Multimorbidity in bronchiectasis: a systematic scoping review

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Shareable abstract (@ERSpublications)
A scoping review demonstrates bronchiectasis multimorbidity is common, and associated with increased mortality, exacerbations and hospitalisation. It negatively impacts lung function. There is a deficit of research in key areas, such as management. https://bit.ly/3W1QUnt

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Abstract

Introduction Multimorbidity, the coexistence of two or more chronic conditions, has been extensively studied in certain disease states. Bronchiectasis aetiology is complex and multimorbidity is insufficiently understood. We performed a scoping review, summarising the existing literature and identifying deficits.

Method A literature search of the electronic databases PubMed, CINAHL and EMBASE was conducted following PRISMA guidelines. Observational, interventional, qualitative, randomised control trials and systematic reviews were included. The main objective was to identify prevalence, prognosis, symptoms, quality of life and management in bronchiectasis multimorbidity. Key findings were analysed descriptively.

Results 40 studies (200 567 patients) met the inclusion criteria, the majority (68%) being cohort studies. Study size ranged from 25 to 57 576 patients, with mean age 30–69 years. 70% of studies investigated the prognosis of comorbidities and 68% prevalence; 70% analysed multiple comorbidities in bronchiectasis. The most frequent comorbid diseases evaluated were COPD (58%), cardiovascular disease (53%) and asthma (40%). COPD and hypertension were the most prevalent conditions (pooled mean 35% and 34% respectively). Multimorbidity was associated with increased mortality, exacerbations and hospitalisation rates. It had a negative impact on lung function. Mortality increased in the following comorbidities: COPD, gastro-oesophageal reflux disease and rheumatoid arthritis.

Conclusion Bronchiectasis multimorbidity is common. Research focuses on a few key aspects and favoured comorbidities (*e.g.* COPD). There is a deficit of research into symptoms, quality of life, interactions and management. High-resolution computed tomography diagnosis is not consistent, and there is no agreed multimorbidity screening questionnaire. Bronchiectasis multimorbidity is of importance; it is associated with morbidity and mortality.

Introduction

Bronchiectasis is a chronic lung disease, in which one or more bronchi become permanently dilated, resulting in mucus retention and airway inflammation. It has a wide range of clinical manifestations, *e.g.* cough, sputum production, sputum purulence, fatigue and recurrent infective exacerbations [1]. Bronchiectasis is characterised by frequent exacerbations and a sustained inflammatory response. The aetiology is varied; however 44.8% of cases are idiopathic [2]. Bronchiectasis is often described as having a vicious cycle of airway inflammation, airway structural damage, infection and dysfunctional mucociliary clearance [3]. Mucociliary clearance is affected by congenital conditions such as primary ciliary dyskinesia [4, 5], or through congenital malformation such as tracheobronchomegaly [1]. Alternatively, acquired conditions, *e.g.* respiratory infection such as pneumonia and tuberculosis or foreign body obstruction, affect mucus clearance [1, 4]. Primary and secondary immunodeficiencies (*i.e.* HIV and hypogammaglobulinaemia [6]) and systemic inflammatory diseases (*e.g.* connective tissue disease) result in immune dysregulation, lung inflammation and bronchiectasis [7, 8]. Lastly, there is a recognised association

between inflammatory airway diseases and bronchiectasis, *e.g.* COPD and asthma [1]. In this scoping review we focus on non-cystic fibrosis bronchiectasis as cystic fibrosis (CF) is a distinct and separate disease.

Historically bronchiectasis has been considered an orphan disease, a disease affecting <5 per 10 000 [9, 10]. Idiopathic bronchiectasis is classified as a rare disease within the Orphanet Report Series [11]; however the prevalence of bronchiectasis now surpasses the threshold for this [12]. Between 2004 and 2013, the prevalence of bronchiectasis in the UK increased by 60% (from 300–350 to 495–566 per 100 000) [13], and the bronchiectasis community acknowledges these figures are likely to be an underestimation. The increasing prevalence may be the result of an ageing population and/or advancements in radiographic imaging.

Clinical tools have been developed to give prognostic information, including the Bronchiectasis Severity Index (BSI) predicting acute hospitalisation and mortality rates [14], the Charlson Comorbidity Index (CCI), which predicts 10-year survival rate [15], and the Bronchiectasis Aetiology Comorbidity Index (BACI) predicting mortality and risk of hospital admissions for severe exacerbation [16]. These clinic tools incorporate comorbid conditions into their design, acknowledging the impact of multimorbidity on outcomes. However this relationship is insufficiently understood.

Multimorbidity (*i.e.* multiple long-term conditions (MLTC)) is defined as the coexistence of two or more chronic conditions [17]. McDonnell *et al.* [16] identified MLTC in a cohort of 986 bronchiectasis patients. The most common coexisting conditions were gastro-oesophageal reflux disease (GORD) (34.3%), hypertension (27.5%), hyperlipidaemia (20.1%) and COPD (17.1%). Other well-recognised MLTC in bronchiectasis include asthma, cardiovascular disease, pulmonary hypertension and psychological disorders.

In other disease states multimorbidity drives polypharmacy, quality of life (QoL), treatment decisions and symptom burden [18]. However the effect on these domains in bronchiectasis is unclear. Importantly, patients with MLTC are often excluded from clinical drug trials treatments, limiting the generalisability and application of results for this cohort [19].

Method

Overview

A scoping review was selected to consolidate knowledge in the area of bronchiectasis with MLTC. We identified that the depth of evidence in this topic required investigation and a scoping review enables key findings to be quickly summarised and disseminated. The review followed the PRISMA guidelines for scoping reviews: 1) identify objectives; 2) identify relevant studies; 3) analyse the literature for relevance; 4) extract key data; and 5) review and report results. A prespecified protocol was used to guide data synthesis.

Identifying objectives

The following main objectives were identified as being key areas of interest: What are the prevalence and patterns of multimorbidity in bronchiectasis? Does multimorbidity in bronchiectasis affect symptoms, prognosis, QoL and management? Are patients with bronchiectasis and multimorbidity included in clinical trials?

Identifying relevant studies

Search strategies and database

A systematic literature search of the electronic databases PubMed, CINAHL and EMBASE was conducted. Boolean operators were included. The broad search terms were as follows: “bronchiectasis” AND “multimorbidity” OR “multimorbidity” OR “comorbidity” OR “comorbidity” OR “long-term condition” OR “coexist” (please see online supplementary material for further details). Searches were limited to human studies, with databases searched from inception to the end of January 2021. Handsearching was conducted to identify studies from alternative sources.

Eligibility criteria

Inclusion criteria were observational studies, randomised controlled studies, interventional studies, qualitative studies and systematic reviews in the language English. Exclusion criteria were case reports, narrative reviews and manuscripts in languages other than English. There were no geographical restrictions. Patients with CF were excluded, as this is a distinct condition with different comorbidities.

Analysing the literature for relevance

Duplicates studies were removed using Endnote (IBM Systems, Armonk, NY, USA). Two independent reviewers assessed each abstract and formulated a list of "relevant" and "of uncertain relevance" studies. The full manuscripts which met either of these criteria were subsequently independently reviewed by the two reviewers and eligible studies identified. When consensus was not met, a third independent reviewer adjudicated.

Extracting key data

A charting form was developed for data extraction. A single reviewer independently extracted the following data from eligible studies: title, author, date, location, study type, methods, study size, mean age, diagnostic method for multimorbidity and bronchiectasis, comorbidities, main objectives and key findings/outcome.

Reviewing and reporting results

A descriptive analysis was conducted in relation to the main objectives identified in the scoping review. The results were analysed with the following categories: scope of conditions investigated, prevalence of multimorbidity, morbidity and mortality, pharmacological management, symptoms with disease severity and lung function, QoL, psychological multimorbidity, patterns of multimorbidity and inclusion in clinical trials. A pooled estimate of the mean prevalence of comorbidity was calculated and the prevalence range.

Results

The initial database search identified 1737 articles. One additional article was obtained from handsearching. 40 studies met the inclusion criteria. The number of studies omitted at each stage and reasons for exclusion are shown in figure 1. The location of the included studies was as follows: Asia 16, Europe 14, USA four, Australia three, multinational two and Egypt one. Of the 40 studies analysed the majority (27) were cohort studies (67.5%), and the remaining (10) cross-sectional (25%) or case–control studies (3) (7.5%). There were no qualitative studies identified relevant to this topic.

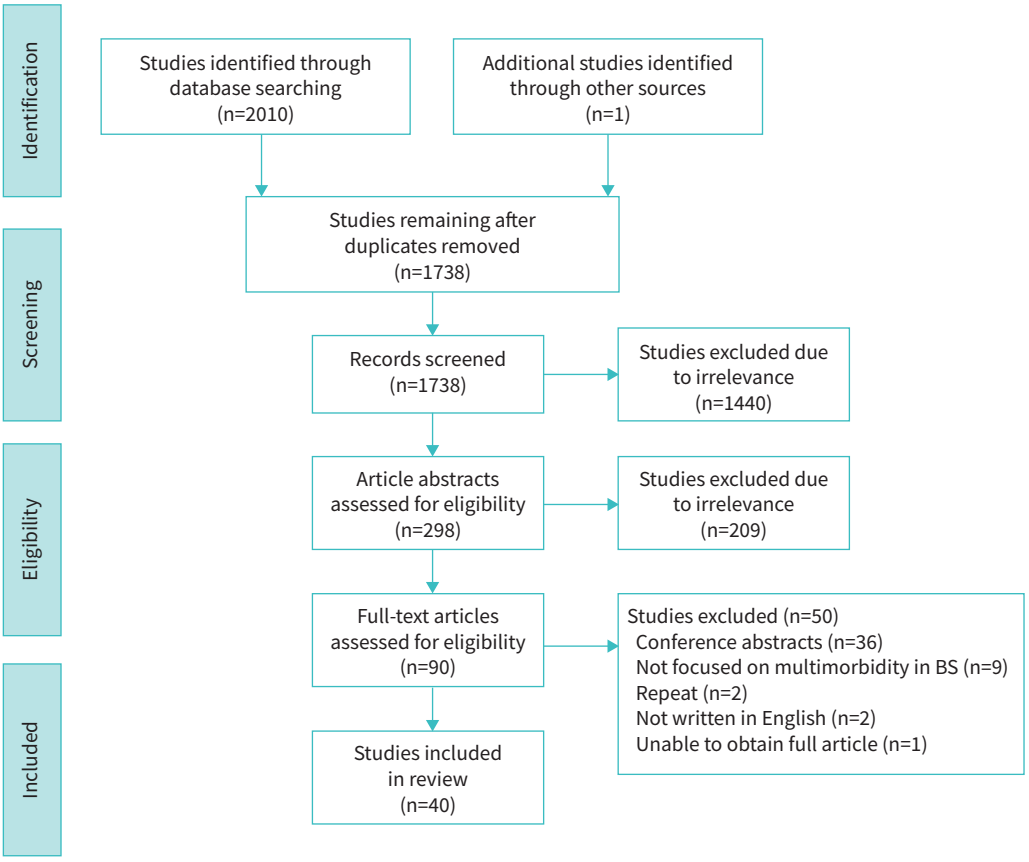

FIGURE 1 PRISMA flow diagram of literature review and selection process. BS: bronchiectasis.

Study sample size ranged from 25 to 57 576. Half (19) of the studies had a sample size of <100. The mean age of studies ranged from 30 to 69 years (demonstrating a significant variability). 24 studies used high-resolution computed tomography (HRCT) as the standard for diagnosis. However, there was a wide range of heterogeneity with other studies defining bronchiectasis *via* a physician diagnosis, presence of symptoms or a standard computed tomography scan.

Supplementary table S1 shows a summary of the key information of each individual study.

Scope of conditions investigated

Table 1 demonstrates the comorbid conditions investigated (more than one condition allowed per study). 12 studies (30%) analysed one comorbidity and its relation to bronchiectasis. 28 studies (70%) analysed more than one comorbidity and bronchiectasis. However those studies looking at multiple comorbid conditions rarely analysed disease interactions. COPD (including emphysema) and cardiovascular disease were the most frequently analysed comorbidities (23 studies (58%) and 21 studies (53%) respectively).

With regards to the focus of each study, prognosis was the most investigated area (28 studies, 70%). Prevalence was also a common focus (27 studies, 68%). Patterns of multimorbidity (7 studies, 18%), QoL (7 studies, 17.5%) and symptoms (2 studies, 5%) were less commonly reviewed.

Prevalence of multimorbidity

27 studies investigated the prevalence of one or more comorbidity. The most common comorbid conditions investigated for prevalence were COPD (17 studies, 43%), cardiovascular disease (13 studies, 33%), hypertension (12 studies, 30%), asthma (12 studies, 30%) and diabetes (11 studies, 28%). The prevalence of coexisting anxiety and depression, GORD, cardiac failure, cerebral vascular disease, osteoporosis and rheumatoid arthritis were less commonly investigated (see figure 2). For further details please see online supplementary material.

TABLE 1 Comorbidity investigated (more than one condition can be shown per study)

Disease	Number of studies
Multiple conditions investigated	28
Single conditions investigated	12
COPD and emphysema	23
Cardiovascular disease	21
Asthma	16
Diabetes	14
Gastro-oesophageal reflux disease, hiatus hernia and peptic ulcer	12
Cerebrovascular disease	9
Rheumatoid arthritis	7
Anxiety or depression	7
Malignancy	6
Osteoporosis and osteopenia	6
Peripheral vascular disease	5
Hyperlipidaemia	4
Chronic kidney disease	3
Rhinosinusitis	2
Tuberculosis	2
Liver disease	2
Pulmonary fibrosis	1
Pulmonary hypertension	1
Connective tissue disease	1
Immune deficiency	1
Allergic bronchopulmonary aspergillosis	1
Osteoarthritis	1
Pneumoconiosis	1
Dementia	1
Anaemia	1
Urinary incontinence	1
Non-tuberculous mycobacteria	1
Irritable bowel disease	1

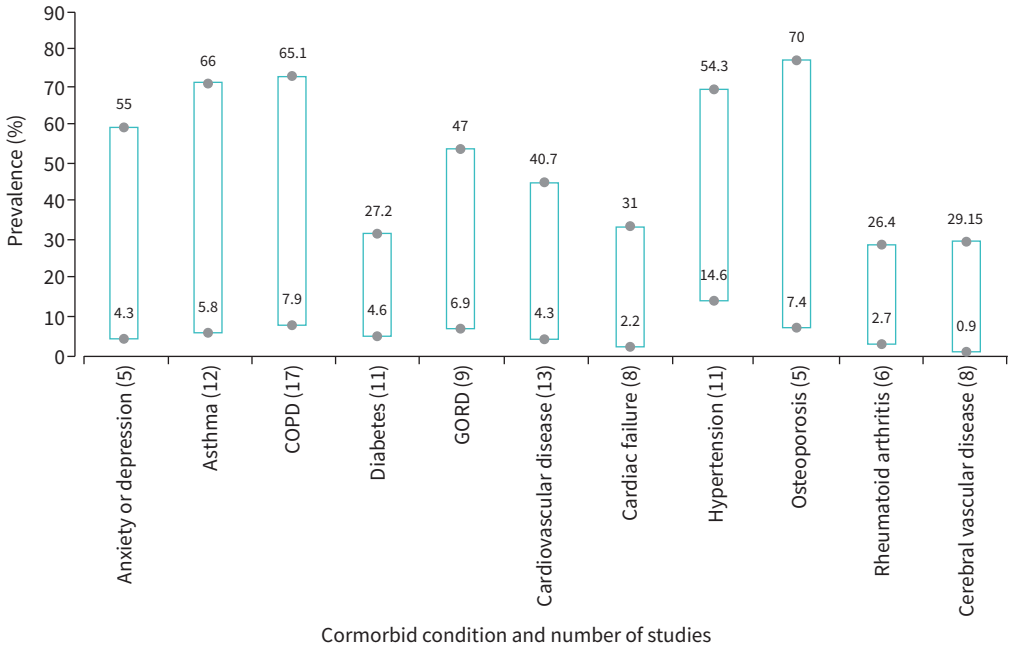

FIGURE 2 Prevalence range for comorbid conditions. GORD: gastro-oesophageal reflux disease.

McDonnell *et al.* [16] performed an international multicentred cohort study which specifically focused on multimorbidity. This demonstrated the median number of comorbid conditions as 4 (IQR=2–6). Male sex was associated with an increased number of comorbid conditions (four *versus* three, p=0.005) [16].

A range of prevalence for each comorbid condition in bronchiectasis is presented in figure 2. Only comorbidities described in ⩾4 separate studies were included. COPD was the most common comorbidity (with a prevalence range of 7.9–65.1%; pooled mean 34.9%). The prevalence range of the comorbid conditions was wide (see figure 2).

Prognosis: morbidity and mortality

Morbidity in bronchiectasis is predominantly defined as both exacerbations and acute hospitalisation.

The frequency of hospitalisation, exacerbation rates, BACI score, lung function severity and ambulatory encounters are increased in bronchiectasis and COPD overlap syndrome (BCOS) [20]. In this study, BCOS was associated with a high rate of previous hospital admissions (58.3% *versus* 25.1%, p<0.05) when compared with idiopathic bronchiectasis, and mean exacerbations/year are also increased (2.7 *versus* 1.8 respectively, p<0.05).

Lung function in BCOS is adversely affected. There is a significantly higher rate of "very severe" lung function impairment (20% *versus* 4.9%, p<0.001) and a significantly lower rate of "normal" or "mild" lung function (3.3% *versus* 38.8%, p<0.001) compared to bronchiectasis alone [21]. The BSI, predicting acute hospitalisation and mortality, is significantly higher in BCOS compared to bronchiectasis (10.4 *versus* 7.1, p<0.05) [20].

Hospitalisation at 1 year was increased in the following comorbidities: heart failure, COPD and diabetes (percentage of patients hospitalised at 1-year follow-up (91.2%, p<0.001, 83.1%, p<0.001, and 82.9%, p=0.002 respectively)) [22]. Bronchiectasis with asthma increases exacerbation rates (OR 2.6, 95% CI 1.15–5.88; p=0.021) [23]. Coexisting GORD with bronchiectasis increased the exacerbation frequency and number of hospitalisations [24]. BSI scores were greater in bronchiectasis and rheumatoid arthritis overlap syndrome (BROS) (7.7 *versus* 7.1, p<0.05), predicting acute hospitalisation and mortality rates [20].

McDonnell *et al.* [16] demonstrated in an international multicentred cohort study that bronchiectasis mortality increases with number of coexisting conditions. Over 5-year follow-up the median number of

associated conditions (at baseline) in survivors was three, *versus* six for non-survivors (p<0.0001). The count of coexisting conditions was associated with mortality rate (HR=1.17, 95% CI 1.12–1.23) [16].

The comorbidities COPD, GORD and rheumatoid arthritis negatively impact mortality rates [16, 20, 24]. Three studies described increased mortality rates in BCOS (HR for mortality or severe exacerbation requiring hospital admission 2.22, 95% CI 1.53–3.23, p<0.0001) [16, 20, 21]. Logistic regression, in a retrospective cohort study, showed mortality (OR 2.5, 95% CI 1.1–7.8) was associated with GORD [24], while the 4-year mortality rate for BROS is higher than in bronchiectasis (18% and 9.3% respectively, p=0.01, HR for mortality 1.88, p=0.01, mortality rates 2.4 times higher) [20].

Other coexisting conditions included in the BACI scoring model, and increasing mortality or risk of hospital admission for severe exacerbation, were diabetes (HR 1.76, 95% CI 1.10–2.80, p=0.02), asthma (HR 1.65, 95% CI 1.00–2.73, p=0.050), connective tissue disease (HR 1.78, 95% CI 1.19–2.68, p=0.005) and metastatic malignancy (HR 6.69, 85% CI 3.53–12.68, p<0.0001) [16].

Not all mortality in bronchiectasis is due to the underlying primary disease. Cardiovascular disease was a major cause of mortality (16%), and 42% of deaths were from a non-respiratory cause [25].

Pharmacological management

Few studies examined the effect of multimorbidity on management; those which did focused on BCOS. Two studies looked at the pharmacological management of BCOS compared to bronchiectasis. Patients with BCOS had more therapy days on corticosteroids (92.2 days *versus* 44.7 days), bronchodilators (58.9 days *versus* 19.4 days) and antibiotics (37.1 days *versus* 26 days) than patients with bronchiectasis alone [26]. BCOS patients were also more likely to be taking inhaled corticosteroids (82.2% *versus* 65.3%, p<0.001), bronchodilators (94.0% *versus* 73.5%, p<0.001) and intravenous antibiotics (89.3% *versus* 77.8%, p=0.004) than patients with bronchiectasis alone [21]. It is important to highlight bronchiectasis is not currently an indication for inhaled corticosteroids unless there is coexisting asthma or COPD.

Symptoms, disease severity and lung function

Seven studies assessed the association between multimorbidity and symptom burden or disease severity.

McDonnell *et al.* [24] found that the coexistence of GORD with bronchiectasis was associated with increased daily sputum production (p=0.040), coughing (p=0.002) and wheezing (p<0.001). However, it has also been found that disease severity does not differ between those with bronchiectasis with GORD, and those without [27].

A number of coexisting conditions decreased lung function. This likely reflects symptom burden, for example lung function may be decreased in cough. The associations between different comorbidities and forced expiratory volume in 1 s (FEV_1) are shown in table 2. The comorbidities with significant reduction in percentage FEV_1 were emphysema, COPD and hiatus hernia [21, 28, 20]. Further studies have demonstrated that coexisting rheumatoid arthritis decreases FEV_1 [29]. However, a large multicentre cohort study found no significant difference in FEV_1 between BROS and idiopathic bronchiectasis (mean FEV_1 % predicted BROS 76% *versus* idiopathic bronchiectasis 76%) [20].

The association between anxiety and depression and bronchiectasis severity (FEV_1 and forced vital capacity (FVC)) was investigated by Olveira *et al.* [30]; patients diagnosed with anxiety or depression

TABLE 2 Association between bronchiectasis (BR) multimorbidity and forced expiratory volume in 1 s (FEV_1)

Multimorbidity	FEV_1 in BR (%)	FEV_1 in BR and multimorbidity (%)	p-value
Depression [30]	69.3	61.9	0.1
Anxiety [30]	68.2	69.2	0.76
Emphysema [28]	69.2	35.0	<0.01
Hiatal hernias [31]	90.4	75.4	0.02
GORD [27]	85.0	73.9	0.23
Asthma [32]	73	54	
COPD [21]	72.8	60.2	<0.001
COPD [20]	76.0	51.0	<0.05
Rheumatoid arthritis [20]	76.0	76.0	

("Hospital Anxiety and Depression Scale" (HADS)-A >11 or HADS-D >11) had reduced FEV_1 and FVC compared to those with lower scores.

Quality of life

We found fewer data on how multimorbidity affects QoL in patients with bronchiectasis, and the available information was frequently limited to depression and/or anxiety. Seven studies (17.5%) assessed QoL in bronchiectasis. Three studies found an association between anxiety and/or depression and decreased QoL and health-related QoL [30, 33, 34]. However this relationship was not always statistically significant [34].

Increased number of multimorbidities (demonstrated *via* an increased CCI) was associated with poorer health-related QoL ($p<0.05$) [33].

One study looking at urinary incontinence in bronchiectasis found this negatively impacted QoL [35].

Psychological multimorbidity

When assessing for the comorbidities anxiety and depression, the screening tool HADS was utilised. Bronchiectasis patients with increased symptoms of depression (higher HADS-D score) had a higher number of comorbidities as measured by a higher CCI (3.11 *versus* 2.17, p=0.030). A statistically significant result was not found in anxiety [30].

Anxiety and depression were found more frequently in patients with bronchiectasis than the general population (18% and 12% *versus* 4% and 6%) [30]. This was also reported by YANG *et al.* [36] who found the prevalence of depression was >three-fold higher in bronchiectasis patients than those without (9.3% *versus* 3%, p=0.015).

Patterns of multimorbidity

Seven (17.5%) of the studies considered which common aetiology factors might correlate with multimorbidity. One study attempted to define clusters of conditions associated with bronchiectasis. This considered 12 variables and defined four clinical phenotypes. Older patients with severe disease who had frequent exacerbations and older patients with severe disease who did not have frequent exacerbations had higher mortality rates [37].

Sex was the most frequently described demographic, with coexistent COPD being more prevalent in men than women (89.9% *versus* 10.1%, p<0.001) [21].

Clinical trials in bronchiectasis multimorbidity

We found no papers that attempted to analyse whether bronchiectasis patients with multimorbidity are being included in clinical trials.

Discussion

We present the first systematic scoping review to expose the associations between bronchiectasis and multimorbidity. The 40 eligible studies analysed have highlighted several important findings.

Multimorbidity in bronchiectasis is common (median number of comorbidities four: males six, females three) [16]. COPD (including emphysema) and cardiovascular disease were the most frequently analysed comorbidities and prognosis the most investigated area. When analysing the results using pooled means, the most prevalent multimorbidities are COPD and hypertension (pooled mean 35% and 34% respectively), with asthma also prevalent (pooled mean prevalence 30%). COPD and asthma had a higher pooled mean prevalence than that found in the UK general population (2% and 12% respectively) [38]. Prevalence did not always reflect depth of research in that area; for example the mean prevalence of osteoporosis was 18.6%, but only five studies researched this. Studies regularly focused on multiple comorbid conditions but rarely analysed how each condition would impact one another.

Multimorbidity has a negative impact on bronchiectasis survival, in particular COPD, GORD and rheumatoid arthritis all significantly increase mortality [16, 20, 24]. As the number of multimorbidities increases, mortality rates also rise [16]. As is seen in the general population, the major causes of death in bronchiectasis include cardiovascular disease and cancer. However, the bronchiectasis population has excess rates of these causes of death, with 42% of deaths in bronchiectasis defined as non-respiratory [25]. This may demonstrate the systemic impact comorbid conditions have on bronchiectasis.

Patients with bronchiectasis with an additional multimorbidity of either emphysema, COPD, hiatus hernia, and anxiety and depression had decreased lung function, suggesting multimorbidity is associated with increased disease severity [20, 27, 28, 30, 31, 39, 40].

QoL in bronchiectasis is poorer than that of the general population [30, 36]. However, there is limited literature regarding the effect of bronchiectasis multimorbidity and QoL. Increased numbers of comorbidities were associated with a reduced health-related QoL [33]; however there is a deficit of knowledge in this field.

We identified a lack of consistency when diagnosing bronchiectasis. The majority of studies used HRCT, but a variety of alternative methods were also identified (*e.g.* chest radiograph, clinical symptoms). The range of diagnostic criteria used reduces the reliability of the data in this field, as inaccurate diagnoses are common in bronchiectasis. Heterogeneity also resulted in a wide prevalence range for each comorbid condition. For example, the prevalence of comorbid COPD and emphysema ranged from 2% to 65.1%. Diagnostic thresholds vary between studies, and BCOS is complex to define. This difference may be due to other factors such as age; however it is probable that the contrasting methodology used to diagnose bronchiectasis and other diseases is the underlying cause for the data variances. Standardised methods of diagnosis should be used in future studies.

Our scoping review demonstrated that there is scant evidence on the impact of multimorbidity on bronchiectasis management. We did not find evidence of clinical trials which specifically investigated the management of bronchiectasis with MLTC. However, we did not undertake analysis of individual trials to review whether included participants had multimorbidity (this work was outside the scoping review remit). We would recommend that investigators and trialists perform sub-analysis on their cohorts to provide much needed data in this area.

Adverse and serious complications may occur if multimorbidity is not considered when prescribing. Medications can alter airway tone, breathing dynamics and compromise the diaphragm–oesophageal interface. This could result in multimorbidity being exacerbated, *e.g.* GORD [41]. There is also no current evidence to support the use of inhaler corticosteroids outside of the diagnosis of BCOS or asthma in bronchiectasis. The side-effect profile for these drugs is high and there is potential to exacerbate other comorbidities [41]. Further research identifying the effects of pharmacotherapy on multimorbidity is required. Including patients with comorbidities in bronchiectasis trials will assist in this inquiry, as any side-effects and pathophysiological interactions between bronchiectasis and comorbidities will be quickly identified.

Limitations of the systematic scoping review include the study size. A significant proportion (19) of the studies had a small sample size (n=100 or less) and were confined to a single centre, meaning they may not be generalised or representative of the bronchiectasis population. The nature of a scoping review always raises the possibility that a small number of relevant studies may not have been included. However, the search strategy for this review was extensive; the rigorous systematic methodology for finding articles, the use of a specific prespecified protocol and two independent reviewers all combined to produce a comprehensive search.

Conclusion

Multimorbidity in bronchiectasis is common. The body of research in bronchiectasis focuses on a few key aspects, *i.e.* prevalence and prognosis, and on favoured comorbidities (*e.g.* COPD). There is a deficit of research into symptoms, QoL, the interactions between multiple comorbid conditions and the effect on management.

HRCT diagnosis is not consistent or mandated and there is no agreed multimorbidity screening questionnaire. In conclusion, we have identified that bronchiectasis multimorbidity is of importance; it is associated with disease morbidity and mortality.

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