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Study Title:

Comorbidities and the risk of mortality in patients with bronchiectasis: an international cohort study

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Running head: Comorbidity index predicting outcomes in bronchiectasis

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Research in context

Evidence before this study

There is limited literature available on the prevalence and impact of comorbidities on mortality and other disease-related outcomes in bronchiectasis.

Added value of this study

In this study, we have confirmed that patients with bronchiectasis are frequently afflicted by comorbidities which may drive disease, many of which confer an independent risk of death and may be missed unless specifically searched for. We have developed a quantitative risk stratification tool, the Bronchiectasis Aetiology and Comorbidity Index (BACI) from a large multicentre derivation cohort of 986 bronchiectasis patients with validation in two independent cohorts with 5 and 19 years of follow-up. Our data demonstrate that measurements of comorbidities as captured by the BACI improve the prognostic accuracy for mortality, when used independently, or in conjunction with the Bronchiectasis Severity Index (BSI), to identify patients at risk of future mortality, hospitalisations and exacerbations across different healthcare

systems. The BACI also carries independent prognostic value relating to future disease outcomes including future exacerbations, hospitalization for severe exacerbations and *Pseudomonas aeruginosa* infection. The BACI performs significantly better than any comorbidity scores currently available including the Charlson Comorbidity index and a simple comorbidity count suggesting that a disease-specific comorbidity score is useful in this patient population.

Implications of all the available evidence

The BACI may be a useful clinical predictive tool, when used independently, or in conjunction with the BSI, to risk-stratify patients and assist clinical decision making and personalised medicines approaches in bronchiectasis. The identification of "risky" comorbidities that may lead to stricter follow up of these patients may provide a practical viewpoint for clinicians beyond the BACI score calculation. Future interventions and treatment approaches should consider multiple comorbidities in these patients in order to maximise outcome and reduce the illness burden associated with this disease.

140 character summary: The Bronchiectasis Aetiology and Comorbidity Index (BACI) identifies patients at risk of future mortality, hospitalisations, exacerbations and other outcomes.

Abstract: (250 words)

Background: Patients with bronchiectasis often suffer from concurrent comorbidities but their nature, prevalence and impact on disease severity and outcome is poorly understood. We aimed to evaluate comorbidities in bronchiectasis patients and determine their prognostic value on disease severity and mortality.

Methods: An observational cohort analysis of 986 bronchiectasis patients across four European centres was performed for score derivation. Comorbidity diagnoses were based on standardised definitions obtained on full review of hard copy and electronic records, prescriptions and investigator definitions. Weibull parametric survival analysis was used to model the prediction of 5-year mortality to construct the Bronchiectasis Aetiology Comorbidity Index (BACI). We tested the BACI as a predictor of outcomes and explored whether the BACI added further prognostic information when used alongside the Bronchiectasis Severity Index (BSI).

Findings: Median number of comorbidities per patient was 4 (IQR 2-6), range 0-20. Thirteen comorbidities independently predicting mortality were integrated into the BACI. The overall hazard ratio for death conferred by a one point increase in the BACI was 1.18 (1.14-1.23), $p<0.0001$. The BACI predicted 5-year mortality, hospitalisations, exacerbations and health-related quality of life across all BSI risk strata ($p<0.0001$). When used in conjunction with the BSI, the combined model was superior to either model alone. The BACI was validated in two independent international cohorts.

Interpretation: Multimorbidity is frequent in bronchiectasis and can negatively influence survival. The BACI complements the BSI in assessing mortality and disease outcomes in patients with bronchiectasis.

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Introduction

Bronchiectasis is a chronic airway disease showing an increasing prevalence over the past decade with an associated growing morbidity and mortality worldwide.[1] As a complex multi-component disease, bronchiectasis is characterised by chronic systemic inflammation that frequently co-exists with comorbidities, which may be causative, synergistic, or coincidental, depending on the manner in which they interact.[2]

In addition to known aetiologies of bronchiectasis, several other diseases may occur at any stage of bronchiectasis and are likely major contributors to increased hospitalisations, healthcare utilisation and socioeconomic costs.[3] These include cardiovascular disorders, gastro-oesophageal reflux disease (GORD), psychological illnesses, pulmonary hypertension, cognitive impairment, and lung, oesophageal and hematological malignancies.[4-12] A few studies have explored bronchiectasis-related comorbidities and suggest that, compared with age and sex-matched controls, some comorbidities are more likely to coexist with bronchiectasis[4-12] with a relevant impact on different outcomes, such as exercise capacity,[4] exacerbation frequency,[6,8] lung function,[7,11] health-related quality of life,[6,8,9,11] healthcare utilisation,[8] and mortality.[10,12] Few studies have systematically evaluated the prevalence and role of comorbidities in bronchiectasis; several were performed in single centres with small patient numbers[4-6,10,11] or utilised retrospective databases or cross-sectional designs[7-9,12] limiting the applicability of their findings. However, none have systematically evaluated how comorbidities impact on prognosis in a prospective study.

It is suggested that individual comorbidities and aetiologies of bronchiectasis, such as chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (RA), confer an increased severity and mortality compared to other aetiologies despite targeted treatment of underlying conditions.[13,14] Recent literature has also shown that in approximately 30-40% of patients with bronchiectasis, the primary cause of death is attributed to non-respiratory disease.[15] However, current guidelines fail to provide clear recommendations on how comorbidities should be identified, assessed and treated

within the context of bronchiectasis. Neither of the two prognostic scoring indices recently developed to estimate mortality in patients with bronchiectasis (the bronchiectasis severity index – BSI- and the FACED score-see online supplement for calculation of scores) were planned to systematically evaluate the prevalence and role of comorbidities.[16,17]

In view of this lack of data, we designed a study which aimed to determine not only the prevalence of individual comorbidities in bronchiectasis patients but also the strength of association between the number and nature of comorbidities and risk of death over time. We further aimed to develop a disease-specific comorbidity index and explore if this could provide additional prognostic information to that provided by the BSI.

Our hypothesis was that multiple comorbidities would be a common finding acroos national cohorts, that these would contribute significantly to mortality and that it was practicable to apply a standardized assessment to assess the role of comorbities in the mortality of patients with bronchiectasis.

Methods

Data collection

This study included data from four databases of prospectively enrolled outpatients with bronchiectasis in Dundee (UK), Galway (Ireland), Leuven (Belgium) and Monza (Italy). Consecutive patients aged ≥18 years were enrolled on the basis of a radiological diagnosis made on high-resolution computed tomography (HRCT) and a clinical history consistent with bronchiectasis. Patients with cystic fibrosis or traction bronchiectasis due to pulmonary fibrosis were excluded in all four cohorts. Data from each cohort was collected independently following individual ethics approval and collated for statistical analysis. Standardised assessment and diagnostic work-up according to the 2010 British Thoracic Society (BTS) guidelines was

performed at each site as detailed in the online supplement. Enrolment into the study required that all variables required to calculate clinical prediction scores and the key relevant outcomes of mortality, hospitalisations and exacerbations on follow-up were available. Exacerbations and hospitalisations were defined according to BTS guidelines, and mortality, evaluated at the end of the 5-year follow-up period, was confirmed in 100% of participants.[18] This cohort is entirely independent from the cohorts used to derive the BSI or FACED scores.[16,17]

Comorbidities

All comorbidity diagnoses were systematically recorded according to standardised definitions and were retrospectively obtained on full review of hard copy or electronic records, patients' prescriptions and review of confirmatory tests where available. The 19 conditions included in the Charlson Comorbidity Index (CCI) were included in data collection *plus* any other identified comorbidity.[19] Conditions that had completely resolved, e.g. pneumonia, were excluded. Objective confirmation of diagnoses was sought in each case where possible. Self-reported diagnoses consisted of GORD, depression and anxiety as per standard practice internationally. Further details of comorbidity assessment are available in the online supplement.

Statistical Analysis and Derivation of Clinical Prediction Tool

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate, and categorical data as frequencies and percentages. The Mann Whitney U and chi-squared test were used for comparison of numerical and categorical data, respectively. For comparisons of more than two groups, one-way analysis of variance or the Kruskal-Wallis test were used as appropriate. Weibull parametric survival analysis was used to model the prediction of 5-year mortality. Three candidate comorbidity scores were considered and

compared to the CCI, BSI and FACED scores: (a) The Comorbidity count - a simple sum of the number of comorbidities per individual patient; (b) The Bronchiectasis Comorbidity Index (BCI) - a weighted comorbidity score without those conditions regarded as potential underlying aetiologies of bronchiectasis; (c) The Bronchiectasis Aetiology Comorbidity Index (BACI) - a weighted comorbidity score including conditions regarded as underlying aetiologies.

Based on Peduzzi's modelling, a maximum of 13 variables could be incorporated into the multivariable models in order to comply with statistical norms based on the number of outcomes in our cohort.[20] Comorbidities with <1% prevalence or those with significant collinearity were excluded. Variables were included in the model using a backward stepwise approach requiring a $p<0.2$ for retention in the model. All models were adjusted for age and gender. These variables were then formed into prediction tools using the rounded averaged β-coefficient to award "points" for each variable as previously described.[16] The sum of the points intends to capture the individual or combination of diseases affecting each patient. The performance of the resulting models for mortality was assessed using the area under the receiver operator characteristic curve (AUC) with the exception of the UK validation cohort which had a much longer follow up of 20 years, whereby Kaplan-Meier analysis was performed to avoid favoring fixed effects at the expense of modifiable risk factors that may increase short-term risk but not necessarily guarantee long-term risk. We subsequently tested the predictive ability of the optimal model to determine future disease outcomes using Spearman's rho correlation and explored if it could add further prognostic information when used alongside the BSI and FACED mortality index. Some endpoints, such as quality of life, were only available in 2 cohorts (Dundee and Monza). Such analyses were only conducted in patients with available data – no imputation or other methods of handling missing data were used. For all analyses, $p< 0.05$ was considered statistically significant. All analyses were performed using SPSS Version 21 (SPSS, Chicago, IL, USA) for Windows platform and Graph Pad Prism Version 5 (Graph Pad Software, Inc. San Diego, CA, USA). The reporting of this study conforms to STROBE and TRIPOD recommendations.[21 22]

Validation cohorts

The derived index was subsequently validated in two independent cohorts. One was a historical cohort of patients recruited for the validation of the SGRQ in bronchiectasis.[15] This cohort was selected as a prospective study with the longest duration of follow-up available in the literature to date, where data on comorbidities was systematically collected. The other validation cohort consisted of prospectively recruited bronchiectasis patients in Serbia in Eastern Europe, enabling further assessment of the generalisability of the score.

Role of the funding source

The funding source had no role in study design, data collection, analysis or interpretation or in the writing of the report. The corresponding and lead senior authors had full access to all of the data and the final responsibility to submit for publication."

Results

Characteristics of the cohort and comorbidities

The demographic and baseline characteristics of the 986 patients included in the analysis are summarised in Table 1 and are consistent with other published series in terms of older age, female predominance and bacterial colonisation rates. The cohort consisted primarily of Caucasian females with a median FEV_1% predicted of 75% (54-95) and a median FEV1/FVC% predicted of 70% (59-79) demonstrating moderate airflow limitation. The median BSI was 6 (4-10) and all BSI tertiles (mild, moderate and severe) were evenly represented. Mortality, n (%) at 1, 2, 3 and 5 years

of follow-up were 37 (3.7), 47 (4.8), 85 (8.6) and 122 (12.4), respectively. No patients received lung transplantation during follow-up.

A total of 81 comorbidities were reported in this cohort. The median (IQR) number of comorbidities was 4 (2-6) per subject for the whole cohort with a range of 0-20; males had significantly more co-morbidities than females, median 4 (2-6) for males and 3 (2-5) for females, p=0.005. . The median number of comorbidities was higher for non-survivors compared with survivors [6 (4-9) vs 3 (2-5) respectively, p<0.0001. A significant association was also observed between the median number of comorbidities and the BSI score (low risk: 3; intermediate risk: 3; high risk: 4; p<0.0001).

The distribution of the most prevalent (>1%) and significant comorbidities is shown in Figure 1. There is a heavy tailed distribution, ranging from 34% to less than 1%. 26 comorbidities had a significantly higher prevalence in non-survivors compared with survivors (the majority are shown here by the presence of asterisks in Figure 1 with full details in Table S1 in the online supplement).

Comorbidity scores

The Comorbidity Count

In its simplest form, the comorbidity count, i.e. the sum of the number of comorbidities per patient, was significantly associated with mortality, with a hazard ratio (HR) of 1.17, 95% CI 1.12-1.23 on univariate analysis, suggesting that an increase of 1 comorbidity in the count equates to a 17% increase in mortality. When adjusted for BSI, the HR (95% CI) was still significant at 1.13 (1.08-1.18).

The Bronchiectasis Aetiology Comorbidity Index (BACI)

The comorbidities included in the BACI are shown in Table 2. COPD, connective tissue disease, inflammatory bowel disease and asthma were all included in the final model predicting mortality

and are recognised aetiologies of bronchiectasis that may be associated with poorer outcomes. Overall, the HR (95% CI) for death conferred by a one-point increase in the BACI score was 1.18 (1.14-1.23), p<0.0001. Interestingly, this is higher than the adjusted HR for the BSI of 1.10 (1.06-1.14), p<0.0001 suggesting that the BACI has independent prognostic value comparable to the BSI.

The Bronchiectasis Comorbidity Index (BCI)

As a sensitivity analysis, we evaluated a model excluding the above conditions thought to be associated with bronchiectasis, producing similar results (Table S2 in online supplement). The HR for the BCI was comparable at 1.17 (1.12-1.23), confirming the importance of comorbidities in bronchiectasis prognosis.

Comparison of comorbidity scores to predict 5-year mortality

Comparative AUC (95% CI) scores for the BACI and BCI with the widely validated BSI can be seen in figure 2(a). The BACI has the highest overall predictive ability in this cohort to predict 5-year survival with an AUC score of 0.79 (0.75-0.83) *versus* 0.74 (0.69-0.78) for the BCI, 0.78 (0.73-0.84) for the BSI and 0.71 (0.66-0.75) for the FACED score, respectively. The CC and CCI (figure 2(b)) showed AUC scores of 0.72 (0.67-0.76) and 0.74 (0.69-0.78) respectively, which were inferior to the BACI (p=0.0001 on comparing AUC values), suggesting that a specific comorbidity index for bronchiectasis is appropriate.

The BACI performed consistently better than all scores in predicting 2, 3 and 5-year mortality in this cohort, with AUC scores of 0.75, 0.76 and 0.79 respectively, indicating that the score works similarly for annual prediction as for longer term prediction.

The AUC was used to identify the level of the BACI with the greatest predictive value for death in patients with bronchiectasis. Patients were classified into tertiles designated no high-risk comorbidities (for patients with a score of zero, n=402), intermediate risk comorbidities (for

patients with ≥1 and <6 points, n=398) and high-risk comorbidities (for patients with a score ≥ 6 points, n=186). The relationship between these risk groups and mortality and morbidity are shown in Figure 3.

The sensitivity and specificity values for the BACI, BCI and the BSI are shown in table 3.

The BACI, BSI and mortality

Comparable with previous studies, the BSI was a significant predictor of death in patients with bronchiectasis. To demonstrate the predictive contribution of the BACI to the BSI, Kaplan-Meier survival curves of the BACI groups stratified according to BSI severity are shown in Figure 4. All between group comparisons were statistically significant at $p<0.001$.

A prediction model incorporating both the BSI and the BACI was superior to either model alone for the prediction of 5-year mortality in this cohort with an AUC (95% CI) of 0.83 (0.79-0.87).

The BACI and other disease outcomes

Significant correlations of the BACI with a number of baseline demographic variables and important clinical outcomes were noted. The BACI correlated with both the BSI and FACED disease severity scores as well as lung function, radiological scores, dyspnoea scores, prior exacerbations and hospitalisations. Of note, it also predicts subsequent exacerbations and hospitalisations on follow-up and is independently correlated with *Pseudomonas aeruginosa* colonisation, offering further predictive potential in the clinical setting and suggesting that co-morbidities directly influence pulmonary outcomes (Table 4).

Independent validation cohorts

The Serbian validation cohort consisted of 113 patients, mean age 62 years (13) at diagnosis, 70% female. 5-year mortality was 17.7%. The AUC for predicting 5 year mortality in the Serbian cohort was 0.74 (95% CI 0.63-0.86). The UK validation cohort included 88 patients, mean age (SD) 51 years (12.1) at enrolment, with 57% female. Mortality at 20 years was 40.9%. The BACI was significantly associated with mortality at 20 years, p=0.004 (Kaplan-Meier), (figure 5).

Discussion

The present study is the first multicentre international observational study to systematically describe the prevalence and associations of comorbidities on mortality in patients with bronchiectasis. A new disease-specific comorbidity risk index (the BACI) was derived to help predict which patients with bronchiectasis are at increased risk of death independently of their baseline physiological state. The BACI accurately stratified the risk of mortality and hospitalisations whilst demonstrating that comorbidities contribute to exacerbation frequency and impaired quality of life. The BACI may be a useful clinical predictive tool, when used independently, or in conjunction with the BSI, to risk-stratify patients and assist clinical decision making and personalised medicines approaches in bronchiectasis.

This is one of the largest cohort studies performed to date in bronchiectasis and is in keeping with other studies in bronchiectasis and other comorbidity derivation tools. In bronchiectasis, the BSI and FACED consisted of 608 and 397 patients respectively in their derivation cohorts.[16,17] The Charlson Comorbidity Index, which is perhaps one of the most widely utilised comorbidity assessment tools worldwide, consisted of 604 patients in their derivation cohort.[19] Therefore, our sample size of 986 is more than adequate to derive this score.

Most respiratory diseases have disease-specific assessment tools, designed to identify patients at high risk of complications who may benefit from early treatment intensification. There is accumulating evidence that patients with bronchiectasis, similar to COPD, are prone to develop other important diseases, over and above what can be expected in an age and sex-matched general population, including cardiovascular disease, pulmonary hypertension and lung cancer, among others.[4,10,12] With bronchiectasis, there is a "double hit" as many patients may already have an underlying aetiology that led to the development of bronchiectasis, potentially increasing the likelihood of developing further complications. For example, patients with rheumatoid arthritis and bronchiectasis may be receiving immunosuppressive treatments that increase the likelihood of complications, or patients with COPD-associated bronchiectasis may be at increased risk of lung cancer due to synergistic effects of airway inflammation and smoking.[23]

Systemic inflammation has been proposed as a potential explanation of the mechanistic pathway relating bronchiectasis with its comorbidities, in part due to the ageing process, which is strongly associated with an increased likelihood of developing multiple chronic conditions.[24] The association between biomarkers of systemic inflammation and outcomes in bronchiectasis, including comorbidities, has not been well documented. In COPD, studies have demonstrated that elevated baseline inflammatory markers are associated with an increased risk of myocardial infarction, diabetes mellitus, lung cancer and pneumonia with the "inflamed comorbids" having the lowest survival in COPD populations.[25] Addressing this knowledge gap may allow us to identify pathway-specific treatment targets that could be beneficial in the treatment of multi-diseased bronchiectasis patients. Statins and macrolides have both been shown in randomised controlled trials to modify disease prognosis and improve clinical outcomes in bronchiectasis, owing to their anti-inflammatory effects; the development of new selective anti-inflammatory agents may hold promise for the future.[26,27]

A total of 81 different comorbidities were identified during the 5-year follow-up of these patients. As expected, not all comorbidities were equally prevalent and there were highly varying strengths of association with mortality. Healthcare providers are often limited in their assessment of patients due to time constraints and high patient numbers, therefore guidance that could identify comorbidities at highest risk of worse outcomes could optimise patient care. Our results show that, of the 81 comorbidities identified, 26 differed significantly between survivors and non-survivors. This is far higher than the 15 identified in the derivation of the CO-morbidity TEst (COTE) in COPD.[28] The 13 comorbidities associated with the highest risk of death on multivariate analysis were incorporated into the BACI. Similar to those in COPD, these could constitute a core of "red flag" comorbidities that healthcare providers should pay increased attention to in guiding a targeted personalised screening and treatment approach in patients with bronchiectasis.[28] Some, such as cardiovascular disease, pulmonary hypertension, cognitive impairment, and lung, oesophageal and hematological malignancies, are highly consistent with the little information relating to comorbidities in bronchiectasis that is currently available.[4-7,10-12] However, the increased risk of death conferred by iron deficiency anemia, diabetes mellitus and peripheral vascular disease in this population is less well described. These findings therefore raise the possibility of a shared common biological pathway among these diseases, which requires further exploration.

Although hypertension, high cholesterol and osteoporosis were in the top five most prevalent comorbidities, the direct risk of mortality conferred by these conditions was not significant. Whether this is because they are all treatable or they are risk factors for other potentially more harmful diseases, such as myocardial infarction, is unclear. However, selected solid tumors, such as lung and oesophageal cancer, conferred a significant increased risk of death with prevalence rates of 5% vs. 1% and 3.5% vs. 0.5% in non-survivors *versus* survivors (p=0.004 and p=0.01), respectively (Figure S2 in online supplement for breakdown of prevalence of solid tumors). Hematological malignancies, including lymphoma and leukemia, were also associated with a significantly increased mortality risk in this patient population. These findings have previously

been demonstrated in a nationwide cohort study of >53,000 bronchiectasis patients in Taiwan compared to >215,000 age and sex-matched controls whereby a 2.5 fold increased risk of lung cancer and a 2-fold increased risk of oesophageal and hematological malignancies was demonstrated.[12]

A novel finding in this study was the relatively high prevalence of peripheral vascular disease (9%) and its strong independent association with risk of death, the mechanism of which remains unclear. Diabetes and iron deficiency anemia have both been described in COPD, the former possibly linked to overuse of inhaled corticosteroids in this patient population but more likely, both support the systemic inflammation hypothesis due to repeated infection, inflammation and chronic immune activation.[25,29] Correction of anaemia could improve symptoms of fatigue and dyspnoea, thereby improving patients' QoL and exercise capacity, reducing hospitalisations and improving overall survival. Anxiety and depression have been reported to be highly prevalent among bronchiectasis patients correlating with quality of life measures.[8,9] In COPD, anxiety is an independent risk factor for mortality but no association of depression or anxiety with mortality was identified in this patient cohort.[28]

This study confirms that patients with bronchiectasis are frequently afflicted by comorbidities which may drive disease, many of which confer an independent risk of death and may be missed unless specifically searched for. Although the data may be somewhat intuitive, our finding that COPD, inflammatory bowel disease, connective tissue diseases and asthma are associated with a higher mortality risk may inform decisions about which patients with bronchiectasis should be followed up more closely. Health care providers caring for these patients should routinely screen for the comorbidities outlined in the BACI because there may be effective interventions or changes in management that could reduce the risk of death. Further follow up studies are needed as with the development of any score to substantiate its utility, and determine how this score may impact clinical practice. It would also be interesting to further explore the relationship between high BACI

scores and lung or systemic inflammation in light of the association between higher exacerbations and *Pseudomonas* colonisation in co-morbid patients.

The BACI is a quantitative risk stratification aetiology and comorbidity index for clinicians and researchers to quantify and prioritise comorbidities in bronchiectasis. Our data demonstrate that measurements of comorbidities as captured by the BACI improve the prognostic accuracy for mortality, particularly when used in conjunction with the BSI.[19] The BACI captures diseases not included in the CCI and carries independent prognostic value relating to future disease outcomes such as future exacerbations, hospitalisations and *Pseudomonas* colonisation. Combining the BACI and BSI equips healthcare workers and researchers to better stratify patients and provides a platform for comparative effectiveness research.

This study has several limitations: firstly, there is the potential for missed or as yet, undiagnosed comorbidities. For example, we experienced a somewhat lower prevalence of depression and anxiety in our cohort compared with studies that utilised the Hospital Anxiety and Depression Score to assess psychological wellbeing. However, in clinical practice, depression and anxiety are diagnosed upon history-taking and therefore this should not influence the results of the study. Similarly, there is no objective assessment for GORD, as we rely heavily on questionnaires for diagnosis in the clinical setting, often only resorting to the gold-standard 24h pH-impedance studies in refractory cases due to cost constraints. We may also have underestimated the prevalence of other conditions, such as pulmonary hypertension, in patients who had not had an adequate work-up for the same but who may in fact, still have co-existing disease. There may have been variation between diagnostic criteria used in diagnosing comorbidities due to changes in guidelines throughout the study time period and variation in clinical practice between primary and secondary care and different healthcare institutions.

Secondly, although a small number of patients in our derivation cohort had undergone transplant assessment, none of the patients in our derivation or validation cohorts had received a transplant

therefore we are unable to comment on the utility of the score in this patient population.[30] Comorbidity assessment is routine in the assessment of lung transplant candidates in order to determine suitability. The BACI score may highlight comorbidities that could negate transplant, e.g. in the case of metastatic malignancy, or perhaps delay transplant, e.g. with cases of iron deficiency anaemia where additional treatment may be needed beforehand. However, the BACI would not be considered in isolation in the assessment of transplant suitability and, as with any clinical prediction tool, it needs to be considered in the context of all other available information.

Thirdly, with regards to our validation cohorts, we were unable to account for potential recruitment bias in the younger less co-morbid patients recruited to the original Brompton cohort of 19 years follow up compared to the Serbian cohort. Nevertheless, it is reassuring to see that the BACI works well in different cohorts among different healthcare systems.

Finally, our derived score is relatively complex, awarding different points for each comorbidity. To aid calculation of the score, an online calculator is accessible at http:\\www.bronchiectasisseverity.com. This assigns a total on inputting the relevant data in sequential order and can therefore be completed in a very short space of time in the clinical setting. The BACI requires validation in US and developing countries to further substantiate its utility, and further studies determining how this score may impact clinical practice are now needed. In support of our findings, however, our large representative derivation cohort was made up of almost 1000 patients of varying severity across different healthcare systems in four European countries, with external validation in two independent cohorts, one with 19-years follow-up and one from Eastern Europe, which should make these results generalisable to the majority of bronchiectasis clinics worldwide.

Conclusions

Comorbidities in bronchiectasis are common and significantly contribute to disease burden and mortality. Surprising links with certain comorbidities may provide new insights into the underlying pathogenesis of this disease. We have derived a disease-specific bronchiectasis aetiology and comorbidity assessment tool for predicting future risk of mortality in bronchiectasis. Greater focus is needed to identify, assess and manage comorbidities in bronchiectasis in both clinical and research settings. Future interventions and treatment approaches should consider multiple comorbidities in these patients in order to maximise outcome and reduce the illness burden associated with this disease.

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Figure legends:

Figure 1 legend: Comorbidites in order of overall prevalence among survivor and non-survivor bronchiectasis patients. The figure also includes those comorbidities with a significantly higher prevalence in non-survivors compared with survivors regardless of their absolute prevalence (asterisk). *Definitions of abbreviations:* GORD: Gastro-oesophageal reflux disease; HTN: hypertension; COPD: Chronic obstructive pulmonary disease; CTD: Connective tissue disease; MI: myocardial infarction; CHF: Chronic heart failure; PVD: Peripheral vascular disease; CKD: Chronic kidney disease; CVA: Cerebrovascular attack; RA: Rheumatoid arthritis; ABPA: Allergic bronchopulmonary aspergillosis; TB: Tuberculosis; OSA: Obstructive sleep apnea.

Figure 2 legend: (a) The performance of the Bronchiectasis Aetiology Comorbidity Index (BACI) in relation to the Bronchiectasis Comorbidity Index (BCI) without aetiologies and the widely validated Bronchiectasis Severity Index (BSI) using area under the receiver operator characteristic curve (AUC) scores. (b) The performance of the BACI in relation to the Comorbidity Count and the widely validated Charlson Comorbidity Index (CCI) using area under the receiver operator characteristic curve (AUC) scores.

Figure 3 legend: The performance of the Bronchiectasis Aetiology Comorbidity Index (BACI) in predicting mortality, hospitalisations, exacerbation frequency and quality of life across all risk strata. All between group comparisons for mortality and hospitalisations were statistically significant at $p<0.001$. Between group comparisons for exacerbations were statistically significant at $p=0.03$. Correlation between the BACI and St George's Respiratory Questionnaire (SGRQ) assessing quality of life was statistically significant at $p<0.01$.

Figure 4 legend: Kaplan-Meier survival curves representing survival probability at 5 years. (a) Kaplan-Meier survival curve according to the Bronchiectasis Severity Index (BSI) with mild (0-4 points), moderate (5-8 points) and severe (≥ 9 points). To demonstrate the predictive contribution of the Bronchiectasis Aetiology Comorbidity Index (BACI) to the BSI, the survival curves were represented for each BSI tertile (b) mild disease, (c) moderate disease, and (d) severe disease. BACI group 1 = score of O, BACI group 2 = score <6, BACI group 3 = score ≥ 6. Survival is significantly lower in BACI groups 2 and 3 compared to group 1 which represents no high risk comorbidities. The gap between groups becomes much more evident as disease severity increases.

Figure 5 legend: Validation of the Bronchiectasis Aetiology Comorbidity Index (BACI) in two independent cohorts: (a) Kaplan-Meier survival curves representing survival probability in BACI groups at 20 years in UK population, p=0.004; (b) Area under the receiver operator characteristic curve (AUC) score of BACI score in the Serbian cohort.

Comorbidity paper tables

Table 1: Derivation Cohort Patient Characteristics

Patient characteristics	Derivation Cohort (n=986)
Demographic variables	
Age, Years, Median (IQR)	67 (57-74)
Female, n (%)	589 (59.7)
Body Mass Index, Median (IQR)	24.6 (21.2-27.8)
Smokers / Ex-smokers, n (%)	379 (38.4)
Clinical status	
MRC, Median (IQR)	2 (1-3)
Exacerbations in the previous year, Median (IQR)	2 (1-3)
At least one hospitalisation in the previous year, n (%)	224 (22.7)
Lung function	
FEV_1 % predicted, Median (IQR)	75 (54-95)
Radiology status	
Reiff score, Median (IQR)	4 (2-6)
Microbiological status	
Pseudomonas colonisation, n (%)	122 (12.4)
Other colonisation, n (%)	229 (25.3)
Disease severity	
BSI score, Median (IQR)	6 (4-10)
BSI 0-4 (mild), n (%)	312 (31.6)

BSI 5-8 (moderate), n (%)	351 (35.6)
BSI ≥ 9 (severe), n (%)	323 (32.8)
Comorbidities	
No. of comorbidities, Median (IQR)	4 (2-6)
Range	0-20

Definition of abbreviations: MRC: Medical Research Council dyspnoea score, FEV_1%: forced expiratory volume in 1 second % predicted; BSI: Bronchiectasis Severity Index.

Table 2: Derivation of the Bronchiectasis Aetiology Comorbidity Index (BACI) and Point Allocation

Definition of abbreviations: COPD: Chronic Obstructive Pulmonary Disease, RA: Rheumatoid arthritis.

Comorbidity	Hazard Ratio	95% CI	P value	Points
Metastatic malignancy	6.69	3.53-12.68	<0.0001	12
Haematological malignancy	2.85	1.17-6.97	0.02	6
COPD	2.22	1.53-3.23	<0.0001	5
Cognitive impairment	2.21	0.82-6.01	0.12	5
Inflammatory bowel disease	2.01	0.75-5.40	0.17	4
Liver disease	1.94	0.80-4.72	0.14	4
Connective tissue disease	1.78	1.19-2.68	0.005	3
Iron deficiency anaemia	1.78	0.80-2.68	0.16	3
Diabetes	1.76	1.10-2.80	0.02	3

Asthma	1.65	1.00-2.73	0.050	3
Pulmonary hypertension	1.58	0.88-2.84	0.12	3
Peripheral vascular disease	1.50	1.00-2.25	0.052	2
Ischaemic heart disease	1.31	0.91-1.89	0.14	2

Table 3: Sensitivity and specificity values for derived clinical prediction tools

Organisms	PLR	NLR	Sensitivity	Specificity	PPV	NPV
BACI						
Grp 2 and 3 vs Grp 1	1.61 (1.47-1.75)	0.26 (0.16-0.42)	88.5 (81.5-93.6)	44.9 (41.6-48.3)	18.5 (15.4-21.9)	96.5 (94.2-98.1)
Grp 3 vs Grp 1 and 2	3.80 (3.01-4.81)	0.54 (0.45-0.66)	53.3 (44.0-62.4)	86.0 (83.5-88.2)	34.9 (28.1-42.3)	92.9 (90.9-94.6))
BCI						
Grp 2 and 3 vs Grp 1	1.57 (1.42-1.74)	0.35 (0.23-0.53)	83.6 (75.8-89.7)	46.9 (43.5-50.3)	18.2 (15.1-21.6)	95.3 (92.8-97.1)
Grp 3 vs Grp 1 and 2	4.68 (3.27-6.69)	0.73 (0.65-0.83)	32.0 (23.8-41.0)	93.2 (91.3-94.8)	39.8 (30.0-50.2)	90.7 (88.6-92.5)
BSI						
Mod/severe vs mild	1.37 (1.26-1.48)	0.31 (0.18-0.52)	89.3 (82.5-94.2)	34.6 (31.4-37.9)	16.2 (13.5-19.2)	95.8 (92.9-97.8)
Severe vs Mod/mild	2.18 (1.83-2.59)	0.53 (0.42-0.67)	62.3 (53.1)	71.4 (68.3-74.4)	23.5 (19.0-28.5)	93.1 (90.9-94.9)

Definition of abbreviations: BACI: Bronchiectasis Aetiology and Comorbidity Index; BCI Bronchiectasis Comorbidity Index; BSI: Bronchiectasis Severity Index

Table 4: Correlation of the BACI with clinical scores and severity indices

Patient characteristics (n=986)	Spearman's Rho	P value
BSI	0.23	<0.0001
FACED	0.24	<0.0001
Age	0.20	<0.0001
Male gender	0.20	<0.0001
Smoking history	0.33	<0.0001
Reiff radiological score	0.08	0.008
MRC dyspnoea score	0.31	<0.0001
LTOT	0.23	<0.0001
Prior exacerbations	0.12	0.0002
Prior hospitalisations	0.13	<0.0001
FEV1 %	-0.26	<0.0001
Pseudomonas colonisation	0.078	0.01
Exacerbations on follow-up	0.11	0.0006
Hospitalisations on follow-up	0.22	<0.0001

Definition of abbreviations: BSI: Bronchiectasis Severity Index, FACED: Acronym for a 5-component disease severity score; MRC: Medical Research Council, LTOT: long term oxygen therapy, FEV_1%: Forced expiratory volume in 1 second % predicted.

Online supplementary data

Study Title:

Comorbidities and the risk of mortality in patients with bronchiectasis: an international cohort study

Material contained in this document:

- Process to define bronchiectasis aetiologies
- Data collection procedure at each site
- Standardised definitions of comorbidities
- Guide to interpretation of Spearman's rho correlation coefficient
- Table S1: Comorbidities prevalence for the full cohort and prevalence comparison between survivors and non-survivors
- Figure S1: Solid tumour prevalence chart
- Table S2: Derivation of the bronchiectasis comorbidity index (BCI)

Process to define bronchiectasis aetiologies

Patients in each site underwent the same comprehensive diagnostic work-up as suggested by the 2010 British Thoracic Society (BTS) guidelines including: full blood count, serum electrophoresis, serum immunoglobulin (Ig) G, IgA, IgM, total IgE, specific IgE and precipitins for A. fumigatus, and pulmonary function testing with reversibility testing and diffusion capacity test.[18] If there was a clinical suspicion of primary ciliary dyskinesia, such as recurrent sinusitis and/or chronic otitis media, patients were referred for further testing with nasal mucociliary clearance measured by the saccharin test and/or nasal nitric oxide at specialist primary ciliary dyskinesia centres. $Alpha_1$-antitripsin deficiency was evaluated in the presence of emphysema affecting lower lobes on high-resolution computed tomography (HRCT) scan and/or significant family history. Autoimmunity testing including anti-nucleolar antibodies, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, rheumatoid factor and anti–citrullinated protein antibody were requested if a rheumatological disease was clinically suspected. Sweat test and cystic fibrosis (CF) transmembrane conductance regulator genetic testing were requested if there were signs and symptoms suggestive for CF as suggested by BTS guidelines.[18]

An evaluation of CT images and testing results was performed, including immunoglobulins, skin prick testing or serum IgE resting to *A. fumigatus* and *Aspergillus* precipitins, and serum electrophoresis, in order to differentiate patients into categories of congenital abnormalities, post-obstructive bronchiectasis, primary or secondary immunodeficiency, $alpha_1$-antitrypsin deficiency or allergic bronchopulmonary aspergillosis (ABPA). If all of the above tests were negative, a history of prior severe respiratory infections was investigated, including previous infection with tuberculosis or non-tuberculous mycobacteria. If no history of previous respiratory infections was present, an association between bronchiectasis and other diseases, such as COPD, asthma, inflammatory bowel disease (IBD), overt aspiration on barium studies

or connective tissue disease (CTD) was investigated. If tests were negative and no association with other diseases was found, a diagnosis of idiopathic bronchiectasis was made.

A serum IgE of >1000 IU/ml, positive *Aspergillus* precipitins and skin prick, blood eosinophilia of >0.4 and compatible radiology was required to fulfil the diagnosis of ABPA.[31] Post-infective bronchiectasis (PIB) was diagnosed in patients reporting a history of symptom onset within 5 years of a severe respiratory tract infection, such as pneumonia, whooping cough or complicated measles infection. Where a patient reported a history of severe respiratory infections, but with a five-year symptom free period, the post-infective diagnosis was not attributed. Post- tuberculous bronchiectasis was diagnosed in patients with clearly documented prior tuberculosis and compatible radiology. COPD-associated bronchiectasis was classified in the presence of significant smoking history and airflow obstruction according to GOLD criteria.[32] Bronchiectasis associated with asthma was diagnosed in patients without post-infective bronchiectasis and with normal or negative results of blood investigations, according to GINA guidelines.[33] Bronchiectasis associated with IBD was diagnosed if patients had ulcerative colitis or Crohn's disease and no other suggested aetiology for bronchiectasis. In the presence of a diagnosis of both bronchiectasis and CTD, including rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, psoriatic arthritis, ankylosing spondylosis or mixed CTD, a diagnosis of CTD-associated bronchiectasis was made. Yellow nail syndrome was diagnosed when examination showed yellow discoloration of dystrophic nails together with bronchiectasis and sinusitis, whether or not patients had other features of the syndrome. Young's syndrome was diagnosed when there was a history of bronchiectasis, sinusitis and azoospermia in males and negative CF testing.[34] A diagnosis of IB was made by exclusion of any known cause.

Data collection

Demographics, comorbidities, disease severity, bronchiectasis aetiology, symptoms, sputum evaluation, baseline radiological, functional and laboratory findings, quality of life, and long-term treatments and outcomes - including exacerbations, hospitalisations and mortality - over a five-year follow-up period were recorded in each site. Radiological severity was assessed using the modified Reiff score incorporating number of lobes and degree of dilatation as previously described.[16] Bronchiectasis severity was evaluated according to the BSI.[16] Quality of life was assessed using the St. George's Respiratory Questionnaire (SQRQ).[35] Microbiological examinations were performed on sputum, bronchial aspiration or bronchoalveolar lavage during stable state. Identification of microorganisms and susceptibility testing were performed according to standard methods. Chronic infection was defined by the presence of pathogenic bacteria in sputum culture on two or more occasions at least three months apart over a one-year period.[36] The predominant pathogen was the organism grown most frequently over the study period. Patients who were unable to provide sputum samples due to absence of a productive cough were classified as not having chronic infection for the purposes of analysis.

Study outcomes

Exacerbations: An exacerbation of bronchiectasis was defined as a clinical diagnosis of exacerbation for which antibiotics were prescribed in the presence of at least one (and usually more than one) of the following symptoms: increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnea, increased fatigue/malaise, fever, and hemoptysis.[18]

Hospitalization for severe exacerbations: Severe exacerbations were defined according to the BTS guidelines, and unscheduled hospitalizations or emergency department visits for severe

bronchiectasis exacerbations or complications were recorded from patient histories and verified using administrative databases that record admissions.[16,18]

Mortality: All-cause mortality up to 5 years of follow up was evaluated.

Details of each individual cohort are displayed below:

Dundee, United Kingdom

This cohort consisted of 286 consecutive bronchiectasis patients attending a specialist bronchiectasis clinic in Tayside, Scotland, UK. Patients in this cohort were included in 2011 with follow-up data to September 2015. Patients were assessed according to a standardised protocol based on the British Thoracic Society (BTS) guidelines including standardised testing for aetiology. Clinic data were recorded at baseline and subsequent clinic review. All bacteriology was performed on early morning sputum samples. Patients were routinely asked to provide sputum samples at least twice a year at clinic reviews. Data on exacerbations were obtained from patient histories and verified against electronic general practice prescribing data to ensure all exacerbations treated with antibiotics were captured. Hospital admissions and mortality data were obtained from patient follow-up and verified by electronic medical records containing all hospital admissions and deaths regionally. Follow-up status was verified in 100% of participants. Outcomes available in this database were 5-year mortality, subsequent hospital admissions and exacerbations, and quality of life data.

Galway, Ireland

This database included 280 consecutive patients attending respiratory clinics at Galway University Hospitals and Merlin Park University Hospitals in Galway, Ireland. Patients in this cohort were included in 2009-2011 with follow-up data to September 2015. All patients undergoing diagnostic investigation for bronchiectasis were assessed according to BTS

guidelines including standardised testing for aetiology. In this centre, all patients referred for investigation routinely undergo bronchoscopic evaluation and lavage as part of their work-up. Clinic data were recorded at baseline and subsequent review. Patients were asked to provide 6-mpnthly samples of sputum where possible for microbiological surveillance. Data on exacerbations, hospitalisations and mortality were obtained from patient histories and full review of medical and electronic records. Data on exacerbations and hospitalisations was verified against prescribing practices and admission records. Data pertaining to mortality and causes of death were verified against the Health Service Executive Civil Register. Follow-up status was verified in 100% of participants. Outcomes available in this database were 5-year mortality, subsequent hospital admissions and exacerbations.

Leuven, Belgium

The bronchiectasis cohort from the University of Leuven, Belgium, contains data on 190 patients seen at the department with a radiological and clinical diagnosis of bronchiectasis from June 2006 to October 2012. All patients had a high resolution CT scan confirming the presence of bronchiectasis. Patients underwent testing for aetiological causes in accordance with British Thoracic Society guidelines. Clinical data were collected at baseline and survival data determined for a mean of 49 months. The definitions of colonisation and the assessments of radiological severity were in accordance with those used in the other derivation cohorts. Outcomes available in this cohort were 5-year mortality, subsequent hospital admissions and exacerbation frequency.

Monza, Italy

This cohort included 230 consecutive patients with bronchiectasis (defined by clinical history and high-resolution computed tomography scan) attending respiratory clinics at the San Gerardo Hospital in Monza, Italy. Patients in this cohort were included in 2011 and 2012 with

follow up data to September 2015. As with other cohorts, patients with cystic fibrosis or traction bronchiectasis secondary to pulmonary fibrosis were excluded. Patients were assessed according to a standardised protocol based on BTS guidelines including standardised testing for aetiology. Data on exacerbations, hospital admissions and mortality were obtained from patient histories and follow-up. Follow-up status was verified in 100% of participants. Outcomes available in this cohort were 5-year mortality, subsequent hospital admissions and exacerbation frequency.

Comorbidity assessment

Comorbidity assessment was performed according to standardized definitions with review of objective assessment and confirmatory tests to verify diagnosis where possible. Below are a few examples of how comorbidity was determined in the most prevalent or significant comorbidities among this patient population.

Gastro-esophageal reflux disease (GERD): Based on a presumptive diagnosis of GERD in the setting of typical symptoms of heartburn and regurgitation or by improvement in symptoms after trial of therapy as per American College of Gastroenterology recommendations. Patients were considered to have GERD where a diagnosis of GERD was recorded in the notes by a primary or secondary care physician, or in a patient taking a prescribed anti-reflux medication.

Hypertension: Based on previous guidelines of clinic blood pressure readings of >140/90mmHg on three separate occasions taking the lowest of at least two readings at each visit. Note: since 2011 guidelines, ambulatory and/or home blood pressure measurements are included in the diagnosis of arterial hypertension according to the British Hypertension and European Society of Cardiology guidelines. Patients were considered to have hypertension

where a diagnosis of hypertension was recorded in the notes by a primary or secondary care physician, or in a patient taking a prescribed anti-hypertensive medication.

High cholesterol: Based on an objective fasting total cholesterol level of >5 mmol/L for healthy adults and/or >4 mmol/L in high risk patients and/or a ratio of total cholesterol to HDL above 4.The 2014 guidelines allow measurement of cholesterol in non-fasting samples. Patients were considered to have high cholesterol where a diagnosis of high cholesterol was recorded in the notes by a primary or secondary care physician AND objective evidence of cholesterol levels could be assessed, or in a patient taking a prescribed cholesterol medication for primary or secondary prevention.

COPD: Based on the presence of a significant smoking history of >10 pack years and objective confirmation of airflow obstruction according to GOLD criteria. Patients were considered to have COPD where a diagnosis of COPD was recorded in the notes in patients with a significant smoking history AND objective evidence of airflow obstruction in primary or secondary care. In patients prescribed inhaled medications without objective evidence of airflow limitation, a diagnosis of COPD was not recorded.

Osteoporosis: Based on a bone mineral density that is 2.5 SD or more below that of a "young normal" adult (T-score at or below -2.5) on DEXA scanning and/or clinical diagnosis in at-risk individuals who have sustained a low-trauma fracture according to World Health Organization guidelines. Patients were considered to have osteoporosis where a diagnosis of osteoporosis was recorded in the notes by a primary or secondary care physician AND objective evidence on DEXA scanning or in patients taking bisphosphonate treatment.

Connective tissue disease: Based on assessment by an expert rheumatologist according to American College of Rheumatology guidelines incorporating history, physical examination, laboratory and radiographic findings according to individual disease.

Myocardial infarction: Based on a rise and/or fall of cardiac biomarker values plus at least one of: symptoms of ischemia, new or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB), development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality and/or identification of an intracoronary thrombus by angiography or autopsy according to the universal definition in the European Cardiac Society guidelines. Patients were considered to have had a myocardial infarction where a diagnosis was recorded in the notes AND objective evidence in the form of blood tests, ECG or imaging studies was available.

Chronic heart failure: Based on the presence of symptoms and signs of heart failure with measurement of ejection fraction on echocardiography to determine if reduced or preserved and to determine the presence of structural heart disease or diastolic dysfunction in the presence of a preserved ejection fraction according to the European Society of Cardiology guidelines. Patients were considered to have heart failure where a diagnosis of heart failure was recorded in the notes or patients were prescribed heart failure medications AND objective evidence on echocardiography was available.

Depression: Based on the presence of at least four out of ten depressive symptoms, present for at least 2 weeks for most of every day according to ICD-10 criteria. Patients were considered to have depression where a diagnosis of depression was recorded in the notes by primary or secondary care physicians or in patients prescribed anti-depressant medications.

Solid tumor/metastatic malignancy: Based on assessment by an expert physician and/or oncologist with appropriate objective staging imaging and histopathological investigations.

Peripheral vascular disease: Based on the presence of symptoms and signs of peripheral vascular disease, objective measurement of ankle brachial pressure indices in primary care setting or confirmatory imaging investigations such as Doppler ultrasound, angiography or

digital subtraction arteriography according to European Society of Cardiology guidelines. Patients were considered to have peripheral vascular disease where a diagnosis of peripheral vascular disease was recorded in the notes AND objective evidence was available.

Atrial fibrillation: Based on an irregular heart rate with ECG confirmation. Patients were considered to have atrial fibrillation where a diagnosis of atrial fibrillation was recorded in the notes by a primary or secondary care physician AND objective ECG evidence was available.

Chronic kidney disease: Based on objective reduced eGFR values for staging of chronic kidney disease as per national and international guidelines.

Diabetes mellitus: Based on plasma glucose criteria, with fasting glucose >7.0 mmol/L, random or 2-h glucose post-oral glucose tolerance test > 11.1 mmol/L, or HbA1C ≥6.5% according to the American Diabetes Association guidelines. Patients were considered to have diabetes mellitus where a diagnosis of diabetes mellitus was recorded in the notes by a primary or secondary care physician AND objective blood glucose levels were available.

Cerebrovascular accident/Transient ischemic attack: Based on the presence of symptoms and signs with confirmatory imaging findings on CT brain, MRI brain, Doppler USS neck or other investigations according to the American Heart Association/ American Stroke Association guidelines. Patients were considered to have a CVA/TIA where a diagnosis was recorded in the notes, patients were prescribed anticoagulant medications AND objective evidence on imaging was available.

Rheumatoid arthritis: Based on assessment by an expert rheumatologist according to American College of Rheumatology guidelines incorporating history, physical examination, laboratory and radiographic findings with four of seven of the diagnostic criteria present, one of which must have been present for a minimum of 6 weeks.

Pulmonary hypertension: Based on an increase in mean pulmonary arterial pressure ≥25 mmHg at rest as assessed by right heart catheterization or echocardiography. Patients were considered to have pulmonary hypertension where a diagnosis was recorded in the notes AND objective evidence on imaging was available.

Thromboembolic disease: Based on objective confirmation of deep vein thrombosis on Doppler ultrasound or pulmonary embolism on CTPA. Patients were considered to have thromboembolic disease where a diagnosis was recorded in the notes, patients were prescribed anticoagulant medications AND objective evidence on imaging was available.

Overt aspiration: Based on objective confirmation of aspiration on barium swallow studies. Patients were considered to have overt aspiration where a diagnosis was recorded in the notes AND objective evidence on imaging was available.

Leukemia: Based on assessment by an expert oncologist according to World Health Organization guidelines incorporating history, physical examination, full blood count and film, imaging, bone marrow biopsy and cytogenetic abnormality conformation.

Lymphoma: Based on assessment by an expert oncologist according to World Health Organization guidelines incorporating history, physical examination, full blood count and film, imaging and histopathological confirmation.

Iron deficiency anemia: Based on objective low iron stores and a hemoglobin level two standard deviations below normal as per national and international guidelines.

Cognitive impairment: Based on a clinical diagnosis by a primary or secondary care physician whereby acquired cognitive deficits in more than one area of cognition interfere with normal activities of daily living and represent a decline from a previously higher level of functioning. Patients were considered to have cognitive impairment where a diagnosis was recorded in the

notes, deficits on structured memory tests were noted, and/or patients were prescribed medications to treat dementia.

Guide to interpretation of Spearman's rho correlation coefficient

Interpretation of Spearman's rho correlation coefficient: Spearman's correlation coefficient is a statistical measure of the strength of the relationship between paired data. The closer the value is to 1, the stronger the relationship. Correlation is an effect size; the strength of the correlation can therefore be described using the following guide for the absolute value Spearman's rho: ≤0.19 - very weak; 0.2-0.4 weak; 0.40-0.59 moderate; 0.60-0.79 strong; ≥ 0.80 very strong.

Table S1: Comorbidities prevalence for the full cohort and prevalence comparison between survivors and non-survivors.

	Comorbidity prevalence	Total cohort (n=986) %	Survivors (n=864) %	Non-survivors (n=122) %	P value
1	*GERD	34.3	32.4	47.6	0.001
2	HTN	27.5	26.5	34.4	0.080
3	High cholesterol	20.1	19.6	23.8	0.281
4	*COPD	17.1	14.2	37.7	<0.001
5	Osteoporosis	15.9	15.2	20.5	0.147
6	Rhinosinusitis	13.1	13.5	9.8	0.315
7	Asthma	12.4	12.5	11.5	0.883
8	*CTD	12	10.9	19.7	0.010
9	*MI	11.7	10.3	21.3	0.001
10	*CHF	10	8.7	19.7	<0.001
11	Depression	9.3	9.1	10.7	0.496
12	*Solid tumour	9.1	8.7	12.3	0.028
	*Lung cancer	1.4	0.9	4.9	0.004
	*Oesophageal cancer	0.8	0.5	3.3	0.010
13	*PVD	8.9	6.8	23.8	<0.001
14	*PUD	8.9	6.8	23.8	<0.001
15	*Atrial fibrillation	8.7	7.6	16.4	0.003
16	Anxiety	8.4	8.2	9.8	0.372
17	*CKD	8.2	6.8	18.1	<0.001
18	*Diabetes Mellitus	7.1	6.0	14.8	0.002
19	Immunodeficiency	6.8	6.7	7.4	0.704
20	*CVA	6.1	5.2	12.3	0.007
21	ABPA	5.8	6.1	3.3	0.298
22	*RA	5.7	4.9	11.5	0.007
23	Osteoarthritis	5.6	5.6	9	0.151
24	Thyroid disorder	5.6	5.9	4.9	0.836
25	*Pulmonary HTN	4.4	3.5	10.7	0.001
26	TB	4.1	3.8	6.6	0.151
27	Childhood infection	4	3.9	4.1	0.808
28	Valvulopathy	3.5	3.1	6.6	0.066
29	*Thromboembolic disease	3.4	2.9	6.6	0.028
30	Liver disease	3.4	3.5	3.3	1.000
31	Sarcoidosis	2.5	2.7	0.8	0.346
32	IBD	2.4	2.4	2.5	1.000
33	Morbid obesity	2.3	2.1	4.1	0.191
34	Overt aspiration	1.9	1.8	2.5	0.721
35	*Psoriasis	0.7	0.5	2.5	0.045
36	*Metastatic malignancy	1.8	0.9	8.2	<0.001
37	Spinal problems	1.8	1.5	4.1	0.061
38	OSA	1.6	1.6	1.6	1.000
39	Pulmonary nodules	1.5	1.6	0.8	0.710

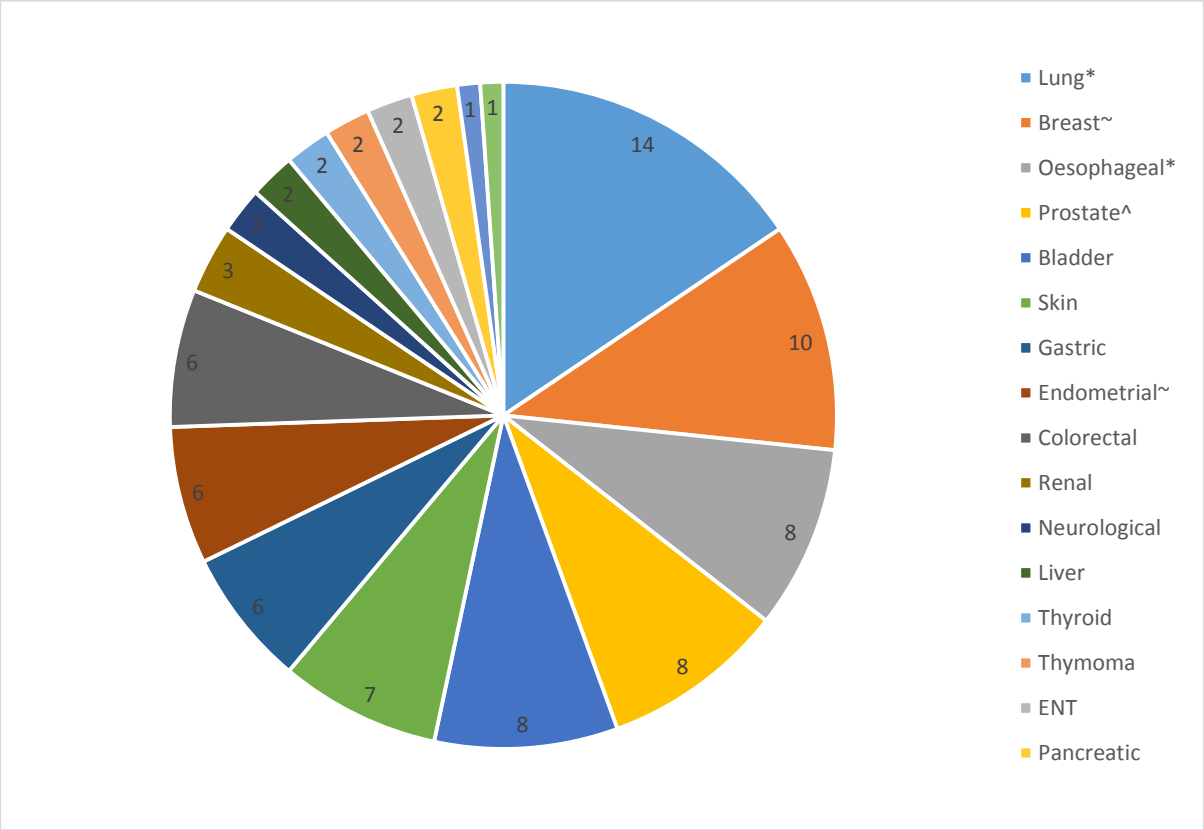
40	*TIA	1.5	1	4.9	0.006
41	*Leukaemia	1.4	1.1	3.3	0.021
42	BPH	1.4	1.0	2.5	0.177
43	PCD	1.3	1.5	0	0.388
44	*Iron deficiency anaemia	1.3	0.9	4.1	0.015
45	Gout	1.3	1.2	2.5	0.211
46	Cataracts	1.3	1.3	1.6	0.669
47	*Cognitive impairment	1.1	0.8	2.6	0.010
48	*Lymphoma	1.1	0.4	2.6	0.006
49	Vasculitis	1.1	1	1.7	0.635
50	PMR	1.1	1.2	0.8	1.000
51	Recurrent cystitis	1.1	0.9	2.5	0.145
52	A1AT deficiency	1	1.2	0	0.621
53	Diverticular disease	1	0.8	2.5	0.116
54	Gallstones	0.9	1	0	0.611
55	Congenital disorders	0.8	0.8	0.8	1.000
56	Other psychological disorder	0.6	0.7	0	1.000
57	Epilepsy	0.6	0.5	1.6	0.163
58	Postural hypotension	0.6	0.5	1.6	0.163
59	*Multiple myeloma	0.6	0.3	2.5	0.028
60	Coeliac disease	0.5	0.3	1.7	0.118
61	Pernicious anaemia	0.5	0.3	1.6	0.118
62	Parkinson’s disease	0.5	0.4	0.9	0.484
63	Pneumothorax	0.4	0.2	1.6	0.077
64	Hemochromatosis	0.4	0.5	0	1.000
65	Fibromyalgia	0.4	0.2	1.6	0.077
66	Primary renal disease	0.4	0.2	1.6	0.077
67	Migraine	0.4	0.3	0.8	0.411
68	Other neurological disorders	0.4	0.2	1.6	0.077
69	Glaucoma	0.4	0.3	0.8	0.411
70	Haemangioma	0.4	0.5	0	1.000
71	AIDS	0.2	0	0.2	1.000
72	Cardiomyopathy	0.2	0.1	0.8	0.232
73	*AAA	0.2	0	1.6	0.015
74	Ovarian problems	0.2	0.2	0	1.000
75	Syphilis	0.2	0.2	0	1.000
76	Asbestosis	0.1	0.1	0	1.000
77	Spinal muscular atrophy	0.1	0.1	0	1.000
78	Myasthenia gravis	0.1	0.1	0	1.000
79	Pancreatitis	0.1	0.1	0	1.000
80	Tracheomalacia	0.1	0.1	0	1.000
81	Swyer James Macloud	0.1	0.1	0	1.000

Definition of abbreviations: GERD: gastro-oesophageal reflux disease; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CTD; connective tissue disease; MI:

myocardial infarction; CHF: congestive heart failure; PVD: peripheral vascular disease; PUD: peptic ulcer disease; CKD: chronic kidney disease; CVA: cerebrovascular attack; ABPA: allergic bronchopulmonary aspergillosis; RA: rheumatoid arthritis; TB: tuberculosis; IBD: inflammatory bowel disease; OSA: obstructive sleep apnoea; TIA: transient ischaemic attack; BPH: benign prostatic hyperplasia; PCD: primary ciliary dyskinesia; PMR: polymyalgia rheumatica; A1AT: Alpha$_{-1}$ anti-trypsin deficiency; AIDS: acquired immunodeficiency syndrome; AAA: abdominal aortic aneurysm.

Figure S1: Solid tumour prevalence chart

Solid tumours were identified in 90 (9.1%) of total cohort. This pie chart provides a breakdown of the prevalence of tumor type among these patients.



Definition of abbreviations: ENT = Ears, nose and throat cancers.

*Represents statistically significant difference between survivors and non-survivors. ~Represents female-specific malignancies. ^Represents male-specific malignancies.

Table S2: Derivation of the Bronchiectasis Comorbidity Index (BCI) and Point Allocation

Comorbidity	Hazard Ratio	95% CI	P value	Points
Metastatic malignancy	5.21	2.83-9.58	<0.0001	**10**
Iron deficiency anaemia	2.52	1.15-5.55	0.02	**6**
Liver disease	2.21	0.91-5.37	0.08	**5**
Haematological malignancy*	1.87	0.79-4.45	0.16	**4**
Diabetes mellitus	1.77	1.13-2.79	0.01	**3**
Solid tumour	1.60	1.00-2.57	0.048	**3**
Pulmonary hypertension	1.56	0.87-2.80	0.14	**3**
Peptic ulcer disease	1.49	0.85-2.59	0.16	**2**
Peripheral vascular disease	1.44	0.97-2.15	0.07	**2**
GORD	1.31	0.96-1.79	0.09	**2**
IHD	1.31	0.91-1.87	0.14	**2**

*Although haematological malignancy can be a cause of bronchiectasis, we retained this in the model where haematological malignancy was not considered by the clinician as the underlying aetiology after testing.

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