TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2016) 46: 1838-1845

doi:10.3906/sag-1511-137

The factors affecting survival in patients with bronchiectasis

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Received: 23.112015 • **Accepted/Published Online:** 27.03.2016 • **Final Version:** 20.12.2016

Background/aim: There is limited information about the rate and modifiers of mortality in noncystic fibrosis bronchiectasis.

Materials and methods: This study enrolled a total of 56 bronchiectasis patients. Patients' body mass index, smoking habit, previous therapies, comorbid disorders, history of vaccination, bronchiectasis type and radiological extent, arterial blood gas analysis, respiratory function tests, and laboratory results were recorded.

Results: After a follow-up of 65.38 ± 18.62 months the overall mortality rate was 35.7%. The mean survival duration was 46.42 ± 8.25 months. Advanced age significantly increased mortality (HR: 2.031; CI: 0.991–4.072, P = 0.035). A significant correlation was found between mortality rate and the partial oxygen pressure level (HR: 0.886 (CI: 0.817–0.960); P = 0.039). Pulmonary artery pressure was directly proportional to mortality rate (HR: 9.015 (CI: 3.272–94.036); P = 0.03). There was also a significant correlation between *Pseudomonas aeruginosa* proliferation in sputum and mortality (HR: 7.014 (CI: 2.812–17.962); P = 0.00). Comorbidities increased mortality (HR: 1.984 (CI: 0.972–2.996); P = 0.04).

Conclusion: Bronchiectasis is a disease with high mortality. Advanced age, comorbid conditions, reduced partial oxygen pressure, pulmonary hypertension, and *Pseudomonas aeruginosa* proliferation in sputum increase its mortality rate.

Key words: Bronchiectasis survival, mortality, *Pseudomonas aeruginosa*

1.Introduction

Bronchiectasis is a rare disorder originating from irreversible dilatation of segmental and subsegmental airways as an abnormal and continuous distortion of one or more conductive bronchi or airways (1). Injured airways give rise to recurrent bacterial infections that become chronic in some cases. The inflammatory response in the host leads to tissue injury, which causes a vicious cycle. It is unclear why some cases rapidly progress despite the slow nature of progression in the majority of cases (2). Prediction of the mortality rate of bronchiectasis is very challenging owing to the difficulty in estimating the disease's exact prevalence and the scarcity of descriptive studies so far reported. Moreover, risk factors for mortality are yet to be clearly defined (3). The estimated annual incidence of noncystic fibrosis bronchiectasis (NCFB) has been reported as 1.3/1000, and it tends to be higher in regions with low socioeconomic level (4).

It is currently unknown how radiological extent and clinical signs of the disease or other factors affect mortality rate although some domestic and foreign studies have been previously published on this subject (5,6). Although a number of studies have linked the disease extent in high resolution computed tomography (HRCT) to mortality and some others have even developed an index combining HRCT findings and a number of other parameters, an association between the number of involved lobes or segments and disease severity was rejected by some other studies (7–9).

Determination of individuals at risk for future mortality is central to clinical management of this disorder. An increasing number of clinical trials of inhaled and oral therapies are ongoing in bronchiectasis (10–13), and there is a growing need to define which patients are most likely to benefit from new treatments.

Determining potential factors affecting mortality and thus estimating certain groups with higher mortality could theoretically allow therapies to target patients who are most likely to benefit from them.

This study therefore grouped bronchiectasis patients into survivor and deceased groups after a follow-up of almost 8 years to determine factors affecting mortality.

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2. Materials and methods

2.1. Patients and clinical evaluation

This retrospective cohort study enrolled a total of 56 patients (27 men, 29 women) who were diagnosed with bronchiectasis at the outpatient clinic of a university hospital between January 2000 and December 2004. The study was approved by Ankara University School of Medicine Clinical Researches Ethical Committee (No: 23-052014).

All patients had bronchiectasis confirmed by a HRCT scan; patients with a definitive diagnosis of cystic fibrosis were excluded. An informed consent was obtained from each subject. The subjects were clinically and radiologically followed until December 2008. During the first visit, the subjects' age, sex, body mass index, smoking habit, previous therapies, comorbid disorders, history of tuberculosis, history of regular vaccination (influenza and pneumococcus vaccines), previous thoracic surgery or resection history, bronchiectasis-related complications (respiratory failure, cor pulmonale, empyema, metastatic abscess, amyloidosis, hemoptysis), and types, dosages, and durations of medications (antibiotics, inhaled corticosteroids, inhaled long acting beta-2 agonists, inhaled anticholinergics, and oral N-acetyl cysteine) were recorded. The etiological factors for developing bronchiectasis were questioned. Arterial blood gas analysis, respiratory function tests, and laboratory blood tests (hemogram, albumin, total protein, erythrocyte sedimentation rate, C-reactive protein level) were performed. The bacteriological examinations were performed from early-morning sputum samples.

Type (cystic, cylindrical, or varicose) and localization of bronchiectasis were determined according to thoracic HRCT. The radiological extent of the disease was determined using the Thoracic HRCT scale (14). In this scale, a normal radiological examination was assigned 0 points, bronchiectasis at one or less bronchopulmonary segment 1 point, bronchiectasis at more than one bronchopulmonary segment 2 points, and diffuse bronchiectasis 3 points.

The Charlson Comorbidity Index was used to calculate the comorbidity scores and the 10-year survival rate (15).

During the follow-up period the number of exacerbations, results of sputum cultures sampled during the exacerbations, and the number of hospitalizations during follow-up were recorded. An exacerbation was defined as an increase in dyspnea and the amount or purulence of sputum (16).

Pulmonary hypertension was diagnosed on the basis of clinical examination, radiological imaging, and Doppler echocardiography in patients with clinical signs of cor pulmonale. Subjects with a partial oxygen pressure (PaO_2) below 60 mmHg in arterial blood gas analysis were considered as having hypoxemic (Type 1) respiratory failure, and those with a partial carbon dioxide pressure ($PaCO_2$) over 45 mmHg as having hypercapnic (Type 2) respiratory failure. Patients not attending planned follow-up visits were contacted by telephone and information about their survival was obtained.

The factors associated with survival in a period of 8 years were evaluated in December 2008 by comparing the data of the survivors and the deceased patients among the subjects diagnosed between 2000 and 2004.

2.2. Statistical analysis

Statistical analysis was performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation or number (percentage). Student's t-test and the chi-square test were used to compare continuous variables and categorical variables, respectively. Kaplan–Meier survival analysis was used to determine the survival status. The log-rank test was used to test differences in the cumulative survival curves. Cox proportional hazard model analysis was used to determine the relative mortality risks of different factors. Univariate analysis was used to determine individual variables predicting mortality; multivariate analysis was used to determine independent variables predicting mortality. Significance level was set at $P < 0.05$.

3. Results

The baseline demographic characteristics of the 56 bronchiectasis patients are presented in Table 1.

Table 1. General demographics of the bronchiectasis group.

Variable	
Subjects, n	56
Age, years	60.54 ± 12.43
Male	27 (48.2)
BMI, kg/m^2	28.45 ± 6.27
Smoking history, pack-years	27.12 ± 12.88
Previous tuberculosis	15 (26.8)
Sputum culture positivity	21 (37.2)
Bronchiectasis types	
Cylindrical	17 (30)
Varicose	24 (43)
Cystic	15 (27)
PaO_2, mmHg	56.42 ± 11.2
$PaCO_2$, mmHg	44.98 ± 10.04
FEV1, % predicted	44.78 ± 15.22
FVC, % predicted	58.73 ± 17.37
FEV1/FVC,%	65.79 ± 11.74
TLC, % predicted	89.4 ± 14.5
PAPs	38.71 ± 13.29
Hematocrit, mg/dL	43.2 ± 5.26
CRP, mg/L	16.53 ± 13.47
ESR, h	31.41 ± 12.59

Data are presented as number (%) or mean ± SD. BMI: Body mass index; PaO_2: Partial oxygen pressure; $PaCO_2$: Partial carbon dioxide pressure; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; TLC: Total lung capacity; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate, PAPs: Pulmonary artery systolic pressure

The mean age of the study population was 60.54 ± 12.43 years. Twenty-seven (48%) men and 29 (52%) women were included. The mean follow-up duration was 65.38 ± 18.62 months. The mortality rate was 35.7% and the mean survival time was 46.42 ± 8.25 months. Seventeen (30.3%) subjects were current smokers, 23 (41.1%) were nonsmokers, and 16 (28.6%) were former smokers. At the first visit, the information was obtained that five (9%) of the patients had been regularly vaccinated against influenza and 12 (21%) had been vaccinated against *Streptococcus pneumoniae* with polyvalent vaccine at least once in their lifetime after being diagnosed. At every visit all patients with bronchiectasis were advised to get influenza and pneumococcal vaccinations. In 2008 the information was obtained that 22 (39.3%) patients had been regularly vaccinated against influenza, 20 (35.7%) patients had been irregularly vaccinated against influenza, and 14 (25%) patients had never been vaccinated against influenza. At the same date it was also noted that 25 (44.6%) patients had been vaccinated against pneumococcal disease within 5 years. The etiology of bronchiectasis was unclear in 24 (43%) patients, while it was lung tuberculosis in 11 (20%) patients, nontuberculous infections in 19 (34%) patients, and alpha-1 antitrypsin deficiency in 2 (3%) patients.

As for complications of bronchiectasis, only a 58-year-old woman had been operated on with lobectomy for recurrent hemoptysis; and she died in the sixth year of follow-up. The analysis of the microbiological proliferation in the sputum cultures revealed *Pseudomonas aeruginosa* proliferation in 8 (14%) subjects, *Haemophilus influenzae* in 5 (9%), *Streptococcus pneumoniae* in 4 (7%), *Klebsiella pneumoniae* in 3 (5%), and *Stenotrophomonas maltophilia* in 1 (2%). The most commonly observed comorbidities in descending order were hypertension (n = 19; 33%), diabetes mellitus (n = 12; 21%), and coronary artery disease (n = 9; 16%).

The cumulative survival plot of the bronchiectasis cases is shown in Figure 1.

Twenty (35.7%) patients died by the end of the study. The patients with bronchiectasis were categorized into survivor and deceased groups to compare their characteristics (Table 2). The two groups were similar in terms of gender distribution. The mean age of the survivors was 56.05 ± 10.22 and the deceased patients was 66.18 ± 10.37 years (P = 0.0087). There was no significant difference between the two groups with respect to smoking status, vaccination rates with both vaccines, and initial therapies. At the start of the study hypoxemic respiratory failure was detected in 10 (50%) subjects in the deceased group and 16 (44%) subjects in the survivor group (P > 0.05). Arterial blood gas analysis at the final visit revealed a lower PaO_2 level in the deceased group (P = 0.041). The deceased group had a significantly higher rate of cor pulmonale (P = 0.036). The two groups did not significantly differ with regard to $PaCO_2$ level at the first and final visits. There were also no significant differences between the respiratory function tests of the two groups. The survivor and deceased groups did not significantly differ with respect to the radiologic extent of the disease. The rate of bacterial culture positivity was significantly higher in the deceased group (P = 0.046). Eight subjects, all of whom were in the deceased group, had *Pseudomonas aeruginosa* proliferation in sputum samples. The deceased group had a significantly higher rate of *Pseudomonas* proliferation (P = 0.043).

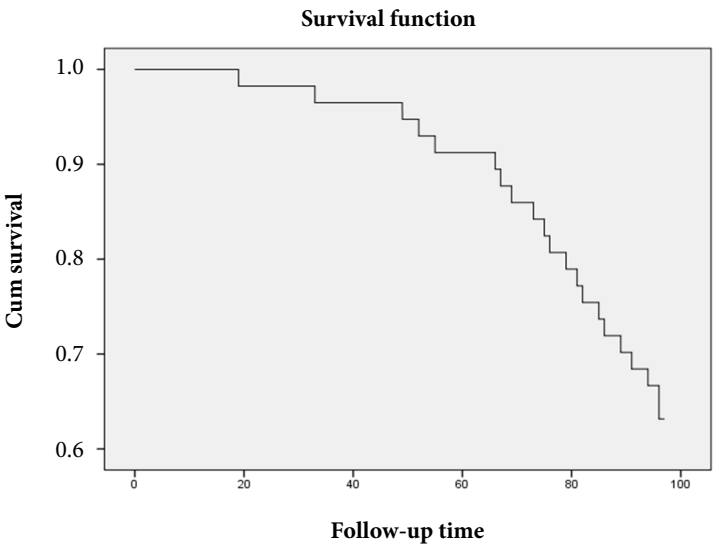

Figure 1. The Kaplan–Meier cumulative survival plot demonstrating survival rates of subjects with bronchiectasis during 8-year follow up.

Table 2. General characteristics of the survivor and deceased groups.

Variable	Deceased patients	Survivors	P value
Subjects, n	20 (35.7)	36 (64.3)	
Age	66.18 ± 10.37	56.05 ± 10.22	0.0087
Male	11 (55)	16 (44)	>0.05
Smoking status			
Current smoker	6 (30)	11 (30.5)	>0.05
Former smoker	6 (30)	10 (27.7)	>0.05
Nonsmoker	8 (40)	15 (41.7)	>0.05
Vaccination			
Influenza vaccinated regularly	9 (45)	13 (36.1)	>0.05
Influenza vaccinated irregularly	6 (30)	14 (38.9)	>0.05
Influenza nonvaccinated	5 (25)	9 (25)	>0.05
Pneumococcal vaccination	8 (40)	17 (47.2)	>0.05
Treatment			
Inhaled long acting beta-2 agonists	14 (70)	21 (58.3)	>0.05
Inhaled anticholinergics	11 (60)	17 (47.2)	>0.05
Inhaled steroids	6 (30)	11 (30.5)	>0.05
Oral N-acetylcysteine	17 (85)	28 (77.7)	>0.05
Sputum bacterial culture results			
Pseudomonas aeruginosa	8 (40)	0	0.043
Haemophilus influenzae	3 (15)	2 (5.5)	>0.05
Streptococcus pneumoniae	3 (15)	1 (2.8)	>0.05
Klebsiella pneumoniae	2 (10)	1 (2.8)	>0.05
Stenotrophomonas maltophilia	0	1 (2.8)	>0.05
PaO_2, mmHg	55.9 ± 12.08	56.7 ± 10.8	>0.05
$PaCO_2$, mmHg	45.7 ± 10.2	44.5 ± 10.1	>0.05
FEV1, % predicted	46.05 ± 14.09	44.15 ± 15.93	>0.05
Hypoxemic respiratory failure	10 (50)	16 (44)	>0.05
Cor pulmonale	8 (40)	4 (11.1)	0.036
Charlson estimated 10-year survival %	46.15 ± 33.83	76.52 ± 23.56	0.0065
Charlson comorbidity index	4.10 ± 1.22	2.15 ± 1.26	0.0072
No. of hospitalizations during follow up	3.10 ± 1.71	2.83 ± 0.47	>0.05
Location of bronchiectasis			
Right upper lobe	5 (25)	6 (16.7)	>0.05
Right middle lobe	8 (40)	12 (33.3)	>0.05
Right lower lobe	9 (45)	17 (47.2)	>0.05
Left upper lobe	5 (25)	8 (22.2)	>0.05
Lingula	6 (30)	10 (27.8)	>0.05
Left lower lobe	10 (50)	19 (52.7)	>0.05
Bronchiectasis in one or less bronchopulmonary segment	5 (25.0)	9 (25.0)	>0.05
Bronchiectasis in more than one bronchopulmonary segment	9 (45.0)	15 (41.7)	>0.05
Diffuse bronchiectasis	6 (30.0)	12 (33.3)	>0.05

Data are presented as number (%) or mean ± SD. PaO_2: Partial oxygen pressure; $PaCO_2$: Partial carbon dioxide pressure; FEV1: Forced expiratory volume in 1 s

A significant correlation was found between the radiological extent of the bronchiectasis and the presence of respiratory failure (P = 0.041). Similarly, the extent of bronchiectasis was significantly greater in the subjects with cor pulmonale than in those without (P = 0.039).

Cox proportional hazard model analysis was used to determine relative risk of death with different variables (Table 3). According to that analysis, advanced age (HR: 2.031 (CI: 0.991–4.072); P = 0.035), final PaO_2 level (HR: 0.886 (CI: 0.817–0.960); P = 0.039), systolic pulmonary artery pressure (HR: 9.015 (CI: 3.272–94.036); P = 0.03), and *Pseudomonas aeruginosa* proliferation (HR: 7.014 (CI: 2.812–17.962; P = 0.00) significantly increased the risk of death, whereas microorganisms other than *Pseudomonas* species and disease duration did not. As shown by a Kaplan–Meier cumulative survival plot, the survival rate was significantly lower in patients with *Pseudomonas* proliferation than in those without (Figure 2). The Charlson Comorbidity Index and Charlson estimated 10-year survival percentage significantly increased the risk of death (HR: 1.984 (CI: 0.972–2.996); P = 0.04).

4. Discussion

There is limited information about the mortality rate of bronchiectasis, which is considered an orphan disease despite being commonly encountered. In the present study, age, comorbid conditions, PaO_2 level, presence of cor pulmonale, and bacterial infections significantly increased the mortality rate associated with the disease, which was found to be 35.7% during a follow-up time of 18 to 96 months. Onen et al. reported a mortality rate of 16.3% after a median follow-up of 4 years (17). In that study the

Table 3. Cox proportional hazard analysis of significant predictors of mortality.

	HR	95% CI	P value
Age, years	2.031	0.991–4.072	0.035
PaO_2, mmHg	0.886	0.817–0.960	0.03
PAPs	9.015	3.272–94.036	0.03
Pseudomonas aeruginosa proliferation	7.014	2.812–17.962	0.000
CCI	1.984	0.972–2.996	0.04

CI: confidence interval, PaO_2: Partial oxygen pressure, PAPs: Pulmonary artery systolic pressure, CCI: Charlson comorbidity index

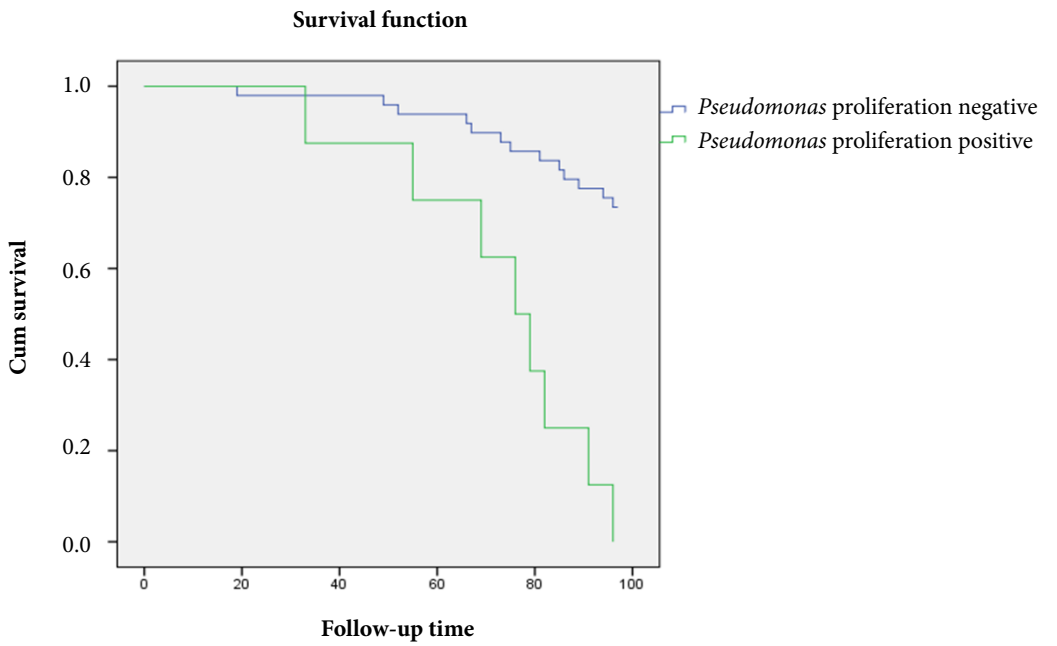

Figure 2. The Kaplan–Meier cumulative survival plot demonstrating significantly higher mortality in patients with *Pseudomonas* proliferation in sputum culture.

Table 4. Comparison of the first and final visit characteristics of the study subjects.

	First visit			Final visit		
Variable	Deceased patients	Survivors	P value	Deceased patients	Survivors	P value
Subjects, n	20	36		20	36	
PaO_2, mmHg	55.9 ± 12.08	56.7 ± 10.8	>0.05	43.25 ± 8.14	55.18 ± 12.3	0.041
$PaCO_2$, mmHg	45.7 ± 10.2	44.5 ± 10.1	>0.05	47.12 ± 8.21	45.16 ± 10.03	>0.05
FEV1, % predicted	44.15 ± 15.93	46.05 ± 14.09	>0.05	43.17 ± 13.2	47.14 ± 9.05	>0.05
FVC, % predicted	49.17 ± 12.16	52.19 ± 13.27	>0.05	45.28 ± 10.15	50.17 ± 11.12	>0.05
FEV1/FVC, %	62.12 ± 18.13	66.31 ± 10.21	>0.05	65.16 ± 20.17	64.16 ± 16.03	>0.05
6-MWT, m	410.25 ± 65.32	540.18 ± 62.24	>0.05	320.14 ± 48.11	527.37 ± 85.16	0.045
PAPs, mmHg	44.32 ± 8.27	29.41 ± 5.19	0.037	48.16 ± 6.12	31.19 ± 5.27	0.033

Data are presented as mean ± SD. PaO_2: Partial oxygen pressure, $PaCO_2$: Partial carbon dioxide pressure, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, 6MWT: 6-min walking test, PAPs: Pulmonary artery systolic pressure

female-to-male ratio, body mass index, and PaO_2 levels were greater than in our study population. Goemminne et al. reported an overall mortality rate of 20.4% after a median follow-up of 5.18 years (7). In that study, the age range and the sex distribution of the patient population were similar to in our study although the number of subjects with COPD was significantly higher.

Not surprisingly, previous reports have reported a higher mortality rate in the elderly. Dupont et al. reported that mortality was increased more than twofold in patients with bronchiectasis aged above 65 years (relative risk [RR], 2.70; 95% confidence interval [CI], 1.15 to 6.29) (18,19). Age > 65 years, comorbidities, and treatment noncompliance may underlie an increased mortality rate (20–22).

The number of vaccinated patients was quite low at the start of our study. Moreover, during the follow-up, vaccination rates remained low despite the patients having been informed about vaccination and being advised to get vaccinated. No significant correlation was found between vaccination with influenza and pneumococcal vaccines and overall mortality. In fact, we expected a mortality reduction by lowering the rates of exacerbations, disease complications, and the number of hospitalizations by vaccination. The failure to detect such a finding may be a result of the small sample size.

Smoking status did not affect mortality in our study. Loebinger et al. showed that the mortality rate was not increased in smokers (RR: 1.78 (CI: 0.87 – 3.63), P = 0.120) (2). Onen et al. reported that smoking history and the presence of COPD as a comorbid condition did not have an influence on mortality from bronchiectasis (17).

Bacterial proliferation occurred in 21 subjects from the sputum samples taken during the first visit. As recently reported by others, the most frequently proliferated bacterial pathogen was *Pseudomonas aeruginosa* in the present study (23). The culprit bacteria were *Pseudomonas aeruginosa* species in eight subjects, all in the deceased group. The mortality rate was increased by the presence of bacterial colonization. Particularly, the rate of *Pseudomonas aeruginosa* infection was significantly higher in the deceased group. It is already known that patients with bronchiectasis are more susceptible to *Pseudomonas aeruginosa* infection due to impaired airway mucus clearance as a result of chronic bronchial dilatation. Being one of the most common agents of infection, *Pseudomonas* species adversely affect the immune system. Inflammation causes increased interleukin 8 synthesis, which in turn interacts with chemokine receptor CXCR1 to attract neutrophils to the site of inflammation. Proteases secreted by pseudomonas impair CXCR1's functions and interfere with neutrophil aggregation, events that ultimately prevent bacterial killing. The increased rate of isolation of *Pseudomonas* in patients with bronchiectasis is associated with worsened disease severity, airway obstruction, and quality of life (24–26).

Our data showed that there was no significant relationship between radiological extent of the disease and mortality. We also did not find any significant correlation between the radiological extent of the disease and respiratory functions or bacterial proliferation rates. Chalmers et al. failed to show any significant correlation between the radiological extent and mortality (8). Nevertheless, in that study the radiological severity

of bronchiectasis was assessed using a modified Reiff score (27) that takes into account the number of lobes involved and the degree of bronchial dilatation. That study demonstrated a significant relationship between the Reiff score and hospital admissions (8,27). This suggests that not the number of affected lobes alone, but other factors such as bronchial dilatation severity may be important points for radiological assessment.

Our study also importantly showed that although the radiological extent of the disease was not directly related to survival, it indirectly increased mortality by worsening respiratory failure and cor pulmonale.

The patient population in the present study had a strikingly higher comorbidity rate. Charlson comorbidity indexes and estimated 10-year survival rates as determined by comorbidity analysis showed a significant correlation with mortality. Considering the impact of comorbidities on the prognosis, progression, and mortality of the disease, it may be hypothesized that bronchiectasis itself may create a systemic inflammatory state (27). Monitoring and treatment of accompanying comorbid conditions may contribute to reduce the mortality rate of bronchiectasis.

The deceased group was more often diagnosed with cor pulmonale compared to the survivors. The pathophysiology of pulmonary hypertension in chronic lung disease is multifactorial and includes hypoxic pulmonary vasoconstriction, pulmonary vascular remodeling, small vessel destruction, and fibrosis. Pulmonary hypertension in bronchiectasis is typically of mild-to-moderate severity. Development of pulmonary hypertension is a poor prognostic sign in chronic lung disorders. In severe bronchiectasis perfusion is impaired secondary to capillary bed injury and left-to-right shunting, which impair cardiac functions and pulmonary gas exchange. This may explain why pulmonary hypertension is a poor prognostic sign in bronchiectasis.

In our study the initial PaO_2 level was not a prognostic factor. Our hypotheses for this finding are the following. We only measured resting PaO_2 levels of our patients. However, they may have exercise hypoxemia leading to pulmonary hypertension. The latter can also originate from fibrosis that develops in secondary bronchiectasis due to recurrent infections. Hence, there is a mixed type airflow limitation. PaO_2 level tended to be lower during exacerbations of bronchiectasis, which contributes to the progress of pulmonary hypertension. A reduced PaO_2 level at the final visit significantly increased mortality.

The main limitation of our study is its small sample size. This caused the number of factors affecting mortality to be small among the overall sample, reducing the statistical power and producing weaker statistical correlations between the study parameters.

In conclusion, this analysis revealed a bronchiectasis mortality rate of 35.7% during a follow-up of almost 8 years. The variables related to increased mortality were advanced age, a high Charlson comorbidity score, PaO_2, cor pulmonale, and *Pseudomonas* proliferation.

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