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The emerging association between bronchiectasis and systemic sclerosis: assessing prevalence and potential causality

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MAIN TEXT

Introduction

Systemic sclerosis (SSc) is an autoimmune condition characterised by cutaneous fibrosis and variable internal organ involvement. SSc can be limited or diffuse. In limited SSc the cutaneous fibrosis affects the face and distal extremities, whereas in diffuse SSc the cutaneous fibrosis extends proximally to the elbows and/or knees. In both conditions, a vasculopathy, fibrosis and excessive collagen and other ground substance deposition is described. The result is a varying degree of organ involvement, namely cardiorespiratory, gastrointestinal and renal disease.[1]

SSc is uncommon in Australia, however there has been an apparent increase in prevalence in the last three decades. The Australian prevalence estimates per 10,000 have increased from 0.4-0.9 in 1975-1988[2], to 1.47 in 1993[3], to 2.4 in 2007.[4] There is reported to be a similar prevalence between Aboriginal and non-Aboriginal Australians.[5] Since the 1970s, cardiorespiratory manifestations have overtaken renal crisis as the leading cause of SSc related mortality, with pulmonary arterial hypertension (PAH) accounting for 27% and interstitial lung disease (ILD) accounting for 33% deaths.[6]

PAH is reported to occur in 10% to 13% of those with SSc.[7,8] ILD is seen in up to 30%.[9] Tractional airway dilatation, referred to as traction bronchiectasis, is a common mechanical consequence of lung fibrosis. A number of studies report an association between *non-traction* or primary bronchiectasis and SSc.[7,10,11,12] However, these studies are limited in scope and confounded by selection bias, with prevalence rates of 3.3%[7] to 59.1%[10] reported.

The prevalence of bronchiectasis in the Australian population is not accurately known. Established in 2015, The Australian Bronchiectasis Registry aims to provide comprehensive bronchiectasis prevalence data. At the time of writing its prevalence data have not been released. Several studies from high-income countries have reported a higher than expected prevalence, ranging from 0.2% to 10.3%, in Indigenous populations.[13,14,15]

Oesophageal dysmotility is very common in SSc, with abnormal manometry reported in 68.1% to 100% of patients.[16,17,18] Abnormal manometry is characterised by a decreased amplitude of oesophageal peristalsis and decreased lower oesophageal sphincter tone. An impedance planimetry study in 2001 enrolled participants with SSc and controls for evaluation of these parameters. In the group with SSc, a significantly decreased contraction frequency of secondary peristalsis was seen in the distal oesophagus as well as significantly decreased lower oesophageal tone.[19] Patients with SSc are also known to have an increased distal oesophageal cross sectional area[19] and prominent reflux symptomatology.[16,17,20]

Oesophageal dysmotility can be associated with the aspiration of upper gastro-intestinal contents into the airways. A videofluroscopy study of 51 patients with SSc demonstrated swallowing disorders in 25.5%, with abnormal swallow being more prevalent in those with oesophageal dysmotility.[21] Aspiration of gastro-intestinal contents may result in local bronchial inflammation, immune cell recruitment and free radical release. The resulting bronchial wall damage can lead to the irreversible abnormal bronchial wall dilatation characteristic of bronchiectasis.[22]

Although oesophageal dysmotility is widely reported in SSc, and aspiration is a recognised risk factor for bronchiectasis, no study has assessed the role of oesophageal dysmotility in bronchiectasis development in an SSc population.

The aims of this study were to determine:

1. The prevalence of bronchiectasis in a large well-characterised SSc cohort.
2. The frequency of oesophageal dysmotility in this cohort and whether it is correlated with bronchiectasis development.
3. Whether bronchiectasis in this cohort is more common as disease duration lengthens.
4. Whether demographic variables or SSc subclass are correlated with bronchiectasis development in this cohort.

Methodology

Participants were recruited from the Australian Scleroderma Cohort Study (ASCS). This is a prospective study coordinated by the Australian Scleroderma Interest Group (ASIG). All ASCS participants received a diagnosis of SSc as per the European League Against Rheumatism/American College of Rheumatology criteria.[23] A research proposal was submitted to ASIG and data access granted. The following participant details were obtained: age; SSc diagnosis date; gender; race; SSc subclass; immunosuppressant use; spirometry results and symptoms (reflux and dysphagia). The first recording of a non-Raynaud's manifestation of SSc was used for the SSc diagnosis date. Where a participant had more than one spirometry result, the most recent was used for analysis. Spirometry was categorised as "obstructive", "restrictive" or "normal" using the Global Initiative for Chronic Obstructive Lung Disease criteria.[24]

Participants are enrolled in the ASCS irrespective of respiratory symptoms and do not routinely have thoracic radiology performed. We included participants into our study if they had a digital high-resolution computed tomography (HRCT) thorax scan, subsequent to their SSc diagnosis, at a participating study site. These sites were: St. Vincent's Hospital, Melbourne; Monash Medical Centre, Melbourne and Royal Adelaide Hospital, Adelaide. The SSc diagnosis duration was calculated by taking into account both the SSc diagnosis date and the HCRT thorax scan date. Ethical approval for this study was obtained through

the University of Notre Dame, Western Australia. Site-specific approvals were granted for each participating study site. All participants had given their informed consent to the ASCS.

Digital HRCT thorax images were collected from participating sites and reported by the study's radiologists. Both radiologists have a specific interest in respiratory imaging. Bronchiectasis was noted and scored for severity as per the modified Reiff score.[25] This requires assessment of the number of lobes involved and the degree of bronchiectatic dilatation (tubular, varicose or cystic). It has been validated to show correlation with significant sputum microbiology and a decreased forced expiratory volume in one second.[26] Where airway dilatation was seen in co-location to fibrosis, this was defined as traction bronchiectasis and was recorded as a separate entity for the purpose of this study. Distortion of the airways by co-located fibrosis added further support to the reporting of traction bronchiectasis. An exception to this general rule of co-location was allowed if bronchiectasis was co-located but disproportionate to the degree of fibrosis, in which case primary bronchiectasis was favoured. The radiologists also recorded findings of oesophageal dilatation and ILD. For data analysis "oesophageal dysmotility" was defined as the presence of reflux and/or dysphagia and/or oesophageal dilatation.

All data were recorded in Stata. This was used for bi-variate analysis of bronchiectasis against independent variables. Fisher's exact test was applied to calculate *p*-values for categorical variables. A Student's t-test was applied to

continuous variables. Given the large number of possible variables associated with bronchiectasis a logistic regression analysis was also performed.

Results

The ASCS had 1,632 participants enrolled at the time of data collection in 2017. Of these, 260 participants had a digital HRCT thorax available at a participating study site. Four participants had bronchiectasis that could not clearly be classified as traction or non-traction and these were excluded from further analysis. The ages of the remaining 256 participants and the duration of their SSc diagnoses are summarised in Table 1. Other demographics, disease characteristics and HRCT thorax findings are summarised in Table 2.

Of the 256 participants, 16.4% (n=42) had bronchiectasis. A further 42.2% (n=108) had traction bronchiectasis, which was not included in the bronchiectasis definition for the purpose of this study. Traction bronchiectasis was, as per its definition, always associated with ILD. However, 12 participants were found to have ILD and airway dilatation disproportionate to or not co-located with fibrosis. These participants were considered to have ILD and co-existent primary bronchiectasis. All except three participants with primary bronchiectasis had multilobar disease, with slight lower zone predominance [Table 3]. Using the modified Reiff scoring system, 41 of the 42 participants with bronchiectasis had mild disease (modified Reiff score 1-6) and one participant had moderate disease (modified Reiff score 7-12). The median modified Reiff score was two, with a range of one to 10.

Most participants (92.1% (n=234)) had symptoms of reflux and/or dysphagia, whilst a majority (62.5% (n=160)) had oesophageal dilatation on HRCT. Collectively 95.7% (n=245) had oesophageal dysmotility as it was defined for the purpose of this study. A significant association was not seen between oesophageal dysmotility and bronchiectasis (p=0.396). There was no association between the presence of bronchiectasis and symptomatic reflux and/or dysphagia (p=0.342). Further, the presence of oesophageal dilatation was not associated with bronchiectasis (p=0.728). [Table 2]

Participants were aged between 26 and 89 years. A Student's t-test suggested that older age, in our cohort, was associated with an increased prevalence of bronchiectasis (p=0.023). [Figure 1] A longer SSc diagnosis duration was not associated with bronchiectasis (p=0.679). [Figure 2] 83.2% (n=213) of participants were female. 253 participants declared their racial background. The majority (87.0% (n=220)) identified as Caucasian. Neither gender (p=0.372) nor race (p=0.162) were associated with bronchiectasis. [Table 2]

SSc subclass data was available for all participants. 59.8% (n=153) had limited disease. Limited SSc was associated with a slight increase in bronchiectasis prevalence, but this did not meet significance (p=0.121). [Table 2]

Immunosuppressant medication use was common in our cohort, with 72.7% of participants (n=186) bring prescribed immunosuppressants since their

enrollment in the ASCS. Prednisolone exposure was the most common (n=154), followed by exposure to methotrexate (n=72) and mycophenolate (n=62). The use of two or more immunosuppressant agents was recorded for 42.2% (n=108) of our participant cohort. The use of immunosuppressant therapy was not associated with the presence of bronchiectasis (p=0.573). [Table 2]

Logistic regression analysis was performed for the variable of bronchiectasis. [Figure 1] The only variable showing a significant association with bronchiectasis was absence of ILD (p=0.009, odds ratio 0.322, 95% confidence intervals 0.137-0.756). ILD was observed in 55.9% (n=143) of the HRCT thoraces reported for this study.

Spirometry results were available for 254 of the 256 participants in our cohort, including for 41 of the 42 participants with bronchiectasis. Of those with bronchiectasis, four had an obstructive deficit, eight had a restrictive deficit and 29 had normal spirometry. Bronchiectasis in our cohort appeared to be associated with normal spirometry (p=0.031).

A number of secondary findings pertaining to SSc subclass were returned from our cohort of participants with SSc and an HRCT thorax. Diffuse SSc was seen more often in younger participants. The mean age of participants with limited SSc was 66.1 years, compared to a mean age of 58.5 years in the diffuse SSc group (p<0.001). As expected, diffuse SSc was strongly associated with ILD

(p=0.001). Oesophageal dilatation was also seen more often in the diffuse SSc group, although this association did not meet significance (p=0.149).

Discussion

At the time of writing, this is the largest study reporting on bronchiectasis prevalence in an SSc population. Bronchiectasis was identified in 16.4% (n=42) of the ASCS participants with an HRCT thorax. Clearly, not all ASCS participants had an HRCT thorax and it is likely that the true prevalence of bronchiectasis in the entire SSc population may be lower.

On the other hand, the true prevalence of bronchiectasis *in our study population* is likely to be higher than 16.4%. The majority of study participants with ILD were deemed to have traction bronchiectasis if abnormal airway dilatation was seen. There are no objective criteria that can be applied to determine whether bronchiectasis is related to traction and a certain amount of interpretation is required. Our radiologists were instructed to adopt a conservative approach and only record primary bronchiectasis if the airway dilatation clearly met the criteria detailed. It is plausible that some of the 108 participants who were classified as having traction bronchiectasis did in fact have primary bronchiectasis as well as tractional dilatation related to their ILD.

That said, the finding of bronchiectasis in 16.4% of our study participants falls within the wide range of 3.3%[7] to 59.1%[10] reported by smaller studies in the literature. In 2001 a study of 22 patients, 13 with diffuse and nine with limited

SSc, showed a bronchiectasis prevalence of 59.1%. All participants were attendees at a rheumatology out-patient clinic and had, amongst other investigations, an HRCT thorax performed for the study.[10] This was limited by its small size and importantly, in our view, the authors did not distinguish between traction and non-traction bronchiectasis. 42% (n=9) of their participants had lung fibrosis and many of these would have had associated traction bronchiectasis, likely explaining the high prevalence of bronchiectasis reported overall.

In 2009, 184 participants with SSc were enrolled in a Western Australian study, which aimed to determine the prevalence of PAH in an SSc population. HRCT thorax images were examined if they were available.[7] As a secondary outcome, 3.3% of the study participants were found to have bronchiectasis, although as many of the participants did not have a HRCT thorax, this prevalence is likely an underestimate.

We defined oesophageal dysmotility as the presence of reflux and/or dysphagia and/or oesophageal dilatation. Based on this arguably very broad definition, oesophageal dysmotility was almost universal in our study population (95.7% (n=245)). Subjective reports of symptoms are not always well correlated with either abnormal manometry or abnormal videofluroscopy.**Error! Bookmark not defined.**,[21] Nonetheless, 92.1% (n=234) of the SSc population included in our study had symptoms of reflux and/or dysphagia and 62.5% (n=160) has oesophageal dilatation. Neither symptoms nor oesophageal dilatation were

independently associated with bronchiectasis in our study cohort (p=0.342 and p=0.728 respectively). Due to the almost universality of symptoms and/or oesophageal dilatation in our cohort, we believe that no conclusion can be drawn regarding oesophageal dysmotility as a causative factor in the development of bronchiectasis associated with SSc.

Participants in the ASCS database do not routinely have an HRCT thorax performed. It is possible that those who required an HRCT thorax on clinical grounds, self-selected as more likely to have oesophageal symptomatology. This remains conjecture on our part, however, it should be noted that a large study of 17,838 participants with SSc from four multicentre registries, including the ASCS, reported a similar reflux prevalence when all-comers (not only those with an HRCT thorax) were in included in the sample; reflux was reported in 85.0% of participants with limited SSc and in 85.5% of participants with diffuse SSc.[27]

A significant association was seen between older age and bronchiectasis on bi-variate analysis (p=0.023). This significance was not maintained in the logistic regression analysis. SSc diagnosis duration was not associated with the development of bronchiectasis (p=0.679). The participant with bronchiectasis and the shortest SSc diagnosis duration had been diagnosed with SSc 11 days before their HRCT thorax. We postulate that, since bronchiectasis was established on this and other early HRCT thoraces, bronchiectasis may pre-date SSc diagnosis in some instances. We defined SSc diagnosis as the

emergence of the first non-Raynaud's manifestation of SSc, which was often skin thickening in our participant cohort. Participants with the finding of bronchiectasis early in their SSc disease course may have had bronchiectasis related to other inherited or acquired risks. Data on screening for these was not available and beyond the scope of this study. It is however possible that bronchiectasis, as a manifestation of SSc, may appear early in the disease course, before skin thickening has manifest.

Immunosuppressant use for SSc was common in our participant cohort, with 72.7% (n=186) being exposed since their entry onto the ASCS register. The dosing, duration and compliance with medication was not available and, as such, the degree of immunosuppression from medications, as well as the timing of this in relation to HRCT thorax, is difficult to determine. For this reason prior documentation of immunosuppressant medication use was not included in the logistic regression analysis. However, it is likely that participants with a longer SSc duration would have had a heavier lifetime exposure to immunosuppressant therapy. Since bronchiectasis was not seen more often in participants with a longer duration of SSc, we believe that bronchiectasis in our cohort was not related to immunosuppressed states alone.

Neither gender nor race were significantly associated with bronchiectasis (p=0.378 and p=0.161 respectively). Studies from high-income countries have demonstrated increased bronchiectasis prevalence in their Indigenous populations.[13,14,15] Although this study did not demonstrate the same finding,

only six participants identifying as Aboriginal or Torres Strait Islander were included in the participant population.

On logistic regression analysis, bronchiectasis was negatively associated with ILD (p=0.009, odds ratio 0.322, 95% confidence intervals 0.137-0.756). We believe that this reflects the challenge of identifying primary bronchiectasis in the setting of co-existent traction bronchiectasis. Alternatively, patients may select out as developing ILD *or* bronchiectasis, although the mechanism of a dichotomy is unclear to us from the data available.

We did not include data on chronic cough, sputum production, recurrent chest infections nor hospitalisations as this was not available. Whilst bronchiectasis can occur without symptoms,[28,29] participants in the ASCS database do not routinely have an HRCT thorax performed. Imaging for our cohort had been organised based on respiratory symptomatology, clinical signs or abnormal lung physiology. Overall, bronchiectasis in our cohort was associated with normal spirometry (p=0.031) with a minority of participants having obstructive or restrictive deficits. Complete pulmonary function testing, which may have better predicted the clinical importance of the bronchiectasis seen in our cohort, was not available.[30]

Significant secondary findings were that diffuse SSc was more likely to be seen in younger participants (p<0.001) and was more likely to be associated with ILD (p=0.001). These findings are consistent with the available literature.[31,32]

Conclusion

In summary, in the largest such study to date, we found that primary bronchiectasis is common in SSc, independent of tractional bronchiectasis seen in association with ILD. Neither SSC duration nor subclass appear to correlate with bronchiectasis.

Oesophageal dysmotility was very common in the study population (95.7%). The near universality of reflux and/or dysphagia meant that very few participants did not meet the definition of oesophageal dysmotility outlined in this study. This is a clear limitation and it follows that no firm conclusions can be drawn about the role of oesophageal dysmotility in bronchiectasis development associated with SSc. Future studies into the association between SSc and bronchiectasis, with a view to determining its cause, may combine HRCT thorax with the findings of oesophageal manometry, as an alternative and validated objective measure of oesophageal dysmotility.

Our paper has clearly shown that those with SSc appear to be at higher risk than the general population for symptomatic bronchiectasis, however the extent of the impact on patient outcomes requires exploration in future studies. We believe that consideration of the cardiorespiratory manifestations of SSc should now include bronchiectasis alongside PAH and ILD.

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Table 1

Participant ages and duration of systemic sclerosis diagnosis.

Variable	Mean (years)	Standard deviation	Minimum to maximum (years)
Age (n=256)	63.0	12.3	26.9 – 89.1
SSc duration (n=236)	12.5	10.2	0.0 – 45.8

Legend: SSc=systemic sclerosis

Table 2

Participant demographics (excluding age) and disease characteristics.

Variable	Total number (%)	Number with bronch-iectasis (%)	Number without bronch-iectasis (%)	Fisher's exact analysis against bronchiectasis (*p*-value)
Gender (n=256)				0.372
Male	43 (16.8)	9 (3.5)	34 (13.2)	
Female	213 (83.2)	33 (12.9)	180 (70.3)	
Race (n=253)				0.162
Aboriginal or TSI	6 (2.4)	2 (0.8)	4 (1.6)	
Asian	21 (8.3)	1 (0.4)	20 (7.9)	
Caucasian	220 (87.0)	37 (14.6)	183 (72.3)	
Hispanic	4 (1.6)	0 (0.0)	4 (1.6)	
Other	2 (0.8)	1 (0.4)	1 (0.4)	
SSc subclass (n=256)				0.121
Limited				
Diffuse	153 (59.8)	30 (11.7)	123 (48.0)	
	103 (40.2)	12 (4.8)	91 (35.5)	
Immunosuppressant use				0.573

Yes	186 (72.7)	29 (11.3)	157 (61.3)	
No	70 (27.3)	13 (5.1)	57 (22.3)	
Reflux (n=254)				0.594
Yes	225 (88.6)	36 (14.2)	189 (74.4)	
No	29 (11.4)	6 (2.4)	23 (9.1)	
Dysphagia (n=237)				0.858
Yes	146 (61.6)	24 (10.1)	122 (51.5)	
No	91 (38.4)	14 (5.9)	77 (32.5)	
Symptoms (reflux and/or dysphagia) (n=254)				0.342
Yes	234 (92.1)	37 (14.6)	197 (77.6)	
No	20 (7.9)	5 (2.0)	15 (5.9)	
OD (n=256)				0.728
Yes	160 (62.5)	25 (9.8)	135 (52.7)	
No	96 (37.5)	17 (6.6)	79 (30.9)	
Oesophageal dysmotility (symptoms and/or OD) (n=256)				0.396
Yes				
No	245 (95.7)	39 (15.2)	206 (80.5)	
	11 (4.3)	3 (1.2)	8 (3.1)	
ILD (n=256)				<0.001**
Yes	143 (55.9)	12 (4.7)	131 (51.2)	

No	113 (44.1)	30 (11.7)	83 (32.4)

Legend: TSI=Torres Strait Islander, SSc=systemic sclerosis, OD=oesophageal dilatation, ILD=interstitial lung disease, **=strongly significant p-value

Table 3

Distribution of bronchiectasis by lung lobe in the participant group with primary bronchiectasis (n=42).

Left upper lobe	**Lingula**	**Left lower lobe**	**Right upper lobe**	**Right middle lobe**	**Right lower lobe**
23/42 (54.8%)	32/42 (76.2%)	37/42 (88.1%)	22/42 (52.4%)	32/42 (76.2%)	36/42 (85.7%)

Figure 1
Age spread of those with and without bronchiectasis (Student's t-test p=0.023).

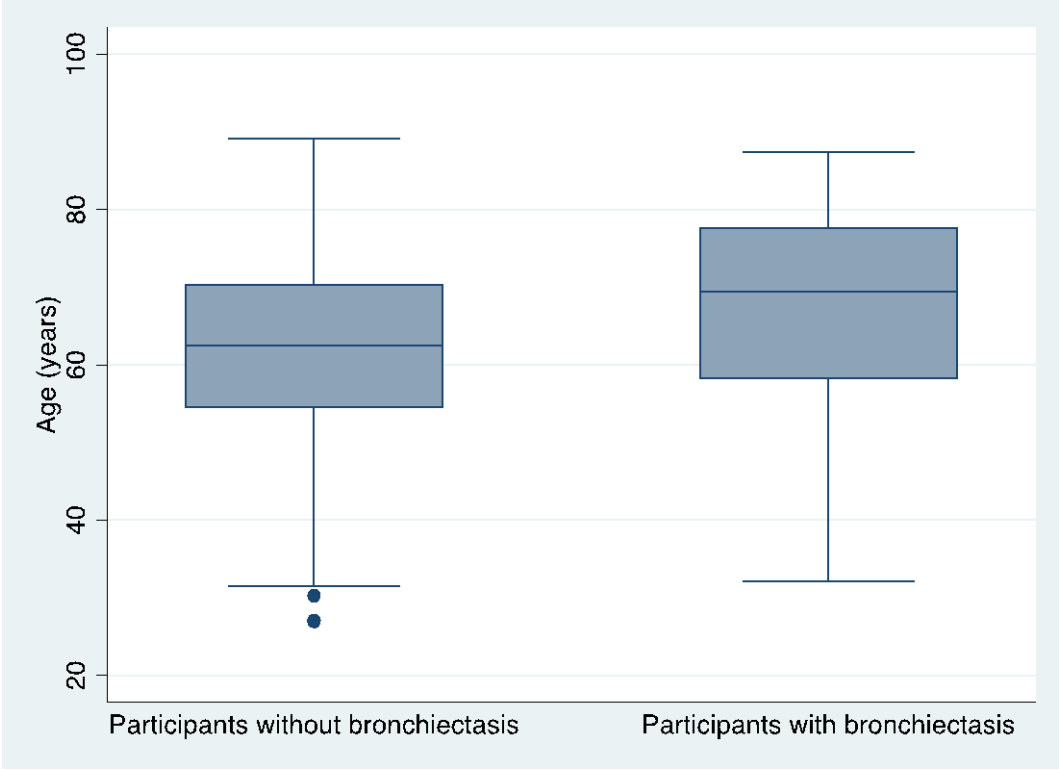
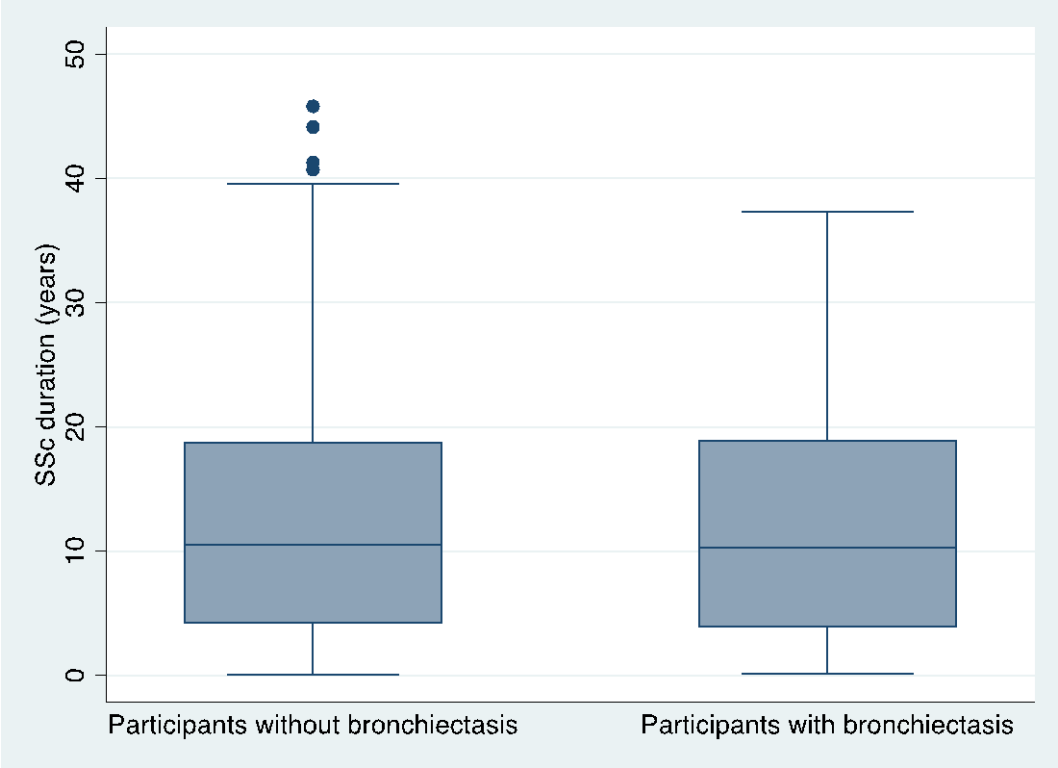


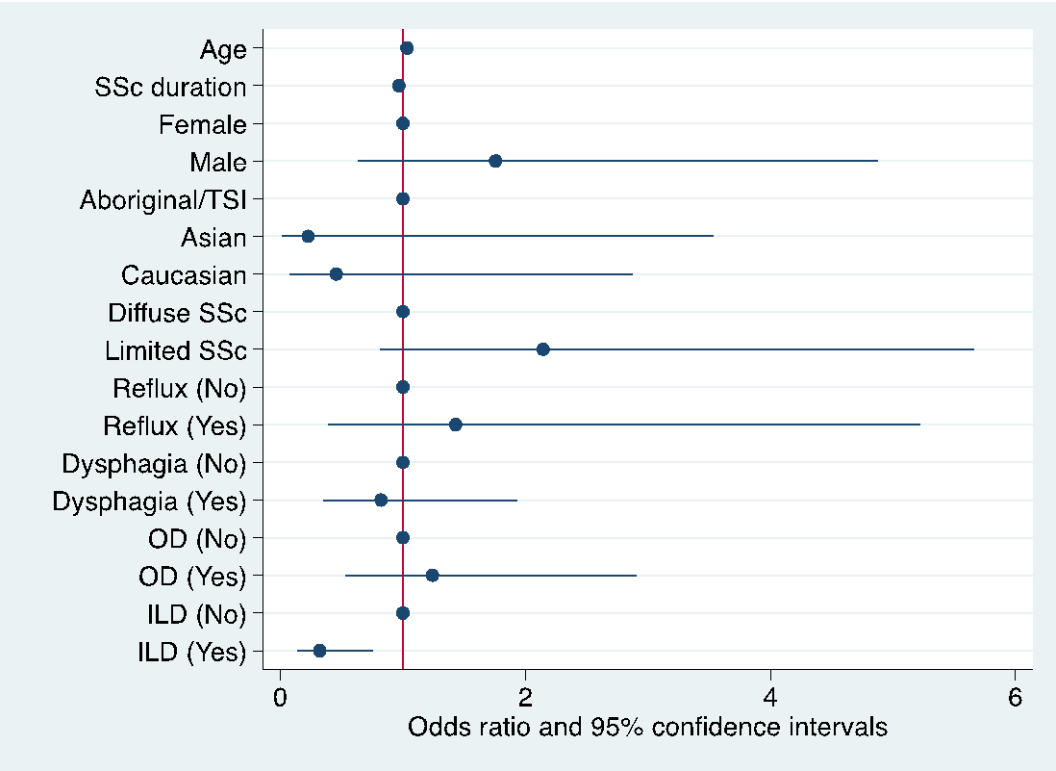
Figure 2
SSc diagnosis duration spread of those with and without bronchiectasis (Student's t-test p=0.679).



Legend: SSc=systemic sclerosis

Figure 3

Logistic regression analysis performed for bronchiectasis.



Legend: SSc=systemic sclerosis, TSI=Torres Strait Islander, OD=oesophageal dilatation, ILD=interstitial lung disease

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The emerging association between bronchiectasis and systemic sclerosis: assessing prevalence and potential causality

ABSTRACT

Background

Bronchiectasis has been observed in association with systemic sclerosis (SSc). Theorised aetiology includes aspiration related to oesophageal dysmotility, immunosuppressant medication use and the direct effect of collagen deposition on airway calibre.

Aims

In this study we detail bronchiectasis prevalence in an SSc population who have had a high-resolution computed tomography (HRCT) thorax. We assessed whether oesophageal dysmotility, demographic variables, SSc duration or subclass were associated with bronchiectasis.

Methods

Participants in the Australian Scleroderma Cohort Study (ASCS) with an HRCT were included. The ASCS provided demographic and clinical data. HRCT studies were reviewed for bronchiectasis, oesophageal dilatation and interstitial lung disease (ILD). Traction bronchiectasis associated with ILD was recorded as a separate entity to bronchiectasis. Oesophageal dysmotility was defined by symptoms and/or oesophageal dilatation.

Results

16.4% (n=42) of the 256 participants had bronchiectasis. Logistic regression analysis revealed no significant association between bronchiectasis and oesophageal dysmotility (observed in 95.7%), any demographic variable, SSc duration or subclass. A negative association between bronchiectasis and ILD was observed (p=0.009, odds ratio 0.322, 95% confidence intervals 0.137-0.756).

Discussion

Those with SSc appear to have an increased risk for bronchiectasis. Since bronchiectasis was not more frequent in participants with a longer duration of SSc, we hypothesise that its development is not related to immunosuppression alone. Oesophageal dysmotility was almost universal in our population such that its effect on bronchiectasis development could not be concluded. A negative association between bronchiectasis and ILD reflects that bronchiectasis occurring alongside ILD was recorded as a separate entity.

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3. Support for travel to meetings for the study or other purposes	☑	☐	☐	• St Vincents Hospital Melbourne Research Endowment Fund		X ADD
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5. Payment for writing or reviewing the manuscript	☑	☐	☐			X ADD
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4. Expert testimony	☑	☐	☐		
5. Grants/grants pending	☐	☑	☐	National Health and Medical Research Council investigator Grant	Awarded to Dr Nikpour (GTN 1176538)
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The emerging association between bronchiectasis and systemic sclerosis: assessing prevalence and potential causality

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