

## Health status measured with the CRQ does not predict mortality in COPD

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**ABSTRACT:** One purpose of measuring health status is to predict future outcomes. The aim of this study was to investigate the ability of health status derived from the Chronic Respiratory Disease Questionnaire (CRQ) to predict mortality in chronic obstructive pulmonary disease (COPD).

One-hundred and forty-three patients with COPD were recruited. Health status, using the CRQ, and pulmonary function were measured at entry. Mortality after 7 yrs was then assessed. Univariate and multivariate Cox proportional hazards analyses were performed to predict those factors related to mortality.

Of all the patients, 13 could not be followed up and 40 had died. The survival rate was 69% at 7 yrs. Univariate regression analyses revealed that the dyspnoea and emotional function domains and the total score of the CRQ were weakly but significantly correlated with mortality from all causes. However, multivariate regression analyses revealed that age and forced expiratory volume in one second were the strongest predictors of mortality, and health status was not a significant factor.

Although there was a weak but significant relationship between health status and subsequent mortality in chronic obstructive pulmonary disease, it was not significant after an adjustment for age and pulmonary function. Mortality cannot be predicted from Chronic Respiratory Disease Questionnaire scores.

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Health status or health-related quality of life (HRQL) measurement is a means of quantifying, in a standardised and objective manner, the impact of a disease on patients' daily life, health and well being [1]. It contains three properties [2, 3]. First, health status measures can differentiate between people who have better health status and those with worse health status (a discriminative property). Secondly, they can measure how much health status changes (an evaluative property). Thirdly, they can predict the future outcomes of patients (a predictive property). However, in comparison to the first two properties, the predictive property of health status instruments has not been fully evaluated in some disorders.

Chronic obstructive pulmonary disease (COPD) is a progressive disorder for the most part, and its long-term survival rate is so poor that it is ranked high as a cause of death in developed countries [4]. Some researchers have reported the predictive significance of impaired health status on emergent hospital use [5] or hospital re-admission [6] in patients with COPD. However, in spite of the importance of mortality as an outcome, the ability of health status to predict mortality in COPD has not yet been established, although factors associated with mortality in COPD have often been examined [7–9]. Both positive and negative relationships between health status and

mortality have recently been reported in advanced pulmonary disease [10], chronic respiratory failure [11] and COPD [12], and therefore, further study is needed.

The association between health status and subsequent mortality has been frequently reported in patients with cancer [13–15]. The present authors hypothesised that health status would also be a predictor of mortality in patients with COPD. Therefore, in the present study, the baseline health status as well as pulmonary function of patients with COPD was examined, and then the relationship between health status and their mortality after 7 yrs was investigated.

### Methods

#### Subjects

A total of 143 consecutive patients with stable COPD, based on the definition by the American Thoracic Society (ATS) [16], were recruited from the outpatient clinic of the Kyoto University Hospital, Kyoto, Japan from October 1993 to September 1994. Their mortality over 7 yrs from the entry into the present study was prospectively examined. The entry

criteria for the study included: 1) a smoking history of >20 pack-yrs; 2) regular attendance at the authors' clinic for >6 months; 3) chronic fixed airway obstruction; 4) no changes in treatment regimen for >4 weeks; 5) no exacerbations of COPD over the preceding 6 weeks; and 6) no other uncontrolled comorbidity factors which could affect the patient's prognosis. In particular, patients with malignant disorders or cardiovascular diseases at entry were excluded from the study, as they are the most important non-respiratory causes of death [7]. Chronic fixed airway obstruction was defined as a maximal ratio of forced expiratory volume in one second (FEV<sub>1</sub>) to forced vital capacity (FVC) of <0.7 for all measurements during the prior 6 months. At entry, pulmonary function, health status, smoking habits, age, height and weight were evaluated on the same day. The body mass index (BMI) was calculated as weight/height<sup>2</sup> (kg/m<sup>2</sup>). Verbal informed consent was obtained from all patients.

### *Pulmonary function*

Pulmonary function tests were performed  $\geq 12$  h after the withdrawal of inhaled bronchodilators for COPD. According to the method recommended by the ATS [16], the subjects underwent spirometry using a spirometer (AUTOSPIRO AS-600; Minato Medical Science Co. Ltd, Osaka, Japan) before and 15 and 60 min after the inhalation of 400  $\mu$ g (four puffs) of salbutamol and 80  $\mu$ g (four puffs) of ipratropium bromide. These doses were the average doses of each drug that the patients generally received. Spirometric testing was performed three times on each occasion, and the largest FEV<sub>1</sub> and FVC values were then analysed. The total lung capacity (TLC) was measured by body plethysmography (MBR-600; Nihon Koden Co., Tokyo, Japan). The carbon monoxide transfer coefficient (KCO) was measured using the single-breath technique (CHESTAC-65V; Chest, Tokyo, Japan). The predicted values for pulmonary function were those established by the Japan Society of Chest Diseases [17].

### *Health status*

Health status was measured by the Japanese version of the Chronic Respiratory Disease Questionnaire (CRQ) [18]. This questionnaire was translated into Japanese according to the standardised methodology, and the Japanese version of the CRQ has previously been validated [19]. The CRQ consists of 20 items, which can be divided into four domains: dyspnoea (five items), fatigue (four items), emotional function (seven items) and mastery (four items). The patients were asked to rate each item on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). Each domain of the CRQ was then scored as the sum. In addition, the total score of the CRQ was calculated as the sum of the scores from all four domains. Although the original version of the CRQ did not introduce the

idea of the total score, this has been used in previous studies.

### *Seven-year prospective observation*

Seven yrs after entry into the present study, the survival status of all subjects registered was assessed. For those subjects who did not attend the outpatient clinic, efforts were made to contact their families or their primary care physicians by telephone or mail to obtain information about their mortality. When the causes of death were uncertain, they were defined as unknown. Those who could not be reached were considered to be drop-outs. The period of time from entry to the last attendance or death was recorded for the analysis.

### *Statistical analysis*

The results are presented as mean $\pm$ SD, unless otherwise stated. The relationship between two sets of data was analysed by Spearman's rank correlation tests. The survival time was calculated using the life table method.

Univariate and multivariate regression analyses of the factors related to mortality were performed using the Cox proportional hazards ratio model. Scores from the CRQ, age, BMI, FEV<sub>1</sub>, TLC and KCO were used as continuous variables, whereas the categorical variable of smoking status was coded as 1 or 0 for the analysis. The percentage of the predicted FEV<sub>1</sub> after bronchodilators was used for the analysis as a measure of airway obstruction, since it has been regarded as a stronger predictor of survival [8].

The results of the regression analyses are presented in terms of the estimated relative risks with corresponding 95% confidence intervals (CI). A p-value of <0.05 was considered to be statistically significant for all analyses.

## **Results**

The baseline characteristics of the 143 patients with COPD enrolled are presented in table 1. Pre- and post-bronchodilator FEV<sub>1</sub> were 1.16 $\pm$ 0.52 L and 1.39 $\pm$ 0.55 L, respectively, since the present study included those with mild-to-severe airway obstruction. Forty-four patients (31%) were current smokers. Four patients received no medications. One-hundred and thirty-nine patients (97%) were treated with both inhaled  $\beta_2$ -agonists and anticholinergic agents. Oral theophylline (400–800 mg·day<sup>-1</sup>) was administered to 21 patients (15%). In addition, 66 patients (46%) were treated with high doses (1,600–2,400  $\mu$ g·day<sup>-1</sup>) of inhaled beclomethasone dipropionate, and 8 patients (6%) were treated with additional oral corticosteroids (prednisolone, 2.5–10 mg·day<sup>-1</sup>). Five patients were managed with long-term domiciliary oxygen therapy.

Among the enrolled patients, 13 could not be followed up and were considered to be drop-outs (follow-up rate 91%). Of the 130 patients available for

Table 1.—Baseline characteristics of 143 patients with chronic obstructive pulmonary disease

Characteristic	
Sex M:F	139:4
Age yrs	68.6±7.0 (48–89)
Smokers former:current	99:44
BMI kg·m <sup>-2</sup>	20.6±2.8 (13.5–28.0)
Prebronchodilator FEV <sub>1</sub> L	1.16±0.52 (0.21–2.95)
Prebronchodilator FEV <sub>1</sub> % pred	43.7±18.1 (7.9–89.8)
Prebronchodilator FVC % pred	72.9±18.5 (29.6–125.0)
Postbronchodilator FEV <sub>1</sub> L	1.39±0.55 (0.34–3.20)
Postbronchodilator FEV <sub>1</sub> % pred	52.8±19.6 (13.6–98.3)
Postbronchodilator FVC % pred	92.7±22.6 (31.4–143.1)
Vital capacity L	2.99±0.74 (1.18–5.69)
Total lung capacity L	5.84±1.04 (2.86–8.87)
Total lung capacity % pred	107.8±16.8 (53.8–154.6)
KCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·L <sup>-1</sup>	1.28±0.52 (0.54–3.17)
KCO % pred	84.8±26.0 (37.0–179.7)
CRQ	
Dyspnoea (5–35)	25.1±6.3 (11–35)
Fatigue (4–28)	19.4±4.7 (6–28)
Emotional function (7–49)	38.0±7.1 (17–49)
Mastery (4–28)	21.0±4.2 (8–28)
Total (20–140)	103.6±19.2 (52–140)

Data are presented as mean±SD (range) unless otherwise stated. The numbers in parentheses indicate the theoretical score range; M: male; F: female; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; KCO: carbon monoxide transfer coefficient; CRQ: Chronic Respiratory Disease Questionnaire.

the 7-yr follow-up, 40 patients (31%) had died. Among them, 20 died of COPD or COPD-related disease, eight died of malignant disorders, including lung cancer in two cases, which developed after the start of the present study, and two died of cerebrovascular disease. Encephalitis and hepatic failure was the cause of death in one patient each, respectively. Two patients died suddenly and six deaths were due to unknown causes. The overall survival rates were 98%, 89%, 79%, and 69% at 1, 3, 5 and 7 yrs, respectively.

Table 2 shows the results of the univariate Cox proportional hazards model to analyse the factors related to mortality. The dyspnoea and emotional function domains and the total score of the CRQ were weakly but significantly correlated with mortality from all causes (relative risk (RR)=0.946, p=0.02; RR=0.956, p=0.04; and RR=0.981, p=0.02, respectively). However, no domains of the CRQ were significantly correlated with COPD-related mortality. Among the clinical and physiological factors, BMI, FEV<sub>1</sub> and KCO were strong predictors of mortality from all causes and COPD. The current smoking status at baseline was not related to mortality.

The multivariate Cox proportional hazards analyses were performed to investigate the factors related to mortality (table 3). This demonstrated that age and FEV<sub>1</sub> were the strongest predictors of mortality, and that BMI was also independently strongly related to COPD mortality. The total CRQ score was not a significant factor among the variables. When the other domains of the CRQ were entered into the multivariate

Table 2.—Results of the univariate Cox proportional hazards analyses of the predictors of mortality in patients with chronic obstructive pulmonary disease (COPD)

	RR	95% CI	p-value
All deaths			
CRQ			
Dyspnoea	0.946	0.902–0.993	0.02
Fatigue	0.943	0.880–1.010	0.09
Emotional function	0.956	0.916–0.997	0.04
Mastery	0.944	0.877–1.017	0.13
Total	0.981	0.965–0.997	0.02
Age yrs	1.089	1.037–1.143	<0.001
BMI kg·m <sup>-2</sup>	0.778	0.691–0.876	<0.001
Current smoking	0.862	0.452–1.657	0.66
Postbronchodilator FEV <sub>1</sub> % pred	0.969	0.952–0.987	<0.001
Total lung capacity % pred	1.020	1.001–1.038	0.04
KCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·L <sup>-1</sup>	0.102	0.034–0.306	<0.001
COPD deaths			
CRQ			
Dyspnoea	0.945	0.883–1.011	0.10
Fatigue	0.968	0.876–1.071	0.53
Emotional function	0.957	0.898–1.019	0.17
Mastery	0.914	0.813–1.027	0.13
Total	0.981	0.957–1.005	0.12
Age yrs	1.076	0.997–1.162	0.06
BMI kg·m <sup>-2</sup>	0.648	0.536–0.782	<0.001
Current smoking	0.964	0.371–2.510	0.94
Postbronchodilator FEV <sub>1</sub> % pred	0.937	0.909–0.966	<0.001
Total lung capacity % pred	1.032	1.006–1.058	0.01
KCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·L <sup>-1</sup>	0.052	0.009–0.312	0.001

All deaths (n=143); COPD deaths (n=123). RR: relative risk; CI: confidence interval; CRQ: Chronic Respiratory Disease Questionnaire; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: % predicted; KCO: carbon monoxide transfer coefficient.

analyses instead of the total CRQ score, they were found not to be significant (data not shown).

## Discussion

The purpose of the present study was to investigate the relationship between health status evaluated by the CRQ and the subsequent mortality after 7 yrs in patients with COPD. The authors found that there was a significant association between them in the all causes analysis, but it was so weak that the relationship became insignificant after an adjustment for age and pulmonary function. Postbronchodilator FEV<sub>1</sub> and age have often been reported to be the best predictors of mortality in patients with COPD [8], and health status derived from the CRQ was unable to supersede them in the present study.

The predictive property is one purpose for which health status is measured [2, 3], although the evaluative property is more practically stressed in respiratory medicine. Among various diseases, the ability of health status to predict mortality has been reported

Table 3.—Results of the multivariate Cox proportional hazards analyses of the predictors of mortality in patients with chronic obstructive pulmonary disease (COPD)

	RR	95% CI	p-value
All deaths			
CRQ Total	1.005	0.987–1.022	0.60
Age yrs	1.091	1.037–1.147	<0.001
BMI kg·m <sup>-2</sup>	0.878	0.765–1.008	0.06
Postbronchodilator FEV <sub>1</sub> % pred	0.968	0.949–0.987	0.001
Total lung capacity % pred	0.994	0.974–1.015	0.58
KCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·L <sup>-1</sup>	0.227	0.063–0.811	0.02
COPD deaths			
CRQ Total	0.991	0.964–1.019	0.54
Age yrs	1.136	1.035–1.248	0.007
BMI kg·m <sup>-2</sup>	0.699	0.563–0.868	0.001
Postbronchodilator FEV <sub>1</sub> % pred	0.922	0.890–0.955	<0.001
Total lung capacity % pred	0.997	0.960–1.036	0.87
KCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·L <sup>-1</sup>	0.113	0.010–1.275	0.08

Total deaths (n=143); COPD deaths (n=123). RR: relative risk; CI: confidence interval; CRQ: Chronic Respiratory Disease Questionnaire; BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: % predicted; KCO: carbon monoxide transfer coefficient.

most often in cancer trials [13–15]. However, with regard to mortality in COPD patients, the predictive significance of health status has not been well evaluated.

GERARDI *et al.* [10] reported that quality of life evaluated by the CRQ was unrelated to the 3-yr survival in patients with advanced pulmonary disease following comprehensive pulmonary rehabilitation, except for a weak but significant association between the increased dyspnoea and respiratory mortality. In comparison, strong significant relationships between health status and mortality were recently reported for chronic respiratory failure [11] and COPD [12] in larger-scaled studies, using the St. George's Respiratory Questionnaire (SGRQ) [20]. Therefore, there is a possibility that the ability of the CRQ to predict mortality was weaker than the SGRQ, although this is difficult to conclude due to differences in the study settings. The CRQ includes only 20 items in total, which is much less than the 50 items on the SGRQ. Therefore, the CRQ might not be suitable for prolonged follow-up studies of this kind, although it would be appropriate as an evaluative instrument, because it has seven responses to each item.

JONES [1] recently summarised health status measurements in COPD, and stated that health status represents the sum of the effects of multiple processes. There are also functional performance questionnaires that are partially similar in some respects to health status measures. BOWEN *et al.* [21] reported that the Pulmonary Function Status Scale (PFSS) functional activities subscore was predictive of 4-yr survival in patients with advanced pulmonary disease following pulmonary rehabilitation. Functional performance

measures concentrate on interference activities performed, whereas health status measures emphasise the patient's subjective reaction to this interference, including the emotional and psychological effects of the disease as well as the physiological. Therefore, functional status might be more directly related to mortality than the scores from health status measures. However, one problem with the present study is that the CRQ may not measure the activity limitations well due to the lesser number of items included. According to the report by HAJIRO *et al.* [19], psychological status and dyspnoea, rather than pulmonary function or exercise capacity, are the major determinants of the total score of the CRQ.

Patients with COPD manage to maintain their health status by changing their lifestyle or by adding the use of bronchodilators while their airflow obstruction progresses. A worsening of health status may progress very rapidly as death approaches when the patient cannot cope with the deterioration of their situation. Therefore, health status might better predict mortality of patients with more advanced COPD. CARONE *et al.* [11] recently reported that health status evaluated by the SGRQ was a better predictor of mortality than functional measures in patients with chronic respiratory failure with mean FEV<sub>1</sub> of 37% predicted.

The 3-yr survival rate in the present study was 89%, which was better than the 3-yr survival rate in the study by GERARDI *et al.* [10] (80%) or the study by BOWEN *et al.* [21] (85%). However, these studies targeted patients with advanced pulmonary disease who experienced pulmonary rehabilitation. Therefore, this difference in the study setting might have caused the difference in the survival rate.

With respect to the causes of death, COPD was the most important in the present study. Among the nonrespiratory causes, cardiovascular disease deaths are considered to be the main cause of death in Western countries [7, 10, 21]. In the studies by GERARDI *et al.* [10] and BOWEN *et al.* [21], these deaths accounted for 16% and 30% of all deaths, respectively. ZIELINSKI *et al.* [22] reported that heart failure (13%) was the major cause of death after acute-on-chronic respiratory failure (38%) in patients with COPD and chronic respiratory failure. In contrast, malignant disorders were the most prominent (20%) as a nonrespiratory cause in the present study. This trend may be a typical association in Japan between smoking and higher death rates from malignant disorders rather than coronary heart disease [23].

One limitation of the present study was that the ratio of males to females was higher than that of Western countries. This observation can be attributed to the sex difference in the past smoking trends in Japan, and reflects the present characteristics of Japanese patients with COPD. Therefore, a generalisation of these results to females with COPD is unwarranted.

The present study demonstrated a significant but weak relationship between health status evaluated by the CRQ and the subsequent mortality in patients with COPD. However, this significant relationship became nonsignificant after an adjustment for age and

pulmonary function. One of the purposes of measuring health status is to predict the future outcomes of patients. The present negative result might have been due to the choice of questionnaire, and further study should be pursued.

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