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Original Article

Managing Bronchiectasis: 13 Years of Experience from Sputum to Lung Transplantation

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Abstract

OBJECTIVES: Bronchiectasis and especially related mortality has gained growing interest in recent years.The aim of our retrospective study was to determine the factors which may influence and indicate mortality in our bronchiectasis patients throughout 13 years.

MATERIAL AND METHODS: Patients with ICD-10 code J47 depicting bronchiectasis between 1.1.2003 to 31.12.2015 were evaluated using database of our hospital.694 out of 1470 patients who had high-resolution computed tomography (HRCT) scan confirming the presence of bronchiectatic lesions were included.

RESULTS: Female/male ratio was 1.09. Mean age of the patients was 45.9±15.7 years. Sputum culture results were available in 365 (52.6%)of the patients.Pseudomonas aeruginosa was the leading pathogen, which was found in 68 (20.7%) patients.28 (4%) patients have died during the 13 year period, and the overall survival was 125,3 months. In general 5 (4.4%) out of 112 patients who underwent surgery were lost, 3 of them belonging to the transplantation group. 3 out of 9 patients (33%) who underwent lung transplantation were lost within 3 years.There was no statistically significant difference in survival between patients who underwent surgery or not (p>0.05). In univariate Cox regression mortality analysis age, FEV1, P. aeruginosa, E.coli, hospitalisation and ICU admission had p value <0.01. When these factors were evaluated in the multivariate analysis, only P.aeruginosa reached statistical significance in predicting mortality.

CONCLUSION: Isolation of P.aeruginosa in a patient with bronchiectasis should be taken seriously. It can be suggested that eradication treatment according to guidelines will help reduce mortality of bronchiectasis worldwide. Surgery is still an option of treatment in severe bronchiectasis and lung transplantation may be a life-saving way of managing end-stage disease.

KEYWORDS: Bronchiectasis, mortality, microbiology, surgery

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INTRODUCTION

Bronchiectasis is a chronic lung disease characterized by clinical symptoms of cough, sputum production, and also bronchial infection. It is defined radiologically by permanently dilated bronchi, leading to impaired mucociliary clearance, chronic airway inflammation, and bacterial colonization. The aims of treatment are to prevent exacerbations, reduce symptoms, improve quality of life, and stop disease progression as stated in the European Respiratory Society guidelines for the management of adult bronchiectasis [1]. Bronchiectasis may also lead to life-threatening hemoptysis, respiratory failure, and death. Nowadays, two scoring systems are used to predict severity and mortality of bronchiectasis [2]. They include age, airway obstruction, body mass index, dyspnea, affected lobe quantity, exacerbations, hospitalization, and microbiological status as variables predicting mortality. Several retrospective and prospective studies targeting different factors related to mortality have been published in the last decade [3-5]. Recent studies focusing specifically on *Pseudomonas aeruginosa* and its role in bronchiectasis present valuable data which can direct future direction in this field. In general, sputum microbiology, radiological severity, age, and hospitalizations are the most commonly encountered factors related to mortality [6, 7]. Surgical removal of the affected site or lung transplantation are non-medical options in patients with bronchiectasis who have severe suppurative complications, life-threatening hemoptysis, and respiratory insufficiency. The recent guidelines from the British Thoracic Society (BTS) specifically note scarce data on the results of surgery and specifically lung transplantation for bronchiectasis [8]. It is still debatable which patients should be referred for surgery and when to operate. Resections and lung transplantation may save lives in this population. The aim of our study was to determine the role of clinical factors and surgery including lung transplantation in mortality in patients with bronchiectasis through 13 years in a single institution.

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MATERIALS AND METHODS

Patients with ICD-10 code J47 depicting bronchiectasis between 1.1.2003-31.12.2015 were retrospectively evaluated using electronic database of our hospital. The study included only the patients who had thoracic high resolution computed tomography (HRCT) and was diagnosed at our hospital with a minimum follow-up time equal to or more than 12 months. A total of 1470 patients were found to have the diagnosis of bronchiectasis; however, 776 of them did not have HRCT confirming the diagnosis or had a follow-up time less than 12 months; therefore, 694 out of 1470 patients who had HRCT scan confirming bronchiectatic lesions and were followed at least 12 months were included in our study. The status of survival was determined in December 2016 using 'Declaration of Death Online System' of the Ministry of Health, Turkey. The study received approval from the Ethical Committee of our hospital with registration number 2016/08. As the study was planned as a retrospective cohort, no informed consent was obtained from patients. Images obtained using 1 mm collimation at full inspiration were reviewed, and bronchiectasis was determined to be present if there was one or more of the following criteria: a broncho-arterial ratio greater than 1, lack of tapering of the bronchi, and visualization of bronchi within 1 cm of costal or paravertebral pleura or abutting the mediastinal pleura. The results of the sputum culture were obtained from the database of our hospital. Any sputum culture results at any time - whether normal flora or pathological growth – was included in the study. Clinical data, radiological localization, sputum culture, surgical treatment, and mortality were investigated.

Statistical Analysis

Data were expressed as mean with standard deviation (SD) and 95% confidence intervals (CI). The Chi-squared test and Mann-Whitney U test were used for comparison of categorical and numerical data, respectively. For percent survival and presentation of the figures on total mortality and mortality sub-analysis, a Kaplan-Meier analysis was performed with a log-rank test to compare different etiology subgroups. For the univariate mortality analysis, Cox proportional hazard regression analysis was used to estimate hazard ratios (HR) and their 95% CI of several parameters possibly predicting mortality. For multivariate analysis of factors associated with mortality, a multivariate Cox regression analysis was performed. Variables that were significant in the univariate model were included in the multivariate analysis. Analysis was performed using the Statistical Package for Social Sciences version 20.0. (IBM SPSS Corp., Armonk, NY, USA). P values were considered to be significant if lower than 0.05 and two-tailed testing was performed.

MAIN POINTS

- The management of bronchiectasis has been empirical for a long time.
- With accumulating knowledge and experience, patients with bronchiectasis get better follow-up plans and P. aeruginosa eradication plays an important role in reducing mortality.
- Surgery is still a treatment option in severe bronchiectasis, and lung transplantation may be life-saving in managing end-stage disease.

RESULTS

There were 362 female (52.2%) and 332 male (47.8%) patients. The female/male ratio was 1.09. Mean age of the patients was 45.9±15.7 years. Median duration of follow-up of the patients was 59±32 months, and 23.6% of the patients smoked cigarettes at some time during their life. More than half of the patients were never smokers (59.2%). Sputum culture results were available in 337 (48.5%) of the patients. Details about microbiological spectrum including culture positivity in more than 1% of the patients are given in Table 1. *P. aeruginosa* with two different bacteria was detected in 12 patients and *P. aeruginosa* with three different bacteria in six patients. Mixed double isolation was detected in 19 patients, and mixed triple isolation in 9 patients. Spirometry results were available in 251 (36%) of the patients. The spirometry results were within reference limits in 17.6% of the patients (n=92). The majority of patients had a combined ventilatory defect with a proportion of 38.4% (n=201). Obstructive ventilatory defect was found in 21.2% (n=111) and restrictive defect was found in 22.9% (n=120) of the study population. FEV1 level was 65% with a SD of ±24.8. In 58.2% (n=405) of the patients, the disease was unilaterally located. In 41.8 % (n=292) of the patients, both lungs were involved. In 40.1 % of the patients, the disease was confined to only one lobe. Two lobes were affected in 29.7% of the patients. In 3.7% of them, all the lobes in both lungs were affected. Left lower lobe was the predominant location of bronchiectasis (62.2%), followed by right lower lobe (40.6%), right upper lobe (31.6%), left upper lobe (28.4%). Right middle lobe (28.2%) and lingula (22.5%) were the least commonly diseased lobes. Table 2 summarizes the operations performed during 13-year period; 69 (61.6%) of the operations were left-sided. Left lower lobectomy at 36.6 % (n=41) was the most commonly performed surgery, followed by right lower lobectomy at 10.7% (n=12). Nine patients had bilateral lung transplantations because of the involvement of both lungs leading to respiratory insufficiency. Lung transplantation

Table 1. Microbiological examination of the patients' sputum

Normal sputum flora	55.6% (n=183)
P.aeruginosa	20.7% (n=68)
H.influenzae	7.6% (n=25)
S.pneumoniae	6.1% (n=20)
E.coli	4% (n=13)
M. tuberculosis	3.6% (n=12)
S. aureus	3.3% (n=11)
E.cloaca	3.3% (n=11)
K.pneumoniae	2.4% (n=8)
A. baumanni	1.2% (n=4)
M. catarrhalis	1.2% (n=4)
Two different bacteria	5.6% (n=19)
Three different bacteria	2.6% (n=9)

was first performed in our institution in 2013. Five patients were operated upon in 2013 and two patients in 2014. The remaining two patients received bilateral transplantation in 2015 and in 2016, respectively.

In general, five (4.4%) out of 112 patients who underwent surgery died, and three of them underwent transplantation. Three out of nine patients (33%) who underwent lung transplantation died within three years of the surgery. The causes of death were as follows: One patient (a 56-year-old male) died due to respiratory insufficiency after one month following surgery; another patient (a 35-year-old female) underwent a re-transplantation after two years of the first procedure because of chronic rejection and died of septic complications more than one month following the second surgery; the third patient (a 48-year-old female) died two years post transplantation due of respiratory insufficiency. Sputum cultures of the two female patients were positive for *P.aeruginosa,* and the male patient had *E.coli* growth in sputum culture. Table 3 summarizes the microbiological spectrum of patients who were operated upon. The first patient (a 58-year-old male) from the non-transplant group died after emergent massive hemoptysis-related left-sided thoracotomy. The second patient (a 61-year-old male) died ten years after a left-sided thoracotomy due to ischemic heart disease. Sputum cultures were positive for *K. pneumoniae* and *P. aeruginosa*, respectively. The disease related mortality rate in the non-transplant group was 1/103, namely 0.97%. Twenty-eight (4%) patients have died during the 13-year period, and the overall survival was 125.3 months (95% CI; 123.1-127.5). The case fatality rate in 12 months was 3/694 (0.43 %); 9/694 in 36 months (1.3%); in 60 months 16/694 (2.3%); and 4% in 120 months. There was no statistically significant difference in survival between patients who underwent surgery or those who did not ($p > 0.05$). The cause of death in 14 of the patients was recorded as respiratory insufficiency in different hospitals. We were not able to determine the real causes of death in nine patients. In univariate Cox regression mortality analysis age, FEV1, *P. aeruginosa*, *E.coli*, hospitalization, and ICU admission had a p value less than 0.01. There were significant mortality rates in ≥30 years group; however, there have been no fatalities in patients younger than 30 years of age ($p<0.005$). The involvement of three or more lobes of the lung was found in 209 (30%) patients. and this had a relationship with poor survival in patients older than 30 years ($p=0.032$). The overall survival in patients with less than three lobes involvement was 127.5 months (95% CI; 125.6-129.4), and in patients with three or more lobes involvement was 122.5 months (95% CI; 118.5-126.4); 440 patients were treated as outpatients during follow-up; 138 have been hospitalized only once; and 116 had multiple hospitalizations. The survival times were 128.4 months (95% CI; 126.7-130), 125.5 months (95% CI; 122.2-128.8), and 118.1 months (95 CI%; 112.3-123.8) ($p<0.005$), respectively. Thirty patients had one or more ICU admissions. The survival was the worst in this group with a mean of 90.7 months (95% CI; 73.3-108.0) ($p<0.005$). The presence of *P. aeruginosa* was associated with poor prognosis with a survival rate of 109.3 months (95% CI; 99.8-118.8) ($p<0.005$). On the other hand, the presence of *P. aeruginosa* was not associated with surgical treatment of the bronchiectasis ($p=0.9$). Apart from this, the presence of *E. coli* in sputum was also associated with poor survival in our patients ($p<0.01$). When all these factors were evaluated in the multivariate analysis, only *P.aeruginosa* reached statistical significance in predicting mortality.

Table 2. Types of bronchiectasis-related surgical treatment

Left lung segmentectomy	6.3% (n=7)
Left upper lobectomy	0.9% (n=1)
Left lower lobectomy	36.6% (n=41)
Lingulectomy + Left lower lobectomy	7.1% (n=8)
Left pneumonectomy	9.8% (n=11)
Lingulectomy	0.9% (n=1)
Right lung segmentectomy	3.6% (n=4)
Right upper lobectomy	4.5% (n=5)
Right middle lobectomy	3.6% (n=4)
Right lower lobectomy	10.7% (n=12)
Right bilobectomy	3.6% (n=4)
Right pneumonectomy	4.5% (n=5)
Bilateral lung transplantation	8% (n=9)
Total	n=112

Table 3. Microbiological spectrum of the patients who underwent surgery

Normal sputum flora	32% (n=33)
P. aeruginosa	8.7% (n=9)
H. influenzae	6.8% (n=7)
S. pneumoniae	4.9% (n=5)
E. coli	1.9% (n=2)
M. tuberculosis	2.9% (n=3)
K. pneumoniae	1% (n=1)
M. catarrhalis	2.9% (n=3)
A. baumanni	1.9% (n=2)
Enterobacter spp.	1.9% (n=2)

DISCUSSION

Our results show that during 13 years, 4% of our patients died. Univariate analysis showed higher mortality according to age, FEV1, radiological extent/severity, *P. aeruginosa*, *E. coli*, hospitalization, and ICU admission. Multivariate analysis showed that the major risk factor for higher mortality was the existence of *P. aeruginosa*. Our mortality rate was relatively lower when compared to other similar studies. Loebinger et al. [4] reported 8.8-year mortality as 16.5 % and in the study by Goeminne et al. [3], the mortality was 20.4% in a median follow-up of 5.18 years. Önen et al. [5] detected 16.3% mortality during 4-year follow-up of the patients. Our study population was comparable with the recent literature in terms of age and gender distribution [1, 3-5]. More than half of the patients were never smokers (59.2%) which was higher than in the study by Goeminne et al. [3], but lower than in the study population of Önen et al. [5], which was 75.5%. It

must be noted that we have missing data due to heterogeneity of our file system. The involvement of three or more lobes of the lung was found in 209 (30%) patients. This is lower than the study population of Goeminne et al. [3], which may partly explain the higher mortality rate in their study. Lateralization of disease showed predominance in favor of the left lower lobe, but this had no association with mortality. Hospitalization rates may be misleading when comparing patient outcomes as the specifications of the institution – reference center/training hospital or general hospital-bed availability, and indications for inpatient treatment may differ. More than half of our study population was treated as outpatients. The higher rate of mortality in hospitalized patients is expected as more severe patients with exacerbations, lower respiratory capacity, colonization with strong pathogens, and hemoptysis constitute this group. Multiple hospitalizations had a significant negative impact on survival in our population, and this was in accordance with scoring systems predicting mortality [2]. ICU admission was also associated with mortality. The indications for ICU admission rely on generally defined objective criteria. The association of this fact with higher mortality is therefore beyond dispute. Of the patients who had spirometric evaluation (75.5%), the majority had either combined or obstructive ventilatory defect with a mean FEV1 of 65%±24.8. Although being a factor related to mortality in univariate analysis, FEV1 lost this significance in multivariate analysis. It still has its place in FACED score and bronchiectasis severity index with age and hospitalization, where they proved to be even stronger in predicting mortality over a longer period than originally described [3]. *P. aeruginosa* is an opportunistic pathogen. It is well known that in cystic fibrosis (CF) bronchiectasis, *P. aeruginosa* colonization leads to rapid decline in lung function and premature mortality. This bacterium rapidly adapts to chronic infection in lung and develops resistance. Finch et al. [6] made a systematic review to determine whether colonization with *P. aeruginosa* influences prognosis and/or is associated with cross-sectional features of severity. They included studies with a total of 3683 patients. *P. aeruginosa* was significantly linked to mortality, hospital admissions, and exacerbations of bronchiectasis. The risk of death was found to be threefold. Thus, this pathogen proved to be both a marker of severe disease and associated with a poor prognosis. In our retrospective study, we were unable to determine colonization, the most frequent definition of which is two positive cultures at least 3 months apart over the course of 12 months. The presence of *P. aeruginosa* at any time in the sputum culture was related significantly to mortality and was associated with poor prognosis with a survival rate of 109.3 months (95% CI; 99.8-118.8) ($p<0.005$). This finding is in accordance with the analysis of Finch et al. [6], supporting their conclusion that patients with *P. aeruginosa* deserve specific treatment to reduce the risk of mortality. Wang et al. [7] recently published a retrospective study to evaluate the clinical characteristics and prognostic value of *P. aeruginosa* in adult patients with bronchiectasis. *P. aeruginosa* was the most commonly isolated pathogen (43.3%) in 1188 patients with sputum or bronchoalveolar lavage fluid (BALF) data. This was relatively higher than in our study population where we had *P. aeruginosa* growth in 20% of the patients with sputum culture. This study and ours had some common features like being a single and specialized center and taking all-cause mortality as an endpoint. They found that the isolation of *P. aeruginosa* was related to poor clinical and radiological conditions, worsening lung function, more exacerbations, and higher mortality. Depending on similar results, Pasteur MC et al. [9] proposed in BTS guideline for non-CF bronchiectasis that *P. aeruginosa* colonization status should play a key role in the assessment of disease severity. In our study, 4 (3.6%) out of 110 patients who underwent surgery died. This was not an immediate postoperative mortality, but again 'all-cause mortality' due to retrospective design. Fan et al. [8] designed a meta-analysis to evaluate the efficiency and safety of surgery in the management on non-CF bronchiectasis. The overall pooled mortality was calculated as 1.5% of a total of 38 studies from 1969 to 2014. The lower mortality can be explained by the fact that both children and adults were included and elective rather than emergency surgeries predominated. Three out of nine patients (33%) who underwent lung transplantation died within 3 years. Sputum cultures of the two female patients were positive for *P. aeruginosa* and the male patient had *E. coli* growth in sputum culture. Data on transplantation in bronchiectasis are limited. Rademacher J et al. [10] published a retrospective analysis of 34 patients who underwent lung transplantation with a primary diagnosis of bronchiectasis. The most common organism of pre-and post-transplant chronic airway infection was *P. aeruginosa*. Fifteen of the 34 patients (44%) died within the study period, but early deaths – those within one year – were attributed to immunodeficiency. Overall survival of patients with bronchiectasis after transplantation was comparable to other diseases. Thus we suggest that with growing experience, lung transplantation will gain prominence in treating patients with severe bronchiectasis.

There are a few limitations in our study. As it based on retrospective data, we could not determine some parameters like the load of active smoking, associated comorbidities, exacerbation rates, the details of microbiological studies (infection in exacerbation or colonization), the details of the treatment (eradication therapy, long-term antibiotic therapy, changes in the treatment according to culture results, the availability of pulmonary rehabilitation including airway clearance techniques), investigations concerning the etiology of bronchiectasis (CF, immune deficiencies, etc.), and the actual cause of death in some patients. Malnutrition data including body mass index, which is an important determinant of mortality is also missing in our study. As our hospital is a referral center for pulmonary diseases in our country, probably more severe patients are treated here and our patients may not reflect the real spectrum of bronchiectasis in patients in general, and this may have resulted in some selection bias. In addition, we used 'all-cause mortality' instead of 'bronchiectasis-related mortality' and this might lead to exaggerated influence of *P. aeruginosa* infection on mortality. We were not able to define the groups which were colonized or infected with *P. aeruginosa*. Apart from this, there is a lack of data both worldwide and concerning this study describing the effect of organisms other than *P. aeruginosa* on prognosis. Only the presence of *E.coli* in sputum culture showed association with mortality in the univariate analysis but lost its significance in multivariate analysis thereafter. Other organisms may influence the out-

come of these patients to a lesser extent than *P. aeruginosa*, which also found its place in the Bronchiectasis Severity Index [11].

Our study may fill a gap in the literature by contributing a large population of patients with bronchiectasis from Turkey. As our hospital is a referral center for pulmonary diseases and thoracic surgery, this pooled experience can be further improved by prospectively following the patients of this cohort. Our study had 694 patients, which is more than the study population on which Bronchiectasis Severity Index and FACED score were based [2]. In the light of accumulating data and the results of our study, all patients with bronchiectasis should have sputum microbiological results in order to detect *P. aeruginosa* as soon as possible. As *P. aeruginosa* accompanies severe disease and mortality depends on multiple factors, the method to conclusively prove the isolated effects of this organism on outcome is through a large randomized controlled trial of eradication treatment, which is recommended clearly in the last consensus statement by EMBARC [12]. We do not know why some patients become colonized with *P. aeruginosa*. This fact is also highlighted by Aliberti et al. [12] and shows why we need more studies investigating the genetic, microbiological, inflammatory, and clinical susceptibility factors for colonization. In summary, we can conclude that isolation of *P. aeruginosa* in a patient with bronchiectasis should be taken seriously. We believe that eradication treatment according to guidelines will help reduce mortality from bronchiectasis worldwide. Surgery is still a treatment option in severe bronchiectasis, and lung transplantation may be life-saving in managing end-stage disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital with registration number 2016/08.

Informed Consent: Written informed consent was not taken because of retrospective design.

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