Predictors of long-term survival in patients with chronic obstructive pulmonary disease

Oznur A. Yildiz, MD, Zeynep P. Onen, MD, Elif Sen, MD, Banu E. Gulbay, MD, Kenan Kose, MD, Sevgi Saryal, MD, Gulseren Karabiyikoglu, MD.

ABSTRACT

Objectives: To analyze the factors affecting survival of patients with chronic obstructive pulmonary disease (COPD) during the follow-up period using a 4-year prospective study.

Methods: The study included 276 out-patients with COPD. The study took place in Ankara University, Cebeci Hospital, Ankara, Turkey between September 2000 and January 2005. We used cox proportional hazards model in investigating the effects of clinical variables on survival. Risk factors related with mortality were analyzed.

Results: Forty-nine patients (17.8%) died and the mean survival time was 43.40 ± 0.65 months. The survival rates were 97% at one year, 89% at 2 years, 84% at 3 years, and 73% at 4 years. Cox proportional hazard model revealed that long-term mortality was significantly associated with age (relative risks [RR]: 1.13, 95% confidence interval: 1.09-1.17), the level of dyspnea (RR: 1.99, 95% confidence interval: 1.44-2.74), the number of hospital admission for acute exacerbation of COPD (RR: 1.33, 95% CI: 1.07-1.67) and the number of scheduled physician visits (RR: 0.75, 95% CI: 0.58-0.95). Also, the presence of hypoxemia was correlated with survival of COPD patients (RR: 0.99, 95% CI: 95-1.00).

Conclusion: Patient's age, level of dyspnea, hypoxemia and the number of hospital admission were more closely correlated with mortality in COPD. The regular follow-up patients increased the survival of this disease. According to this study patients with COPD may be followed in the specialized out-patient COPD clinics to decrease their morbidity and mortality rates.

Saudi Med J 2006; Vol. 27 (12): 1866-1872

Chronic obstructive pulmonary disease (COPD) is recognized as a major cause of death in developed countries, as it is currently the fourth leading cause of death in the world. By the year 2020, COPD might become the third-leading cause of combined mortality and disability worldwide.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defined COPD as a disease that is characterized by airflow limitation that not fully reversible and carried out that is usually slowly progressive.[2] Although multiple observational studies have identified predictors of COPD progression, there are no uniformly accepted parameters to use in monitoring COPD progression. Forced expired volume in one second (FEV_1) is used to define the staging of disease severity in recent guidelines. For past several decades, low FEV_1 and age were accepted as the most important factors related to mortality.[3,4] However, in recent studies, it has been shown that mortality rates were also associated with other factors such as cigarette smoking, baseline hypercapnia, untreated hypoxemia, body mass index

From the Department of Chest Diseases (Yildiz, Onen, Sen, Gulbay, Saryal, Karabiyikoglu), and the Department of Biostatistics (Kose), School of Medicine, Cebeci Hospital, Ankara University, Ankara, *Turkey*.

Received 30th April 2006. Accepted for publication in final form 15th August 2006.

Address correspondence and reprint request to: Dr. Oznur A. Yildiz, Department of Chest Diseases, School of Medicine, Cebeci Hospital, Ankara University, Ankara, *Turkey*. Tel. +90 (312) 3623030. E-mail: akkoca@medicine.ankara.edu.tr

(BMI), health related quality of life, dyspnea level and exercise intolerance.[5-11] Celli et al[10] proposed multi-dimensional disease staging in COPD patients and this grading system (based on degree [BODE] index of airflow limitation dyspnea 6 min. walking distance and BMI) showed to be mostly useful at predicting the risk of death from respiratory cause among patients with COPD. Besides the impact of COPD, mortality depends on the interactions of the disease with comorbid conditions.[12] Hospitalization for acute exacerbation of COPD carries both an immediate and long term risk for mortality.[5,7] The effect of smoking on gender-specific mortality has been examined on a number of occasions and the results may be related to mortality because smoking had greater impact on the lung function of females than males and females with COPD lose more years of their lives than males.[13,14] Several studies have been performed to establish parameters associated with an increased risk of death in COPD patients; however, there is not enough prospective and long-term follow-up survival analyses. For this reason, the present report was designed to assess the survival analyses and potential determinants of mortality during the follow-up period in patients with COPD using a 4 year prospective study with scheduled physician visits, in the COPD out-patient clinic.

Methods. Three hundred-thirty out-patients were prospectively recruited but 40 patients were excluded due to other obstructive pulmonary disease such as bronchial asthma, uncontrolled systemic disease, uncontrolled malignancy, uncontrolled cardiovascular disease and also 14 patients did not attend regular follow up. Thus, 276 out-patients with COPD (24 females and 252 males) were included in the study from September 2000 to January 2005 and all patients were regularly followed during the study period. Chronic obstructive pulmonary disease was defined according to the standards of GOLD and also the patients were staged according to GOLD criteria with revisions due to upgrades in every single year.[2] Entry criteria included: 1) FEV_1/Forced vital capacity (FVC) ratio of <0.70, 2) Regular attendance >3 to 6 months. At the time of the first visit, clinical, physiologic and radiographic features of patients were examined. The participating chest physicians confirmed that the treatment for each patient was performed in GOLD standards. Informed consents were completed. The following data were collected: anthropometric parameters (including age, gender, BMI), medical history (respiratory symptoms, duration of disease), smoking status, presence of comorbidity, previous treatment, frequency of COPD exacerbation per year, previous number of hospital admission per year and educational level. These data were recorded on standardized forms from patient charts. The BMI was calculated by dividing the patient's weight in kg by height squared (m^2). The number of cigarette pack per year was calculated as the product of the period of tobacco use (in years) and the average number of cigarettes smoked per day. Symptoms of chronic bronchitis were considered to be present when cough and sputum had lasted at least 3 months for >1 year. Dyspnea was evaluated according to the Medical Research Council (MRC) scale. Medical Research Council 5-grade scale is a 5-point scale based on degrees of various physical activities that precipitate dyspnea. Comorbidity was determined by standard methods (defined as the existence of malignancies, cardiovascular disease, diabetes mellitus and rheumatologic disease). Previous treatment (use of inhaled or oral steroid, theophylline and bronchodilators) and the frequency of exacerbations per year were also recorded. Besides, the date of hospital admission was recorded and verified by hospital records in the first visit. Pulmonary function tests (PFT) were performed according to ATS criteria,[15] including spirometric parameters (FEV_1, FVC, FEV_1/FVC% predicted, PEFR, FEF_{25-75}) were measured, using "Vmax 229 Pulmonary Function/Cardiopulmonary Exercise Testing Instruments" (SensorMedics, Bilthoven, The Netherlands) in all patients. All of the tests were performed in sitting position and the best of 3 attempts were evaluated. Predicted values were calculated using European Community for Steel and Coal (ECCS) reference values.[16] Arterial blood gas (ABG) analyses were performed at rest and in room air with a Rapid lab 348 pH/blood gas analyzer (Chiron Diagnostics Ltd., Essex, UK). Partial pressure of oxygen in arterial blood pressure of carbon dioxide ($PaCO_2$), pH, and arterial oxygen saturation (SaO_2) were measured while breathing on room air. Chest radiography was examined by 3 chest physicians. We prospectively included in the study all patients who had been admitted in specialized out-patient clinic of COPD in our university hospital between September 2000 and January 2004. January 2004 was chosen as the end point of inclusion in the study. The date of end point of follow-up time was January 2005. Follow-up time ranged from 12 to 51 months among survivors. In our COPD out-patient clinic the regular follow-up of each patient were organized according to the scheduled physician visits, and patients were usually examined at per 3-6 months which depends on the situation of the patients. For patients who could not be followed up, an effort was made to contact the patient

by telephone to obtain information regarding survival. Also, survival rates were determined at 1, 2, 3 and 4 years. Information regarding mortality and cause of death (due to COPD and COPD related disease) was obtained from the medical data or hospital records. We examined the clinical course and prognosis of the registered patients. We recorded severity of respiratory symptoms, treatment history, comorbidity, frequency of COPD exacerbation, number of hospital admission for acute exacerbation of COPD per year. Exacerbations were defined by the presence of one or more of the symptoms including increase in sputum volume or dyspnea, sputum purulence. Also, number of scheduled physician visits per year was recorded for each year during the follow-up time. Long term use of oxygen therapy (LTOT) was defined as duration of oxygen administration >15 hours/day.

All statistical measurements were made using SPSS Package for the Social Sciences, Version 11.0 for Windows (SPSS Inc., Chicago, IL). Descriptive data were presented as mean ± standard deviation or number (percentage). The survival status of all subjects after 4 years was assessed. The duration from entry to the last attendance or death was recorded. The Kaplan-Meier method was used for the evaluation of prognosis, and the survival time was calculated using this method. The Cox proportional hazards model was used to investigate the effects of clinical variables on survival. The clinical variables were used as continuous variables, except that the categorical variables of gender, comorbidity, the use of oxygen therapy were coded as one or zero for the analysis. Relative risks (RR) were calculated for the following risk factors; age, gender, BMI, smoking status, comorbidity, COPD stage based on GOLD, MRC scale, PFT parameters, ABG analysis parameters, hematocrit (Htc), frequency of COPD exacerbations, frequency of hospital admissions, number of scheduled physician visits, long term oxygen therapy. Results of the analysis were presented in terms of the estimated RRs with corresponding 95% confidence intervals; probability values of less than 0.05 were considered statistically significant.

Results. The characteristics of 276 patients with COPD registered in the study were summarized in **Table 1**. There was male dominance in the study group. Thirty-one patients (11.2%) had never smoked but they had other environmental factors. All of the smoking patients were heavy smokers (49.80 ± 27.62 pack/year). One hundred-fifty patients (54.3%) had comorbid disease (majority of the comorbid diseases were cardiovascular diseases). Patients had moderate or severe disease according to GOLD criteria (mean FEV_1 (%): 43.01 ± 15.38). When the patients were classified according to COPD severity based on airflow limitation defined by GOLD, 18 patients (6.5%) were in stage I, 77 patients (27.9%) were in stage II, 104 patients (37.7%) were in stage III and 77 patients (27.9%) were in stage IV. The mean survival time for patients was 43.40 ± 0.65 months which was estimated by the Kaplan-Meier method. The Kaplan–Meier survival curve was shown in **Figure 1**. Forty-nine patients (17.8%) died during the follow up period. Majority of the deaths were due to cardio-respiratory diseases (frequently, COPD and COPD related conditions such as respiratory insufficiency or right heart failure). For follow-up times, the loss in life expectancy was 97% at one year, 89% at 2 years, 84% at 3 years, and 73% at 4 years. The results of the Cox proportional hazards model analysis were shown in **Table 2**. Relative risks for death were calculated for each of clinical variables. This analysis demonstrated

Table 1 - General characteristics of patients with chronic obstructive pulmonary disease (COPD).

Characteristics	Data
Number of patients	276
Age (year)	63.55 ± 11.39
Gender (Female/male)	24 / 252
Body mass index (kg/m^2)	25.66 ± 5.08
Current/former/never smoker	20/225/31
Smoking (pack/year)	49.80 ± 27.62
Comorbidity (%)	150 (54.3)
Cardiovascular	40 (14.4)
Hypertension	27 (9.8)
Bronchiectasis	17 (6.2)
BPH	14 (5.1)
Diabetes mellitus	9 (3.3)
Other comorbidity	43 (17.5)
FEV_1 (%)	43.01 ± 15.38
FVC (%)	57.50 ±16.28
FEV_1/FVC%	57.36 ± 11.43
PaO_2 (mm Hg)	62.44 ± 11.97
$PaCO_2$ (mm Hg)	38.91 ± 6.46
Hematocrit (%)	45.13 ± 4.77
MRC dyspnea scale	2.11 ± 0.80
COPD exacerbations/year)	2.00 ± 1.87
Hospital admissions/year	0.45 ± 1.38
Scheduled physician visits/year)	2.89 ± 1.18
Death (%)	49 (17.8)

Data presented as mean ± SD or number (percentage).
FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, PaO_2 - partial pressure of oxygen in arterial blood, partial $PaCO_2$ - pressure of carbon dioxide.
MRC - Medical Research Council

an increased mortality risk in elderly patients (RR: 1.13, 95% CI: 1.09-1.17). The MRC dyspnea scale was significantly associated with mortality rate (RR: 1.99, 95% CI: 1.44-2.74). The one score increase in MRC scale led to a 2-fold increase in risk of mortality. Also, the number of hospital admission for acute exacerbation of COPD and the number of scheduled physician visits were significantly associated with increased mortality. The risk decreased by 25.4% for each number of scheduled physician visits per year (RR: 0.75, 95% CI: 0.58-0.95). On the other hand, greater number of hospital admission for acute exacerbation of COPD per year was associated with decreased survival by 1.33 fold for each hospitalization per year (RR: 1.33, 95% CI: 1.07-1.67). Smoking intensity (number of pack-years of cigarette smoking), comorbidity, BMI, PFT parameters (FEV_1, FVC, FEV_1/FVC% predicted), PaO_2, $PaCO_2$, COPD stages, hematocrit and the LTOT were not significant predictors of survival. Patients with hypoxemia had a loss in life expectancy of 22%, and this is on the verge of significance (RR: 0.99, 95% CI: 95-1.00) (p=0.052).

Discussion. This prospective study demonstrated that patient's age and level of dyspnea were more closely correlated with mortality of COPD. Also, the number of hospital admission for acute exacerbation of COPD was significantly associated with increased mortality. The regular follow-up (as scheduled physician visits) in specialized out-patient clinic of each COPD patient had an influence on the survival rate of COPD. Chronic obstructive pulmonary disease is a common disease whose prevalence and mortality rate is increasing worldwide. Chronic obstructive pulmonary disease results in an economic and social burden that is both substantial and increasing. Mortality data for COPD are inaccurate because of inconsistent use of terminology.[2] Studies on the prognosis of the patient with COPD have utilized various indexes as factors related to survival. Age and FEV_1 are useful prognostic factors but still there is considerable variability. In distinctive studies, it has been shown that age is the most important predictor factor in the survival in patients with COPD.[7,9,14,17,18] Chronic obstructive pulmonary disease death rates are very low <45 years and increase steeply with age.[2] Oswald-Mammoser et al[18] demonstrated that survival was statistically decreased in patients >63, among 84 COPD patients receiving LTOT. Also age was more important prognostic factor found in our study and the relative risks were raised with age, from year to year. Although airflow limitation has been traditionally used as the index of disease severity in COPD, there are lots of debates about the mortality rate adjustment with low FEV_1 in COPD patients. Our study group was relatively homogeneous, almost all of the included patients had moderate to severe disease according to GOLD

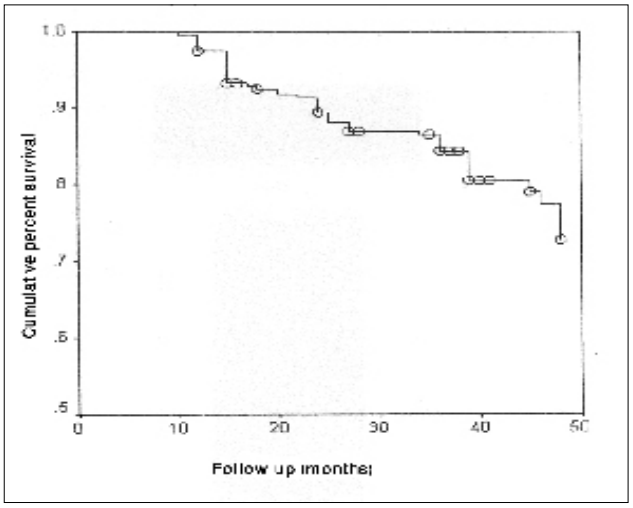

Figure 1 - Cumulative survival rate of the 276 chronic obstructive pulmonary disease patients included in our study.

Table 2 - Cox proportional hazards analysis in patients with chronic obstructive pulmonary disease (COPD).

Parameters	RR (95% CI)	*P*-value
Age (year)	1.13 (1.09-1.17)	<0.001
Gender (Female/male)	0.72 (0.31-1.70)	0.45
Body mass index (kg/m^2)	1.02 (0.97-1.08)	0.39
Smoking (pack/year)	1.00 (0.99-1.01)	0.51
Comorbidity	1.46 (0.82-2.61)	0.20
FEV_1 (%)	1.01 (0.99-1.02)	0.50
FVC (%)	1.00 (0.99-1.02)	0.70
FEV_1/FVC%	1.02 (0.99-1.04)	0.16
PaO_2 (mm Hg)	0.99 (0.95-1.00)	0.05
$PaCO_2$ (mm Hg)	1.02 (0.98-1.06)	0.38
COPD stage	0.93 (0.69-1.27)	0.66
Htc (%)	0.96 (0.90-1.02)	0.14
MRC dyspnea scale	1.99 (1.44-2.74)	<0.001
COPD exacerbation/year)	1.10 (0.97-1.24)	0.14
Hospital admission/year)	1.33 (1.07-1.67)	<0.05
Scheduled physician visits/year)	0.75 (0.58-0.95)	<0.05
Use of LTOT	1.15 (0.64-2.06)	0.64

RR - relative risk, FEV_1 - Forced expiratory volume in one second, FVC - Forced vital capacity, PaO_2 - partial pressure of oxygen in arterial blood, partial $PaCO_2$ - pressure of carbon dioxide. MRC - Medical Research Council, LTOT - long-term oxygen therapy, Htc - hematocrit, CI - confidence interval

criteria (mean FEV_1: 43%). We thought that, this was the main point why we were not able to detect an association between low FEV_1, FVC, FEV_1/FVC and mortality with Cox proportional Hazard Model analysis. Oswald-Mammoser et al[18] demonstrated that there was no relation between the FEV_1, FEV_1/VC and the mortality. Dubois et al[19] included 217 patients with COPD, and reported that there were no difference in FEV_1 between those who died and those who were living. Besides, Hersh et al[20] reported, in severe, early onset COPD patients, a 1% increase in FEV_1 percentage of predicted led to an 8% decrease in the risk of mortality. It appears that there are the discrepancies between the results reported in literature. In COPD, dyspnea is one of the major symptoms that gives impact to the patient's quality of life which is a result of complex and multifocal mechanisms in patients with COPD. Even though dyspnea is a subjective perception of respiratory discomfort, it can be quantified using an appropriate method in practical setting. Also, patients with COPD can be categorized into subgroups based on their level of dyspnea. Medical Research Council dyspnea scale is simple to administer and it correlates with degree of dyspnea in patients with COPD.[10] The dyspnea grades may give a better estimate of quality of life in patients with COPD than disease severity alone.[21] In a multicenter prospective study, it has been shown that categorizing patients with COPD on the basis of the level of dyspnea was closely correlated with survival than classification on the basis of disease severity as assessed by the percentage of predicted FEV_1.[6] In our study, the MRC dyspnea scale was significantly associated with risk of mortality ($p<0.001$) and the one score increase in MRC scale led to a double fold increase in risk of mortality. Therefore, the level of dyspnea may be useful determinant in prediction of survival. The prognosis of patients with COPD has also been reported to be related to nutritional status. Several studies have shown that a low body weight, expressed as BMI, is associated with an increased overall mortality.[8,9,22,23] Chailleux et al[24] found a 5-year survival of 24% for those patients with severe COPD who had a BMI of <20 kg/m^2.[24] Contrary, in some studies, BMI was not a significant predictor for mortality risk.[9,24,25] In our study, BMI was not a significant prognostic factor which was parallel with the studies of Bowen and Nizet. Those previous studies of mortality in patients with COPD have yielded results compatible with ours. Mean BMI of our patients was 25.7 kg/m^2, which was similar to the mean BMI described in the studies of Bowen et al[24] (24.8 kg/m^2) and Nizet et al[25] (25.6 kg/m^2). Comorbidity was present at entry of study in 54.3% of our patients. The most common comorbidities found were cardiovascular disease (14.4%), followed by hypertension (9.8%) and bronchiectasis (6.2%). However, these comorbidities were not associated with increased mortality in our study. In contrast to our results; Nizet et al[25] found that the presence of comorbidity (38.3% of patients) predict survival in patients with COPD.Comorbidities could not be a determinant factor of survival in our patients because more than half of them had comorbidity. Severe COPD is often accompanied by failure in gas exchange. Chronic hypoxemia usually leads to pulmonary hypertension and cor pulmonale. Therefore, the presence of hypoxemia and hypercapnia in patients with COPD are considered to be related to poor prognosis.[11,23,25] Nizet et al[25] observed a cohort of 47 chronic hypercapnic COPD patients for 3.8 years on average. A higher partial pressure of oxygen in arterial blood (PaO_2) affected survival positively. Partial pressure of oxygen in arterial blood tended to be lower in survivors, but this did not reach statistical significance.[25] In our study, almost of the patients had mild to moderate hypoxemia with normocapnia, which resembles the results of Nizet et al (PaO_2: 62.4 ± 11.9 mm Hg, $PaCO_2$: 38.9 ± 6.5 mm Hg; PaO_2: 61.5 ± 8.3 mm Hg, $PaCO_2$: 48.8 ± 4.5 mm Hg). On the other hand, our results demonstrated a higher PaO_2 showed a tendency toward decreasing the mortality rate. Patients with hypoxemia had a loss in life expectancy of 22%, this is on the verge of significance (RR: 0.99) ($p=0.052$). Costello et al constructed a survival analysis after dividing the group into chronic hypercapnic patients, reversible hypercapnic patients and normocapnic COPD patients. Five-years survival in chronic hypercapnic COPD patients was significantly lower where as in normocapnic COPD patients 5-year survival rates was higher.[11] However, in our study, analysis revealed that the level of $PaCO_2$ was not significantly predictive. In contrast to previous studies, only 14% of our patients had an initial hypercapnia, because of this low rate we thought that it may not be possible to show $PaCO_2$ as a mortality determinant. Also in the previous 2 studies (Nocturnal Oxygen Therapy Trial and Medical Research Council Trial) use of LTOT for COPD showed that LTOT improved the survival.[26] Statistical analysis of our hypoxemic patients did not show better survival rates among those receiving LTOT. Forty percent of our patients had PaO_2 <60 mm Hg (24% of the patients PaO_2 <55 mm Hg) and 31.5% of patients were receiving LTOT during the follow-up, 21% of them died. Increased mortality

rate in patients, who specially had PaO_2 <55 mm Hg and received LTOT, has to be considered as the impact of gas exchange on the mortality of COPD patients. Hospitalization for acute exacerbations represents a major component of the socioeconomic burden related to COPD. The risk of hospital admission increases with decreasing lung function and when chronic respiratory symptoms are present. Hospital admission carries both an immediate and long term risk of mortality.[2,5] Groenewegen et al, included 171 patients admitted to the hospital with an acute exacerbation, showed that the mortality rate was 8%, increasing to 23% after one year of follow-up. In addition to several factors, hospital readmission was also contributed to the increased mortality rate.[7] Gunen et al[27] demonstrated an increase in mortality rate, year by year, in COPD patients related to hospitalization with acute exacerbation of COPD (33% at one year, 39% at 2 years, and 49% at 3, years.[27] Both of the studies have similar and higher mortality rates from the other published studies, which included out patient.[11,18,20,26] In our study, the mean hospital admission frequency with acute exacerbation of COPD per year was 0.50. Higher number of hospital admission for acute exacerbation of COPD per year was associated with decreased survival (p<0.05). The presence of moderate and severe COPD at baseline was associated with an increased risk of death.[28] In our study, the mean survival time for patients was 43.40 ± 0.65 months. The survival rates were 97% at one year 89% at 2 years, 84% at 3 years, and 73% at 4 years. Many published studies, including Nishimura et al, also found similar survival rates (95% at one year, 90% at 2 years, 83% at 3 years, 78% at years, 73% at 5 years).[6,11,18,20,26] The present study is the first to show that following patients with COPD in a specialized out-patient clinic with scheduled physician visits significantly improves the survival rate. Our intention was to construct a specialized out-patient COPD clinic and follow the patients regularly (2-4/year) with the same and specialized doctors and staff. We are expecting patients with COPD to understand the nature of their disease, the risk factors for progression, their role and the role of health care workers. On the other hand, regular follow-up visits play an important role in the improvement of their diseases by realizing the changes of symptoms and complications related to COPD as early as possible. Also suggestion of appropriate treatment according to guidelines and follow-up strategy must be determined during their visits. Current evidence indicates that appropriate treatment can make a major difference in health outcomes in COPD patients. The present results suggest that, regular visits independently decrease the mortality rate. Thus, we believe that patients with COPD need to be followed in the specialized out-patient COPD clinics to decrease their morbidity and mortality rates. The frequency and intensity of follow up depend on the individual patient's disease status and course, as well as the local healthcare system. However, there are no studies that have addressed the specific schedules more likely to results in positive outcome. The current analysis must be validated in future studies. Although there are no routine accepted parameters to use in monitoring COPD progression, several clinical variables may be used to estimate mortality risk. Patient's age, level of dyspnea, presence of hypoxemia and the number of hospital admission for acute exacerbation of COPD were more closely correlated with mortality in COPD. The regular follow-up in COPD out-patient clinic of each COPD patient increased the survival of this disease.

References

1. Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. ***Chest*** 2000; 117: 1s-4s
2. Global Initiative for Chronic Obstructive Lung Disease. GOLD workshop report update 2004. Available from URL: http://www.goldcopd.com
3. Celli BR, Snider GL, Heffner J, Tiep B, Ziment I, Make B et al. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. ***Am J Respir Crit Care Med*** 1995; 152: s77-s120.
4. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. ***Am Rev Respir Dis*** 1986; 133: 14-20.
5. Stephen D, Varkey B. Prognostic factors in chronic obstructive pulmonary disease. ***Curr Opin Pulm Med*** 2005; 11: 149-152.
6. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. ***Chest*** 2002; 121: 1434-1440.
7. Groenewegen KH, Schols AMW, Wouters EFM. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. ***Chest*** 2003; 124: 459-467.
8. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. ***Am J Respir Crit Care Med*** 1999; 160: 1856-1861.
9. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease. Role of exercise capacity and health status. ***Am J Respir Crit Care Med*** 2003; 167: 544-549.
10. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA et al. The body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. ***N Engl J Med*** 2004; 350: 1005-1012.
11. Costello R, Deegan P, Fitzpatrick M, McNicholas T. Reversible hypercapnia in chronic obstructive pulmonary disease: A distinct pattern of respiratory failure with a favorable prognosis. ***Am J Med*** 1997; 103: 239-244.

12. Pinckney RG, O'Brien R, Piccirillo JF, Littenberg B. Evaluation of co-morbidity indices in patients for chronic obstructive pulmonary disease. ***Monaldi Arch Chest Dis*** 2004; 61: 209-212.
13. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. ***Eur Respir J*** 1997; 10: 822-827.
14. Ringbeak T, Seersholm N, Viskum K. Standardised mortality rates in females and males with COPD and asthma. ***Eur Respir J*** 2005; 25: 891-895.
15. American Thoracic Society. Standardization of spirometry (1994 Update). ***Am J Respir Crit Care Med*** 1995; 152: 1107-1136.
16. Quanjer P, Tammeling FJ, Cotes JE. Standardised lung function testing; lung volumes and forced ventilatory flows. ***Eur Respir J*** 1993; 6 (Suppl 16): 5-40.
17. Foucher P, Baudouin N, Merati M, Pitard A, Bonniaud P, Reybet-Degat O et al. Relative survival analysis of 252 patients with COPD receiving long-term oxygen therapy. ***Chest*** 1998; 113: 1580-1587.
18. Oswald-Mammoser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. ***Chest*** 1995; 107: 1193-1198.
19. Dubois P, Machiels J, Smeets F, Delwiche JP, Lulling J. CO transfer capacity as a determining factor survival for severe hypoxemic COPD. ***Eur Respir J*** 1990; 3: 1042-1047.
20. Hersh CP, DeMeo DL, Al-Ansari E, Carey VC, Reilly JJ, Ginns LC et al. Predictor of survival in severe, early onset COPD. ***Chest*** 2004; 126: 1443-1451.
21. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. ***Chest*** 1999; 116: 1632-1637.
22. Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy. ***Chest*** 2003; 123: 1460-1466.
23. Schols AMW, Slangen J, Volovics L. Weight loss is a reversible factor in the prognosis of COPD. ***Am J Respir Crit Care Med*** 1998; 157: 1791-1797.
24. Bowen JB, Votto JJ, Thrall RS, Hagerty MC, Stockdale-Woolley R, Bandyopadhyay T et al. Functional status and survival following pulmonary rehabilitation. ***Chest*** 2000; 118: 697-703.
25. Nizet TAC, van den Elshout FJ, Heijdra YF, Van de ven MJT, Mulder PGH, Folgering HM. Survival of chronic hypercapnic COPD patients is predicted by smoking habits, comorbidity and hypoxemia. ***Chest*** 2005; 127: 1904-1910.
26. Nishimura K, Tsukino M. Clinical course and prognosis of patients with chronic obstructive pulmonary disease. ***Curr Opin Pulm Med*** 2000; 6: 127-132.
27. Gunen H, Hacıevliyagil SS, Kosar F, Mutlu LC, Gülbag G, Pehlivan E et al. Factors affecting survival of hospitalized patients with COPD. ***Eur Respir J*** 2005; 26: 234-241.
28. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States:data from the First National Health and Nutrition Examination Survey follow up study. ***Thorax*** 2003; 58: 388-393.