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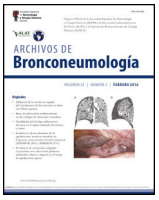

Scientific Letters

Factors Associated With One-Year Mortality in Hospitalised Patients With Exacerbated Bronchiectasis

To the Director,

Non-cystic fibrosis bronchiectasis is characterised by a chronic pathologic dilation of the bronchi and bronchioles. The condition results from a cycle of inflammation, infections causing structural damage, and recurrent exacerbations.[1] Severe and frequent exacerbations are associated with worse quality of life and respiratory function, more hospital admissions, higher mortality and increased economic burden. The mean annual hospitalisation rate per patient ranges between 0.3 and 1.3, whilst the mean annual age-adjusted hospitalisation rate varies between 1.8 and 25.7 per 100,000 inhabitants. Hospitalisation costs are the leading driver behind the economic burden caused by bronchiectasis.[2]

Previous studies have reported that survival rates of patients with bronchiectasis were 97%, 89%, 76% and 58% at 1-, 2-, 3- and 4-year follow-up timepoints, respectively. The mean survival time was 44.06 ± 1.6 months. Mortality for both males and females with bronchiectasis is more than twice that of the general population, independent of age (the age-adjusted mortality rate for males and females with bronchiectasis was 1437.7 and 1914.6 per 100,000, respectively).[3]

Currently, there is a lack of information about the factors associated with mortality after hospitalisation due to exacerbated bronchiectasis. Several factors may contribute to negative clinical outcomes in this series of patients. Neutrophil-to-lymphocyte ratio (NLR) and absolute neutrophil count may be viable biomarkers to show acute exacerbations.[4] Male sex, elevated creatinine, decreased forced expiratory volume in the first second (FEV_1%) predicted, mechanical ventilation, smoking history and acute use of systemic steroids during hospitalisation have been associated with an increased risk of mortality.[5] However, no clear predictors have yet to be identified.

The aim of this study was to evaluate the association between mortality, and clinical and microbiologic characteristics of patients with severe exacerbation of bronchiectasis during a one-year period.

We conducted a prospective observational study at two university hospitals in Spain (Hospital Clínic in Barcelona and Hospital Universitario y Politécnico La Fe in Valencia) between 2011 and 2015 (local ethics committees: Hospital Clínic, Barcelona N° 2013/8071; Hospital Universitario y Politécnico La Fe, Valencia N° 2011/0342). The study was carried out according to the principles set forth by the Declaration of Helsinki. We included consecutive adult patients (aged > 18 years) admitted to hospital for an exacerbation of bronchiectasis.[6,7] The attending physician in the emergency department determined the need for hospital admission based on the presence or absence of acute clinical, analytical and radiographic findings.

The main inclusion criteria were a clinical history compatible with bronchiectasis and confirmed diagnosis by high-resolution computerised tomography (CT) scan before recruitment. Disease aetiology was established according to Spanish guidelines.[8]

We applied the following exclusion criteria: (a) diagnosis of cystic fibrosis, ciliary dyskinesia, pulmonary interstitial diseases, active tuberculosis or non-tuberculosis mycobacterial infection during treatment; (b) exacerbation of any comorbidity; and (c) participation in any clinical trial that included changes in pharmacologic treatment within the preceding six months. All enrolled patients were required to provide written informed consent.

We collected clinical and demographic data, including information about smoking habits, comorbidities, vaccine status, previous chronic infections, number of exacerbations and hospitalisations due to bronchiectasis in the previous year, lobes affected on CT, chronic medication, and bronchiectasis severity scores.

Microbiologic diagnoses, as well as sputum cultures for bacterial, fungal and mycobacterial pathogens, were performed within the first 24 h of the exacerbation. Laboratory tests were reported at days 1 and 5 of hospitalisation. We also recorded length of hospital stay, intensive care unit (ICU) admission, invasive and non-invasive mechanical ventilation (NIV), septic shock, severe sepsis and complications. All surviving patients underwent a 1-year follow-up after hospital discharge for mortality assessment purposes.

Descriptive statistics were used for basic features of study data, and appropriate statistical tests were performed to compare groups. Cox proportional hazard regression analyses were done to examine factors associated with 1-year mortality in hospitalised patients with bronchiectasis.

We enrolled 185 hospitalised patients with bronchiectasis (94 females, 71.8 ± 11.8 years, 66.5% Bronchiectasis Severity Index, BSI, stage severe). Twenty-three (12.4%) patients died during the 1-year follow up. The major causes of death were respiratory-related (68%), cardiovascular (18%) and septic shock (14%). Compared to survivors, non-survivors showed a greater number of hospitalisations in the previous year, more comorbidities, more severe BSI scores and a higher incidence of NIV during hospitalisation.

At 1-year follow-up, non-survivors presented a significantly higher NLR at days 1 and 5 than those who survived. Univariable analyses were performed to assess the main characteristics of patients who died during the year following hospitalisation; several variables were significantly associated with 1-year

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Table 1
Significant univariable and multivariable Cox regression analyses of factors associated with 90-day mortality in hospitalised patients with bronchiectasis.

Variable	Univariable[a]			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex (male)	2.45	1.01–5.95	0.048	–	–	–
Long-term oxygen therapy	2.90	1.23–6.84	0.015	–	–	–
Influenza vaccination	0.50	0.22–1.14	0.100	–	–	–
FACED severity[b]			0.071			–
Mild	1.00	–	–	–	–	–
Moderate	1.93	0.65–5.76	0.24	–	–	–
Severe	3.55	1.19–10.61	0.023	–	–	–
Neutrophil/Lymphocyte ratio at day 5 ≥6.95[c]	4.34	1.61–11.69	0.004	3.842	1.41–10.48	0.009
Previous hospitalisation (due to BE)	2.71	1.11–6.59	0.028	2.494	1.02–6.11	0.045
Complication: NIV	16.22	5.42–48.49	<0.001	13.246	4.25–41.24	<0.001
Complication: Intubation/MV	5.90	0.79–43.97	0.083	–	–	–

Abbreviations: BE: bronchiectasis; CI: confidence interval; FACED: Forced expiratory volume in 1 s (FEV1); Age; Chronic colonisation; Extension; and Dyspnoea; HR: hazard ratio; MV: mechanical ventilation; NIV: non-invasive ventilation. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 90-day mortality group. The HR is defined as the ratio of the hazard rates corresponding to the conditions described by two levels of an explanatory variable (the hazard rate is the risk of death; given that the patient has survived up to a specific time). The *p*-value is based on the null hypothesis that all HRs relating to an explanatory variable equal unity (no effect).

[a] The variables analysed univariately were age, sex, smoking habit, influenza vaccination, pneumococcal vaccination, primary aetiology, long-term oxygen therapy, exacerbations in last year, pneumonia episodes in last year, previous hospitalisation (due to BE) in the last year, FACED severity, place of initial treatment during acute episode, acute episode severity, polymicrobial *Pseudomonas aeruginosa*, number initial antibiotic treatment, poor response or clinical deterioration, correct initial treatment, complication: Intubation/MV, complication: NIV, complication: severe sepsis, complication: septic shock, complication: acute myocardial infarction, complication: atrial fibrillation/arrhythmia, neutrophil/lymphocyte ratio at day 5.

[b] The *p*-value corresponds to differences amongst the three groups (mild, moderate or severe).

[c] Optimal cut-off value to predict 90-day mortality, using ROC curves.

mortality. However, when all variables with a *p*-value < 0.2 in the univariable analyses were placed in the multivariable model (backward stepwise selection model), only three factors remained independently associated with mortality, including: NLR at day 5 ≥6.95 (HR 3.84 (95% CI 1.41–10.48)); previous hospitalisation (due to bronchiectasis) (HR 2.49 (95% CI 1.02–6.11)); and the need for NIV during hospitalisation (HR 13.25 (95% CI 4.25–41.24)) (Table 1).

For patients admitted to ICU due to exacerbated bronchiectasis, one-year mortality in our study was lower than that reported by Dupont et al. (40%)[9] and Alzeer et al. (34%).[10] This difference in findings is explainable, given that our patients were predominantly admitted to hospital ward and only seven required ICU admission.

In this study, we also found that NLR at day 5 ≥6.95 was associated with increased mortality. In previous studies, NLR has been shown to be a possible biomarker of airway inflammation in cases of bronchiectasis. Nacaroglu HT et al.[4] demonstrated that leucocyte, platelet and absolute neutrophil count, as well as NLR can be used to show chronic inflammation in bronchiectasis. However, only NLR and absolute neutrophil count are possible, viable biomarkers to show acute exacerbations. Furthermore, Georgakopoulou VE et al.[11] reported that NLR can be used to predict positive cultures in patients with bronchiectasis exacerbation. To the best of our knowledge, this is the first study to evaluate the role of NLR in predicting 1-year mortality in hospitalised patients with bronchiectasis. As NLR could serve as a biomarker of chronic inflammation in bronchiectasis, it could also prove useful in identifying a more severe pathology.

Previous studies have demonstrated that history of hospitalisations increase the risk of both further hospital admission due to bronchiectasis exacerbation and in-hospital mortality.[12] In our study, non-survivor patients presented almost one hospitalisation in the previous year compared to survivors. Greater systemic inflammation was observed during day 1 of hospitalisation, perhaps contributing to perpetuating the infection-inflammation cycle and incurring a negative effect on prognosis.[13]

Although admission to the ICU is unusual in patients with bronchiectasis, it is becoming increasingly frequent. As shown by Navaratnam et al.,[14] it carries a substantial mortality rate. Our model found that the need for NIV during hospitalisation was associated with an increased risk of mortality, contrasting with a study by Benhamou et al. wherein the multivariable analysis showed that the survival rate was not correlated with NIV treatment.[15] On the other hand, MV was not associated with mortality in our study. A possible explanation for this result is the small number of patients who died during the 1-year follow-up.

In conclusion, our pilot study aims to define factors associated with mortality after hospital admission due to an exacerbated bronchiectasis. This study may also provide a starting point for improving management of this disease, better establishing the role of mechanical ventilation during care. Similar yet larger studies are needed to identify clear predictors for mortality in cases of exacerbations of bronchiectasis.

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Conflict of interest

The authors have no conflicts of interest to declare.

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G. Scioscia [a,1], V. Alcaraz-Serrano [b,1], R. Méndez [c], A. Gabarrús [d], L. Fernández-Barat [d], R. Menéndez [c], P. Tondo [a], L. Bueno [d], A. Torres [d,e,*]

[a] *Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy*
[b] *Fundació Clínic per la Recerca Biomèdica (Hospital Clínic de Barcelona), Facultat Ciències de la Salut Blanquerna – Universitat Ramon Llull, Barcelona, Institut de Salut Global de Barcelona (ISGlobal), Spain*
[c] *Pneumology Department, La Fe University and Polytechnic Hospital, La Fe Health Research Institute, Valencia, Spain*
[d] *Fundació Clínic per la Recerca Biomèdica (FCRB), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Biomedical Research Networking Center on Respiratory Diseases (CIBERES), Hospital Clínic of Barcelona, Barcelona, Spain*
[e] *Institute of Respiratory Disease, Hospital Clínic of Barcelona, Barcelona, Spain*

Corresponding author.
E-mail address: atorres@clinic.cat (A. Torres).
[1] Co-first authors.