Analysis of the Factors Related to Mortality in Chronic Obstructive Pulmonary Disease

Role of Exercise Capacity and Health Status

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In this study, we analyzed the relationships of exercise capacity and health status to mortality in patients with chronic obstructive pulmonary disease (COPD). We recruited 150 male outpatients with stable COPD with a mean postbronchodilator FEV_1 at 47.4% of predicted. Their pulmonary function, progressive cycle ergometry, and health status using the Chronic Respiratory Disease Questionnaire, the St. George's Respiratory Questionnaire (SGRQ), and the Breathing Problems Questionnaire were measured at entry. Among 144 patients who were available for the 5-year follow-up, 31 had died. Univariate Cox proportional hazards analysis revealed that the SGRQ total score and the Breathing Problems Questionnaire were significantly correlated with mortality; however, with the Chronic Respiratory Disease Questionnaire, the total score was not significantly correlated. Multivariate Cox proportional hazards analysis revealed that the peak oxygen uptake and the SGRQ total score were both predictive of mortality, independent of FEV_1 and age. Stepwise Cox proportional hazards analysis revealed that the peak oxygen uptake was the most significant predictor of mortality. We found that exercise capacity and health status were significantly correlated with mortality, although different health status measures had different abilities to predict mortality. These results will have a potentially great impact on the multidimensional evaluation of disease severity in COPD.

Keywords: chronic obstructive pulmonary disease; mortality; exercise capacity; health status

Mortality has been an important outcome in chronic obstructive pulmonary disease (COPD), as it is currently the fourth leading cause of death in the world (1). The disease severity of COPD has been based on the degree of airflow limitation, as defined by FEV_1 because FEV_1 has been regarded as the most important predictor of mortality in addition to age (2). However, although many studies investigating factors related to mortality have been performed in COPD, the relationships of exercise capacity and health status to mortality have rarely been evaluated.

There has recently been some debate about the use of FEV_1 as the main single evaluative parameter for COPD. Van Schayck commented that when the effects of medication are evaluated, the effects on quality of life and functional status are probably much more important than effects on airflow limitation alone (3). Nishimura and coworkers have recently reported that categorizing patients with COPD on the level of dyspnea was more closely correlated with mortality than classification based on disease severity, as assessed by the percentage of predicted FEV_1 (4). Celli proposed a systemic evaluation of COPD patients and stressed that there is a need to seek candidates for multidimensional disease staging (5). Exercise capacity and health status may also be important clinical indices to evaluate disease impairment in addition to FEV_1.

Although airflow limitation is the most obvious manifestation of COPD, COPD has other extrapulmonary features and should be regarded as a systemic disorder (6). This multipathophysiologic aspect of COPD can influence exercise capacity (7) and health status (8). Therefore, we hypothesized that they could predict mortality in COPD. In this study, we investigated the relationships between various clinical parameters, including exercise capacity and health status, and mortality in patients with COPD after 5 years. In addition, we examined which clinical parameter was the most important when regarding mortality as the reference outcome.

METHODS

Patients

We recruited 150 consecutive male outpatients with COPD from September 1995 to January 1997 at the Kyoto University Hospital. Entry criteria included (*1*) smoking history of more than 20 pack-years; (*2*) maximal FEV_1/FVC ratio of less than 0.7 and prebronchodilator FEV_1 of less than 80% of the predicted value; (*3*) no uncontrolled comorbidities likely to affect mortality such as malignant disorders, cardiovascular diseases, or cerebrovascular diseases; (*4*) regular attendance over 6 months; and (*5*) no exacerbations in the preceding 6 weeks. Pulmonary function, exercise capacity, health status, smoking status, and body mass index (BMI) were evaluated on the same day. Pulmonary function tests were performed at least 12 hours after the withdrawal of inhaled bronchodilators. According to the recommended method (9), subjects underwent spirometry before and at 15 and 60 minutes after inhaling salbutamol (400 μg) and ipratropium bromide (80 μg) using a metered-dose inhaler with a spacer device (InspirEase; Schering-Plough K.K., Osaka, Japan) (10). The predicted values were those established by the Japan Society of Chest Diseases (11). Self-reported smoking status was confirmed by using a smokerlyzer and measuring plasma cotinine levels as explained elsewhere (12). BMI was calculated by dividing the patient's weight in kg by height squared (m^2). Although all patients were advised to exercise during daily living, no established rehabilitation program was administered. Verbal informed consent was obtained from all patients.

Measurements

Symptom-limited progressive cycle ergometry was performed 60 minutes after the inhalation of bronchodilators on a calibrated, electrically braked cycle ergometer (13). Patients wore a face mask and began unloaded pedaling for 3 minutes, after which the workload was increased progressively by increments of 1 W every 3 seconds to the limit of tolerance. The exercise data were recorded with an automated exercise testing system. The peak oxygen uptake ($\dot{V}O_2$) that was reached during exercise was calculated.

Health status was measured by three disease-specific measures: the Chronic Respiratory Disease Questionnaire (CRQ) (14), the St. George's Respiratory Questionnaire (SGRQ) (15), and the Breathing

(*Received in original form June 20, 2002; accepted in final form November 18, 2002*)

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Am J Respir Crit Care Med Vol 167. pp 544–549, 2003
Originally Published in Press as DOI: 10.1164/rccm.200206-583OC on November 21, 2002
Internet address: www.atsjournals.org

TABLE 1. BASELINE CHARACTERISTICS IN 150 MALE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Characteristics	Mean ± SD or Number	Range
Age, yr	68.7 ± 6.9	48–89
Smokers, former/current	115/35	
Cumulative smoking, pack-years	58 ± 31	20–210
Body mass index, kg/m^2	21.1 ± 2.9	14.0–29.0
Prebronchodilator FEV_1, L	1.01 ± 0.44	0.34–2.52
Prebronchodilator FEV_1, % predicted	38.1 ± 15.7	14.7–78.0
Postbronchodilator FEV_1, % predicted	47.4 ± 17.4	15.7–83.6
D_{LCO}, % predicted	64.8 ± 20.2	30.5–131.2
D_{LCO}/V_A, ml/min/L/mm Hg	3.37 ± 1.17	1.29–7.11
Peak $\dot{V}O_2$, ml/min	833 ± 265	202–1,625
Health status measures		
CRQ dyspnea (5–35)	26.0 ± 5.8	11–35
Fatigue (4–28)	19.9 ± 5.1	4–28
Emotional function (7–49)	39.5 ± 7.0	19–49
Mastery (4–28)	22.0 ± 4.3	11–28
Total (20–140)	107.5 ± 18.3	65–140
SGRQ symptoms (0–100)	52.4 ± 19.9	9.7–100.0
Activity (0–100)	42.2 ± 21.1	0.0–94.0
Impact (0–100)	24.7 ± 16.9	0.0–75.4
Total (0–100)	36.1 ± 16.7	2.5–80.0
BPQ Total (1–103)	18.1 ± 12.9	1–62

Definition of abbreviations: BPQ = Breathing Problems Questionnaire; CRQ = Chronic Respiratory Disease Questionnaire; D_{LCO} = diffusing capacity for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire; V_A = alveolar volume; $\dot{V}O_2$ = oxygen uptake.

* The numbers in parentheses indicate the theoretical score range.

On the CRQ, higher scores indicate better health status, and vice versa on the SGRQ and BPQ.

Problems Questionnaire (BPQ) (16). The Japanese versions of these questionnaires have been previously validated (12). The CRQ consists of 20 items that were divided into four domains: dyspnea, fatigue, emotional function, and mastery. Each question was scored on a seven-point scale, and each domain and the total score were calculated as the sum. The SGRQ consists of 50 items divided into three components of symptoms, activity, and impacts, and the total score was also calculated, with scores ranging from 0 to 100. The BPQ has 33 items, and its total score was calculated using a scale of 1 to 103. Higher scores indicate less impairment on the CRQ, and the opposite is true of the SGRQ and BPQ.

Statistical Analysis

Results are presented as mean ± SD unless otherwise stated. The survival status of all subjects after 5 years was assessed. The duration from entry to the last attendance or death was recorded. The survival time was calculated with the life table method.

Univariate and multivariate Cox proportional hazards analyses were performed to investigate the relationship between the clinical indices and mortality. Postbronchodilator FEV_1 was used as an index of airflow limitation because it is regarded as a better predictor of mortality than prebronchodilator FEV_1 (2). Clinical variables were used as continuous variables, except that the categoric variables of smoking status and the use of inhaled corticosteroids were coded as one or zero for the analysis. Results of the regression analysis were presented in terms of the estimated relative risks (RRs) with corresponding 95% confidence intervals; p values of less than 0.05 were considered to be statistically significant.

RESULTS

The baseline characteristics of the 150 male COPD patients are presented in Table 1. Their age averaged 68.7 ± 6.9 years, and postbronchodilator FEV_1 was 47.4 ± 17.4% predicted. Five patients received no medications, and 145 patients were treated with both inhaled short-acting β_2-agonists and anticholinergic agents. Sixteen patients (11%) received oral theophylline (400 to 800 mg/day). In addition, 74 patients (49%) were treated with high doses (1,600 to 2,400 μg/day) of inhaled beclomethasone dipropionate. Additional oral corticosteroids (prednisolone; 2.5 to 10 mg/day) were administered to six patients (4%). Long-acting β_2-agonists and inhaled corticosteroids other than beclomethasone dipropionate were not available during the study period.

When the patients were classified according to COPD severity based on airflow limitation defined by the American Thoracic Society, 63 patients (42%) were in stage I (50% or more predicted). Forty-eight (32%) were in stage II (35–49% predicted), and thirty-nine (26%) were in stage III (less than 35% predicted). Kaplan-Meier survival curves based on the severity of airflow limitation are presented in Figure 1.

Among the 150 patients enrolled, 6 were unavailable for

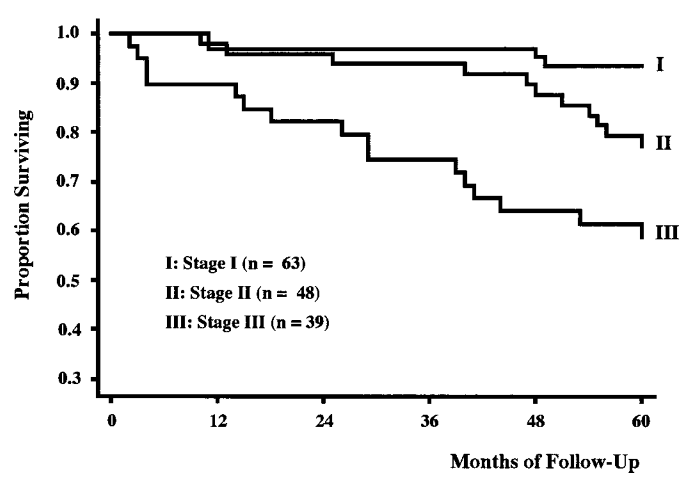

Figure 1. Kaplan-Meier survival curves based on the severity of airflow limitation (n = 150). Stage I: FEV_1, 50% predicted or greater; stage II: FEV_1, 35–49% predicted; and stage III: FEV_1, less than 35% predicted.

TABLE 2. UNIVARIATE COX PROPORTIONAL HAZARDS ANALYSIS IN MALE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Relative Risk	95% Confidence Interval	p Value
Age, yr	1.091	1.032–1.153	0.0021
Current smoking	0.768	0.315–1.873	0.56
Cumulative smoking, pack-years	1.010	1.002–1.019	0.022
Use of inhaled corticosteroids	1.575	0.764–3.245	0.22
Body mass index, kg/m^2	0.785	0.685–0.900	0.0005
Postbronchodilator FEV_1, % predicted	0.940	0.914–0.966	< 0.0001
D_{LCO}/V_A, ml/min/L/mm Hg	0.413	0.269–0.633	< 0.0001
Peak $\dot{V}O_2$, ml/min	0.994	0.992–0.996	< 0.0001
Health status measures			
CRQ dyspnea	0.921	0.869–0.975	0.0047
Fatigue	0.961	0.901–1.025	0.23
Emotional function	0.997	0.948–1.049	0.92
Mastery	0.980	0.906–1.059	0.60
Total	0.987	0.969–1.005	0.17
SGRQ symptoms	1.000	0.982–1.018	0.97
Activity	1.038	1.018–1.058	0.0001
Impact	1.029	1.010–1.048	0.0023
Total	1.033	1.012–1.055	0.0017
BPQ total	1.035	1.011–1.059	0.0044

Definition of abbreviations: BPQ = Breathing Problems Questionnaire; CRQ = Chronic Respiratory Disease Questionnaire; D_{LCO} = diffusing capacity for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire; V_A = alveolar volume; $\dot{V}O_2$ = oxygen uptake.

follow-up over the 5-year period (follow-up rate 96%), and 31 had died. The survival rates at 1, 3, and 5 years were 95%, 90%, and 80%. Of the causes of deaths, 20 patients died due to COPD or COPD-related diseases, 4 due to malignant disorders, including 2 lung cancer cases, and 1 each due to myocardial infarction and hepatic failure, respectively. Five deaths were due to unknown reasons.

Univariate Cox proportional hazards analysis was performed to investigate the relationship between the clinical measures and mortality (Table 2). Age, BMI, FEV_1, diffusing capacity for carbon monoxide/V_A, and peak $\dot{V}O_2$ were all significantly related to survival (RR = 1.091, p = 0.0021; RR = 0.785, p = 0.0005; RR = 0.940, $p < 0.0001$; RR = 0.413, $p < 0.0001$; and RR = 0.994, $p < 0.0001$, respectively). Although the relationship between smoking status at baseline and mortality was not significant (p = 0.56), cumulative smoking evaluated by the total pack-years was significantly correlated with mortality (RR = 1.010, p = 0.022). Regarding health status, the CRQ dyspnea domain was significantly correlated with mortality (RR = 0.921, p = 0.0047); however, the other three domains and the total score on the CRQ were not correlated with mortality. In contrast, activity, impacts, and the total scores on the SGRQ and the total score on the BPQ had strong relationships with mortality (RR = 1.038, p = 0.0001; RR = 1.029, p = 0.0023; RR = 1.033, p = 0.0017; and RR = 1.035, p = 0.0044, respectively).

To compare the ability of exercise capacity and health status to predict mortality versus that of airflow limitation and age, which have been considered to be the best predictors of mortality (2), multivariate regression analysis was performed (Tables 3 and 4). With respect to exercise capacity, when entering peak $\dot{V}O_2$, age, and FEV_1 as explanatory variables, peak $\dot{V}O_2$ turned out to be more strongly correlated with mortality than age or FEV_1 (Table 3). Regarding health status, the SGRQ total score was used as an index because it was more significantly related to mortality than the total scores on the CRQ or BPQ. When entering the SGRQ total score, age, and FEV_1 as explanatory variables, all were significantly correlated with mortality (Table 4). However, the relationship between the SGRQ total score and mortality was weaker as compared with age and FEV_1.

To analyze which index was the most significantly correlated with mortality, stepwise Cox proportional hazards analysis was performed using age, cumulative smoking, BMI, FEV_1, diffusing capacity for carbon monoxide/V_A, peak $\dot{V}O_2$, and the SGRQ total score. This analysis revealed that peak $\dot{V}O_2$ and age were the most significant factors related to mortality (RR = 0.994, $p < 0.0001$; RR = 1.077, p = 0.024, respectively) (Table 5). Figure 2 shows Kaplan-Meier survival curves using quartiles of the peak $\dot{V}O_2$ distribution.

DISCUSSION

We have evaluated the factors related to mortality in COPD, particularly the relationships of exercise capacity and health status to mortality. We have found that exercise capacity and health status were significantly predictive of mortality in COPD, independent of airflow limitation or age. In addition, this study indicates that exercise capacity can be the best predictor of mortality in patients with COPD. Furthermore, the ability of

TABLE 3. MULTIVARIATE COX PROPORTIONAL HAZARDS ANALYSIS TO INVESTIGATE THE RELATIONSHIPS BETWEEN EXERCISE CAPACITY, AGE, AND AIRFLOW LIMITATION WITH MORTALITY IN MALE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Relative Risk	95% Confidence Interval	p Value
Age, yr	1.090	1.021–1.163	0.0093
Postbronchodilator FEV_1, % predicted	0.972	0.943–1.001	0.059
Peak $\dot{V}O_2$, ml/min	0.995	0.993–0.998	< 0.0001

Definition of abbreviation: $\dot{V}O_2$ = oxygen uptake.

TABLE 4. MULTIVARIATE COX PROPORTIONAL HAZARDS ANALYSIS TO INVESTIGATE THE RELATIONSHIPS BETWEEN HEALTH STATUS, AGE, AND AIRFLOW LIMITATION WITH MORTALITY IN MALE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Relative Risk	95% Confidence Interval	p Value
Age, years	1.134	1.069–1.204	< 0.0001
Postbronchodilator FEV_1, % predicted	0.940	0.915–0.966	< 0.0001
SGRQ total	1.035	1.008–1.063	0.012

Definition of abbreviation: SGRQ = St. George's Respiratory Questionnaire.

health status to predict mortality turned out to be different depending on the instruments used.

Regarding exercise capacity, one novel finding in this study was that it could be the most significant criterion related to mortality among age, pulmonary function, BMI, or health status when using peak $\dot{V}O_2$ as an index. Exercise capacity of COPD patients is affected by important, complex factors, including ventilation, gas exchange, circulation, muscular function, nutritional status, and their symptoms (7); hence, COPD can be regarded as a systemic disorder (6). Exercise capacity may thus evaluate the severity of COPD more comprehensively and objectively than airflow limitation defined by FEV_1. Furthermore, exercise capacity cannot be accurately predicted from resting physiologic variables (7). Therefore, in addition to resting spirometric testing, exercise capacity can be measured as an index of disease severity from the perspective of mortality in patients with COPD.

A few studies have reported the importance of exercise capacity as a predictor of mortality in COPD (2, 17, 18). However, the indices of exercise capacity in these studies were the maximal work rate (2) and the walking distance (17, 18), and an analysis of the gas expired during exercise was not performed. Peak $\dot{V}O_2$ is the primary measure of exercise capacity; the prognostic significance of peak $\dot{V}O_2$ has not, however, been previously evaluated in COPD. When investigating the relationship with mortality in COPD, peak $\dot{V}O_2$ might be preferable, as it was more significantly correlated to mortality than any of the other measures.

This study demonstrated that health status had a significant correlation with mortality independent of airflow limitation or age. The role of health status in predicting mortality has not been previously evaluated well in COPD, although the association between health status and subsequent mortality has been frequently reported for cancer (19, 20). In addition, a novel finding was the different abilities of health status measures to predict mortality. Predicting future outcomes is one important objective of measuring health status (21), and therefore, it may be insightful to compare different measures from the viewpoint of their predictive properties. In this study, the total scores on the SGRQ and the BPQ were strongly and significantly correlated with mortality; however, the CRQ total score was not significantly correlated. Gerardi and coworkers (17) also failed to show a significant relationship between the CRQ and the 3-year survival rate after pulmonary rehabilitation in patients with advanced pulmonary disease. However, recent studies have reported a significant relationship between health status and mortality using the SGRQ (22, 23).

Why was the CRQ less correlated to mortality than the SGRQ and the BPQ? First, the CRQ does not examine activity restrictions, unlike the SGRQ and BPQ (24). Therefore, the patients may not be well discriminated based on the severity of their functional status, which is a significant factor closely correlated with mortality (18). Wijkstra and coworkers (25) also reported that functional exercise capacity was not adequately evaluated by the CRQ. In addition, Hajiro and coworkers (12) showed that the CRQ had relatively lower correlations with pulmonary function, exercise capacity, and dyspnea but was more influenced by psychologic status than the SGRQ or BPQ. These differences in the physical versus psychologic aspects might have contributed to these results. Second, the CRQ has a seven-point Likert scale but includes only 20 items. In comparison, the SGRQ and BPQ have a lower response range to each item but more items than the CRQ. Therefore, the CRQ would be better at investigating the changes within individuals but weaker at discriminating between patients based on various aspects for assessing health status. This point might also have affected the ability of the CRQ to predict mortality.

In this study, BMI was not a significant prognostic factor in the multivariate analysis as observed by Bowen and coworkers (18), although some studies have reported a significant relationship (26, 27). In the Copenhagen City Heart Study (26), the association between BMI and mortality was especially significant in severe COPD and differed according to the severity of airflow limitation. We made only an overall analysis of COPD due to the smaller sample size in this study. In contrast, we included some detailed potential prognostic factors such as exercise capacity and diffusing capacity, which have been shown to be related

TABLE 5. STEPWISE MULTIVARIATE COX PROPORTIONAL HAZARDS ANALYSIS TO INVESTIGATE THE MOST SIGNIFICANT PREDICTOR OF MORTALITY IN MALE PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Relative Risk	95% Confidence Interval	p Value
Peak $\dot{V}O_2$, ml/min	0.994	0.992–0.996	< 0.0001
Age, yr	1.077	1.010–1.149	0.024
Postbronchodilator FEV_1, % predicted			0.056
D_{LCO}/V_A, ml/min/L/mm Hg			0.089
Body mass index, kg/m^2			0.21
Cumulative smoking, pack-years			0.32
SGRQ total			0.42

Definition of abbreviations: D_{LCO} = diffusing capacity for carbon monoxide; SGRQ = St. George's Respiratory Questionnaire; V_A = alveolar volume; $\dot{V}O_2$ = oxygen uptake.

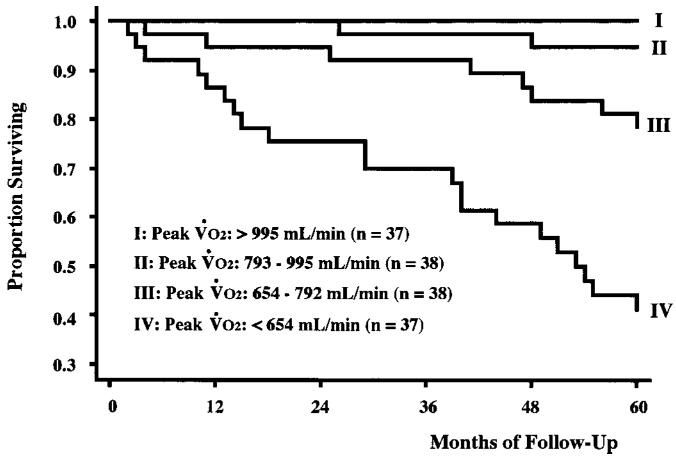

Figure 2. Kaplan-Meier survival curves using quartiles of the peak $\dot{V}O_2$ distribution (n = 150).

to nutritional status (28). These may explain the insignificant relationship to BMI in this study.

This study demonstrated that cumulative smoking was a significant predictor of mortality in the univariate analysis but that smoking status at baseline was not. The effects of smoking cessation on lung function and respiratory symptoms have been demonstrated in patients with mild to moderate COPD in the Lung Health Study (29, 30), and a relationship between smoking cessation and improved mortality was anticipated. However, the effects of smoking cessation in patients with severe COPD may not confirm this observation (31). Symptomatic patients with severe COPD spontaneously tended to quit smoking, and smoking status in some patients may have changed during the 5-year follow-up period in this study. These may be some of the reasons for the insignificant relationship between smoking status and mortality in this study.

The use of inhaled corticosteroids was not related to mortality, although Sin and Tu (32) suggested that it was associated with reduced COPD-related morbidity and mortality in patients with COPD. In this study, although half of the patients were treated with inhaled corticosteroids, they had more severe airflow limitation than patients who were not because our pharmacologic treatment was somewhat based on the degree of airflow limitation. In addition, our sample was much smaller than that of the Sin and Tu study (32). Furthermore, the use of inhaled corticosteroids was not comprehensively evaluated during the 5-year follow-up period, and inhaled corticosteroid therapy was initiated in some patients. Therefore, it was impossible to demonstrate the effects of inhaled corticosteroids on mortality in this study.

In addition to this study, we have recently completed two different prospective studies regarding mortality in COPD patients (4, 33). Although some patients were included in more than one of studies, there was no data overlap between the various studies. Moreover, this study has collected additional baseline information on these patients. Notably, only this study included exercise data at baseline, and this study showed that exercise capacity predicted mortality in COPD most significantly.

Some limitations of this study should be mentioned. First, as the entry criteria excluded the major comorbidities that might affect mortality, we did not investigate the significance of comorbidity factors fully. Comorbidity has been reported to play an important role in the prediction of survival of COPD patients (34). Therefore, we should have searched for a better way to investigate the relationship between comorbidities and survival. Second, it is not well known how accurate a face mask is in the determination of peak $\dot{V}O_2$ in comparison to a mouthpiece. Although breathing pattern may change according to types of breathing assembly (35), it was reported that this did not alter maximal exercise (36). To find the individual maximal $\dot{V}O_2$ is difficult because peak $\dot{V}O_2$ will change depending on exercise apparatus, incremental work rate, and so on (37). However, we believe that the more accurately peak $\dot{V}O_2$ is calculated, the stronger the significant relationship between peak $\dot{V}O_2$ and mortality becomes.

In conclusion, we demonstrated significant relationships of exercise capacity and health status to mortality in COPD patients, independent of FEV_1 or age. Laboratory exercise capacity using the cycle test could be the most significant predictor of mortality in COPD. With respect to health status, the ability of the CRQ to predict mortality was weaker than the SGRQ or BPQ. Although airflow limitation has been traditionally used as the index of disease severity in COPD, as it is regarded as the most significant predictor of mortality, the findings of this study will have a potentially great impact on the multidimensional evaluation of the disease severity in COPD from the perspective of mortality.

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