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Analysis of the factors related to mortality in patients with bronchiectasis ☆

Zeynep Pınar Onen*, Banu Eris Gulbay, Elif Sen, Öznur Akkoca Yildiz, Sevgi Saryal, Turan Acican, Gülseren Karabiyikoglu

Department of Pulmonary Diseases, School of Medicine, Ankara University, Ankara, Turkey

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Summary
Background: Bronchiectasis is a common disabling but rarely fatal disease. However the long-term prognosis and risk factors for mortality are not well known.
Objective: The aim of this study was to determine prospectively the survival and predictive factors of mortality in patients with bronchiectasis, during 4-year follow-up.
Patients and methods: From September 2000 to January 2005 survival of bronchiectasis (as evaluated by computed tomography) and predictors of mortality were assessed in 98 outpatients. Fifty-one of the patients had self-reported history of pulmonary infection including tuberculosis. Baseline data, reevaluated in every single year according to scheduled visits.
Results: The mean age was 61 ± 10 and 74% of the patients were female. In total, 16 patients (16.3%) died; mean survival time was 44.06 ± 1.6 months. The survival rates were 97%, 89%, 76%, 58% at 1, 2, 3 and 4 years, respectively. Cox proportional hazard model revealed that long-term mortality was significantly associated with age, body mass index (BMI), Medical Research Council (MRC) dyspnea scale, vaccination, radiographic extent, hypoxemia, hypercapnia and functional parameters. However, MRC and BMI had more significant effects on the mortality than the functional parameters.
Conclusions: These results suggest that high BMI, regular vaccination and scheduled visits may have beneficial effects on the survival of bronchiectasis. Besides, presence of hypoxemia, hypercapnia, dyspnea level and radiographic extent were more closely correlated with mortality.
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*Corresponding author. Ankara Üniversitesi, Tıp Fakültesi, Göğüs Hastalıkları ABD. Cebeci Hastanesi, PK:06100 Cebeci/Ankara, Türkiye. Tel.: +90 312 595 60 88.
E-mail address: zponen@yahoo.com (Z.P. Onen).

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Introduction

Bronchiectasis is defined as an irreversible dilatation of a portion of the bronchial tree with destruction of the elastic and muscular components of their walls, usually due to recurrent or severe infections. This predisposes to reduction in the clearance of mucoid and mucopurulent secretions which causes to reduction in the expiratory flow of air from the lungs[1,2] Bronchiectasis is the result of a broad range of pathological processes, including primary disorders of bronchial structure, diseases of mucus clearance, infectious causes and inflammatory disorders. However, in more than half of the cases no cause could be found; in an additional 29%, the disease was deemed to be post infectious.[3] Regardless of etiology, symptoms include chronic cough, mucopurulent sputum production, hemoptysis, dyspnea and tiredness.

High-resolution computed tomography (HRCT), as a non-invasive gold standard in diagnosis, has revealed that bronchiectasis has been under diagnosed. For this reason the exact prevalence of bronchiectasis is unknown but the incidence has decreased in developed countries with declining incidence of pulmonary tuberculosis, immunization and effective antibiotic treatment in childhood infections.[2,4] The average age at death has also increased during the last decades and the causes of mortality are now mostly related to respiratory failure.[5] However, it is important to mention that bronchiectasis remains more common and still the frequent leading causes of death in many developing nations. In addition, so many studies have analyzed the effects of microorganisms in the sputum of patients with bronchiectasis, a few studies used some of the quality of life questionnaires to assess the health-related quality of life status but to date no study has assessed the prospective long-term predictors and survival analysis of the patients with bronchiectasis.[6–8]

The present study was designed to assess prospectively the mortality rates and potential determinants of mortality in patients with bronchiectasis during 4-year follow-up. Therefore patient characteristics related to an increased mortality rate and preventive factors such as vaccination were analyzed.

Material and methods

Patients

Subjects were recruited from consecutive patients referred to the outpatient clinics of a university hospital for investigation of possible bronchiectasis between September 2000 and January 2004. *All of the patients were Caucasians*. We prospectively included all patients who had been admitted for cough, chronic sputum production and radiological changes consistent with bronchiectasis, in the study. However, patients with confirmed diagnosis of chronic bronchitis, bronchial asthma, allergic bronchopulmonary aspergillosis, cystic fibrosis and previous history of lobectomy or pneumonectomy were excluded. The final study population consisted of patients with bronchiectasis who had HRCT scan and formal pulmonary function tests (within 1 month time interval), as a result 98 patients (idiopathic bronchiectasis $n = 43$, postinfective $n = 51$; 27 of them had prior tuberculosis, primary ciliary dyskinesia $n = 2$, α1-antitrypsin deficiency $n = 2$) were included and followed until January 2005. There were 73 females and 25 males with the mean age (SD) of 61.76 ± 10.79 and 74 of them were non-smoker. All patients gave written informed consent to participate in the study.

Clinical data

The data as follows were recorded for each patient: anthropometric parameters (including age, gender), medical history (respiratory symptoms, duration of disease), smoking history, self-reported comorbidity, previous treatment protocols, frequency of infectious exacerbation per year, previous number of hospital admission because of respiratory problems per year and education level. Weight and height were measured individually, at each visit. Body mass index (BMI) was calculated by dividing each participant's weight in kilograms by the square of the height in meters. According to calculations, the following standard classifications were used: $<20\,kg/m^2$ (underweight), $\geqslant 20$–$24\,kg/m^2$ (normal), $\geqslant 25\,kg/m^2$ (overweight). If there were former or current smoking history; the number of cigarette pack-year was calculated as the product of the period of tobacco use (in years) and the average number of cigarettes smoked per day. Dyspnea was evaluated according to Medical Research Council (MRC) scale, modified by American Thoracic Society, which is a 5-point scale based on degrees of various physical activities that precipitate dyspnea.[9] Entire of the patients were instructed about the cough, daily sputum production and according to their expressions average of the sputum amount with color were recorded. Comorbidity was determined by standard methods (defined as the existence of malignancies, cardiovascular disease, diabetes mellitus and rheumatologic disease). Former treatments (such as use of antibiotics, inhaled or oral steroid, theophylline and bronchodilators) and the frequency of infectious exacerbations per year were also recorded from medical data. Besides, the date of hospital admission was recorded and verified by hospital records in the first visit.

Pulmonary function tests and arterial blood gas analysis

The functional indices measured were forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow rate (PEFR), midexpiratory flow rate ($FEF_{25–75}$), total lung capacity (TLC), carbon monoxide diffusing capacity of the lung (DLCO) and adjusted for alveolar volume (DLCO/VA) were expressed as percentages of values predicted for the patient's age, sex and height using European Community for Steel and Coal (ECSC) references values.[10] Spirometric parameters were measured using a ''Vmax 229 pulmonary function/cardiopulmonary exercise testing instruments'' (SensorMedics, Bilthoven, The Netherlands) in all patients.

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). PaO_2, $PaCO_2$, pH, and SaO_2 were measured while breathing on room air.

Radiology

Computed tomography (CT) scans were obtained on an electron beam CT scanner (General Electric, USA). Sections of 1.5 or 3 mm thickness were acquired at full inspiration (10 mm intervals) in the supine position. The breath-holding technique was rehearsed before the HRCT examination and consecutive scans were of the same section thickness in individual patients. A high spatial resolution algorithm was used to reconstruct images that were photographed at appropriate window settings (level −700 Hounsfield units (HU); width 1000 HU).

Two observers, 1 radiologist and 1 pulmonologist, independently scored each of 6 lobes (the lingula was regarded as a separate lobe) at the initial CT scanning, as previously described[11–14] using modification of Bhalla system.[11] The presence and extent of bronchiectasis was determined according to established CT criteria[15,16] using a scoring system as follows: grade 1 = localized bronchiectasis affecting 1 or part of 1 bronchopulmonary segment, grade 2 = bronchiectasis in more than 1 bronchopulmonary segment (extensive), grade 3 = generalized cystic bronchiectasis.

Follow-up study

In our specialized outpatient clinic the regular follow-up of each patient were organized according to the scheduled physician visits and individual cases were usually examined at for 3–6 months which depends on the situation of the patients disease status and course. 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 1–4 years. Information regarding mortality and cause of death (due to bronchiectasis and bronchiectasis-related diseases) 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 infectious exacerbation, number of hospital admission because of bronchiectasis per year. Exacerbations were defined by the presence of 1 or more of the symptoms including increase in sputum volume or dyspnea, sputum purulence. Entire of the tests, except HRCT and detailed lung volumes with diffusing capacity, which were described above was assessed once a year for every patient. Also, number of scheduled physician visits per year was recorded for each year during the follow-up time. Vaccination against influenza and pneumococci were suggested in every single year and every 5 years, respectively. Patients were advised to perform postural drainage at least once a day and increase the frequency from 2 to 3 times if they suffer an exacerbation.

Statistical analysis

All statistical measurements were made using SPSS Package for the Social Sciences, Version 11.0 for Windows; SPSS Inc., Chicago, IL.

Descriptive data are 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 with 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 sex, comorbidity, the use of oxygen therapy, extent of bronchiectasis, vaccination were coded numerically as nominal data for the analysis. Relative risks (RR) were calculated for the following risk factors; age, sex, BMI, comorbidity, MRC scale, PFT parameters, ABG analysis parameters, radiological extent of bronchiectasis, vaccination, frequency of infections per year, 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; p values of less than 0.05 were considered to be statistically significant.

Results

Patient demographics and data at presentation

Baseline characteristics, including demographic parameters, of the 98 bronchiectasis patients at study entry are given in Table 1. More than 3 quarters of the patients, 75.51%, were lifetime non-smoker, while the average smoker had an 8.69 ± 18.11 pack-year history. A considerably larger proportion of the women were non-smokers and had a higher mean BMI than the men ($p < 0.001$). At the referral time, highest frequency of patients had 2nd level of dyspnea according to MRC ($n = 56$). Almost all patients had a wide range of airway obstruction with mild hypoxemia. None of the patients had a previous vaccination for influenza or pneumococci. Only 12.2% of the patients had localized type of bronchiectasis where as 46.9% of them had bilateral radiographic extent with cystic bronchiectasis. Additionally half of the patients had any kind of school education.

Long-term follow up

Follow-up time ranged from 12 to 51 months in overall the cohort, according to survival time. The pattern of the functional impairement was combination of obstruction and restriction. Nevertheless airflow obstruction was the predominant finding (mean FEV_1/FVC 68% predicted and FEV_1 45.90% predicted) with radiological extent of bronchiectasis and there were no significant changes from baseline in any of the functional variables, which were analyzed during 4-year study. MRC level was improved in 22 of the patients whereas 2 significant deterioration were reported. At the referral time all of the patients had at least 1 hospitalization history per year but after regular follow-up this became infrequent. Additionally, 26 of the patients were not hospitalized because of respiratory symptoms. In serial chest X-ray observations of 89 patients for each year no

Table 1 General characteristics of patients with bronchiectasis.

Patients number (*n*)	98
Age (yr)	61.76±10.79
Sex (female/male)	73/25
BMI (kg/m^2)	27.62±6.36
Current/former/never smoker (*n*)	3/21/74
Smoking (pack-year)	8.69±18.11
Comorbidity (%)	53(56.1%)
Cardiovascular	19 (19.4%)
Hypertension	21 (21.4%)
Diabetes mellitus	5 (5.1%)
Other comorbidity	8 (10.2%)
FEV_1% predicted	45.9±17.1
FVC % predicted	55.3±17.1
FEV_1/FVC % predicted	68.2±13.2
TLC %	92.8±15.0
DLCO %	73.2±12.8
PaO_2 (mmHg)	60±12
$PaCO_2$ (mmHg)	41±7
MRC dyspnea score	2.33±0.81
Infectious exacerbations in previous years (/yr)	2.40±1.64
Hospital admissions in previous years (/yr)	1.63±1.83
Scheduled physician visits (/yr)	2.87±1.27

Data are presented as mean±SD or number (percentage).
FEV_1: Forced expiratory volume in 1 s.
FVC: Forced vital capacity.
TLC: Total lung capacity.
DLCO: Diffusing capacity for carbon monoxide.

radiographic deterioration were reported. Furthermore, 84 of the patients had regular vaccination for influenza and pneumococci.

Survival

There had been 16 deaths (16.3%) by the end of the study and all of these non-survivors died because of bronchiectasis or bronchiectasis-related disorders (especially respiratory failure) (Table 2). The mean survival time was 44.06±1.6 months. The cumulative survival rates were 97%, 89%, 76%, 58% at 1, 2, 3 and 4 years, respectively. Clinical data of survivors and non-survivors at the 1st registration are compared in the Table 3. The Kaplan–Meier cumulative survival plot for the study population is shown in Fig. 1.

Risk factors for mortality in bronchiectasis

Table 4 shows the results of the univariate analysis for the influence of risk factors on survival. Mortality was highest in underweight subjects and decreased with increasing BMI in both men and women. High values for age, $PaCO_2$, MRC level and low values for FEV_1, FVC and PaO_2 were significantly associated with increased mortality. Furthermore, vaccination and frequent scheduled physician visits had protective role whereas mortality was higher with increasing radiographic extent. On the other hand there was no significant correlation between the treatment protocols including antibiotics and mortality rates.

Discussion

The main findings of the present study, among non-survivors were; advanced age, hypoxemia, hypercapnia, functional parameters, dyspnea level and radiographic extent were associated with increased mortality risk. Among survivors preventive medicine such as vaccination, scheduled visits and high BMI may have beneficial effects on the survival rate of the bronchiectasis patients.

Since 1990s, very limited studies have focused on the risk factors that influence mortality in patients with bronchiectasis and most of them had a great interest in the respiratory failure or coexistence with COPD.[3,8,18,19] Some of the other studies have mentioned the microbiologic characterization or the radiological features of the disease.[14,20] Consequently, data on long-term outcomes including preventive medicine, BMI and dyspnea in outpatients are lacking for bronchiectasis.

In this study, gender of the cohort was similar to the recent studies of Nicotra and Dupont[18,20] but contrast to earlier studies.[21,22] Besides, never-smoked patients were higher and the mean age of the total was older than the reported mean age of the bronchiectasis patients.[18,20–23] Our results suggest that non-smoker female dominance is getting higher day by day without an influence on mortality of the bronchiectasis. For the same reason, data from the current study support previous finding that published by Pasteur et al.[3] who demonstrated that 'lung damages in bronchiectasis progress at the same rate in both sex.'

The etiology of the bronchiectasis, in a significant proportion (52%), of our patients was postinfective, including tuberculosis. The higher rates of postinfective etiology that we found may depend on the insufficient childhood vaccination and tuberculosis disease, which was endemic in our country.[24] This hypothesis could also be supported by the educational status of our cohort that distinguishes the self-preventive health care system. Additionally, more than half of our patients had comorbidity at the referral time and this percentage was higher than the recent intensive care unit patients' of Gursel.[8] However, we did not find any influence of etiology or comorbidity on survival of bronchiectasis. Our findings could be explained by the fact that our cohort was perhaps similar in etiology and comorbidity to allow us to detect the influence of these 2 factors on survival.

The main cause of the death in this study was respiratory failure, which was considered as directly related to bronchiectasis. One study on mortality among patients with bilateral bronchiectasis had reported that the 1-year mortality rate after intensive care unit stay was 40% and also the main cause of the death was respiratory failure.[18] In another study, Keistinen et al.[17] took into account a higher number of patients ($n = 842$) which were gathered from multiple hospitals of the country and the 9 years mortality rate was 25%. The current findings regarding long-term mortality are somewhat different. This difference may be due to different methodologies employed, use of longer follow-up period and stage of the disease. Furthermore, the

Table 2 Characteristics of non-survivor patients with bronchiectasis.

Patient	Age (yr)	Follow-up time (months)	Place of death	Cause of death, from death certificate
1	75	41	Hospital	Pulmonary arrest
2	75	50	Hospital	Pulmonary arrest
3	70	27	Hospital	Pulmonary arrest
4	73	28	Hospital	Pulmonary arrest
5	74	24	Hospital	Pulmonary arrest
6	75	27	Hospital	Cardio-pulmonary arrest
7	51	48	Hospital	Pulmonary arrest
8	70	24	Hospital	Cardio-pulmonary arrest
9	73	36	Hospital	Pulmonary arrest
10	72	14	Hospital	Pulmonary arrest
11	62	12	Home	Cardio-pulmonary arrest
12	70	24	Hospital	Pulmonary arrest
13	85	27	Hospital	Pulmonary arrest
14	58	24	Hospital	Cardio-pulmonary arrest
15	73	18	Hospital	Pulmonary arrest
16	77	27	Hospital	Pulmonary arrest

Cause of death: There was no additional cause for pulmonary or cardiopulmonary arrest other than bronchiectasis.

Table 3 Comparison of backgrounds of survivors and non-survivors.

Variables	Survivors ($n = 82$)	Non-survivors ($n = 16$)	p value
Age (yr)	59.74 ± 10.11	72.06 ± 8.07	< 0.0001
Female/male (n)	61/21	12/4	1.0
BMI (kg/m^2)	29.54 ± 4.94	17.68 ± 2.06	< 0.0001
MRC dyspnea score	1.69 ± 0.62	3.81 ± 0.40	< 0.0001
FEV_1 (%)	46.99 ± 17.75	40.50 ± 12.50	0.09
FVC (%)	56.36 ± 17.68	50.00 ± 13.27	0.11
FEV_1/FVC	68.29 ± 12.90	67.73 ± 15.14	0.87
PaO_2 (mmHg)	62.26 ± 12.11	52.57 ± 9.17	0.001
$PaCO_2$ (mmHg)	40.86 ± 6.95	45.54 ± 6.78	0.01
Infectious exacerbations in previous years (/yr)	2.42 ± 1.69	2.31 ± 1.35	0.77
Radiographic extent (1/2/3)*	12/38/32	0/2/14	0.002
Vaccinated/non-vaccinated patients (n)	79/3	5/11	< 0.0001

Data presented as mean ± SD or number (percentage).
*1 = localized bronchiectasis, 2 = bronchiectasis in more than one bronchopulmonary segment, 3 = generalized cystic bronchiectasis.

survival of our patients remains poor with a 4-year cumulative survival rate of 58%.

A few studies have referred to the nutritional status in respiratory failure including bronchiectasis patients but it has not been demonstrated that malnutrition is associated with poor prognosis in patients with bronchiectasis.[25] Additionally, results of our study are in contrast to those of Dupont who found low BMI, was not associated with mortality in their retrospective analysis of intensive care unit patients with bilateral bronchiectasis.[18] A possible explanation could be that entire of their study population had edema related to right ventricular failure at the referral time. For this reason BMI may has been overestimated and has lacked predictive ability in the survival of their study cohort. In our study population, BMI was independently significant predictor of survival and long-term mortality; the critical level appeared to be 20 kg/m^2, below which mortality rate increased. The suggested mechanism for higher long-term mortality in patients with lower BMI may be impaired immune response with respiratory muscle weakness. Also, this situation may be attributable to the raised systemic markers of inflammation such as high sensitive CRP but in our study population the relationship was not significant. We have not specifically measured the influence of inflammation and future studies should investigate the impact of systemic inflammation on long-term mortality of bronchiectasis.

Although, dyspnea is 1 of the main symptoms of the bronchiectasis, until know limited studies have suggested that dyspnea could be used as 1 of the prognostic factors in patients with bronchiectasis. Garcia reported that the dyspnea is the most relevant health-related quality of life

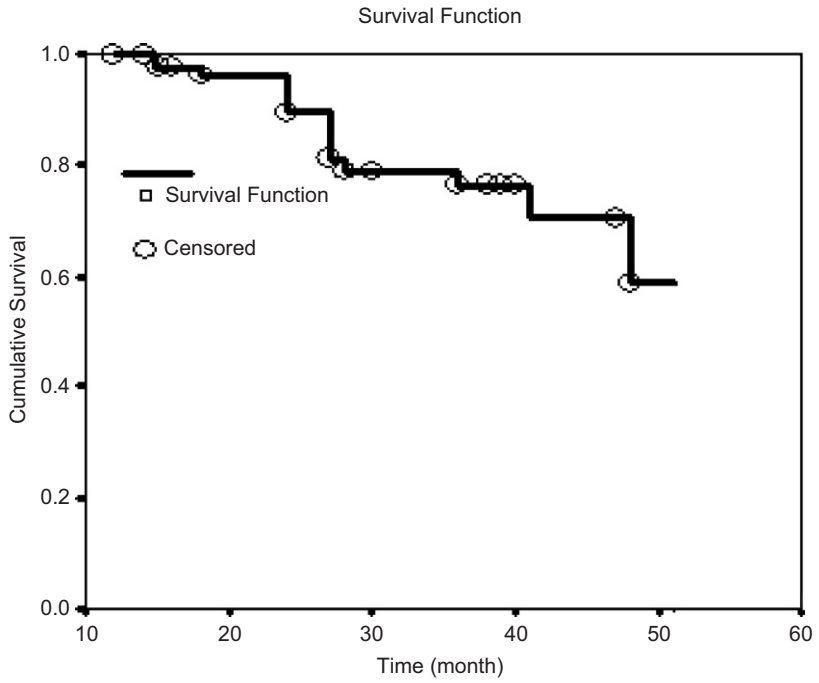


Figure 1 Kaplan–Meier curve showing cumulative survival rates of 98 patients with bronchiectasis during study period.

Table 4 Cox proportional hazards analysis for factors associated with mortality in bronchiectasis.

Parameters	RR (95% CI)	*p* value
Age (yr)	1.14 (1.07–1.21)	<0.001
BMI (kg/m^2)	0.71 (0.61–0.83)	<0.001
FEV_1 (%)	0.98 (0.91–1.00)	0.05
FVC (%)	0.96 (0.93–1.00)	0.04
PaO_2 (mmHg)	0.94 (0.90–0.99)	0.01
$PaCO_2$ (mmHg)	1.11 (1.03–1.2)	0.007
Radiographic extent	5.29 (1.19–23.54)	0.02
MRC dyspnea scale	5.73 (2.55–12.85)	<0.001
Scheduled physician visits (/yr)	0.41 (0.25–0.67)	<0.001
Vaccination	10.1 (3.41–29.88)	<0.001

Data presented as mean ± SD or number (percentage).
CI = confidence interval.

(HRQL) as assessed by the St. George's Respiratory Questionnaire (SGRQ) and scale of MRC in stable bronchiectasis.[6] In our study population, functional dyspnea; as measured by the modified MRC scale correlated similarly with mortality at the initial visit. Besides, MRC scale was also associated with an increased risk of death at the end of the follow-up time period. The present study suggest that categorization by the level of dyspnea may be useful in the prediction of survival in bronchiectasis.

To date limited studies on the prognosis of patients with bronchiectasis have utilized a few objective radiological indexes as factors related to survival.[12] After the confirmation of the diagnosis of bronchiectasis, radiological extent may be preferred for the estimation of survival rate. Leading practical theories for determining the radiological extent can be modified by Bhalla system,[11] which may be performed by clinicians. To the authors' experience, observer variation for HRCT features was generally acceptable in this system. Although convincing explanation for these results are difficult to construct, almost half of the patients had high modified Bhalla scores, which increased the mortality rates 5.29 folds compared with the patients who had low scores, those may be responsible for the results.

An interesting finding in our analysis was that, among all predictor factors, impact of concerning spirometric data on mortality was poor or not influential with univariate analysis. On the other hand, authors were expecting to see restrictive changes more frequently than the obstruction in pulmonary function, according to underlying abnormality. The precise mechanisms are unknown but may be related to the radiological features and extent of

the bronchiectasis. In more diffuse disease the functional pattern is obstructive, whereas in the presence of atelectasis the abnormality in function may be restrictive. Another possibility is that, there was no significant alteration from the baseline in the spirometric data during follow up. In any case, our results would confirm the recent hypothesis of Garcia et al.[6] that, the FEV_1 was the weakest predictive factor on mortality of bronchiectasis.

Among non-survivors, 75% of the patients had hypercapnia whereas 17% of the survivors had hypercapnia. A high $PaCO_2$ was found to be a risk factor for mortality in our population and this is in line with other reports.[26] The level of hypercapnia reflects the severity of the underlying condition. Because of this reason, patients with chronic hypercapnia during follow-up time have a worse prognosis than patients with normocapnia. On the other hand, PaO_2 has also correlated with survival and confirmed the results of Ström and Boe[27] Among all predictive factors on long-term improvement investigated by univariate analysis PaO_2 and $PaCO_2$ were found independently prognostic factors.

The most surprising finding in the present study was the strong independent association between regular vaccination and preventive influence on the mortality of bronchiectasis. Although, numbers of respiratory infections were associated with an inflammatory response and the release of proteolytic enzymes, which results in damage to the airway wall, the relationship between immunization and survival has not been researched. Besides, the prognostic value of regular vaccination in patients who were treated with conventional treatment is more difficult to explain, because there is not enough study available to compare with the present study in directly addressing immunization and the long-term survival of bronchiectasis patients.

Although the present study has the advantage of being based on a large and prospectively examined population with a long duration of long-term follow-up it also has shortcomings. First, some factors that probably could be predictors of reduced survival, such as bacterial colonization of sputum, 6 min walking test and pulmonary arterial pressure were not assessed. Second, our study was not designed to test whether the inhaled steroids and antibiotic treatments were different in their predictive validity.

On the basis of the present study of subjects with bronchiectasis we conclude that underweight and MRC scale are important independent risk factors for mortality, both of them are simple to calculate and requires no special equipment or time. Although, functional parameters had a significant influence on the mortality, the findings of this study will have a potentially great impact of the radiological extent in bronchiectasis from the perspective of survival. In addition to this, vaccination and scheduled physician visits had preventive effects on the mortality but we do not know whether these would be useful indicators of the outcome in clinical trials. Moreover, future studies should focus on preventive medicine that will improve health-related quality of life in bronchiectasis.

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