

# The influence of comorbidities on mortality in bronchiectasis: A prospective, observational study

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## Abstract

**Background.** Bronchiectasis is a progressive chronic disease associated with an increased risk of mortality.

**Objectives.** To identify the prevalence of comorbidities in patients with bronchiectasis and the impact of these comorbidities on mortality.

**Materials and methods.** A cohort of 93 patients with computed tomography (CT)-confirmed bronchiectasis admitted consecutively to a tertiary teaching hospital was observed over a period of 5 years. All patients were carefully observed for comorbidities and mortality.

**Results.** A total of 43 men (46.2%) and 50 women (53.8%) with a median age of 66.0 years (interquartile range (IQR) 59.7–74.0 years), and a median of 3 comorbidities at baseline (IQR 1–5) were observed. The mortality rate during the observation period was 16%. The median number of comorbidities was significantly higher in the group of non-survivors (5 (IQR 3–5.75)) compared with survivors (3 (IQR 1–4);  $p = 0.0100$ ). The burden of comorbidities was associated with an increased hazard of death: having 4 or more comorbidities was associated with an increased risk of death compared to patients with 2 or 3 coexisting illnesses (hazard ratio (HR) = 1.35 (95% confidence interval (95% CI) [0.41, 4.41]);  $p = 0.0494$ ). The Bronchiectasis Aetiology Comorbidity Index (BACI) was a significant predictor of death in patients with severe bronchiectasis.

**Conclusions.** We found a significant number of comorbidities in patients with bronchiectasis. In these patients, the comorbidity burden has an impact on mortality. The BACI is a useful tool for the clinical assessment of patients with severe bronchiectasis.

**Key words:** survival, bronchiectasis, comorbidities, mortality

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## Background

Bronchiectasis is a progressive chronic disease associated with an increased risk of mortality. In recent years, several prospective studies assessing the survival of patients with non-cystic fibrosis (CF) bronchiectasis have been conducted. A Turkish study found a 16.3% mortality rate during 4 years of follow-up.<sup>1</sup> In the UK, the mortality rate was 29.7% during 13 years of follow-up,<sup>2</sup> and a single-center study in Belgium found a mortality rate of 20.4% after 5.18 years of follow-up.<sup>3</sup>

Subsequently, multicenter studies assessing factors affecting mortality allowed for the preparation of complex tools that help in estimating the risk of death. The FACED (FEV1, age, *Pseudomonas aeruginosa* colonisation, radiological extension, and dyspnoea) score<sup>4</sup> and the Bronchiectasis Severity Index (BSI)<sup>5</sup> were thus generated, and they have proven to be clinically helpful in assessing the individual risk of death. Recently, the attention has also been directed to the impact of another factor that significantly affects the prognosis of bronchiectasis patients: comorbidities. The occurrence of cardiovascular disease (CVD),<sup>6</sup> infections or kidney diseases,<sup>7</sup> and rheumatological diseases<sup>8</sup> increase the mortality of patients with bronchiectasis.

The multiple comorbidities that are frequent in bronchiectasis patients and can negatively affect survival, prompted McDonnell et al. to develop the Bronchiectasis Aetiology Comorbidity Index (BACI), a new tool prepared to assess the individual risk of mortality.<sup>9</sup>

However, studies assessing the impact of comorbidities on the mortality of bronchiectasis patients are still scarce. Further research is needed, particularly regarding the validation of existing clinical prediction scores in independent prospective studies.

## Objectives

In this observational study, our aim was to identify the prevalence of comorbidities in patients with bronchiectasis and the impact of these comorbidities on mortality.

## Materials and methods

This study was performed in the tertiary teaching hospital. We designed an observational, prospective study involving a Polish center specialized in the treatment of patients with non-CF bronchiectasis. During the five-year study (2015–2019), 100 consecutive patients aged  $\geq 18$  years with a confirmed diagnosis of non-CF bronchiectasis were enrolled.

Before being included in the study, all study participants signed a consent to participate in the study. The study protocol was reviewed and approved by the research ethics committee of the Institute of Tuberculosis and Lung Diseases in Warszawa, Poland. All procedures involving

human participants and the written consent submitted by participants followed the scientific ethical standards of the 1964 Declaration of Helsinki and its later amendments.

All patients were assessed according to the current guidelines of the British Thoracic Society (BTS) and the European Respiratory Society (ERS). The diagnosis of bronchiectasis was based on high-resolution computed tomography (HRCT) scans performed prior to the study.<sup>10</sup> Patients with CF were not included. All participants were carefully examined for comorbidities. Comorbidity was defined as a disease coexisting with the primary disease of interest, as suggested by Sin et al.<sup>11</sup> Diagnoses were made by a group of respiratory and internal medicine specialists and were established following the current relevant international guidelines. Diseases that resolved completely during the hospital stay were excluded from the assessment. The list of diagnoses for each patient, including comorbidities, was recorded in an electronic database.

The diseases were counted and grouped into typical comorbidity groups, as proposed by Charlson et al. investigating comorbidities in respiratory medicine.<sup>12</sup>

The BACI was calculated as proposed by McDonnell et al.<sup>9</sup> For the assessment of comorbidities, all physicians were free to review the patients' medical files and to order any additional tests, including radiology and biochemistry tests.

## Statistical analyses

Results are expressed as a median quartile range, as numbers, and as relative frequency (n, %). Dichotomous variables were compared using the  $\chi^2$  test. The Kolmogorov–Smirnov test was used to check the normality of variable distribution. As the presented data did not meet the assumptions for the parametric tests, the Mann–Whitney U test was used to test the differences between the dichotomous groups, and the Kruskal–Wallis test was used to compare more than 2 groups. Survival analysis was performed with the Kaplan–Meier estimate. The log-rank test with post hoc Bonferroni correction was used for comparisons of the survival curves. Results were considered to be statistically significant at  $p < 0.05$ . The Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) recommendations for observational studies were followed during protocol preparation.<sup>13</sup> All statistical calculations were performed with MedCalc software v. 19.1.6 (MedCalc, Ostend, Belgium).

## Results

### Characteristics of the group and comorbidities

Initially, 100 unselected consecutive patients with confirmed non-CF bronchiectasis were enrolled in the study.

From this group, 7 patients were excluded due to a lack of proper written consent, being lost to follow-up, or due to the withdrawal of consent during the observation period. Mortality was evaluated in the remaining patients at the end of the five-year follow-up period. The final assessment included a group of 93 patients: 43 men (46.2%) and 50 women (53.8%) with a median age of 66.0 (59.7–74.0) years.

**Table 1.** Characteristics of the study group. The data are reported as median with interquartile range (IQR) or number with prevalence

Demographics	Cohort (n = 93)
Age [years]	66.0 (59.7–74.0)
Female sex, n (%)	50 (53.8)
BMI [kg/m <sup>2</sup> ]	25.9 (21.9–29.6)
Ex-smokers, n (%)	47 (50.5)
Current smokers, n (%)	15 (16.1)
Never smokers, n (%)	31 (33.3)
Etiology	
ABPA, n (%)	1 (1.1)
Alpha1 antitrypsin deficiency, n (%)	1 (1.1)
Asthma, n (%)	2 (2.2)
COPD, n (%)	6 (6.5)
Idiopathic, n (%)	56 (60.2)
IgG subclass deficiency, n (%)	1 (1.1)
Mounier–Kuhn syndrome, n (%)	1 (1.1)
Nontuberculous mycobacteria, n (%)	2 (2.2)
Postinfective, n (%)	11 (11.8)
Post-tuberculous, n (%)	9 (9.7)
Primary ciliary dyskinesia, n (%)	1 (1.1)
Yellow nail syndrome, n (%)	2 (2.2)
BSI score risk class	
Mild, n (%)	28 (30.1)
Moderate, n (%)	28 (30.1)
Severe, n (%)	37 (39.8)
Clinical status	
Sputum volume [mL/day]	10 (10–20)
MRC dyspnea score [points]	2 (1–2)
Exacerbations not requiring secondary care in the previous year, n	1 (0–2)
At least 1 hospitalization in the previous year, n (%)	46 (49.5)
Functional status	
FEV <sub>1</sub> , % predicted	79.8 (53.7–98.6)
Microbiology	
<i>P. aeruginosa</i> infection, n (%)	12 (12.9)
Comorbidity burden	
Number of comorbidities at baseline, n	3 (1–5)
Number of comorbidities range, n	0–8

BMI – body mass index; COPD – chronic obstructive pulmonary disease; TB – tuberculosis; ABPA – allergic bronchopulmonary aspergillosis; BSI – bronchiectasis severity index; MRC – Medical Research Council; FEV<sub>1</sub> – forced expiratory volume in 1 s; *P. aeruginosa* – *Pseudomonas aeruginosa*; IgG – immunoglobulin G.

**Table 2.** Most prevalent comorbidities in the study group

Comorbidity	Number of patients	Prevalence (%)
Cardiovascular diseases	61	65.5
COPD	48	51.6
Hypertension	32	34.4
Asthma	25	26.9
Obesity	22	23.6
Coronary heart disease	18	19.4
Diabetes	16	17.2
Cancer/neoplasm	12	12.9
Congestive heart failure	12	12.9
Chronic respiratory failure	11	11.8
Osteoporosis	9	9.7
Tuberculosis in anamnesis	9	9.7
Chronic atrial fibrillation	8	8.6
Pulmonary hypertension	7	7.5
Anxiety/depression	7	7.5
Anemia	5	5.4
Chronic renal disease	4	4.3
Liver cirrhosis	3	3.2
Other arrhythmia	2	2.2
Aortic aneurysm	1	1.1
Sarcoidosis	1	1.1

COPD – chronic obstructive pulmonary disease.

The anthropometric data and comorbidities of the patients are shown in Table 1 and Table 2, respectively.

The group consisted predominantly of middle-aged Caucasians with a median forced expiratory volume in 1 s (FEV<sub>1</sub>) predicted of 79.8% (53.7–98.6%). The 3 BSI groups were evenly represented: 28 (30.1%) patients displayed mild bronchiectasis, 28 (30.1%) had moderate symptoms and 37 patients (39.8%) had severe symptoms. Bronchiectasis was considered idiopathic in most of the patients (60.2%), but it was classified as post-tuberculosis bronchiectasis in 9.7% of patients. Other, less common causes of bronchiectasis were identified in the remaining patients.

Half of the patients required hospital treatment in the previous year. Twelve patients (12.9%) were chronically colonized with *Pseudomonas aeruginosa*. The median number of comorbidities at baseline in the whole group was 3 (interquartile range (IQR) 1–5).

## Mortality

The total observation period in our group was 50 months, but because patients were enrolled consecutively in the study, the median follow-up period for the whole group was 31.0 (IQR 18.5–42.0) months. During the observation period, 15 patients died (16.1%). The median survival period in non-survivors was 14.0 (IQR 5.2–23.0) months, with a range of 2.0–46.0 months. The median follow-up

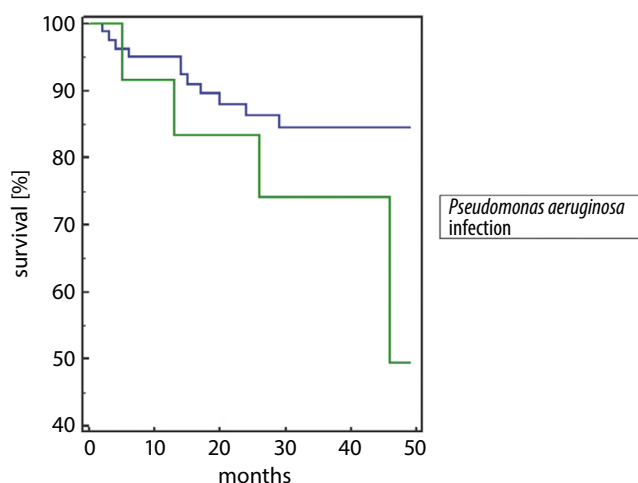


Fig. 1. Kaplan–Meier survival curves demonstrating the survival of patients with non-cystic fibrosis bronchiectasis, with and without *Pseudomonas aeruginosa* infection

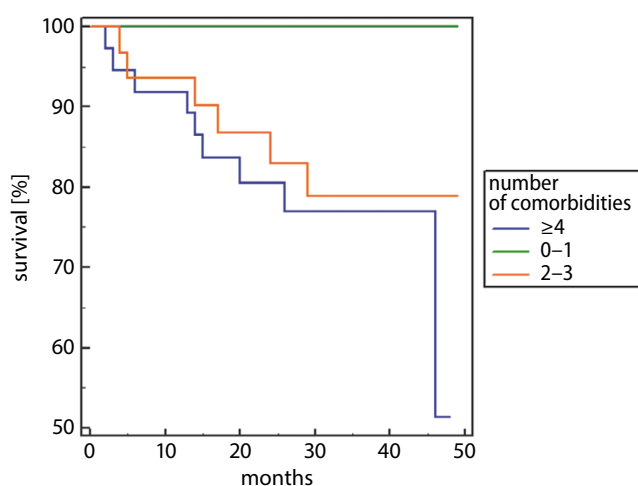


Fig. 2. Kaplan–Meier survival curve showing the survival rates of bronchiectasis patients with different number of comorbidities

for the survivors was 33.0 (IQR 23.0–43.0) months, with a range of 2.0–49.0 months.

The Kaplan–Meier survival curves for the whole group are shown in Fig. 1. The survival curves of patients colonized with *P. aeruginosa* and those not colonized are shown separately because the colonization by *P. aeruginosa* is known to affect the survival.

The number of patients who tested positive for *P. aeruginosa* was small ( $n = 12$ , 12.9%), and the comparison of survival curves between infected and non-infected patients showed that the difference was not statistically significant ( $p = 0.1586$ , log-rank test,  $\chi^2 = 1.9878$ ). The hazard ratio (HR) for death in the group with *P. aeruginosa* infection was 2.86 (95% confidence interval (95% CI) [0.66, 12.35]) when compared with the group without *P. aeruginosa* infections.

The median number of comorbidities was significantly higher in the group of non-survivors (5 (IQR 3–5.75)) than in the group of survivors (3 (IQR 1–4);  $p = 0.0100$ , Mann–Whitney U test,  $U = 341.5$ ).

Although the total number of deaths was relatively low, and therefore comparisons are difficult, the burden of comorbidities was associated with an increased hazard of death. Having 4 or more comorbidities was associated with an increased risk of death (HR = 1.35 (95% CI [0.41, 4.41])) compared with patients with 2 or 3 coexisting illnesses ( $p = 0.0494$ ; for HR test, Fig. 2).

## BSI and BACI scores

The comparison of the patients' survival curves, grouped according to the BSI score risk classes did not show statistically significant differences between the groups ( $p = 0.9682$ , log-rank test,  $\chi^2 = 0.0645$ ). During the observation period, 15 patients died. In this group of non-survivors, 4 patients had a BSI score in the range of 0–4 points, 4 patients in the range of 5–8 points and 7 patients had a score over 9 points. The death HR for patients with a BSI score in the range of 0–4 points was similar to that of patients with a BSI score of more than 9 points (HR = 1.16 (95% CI [0.34, 3.91]);  $p = 0.9176$ ; for HR test (Fig. 3)).

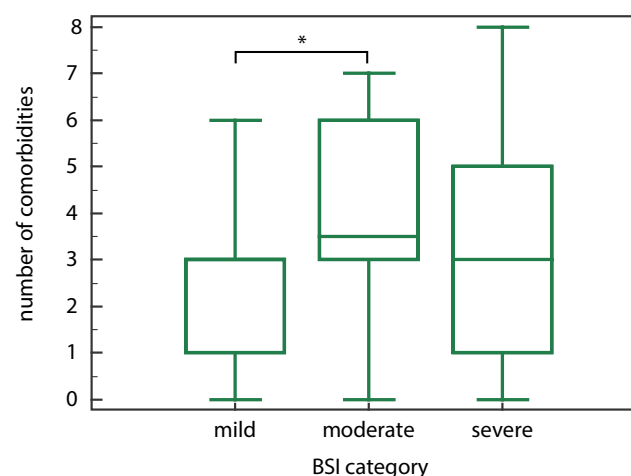
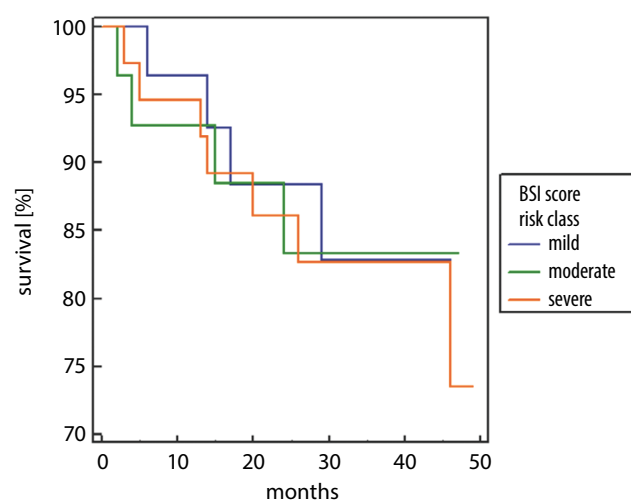


Fig. 3. A. Kaplan–Meier survival curves showing the probability of survival in bronchiectasis patients grouped according to the Bronchiectasis Severity Index (BSI) risk classes; B. The number of comorbidities against the Bronchiectasis Severity Index (BSI) risk classes. The asterisk indicates a statistically significant difference between the groups joined by the line

A significant, although moderate relationship was observed between the median number of comorbidities and the BSI score. Patients with a BSI score in the “moderate” category had a statistically significantly higher number of comorbidities than patients with a BSI score in the “mild” category ( $p = 0.0367$ , Kruskal–Wallis test) (Fig. 3, Supplementary Table 1).

The BACI index classes were analyzed across the survival data. While a high risk BACI score suggested an increased risk of death, this parameter did not reach statistical significance while considering the whole study group ( $HR = 1.69$  (95% CI [0.24, 11.62]);  $p = 0.4352$  for HR test). However, when the analysis of the BACI index classes was conducted in the group of patients with the most severe bronchiectasis symptoms (BSI severe class), the BACI was found to be a significant predictor of death ( $HR = 7.5$  (95% CI [1.57, 36.29]);  $p = 0.0433$  for HR test) (Fig. 4).

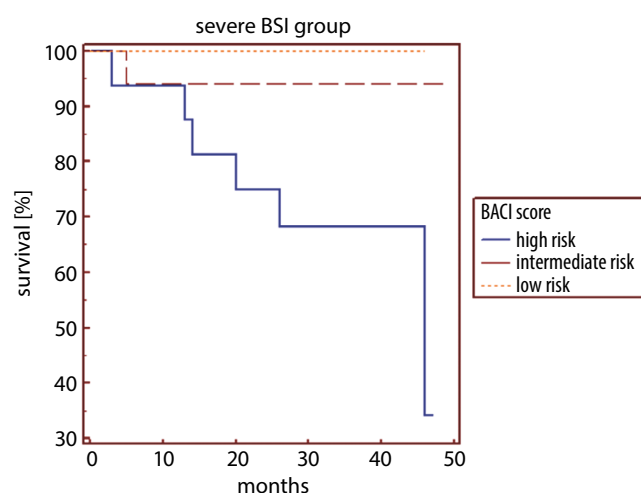


Fig. 4. Kaplan–Meier survival curve showing patient survival against the Bronchiectasis Aetiology Comorbidity Index (BACI) risk classes in the group of patients with severe Bronchiectasis Severity Index (BSI)

## Discussion

The 1<sup>st</sup> and main finding from this single-center longitudinal prospective study was the impact of the comorbidity burden on mortality in non-CF bronchiectasis. The 2<sup>nd</sup> finding was the usefulness of the BACI in the prognosis assessment of bronchiectasis patients, which agrees with the previous observations from a multicenter trial.<sup>9</sup> The 3<sup>rd</sup> finding was the usefulness of a simple counting of comorbidities in the prediction of the five-year mortality risk in bronchiectasis patients.

## Mortality in bronchiectasis

In our study, we found a 16% mortality rate over a 50-month follow-up period. These results are consistent with other studies. Onen et al. found that 16.3% of patients died during an observation period of 44.6 months. The survival rates they observed at 1, 2, 3, and 4 years were

97%, 89%, 76%, and 58%, respectively.<sup>1</sup> Loebinger et al. reported survival rates of 91% at 4 years, 83.5% at 8.8 years and 68.3% at 12.3 years.<sup>2</sup>

In a multicenter study by Chalmers et al., there were 62 deaths in over 4 years (10.2%) in a cohort of 608 patients. In another multicenter study, the overall mortality after 1, 2, 3, and 5 years of follow-up was 3.7%, 4.8%, 8.6%, and 12.4%, respectively.<sup>5</sup>

Our study was a single-center observational study. Therefore, before assessing our results in the context of mortality, we should evaluate whether our study group is similar to other described groups. Our group of patients is comparable to the abovementioned cohorts in terms of age, sex distribution, the etiology of bronchiectasis, and the functional respiratory parameters, such as FEV<sub>1</sub>% predicted. Numerous observational studies have reported that colonization with *P. aeruginosa* significantly affects the prognosis of bronchiectasis patients by increasing the mortality rate.<sup>9,14</sup> In our study, 12.9% of patients were colonized with *P. aeruginosa*, which is a slightly smaller percentage compared to other analyzed cohorts. For example, Chalmers et al. and Pasteur et al. reported a 20–40% prevalence of *P. aeruginosa* in UK cohorts.<sup>5,15</sup> We observed a possible effect of colonization by *P. aeruginosa*. However, the difference in survival rates between the colonized and non-colonized groups was not statistically significant. One reason for this could be the small size of the study group. Another possible explanation is the low percentage of colonized patients in our group, which could be due to geographical differences in the distribution of the microorganism.<sup>16</sup>

## The number and type of comorbidities

We found a significant number of comorbidities in the study group, with a significantly higher number in the group of non-survivors than in the group of survivors. This observation is consistent with the study by McDonnell et al.,<sup>9</sup> who reported that even a simple count of the number of comorbidities has some importance in estimating the risk of death in bronchiectasis patients. Moreover, we found that the risk of death increased significantly with the number of comorbidities: patients with 4 or more comorbidities had a 35% higher risk of death than patients with 2 or 3 comorbidities.

The number and type of comorbidities in our group of patients is consistent with those described by other research groups. The most frequent comorbidity in our patients was the CVD. It occurred in 65% of patients, which is similar to the previous observations by other research groups.<sup>17,18</sup> By analogy with chronic obstructive pulmonary disease (COPD), another important bronchial disease, the chronic inflammation in bronchiectasis could result in an increased risk of the CVD through the “spill-over” of inflammatory factors from the bronchial tree into the bloodstream.<sup>19</sup>

In our study, a significant percentage of patients with bronchiectasis were also diagnosed with COPD (51.6%).



There is an ongoing discussion regarding the relationship between COPD and bronchiectasis,<sup>20,21</sup> and statistical analyses sometimes give divergent results. In our study, the reason for the frequent coexistence of bronchiectasis and COPD may be local Polish conditions, which are linked to the socioeconomic factors. In Poland, diagnosing COPD allows doctors to prescribe cheaper drugs with better reimbursement for patients, thereby prompting doctors to diagnose COPD more often in patients with bronchiectasis.

The incidence of other comorbidities does not differ significantly from the observations of other researchers, both in retrospective and prospective studies.<sup>5,9</sup>

## Outcome prediction tools – BSI and BACI

We did not find any statistically significant relationship between the severity of bronchiectasis assessed with the BSI and an increased risk of death. Others have reported the BSI to be a good parameter to estimate the risk of death in bronchiectasis patients, but the analysis of the Kaplan–Meier curves in our study did not confirm these results. This may be due to the small size of our study group and the relatively low number of deaths we observed. It may also be a confirmation of the important role that comorbidities play in the increasing the risk of death in bronchiectasis patients. This observation seems to be confirmed by the BACI scale analysis.

Despite our small group size, we found that patients with severe bronchiectasis and high BACI classes had an increased risk of death compared to the patients with a severe BSI assessment but a lower number and severity of comorbidities. In our opinion, this confirms the usefulness of the BACI in the clinical assessment of patients with bronchiectasis.

## Limitations

This study was not designed as an epidemiological study. Therefore, the overall results of bronchiectasis mortality in our group should be assessed in the context of the study setting. Nevertheless, bronchiectasis requires a multi-dimensional assessment; coexisting illnesses should be carefully treated in all affected patients. New tools, such as the BSI, FACED and BACI, may prove useful for the clinical assessment of bronchiectasis patients.

## Conclusions

We found a significant number of comorbidities in patients with bronchiectasis. The comorbidity burden has an impact on mortality in patients with bronchiectasis. The Bronchiectasis Aetiology Comorbidity Index (BACI) is a useful tool for the clinical assessment of patients with severe bronchiectasis.

**Supplementary Table 1.** Number of comorbidities against severity of bronchiectasis expressed in Bronchiectasis Severity Index (BSI) results (mild, moderate, severe)

### A. Kruskal–Wallis test

Data	Number of comorbidities
Factor codes	BSI categories
Sample size	93

### B. Descriptive statistics

BSI category	n	Minimum	25 <sup>th</sup> percentile	Median	75 <sup>th</sup> percentile	Maximum
Mild	28	0.0000	1.000	3.000	3.000	6.000
Moderate	28	0.0000	3.000	3.500	6.000	7.000
Severe	37	0.0000	1.000	3.000	5.000	8.000

### C. Kruskal–Wallis test

Test statistic	6.4395
Corrected for ties	6.6088
Degrees of freedom (df)	2
Significance level	p = 0.036720

### D. Post hoc analysis (Conover)






BSI category	n	Average rank	Different (p < 0.05) from factor No.
Mild	28	37.93	(2)
Moderate	28	56.23	(1)
Severe	37	46.88	–

**Supplementary Table 2.** Comorbidities summary statistics in the whole group**A. Comorbidities summary**

Variable	Comorbidities, n
Sample size	93
Lowest value	0.0000
Highest value	8.0000
Arithmetic mean	3.2043
95% confidence interval (95% CI) for the arithmetic mean	[2.7764, 3.6322]
Median	3.0000
95% CI for the median	[3.0000, 3.0000]
Variance	4.3165
Standard deviation (SD)	2.0776
Relative standard deviation	0.6484 (64.84%)
Standard error of the mean (SEM)	0.2154
Coefficient of skewness	0.2710 (p = 0.2685)
Coefficient of kurtosis	−0.7375 (p = 0.0348)
Kolmogorov–Smirnov test <sup>a</sup> for normal distribution	D = 0.1521 reject normality (p < 0.0001)

<sup>a</sup> Lilliefors significance correction.**B. Distribution of the number of comorbidities**

Percentiles	Median number of comorbidities	95% confidence interval (95% CI)
2.5	0.0000	–
5	0.0000	[0.0000, 0.6356]
10	0.8000	[0.0000, 1.0000]
25	1.0000	[1.0000, 2.0000]
75	5.0000	[4.0000, 6.0000]
90	6.0000	[6.0000, 7.0000]
95	6.8500	[6.0000, 8.0000]
97.5	7.1750	–

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