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Bronchiectasis Rheumatoid overlap syndrome (BROS) is an independent risk factor for mortality in patients with bronchiectasis: A multicentre cohort study

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Running head: Rheumatoid associated bronchiectasis and outcomes

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Abstract

Introduction

We studied if Bronchiectasis (BR) and Rheumatoid arthritis (RA) when manifesting as an overlap syndrome (BROS) was associated with worse outcomes than other BR aetiologies applying the Bronchiectasis Severity Index (BSI).

Methods

We interrogated the Bronchiectasis Severity Index (BSI) databases of 1716 patients across 6 centres: Edinburgh, UK (608 patients), Dundee, UK (N=286), Leuven, Belgium (N=253), Monza, Italy (N=201), Galway Ireland (N=242) and Newcastle, UK (N=126). Patients were categorised as BROS (those with RA and Bronchiectasis without interstitial lung disease), idiopathic bronchiectasis, Bronchiectasis-COPD overlap syndrome (BCOS) and "other" BR aetiologies. Mortality rates, hospitalisation and exacerbation frequency were recorded.

Results

We identified 147 patients with BROS (8.5% of cohort). There was a statistically significant relationship between BROS and mortality although this was not associated with higher rates of bronchiectasis exacerbations or bronchiectasis-related hospitalisations. The mortality rate over a mean of 48 months was 9.3% for idiopathic BR, 8.6% in patients with "other" causes of BR, 18% for RA and 28.5% for BCOS. Mortality was statistically higher in BROS and BCOS compared with all other aetiologies. The BSI scores were statistically but not clinically significantly higher in those with BROS when compared to idiopathic BR (BSI mean 7.7 vs. 7.1 respectively, $p < 0.05$). BCOS had significantly higher BSI scores (mean 10.4), *Pseudomonas aeruginosa* colonization rates (24%) and prior hospitalisation rates (58%).

Conclusions

Both BROS and BCOS groups have an excess of mortality -the mechanisms for this may be complex but these data highlight that these subgroups require additional study to understand this excess mortality.

=250words

Introduction

Non-cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis-BR) is a chronic respiratory disorder characterised by recurrent cough, sputum production and respiratory infections[1] Pathologically, patients have abnormally dilated bronchi leading to impairment of host defence, chronic infection with bacteria and airways inflammation.[2,3]

Rheumatoid arthritis (RA) is a common auto-immune disease associated with many extra-articular features. RA has numerous pulmonary complications including interstitial lung diseases that may lead to "traction bronchiectasis" whilst the association between RA and bronchiectasis without interstitial lung disease (hereafter BROS) is well recognised. Recent studies note a significantly higher prevalence of symptomatic bronchiectasis in RA subjects (approximately 3%) as compared to 0.03% in the general population [4]. Supporting this are high resolution CT scanning (HRCT) studies consistently reporting high prevalence of up to 30% of radiological evidence of BR in RA populations [5,6].

Historical single centre studies have suggested that patients with BROS may have a worse clinical course than those patients with bronchiectasis due to other aetiologies. Recently we have identified that when compared to patients with RA alone, BROS patients have a higher indices of RA activity e.g. disease activity scores (DAS-28) demonstrating worse rheumatoid arthritis and higher levels of RA seropositivity [7]

We therefore wished to explore if BROS was associated with poorer outcomes compared to BR without RA. Defining the clinical severity of bronchiectasis has been problematic until recent scoring indices such as the Bronchiectasis Severity Index (BSI) became available[8]. We therefore aimed to assess mortality, frequency of exacerbations, hospital admissions, reported health related quality of life and BSI scores in an international

cohort comparing BROS to BR without RA. Idiopathic bronchiectasis was used as a benchmark due to its prevalence and a perception that this aetiological group may have better outcomes.[1] As bronchiectasis and COPD overlap syndrome (BCOS) has been linked to excess mortality we used this second group as an additional reference group[9].

Methods

Multicentre assessment of bronchiectasis severity

Six independent cohorts of patients were collected from specialist Bronchiectasis services in Edinburgh, Dundee and Newcastle (UK), Leuven (Belgium), Monza (Italy) and Galway (Ireland) with an average follow up of 4 years[8,10]. Consecutive adult patients were enrolled on the basis of a diagnosis of bronchiectasis made by high resolution computed tomography (HRCT) and a clinical history consistent with bronchiectasis.[1] Patients were excluded if they had active malignancy at enrolment, cystic fibrosis, active mycobacterial disease (including active non-tuberculous mycobacteria (NTM)), HIV or a primary diagnosis of pulmonary fibrosis/sarcoidosis with secondary traction bronchiectasis. Patients with BCOS were not included within the Edinburgh cohort due to their cohort building protocol. Cohort building was approved at each individual centre; by the South East Scotland Research Ethics Committee, Research ethics service multi-centre ethics - IRAS 12324 and by NRES, UK 12/NE/0298, CA 128 Clinical research committee, Galway [8,10].

Aetiological categorisation

The underlying aetiology of bronchiectasis was determined following testing recommended by the British Thoracic Society (BTS) guidelines [1]. This includes serological and clinical assessment for Rheumatoid arthritis [1].

BROS required a diagnosis of both BR, as above, and Rheumatoid arthritis, defined according to the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) RA criteria [11] and local prevailing clinical guidelines.

Patients were grouped into the BROS category irrespective of which of the two conditions preceded the other.

Patients were pragmatically categorised as BCOS based on evidence of airflow obstruction and smoking greater than 20 pack years. The presence of emphysema on CT scan was not a pre-requisite.

Post-infectious causes were attributed when a clear history of bronchiectasis after an acute infectious episode was reported[1]. Inflammatory bowel disease and ABPA associated aetiological categories were applied when a clear history and/or appropriate serological and history were reported respectively. Idiopathic was attributed as a diagnostic grouping in the absence of any recognised aetiology. "Other bronchiectasis" was a grouping of categories that included all remaining aetiological groups (e.g. immunodeficiency associated bronchiectasis- including those on immunoglobulin replacement, ciliary dyskinesia etc).

Clinical assessments

At the time of clinical assessment all patients were clinically stable with no antibiotic use in the preceding 4 weeks. All patients underwent spirometry (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) according to ERS guidelines with the highest of three technically satisfactory measurements recorded).

Radiological severity

Radiological severity of bronchiectasis was assessed using a modified Reiff score which has been used previously bronchiectasis studies.[8,12,13] The score assesses the number of lobes involved (with the lingula considered to be a separate lobe) and the degree of bronchial dilatation (tubular-1, varicose-2 and cystic-3) with a maximum score of 18 and minimum score of 1. There was no minimum Reiff score for patients to be entered into the cohorts.

Bacteriology

As previously described all bacteriology was performed using local culture protocols on spontaneous early morning sputum samples.[3] The definition of chronic persistent infection, was the isolation of potentially pathogenic bacteria in sputum culture on 2 or more occasions, with at least 3 months apart in a one year period.[13,14,15] The micro-organism grown most frequently over the study period was classed as the predominant pathogen. The clinical standards were sputum sampling at 6 monthly or more frequent intervals at clinic reviews.

BSI scores

As previously described, BSI scores were grouped as follows; scores 0-4 represents mild bronchiectasis, scores 5-8 moderate bronchiectasis and scores >8 represents severe bronchiectasis.[8]

End-points

Mortality: At the end of the follow-up periods, mortality was determined through notes review and interrogating national death records. Survival status was confirmed for 100% of participants although exact date of death was not available for all deceased patients.

Exacerbations were defined according to the BTS definition as an acute deterioration with worsening and/or systemic upset[1]. Severe exacerbations were defined as those needing hospitalisation. The frequency of exacerbations requiring antibiotic treatment were determined from clinic records and patient histories and verified against primary care prescription records.

Statistical analysis

Normally distributed data are presented as mean with standard deviation, whilst non-normally distributed data are presented as median with interquartile range. The Chi square test and Mann Whitney U test were used for comparison of categorical and numerical data respectively. For comparisons of more than 2 groups, one way ANOVA or the Kruskal-Wallis test were used as appropriate. For all analyses a value of $p<0.05$ was considered statistically significant. Independent relationships between BROS and BCOS with mortality were assessed using multivariable logistic regression, adjusting for the BSI. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Kaplan Meier survival curves and Cox-proportional hazards regression were performed for survival. The discrimination of the BSI for predicting mortality in BROS was assessed using the area under the receiver operator characteristic curve (AUC). We performed sensitivity analyses to determine if outcomes were different across all 3 BSI categories (mild, moderate and severe). Additionally we applied calibration analysis - an analysis to determine whether scoring systems perform similarly in a different population compared to the baseline population. As a sensitivity analysis to determine the validity of pooling cohorts, the authors used random effects meta-analysis. Data were pooled using the Mantel-Haenszel method and heterogeneity assessed using Higgins I^2 test and Cochrans Q test.

Results

Multi-centre assessment

We collected data from 1716 adult patients with bronchiectasis across 6 centres in Western Europe. The data is displayed in Table 1 and Figure 1. The median age was 65 years with a female predominance and the commonest aetiological groups were idiopathic and post-infectious suggesting these were broadly representative of bronchiectasis cohorts previously reported.[1]

Overall BROS was present in 8.5% of the cohort whilst BCOS was present in 12% of the cohorts that included BCOS during cohort building. The mean exacerbation frequency was greater than 2 exacerbations per year and all cohorts reported a prior history of hospitalisation in at least 20% of patients. Chronic *Pseudomonas aeruginosa* infection was present in a mean of 13% of patients overall. The mean BSI scores for each centre ranged from 6-9. Prior data has demonstrated this is consistent with patients with moderate to severe bronchiectasis [8]. The centre with the highest hospital admission rate (Newcastle) also had the highest observed mean BSI score 9.6.

Comparison between BROS and non-RA patients with bronchiectasis

The comparisons between BROS and other groups are shown in table 2. In general the BROS patients were similar in terms of age and gender distribution except when compared to the BCOS group who were significantly older and significantly more likely to be male. The BSI scores were statistically significantly higher in the BROS group as compared to idiopathic and other BR though all remained within the moderate severity category of the BSI (scores 5-8). Radiological burden of disease was not significantly different across all groupings with

3 lobes involved as an average. Notably both BCOS and BROS groups had statistically significantly more exacerbations and prior bronchiectasis-related hospitalisations than the idiopathic bronchiectasis group (mean/ median 2.4 and 2.7 vs 1.8 p <0.05 and 26.1 and 58.4% vs 25.1% p<0.05). As expected the mean FEV_1% predicted was both statistically and clinically significantly lower in the BCOS group, in part reflecting the need for airflow obstruction to be present in this diagnostic grouping.

Outcomes in BROS

The mortality rate over a mean of 48 months follow up was 8.6% in patients with "other" causes of BR, 9.3% idiopathic BR, 18% for RA and 28.5% for COPD. There was no significant difference in follow-up duration between any of the four cohorts to explain the differences in mortality (mean 46, 48, 47 and 47 months respectively)- Figure 2.

Using logistic regression, there was a significant univariate association between RA and increased mortality (Odds Ratio (OR) 1.82, 95% Confidence Interval (CI) 1.15-2.89, p=0.01). This persisted after multivariable adjustment for BSI; OR 1.83, 95% CI 1.11-3.02, p=0.01. The relationship was greater in the fully adjusted model (including aetiology, all BSI individual components) - OR 2.03 95 CI 1.19-3.44, p=0.009.

COPD was also independently associated with worse outcome in all models adjusted OR 2.47, 95% CI 1.55-3.92 (in the fully adjusted model). No other aetiologies were independently associated with outcome (Hosner-Lemeshow goodness of fit test p=0.7 indicating excellent model fit).

There was, however, no significant relationship between RA and hospital admission risk during follow-up (OR 0.84, 95% CI 0.42-1.67, p=0.6). There was no significant relationship

between RA and more frequent exacerbations using multiple linear regression (adjusted for BSI, estimate 0.15 std err 0.18, p=0.5).

The results were confirmed using Cox-proportional hazard regression. The Hazard ratio for RA and mortality was 1.88, 95% CI 1.11-3.21, p=0.01. The Kaplan Meier survival curve is shown both for BCOS, BROS (figure 2)

Prediction

Despite clear variations in mortality rates associated with different aetiologies, the BSI showed good discrimination in patients with BROS giving an AUC of 0.77, 95% CI 0.67-0.87, p<0.0001).

Additionally we applied calibration analysis to determine whether the BSI scoring systems perform similarly well in a different population, such as BROS when compared to the overall BR population. Rheumatoid Arthritis was associated with an increased mortality risk across all BSI subgroups – OR 2.57, 95% CI 0.48-13.9 in low risk patients, 2.1 (0.8-5.5) in intermediate risk and 1.64 (0.83-3.3) in high risk patients. Interaction test p=0.8. This analysis indicated that RA increases the risk across the full spectrum of bronchiectasis severity categories and should be considered additive to the BSI.

Validation of the pooled analysis

Using random effects meta-analysis of the 6 cohorts, RA was associated with increased mortality (OR 1.70, 95% CI 1.07-2.70, p=0.02). Importantly there was no heterogeneity in this relationship across all 6 studies. I^2=0%, Cochrans Q test p=0.6.

Discussion

Bronchiectasis (BR) and rheumatoid arthritis (RA) are undoubtedly linked and may present in patients in a variety of temporal and causal ways [4,5,7]. Bronchiectasis appears to predispose to later Rheumatoid arthritis and BRRA could be used to define this syndrome [5]. Patients with RA are known to develop bronchiectasis as their articular disease progresses and could be described as RABR. A third group could include those who coincidentally have both conditions without any causal relationship. Reflecting concerns over recall bias and inaccuracy in pinpointing the onset of a particular condition (in contrast to the time when it was diagnosed) we have opted to use the terminology BROS to encompass all three of these scenarios. This study is the first multi-centre international study to apply the recently validated BSI to define the severity of bronchiectasis in patients with comorbid RA. We report data in almost 150 patients with BROS from a 1716 patient cohort followed over an average of 4 years with bronchiectasis in the largest and only multi-centre study to date to define the impact of RA in BR. We benchmarked this group against a group increasingly recognised to have poorer outcome namely those with Bronchiectasis–COPD overlap syndrome (BCOS) and those often perceived to have more favourable outcomes namely "idiopathic bronchiectasis". We found however that whilst there was a statistically significantly higher BSI score in the BROS group when compared to idiopathic bronchiectasis (BSI mean 7.7 vs. 7.1, $p < 0.05$), this was not likely to be clinically significant as the mean BSI scores were both within the moderate BSI category (BSI score 5-8).

Importantly however, we show that BROS is significantly associated with increased mortality as compared to idiopathic bronchiectasis syndrome. Indeed the mortality in the

BROS overlap syndrome reached towards that seen in BCOS [9,16]. Using multiple modelling methods we show that the mortality risk over 4 years is increased by approximately 80% and when adjusted for all components of the BSI that the odds ratio reached 2.0 indicating a doubling of mortality risk. This effect was replicated in survival analyses confirming that BROS is associated with higher mortality. Importantly this appears independent of the rates of hospitalisation, non-hospitalised exacerbations, spirometric and radiological markers of disease burden.

The co-existence of BR and RA has previously been suggested to have major clinical significance: In 1997, a single centre UK study reported that patients with both BR and RA (BROS) had greatly elevated standardised mortality ratios 7.3 times higher than the general population, 5 times that of patients with RA alone and 2.4 times that of patients with BR over 5 years [17] Our observed mortality rates herein were 18% and the Odds Ratio for mortality was slightly less than that reported in the above study. Careful review of this prior work suggests potential case ascertainment bias with a more severe BROS subgroup selected- only 32 patients with BROS were identified from their RA cohort of 3000 (1%). Their reported prevalence rate is lower than we observed (~8%) and contrasts to more recent studies suggesting prevalence rates ranging from 3% to 30% radiologically. Nevertheless a recent single centre case-control study of patients recruited 1999-2002 reported an excess of mortality over an 11 year period of follow up[18]. The patients with BROS had also a poorer prognosis in terms of survival after RA diagnosis (HR, 8.6; 95% CI, 1.5-48.2; P=0.014) and from birth (HR, 9.6; 95% CI, 1.1-81.7; P=0.039). Divergence in mortality rates was seen within the first 5 years in this study. Collectively these prior data and our international multi-centre observations support BROS as a risk for poorer outcomes.

The reasons for this may be distinct to the pulmonary disease component as suggested by the similar rates of exacerbation and lung function seen between BROS and idiopathic BR

noted herein. This effect may be more clearly seen in those with milder bronchiectasis as suggested by our sensitivity analysis. It is possible that the treatments used for rheumatoid arthritis, which include powerful immunosuppressant drugs, may impact on survival but our study was not designed to define the reasons for poorer outcomes. In this study we did not have funding to collect detailed information on the management of RA and therefore are unable to assess the role this has in the observed increased mortality. Notably however in our prior work we have not seen significantly different rates of disease modifying anti-rheumatic drugs (DMARD) therapy between RA and BROS patients in an intensively characterised UK cohort [19]. We could however demonstrate greater rates of autoantibody seropositivity, inflammatory markers and joint involvement suggesting the BROS syndrome is associated with greater immune activation and systemic inflammation [19,20]. This is noteworthy as RA has been associated with an excess of cardiovascular deaths and is now incorporated as independent risk factor in the cardiovascular Q-RISK2 scoring system [21]. Bronchiectasis has also been recently linked with excessive cardiovascular risk [22] and this may be an underpinning mechanism for excess mortality in BROS with additive cardiovascular risk driven by each pro-inflammatory comorbidity. This requires further mechanistic research that was not possible herein as only limited data collection was possible.

We have also shown that the BSI scoring system still predicts poorer mortality outcomes in those with BROS and that the effects are seen across the range of BSI categories. RA is certainly an additive and independent predictor of severity/death and aetiology may need incorporated into future risk stratification systems.

To benchmark the outcomes in BROS we used a previously described bronchiectasis aetiology associated with poor outcomes.

We show that BCOS has an elevated mortality risk (28% risk of death over 4 years), which is much higher than that reported in the selected population recruited into the TORCH study of COPD (patients who had an average FEV1 of ~60% (15% mortality over 3 years).[23] The mortality rates in the BCOS population were high and in the order of those reported in GOLD stage II/III COPD patients (or those within BODE index quartile 3) in the BODE index cohort and in more recent studies.[24, 25] We extend the findings of Gatheral *et al* demonstrating that BCOS is associated with a high hospital admission rate (58% in this series) and that persistent *Pseudomonas aeruginosa* infection is common in BCOS (24% herein).[25] In contrast to this recent paper from the UK which did not show an excess of mortality in BCOS when compared to COPD alone [26] we confirm work from others [9,16,27] that BCOS is associated with excess mortality when compared to other bronchiectasis aetiologies. These differences may be explained by the comparator groups; Gatheral compared BCOS to relatively severe COPD patients whilst in the other studies and our current study, the comparator group has been bronchiectasis often including those with mild disease [26,27]. Our definition of BCOS may have incorrectly categorised idiopathic bronchiectasis patients who previously smoked as BCOS. Nevertheless our pragmatic definition appears to have confirmed the findings reported from single centres [9,16,27]. There is a consensus on the need to better define bronchiectasis phenotypes and predictors of mortality [28,29]. One area to focus upon is BCOS, a syndrome that is clearly adversely prognostic yet difficult to define precisely and mechanisms leading to adverse outcomes are unclear [reviewed in 29]. BROS clearly is another area also requiring better understanding. We do not have prescription records of immunosuppressive therapies to target rheumatoid arthritis this patient population- such therapies may influence both infection rates and possibly mortality in the setting of BROS. These data will be prospectively collected in UK national and European observational cohorts and should allow future associations to be

explored (www.bronch.ac.uk)[30]. Our study has inherent limitations in addition to those relating to concomitant medications: We excluded patients with active non-tuberculous mycobacterial disease and patients with known RA-related interstitial lung disease. These factors may have contributed to the differences in the BSI scores between groups. We cannot however exclude the possibility of "missed" cases of BROS being incorrectly classified as idiopathic BR in any of the cohorts though serological testing for rheumatoid arthritis was conducted in all cohorts. The pooling of data from multiple centres may be regarded as a limitation, as there was some heterogeneity in the populations, such as the exclusion of BCOS patients from the Edinburgh cohort (that reflected an *a priori* decision at that recruiting centre [8]. Nevertheless in our sensitivity analysis we demonstrate no significant heterogeneity in the relationship between BROS and mortality and therefore we regard the robustness of this finding across multiple centres as a strength and not as a weakness. We did not assess RA serology repeatedly only doing so when at a patients' first clinic review or when new symptoms prompted a clinical suspicion of RA. Therefore it is possible that our BR patients may have inadvertently included some subclinical or early stage RA that should have been placed in the BROS category. Lastly, our mortality data did not compare outcomes in BROS with a cohort of patients with RA alone nor included the recorded cause of death; these data will be highly relevant to future studies.

In conclusion, in the largest cohort studied to date, both BROS and BCOS have both been shown to be associated with poorer outcomes and should be investigated further as a priority in longitudinal and mechanistic studies to assess drivers of mortality [28,29]. The current data support the premise that BROS patients are at higher risk of premature death and a multidisciplinary approach involving chest and rheumatology physicians is needed. Patients with BROS with "mild" bronchiectasis defined radiologically by extent or by using

composite scoring systems may need closer monitoring than those with other aetiologies causing bronchiectasis.

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Table 1 Details of the European Bronchiectasis Cohorts

	Leuven (Belgium)	Galway (Ireland)	Monza (Italy)	Edinburgh (UK)	Newcastle (UK)	Dundee (UK)
Total, n.(%)	253 (100)	242 (100)	201 (100)	608 (100)	126 (100)	286 (100)
Demographic						
Age (median, IQR))	68 (56-78)	63 (53-71)	68 (59-73)	67 (58-75)	61 (54-69)	68 (61-75)
Male Gender	127 (50%)	76 (31%)	80 (39%)	243(40%)	51 (41%)	115 (42%)
Aetiology*						
Idiopathic	78 (31%)	98 (40%)	79 (39%)	261 (42%)	52 (41%)	124 (43%)
Post-infective	50 (19%)	41 (17%)	51 (25%)	207 (34%)	28 (22%)	51 (17%)
ABPA	15 (6%)	5 (2%)	4 (2%)	49 (8%)	8 (6%)	31 (11%)
BCOS	42 (17%)	26 (11%)	49 (24%)	0 (excl)	15 (12%)	7 (2%)
Immuno-deficiency	18 (7%)	13 (5%)	9 (4%)	6 (1)	14 (11%)	16 (6%)
BROS	25 (10%)	55 (23)	2 (1%)	44 (7%)	11 (9%)	10 (4%)
IBD	5 (2%)	4 (2%)	6 (3%)	14 (2%)	2 (1%)	8 (3)
Severity markers						
Exacerbations/yr	1.8 (2.0)	3.2 (1.3)	1.9 (1.9)	1.7 (2.0)	3.4 (1.7)	2.1 (1.8)
Prior hospital admissions – n (%)	67 (26%)	63 (26%)	56 (27%)	133 (21%)	74 (58%)	66 (23%)
%*P. aeruginosa*	20 (8%)	35 (14%)	39 (19%)	70 (12%)	13 (10%)	37 (14%)
Lobes involved on CT	2.9 (1.3)	2.7 (1.3)	2.8 (1.4)	3.0 (1.6)	2.8 (1.4)	3.2 (1.6)

(mean/ SD)						
Mean FEV_1 % pred	70.1 (27)	77.5 (24)	71.7 (35)	72.6 (25)	64.0 (27)	72.1 (26)
Mean BSI score	6.7 (4.8)	7.2 (4.4)	7.2 (4.5)	7.3 (4.8)	9.6 (4.9)	7.1 (4.5)

Key; ABPA allergic bronchopulmonary aspergillosis, BCOS Bronchiectasis-COPD overlap syndrome, BROS bronchiectasis- Rheumatoid arthritis, IBD inflammatory bowel disease, BSI Bronchiectasis severity index, CT – computerised tomography scan. FEV1 Forced expiratory volume 1 second. Less frequent aetiologies not shown. Data are presented as mean (standard deviation) or N(%) unless otherwise stated. Excl- BCOS patients were excluded from this cohort.

Table 2 Comparison between BROS and non-RA patients with bronchiectasis

	BROS	Idiopathic BR	BCOS	Other BR
Age (median-IQR)	69 (60-76)#	67 (58-74)#	73 (65-78)*	64 (55-72)*#
Gender	34.3% male#	38.2% male#	70.0% male*	38.4% male#
Exacerbations/yr	2.4 (1.9)	1.8 (1.9)*#	2.7 (2.0)	2.2 (2.0)
Prior hospital admissions	26.1%#	25.1%#	58.4%*	23.7%#
% *P. aeruginosa*	14.3%#	14.7%#	24.1%*	14%#
Lobes involved on CT	3.0 (1.5)	2.8 (1.5)	3.1 (1.4)	3.0 (1.5)
Mean FEV_1 % pred	76% (25)#	76% (25)#	51% (22)*	74% (25)#
Mean BSI score	7.7 (4.6)#	7.1 (4.6)*#	10.4 (4.5)*	6.9 (4.3)*#

Key; BROS bronchiectasis- rheumatoid arthritis, BCOS Bronchiectasis-COPD overlap syndrome, BSI Bronchiectasis severity index, CT – computerised tomography scan. FEV1 Forced expiratory volume 1 second *= $p<0.05$ compared with BROS, #= $p<0.05$ compared with BCOS. Data are presented as mean (standard deviation) or N(%) unless otherwise stated.

Figure 1 CONSORT diagram

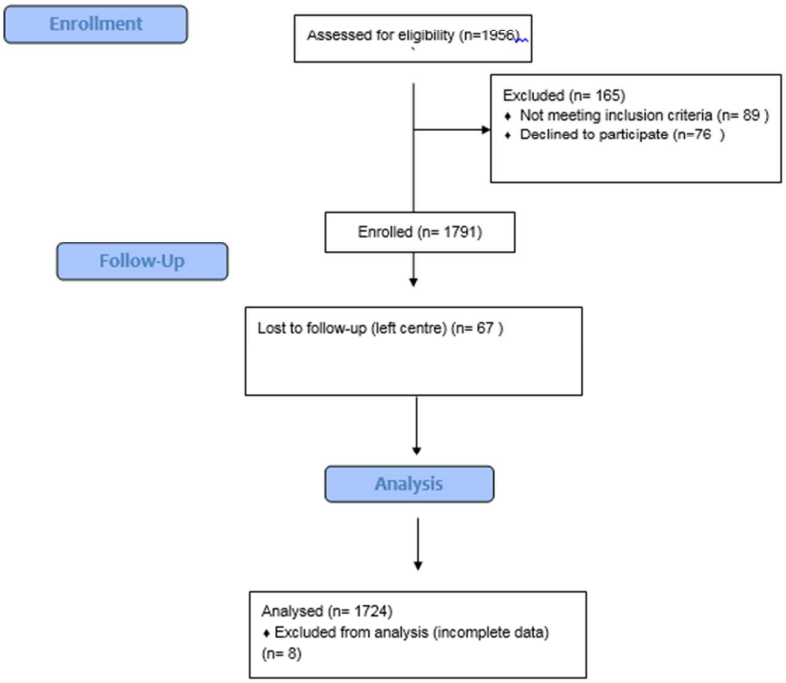

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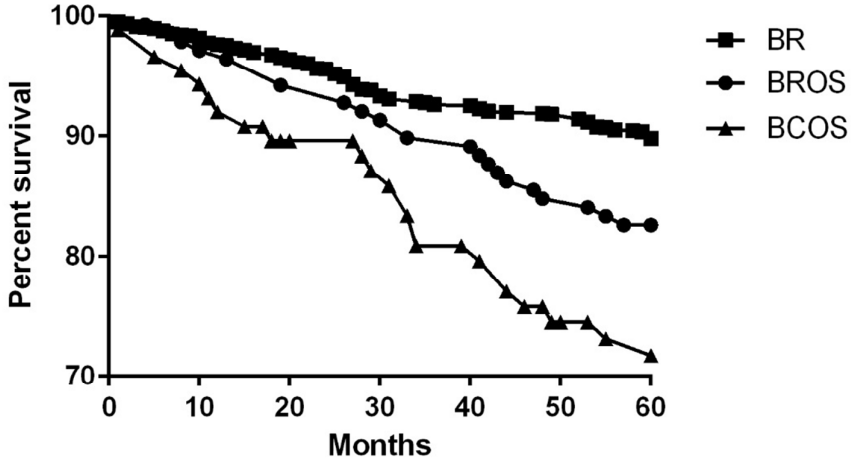
Figure 2. Survival analysis comparing BROS to other aetiologies



The survival analysis was completed using Kaplan Meier analysis comparing BROS (bronchiectasis-rheumatoid arthritis) and BCOS (Bronchiectasis-COPD overlap syndrome) to other causes of bronchiectasis. Both BROS and BCOS had significantly poorer survival than for other aetiologies of BR ($p<0.05$).

Bronchiectasis Rheumatoid overlap syndrome (BROS) is an independent risk factor for mortality in patients with bronchiectasis: A multicentre cohort study

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Running head: Rheumatoid associated bronchiectasis and outcomes

Conflicts of interest: All authors declare no conflicts of interest in relation to the present study.

Abstract

Introduction

We studied if Bronchiectasis (BR) and Rheumatoid arthritis (RA) when manifesting as an overlap syndrome (BROS) was associated with worse outcomes than other BR aetiologies applying the Bronchiectasis Severity Index (BSI).

Methods

We interrogated the Bronchiectasis Severity Index (BSI) databases of 1716 patients across 6 centres: Edinburgh, UK (608 patients), Dundee, UK (N=286), Leuven, Belgium (N=253), Monza, Italy (N=201), Galway Ireland (N=242) and Newcastle, UK (N=126). Patients were categorised as BROS (those with RA and Bronchiectasis without interstitial lung disease), idiopathic bronchiectasis, Bronchiectasis-COPD overlap syndrome (BCOS) and "other" BR aetiologies. Mortality rates, hospitalisation and exacerbation frequency were recorded.

Results

We identified 147 patients with BROS (8.5% of cohort). There was a statistically significant relationship between BROS and mortality although this was not associated with higher rates of bronchiectasis exacerbations or bronchiectasis-related hospitalisations. The mortality rate over a mean of 48 months was 9.3% for idiopathic BR, 8.6% in patients with "other" causes of BR, 18% for RA and 28.5% for BCOS. Mortality was statistically higher in BROS and BCOS compared with all other aetiologies. The BSI scores were statistically but not clinically significantly higher in those with BROS when compared to idiopathic BR (BSI mean 7.7 vs. 7.1 respectively, p <0.05). BCOS had significantly higher BSI scores (mean 10.4), *Pseudomonas aeruginosa* colonization rates (24%) and prior hospitalisation rates (58%).

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Conclusions

Both BROS and BCOS groups have an excess of mortality -the mechanisms for this may be complex but these data highlight that these subgroups ~~may benefit from~~require additional study to understand ~~the drivers for~~this excess mortality.

=~~245~~ 250words

Introduction

Non-cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis-BR) is a chronic respiratory disorder characterised by recurrent cough, sputum production and respiratory infections[1] Pathologically, patients have abnormally dilated bronchi leading to impairment of host defence, chronic infection with bacteria and airways inflammation.[2,3]

Rheumatoid arthritis (RA) is a common auto-immune disease associated with many extra-articular features. RA has numerous pulmonary complications including interstitial lung diseases that may lead to "traction bronchiectasis" whilst the association between RA and bronchiectasis without interstitial lung disease (hereafter BROS) is well recognised. Recent studies note a significantly higher prevalence of symptomatic bronchiectasis in RA subjects (approximately 3%) as compared to 0.03% in the general population [4]. Supporting this are high resolution CT scanning (HRCT) studies consistently reporting high prevalence of up to 30% of radiological evidence of BR in RA populations [5,6].

Historical single centre studies have suggested that patients with BROS may have a worse clinical course than those patients with bronchiectasis due to other aetiologies. Recently we have identified that when compared to patients with RA alone, BROS patients have a higher indices of RA activity e.g. disease activity scores (DAS-28) demonstrating worse rheumatoid arthritis and higher levels of RA seropositivity [7]

We therefore wished to explore ~~the corollary- Is~~if BROS was associated with poorer outcomes compared to BR without RA.~~?~~ Defining the clinical severity of bronchiectasis has ~~until~~ been problematic until recent scoring indices such as the Bronchiectasis Severity Index (BSI) became available[8]. We therefore aimed to assess mortality, frequency of exacerbations, hospital admissions, reported health related quality of life and BSI scores in an

international cohort comparing BROS to BR without RA. Idiopathic bronchiectasis was used as a benchmark due to its prevalence and a perception that this aetiological group may have better outcomes.[1] As bronchiectasis and COPD overlap syndrome (BCOS) has been linked to excess mortality we used this second group as an additional reference group[9].

Methods

Multicentre assessment of bronchiectasis severity

Six independent cohorts of patients were ~~independently~~ collected from specialist Bronchiectasis services in Edinburgh, Dundee and Newcastle (UK), Leuven (Belgium), Monza (Italy) and Galway (Ireland) with an average follow up of 4 years[8,10]. Consecutive adult patients were enrolled on the basis of a diagnosis of bronchiectasis made by high resolution computed tomography (HRCT) and a clinical history consistent with bronchiectasis.[1] Patients were excluded if they had active malignancy at enrolment, cystic fibrosis, active mycobacterial disease (including active non-tuberculous mycobacteria (NTM)), HIV or a primary diagnosis of pulmonary fibrosis/sarcoidosis with secondary traction bronchiectasis. Patients with BCOS were not included within the Edinburgh cohort due to their cohort building protocol. Cohort building was approved at each individual centre; by the South East Scotland Research Ethics Committee, Research ethics service multi-centre ethics - IRAS 12324 and by NRES, UK 12/NE/0298, CA 128 Clinical research committee, Galway [8,10].

Aetiological categorisation

The underlying aetiology of bronchiectasis was determined following testing recommended by the British Thoracic Society (BTS) guidelines [1]. This includes serological and clinical assessment for Rheumatoid arthritis [1].

BROS required a diagnosis of both BR, as above, and Rheumatoid arthritis, defined according to the 2010 American College of Rheumatology (ACR) and European League

Against Rheumatism (EULAR) RA criteria [~~10~~11] and local prevailing clinical guidelines. Patients were grouped into the BROS category irrespective of which of the two conditions preceded the other.

Patients were pragmatically categorised as BCOS based on evidence of airflow obstruction and smoking greater than 20 pack years. The presence of emphysema on CT scan was not a pre-requisite.

Post-infectious causes were attributed when a clear history of bronchiectasis after an acute infectious episode was reported[1]. Inflammatory bowel disease and ABPA associated aetiological categories were applied when a clear history and/or appropriate serological and history were reported respectively. Idiopathic was attributed as a diagnostic grouping in the absence of any recognised aetiology. "Other bronchiectasis" was a grouping of categories that included all remaining aetiological groups (e.g. immunodeficiency associated bronchiectasis- including those on immunoglobulin replacement, ciliary dyskinesia etc).

Clinical assessments

At the time of clinical assessment all patients were clinically stable with no antibiotic use in the preceding 4 weeks. All patients underwent spirometry (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) according to ERS guidelines with the highest of three technically satisfactory measurements recorded).

Radiological severity

Radiological severity of bronchiectasis was assessed using a modified Reiff score which has been used previously bronchiectasis studies.[8,~~11~~12,~~12~~13] The score assesses the number of lobes involved (with the lingula considered to be a separate lobe) and the degree of bronchial

dilatation (tubular-1, varicose-2 and cystic-3) with a maximum score of 18 and minimum score of 1. There was no minimum Reiff score for patients to be entered into the cohorts.

Bacteriology

As previously described all bacteriology was performed using local culture protocols on spontaneous early morning sputum samples.[3] The definition of chronic persistent infection, was the isolation of potentially pathogenic bacteria in sputum culture on 2 or more occasions, with at least 3 months apart in a one year period.[~~12,~~13,14,15] The micro-organism grown most frequently over the study period was classed as the predominant pathogen. The clinical standards were sputum sampling at 6 monthly or more frequent intervals at clinic reviews.

BSI scores

As previously described, BSI scores were grouped as follows; scores 0-4 represents mild bronchiectasis, scores 5-8 moderate bronchiectasis and scores >8 represents severe bronchiectasis.[8]

End-points

Mortality: At the end of the follow-up periods, mortality was determined through notes review and interrogating national death records. Survival status was confirmed for 100% of participants although exact date of death was not available for all deceased patients.

Exacerbations were defined according to the BTS definition as an acute deterioration with worsening and/or systemic upset[1]. Severe exacerbations were defined as those needing hospitalisation. The frequency of exacerbations requiring antibiotic treatment were determined from clinic records and patient histories and verified against primary care prescription records.

Statistical analysis

Normally distributed data are presented as mean with standard deviation, whilst non-normally distributed data are presented as median with interquartile range. The Chi square test and Mann Whitney U test were used for comparison of categorical and numerical data respectively. For comparisons of more than 2 groups, one way ANOVA or the Kruskal-Wallis test were used as appropriate. For all analyses a value of $p<0.05$ was considered statistically significant. Independent relationships between BROS and BCOS with mortality were assessed using multivariable logistic regression, adjusting for the BSI. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Kaplan Meier survival curves and Cox-proportional hazards regression were performed for survival. The discrimination of the BSI for predicting mortality in BROS was assessed using the area under the receiver operator characteristic curve (AUC). We performed sensitivity analyses ~~in those with various BSI categories~~to determine if outcomes were different across all 3 BSI categories (mild, moderate and severe). Additionally we applied calibration analysis - an analysis to determine whether scoring systems perform similarly in a different population compared to the baseline population. As a sensitivity analysis to determine the validity of pooling cohorts, the authors used random effects meta-analysis. Data were pooled using the Mantel-Haenszel method and heterogeneity assessed using Higgins I^2 test and Cochrans Q test.

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Results

Multi-centre assessment

We collected data from 1716 adult patients with bronchiectasis across 6 centres in Western Europe. The data is displayed in Table 1 and Figure 1. The median age was 65 years with a female predominance and the commonest aetiological groups were idiopathic and post-infectious suggesting these were broadly representative of bronchiectasis cohorts previously reported.[1]

Overall BROS was present in 8.5% of the cohort whilst BCOS was present in 12% of the cohorts that included BCOS during cohort building. The mean exacerbation frequency was greater than 2 exacerbations per year and all cohorts reported a prior history of hospitalisation in at least 20% of patients. Chronic *Pseudomonas aeruginosa* infection was present in a mean of 13% of patients overall. The mean BSI scores for each centre ranged from 6-9. Prior data has demonstrated this is consistent with patients with moderate to severe bronchiectasis [8].~~The mean BSI scores across each cohort suggested patients with moderate to severe bronchiectasis were in follow up at such centres.~~ The centre with the ~~highest~~ highest hospital admission rate (Newcastle) also had the highest observed mean BSI score 9.6.

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Comparison between BROS and non-RA patients with bronchiectasis

The comparisons between BROS and other groups are shown in table 2. In general the BROS patients were similar in terms of age and gender distribution except when compared to the BCOS group who were significantly older and significantly more likely to be male. The BSI scores were statistically significantly higher in the BROS group as compared to idiopathic and other BR though all remained within the moderate severity category of the BSI (scores

5-8). Radiological burden of disease was not significantly different across all groupings with 3 lobes involved as an average. Notably both BCOS and BROS groups had statistically significantly more exacerbations and prior bronchiectasis-related hospitalisations than the idiopathic bronchiectasis group (mean/ median 2.4 and 2.7 vs 1.8 p <0.05 and 26.1 and 58.4% vs 25.1% p<0.05). As expected the mean FEV_1% predicted was both statistically and clinically significantly lower in the BCOS group, in part reflecting the need for airflow obstruction to be present in this diagnostic grouping.

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Outcomes in BROS

The mortality rate over a mean of 48 months follow up was 8.6% in patients with "other" causes of BR, 9.3% idiopathic BR, 18% for RA and 28.5% for COPD. There was no significant difference in follow-up duration between any of the four cohorts to explain the differences in mortality (mean 46, 48, 47 and 47 months respectively)- Figure 2.

Using logistic regression, there was a significant univariate association between RA and increased mortality (Odds Ratio (OR) 1.82, 95% Confidence Interval (CI) 1.15-2.89, p=0.01). This persisted after multivariable adjustment for BSI; OR 1.83, 95% CI 1.11-3.02, p=0.01. The relationship was greater in the fully adjusted model (including aetiology, all BSI individual components) - OR 2.03 95 CI 1.19-3.44, p=0.009.

COPD was also independently associated with worse outcome in all models adjusted OR 2.47, 95% CI 1.55-3.92 (in the fully adjusted model). No other aetiologies were independently associated with outcome (Hosner-Lemeshow goodness of fit test p=0.7 indicating excellent model fit).

There was, however, no significant relationship between RA and hospital admission risk during follow-up (OR 0.84, 95% CI 0.42-1.67, p=0.6). There was no significant relationship between RA and more frequent exacerbations using multiple linear regression (adjusted for BSI, estimate 0.15 std err 0.18, p=0.5).

The results were confirmed using Cox-proportional hazard regression. The Hazard ratio for RA and mortality was 1.88, 95% CI 1.11-3.21, p=0.01. The Kaplan Meier survival curve is shown both for BCOS, BROS (figure 2)

Prediction

Despite clear variations in mortality rates associated with different aetiologies, the BSI showed good discrimination in patients with BROS giving an AUC of 0.77, 95% CI 0.67-0.87, p<0.0001).

Additionally we applied calibration analysis to determine whether the BSI scoring systems perform similarly well in a different population, such as BROS when compared to the overall BR population. Rheumatoid Arthritis was associated with an increased mortality risk across all BSI subgroups – OR 2.57, 95% CI 0.48-13.9 in low risk patients, 2.1 (0.8-5.5) in intermediate risk and 1.64 (0.83-3.3) in high risk patients. Interaction test p=0.8. This analysis indicated that RA increases the risk across the full spectrum of bronchiectasis severity categories and should be considered additive to the BSI.

Validation of the pooled analysis

Using random effects meta-analysis of the 6 cohorts, RA was associated with increased mortality (OR 1.70, 95% CI 1.07-2.70, p=0.02). Importantly there was no heterogeneity in this relationship across all 6 studies. I^2=0%, Cochrans Q test p=0.6.

Discussion

Bronchiectasis (BR) and rheumatoid arthritis (RA) are undoubtedly linked and may present in patients in a variety of temporal and causal ways [4,5,7]. Bronchiectasis appears to predispose to later Rheumatoid arthritis and BRRA could be used to define this syndrome [5]. Patients with RA are known to develop bronchiectasis as their articular disease progresses and could be described as RABR. A third group could include those who coincidentally have both conditions without any causal relationship. Reflecting concerns over recall bias and inaccuracy in pinpointing the onset of a particular condition (in contrast to the time when it was diagnosed) we have opted to use the terminology BROS to encompass all three of these scenarios. This study is the first multi-centre international study to apply the recently validated BSI to define the severity of bronchiectasis in patients with comorbid RA. We report data in almost 150 patients with BROS from a 1716 patient cohort followed over an average of 4 years with bronchiectasis in the largest and only multi-centre study to date to define the impact of RA in BR. We benchmarked this group against a group increasingly recognised to have poorer outcome namely those with Bronchiectasis–COPD overlap syndrome (BCOS) and those often perceived to have more favourable outcomes namely "idiopathic bronchiectasis". We found however that whilst there was a statistically significantly higher BSI score in the BROS group when compared to idiopathic bronchiectasis (BSI mean 7.7 vs. 7.1, $p < 0.05$), this was not likely to be clinically significant as the mean BSI scores were both within the moderate BSI category (BSI score 5-8).

Importantly however, we show that BROS is significantly associated with increased mortality as compared to idiopathic bronchiectasis syndrome. Indeed the mortality in the

BROS overlap syndrome reached towards that seen in BCOS [9,~~15~~16]. Using multiple modelling methods we show that the mortality risk over 4 years is increased by approximately 80% and when adjusted for all components of the BSI that the odds ratio reached 2.0 indicating a doubling of mortality risk. This effect was replicated in survival analyses confirming that BROS is associated with higher mortality. Importantly this appears independent of the rates of hospitalisation, non-hospitalised exacerbations, spirometric and radiological markers of disease burden.

The co-existence of BR and RA has previously been suggested to have major clinical significance: In 1997, a single centre UK study reported that patients with both BR and RA (BROS) had greatly elevated standardised mortality ratios 7.3 times higher than the general population, 5 times that of patients with RA alone and 2.4 times that of patients with BR over 5 years [~~16~~17] Our observed mortality rates herein were 18% and the Odds Ratio for mortality was slightly less than that reported in the above study. Careful review of this prior work suggests potential case ascertainment bias with a more severe BROS subgroup selected- only 32 patients with BROS were identified from their RA cohort of 3000 (1%). Their reported prevalence rate is lower than we observed (~8%) and contrasts to more recent studies suggesting prevalence rates ranging from 3% to 30% radiologically. Nevertheless a recent single centre case-control study of patients recruited 1999-2002 reported an excess of mortality over an 11 year period of follow up[~~17~~18]. The patients with BROS had also a poorer prognosis in terms of survival after RA diagnosis (HR, 8.6; 95% CI, 1.5-48.2; P=0.014) and from birth (HR, 9.6; 95% CI, 1.1-81.7; P=0.039). Divergence in mortality rates was seen within the first 5 years in this study. Collectively these prior data and our international multi-centre observations support BROS as a risk for poorer outcomes.

The reasons for this may be distinct to the pulmonary disease component as suggested by the similar rates of exacerbation and lung function seen between BROS and idiopathic BR

noted herein. This effect may be more clearly seen in those with milder bronchiectasis as suggested by our sensitivity analysis. It is possible that the treatments used for rheumatoid arthritis, which include powerful immunosuppressant drugs, may impact on survival but our study was not designed to define the reasons for poorer outcomes. In this study we did not have funding to collect detailed information on the management of RA and therefore are unable to assess the role this has in the observed increased mortality. Notably however in our prior work we have not seen significantly different rates of disease modifying anti-rheumatic drugs (DMARD) therapy between RA and BROS patients in an intensively characterised UK cohort [19]. We could however demonstrate greater rates of autoantibody seropositivity, inflammatory markers and joint involvement suggesting the BROS syndrome is associated with greater immune activation and systemic inflammation [~~18~~19,~~19~~20]. This is noteworthy as RA has been associated with an excess of cardiovascular deaths and is now incorporated as independent risk factor in the cardiovascular Q-RISK2 scoring system [~~20~~21]. Bronchiectasis has also been recently linked with excessive cardiovascular risk [~~21~~22] and this may be an underpinning mechanism for excess mortality in BROS with additive cardiovascular risk driven by each pro-inflammatory comorbidity. This requires further mechanistic research that was not possible herein as only limited data collection was possible.

We have also shown that the BSI scoring system still predicts poorer mortality outcomes in those with BROS and that the effects are seen across the range of BSI categories. RA is certainly an additive and independent predictor of severity/death and aetiology may need incorporated into future risk stratification systems.

To benchmark the outcomes in BROS we used a previously described bronchiectasis aetiology associated with poor outcomes.

We show that BCOS has an elevated mortality risk (28% risk of death over 4 years), which is much higher than that reported in the selected population recruited into the TORCH study of COPD (patients who had an average FEV1 of ~60% (15% mortality over 3 years).[~~22~~23] The mortality rates in the BCOS population were high and in the order of those reported in GOLD stage II/III COPD patients (or those within BODE index quartile 3) in the BODE index cohort and in more recent studies.[~~23~~24, ~~24~~25] We extend the findings of Gatheral *et al* demonstrating that BCOS is associated with a high hospital admission rate (58% in this series) and that persistent *Pseudomonas aeruginosa* infection is common in BCOS (24% herein).[25] In contrast to this recent paper from the UK which did not show an excess of mortality in BCOS when compared to COPD alone [~~25~~26] we confirm work from others [9,~~15~~16,~~26~~27] that BCOS is associated with excess mortality when compared to other bronchiectasis aetiologies. These differences may be explained by the comparator groups; Gatheral compared BCOS to relatively severe COPD patients whilst in the other studies and our current study, the comparator group has been ~~mild~~ bronchiectasis often including those with mild disease [~~25~~26-,~~26~~27]. Our definition of BCOS may have incorrectly categorised idiopathic bronchiectasis patients who previously smoked as BCOS. Nevertheless our pragmatic definition appears to have confirmed the findings reported from single centres [9,16,27]. There is a consensus on the need to better define bronchiectasis phenotypes and predictors of mortality [28,29]. One area to focus upon is BCOS, a syndrome that is clearly adversely prognostic yet difficult to define precisely and mechanisms leading to adverse outcomes are unclear [reviewed in 29]. BROS clearly is another area also requiring better understanding.

We do not have prescription records of immunosuppressive therapies to target rheumatoid arthritis this patient population- such therapies may influence both infection rates and possibly mortality in the setting of BROS. These data will be prospectively collected in

UK national and European observational cohorts and should allow future associations to be explored (www.bronch.ac.uk~~,~~)[~~29~~30]. Our study has inherent limitations in addition to those relating to concomitant medications: We excluded patients with active non-tuberculous mycobacterial disease and patients with known RA-related interstitial lung disease. These factors may have contributed to the differences in the BSI scores between groups. We cannot however exclude the possibility of "missed" cases of BROS being incorrectly classified as idiopathic BR in any of the cohorts though serological testing for rheumatoid arthritis was conducted in all cohorts. The pooling of data from multiple centres may be regarded as a limitation, as there was some heterogeneity in the populations, such as the exclusion of BCOS patients from the Edinburgh cohort (that reflected an *a priori* decision at that recruiting centre [8]. Nevertheless in our sensitivity analysis we demonstrate no significant heterogeneity in the relationship between BROS and mortality and therefore we regard the robustness of this finding across multiple centres as a strength and not as a weakness. We did not assess RA serology repeatedly only doing so when at a patients' first clinic review or when new symptoms prompted a clinical suspicion of RA. Therefore it is possible that our BR patients may have inadvertently included some subclinical or early stage RA that should have been placed in the BROS category. Lastly, our mortality data did not compare outcomes in BROS with a cohort of patients with RA alone nor included the recorded cause of death; these data will be highly relevant to future studies.

In conclusion, in the largest cohort studied to date, both BROS and BCOS have both been shown to be associated with poorer outcomes and should be investigated further as a priority in longitudinal and mechanistic studies to assess drivers of mortality [~~27~~28,~~28~~29]. The current data support the premise that BROS patients are at higher risk of premature death and a multidisciplinary approach involving chest and rheumatology physicians is needed. Patients with BROS with "mild" bronchiectasis defined radiologically by extent or by using

composite scoring systems may need closer monitoring than those with other aetiologies causing bronchiectasis.

Acknowledgements

ADS, JC, SA, PG, MJM designed the study. MJM, ADS and JC drafted the manuscript, ADS, MJM and JC conducted the statistical analyses. The coauthors collected the primary data and revised the drafts. The authors acknowledge ~~Sarah Lonni MD and~~ Alberto Pesci MD from the Health Science Department, University of Milan Bicocca, and Paul McAlinden, Freeman Hospital, Newcastle, UK, for assistance with data collection.

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Table 1 Details of the European Bronchiectasis Cohorts

	Leuven (Belgium)	Galway (Ireland)	Monza (Italy)	Edinburgh (UK)	Newcastle (UK)	Dundee (UK)
Total, n.(%)	253 (100)	242 (100)	201 (100)	608 (100)	126 (100)	286 (100)
Demographic						
Age (median, IQR))	68 (56-78)	63 (53-71)	68 (59-73)	67 (58-75)	61 (54-69)	68 (61-75)
Male Gender	127 (50%)	76 (31%)	80 (39%)	243(40%)	51 (41%)	115 (42%)
Aetiology*						
Idiopathic	78 (31%)	98 (40%)	79 (39%)	261 (42%)	52 (41%)	124 (43%)
Post-infective	50 (19%)	41 (17%)	51 (25%)	207 (34%)	28 (22%)	51 (17%)
ABPA	15 (6%)	5 (2%)	4 (2%)	49 (8%)	8 (6%)	31 (11%)
BCOS	42 (17%)	26 (11%)	49 (24%)	0 (excl)	15 (12%)	7 (2%)
Immuno-deficiency	18 (7%)	13 (5%)	9 (4%)	6 (1)	14 (11%)	16 (6%)
BROS	25 (10%)	55 (23)	2 (1%)	44 (7%)	11 (9%)	10 (4%)
IBD	5 (2%)	4 (2%)	6 (3%)	14 (2%)	2 (1%)	8 (3)
Severity markers						
Exacerbations/yr	1.8 (2.0)	3.2 (1.3)	1.9 (1.9)	1.7 (2.0)	3.4 (1.7)	2.1 (1.8)
Prior hospital admissions – n (%)	67 (26%)	63 (26%)	56 (27%)	133 (21%)	74 (58%)	66 (23%)
%*P. aeruginosa*	20 (8%)	35 (14%)	39 (19%)	70 (12%)	13 (10%)	37 (14%)
Lobes involved on CT	2.9 (1.3)	2.7 (1.3)	2.8 (1.4)	3.0 (1.6)	2.8 (1.4)	3.2 (1.6)

(mean/ SD)						
Mean FEV_1 % pred	70.1 (27)	77.5 (24)	71.7 (35)	72.6 (25)	64.0 (27)	72.1 (26)
Mean BSI score	6.7 (4.8)	7.2 (4.4)	7.2 (4.5)	7.3 (4.8)	9.6 (4.9)	7.1 (4.5)

Key; ABPA allergic bronchopulmonary aspergillosis, BCOS Bronchiectasis-COPD overlap syndrome, BROS bronchiectasis- Rheumatoid arthritis, IBD inflammatory bowel disease, BSI Bronchiectasis severity index, CT – computerised tomography scan. FEV1 Forced expiratory volume 1 second. Less frequent aetiologies not shown. Data are presented as mean (standard deviation) or N(%) unless otherwise stated. Excl- BCOS patients were excluded from this cohort.

Table 2 Comparison between BROS and non-RA patients with bronchiectasis

	BROS	Idiopathic BR	BCOS	Other BR
Age (median-IQR)	69 (60-76)#	67 (58-74)#	73 (65-78)*	64 (55-72)*#
Gender	34.3% male#	38.2% male#	70.0% male*	38.4% male#
Exacerbations/yr	2.4 (1.9)	1.8 (1.9)*#	2.7 (2.0)	2.2 (2.0)
Prior hospital admissions	26.1%#	25.1%#	58.4%*	23.7%#
% *P. aeruginosa*	14.3%#	14.7%#	24.1%*	14%#
Lobes involved on CT	3.0 (1.5)	2.8 (1.5)	3.1 (1.4)	3.0 (1.5)
Mean FEV_1 % pred	76% (25)#	76% (25)#	51% (22)*	74% (25)#
Mean BSI score	7.7 (4.6)#	7.1 (4.6)*#	10.4 (4.5)*	6.9 (4.3)*#

Key; BROS bronchiectasis- rheumatoid arthritis, BCOS Bronchiectasis-COPD overlap syndrome, BSI Bronchiectasis severity index, CT – computerised tomography scan. FEV1 Forced expiratory volume 1 second *= $p<0.05$ compared with BROS, #= $p<0.05$ compared with BCOS. Data are presented as mean (standard deviation) or N(%) unless otherwise stated.

Figure 1 CONSORT diagram

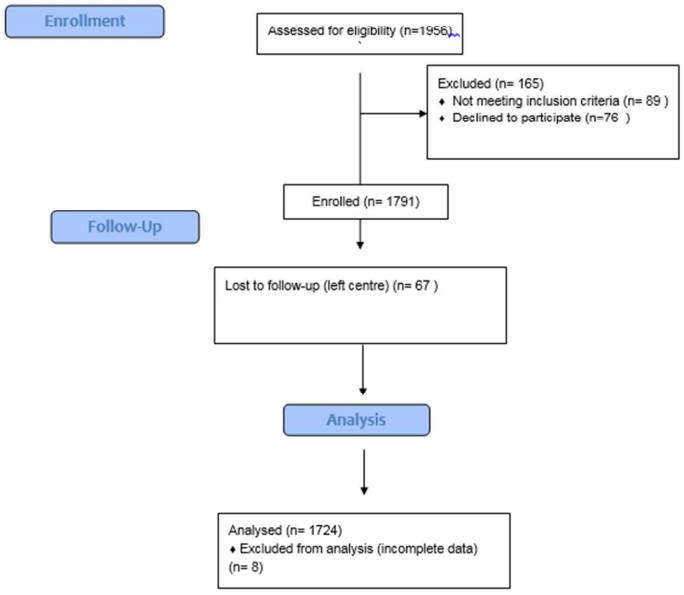

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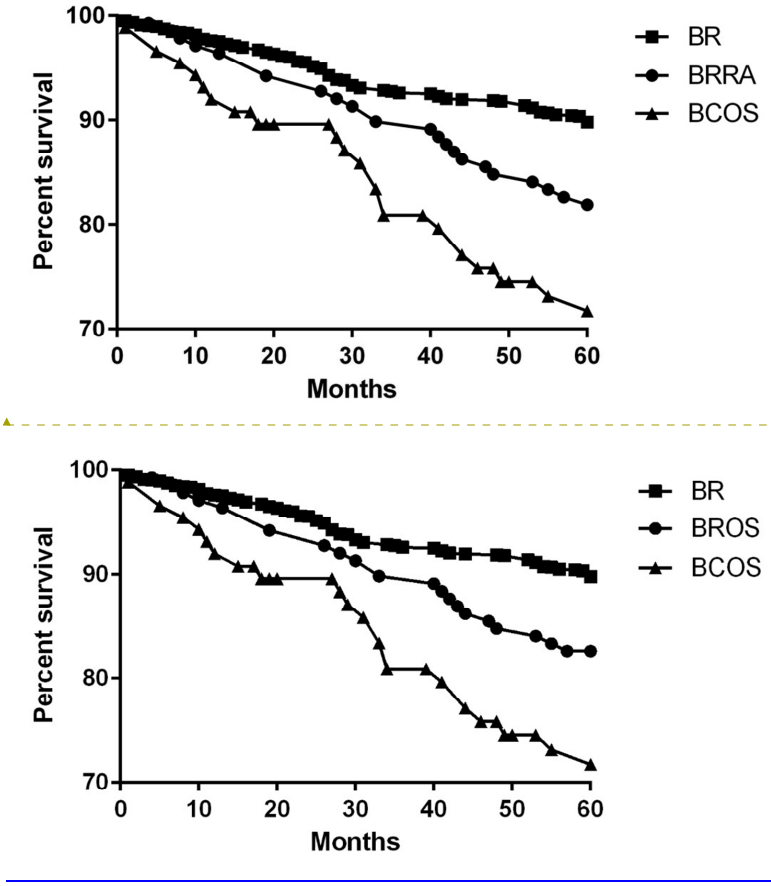
Figure 2. Survival analysis comparing BROS to other aetiologies



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The survival analysis was completed using Kaplan Meier analysis comparing BROS (bronchiectasis-rheumatoid arthritis) and BCOS (Bronchiectasis-COPD overlap syndrome) to other causes of bronchiectasis. Both BROS and BCOS had significantly poorer survival than for other aetiologies of BR ($p<0.05$).

RE Decision Letter (CHEST-16-1964)

Dear Editor;

Many thanks for the opportunity to respond to the reviewers comments

We have amended the manuscript and uploaded clean and marked up versions. We hope the amendments are acceptable. I have responded as requested pointy-by-point to the reviewers comments as below

A De Soyza

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to Author

The manuscript focuses on a novel and unknown topic that is characterization of bronchiectasis associated to AR. The study is well designed and describes BROS in a European multicentre cohort. I think it is worth publishing it since it is of general interest and shows more updated information on a large cohort than in the past but I would like to suggest some minor changes hoping to improve the manuscript.

Q1: Abstract: I would suggest specifying that ILD related bronchiectasis were not included.

R1: We have amended the abstract to clarify this as follows; Patients were categorised as BROS (those with RA and Bronchiectasis without interstitial lung disease), idiopathic bronchiectasis, Bronchiectasis-COPD overlap syndrome (BCOS) and “other” BR aetiologies.

Q2: When authors say BSI scores were statistically but not clinically higher…the meaning is not clear.

The BSI scores were statistically but not clinically significantly higher in those with BROS when compared to idiopathic BR (BSI mean 7.7 vs. 7.1 respectively, $p < 0.05$).

R1; We have expanded upon this in the discussion- statistical testing demonstrated there was a significant difference between BROS and idiopathic bronchiectasis as above but within the bSI scoring system, to date scores of 5-8 map to “ Moderate severity Bronchiectasis” with little difference in outcomes between patients with a score of 5 as compared to 7 (Chalmers et al AJRCCM 2014, McDonell et al Thorax 2016). Therefore we mean the statistical difference observed is not known to have

an important bearing on clinical outcomes as the 2 groups both would be classified as moderate severity.

Q3: The conclusions should focus on BROS and not on BCOS although you can say, “similarly to BCOS” that is only a comparator and not the primary outcome of the study.

R3: We agree and have not increased any emphasis on BCOS in the abstract or discussion

Q4: Introduction: line 48. Is it a “corollary”? I would use another definition for this association. The word “until” is repeated twice line 53

R4: We accept this point and have amended the sentence as follows:

We therefore wished to explore if BROS was associated with poorer outcomes compared to BR without RA?

Q5: Methods: check the ECs approvals since the list seems to be shorter than the number centres involved.

R5: Thank you for raising this point. The EC approvals included multicentre site approvals. We have also referenced this more fully pointing readers to the AJRCCM paper

Q6: Are the patients with BE associated to immunodeficiencies on IgG replacement therapy?

R6: We have clarified this in the text in the methods section- the majority of immunodeficiency patients were CVID patients who were receiving immunoglobulin therapy.

Q7: Radiological score: did the authors use any minimal cut off value of reiff score for patients’ inclusion?

R7: We have clarified within the text that there was no minimal Reiff score required to be eneterd in the cohorts. The entry criteria were “clinical diagnosis of bronchiectasis with radiological confirmation”

Q8: Methods: The sentence on page 10 line 26-27 is not clear: sensitivity analyses in those with various BSI categories… how can a patient be in different categories? Please clarify.

R8: We apologise for the confusing wording. This was intended to say that we evaluated whether BROS was associated with worse outcomes across all 3 BSI groups (mild, moderate and severe). This is now re-worded to be more clear.

Q9: Results and discussion: please use Pseudomonas aeruginosa with italic characters all over the text.

R9: Amended as requested.

Q10: Results: the sentence on page 11 line 30-32 is not clear: what do you mean by "the men BSI scores across each cohort suggested patients with moderate to severe BE were in follow up at such centres"?

R10: We have amended this line for greater clarity as follows;

The mean BSI scores for each centre ranged from 6-9. Prior data has demonstrated this is consistent with patients with moderate to severe bronchiectasis [8].

Q11: Discussion: the reference is missing at the end of the sentence of page 16 line 55 (…Uk cohort).

R11: Amended to denote reference 18

Q12: DMARD therapy is not clear.

R12: This has been clarified wiin text to denote " disease modifying anti rheumatic drugs"

Q13: Do all patients from the cohort were tested for AR (those with and without diagnosis of AR)? If not describe it in methods.

R13; We have improved the methods section to denote that the prevailing British Thoracic society guidleines suggesting serological and clinical testing for rheumatoid arthritis.

Reviewer: 2

Comments to Author

This is a well-conceived study and well-written manuscript from prominent investigators in the field. Using a large database, the investigators report increased mortality in a subset of patients with BROS using the validated BSI. There is

scientific plausibility justifying this study, and the results could lead to better understanding of the syndrome.

Comments:

1) While the focus of this work was BROS, an equally important finding is the increased mortality, increased chronic infection with Pseudomonas, and increased hospitalization associated with BCOS. it would be worth considering highlighting this more prominently, including in the title.

2) This is a philosophical point, but the authors should comment on the choice of the term bronchiectasis- rheumatoid arthritis overlap syndrome (BROS). This suggests that these two processes may simply coexist rather than a possible cause-effect relationship. Perhaps the term should be RA-associated bronchiectasis.

3) The categorization of BCOS based on the presence of airflow obstruction and a 20-pack year smoking history, which was described as pragmatic, may be problematic. The airflow obstruction may be related to the underlying bronchiectasis, rather than true COPD. The authors should elaborate further.

4) Table 1 is quite busy. I would consider splitting the data into 2 tables (Demographics and etiology + severity markers).

5) Figure 2 needs to be corrected. The BROS data line is labeled as BRRA.

6) Unfortunately, the absence of data on cause of death limits any further comment. It may be that death in these patients was from non-pulmonary causes. A prospective study with collection of additional data, including cause of death, would be very helpful. in general, the authors satisfactorily address the limitations of their study.

Comments from Editorial Office:

Please provide the highest academic degree for all of the authors on the title page of the revised manuscript.

Please do not include the figures in the text of the revised manuscript.

Also, please upload the figures as .tiff, .jpg, .png, .ppt, or pptx. Word documents (.doc) or .pdf are not acceptable for figures.

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(DL-7)

Date Sent: 14-Oct-2016