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Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD *

Koichi Nishimura, Takateru Izumi, Mitsuhiro Tsukino and Toru Oga

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Dyspnea Is a Better Predictor of 5-Year Survival Than Airway Obstruction in Patients With COPD*

Koichi Nishimura, MD; Takateru Izumi, MD, FCCP; Mitsuhiro Tsukino, MD; and Toru Oga, MD; on Behalf of the Kansai COPD Registry and Research Group in Japan

Background: **FEV_1 is regarded as the most significant correlate of survival in COPD and is used as a measure of disease severity in the staging of COPD. Recently, however, the categorization of patients with COPD on the basis of the level of dyspnea has similarly been reported to be useful in the prediction of health-related quality of life and improvement in exercise performance after pulmonary rehabilitation.**

Study objectives: **We compared the effects of the level of dyspnea and disease severity, as evaluated by airway obstruction, on the 5-year survival rate of patients with COPD.**

Design and methods: **A total of 227 patients with COPD were enrolled in a 5-year, prospective, multicenter study in the Kansai area of Japan, involving 20 divisions of respiratory medicine from various university and city hospitals.**

Results: **After 5 years, 183 patients were available for the follow-up examination (follow-up rate, 81%). The 5-year cumulative survival rate among patients with COPD was 73%. The effect of disease staging, based on the American Thoracic Society (ATS) guideline as evaluated by the percentage of predicted FEV_1, on the 5-year survival rate was not significant ($p = 0.08$). However, the level of dyspnea was significantly correlated to the 5-year survival rate ($p < 0.001$). The Cox proportional hazards model revealed that the level of dyspnea had a more significant effect on survival than disease severity based on FEV_1.**

Conclusions: **The categorization of patients with COPD on the basis of the level of dyspnea was more discriminating than staging of disease severity using the ATS guideline with respect to 5-year survival. Dyspnea should be included as one of the variables, in addition to airway obstruction, for evaluating patients with COPD in terms of mortality.**

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Key words: airway obstruction; categorization; COPD; dyspnea; mortality

Abbreviations: ATS = American Thoracic Society; DLCO = diffusing capacity of the lung for carbon monoxide; RV = residual volume; TLC = total lung capacity; VA = alveolar volume; VC = vital capacity

COPD is recognized as a major cause of death in developed countries. COPD is characterized by chronic, slowly progressive airway obstruction, and FEV_1 is reported to be the best single correlate of mortality.[1] FEV_1 is also used to define the staging of disease severity in recent COPD guidelines,[1–3] and is used as the main parameter in the evaluation of many other aspects of COPD not related to mortality.

Some researchers have questioned the use of FEV_1 as the best single evaluation parameter, and have pointed out that there is a need to better categorize and systematically evaluate patients with COPD.[4,5] Dyspnea is one potential alternate variable because it is closely related to the patient's life. Hajiro et al[6] reported that categorizing patients with COPD based on their level of dyspnea was more discriminating than the staging of disease severity based on current guidelines with respect to health-related quality of life. Wedzicha et al[7] reported that improvements in exercise performance and health status in patients with COPD after pulmonary reha-

*From the Respiratory Division (Drs. Nishimura and Oga), Kyoto-Katsura Hospital, and the Department of Respiratory Medicine (Drs. Izumi and Tsukino), Graduate School of Medicine, Kyoto University, Kyoto, Japan.

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Correspondence to: Koichi Nishimura, MD, Respiratory Division, Kyoto-Katsura Hospital, 17 Yamadahirao, Nishikyo-Ku, Kyoto, 615-8256, Japan; e-mail: koichi-nishimura@nifty.ne.jp

bilitation depended on the initial degree of dyspnea, even when patients had a similar degree of airway obstruction. The purpose of the present study was to compare the effects of the level of dyspnea with disease severity as defined by airway obstruction on mortality in patients with COPD using a 5-year, multicenter, prospective study in Japan.

Materials and Methods

COPD Case Registration

Case study meetings were held from October 1990 to February 1994 (eight meetings in all). We had asked participating physicians to mail the results of individual case examinations in advance and then distributed them to the participants at the meeting. Ten to 20 chest physicians from a total of 20 facilities participated in each meeting. Each facility presented its case with chest radiographs and CT scans of the patients. During the meeting, clinical, physiologic, and radiographic features were examined. At the time of first registration, the participating chest physicians confirmed that treatment for each case was performed in the standard way. The entry criteria for the study were clinical diagnosis of COPD, presence of emphysema, and suitability for participation in this prospective study. Reasons for exclusions included diseases other than COPD, such as bronchial asthma, diffuse panbronchiolitis, and sequelae of pulmonary tuberculosis; and other uncontrolled comorbidity factors, such as heart disease or severe systemic disease, that could affect patient prognosis. We reached agreement on a total of 227 COPD cases (204 men and 23 women) as positive case examinations. Clinical indexes such as respiratory symptoms, smoking history, pulmonary function (FEV_1, FVC, vital capacity [VC], diffusing capacity of the lung for carbon monoxide [DLCO], residual volume [RV], total lung capacity [TLC]), and PaO_2 and $PaCO_2$ were examined when patients were in clinically stable states. The predicted values for pulmonary function were calculated based on the proposal of the Japan Society of Chest Diseases.[8] Symptoms of chronic bronchitis were considered to be present when cough and sputum had lasted at least 3 months for > 1 year.[9] Dyspnea was evaluated according to the modified 5-point grading scale (I to V) developed by Fletcher et al.[10] Grading was based on patient responses to the following questions[10]: grade I, "Are you ever troubled by breathlessness except on strenuous exertion?"; grade II (if yes), "Are you short of breath when hurrying on the level or walking up a slight hill?"; grade III (if yes), "Do you have to walk slower than most people on the level? Do you have to stop after a mile or so (or after one-quarter hour) on the level at your own pace?"; grade IV (if yes to either), "Do you have to stop for breath after walking about 100 yards (or after a few minutes) on the level?"; and grade V (if yes), "Are you too breathless to leave the house, or breathless after undressing?"

5-Year Prospective Observation

More than 5 years after the first eight meetings were held (*ie*, from September 1995 to February 1999), we held an additional eight meetings to examine the clinical course and prognosis of the registered cases. Contact with patients during the follow-up period was the responsibility of each facility. In the cases that could not be followed up, an effort was made to contact the patient by telephone to obtain information regarding survival. Before each meeting, we sent out and collected follow-up questionnaires, which included questions about prognosis, and then distributed the results at the meeting. Each physician brought chest radiographs and CTs of their patients obtained at the time of first registration in the treatment program and at the time of the final medical examination at the end of the 5-year follow-up period. Physicians then examined each registered case. Information regarding patient death and cause of death was obtained from reports submitted by each facility, and whether the report of cause of death was correct was discussed at the follow-up meeting.

Statistical Analysis

The results are shown as mean ± SD. The Kaplan-Meier method was used for the evaluation of prognosis. An unpaired *t* test and χ^2 test were used to compare backgrounds between the subjects who were successfully followed up and those who were not, and between the nonsurviving group and the surviving group. The effects of FEV_1 and dyspnea on prognosis were analyzed by the log-rank tests. The Cox proportional hazards model was used to investigate the effects of dyspnea grade (II to V) and disease severity based on American Thoracic Society (ATS) staging (stage I to III) on survival. The significance of the differences in the values observed between three groups was determined by a repeated-measures analysis of variance. The groups were delineated on the basis of staging of disease severity as defined by the ATS guideline, which evaluated disease severity by percentage of predicted FEV_1,[1] and on the basis of the level of dyspnea. When a significant difference was noted, *post hoc* analysis was performed using Fisher protected least squares difference method to identify where the differences were significant. The effects of various factors (age, dyspnea, symptoms of chronic bronchitis, FEV_1, DLCO/alveolar volume [VA], and PaO_2) on prognosis were analyzed by the Cox proportional hazards model. To avoid multicollinearity, VC and RV/TLC were not included in the multivariate analysis because they were strongly correlated with FEV_1 (Spearman rank correlation coefficients [Rs] = 0.67, $p < 0.001$, and $Rs = -0.70$; $p < 0.001$, respectively). Age, dyspnea, FEV_1, DLCO/VA, and PaO_2 were expressed as continuous variables, whereas the expression of symptoms of chronic bronchitis was taken as a discrete variable. A p value < 0.05 was considered to be statistically significant for all analyses.

Results

The characteristics of the 227 patients with COPD registered in the study are summarized in Table 1. The male to female ratio was approximately 9:1. Only two patients (0.8%) had never smoked. Symptoms of chronic bronchitis were considered to be present in 132 patients (58%). All patients had a wide range of airway obstruction.

Of the 227 patients enrolled, 183 patients were available for the follow-up examination (follow-up rate, 81%). Participating institutions declined to cooperate in 24 cases, and the patients could not be reached in 20 cases. As a result, 44 case-patients were untraceable and considered dropouts.

A comparison was made of the baseline characteristics between the dropouts (44 cases) and the

Table 1—*Baseline Patient Characteristics (n = 227)**

Characteristics	Data
Age, yr	68 ± 7 (45–85)
Male/female gender, %	90/10
Current/former/never-smoker, %	33/66/1
Cumulative smoking, pack-years	58 ± 30 (0–174)
Symptoms of chronic bronchitis present/absent, %	58/42
Five-point dyspnea grade (I–V)	2.8 ± 0.8 (2–5)
FEV_1, L	1.03 ± 0.46 (0.36–2.72)
FEV_1, % predicted	41.1 ± 17.0 (13.1–98.8)
FEV_1/FVC, %	43.0 ± 10.4 (13.9–71.4)
VC, L	2.67 ± 0.79 (0.93–4.81)
DLCO/VA, mL/min/L/mm Hg	2.50 ± 1.27 (0.39–7.80)
RV/TLC, %	53.4 ± 10.9 (30.0–77.2)
PaO_2, mm Hg	73.0 ± 10.5 (39.0–105.1)
$PaCO_2$, mm Hg	41.7 ± 6.5 (21.6–69.8)

*Data are presented as mean ± SD (range) unless otherwise indicated.

Table 2—*Comparison of the Backgrounds of Survivors and Nonsurvivors**

Variables	Survivors (n = 134)	Non-survivors (n = 49)	p Value
Age, yr	67 ± 6	71 ± 7	< 0.001
Smoking, pack-years	60 ± 33	63 ± 29	0.69
Symptoms of chronic bronchitis present/absent, %	54/46	65/35	0.19
Five-point dyspnea grade (I–V)	2.6 ± 0.6	3.3 ± 0.8	< 0.001
FEV_1, L	1.09 ± 0.49	0.83 ± 0.30	< 0.001
FEV_1, % predicted	42.5 ± 18.1	34.5 ± 11.5	0.005
FEV_1/FVC, %	42.5 ± 10.3	41.2 ± 9.8	0.46
VC, L	2.81 ± 0.74	2.34 ± 0.77	< 0.001
DLCO/VA, mL/min/L/mm Hg	2.66 ± 1.34	1.94 ± 1.10	0.004
RV/TLC, %	51.6 ± 10.7	60.5 ± 9.1	< 0.001
PaO_2, mm Hg	75.2 ± 9.4	67.6 ± 11.3	< 0.001
$PaCO_2$, mm Hg	41.2 ± 6.0	43.9 ± 8.0	0.017

*Data are expressed as mean ± SD unless otherwise indicated.

subjects (183 cases) who were successfully followed up. The dropout group had a lower rate of men (80% vs 92%, respectively; p = 0.02), but there were no significant differences in age, smoking status, dyspnea, or pulmonary function (FEV_1, FVC, VC, DLCO/VA, RV/TLC, PaO_2, and $PaCO_2$).

A total of 134 of the 183 case-patients (73%) were confirmed to be alive. Eight patients were hospitalized in participating or related institutions, and 95 were outpatients. Therefore, 103 case-patients (56%) were receiving continued treatment. Thirty-one patients had not consulted the doctors but were confirmed to be alive by telephone interviews.

Forty-nine patients (27%) were found to be dead. Of these nonsurvivors, 22 patients died of COPD or COPD-related disease, and 10 patients died of malignant disorders, including lung cancer in 6 patients, which developed after registration in the study. In four case-patients, death was attributed to cerebrovascular disease. Each of the following was determined to be the cause of death in one of the patients: cardiac infarction, aortic aneurysmal rupture, acute renal insufficiency, intestinal obstruction followed by multiple-organ failure, and suicide after an operation for stomach cancer. There were eight causes of sudden death or death due to unknown causes. The survival rates were 95%, 90%, 83%, 78%, and 73%, at 1, 2, 3, 4, and 5 years, respectively.

Table 2 compares the clinical data of 134 survivors with 49 nonsurvivors at the time of first registration before the initiation of follow-up examinations. Between these two groups, we found significant differences in age, dyspnea, VC, FEV_1, DLCO/VA, RV/TLC, PaO_2, and $PaCO_2$. We did not, however, find significant differences in the cumulative amount of smoking, the presence of symptoms of chronic bronchitis, and FEV_1/FVC.

Figure 1 shows the 5-year survival rates of patients classified according to the initial staging of disease severity as defined by the ATS guideline.[1] Of the 183 patients analyzed, 42 patients (23%) had stage I (FEV_1 > 50% of the predicted value), 59 patients (32%) had stage II (FEV_1 35 to 49% of the predicted value), and 82 patients (45%) had stage III (FEV_1 < 35% of the predicted value). Among these groups, 6, 15, and 28 patients, respectively, did not survive after 5 years. In the present study, the staging of disease severity did not significantly affect the 5-year survival (p = 0.08). Disease staging based on the percentage of predicted FEV_1 according to the British Thoracic Society[2] and the European Respiratory Society[3] guidelines did not significantly affect the 5-year survival either (data not shown).

Figure 2 shows the 5-year survival rates of patients classified according to the baseline level of dyspnea

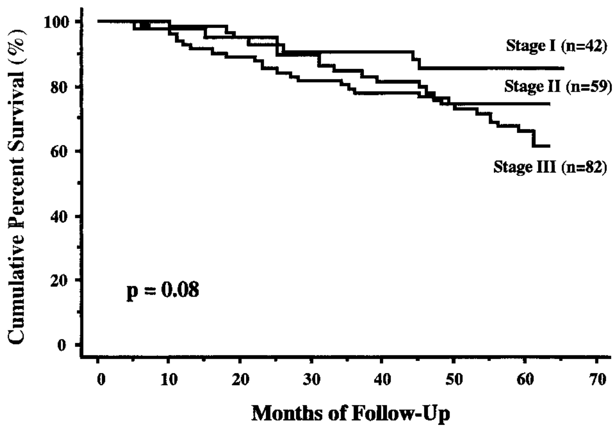

FIGURE 1. Five-year survival according to the staging of disease severity as defined by the ATS guideline evaluated by the percentage of predicted FEV_1.

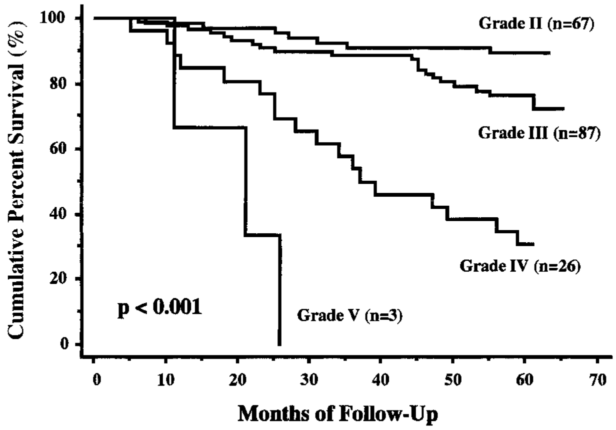

FIGURE 2. Five-year survival according to the level of dyspnea as evaluated by the modified 5-point grading system of Fletcher et al.[10]

evaluated by the 5-point grading system. Of the 183 patients, 67 patients (36%) were classified with grade II, 87 patients (48%) were classified with grade III, 26 patients (14%) were classified with grade IV, and 3 patients (2%) were classified with grade V. Among these patient classifications, 7, 21, 17, and 3 patients were, respectively, nonsurvivors after 5 years. Classification on the basis of the level of dyspnea was significantly correlated with 5-year survivals ($p < 0.001$).

Table 3 shows the results of the Cox proportional hazards model analysis including both dyspnea and FEV_1 as factors. Categorization by the level of dyspnea was more significantly related to survival ($p < 0.001$) than classification of disease severity based on FEV_1 ($p = 0.20$). The relative risk of mortality, in comparison to grade II dyspnea, was 2.21 with grade III, 8.31 with grade IV, and 61.3 with grade V.

Tables 4, 5 compare the backgrounds between groups delineated on the basis of ATS stage (stages I to III) and on the basis of the level of dyspnea (grades II to IV), respectively. There were significant differences in FEV_1, FVC, RV/TLC, and $Pa{CO_2}$ between the three groups delineated on the basis of both sets of criteria. As shown in Table 4, there was no statistically significant difference in dyspnea among patients graded by ATS stage. Age and $Pa{O_2}$ were significantly different between the three groups delineated on the basis of dyspnea level, but these factors were not significantly different among the ATS stage groups.

Table 6 shows the relation of various factors to survival as assessed by the Cox proportional hazards model. In this analysis, age, dyspnea, FEV_1, DLCO/VA, and symptoms of chronic bronchitis were significant factors, but $Pa{O_2}$ was not.

Table 3—*Cox Proportional Hazards Analysis of the Effects of the Levels of Dyspnea and Airway Obstruction on Mortality in Patients With COPD**

Variables	Relative Risk (95% CI)	p Value
Dyspnea		
Grade II	Reference category	< 0.001
Grade III	2.21 (0.93–5.27)	
Grade IV	8.31 (3.41–20.27)	
Grade V	61.3 (13.2–285.4)	
FEV_1		
Stage I	Reference category	0.20
Stage II	2.09 (0.71–6.11)	
Stage III	2.51 (0.92–6.84)	

*CI = confidence interval.

Discussion

This multicenter prospective study demonstrated that categorizing patients with COPD on the basis of the level of dyspnea was more closely correlated with survival than classification on the basis of disease severity as assessed by the percentage of predicted FEV_1. Studies on the prognosis of patients with COPD have utilized various objective indexes as factors related to survival. The present study suggests that categorization by the level of dyspnea may be similarly useful in the prediction of survival.

Most studies[11–13] on mortality among patients with COPD have reported that FEV_1 is the strongest factor related to survival and that other factors, with the exception of age, are minor.[11] Dyspnea, which is the subjective perception of respiratory discomfort, is a result of complex and multifocal mechanisms.[14] These include abnormalities in the respiratory control system, neurochemical receptors, ventilation, respiratory muscles, gas exchange, and so on.[14] Dyspnea can vary among patients with the same degree of airway obstruction.[15] In the present study, there were significant differences in age and arterial blood gas measures as well as pulmonary function between the groups delineated on the basis of the level of dyspnea. As shown in Tables 4, 5, classification by the level of dyspnea was considered to be more discriminating with respect to various factors than classification of disease severity based on airway obstruction. Dyspnea may reflect more comprehensive information than airway obstruction in patients with COPD. Previously, some studies[16] have suggested that dyspnea could be used as one of the prognostic factors in patients with COPD. However, to our knowledge, this is the first report of mortality among patients with COPD that compared the categorization of patients with COPD on the basis of the level of dyspnea vs airway obstruction.

Table 4—*Comparison of the Backgrounds Between the Groups Based on the Staging of Disease Severity According to the ATS Guideline**

Variables	Stage I (n = 42)	Stage II (n = 59)	Stage III (n = 82)	p Value
Age, yr	68 ± 7	68 ± 7	67 ± 7	0.65
Smoking, pack-years	57 ± 29	63 ± 32	60 ± 35	0.71
Dyspnea (I–V)	2.6 ± 0.8	2.7 ± 0.7	3.0 ± 0.7	0.051
FEV_1, L	1.66 ± 0.43	1.06 ± 0.17	0.67 ± 0.14	
FEV_1/FVC, %	51.8 ± 8.5	43.2 ± 8.6†	36.4 ± 7.7†‡	< 0.001
FVC, % predicted	95.6 ± 15.0	76.8 ± 16.3†	57.3 ± 14.3†‡	< 0.001
DLCO/VA, mL/min/L/mm Hg	2.69 ± 1.24	2.27 ± 1.26	2.51 ± 1.41	0.34
RV/TLC, %	44.1 ± 7.0	51.9 ± 9.2†	60.7 ± 9.2†‡	< 0.001
PaO_2, mm Hg	76.3 ± 11.0	72.7 ± 10.3	71.8 ± 10.1	0.085
$PaCO_2$, mm Hg	40.0 ± 7.5	40.3 ± 4.8	44.1 ± 6.9†‡	< 0.001

*Data are expressed as mean ± SD.
†Significant difference from stage I.
‡Significant difference from stage II.

Some researchers[4,5] have questioned the use of FEV_1 alone as an outcome of various interventions or disease severity in patients with COPD. Celli[4] stressed the need for a more comprehensive staging system that would allow for better categorization of patients with COPD. The level of dyspnea can be measured easily in the clinical setting. Dyspnea, in addition to airway obstruction, should be included as one of the variables used to systematically evaluate COPD patients.

Factors related to survival analyzed by the Cox proportional hazards model included age, dyspnea, symptoms of chronic bronchitis, airway obstruction, and DLCO as previously reported correlates of survival.[11, 17] However, the correlation of FEV_1 with the survival rate was weak in the present study. Degree of airway obstruction was not included among the entry criteria, although this factor has been used to screen participants in previous studies such as the Intermittent Positive Pressure Breathing trial.[11] Therefore, the present study might have enrolled more patients with COPD with mild airway obstruction than other studies. This, in turn, might cause underestimation or overestimation of the effect of FEV_1 on the survival rate. Alternatively, the strong correlation between dyspnea and survival may have weakened the degree of correlation between airway obstruction and survival.

The presence of symptoms of chronic bronchitis was a weak but significant factor related to survival, as shown in Table 6. Whether it is related to mortality in patients with COPD remains controversial.[18–20] According to the Copenhagen study,[18] chronic mucus hypersecretion played no major role as a prognostic indicator, although it was significantly associated with hospitalization.[9] The study[18] suggested that predictors of hospitalization might not necessarily be predictors of subsequent prognosis. Although the present study was not performed to investigate the significance of chronic mucus hypersecretion as a prognostic factor, this should be studied in the future.

Table 5—*Comparison of the Backgrounds Between the Groups Based on the Level of Dyspnea (Grade II–IV)**

Variables	Grade II (n = 67)	Grade III (n = 87)	Grade IV (n = 26)	p Value
Age, yr	66 ± 6	68 ± 7†	71 ± 8†	0.007
Smoking, pack-years	55 ± 26	63 ± 35	68 ± 37	0.14
FEV_1, L	1.19 ± 0.50	0.94 ± 0.42†	0.85 ± 0.35†	< 0.001
FEV_1, % predicted	45.6 ± 18.0	37.8 ± 16.3†	35.2 ± 12.7†	0.004
FEV_1/FVC, %	43.2 ± 10.3	41.6 ± 10.0	40.9 ± 11.0	0.53
FVC, % predicted	80.2 ± 20.7	68.9 ± 20.8†	63.8 ± 19.2†	< 0.001
DLCO/VA, mL/min/L/mm Hg	2.68 ± 1.34	2.46 ± 1.35	1.90 ± 1.06	0.074
RV/TLC, %	49.6 ± 10.0	55.9 ± 11.0†	59.2 ± 10.0†	< 0.001
PaO_2, mm Hg	77.7 ± 9.0	73.2 ± 9.3†	63.9 ± 10.4†‡	< 0.001
$PaCO_2$, mm Hg	39.5 ± 5.2	42.3 ± 6.4†	43.8 ± 7.2†	0.002

*Data are expressed as mean ± SD.
†Significant difference from grade II.
‡Significant difference from grade III.

Table 6—*Cox Proportional Hazards Analysis of Prognostic Factors in Patients With COPD**

Variables	Relative Risk (95% CI)	p Value
Age	1.12 (1.05–1.18)	< 0.001
Dyspnea	2.11 (1.23–3.62)	0.007
Symptoms of chronic bronchitis	0.45 (0.21–0.96)	0.040
FEV_1, % predicted	0.97 (0.94–0.99)	0.017
DLCO/VA	0.69 (0.49–0.95)	0.025
PaO_2	0.98 (0.95–1.01)	0.27

*See Table 3 for expansion of abbreviation.

The 5-year survival rate of Japanese patients (73%) in the present study was a little higher than previously reported, because the 5-year mortality rate of patients with COPD typically varies from 40 to 70% depending on disease severity.[21] The morbidity and mortality of patients with COPD can vary with the country or region, and our results are consistent with a past report indicating that COPD mortality was lowest in Japan among 31 developed countries.[22] However, the number of cases analyzed in the present study was less than in other studies,[17] and a more detailed statistical analysis of a larger number of cases may be required to confirm results.

In the present study, the rate of cardiovascular death in this smoking population was lower, compared with the rate of death caused by malignant disorders. Some of the sudden deaths might also have been attributable to the heart. However, the low coronary heart disease death rates and the high deaths from cancer in the Japanese smoking population were consistent with the report by the Seven Countries Study,[23] investigating the association of cigarette smoking with mortality risk. Therefore, this may be a feature of Japanese society in general.

Some limitations of the present study should be mentioned. First, pulmonary function testing was not standardized between hospitals. This may have biased the results of pulmonary function tests. Second, the ratio of men to women in the present study is higher in comparison with Western countries, and generalization of the results of men to women with COPD might be questionable. However, this study population reflects the characteristics of patients with COPD in Japan, and the gender differences likely reflect past trends in smoking. Third, the 81% follow-up rate was somewhat lower than typical for this kind of study. In the Japanese health-care system, patients have free access to health-care facilities, including hospitals, at any time and may choose to change facilities, making follow-up potentially more difficult. However, there were few differences in baseline characteristics between the dropouts and the subjects who were successfully followed up. Therefore, we believe it is unlikely that the high dropout rate reflects increased patient mortality.

In conclusion, the categorization of patients with COPD on the basis of the level of dyspnea was more discriminating than the staging of disease severity with the ATS criteria with respect to 5-year survival. The level of dyspnea, as well as the severity of airway obstruction, provides clinically important prognostic information in the management of patients with COPD. In an attempt to evaluate patients with COPD systematically, dyspnea should be included in addition to airway obstruction as one of the variables affecting mortality.

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