

# Predictive properties of different multidimensional staging systems in patients with chronic obstructive pulmonary disease

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**Background:** Chronic obstructive pulmonary disease (COPD) is considered to be a respiratory disease with systemic manifestations. Some multidimensional staging systems, not based solely on the level of airflow limitation, have been developed; however, these systems have rarely been compared.

**Methods:** We previously recruited 150 male outpatients with COPD for an analysis of factors related to mortality. For this report, we examined the discriminative and prognostic predictive properties of three COPD multidimensional measurements. These indices were the modified BODE (mBODE), which includes body mass index, airflow obstruction, dyspnea, and exercise capacity; the ADO, composed of age, dyspnea, and airflow obstruction; and the modified DOSE (mDOSE), comprising dyspnea, airflow obstruction, smoking status, and exacerbation frequency.

**Results:** Among these indices, the frequency distribution of the mBODE index was the most widely and normally distributed. Univariate Cox proportional hazards analyses revealed that the scores on three indices were significantly predictive of 5-year mortality of COPD ( $P < 0.001$ ). The scores on the mBODE and ADO indices were more significantly predictive of mortality than forced expiratory volume in 1 second, the Medical Research Council dyspnea score, and the St. George's Respiratory Questionnaire total score. However, peak oxygen uptake on progressive cycle ergometry was more significantly related to mortality than the scores on the three indices ( $P < 0.0001$ ).

**Conclusion:** The multidimensional staging systems using the mBODE, ADO, and mDOSE indices were significant predictors of mortality in COPD patients, although exercise capacity had a more significant relationship with mortality than those indices. The mBODE index was superior to the others for its discriminative property. Further discussion of the definition of disease severity is necessary to promote concrete multidimensional staging systems as a new disease severity index in guidelines for the management of COPD.

**Keywords:** COPD, multidimensional staging systems, BODE index, ADO index, DOSE index

## Background

Chronic obstructive pulmonary disease (COPD) is now considered as a respiratory disease with systemic manifestations.<sup>1</sup> COPD first affects the lungs primarily, and then structural and functional changes also take place in other organs. The degree of airflow limitation as defined by forced expiratory volume in 1 second ( $FEV_1$ ) has been used as an index of disease severity, partly because of its significant relationship with mortality.<sup>2,3</sup> Guidelines indicate that some multidimensional staging systems including systemic components in addition to airflow limitation may be used to assess

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disease severity,<sup>1,4</sup> although the definition of disease severity remains elusive.

The BODE index, incorporating measurements of nutrition, airflow limitation, dyspnea, and exercise capacity, has been established for multidimensional staging.<sup>5</sup> It is useful in predicting mortality and hospitalizations and in reflecting disease modification and progression.<sup>6</sup> More simplified indices such as the ADO index, composed of age, dyspnea, and airflow limitation,<sup>7</sup> and the DOSE index, composed of dyspnea, airflow limitation, smoking status, and exacerbation frequency,<sup>8</sup> have been developed recently and have been validated. In two European cohorts, both the ADO index and the updated BODE index significantly predicted the 3-year mortality risk after the first hospital admission due to an exacerbation of moderate-to-severe COPD, although the original BODE index did not accurately predict such a risk.<sup>7</sup> The DOSE index was related to a range of clinically important outcomes of COPD such as health status, hospital admission, or respiratory failure, and was predictive of exacerbations.<sup>8</sup> Although some multidimensional staging systems have been developed recently, these indices have rarely been compared.

More information about the properties of these indices or relationships is needed so that they can be better used in clinical practice or trials and, furthermore, be adopted concretely in the guidelines in future. We hypothesized that the BODE, ADO, and DOSE indices would be useful as predictors of mortality in COPD, but that they would have some different characteristics. We previously examined the factors related to 5-year mortality using multiple measurements in patients with COPD.<sup>9</sup> In the present study, by reviewing those data, we analyzed the discriminative and predictive properties of those multidimensional indices in patients with COPD.

## Materials and methods

### Patients

We previously recruited 150 consecutive male outpatients with COPD and analyzed factors related to mortality.<sup>9</sup> Entry criteria included (1) smoking history of more than 20 pack-years, (2) maximal FEV<sub>1</sub>/forced vital capacity ratio of less than 0.7 and prebronchodilator FEV<sub>1</sub> of less than 80% of the predicted value, (3) regular attendance at Kyoto University, Kyoto, Japan, outpatient clinic over 6 months, (4) no uncontrolled comorbidities, and (5) no COPD exacerbations over the preceding 6 weeks. The study protocol was approved by the institutional ethical committee of Kyoto University.

## Measurements

Pulmonary function tests were performed at least 12 hours after the withdrawal of inhaled bronchodilators.<sup>9</sup> Patients performed spirometry at 15 and 60 minutes after inhaling salbutamol (400 µg) and ipratropium bromide (80 µg) using a metered-dose inhaler with a spacer device.

Exercise tests were performed on symptom-limited progressive cycle ergometry 60 minutes after the inhalation of bronchodilators as described in detail previously.<sup>9–11</sup> Patients wore a face mask and began unloaded pedaling for 3 minutes, after which the workload was increased progressively by an increment of 1 W every 3 seconds to the limit of tolerance. The exercise data were recorded with an automated exercise testing system. Peak oxygen uptake ( $\dot{V}O_2$ ) that was reached during exercise was calculated. Predicted values were calculated using the standard equation.<sup>12,13</sup>

Dyspnea was evaluated by the Japanese version of the modified Medical Research Council (MRC) dyspnea scale, which is a 5-point scale (0–4) based on degrees of various physical activities that precipitate dyspnea.<sup>14,15</sup> Higher scores on the MRC indicate more severe dyspnea. Health status was assessed by the Japanese version of the St. George's Respiratory Questionnaire (SGRQ).<sup>9,16,17</sup> The SGRQ consists of 50 items divided into the three components of symptoms, activity, and impacts, and the total score was calculated with scores ranging from 0 to 100. Higher scores on the SGRQ indicate a more severe health status.

## Multidimensional staging

The BODE index was principally based on the original report<sup>5</sup> whose score comprises the body mass index (BMI), percentage of the predicted FEV<sub>1</sub>, dyspnea by the MRC, and 6-minute walking distance (6MWD) as an exercise capacity component. Scores ranged from 0 (best status) to 3 (worst status) for FEV<sub>1</sub> and MRC, and 0 or 1 for BMI. In the present study, we employed the modified BODE index (mBODE), which used  $\dot{V}O_2$  as % predicted, as tested by the progressive cycle ergometry instead of the 6MWD, and was previously developed and validated.<sup>18,19</sup> The % predicted was scored as follows: score 0 for >70% predicted, score 1 for 60%–69% predicted, score 2 for 40%–59% predicted, and score 3 for 40%< predicted. Points for each component were added together so that the mBODE index ranged from 0 to 10.

The ADO index was calculated based on the original report,<sup>7</sup> with the score comprising age, dyspnea by the MRC, and FEV<sub>1</sub>. Scores ranged from 0 (best status) to 5 (worst status) for age, 0–3 for MRC, and 0–2 for FEV<sub>1</sub>. Points for each component were added so that the ADO index ranged from 0 to 10.

The DOSE index was calculated primarily based on the original report,<sup>8</sup> with scores comprising dyspnea by the MRC, FEV<sub>1</sub>, smoking status, and exacerbation frequency per year. Scores ranged from 0 (best status) to 3 (worst status) for MRC, 0–2 for FEV<sub>1</sub> and the exacerbation frequency, and 0 or 1 for smoking status. In the present study, the modified DOSE (mDOSE) index was calculated using the question “During the last year, how many severe or very unpleasant attacks of chest trouble have you had?” on the SGRQ, instead of exacerbation frequency over the previous year as indicated in the original manuscript.<sup>8</sup> Points for each component were added so that the DOSE index ranged from 0 to 8.

## Statistical analysis

Results were expressed as mean  $\pm$  standard deviation, unless otherwise stated. Relationships between the mBODE, ADO, and mDOSE indices were analyzed by Spearman's correlation coefficient tests. The survival status of all patients after 5 years was assessed. The duration from entry to the last attendance or death was recorded. Univariate and multivariate Cox proportional hazards analyses were performed to investigate the relationships between the clinical measurements and mortality. Results of regression analyses were presented in terms of estimated relative risks (RR) with corresponding 95% confidence intervals. *P*-values of less than 0.05 were considered to be statistically significant.

## Results

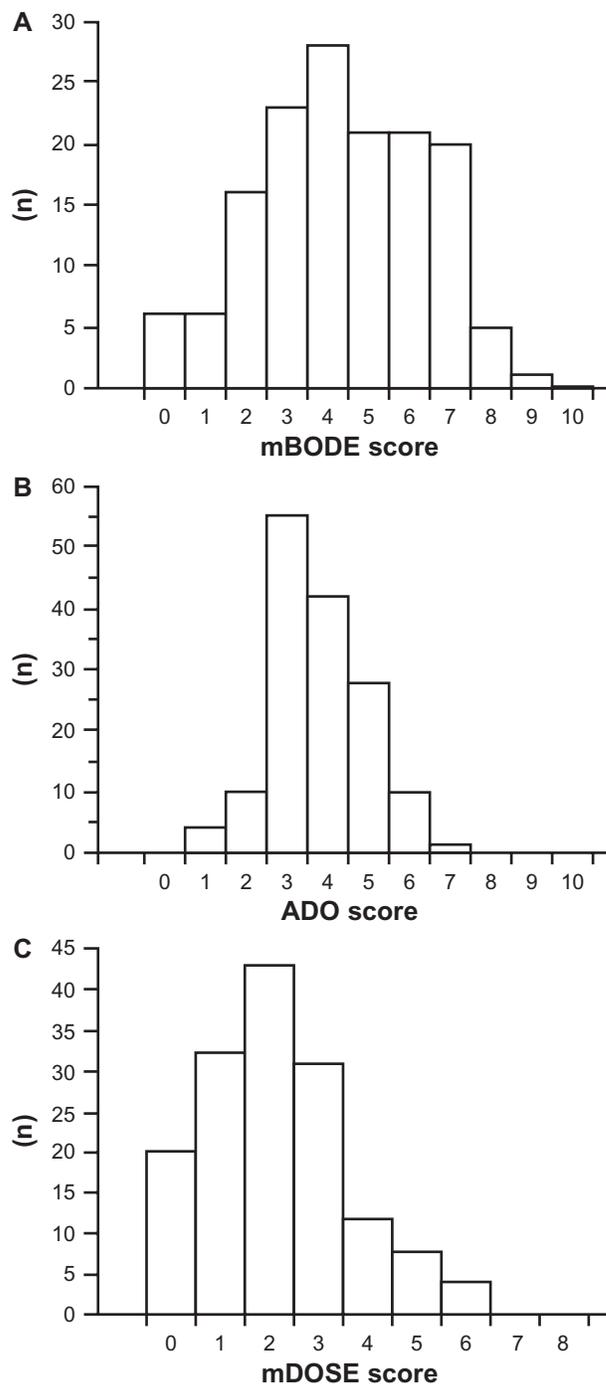
Baseline characteristics of the 150 male patients with stable COPD are shown in Table 1 and elsewhere.<sup>9</sup> Their average age was  $69 \pm 7$  years and the postbronchodilator FEV<sub>1</sub> was  $47.4\% \pm 17.4\%$  predicted. The frequency distributions of mBODE, ADO, and mDOSE scores are shown in Figure 1. The histograms showed widely and virtually normal distribution of the mBODE scores. The ADO scores were more narrowly distributed than the mBODE scores, with 55 patients (37%) and 42 patients (28%) scoring 3 and 4, respectively. The median of the mDOSE score was 2, with the distribution

**Table 1** Multidimensional staging of 150 male patients with chronic obstructive pulmonary disease

Characteristics	Mean $\pm$ SD	Range
mBODE index (0–10)	4.3 $\pm$ 2.0	0–9
ADO index (0–10)	3.8 $\pm$ 1.2	1–7
mDOSE index (0–8)	2.2 $\pm$ 1.5	0–6

**Note:** On the mBODE, ADO, and mDOSE indices, higher scores indicate a more severe status.

**Abbreviations:** ADO, age, dyspnea, and airflow obstruction; mBODE, modified body mass index, airflow obstruction, dyspnea, and exercise capacity; mDOSE, modified dyspnea, airflow obstruction, smoking status, and exacerbation frequency.



**Figure 1** Frequency distributions of the (A) mBODE score, (B) ADO score, and (C) mDOSE score in patients with chronic obstructive pulmonary disease. In each, a higher score indicates a more severe status.

**Abbreviations:** ADO, age, dyspnea, and airflow obstruction; mBODE, modified body mass index, airflow obstruction, dyspnea, and exercise capacity; mDOSE, modified dyspnea, airflow obstruction, smoking status, and exacerbation frequency.

of scores tending to skew toward the lower scores. There were significant relationships between the three indices (mBODE vs ADO, correlation coefficients [ $r_s$ ] = 0.60,  $P < 0.0001$ ; ADO vs mDOSE,  $r_s = 0.55$ ,  $P < 0.0001$ ; and mDOSE vs mBODE,  $r_s = 0.64$ ,  $P < 0.0001$ ).

Of the 150 patients enrolled, six were unavailable for follow-up and 31 patients died.<sup>9</sup> Causes of death were as follows: 20 due to COPD or COPD-related diseases, four due to malignant disorders (two lung cancer cases), one due to myocardial infarction and hepatic failure, respectively, and five due to unknown reasons.

Univariate Cox proportional hazards analyses were performed to investigate the relationship between clinical indices and mortality (Table 2 and elsewhere<sup>9</sup>). Age, BMI, FEV<sub>1</sub>, peak  $\dot{V}O_2$ , MRC, and the SGRQ total score were all significantly related to mortality. All the mBODE, ADO, and mDOSE indices were strongly related to mortality (RR = 1.618,  $P < 0.0001$ ; RR = 2.342,  $P < 0.0001$ ; and RR = 1.521,  $P = 0.0002$ , respectively).

To investigate the abilities of the aforementioned three multidimensional staging methods to predict mortality as compared with airflow limitation, exercise capacity, dyspnea, and health status, multivariate Cox proportional hazards analyses were performed (Table 3). Model 1 includes three analyses investigating the relationships between each index and FEV<sub>1</sub> with mortality. The mBODE and ADO indices were more significantly related to mortality than FEV<sub>1</sub>, but mDOSE index was not. Model 3 includes three analyses investigating the relationships between each index and MRC with mortality. The result was the same with Model 1. These results indicate that predictive properties of mBODE and ADO indices might be stronger than those of FEV<sub>1</sub> and MRC as well as mDOSE index. In contrast, Model 2 includes three analyses investigating the relationships between each index and peak  $\dot{V}O_2$  with mortality. Peak  $\dot{V}O_2$  was more significantly related to mortality than all three indices ( $P < 0.0001$ ), indicating that the predictive property of exercise capacity might be stronger than different multidimensional staging. Model 4 includes three analyses investigating the relationships between each index and SGRQ with mortality. In contrast with Model 2, all three indices were more significantly related to mortality than the SGRQ total score.

To investigate which of the mBODE, ADO, and mDOSE indices was the most significantly correlated with mortality,

stepwise multivariate Cox proportional hazards analysis was performed (Table 4). Both the mBODE and ADO indices were significantly related to mortality (RR = 1.351,  $P = 0.027$ ; and RR = 1.653,  $P = 0.031$ ) but not the mDOSE index ( $P = 0.87$ ).

## Discussion

We evaluated the predictive and discriminative properties of different multidimensional staging systems in patients with COPD. Among the mBODE, ADO, and mDOSE indices, the mBODE index seemed to have the best discriminative property. We found that all three indices were significantly predictive of mortality, although the predictive ability of the mDOSE tended to be inferior to the other two. In contrast, values for the peak  $\dot{V}O_2$  on progressive cycle ergometry were more significantly correlated with mortality than any of the three multidimensional staging systems.

We previously examined predictors of mortality in patients with COPD and reported that exercise capacity, dyspnea, and health status were significantly related to mortality independently of airflow limitation.<sup>9,20,21</sup> These results suggested the need to incorporate these systemic elements in addition to FEV<sub>1</sub> in evaluating patients with COPD. Among the three indices, the mBODE and ADO indices were more strongly predictive of mortality than FEV<sub>1</sub>, MRC, or SGRQ. Thus, these multidimensional staging systems seem to be more useful in prognostic assessments than airflow limitation, dyspnea, or health status alone in patients with COPD. After evaluating their properties well in different study situations, they will be used in clinical settings.

The relationships between the mBODE, ADO, and mDOSE indices were moderate, indicating that they do not necessarily evaluate the same aspects of COPD, although some components are common to all three indices. In fact, the stepwise multivariate Cox proportional hazards analysis showed that both the mBODE and ADO indices were independently related to mortality in patients with COPD. Thus, using more than one index might have some complementarily or additive advantage in prognostic assessment.

There were differences in the discriminative properties among the mBODE, ADO, and mDOSE indices. The mBODE score was more widely and normally distributed than the scores of the other indices examined, indicating its superior discriminative property. In our single population sample, the age component of the ADO index might have varied less widely than the original report of the ADO index,<sup>7</sup> as shown here that about 65% of our patients scored 3 or 4. Regarding the mDOSE index, firstly, its range from 0 to 8 is narrower than the BODE and ADO indices ranging

**Table 2** Univariate Cox proportional hazards analyses in patients with chronic obstructive pulmonary disease

	Relative risk	95% confidence interval	P-value
mBODE index	1.618	1.301–2.013	<0.0001
ADO index	2.342	1.662–3.300	<0.0001
mDOSE index	1.521	1.223–1.890	0.0002

**Abbreviations:** ADO, age, dyspnea, and airflow obstruction; mBODE, modified body mass index, airflow obstruction, dyspnea, and exercise capacity; mDOSE, modified dyspnea, airflow obstruction, smoking status, and exacerbation frequency.

**Table 3** Multivariate Cox proportional hazards analyses in patients with chronic obstructive pulmonary disease

	Relative risk (95% confidence interval)		
<b>Model 1 (airflow limitation and multidimensional staging)</b>			
FEV <sub>1</sub> , %pred	0.972 (0.935–1.012)	0.967 (0.936–0.998) <sup>a</sup>	0.950 (0.920–0.980) <sup>b</sup>
mBODE index	1.379 (1.015–1.874) <sup>a</sup>	NA	NA
ADO index	NA	1.913 (1.248–2.932) <sup>b</sup>	NA
mDOSE index	NA	NA	1.199 (0.916–1.569)
<b>Model 2 (exercise capacity and multidimensional staging)</b>			
Peak $\dot{V}O_2$ , mL/min	0.995 (0.993–0.997) <sup>c</sup>	0.995 (0.993–0.997) <sup>c</sup>	0.994 (0.992–0.996) <sup>c</sup>
mBODE index	1.113 (0.852–1.455)	NA	NA
ADO index	NA	1.328 (0.889–1.983)	NA
mDOSE index	NA	NA	1.119 (0.854–1.467)
<b>Model 3 (dyspnea and multidimensional staging)</b>			
MRC scale	1.163 (0.684–1.977)	1.248 (0.735–2.118)	1.697 (1.029–2.798) <sup>a</sup>
mBODE index	1.556 (1.203–2.012) <sup>c</sup>	NA	NA
ADO index	NA	2.082 (1.334–3.249) <sup>b</sup>	NA
mDOSE index	NA	NA	1.263 (0.955–1.670)
<b>Model 4 (health status and multidimensional staging)</b>			
SGRQ total	1.014 (0.990–1.039)	1.019 (0.997–1.042)	1.014 (0.987–1.041)
mBODE index	1.545 (1.225–1.947) <sup>b</sup>	NA	NA
ADO index	NA	2.169 (1.511–3.115) <sup>b</sup>	NA
mDOSE index	NA	NA	1.384 (1.037–1.845) <sup>a</sup>

**Notes:** <sup>a</sup>P < 0.05, <sup>b</sup>P < 0.01, <sup>c</sup>P < 0.001.

**Abbreviations:** ADO, age, dyspnea, and airflow obstruction; FEV<sub>1</sub>, forced expiratory volume in 1 second; mBODE, modified body mass index, airflow obstruction, dyspnea, and exercise capacity; mDOSE, modified dyspnea, airflow obstruction, smoking status, and exacerbation frequency; MRC, Medical Research Council; NA, not applicable; SGRQ, St. George's Respiratory Questionnaire;  $\dot{V}O_2$ , peak oxygen uptake.

from 0 to 10. Secondly, in the present study, the median score on the mDOSE index was low at 2, and its distribution was skewed toward lower scores, which were consistent with the original report.<sup>8</sup> Thus, although the ADO and DOSE indices are simple and easy assessments for use in primary care settings, as they do not include an exercise capacity component, their discriminative properties may be limited.

In the present study, peak  $\dot{V}O_2$  was more strongly related to mortality than the mBODE, ADO, and mDOSE indices, indicating that peak  $\dot{V}O_2$  is an important factor in COPD in relation to mortality. In addition to studies examining predictors of mortality in COPD,<sup>9</sup> peak  $\dot{V}O_2$  is reported to be a useful prognostic factor in other disorders<sup>22,23</sup> such as interstitial lung diseases,<sup>24</sup> primary pulmonary hypertension,<sup>25</sup> cystic fibrosis,<sup>26</sup> or chronic heart failure.<sup>27</sup> Cardiopulmonary exercise testing has some utility in diagnosis and functional evaluation, and prognostic stratification is considered to be

a major indication for cardiopulmonary exercise testing in patients with pulmonary or cardiac disorders.<sup>23</sup>

In the present study, we compared different multidimensional staging systems from the viewpoint of the relationship of their scores with mortality. Although these or similar indices are sometimes referred to as disease severity indices, strictly speaking, disease severity in COPD has not been defined. When disease severity is considered according to the closeness of death, assessing results of these systems would be appropriate in predicting mortality. However, there are other ideas about defining disease severity, such as its relationship with health status or exacerbations. It seems that multidimensional staging is superior to the current means of disease staging based on the level of FEV<sub>1</sub>.<sup>28,29</sup> A standardized definition of disease severity is needed to eliminate confusion and to officially establish a novel disease severity staging system not based solely on FEV<sub>1</sub> in future.

As a limitation, although several multidimensional staging systems in addition to the BODE, ADO, and DOSE indices have been developed in recent years,<sup>30,31</sup> we did not assess them in the present study.

## Conclusion

We demonstrated that the multidimensional staging systems of the mBODE, ADO, and mDOSE indices were significant predictors of mortality in patients with COPD. The mBODE

**Table 4** Stepwise multivariate Cox proportional hazards analysis in patients with chronic obstructive pulmonary disease

	Relative risk	95% confidence interval	P-value
mBODE index	1.351	1.035–1.765	0.027
ADO index	1.653	1.047–2.610	0.031
mDOSE index			0.87

**Abbreviations:** ADO, age, dyspnea, and airflow obstruction; mBODE, modified body mass index, airflow obstruction, dyspnea, and exercise capacity; mDOSE, modified dyspnea, airflow obstruction, smoking status, and exacerbation frequency.

was superior to other indices for its discriminative property. An understanding of the properties or characteristics of the indices is important when using them in clinical practice, and, at the same time, a definition of disease severity needs to be established in order to propose the indices assessed in this report as a new disease severity index.

## Disclosure

The authors declare that they had no competing interests.

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