPD patient with MRC grade 3 died due to cerebral infarction without

exacerbation. 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 is 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 exacerbations per patient in Japanese individuals may be lower than that in the United States and Europe [17-20]. In our study, 9 (7.3%) and 43 (35.0%) of 123 patients had experienced at least one previous hospitalization and moderate to severe exacerbation during the previous 52 weeks, and the numbers (range) of annual hospitalizations and exacerbations per patient were 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 52 weeks, and the mean numbers (range) of annual hospitalizations and exacerbations per patient were 0.12 (0 to 1) and 0.88 (0 to 6), respectively. Both the frequency of patients who had hospitalizations and exacerbations and the numbers of annual hospitalizations and exacerbations per patient increased after informed consent had been provided. These increases may be associated with physicians and patients being better informed about the study, and the usage of daily journals. We recorded the comorbidities based only on interviews with patients and the physicians' diagnosis, without 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 our study, information about comorbidities was obtained by interviews with patients and the diagnoses made by physicians and therefore some comorbidities may have been missed.

Our study has a number of limitations. First, although we carefully excluded patients with asthma, patients with asthma and ACOS may have been included because we did not investigate changes in pulmonary function, or determine the sputum and blood eosinophil counts, or serum total IgE levels. Second, our assessments of comorbidities associated with exacerbation, such as depression and GERD, were not complete.

Spirometry is thought to be the gold standard for diagnosis of COPD and assessment of its severity. Spirometry still has low worldwide dissemination and use, even though it is an important tool for detection and management of chronic respiratory diseases [24-26]. Our present study demonstrated that the spirometric GOLD classification was an independent factor for predicting the future risks of hospitalization and exacerbation. We believe that assessment using the mMRC scale would provide an easy, safe and useful tool for examination of not only current symptoms but also future risks in patients with COPD. However, longer trials will be necessary 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 risk using the ABCD category classification should be conducted in Japanese patients with COPD.

Conclusion

Our present results indicate that Japanese patients with COPD showing a high mMRC scale grade have a poor prognosis. Assessment of COPD patients using the mMRC scale can predict exacerbation and hospitalization.

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Statement indicating the roles of the authors:

Dr. H. Natori contributed to protocol design, analysis, and writing of the manuscript.

Dr. T. Kawayama contributed to protocol design and editing of the manuscript.

Dr. M. Suetomo contributed to protocol design, data collection, and analysis.

Dr. T. Kinoshita contributed to data collection.

Dr. M. Matsuoka contributed to data collection.

Dr. K. Matsunaga contributed to data collection.

Dr. M. Okamoto contributed to data collection.

Dr. T. Hoshino supervised the protocol design and edited the manuscript.

Conflict of Interest:

Tomotaka Kawayama has received lecture fees from Novartis Pharmaceuticals Japan, GSK Japan, Boehringer Ingelheim Japan, and Astra Zeneca Japan. Tomoaki Hoshino has received a grant from GSK Japan, Novartis Pharmaceuticals Japan and Chugai Pharmaceutical Co. LTD.

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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

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)	
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*	
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)	
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*	
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)	
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	
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)	
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)	
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)	
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*†	
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***†	<
%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***†	<
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***†††† §	<
$\%FEV_1$ 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***†††† ¶	<
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***†††† ¶	<
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)	
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)	
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)	
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)	
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)	

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 expiratory capacity; GOLD, the Global initiative for chronic obstructive lung disease.

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 to414)	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	$0.95x10^6$ (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	$2.19x10^6$ (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	$4.02x10^6$ (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.

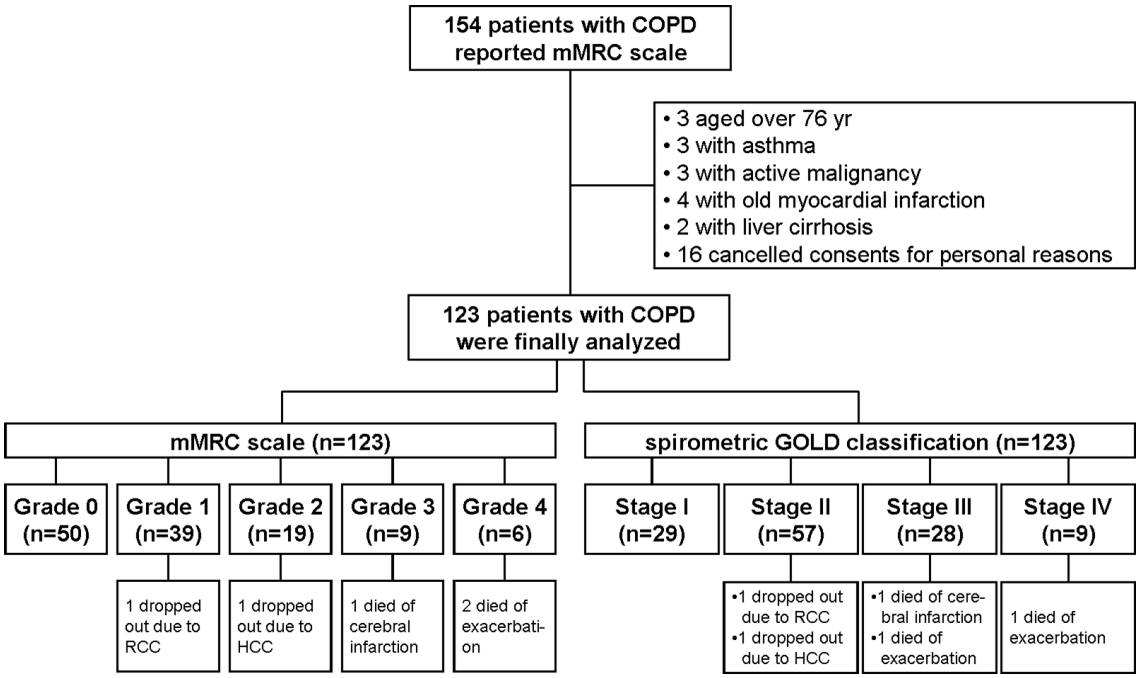
	Frequency of events				Time until first event			
	Hospitalization		Exacerbation		Hospitalization		Exacerbation	
mMRC scale	**Risk ratio (95% CI)**	**p value**	**Risk ratio (95% CI)**	**p value**	**Risk ratio (95% CI)**	**p value**	**Risk ratio (95% CI)**	**p value**
Grade 1	0.37 (0.02 to 4.23)	0.42	2.13 (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	$3.55x10^6$ (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	$2.14x10^6$ (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	$2.32x10^6$ (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

Figure legends

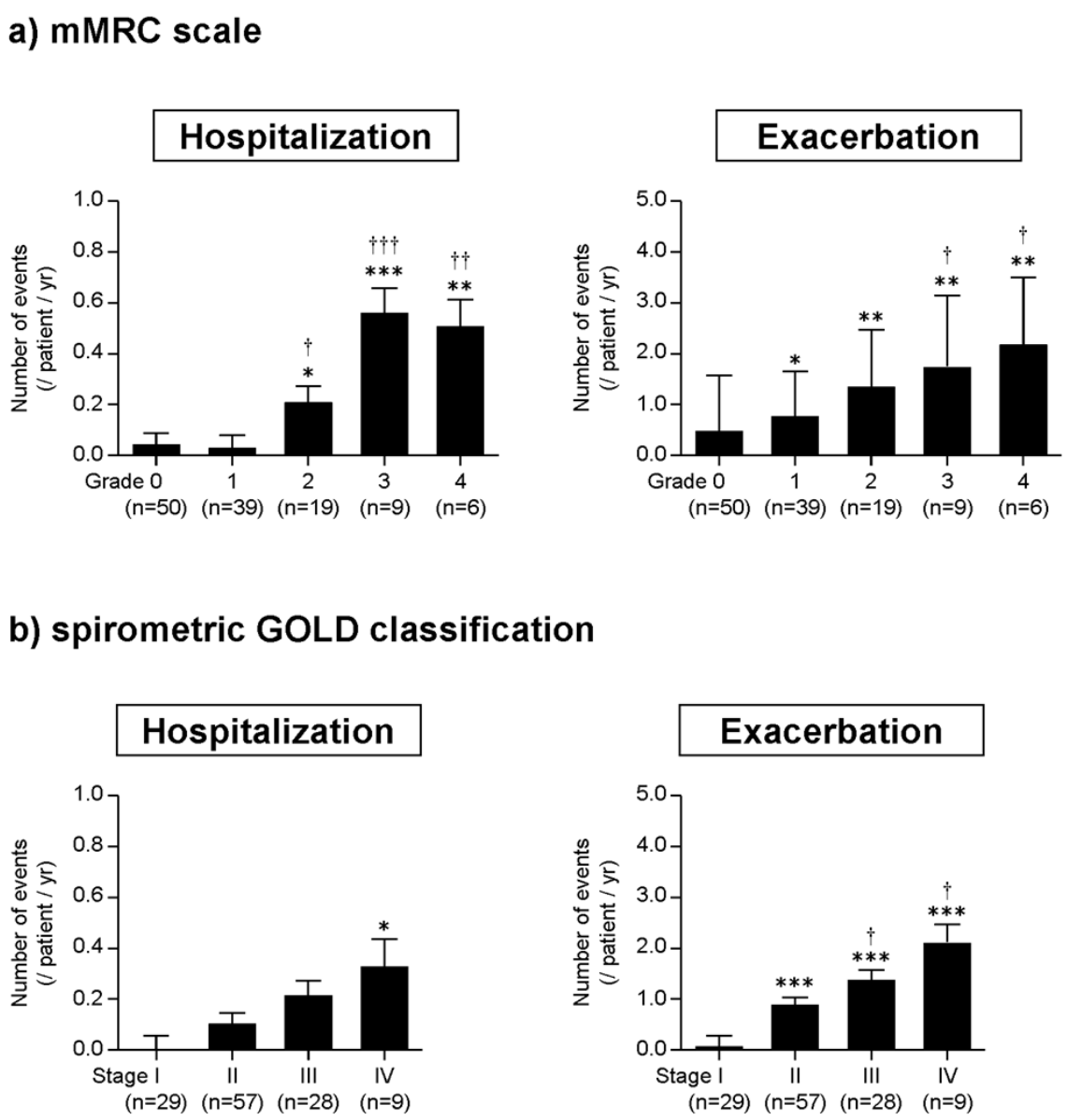
Figure 1. Study design.



One hundred 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. 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

Figure 2. Annual frequency of hospitalization and exacerbation.



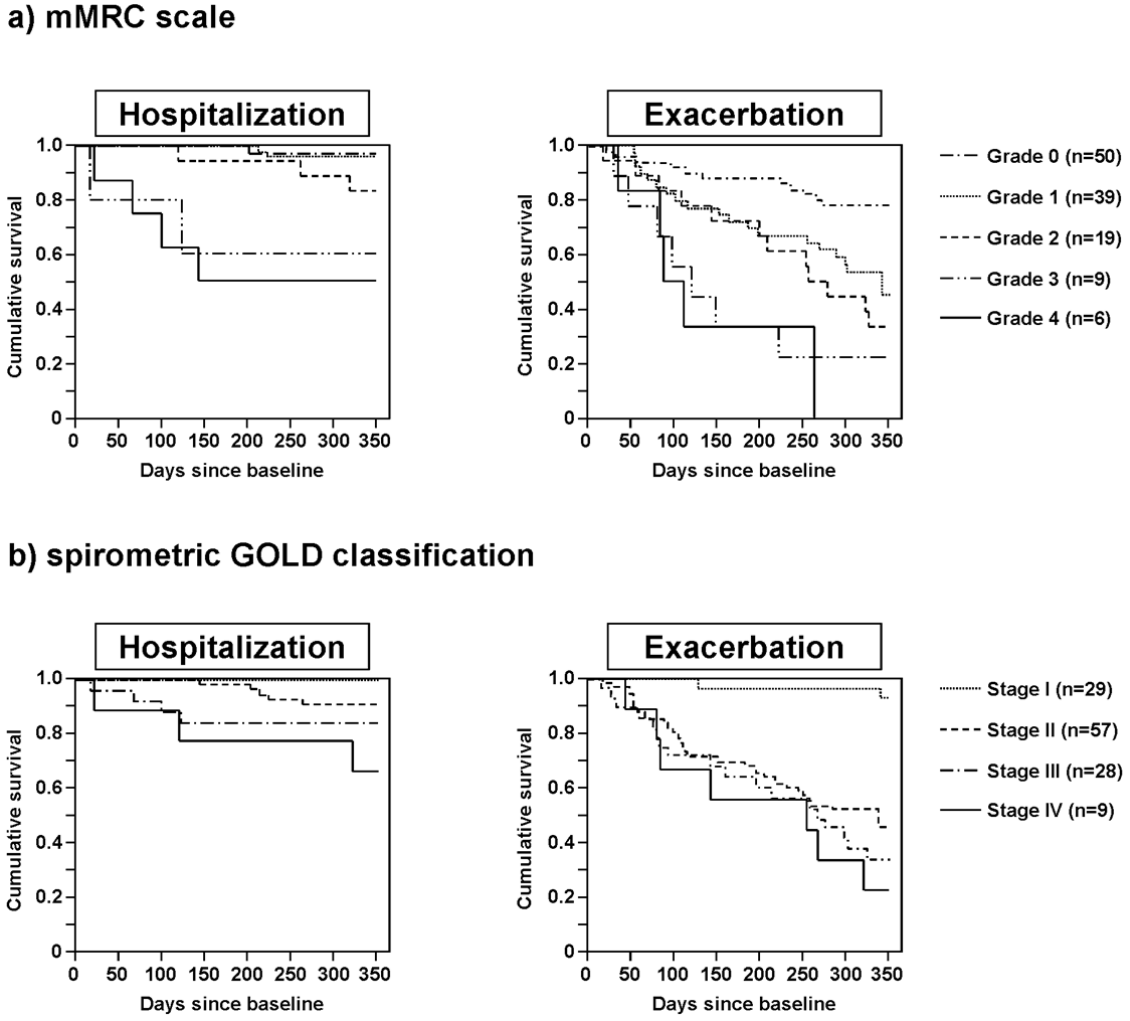
All data are expressed as the frequency (events/patient/yr) of hospitalizations and moderate or severe exacerbations (error bars = standard deviation).

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

Figure 3. Cumulative survival curves for patients with first hospitalization and exacerbation.



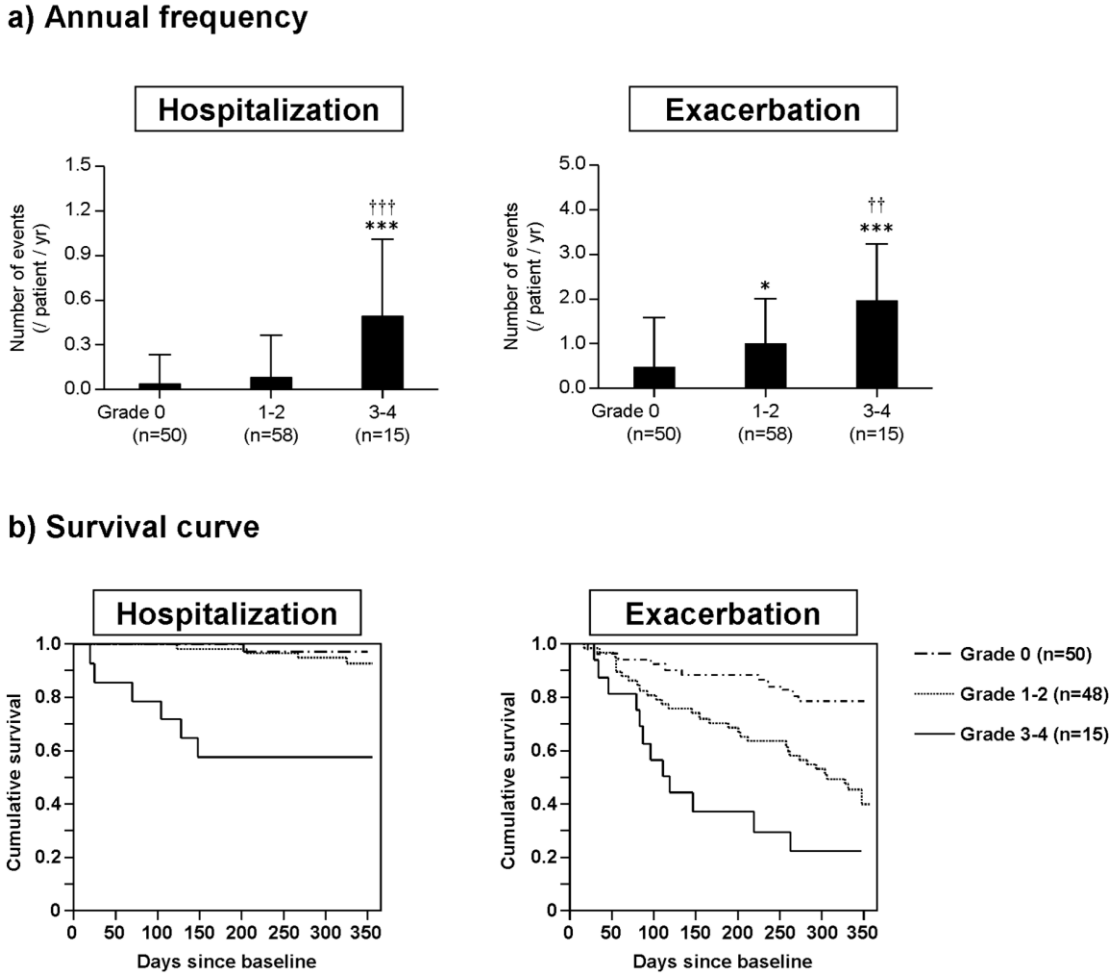
Cumulative survival curves for patients with first hospitalization and moderate or severe exacerbation during the 52-week period.

a) mMRC scale

b) spirometric GOLD classification

mMRC=modified Medical Research Council, GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease

Figure 4. Annual frequency of hospitalization and exacerbation, and cumulative survival curves for patients with first hospitalization and exacerbation.



a) All data are expressed as the frequency (events/patient/yr) of hospitalizations and moderate or severe exacerbations (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 patients with first hospitalization and moderate or

severe exacerbation during the 52-week period.

mMRC=modified Medical Research Council