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Short Communication

Stratifying the risk of COPD exacerbation using the modified Medical Research Council scale: A multicenter cross-sectional CAP study

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Exacerbations are critical events that worsen the prognosis for patients with chronic obstructive pulmonary disease (COPD) [1,2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends the combined use of lung function data and exacerbation history for determination of exacerbation risk [1]. However, it is reported that referral to these guidelines by physicians is limited [3], and there is a need for a simple assessment tool that can be used in everyday practice [4]. The modified Medical Research Council (mMRC) scale is a well-validated questionnaire that uses a simple grading system to quantify disability associated with breathlessness [5], and current guidelines advocate the use of this scale to assess

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symptoms [1]. The mMRC grade correlates well with lung function [6], and it can also predict survival in patients with COPD [7]. However, to date, it remains unclear whether the categories of breathlessness used in the mMRC scale can facilitate stratification of the risk of COPD exacerbation.

This was a multicenter, cross-sectional study that was registered with the University Hospital Medical Information Network (UMIN #000012592) and approved by the ethics committee of Wakayama Medical University (Approval date: May 7, 2014; Approved #: 1410). A total of 1168 patients with COPD, aged 40–95 years, were surveyed at 15 primary or secondary care facilities in Japan. Informed consent for using the data was obtained from all patients. Inclusion criteria were a clinical diagnosis of COPD and a requirement that patients were in a stable condition and had not experienced exacerbation for four weeks prior to the survey. Patients with other pulmonary diseases or with disorders that would prevent them from being able to complete the study assessments were excluded.

The mMRC grades were assessed by the study physicians. The mMRC scale comprises five statements that describe the extent of respiratory disability from no disability (grade 0) to almost complete incapacity (grade 4) [1]. Post-bronchodilator forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured using a dry rolling seal spirometer on the same day. Exacerbation was defined as an acute event characterized by a worsening of respiratory symptoms that was beyond normal day-to-day variations and led to a change in medication [1]. The requirement for systemic corticosteroids or antibiotics and the number of hospitalizations due to COPD during the previous one year were determined by review of medical records [8], and these data were confirmed by patient interview.

To determine the exacerbation risk, the greatest risk according to a GOLD score of ≥ 3 (FEV1 $<50\%$) and/or a history of ≥ 2 exacerbations in the previous one year was selected [1]. The study patients were stratified according to the mMRC scale, and comparisons between different groups were performed by Kruskal–Wallis and Mann–Whitney *U* tests. A receiver operating curve (ROC) was used to determine the cut-off point for the mMRC grade that would identify patients who were at the highest risk for exacerbation.

The results are described in detail in Table 1. The analysis included 1168 patients, 1035 men and 133 women. A majority (96.1%) of the patients were receiving regular pharmacological treatment. In total, 219 patients were untroubled by

Table 1 – Patient characteristics and study results[a]

Age (years)	72.1±8.3
Gender (male/female), *n*	1035/133
Smoking status (never/ex/current), *n*	48/976/144
Use of inhaled long-acting muscarinic receptor antagonist, *n* (%)	868 (74.3)
Use of inhaled long-acting β2-agonist (LABA), *n* (%)	398 (34.1)
Use of inhaled corticosteroids (ICS), *n* (%)	80 (6.8)
Use of combination of ICS and LABA, *n* (%)	431 (36.9)
Use of theophylline, *n* (%)	221 (18.9)
Modified Medical Research Council (mMRC) Scale	
mMRC grade=0, *n* (%)	219 (18.8)
mMRC grade=1, *n* (%)	381 (32.6)
mMRC grade=2, *n* (%)	321 (27.5)
mMRC grade=3, *n* (%)	194 (16.6)
mMRC grade=4, *n* (%)	53 (4.5)
Pulmonary function test[b]	
Forced vital capacity (FVC) (L)	2.90±0.83
Forced expiratory volume in 1 s (FEV1) (L)	1.54±0.62
FEV1/FVC ratio (%)	52.4±12.1
FEV1 % of predicted (%)	59.8±20.6
Severity of airflow limitation (GOLD stage)	
GOLD 1 (mild), *n* (%)	211 (18.1)
GOLD 2 (moderate), *n* (%)	563 (48.2)
GOLD 3 (severe), *n* (%)	304 (26.0)
GOLD 4 (very severe), *n* (%)	90 (7.7)
Previous one year exacerbation history	
Annual rate of exacerbation (events/year)	0.53±0.87
Number of exacerbations=0, *n* (%)	761 (65.2)
Number of exacerbations=1, *n* (%)	259 (22.2)
Number of exacerbations≥2, *n* (%)	148 (12.7)
Patients at risk for COPD exacerbation, *n* (%)[c]	464 (39.7)

[a] Data are presented as means±SD unless otherwise indicated.
[b] All spirometric data were determined after inhalation of 400 μg of salbutamol.
[c] The highest risk according to GOLD stage ≥3 and/or ≥2 exacerbations during the past year was selected.

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breathlessness except on strenuous exercise (mMRC grade 0). There were 381 patients with mMRC grade 1 dyspnea, 321 patients with mMRC grade 2 dyspnea, 194 patients with mMRC grade 3 dyspnea, and 53 patients with mMRC grade 4 dyspnea. All of the patients had FEV1/FVC ratios of <70%, and the mean FEV1 % of predicted value (%FEV1) was 59.8%. There were 211 patients with mild airflow limitation (GOLD stage 1), 563 patients with moderate airflow limitation (GOLD 2), 304 patients with severe airflow limitation (GOLD 3), and 90 patients with very severe airflow limitation (GOLD 4). Among 407 patients who had a history of exacerbation within the previous year, 148 patients had experienced ≥2 exacerbations. Finally, a total of 464 patients (39.7%) were defined as being at risk of exacerbation; 386 had a single risk factor (316 with GOLD score of ≥3 and 70 with history of ≥2 exacerbations during one year) and 78 had a combined risk.

As shown in the figure, there was a marked increase in the proportion of patients at risk of exacerbation across each of the categories of breathlessness used in the mMRC scale (mMRC 0, 12.8%; mMRC 1, 23.1%; mMRC 2, 48.9%; mMRC 3, 72.7%; mMRC 4, 94.3%, $p<0.0001$), and the exacerbation risk was significantly different between groups at all mMRC grades. Significant differences in %FEV1 and exacerbation rates were also found in accordance with the mMRC grade. On ROC analysis, an mMRC grade of ≥2 demonstrated 75% sensitivity and 69% specificity for identifying patients who are at risk of exacerbation (AUC=0.77).

The present study has shown that the mMRC breathlessness scale can provide a simple and valid method of stratifying patients in terms of their risk of COPD exacerbation. In addition, there was a highly significant number of patients with increased risk who had mMRC grade 2 dyspnea or higher. It therefore appears that the correlates of exacerbation risk according to lung function data and exacerbation history may vary with the degree of respiratory disability. The current findings are consistent with a recent population study from Copenhagen in which the survival of COPD patients was better among patients in GOLD group C (poor lung function but less dyspnea) than in GOLD group B (better lung function but more dyspnea) [9]. Moreover, Hurst et al. [10] have reported that an mMRC grade of ≥2 is associated with exacerbations, although they did not provide a detailed analysis of the categories of breathlessness used in the mMRC scale.

The present study has some limitations. Although we carefully excluded patients with any previous diagnosis or clinical history of asthma, we might not have been able to completely exclude COPD patients with an asthmatic component, and this may relate to the finding that 4.1% of the included patients did not have a past smoking history. Because of the size of the study, tests that would have required more strict standardization, i.e., more complex measurements of lung function or measurements of airway responsiveness, were not performed. Next, while significant differences in %FEV1 and exacerbation rates in accordance with the mMRC grade may explain the association between dyspnea and exacerbation risk, the causal relationship between the mMRC grade and the risk for COPD exacerbations remains unclear. A prospective cohort study will be needed to validate the utility of the mMRC scale as a predictor of COPD exacerbation.

Third, in this multicenter study, changes in treatment after exacerbation were left to the discretion of the attending physician. This may have contributed to the relatively higher rate of exacerbation than has been previously reported in data from Japan [11–13].

The present study indicates that disability due to severe dyspnea may reflect a highly vulnerable phenotype, and such patients must be managed with caution. Importantly, it is difficult to distinguish these patients from other patients because exertional dyspnea often causes COPD patients to unconsciously reduce their activities of daily living in order to reduce the intensity of their distress [14]. Furthermore, we showed that risk of exacerbation could be predicted by exacerbation history in only 32% of the patients. Thus, we strongly suggest that the mMRC breathlessness scale should be included in the clinical assessment of COPD populations in everyday practice (Fig. 1).

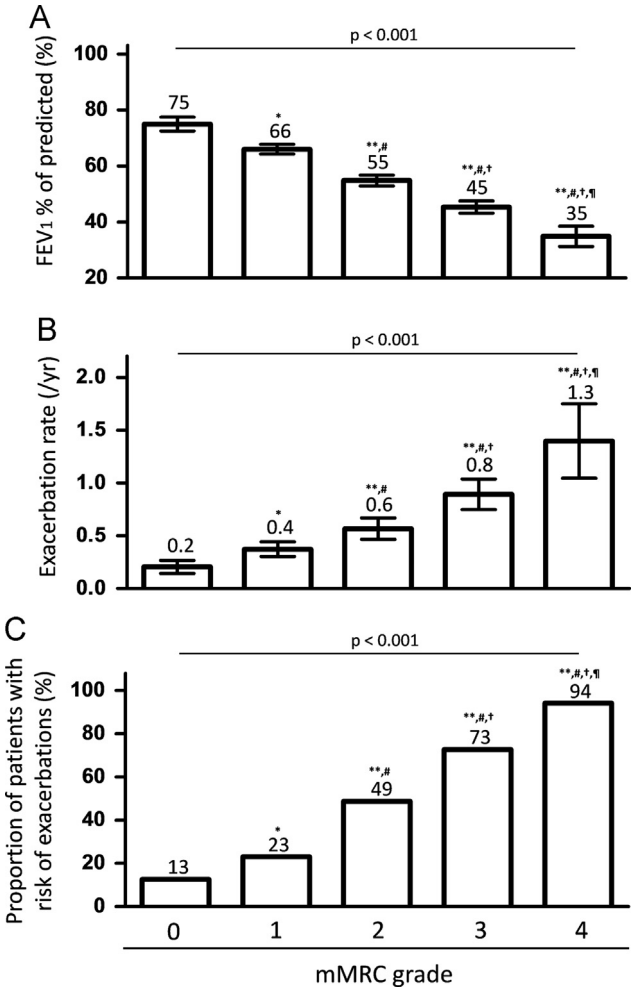

Fig. 1 – (A) Forced expiratory volume in 1 s (FEV1) as % of predicted, (B) exacerbation rate, and (C) the proportion of patients with risk of exacerbation according to mMRC grade. **$p<0.0001$, *$p<0.001$ vs. mMRC 0; #$p<0.001$ vs. mMRC 1; †$p<0.001$ vs. mMRC 2; ¶$p<0.001$ vs. mMRC 3. The error bars represent 95% confidence intervals.

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Author contributions

K.M. conception and design research; K.M., A.H. K.A., T.H., T.T., T.K., T.T., H.N., T.T., S.H., Y.M., Y.S., K.K., U.K., M.M. and M.I. acquisition of data; K.M. performed analysis; K.M. and M.I. interpreted results of analysis; K.M. prepared manuscript; K.M., A.H. K.A., T.H., T.T., T.K., T.T., H.N., T.T., S.H., Y.M., Y.S., K.K., U.K., M.M. and M.I. approved final version of the manuscript.

Conflict of interest statement

The authors have no conflicts of interest.

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