Detection and diagnosis of large airway collapse: a systematic review

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Shareable abstract (@ERSpublications)
CT is mostly used to diagnose LAC, and at a threshold used by most clinicians (*i.e.* ⩾50%) that would classify a large proportion of healthy individuals as being abnormal and LAC in a quarter of patients with chronic airway diseases https://bit.ly/3izAuSk

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Abstract

Large airway collapse (LAC) is a frequently encountered clinical problem, caused by tracheobronchomalacia +/− excessive dynamic airway collapse, yet there are currently no universally accepted diagnostic criteria. We systematically reviewed studies reporting a diagnostic approach to LAC in healthy adults and patients, to compare diagnostic modalities and criteria used. Electronic databases were searched for relevant studies between 1989 and 2019. Studies that reported a diagnostic approach using computed tomography (CT), magnetic resonance imaging or flexible fibreoptic bronchoscopy were included. Random effects meta-analyses were performed to estimate the prevalence of LAC in healthy subjects and in patients with chronic obstructive airway diseases. We included 41 studies, describing 10 071 subjects (47% female) with a mean±SD age of 59±9 years. Most studies (n=35) reported CT findings, and only three studies reported bronchoscopic findings. The most reported diagnostic criterion was a ⩾50% reduction in tracheal or main bronchi calibre at end-expiration on dynamic expiratory CT. Meta-analyses of relevant studies found that 17% (95% CI: 0–61%) of healthy subjects and 27% (95% CI: 11–46%) of patients with chronic airways disease were classified as having LAC, using this threshold. The most reported approach to diagnose LAC utilises CT diagnostics, and at a threshold used by most clinicians (*i.e.*, ⩾50%) may classify a considerable proportion of healthy individuals as being abnormal and having LAC in a quarter of patients with chronic airways disease. Future work should focus on establishing more precise diagnostic criteria for LAC, relating this to relevant physiological and disease sequelae.

Introduction

The term large airway collapse (LAC) is used to describe a phenomenon in which the trachea and/or main bronchi demonstrate excessive inward movement during the expiratory phase of the respiratory cycle. This finding can be associated with troublesome and pervasive clinical features such as a barking cough, exertional dyspnoea and frequent respiratory tract infection [1].

Historically, several terms have been used to describe the entities causing LAC. Most often, the term tracheobronchomalacia (TBM) is used, but is strictly defined as a pathological weakness of the cartilaginous airway wall [2]. The term excessive dynamic airway collapse (EDAC) is used to describe exaggerated invagination of the posterior muscular tracheal membrane during expiration [3, 4].

It is estimated that some form of LAC may be present in approximately one in ten patients undergoing bronchoscopic examination for respiratory symptoms [5] and as many as a third of patients with COPD [6] or severe asthma [7]. In chronic airways disease, loss of elastic recoil combined with positive pleural pressures, especially during exercise or vigorous expiratory manoeuvres, can increase propensity to airway collapse [8]. The appearance of LAC may thus arise as a comorbid entity, in the presence of underlying airway disease, rather than representing a primary pathological problem or disease state *per se*. Regardless, the detection and characterisation of LAC is important, given several studies have now highlighted clinically meaningful improvements in exercise tolerance and quality of life (QoL) with targeted intervention, *e.g.* with the application of continuous positive airway pressure [9] and tracheobronchoplasty [10].

There is currently a lack of consensus regarding the criteria that should be used to diagnose LAC. Accordingly, whilst bronchoscopic or imaging techniques are often employed interchangeably to assess LAC, there is no agreement as to what constitutes an abnormal or "excessive" degree of collapse or how this differs between investigation modalities. The first description of diagnostic criteria for LAC are attributed to RAYL and colleagues [11], now over 50 years ago, reporting that airway collapse was abnormal if the airway lumen was reduced to one half or less during coughing. This magnitude of collapse became increasingly cited as being "diagnostic" of LAC [12, 13] and generally remains the most commonly applied criteria by pulmonologists currently. This degree or severity of collapse has, however, been found in a large proportion of entirely healthy, asymptomatic individuals [14]. Moreover, the diagnostic criteria used for LAC are potentially confounded by variation in the protocols employed to visualise and evaluate airway movement [1]. Thus overall, there is a risk of both potential over- and under-diagnosis, with associated implications for patient management.

The aim of this review was to systematically assess the published literature in this area and report differences in the criteria used in the diagnosis of LAC. A secondary aim was to undertake a synthesis of the literature assessing the prevalence of LAC in healthy individuals and in those with a clinical diagnosis of chronic airways disease. The various cut-off values and diagnostic modalities are critically appraised with the overall aim of helping to inform clinicians and researchers, evaluating this clinical entity and help direct development of future classification systems.

Methods

Protocol and registration

A systematic review of the available literature was performed using two electronic databases (PubMed and Embase). The search criteria employed included all eligible studies between January 1989 and October 2019 using the following keywords (airway collapse OR airway collapsibility OR bronchial collapse OR bronchial collapsibility OR tracheal collapse OR tracheal collapsibility OR expiratory collapse OR expiratory tracheal narrowing OR tracheomalacia OR tracheobronchomalacia OR bronchomalacia). Further detail on the search strategy is summarised in the online supplementary e-table 1. The timeframe for included publications (*i.e.* only studies within the last 30 years) was selected to ensure relatively modern bronchoscopic, imaging equipment and techniques were employed and thus findings were applicable and relevant to current practice. The study was registered with PROPSPERO (CRD42019149347).

Selection criteria

Studies conducted in human subjects and published in English were considered for inclusion, providing they fulfilled the following criteria: 1) LAC had to be evaluated using either CT, magnetic resonance imaging (MRI) or flexible fibreoptic bronchoscopy; 2) the anatomic airway sites for evaluation of LAC had to be the trachea, main bronchi or both; 3) the cut-off values or the magnitude of LAC (TBM or EDAC) or the diagnostic approach had to be clearly reported in the study methodology and/or results section; 4) studies describing findings in children only were excluded; and 5) included case studies/series had to include at least three cases and thus single or double case report studies were excluded.

Data extraction

We extracted the following information: study aim (*e.g.* diagnosis of LAC), study design (*e.g.* prospective or retrospective), population characteristics (*e.g.* healthy adults or patients), diagnostic modality (*e.g.* CT, MRI or bronchoscopy), diagnostic criteria of LAC (*e.g.* >50% collapse in the airway's cross-sectional area; CSA), main findings with prevalence of LAC and conclusions. This information was extracted from the original articles into an Excel spreadsheet (separated into columns such as study aim, study design, *etc.*), which was subsequently used as the data collection form.

Quality assessment

Study quality was assessed for those included in the meta-analysis sections addressing the prevalence of LAC in healthy subjects and patients with chronic airways disease (supplementary e-table 2). As there is no standard tool for assessing the quality of patient-based prevalence studies, we selected and modified items regarding external and internal validity from the assessment tools for population-based prevalence studies [15] and diagnostic studies [16], which included recruitment method, sample size justification, sample representativeness, risk of selection bias, appropriate exclusion criteria and outcome definition. Discrepancies in quality assessment were resolved by discussion between the lead authors.

Statistical analysis and synthesis of results

Estimation of the pooled prevalence of LAC was planned for certain populations (either in healthy controls or chronic airway diseases, where possible), using random effects meta-analyses to account for potential clinical and methodological heterogeneities in observational studies. Subgroup analysis was considered according to different threshold in the diagnostic criteria and modality for LAC. Heterogeneity was first assessed using a visual forest plot inspection and I^2 statistics. We considered funnel plot asymmetry and Egger's tests to assess publication bias if appropriate [17]. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant. All meta-analyses were conducted using software MetaXL 5.3 (EpiGear International Pty Ltd, Brisbane, Australia).

Results

Study selection

The initial search strategy revealed 6446 articles. Following application of the PRISMA criteria, 41 papers satisfied the full selection criteria and were included in subsequent analysis (figure 1). The total sample size from these papers was 10 071 subjects (n=193 healthy), of which 38 studies provided full subject demographic details describing a population with mean age of 59±9 years, 47% of whom were female.

Studies reporting bronchoscopic assessment

Subject characteristics

Three studies describe the use of flexible bronchoscopy to assess LAC (table 1). These studies included 230 patients (age: 56.3±8.8 years; 53% female) with a variety of clinical disease states including COPD, asthma, relapsing polychondritis and sarcoidosis [7, 18, 19]. However, over two-thirds of those identified (88%) were patients with asthma, enrolled into a single trial [7]; with an asthmatic cohort (n=202) and a "control" cohort of subjects undergoing bronchoscopy as a reference group (n=62; age: 38.9±10.4; 38.7% female). The other two studies enrolled small numbers of patients (n=10 and n=18, respectively) [18, 19], and we were unable to find any bronchoscopic studies evaluating LAC in entirely healthy, asymptomatic subjects.

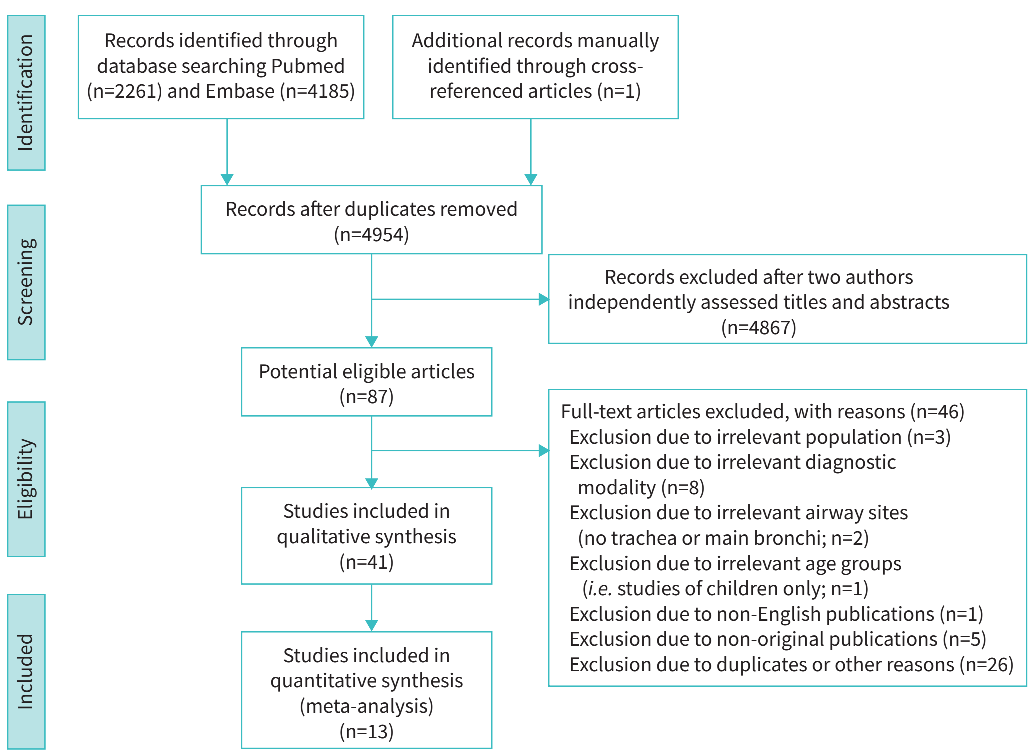

FIGURE 1 PRISMA flow chart for study selection.

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TABLE 1 Bronchoscopic studies

First author/ year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Majid *et al.* 2014 [19]	Prospective single-centre study Assessing inter- and intra-observer agreement in LAC	10 patients (males (n=4), females (n=6); mean age: 65 years, age range: 43–74 years) with various conditions	Dynamic flexible bronchoscopy	TBM or EDAC ⩾50% reduction in the anteroposterior diameter	TBM was found in 70% of patients	There is intra- and interobserver agreement among pulmonologists and trainees with various levels of experience in the evaluation of LAC
Dal Negro *et al.* 2013 [7]	Prospective single-centre study Assessing the prevalence of both TBM and EDAC	202 asthmatics (males (n=91), females (n=111); age: 47.5±13.3 years), and 62 subjects without any obstructive disease (males (n=38), females (n=24); age: 38.9 ±10.4 years)	Dynamic flexible bronchoscopy	TBM or EDAC >50% of airway collapse	TBM and particularly EDAC prevalence are related to asthma severity	The presence of TBM or EDAC should be considered when bronchial asthma persists despite appropriate pharmacological treatment
Murgu & Colt, 2007 [18]	Retrospective single-centre study Assessing a multidimensional classification system (FEMOS) for evaluating patients with expiratory LAC	18 patients (males (n=13), females (n=5); 4 with EDAC and 14 with TBM)	Rigid bronchoscopy	LAC, normal <50%, mild, 50–75%; moderate, 75–100%; and severe, 100% and the airway walls make contact	EDAC and TBM were found in 22.2% and 77.8%, respectively	Using FEMOS, the morphologies and aetiologies of LAC can be identified and stratified objectively based on the degree of functional impairment, extent of disease and severity of airway collapse

LAC: large airway collapse; TBM: tracheobronchomalacia; EDAC: excessive dynamic airway collapse.

Protocols employed

Two studies employed flexible bronchoscopy [7, 19], with the patient in a supine position; and one study utilised both flexible and rigid approach [18]. Scope placement was varied across the studies with evaluation performed at the level of the trachea, carina and main bronchi and under conscious sedation, in the flexible studies [7, 18, 19]. The breathing manoeuvres undertaken during bronchoscopy are described as dynamic or forced inspiration and expiration manoeuvres with luminal dimensions measured at the end of both forced inhalation and exhalation were performed at five sites, namely, proximal, mid- and distal trachea, and at right and left main-stem bronchus [7, 19]. In the study by Majid *et al.* [19], the expiratory phase collapse patients were evaluated by instructing subjects to take a deep breath, hold it and blow it out. In the study by Dal Negro *et al.* [7], collapse was assessed spontaneously and following a physician's instruction to perform deep breathing, forced exhalation and coughing. One study did not report the specific breathing instructions [18], and there were no details providing compliance or non-cooperation during these breathing procedures.

All studies (n=3) defined LAC as a >50% airway collapse and provided a semi-quantitative description of LAC, using pre-defined cut-off thresholds (*i.e.*, normal <50%, mild 50–75%, moderate 75–100% and severe 100%) (figure 2). Murgu and Colt [18] also report a novel scoring system, by combining bronchoscopic findings with a multidimensional classification system (termed the FEMOS classification). In the FEMOS classification, the extent (from normal to diffuse), morphology (TBM type or not) and severity (normal <50%, mild 50–75%, moderate 75–100% and severe 100%) of airway collapse is combined with the functional status of the subject as classified by level of dyspnoea to provide an overall classification score. This classification system was also employed to describe LAC in the 264 subjects in the series of Dal Negro and colleagues [7]. Majid *et al.* [19] utilised pre-defined cut-off thresholds (as described above) to assess the degree of LAC and showed an interobserver and intra-observer interclass correlation coefficient of 0.81 and 0.89, respectively.

Studies reporting imaging-based assessment

Computed tomography

Subject characteristics

The studies (n=35) using CT to assess LAC are presented in table 2. These studies included a total of 10 402 participants of which 10 244 were patients (age: 58.4±9.3 years; 47% female) with conditions such as COPD, asthma, relapsing polychondritis and sarcoidosis. There were also data available in 158 healthy subjects (age: 50.9±4.1 years; 42% female).

Protocols employed

The majority of the protocols describe utilising a helical or spiral CT (27 out of 35 studies) technique, whilst the remaining studies use cine-acquisition. The most commonly utilised breathing manoeuvre described during CT scanning was paired end-inspiratory-dynamic expiratory (used in 33 out of 35 studies). Two studies instructed the patients to cough [20] and to hold their breath [21] during scanning.

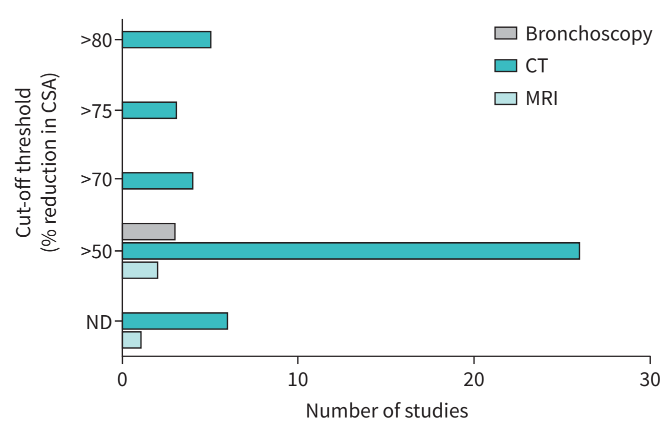

FIGURE 2 Study cut-off thresholds reported for the diagnosis of large airway collapse, based on diagnostic modality. CSA: cross-sectional area; CT: computed tomography; MRI: magnetic resonance imaging.

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TABLE 2 Computed tomographic and magnetic resonance imaging studies

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Bezuidenhout *et al.* 2019 [51]	Retrospective single-centre study To evaluate patients with TBM after undergoing tracheobronchoplasty	18 patients (males (n=5), females (n=13); mean age: 65±12 years) with COPD (n=7), GERD (n=14), OSA (n=8), cardiac disease (n=4)	8-, 16- and 64-MDCT scan	LAC $\geqslant$70% reduction in the CSA	Mean tracheal collapsibility improved by 34% in post-operative CT	Dynamic CT could play an important role in assessing response to tracheobronchoplasty
Nygaard *et al.* 2019 [29]	Retrospective/prospective single-centre study To assess TM over time (2 CT scans) in patients with excessive tracheal collapse	20 patients with respiratory diseases (males (n=6), females (n=14); mean age: 68 years)	high-resolution MDCT scan	TM $\geqslant$50% reduction in the CSA	Seven patients showed a tracheal collapse progression (>10% difference) between the scans	Tracheal collapse regressed in half of the patients over a time period of 2 years
Ciet *et al.* 2017 [31]	Prospective single-centre study Comparison of MRI to MDCT in assessing TBM	12 participants (males (n=5), females (n=7); 9 healthy adults and 3 patients with COPD; mean age: 64.5 years, age range: 45–77 years)	1.5-T Signa MRI 64-MDCT scan	Criterion was not defined	TM was 52% and 77% and BM was 55% and 63% during FVC for healthy and COPD patients, respectively	MRI was found to be a technically feasible alternative to MDCT for assessing TBM
Nygaard *et al.* 2017 [30]	Retrospective single-centre study To compare four different image analysis methods for the diagnosis of tracheal collapse using MDCT	353 patients (males (n=150), females (n=191), mean age: 60 years, age range: 18–88 years) with respiratory diseases (*e.g.* COPD, ILD, bronchiectasis)	64-MDCT scan	LAC >50% and >80% reduction in the CSA	LAC prevalence was ~15.1% when using >50% as a threshold	The different image analysis methods identified LAC in different patients. Thus, the diagnosis of LAC should not solely rely on MDCT images
Leong *et al.* 2017 [6]	Prospective single-centre study To explore the prevalence of ECAC in stable and acute exacerbations COPD (AECOPD) patients	40 COPD patients (males (n=19), females (n=21); age: 70.1±8.2 years); 64 AECOPD (males (n=40), females (n=24); age: 70.2±11.6 years); 53 healthy volunteers (males (n=35), females (n=18); age: 56.6±16.9 years)	320-slice dynamic MDCT	LAC >50%, >75% and >80% reduction in the CSA were compared	ECAC was observed in 35% of COPD, 39% of AECOPD and no healthy individuals when a >50% was used as a criterion	ECAC can be present in up to one third of patients with stable COPD, and the abnormality does not seem to be worsened during AECOPD
Bhatt *et al.* 2016 [44]	Retrospective multicentre study Assessing the association of ECAC to lung disease in smokers	8820 ex- or active smokers (43.7% had COPD and 16.6% had asthma (males (n=4667), females (n=4153); mean age: 59.7 ±6.9 years))	CT scan	ECAC $\geqslant$50% reduction in CSA	ECAC prevalence was 5% in ex- or active smokers and 5.9% in participants with COPD (n=229/3856)	The presence of ECAC was associated with worse respiratory quality of life in current or former smokers
Sindhwani *et al.* 2016 [34]	Prospective single-centre study To assess expiratory wheeze in patients with obstructive airway disorders	25 patients (males (n=14), females (n=11), mean age: 62.7±7.81 years) with COPD	CT scan	TBM/EDAC $\geqslant$50% reduction of the airway lumen	TBM/EDAC was found in 40% of COPD patients	Findings indicate value of screening patients with obstructive airway disease for TBM/EDAC

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TABLE 2 Continued

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
El Sorougi *et al.* 2016 [33]	Prospective single-centre study To determine the prevalence of TM in COPD patients	30 patients with COPD (demographics were not reported)	64-MDCT scan	TM ⩾50% in the tracheal lumen CSA	20% of COPD patients showed evidence of TM	A significant proportion of patients with COPD had features consistent with TM on dynamic CT scanning
Weinstein *et al.* 2016 [52]	Prospective single-centre study To describe the imaging characteristics of people presenting exertional dyspnoea	6 military personnel (males (n=5), females (n=1), mean age: 39.5 years, age range: 24 to 53 years) with no underlying lung disease	CT scan Bronchoscopy at rest and during exercise (cycling; n=2).	EDAC ⩾75% reduction of the airway lumen	EDAC was detected on expiratory images during dynamic CT (n=2)	EDAC may explain "unexplained" exertional dyspnoea and wheeze in military recruits
Represas-Represas *et al.* 2015 [43]	Prospective single-centre study To investigate the prevalence of EDAC in COPD	53 patients (males (n=46), females (n=7), mean age: 65 ±9 years) with COPD	Helicoidal MDCT	EDAC >50% reduction in CSA	Prevalence of EDAC was 9.4%	EDAC in COPD patients is independent of disease severity and may not relate to symptoms
O'Donnell *et al.* 2014 [25][¶]	Prospective single-centre study To determine the tracheal collapse in COPD patients	67 patients (males (n=38), females (n=29); age: 65.1 ±6.5 years) with COPD	64-detector row CT scan	Tracheal collapse ⩾80% reduction in CSA	Average forced expiratory collapse (62±16%) was greater to end-expiratory collapse (17±18%)	COPD patients display a wide range of tracheal collapse at end-expiration
Wielpütz *et al.* 2014 [53]	Prospective single-centre study To assess the feasibility of low-dose MDCT	3 patients (3 males; mean age: 63.3 years) with COPD	4D MDCT scan	TM criterion was not reported	EDAC (n=1), sabre-sheath trachea and TBM (n=1), as well as tracheal stenosis (n=1) were demonstrated	Low-dose MDCT may have equal diagnostic impact as bronchoscopy for tracheal instability
Boiselle *et al.* 2013 [54]	Prospective single-centre study To assess the tracheal collapse in morbidly obese, non-morbidly obese and normal weight COPD patients	100 patients (males (n=52), females (n=48), mean age: 65±7 years) with COPD	64-detector CT scan	LAC criterion was not reported	Expiratory collapse was directly associated with BMI (p=0.002)	Obesity is positively correlated with the degree of expiratory tracheal collapse among COPD patients
O'Donnell *et al.* 2012 [40][#]	Prospective single-centre study To explore the association between forced expiratory tracheal collapse and age or sex	81 healthy volunteers (males (n=41), females (n=40); age: 47±17 years)	64-detector-row CT scan	Tracheal collapse⩾80% reduction in CSA	The mean % collapse was similar for males (55 ±23%) and females (52 ±17%). The mean % collapse was correlated to age (r^2 = 0.40, $p<0.001$) in males	Age and sex should be considered when assessing forced expiratory airway collapse for suspected TM
Boiselle *et al.* 2012 [24][¶]	Prospective single-centre study To determine the prevalence of tracheal collapse in COPD patients	100 patients (males (n=52), females (n=48); age: 65 ±7 years) with COPD	64-detector-row CT scan	Tracheal collapse ⩾80% reduction in CSA	Prevalence of TM was found in 20 participants (20%)	TM is observed in a subset of patients with COPD, but the magnitude of collapse is independent of disease severity

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TABLE 2 Continued

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Boiselle *et al.* 2010 [32]	Prospective single-centre study To assess the reproducibility of MDCT in measuring TM in healthy volunteers over time	14 healthy volunteers (males (n=6), females (n=8), mean age: 48.7 ±13.8 years)	64-MDCT scan	TM criterion was not reported	1st and 2nd year measures of tracheal collapse were strongly associated (r^2=0.98, p<0.001)	MDCT measurements of forced expiratory tracheal collapse in healthy volunteers is highly reproducible over time
Litmanovich *et al.* 2010 [26][#]	Prospective single-centre study To assess the forced expiratory bronchial collapsibility in healthy volunteers	51 healthy volunteers (males (n=25), females (n=26); age: 50±15 years)	64-detector row MDCT scan	Expiratory reduction in CSA of >50% and >80%, were both used	73% of participants met the criterion (>50%) in one or both bronchi	The current data suggest the need for more rigorous criteria for the diagnosis of BM
Wagnetz *et al.* 2010 [28]	Prospective single-centre study To establish the use of a novel MDCT for the evaluation of TM	6 patients (males (n=5), females (n=1); mean age: 53 years, age range: 37 to 70 years) with suspected TM (medical history was not reported)	320-row MDCT scan and fibreoptic bronchoscopy	TM/TBM⩾50% reduction in CSA	All patients demonstrated TM/TBM with varying degrees of airway collapse (50% to >90% of the CSA)	The 4D MDCT, isotropic, isovolumetric and isophasic, of the central airway is promising for the diagnosis of TM/TBM
Boiselle *et al.* 2009 [14][#]	Prospective single-centre study To assess the tracheal collapsibility in healthy volunteers	51 healthy volunteers (males (n=25), females (n=26); age: 50±15 years)	64-detector row MDCT scan	Expiratory reduction in CSA of >50%	78% of healthy volunteers exceeded the current diagnostic criterion for TM	This study emphasises the need for a more rigorous diagnostic criterion to prevent overdiagnosis of TM
McDermott *et al.* 2009 [39]	Prospective single-centre study To determine the prevalence and severity of TM in adults with CF	40 patients (males (n=22), females (n=18); mean age: 28±8, age range: 18–54) with CF and 10 controls	Dynamic cine MDCT with 64-detector row	TM >50% or >75% reduction in CSA during cough	TM was found in 69% of patients with CF during forced expiration and in 29% during coughing	TM depicted at dynamic cine MDCT is a highly prevalent finding in patients with CF
Inoue *et al.* 2009 [45]	Retrospective single-centre study To evaluate the frequency of TBM associated with PE	56 patients (males (n=55), females (n=1); mean age: 68.9 years, age range: 49–87 years) with PE	MDCT scanner with two-detector row	TBM ⩾50% decrease in CSA	Four (7.1%) patients were diagnosed as having TM or BM	TBM might be under-diagnosed in some patients with PE when using the standard criterion (*e.g.* ⩾50%)
Ochs *et al.* 2009 [46]	Retrospective multicentre study To investigate the prevalence of TM in an emphysema cohort	431 patients (males (n=267, mean age: 64 years, range: 41 to 76), females (n=164, mean age: 62 years, range: 41 to 76))	CT scan	LAC ⩾50%, and >70% in the CSA	Prevalence of TM was found in 13.4% participants based on ⩾50% criterion	A large degree of tracheal collapse can be found at end-expiration in patients with emphysema
Ferretti *et al.* 2008 [27]	Prospective single-centre study To compare dynamic and end-expiratory imaging to assess LAC in patients with suspected TBM	70 patients (males (n=43), females (n=27); mean age: 57 years, age range: 12–79 years) with respiratory conditions (*e.g.* COPD)	16-detector row helical CT scan	TBM was not defined	TBM was not found at the end of expiration, but its prevalence was 13% during dynamic expiration	Dynamic expiratory CT demonstrates a greater degree of LAC than the end-expiratory acquisition in patients with suspected TBM

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TABLE 2 Continued

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Lee *et al.* 2007 [50]	Retrospective single-centre study To compare the dynamic expiratory CT against bronchoscopy for detecting airway malacia	29 patients (males (n=12), females (n=17), mean age: 60 years, age range: 36 to 79 years) with COPD and relapsing polychondritis	MDCT helical scan	LAC >50% reduction in CSA	CT findings were concordant with bronchoscopy in 97% of patients	CT is a highly sensitive method for detecting airway malacia and could serve as an effective, noninvasive test for diagnosing LAC
Boiselle *et al.* 2006 [20]	Prospective single-centre study To describe the technical aspects of using 64-MDCT during coughing	17 patients (males (n=6), females (n=11), age range: 62.4 years) with suspected TM	64-MDCT scan	TM >50% reduction in CSA during coughing	64-MDCT during a coughing protocol was technically successful in 94% of patients	64-MDCT is technically feasible and has the potential to make significant contributions to the noninvasive diagnosis of TM
Lee *et al.* 2006 [55]	Retrospective single-centre study To assess the prevalence of expiratory CT abnormalities, including malacia	18 patients (males (n=3), females (n=15), mean age: 47 years; age range: 20–71 years) with relapsing polychondritis	Helical MDCT	LAC >50% reduction in CSA	CT abnormalities were present in 94% and airway malacia in 72% of patients	Dynamic expiratory CT should be considered a standard component of airway evaluation in patients with relapsing polychondritis
Nishino *et al.* 2006 [36]	Prospective single-centre study To evaluate the frequency and severity of BM	46 patients (males (n=10), females (n=36), mean age: 64 years, age range: 44–84 years) with bronchiectasis	Volumetric high-resolution 4- or 8-detector CT	LAC ⩾50% reduction in the CSA	Prevalence of BM was found in 70% of patients at end-expiration	Air trapping in bronchiectasis might be greater in bronchiectasis patients with BM compared to those without
Baroni *et al.* 2005 [38]	Retrospective single-centre study To compare the dynamic- and end-expiratory CT in assessing LAC	14 patients (males (n=11), females (n=3), mean age 53 years old and age range: 19–79 years) with various conditions	Eight-detector row helical CT scan	LAC ⩾50% reduction in the CSA	Collapse was greater in dynamic expiration than in end-expiration ($p<0.004$)	The reliance on end-expiratory imaging alone might result in a high level of false-negative results
Baroni *et al.* 2005 [37]	Prospective single-centre study To describe the role of pre- and post-operative dynamic CT in patients undergoing tracheoplasty	5 patients (males (n=4), woman (n=1); mean age: 62, age range: 56–78)	8-MDCT helical scan	TBM ⩾50% reduction in the CSA	Tracheal collapse was found to be 58.9% pre- and 26.9% post-operatively during dynamic expiration	Dynamic expiratory CT is a potentially valuable tool in the pre- and post-operative evaluations of patients undergoing tracheoplasty
Nishino *et al.* 2005 [35]	Prospective single-centre study To investigate the frequency of BM associated with sarcoidosis	18 patients (males (n=6), females (n=12); mean age: 47 years, age range: 29–64 years) with pulmonary sarcoidosis	High-Resolution CT	LAC >50% reduction in CSA	BM was found in 61% of patients	BM is frequently associated with sarcoidosis

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TABLE 2 Continued

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Heussel *et al.* 2004 [42]	Prospective single-centre study To assess the respiratory lumen diameter, change in the tracheal level during continuous respiration	38 subjects, 23 patients with COPD (age: 59 years, age range: 41–68 years) and 15 healthy adults (age: 62 years, age range: 48 to 74 years)	Cine-MRI	LAC >50% reduction in CSA	A pathological collapse occurred in 33% of volunteers and in 69.6% of patients with COPD	The airway collapse is significantly larger in patients with COPD compared to volunteers
Hasegawa *et al.* 2003 [21]	Retrospective single-centre study To determine the frequency of TM incidentally detected on CT pulmonary angiography (CTPA)	163 (73 males (n=73), females (n=90); mean age: 60 years) with suspected pulmonary embolism	Single detector CT and MDCT (with 4 and 8 detectors)	TM ⩾50% decrease in tracheal lumen	Prevalence of TM was found in 10% of the participants with suspected pulmonary embolism	TM is a relatively common finding in CTPA when assessing patients with suspected pulmonary embolism
Zhang *et al.* 2003 [3]	Prospective single-centre study To compare standard- and low-dose CT images assessing tracheal lumen	10 patients (males (n=5), females (n=5), mean age: 56 ±11 years) with bronchoscopically proved TBM	Multi-section helical MDCT scan	LAC >50% reduction in the CSA	TBM was found in all 10 patients	Paired inspiratory and dynamic expiratory CT images is a promising method for diagnosing TBM
Aquino *et al.* 2001 [56]	Retrospective and prospective single-centre study To explore the measurements of the trachea between inspiration and end-expiration on CT	10 TM patients (males (n=6), females (n=4); mean age: 60 years, age range: 42 to 84 years) and 23 normal control patients (males (n=15), females (n=8); mean age: 40 years, age range: 27 to 57 years)	CT scan	Diagnostic criterion for TM was not reported	Collapsibility in tracheal CSA was significantly greater in patients with TM (1.9±0.9 cm^2) compared to controls (2.4±0.6 cm^2) during end-expiration	Patients with TM demonstrate a higher airway collapse compared to controls
Gilkeson *et al.* 2001 [4]	Prospective single-centre study To examine the role of dynamic inspiratory-expiratory imaging with MDCT in patients with suspected TBM	13 patients (males (n=7), females (n=6); mean age: 49 years and age range: 14–88 years) with respiratory conditions (*e.g.* asthma, chronic cough, smoking)	MDCT scan, bronchoscopy	LAC >50% reduction in the CSA	All patients showed evidence of TBM of different degrees, 50–75% (n=3) 75–100% (n=7), and 100% (n=3)	MDCT with inspiratory-expiratory imaging is a promising method in the evaluation of patients with suspected TBM
Heussel *et al.* 2001 [22]	Prospective (including retrospective analysis) single-centre study To compare CT, MRI bronchoscopy, in the diagnosis of LAC	29 patients (males (n=10), females (n=19); mean age: 61 years, age range: 27–82 years) with suspicion of or previously bronchoscopically verified tracheal collapse	CT scans (spiral and cine), cine-MRI, bronchoscopy	⩾50% collapse of the CSA	Bronchoscopy correlated with cine CT. MRI demonstrated similar time curves of tracheal CSA to cine CT	Cine CT is able to obtain significantly improved evaluation of respiratory collapse. Cine-MRI promises functional information due to free choice of imaging plane

Continued

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TABLE 2 Continued

First author/year	Study purpose and design	Population	Diagnostic modality	Diagnostic criteria	Findings	Discussion
Suto & Tanabe, 1998 [41]	Prospective single-centre study To evaluate tracheal collapsibility during coughing in patients with TM who underwent MRI	6 patients (males (n=4), females (n=2); mean age: 40 years, age range: 44 to 68 years) with suspected TBM and 13 healthy volunteers (males (n=10), females (n=3); mean age: 40 years, age range: 17 to 63 years)	1.5-T superconducting MRI system	Diagnostic criterion for TM was not reported	Collapse was 30±13% and 50±15% in forced expiration, and 38±16% and 75±12% during coughing in healthy and patients with TM, respectively	Collapsibility during forced expiration-inspiration and collapsibility during coughing was not significant in patients with TM during MRI
Stern *et al*. 1993 [57]	Prospective single-centre study To define the range of intrathoracic tracheal diameters and CSA during forced respiration	10 healthy volunteers (males (n=10), age range: 24–31 years)	CT using the model C-100 scanner	TM >70% reduction in the CSA	Trachea significantly decreased (p<0.001) from end-inspiration (280 mm^2) to end-expiration (178 mm^2)	Intrathoracic tracheal shape, sagittal and coronal diameters, and CSA can vary greatly during a forced respiration

[#]The studies by Litmanovich *et al*. 2010 and Boiselle *et al*. 2009 were not analysed as part of the main results as the participants of both studies were included in O'Donnell *et al*. 2012. [¶]The study by Boiselle *et al.* 2013 was not analysed as part of the main results as the participants were included in O'Donnell *et al*. 2014. TBM: tracheobronchomalacia; GERD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea; MDCT: multi-detector CT; LAC: large airway collapse; CSA: cross-sectional area; EDAC: excessive dynamic airway collapse; CT: computed tomography; TM: tracheomalacia; MRI: magnetic resonance imaging; BM: bronchomalacia; FVC: forced vital capacity; ILD: interstitial lung disease; ECAC: excessive central airway collapse; CF: cystic fibrosis; PE: pulmonary emphysema; CTPA: pulmonary angiography.

One of the earliest CT studies included in this review performed both spiral and cine CT scans in patients with a suspicion of tracheal stenosis or collapse [22]. Spiral CT was performed during inspiration and during an end-expiratory breath-hold (lasting ∼20 s) and cine CT was performed during deep and slow breaths. A collapse of >50% was found at significantly fewer levels when using paired spiral CT compared to cine CT (13 *versus* 38%; p<0.001). For this reason and because the results from cine CT correlated better with bronchoscopic findings (from the same study), the authors concluded that cine CT assesses the magnitude of tracheal collapse more reliably than static inspiratory and expiratory imaging [22].

Other studies describe use of a multi-detector (*i.e.* two or more detector rows) CT (MDCT) scan [23–26] to assess LAC in patients with respiratory diseases. This approach allows the entire large airway tree to be scanned in <5 s offering a high standard of temporal resolution during dynamic expiration which is not possible with a slice by slice or single detector CT [27].

Thirteen studies (37%) trained the participants regarding breathing technique, prior to CT examination. Sixteen studies (46%) reported the breathing manoeuvres that were used to assess tendency to airway collapse. Eight studies instructed the participants to breath in, hold (for a count of 2 [28]) and blow out [21, 24, 26, 29–32]. Two studies requested patients to breathe deeply twice, then to exhale as completely as possible before performing a breath-hold, at which point the imaging commenced [33, 34], or to take a deep breath in, blow out all the way and hold breath (four studies; 25%) [35–38]. McDermott *et al.* [39] instructed the patients to perform a maximal inspiration and forceful exhalation, whereas Heussel *et al.* [22] instructed patients to breath slowly and deeply through an open mouth during imaging. Two studies reported that many patients (with suspected pulmonary embolism) were unable to maintain prolonged breath-holds [21], and that inadequate forceful exhalations observed by spirometry trace were repeated [40]. Fourteen studies (out of 35; 40%) did not report the instructed breathing manoeuvres during the airway collapse assessment.

Magnetic resonance imaging

Subject characteristics

MRI has been used to assess LAC in four studies (table 2). These studies included a total of 90 participants of which 53 were patients (mean age: 57.9±6.6 years; 60% female) with COPD, asthma, relapsing polychondritis and sarcoidosis and 37 were healthy volunteers (mean age: 52.3±12.3 years; 23% female; two studies did not report the age).

Protocols employed

The first study to use MRI for the evaluation of tracheomalacia [41] used two-dimensional fast sequences. This approach demonstrated that a significant difference in collapsibility occurs during forced expiration and inspiration (50%±15), and during coughing (75%±12) in patients with tracheomalacia [41]. Moreover, fast acquisition MRI demonstrated excellent temporal resolution, high contrast resolution regardless of imaging plane [41]. A recent study assessed TBM during two 13-s breath-hold end (static)-inspiratory and end-expiratory scans using three-dimensional cine-MRI acquisitions allowing the detection of dynamic TBM in a pseudo real time (*i.e.* high-speed imaging similar to real time) [31].

All MRI studies included in the review defined LAC as a >50% reduction in the CSA (figure 2). One of the studies reported a mean CSA upper tracheal collapse of 42% (but with a range 20–83%) in healthy adults and 64% (range 29–100%) in COPD patients when evaluating LAC using cine-MRI [42]; however, it did not report the prevalence of LAC, based on a >50% reduction in CSA cut-off, in healthy subjects. To elicit expiratory collapse patients were instructed to either breath in, hold and blow out [31] or to breath slowly and deeply through an open mouth during imaging [22, 42]. There were no reports of breathing manoeuvre training prior to the MRI examination or indeed patient cooperation during imaging.

Meta-analyses of LAC prevalence

Healthy controls

The most commonly used criterion to define LAC was a >50% reduction in the airway lumen or in the CSA (figure 2). After exclusion of duplicate inclusion of subjects in different studies (see Boiselle *et al.* [14, 24], Litmanovich *et al.* [26]), five studies were found to report the prevalence of LAC in healthy volunteers (supplementary e-table 3) [6, 7, 39, 40, 42]. In a random effects meta-analysis of the four studies using the criterion of >50% reduction [6, 39, 40, 42], LAC was found in 17% (95% CI: 0–61%; I^2=96%) (figure 3) of healthy subjects. One study using a >70% reduction in CSA criterion reported that LAC was present in only 2% (95% CI: 0–7%) [7]. For the studies that were included in the meta-analysis, the mean CSA collapsibility for healthy controls was 39±17%. There was a considerable heterogeneity among the studies (I^2>90%; figure 3), which could be attributed to the different protocols that were

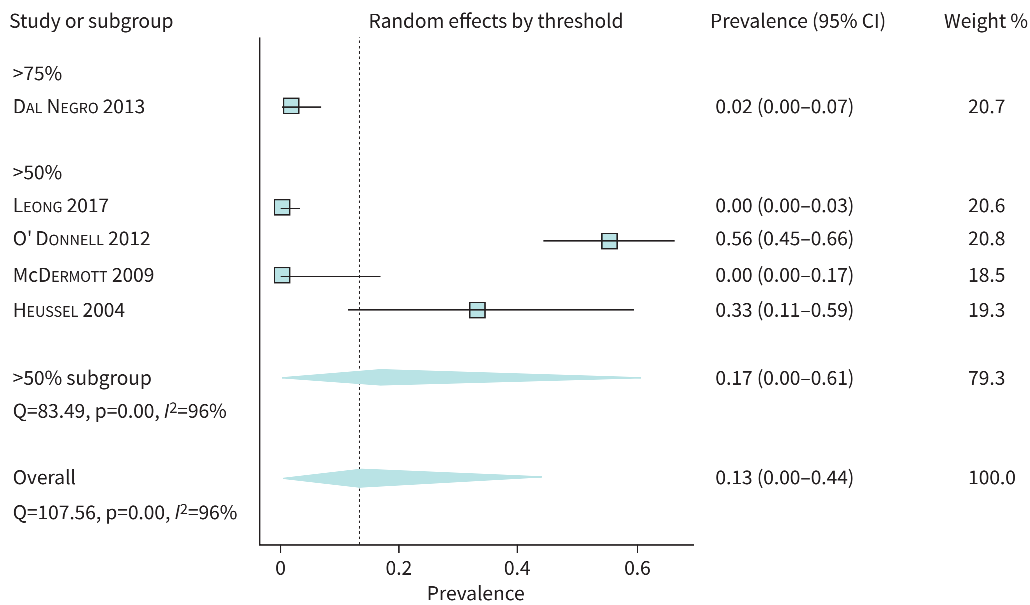

FIGURE 3 Forest plot of the prevalence of large airway collapse in healthy subjects. Random effects meta-analysis was done to estimate the pooled prevalence. Details of included studies, including population, diagnostic modality and threshold, are summarised in table 1.

employed to assess LAC such as the breathing manoeuvres (*e.g.* forced exhalation, breath-hold, coughing) and technical features (*e.g.* spiral or cine CT with single or multi-detectors).

Patients with chronic airway diseases

Thirteen studies reported the prevalence of LAC in patients with chronic airway diseases or smokers, including COPD [6, 7, 24, 33, 34, 42, 43, 44], asthma [7, 34], cystic fibrosis [39], emphysema [45, 46], bronchiectasis [36] or pulmonary sarcoidosis [35]. We performed a meta-analysis for LAC prevalence in eight studies of patients either with COPD or asthma, as the number of studies on other respiratory conditions such as cystic fibrosis, emphysema or bronchiectasis was too small. The studies included in the meta-analysis are summarised in supplementary e-table 4, and most of them utilised a >50% reduction [6, 7, 33, 34, 42, 43, 44]. LAC was found in 27% (95% CI: 11–46%; I^2=97%) of the included patients (figure 4). One study using the >80% criterion found that LAC was present in 20% (95% CI: 13–28%) in a COPD patient population [24]. For the studies that were included in the meta-analysis, the mean CSA collapsibility for patients with chronic airway diseases was 52±17%. Heterogeneity among the studies (I^2>90%; figure 4) was found to be substantial. This could be explained by the fact that in patients with chronic airway diseases, clinical factors, such as age, disease severity or lung function, are relevant in heterogeneity [7].

Discussion

It is apparent from this systematic review that over the past 30 years, a wide variety of approaches have been evaluated in the diagnostic evaluation of LAC. Bronchoscopy has long been considered the "gold standard" diagnostic test by clinicians; however, our review process reveals that CT has actually been the most commonly reported modality in the published literature over this time period. Indeed, CT has been utilised in 80% of all published LAC studies and there are only three papers detailing bronchoscopic evaluation of LAC, within the contemporary literature. The review process also reveals that, to the best of our knowledge, there are no published data describing the "normal" or healthy large airway response to expiratory manoeuvres, using bronchoscopic techniques. In addition, although a >50% reduction in large airway calibre appears to be, at least anecdotally, the most widely used diagnostic criterion in clinical practice, and indeed is reported in half of the papers included in this review, this degree of LAC was encountered in one in five asymptomatic and entirely healthy subjects undergoing dynamic expiratory CT imaging. Overall, the findings thus might challenge several assumptions widely held, with respect to the most widely researched diagnostic technique and cut-off values used for the diagnosis of LAC.

Accurate detection and diagnosis of LAC is important to facilitate selection and delivery of treatments that may improve patient QoL and reduce healthcare utilisation [47, 48]. Recent work has highlighted

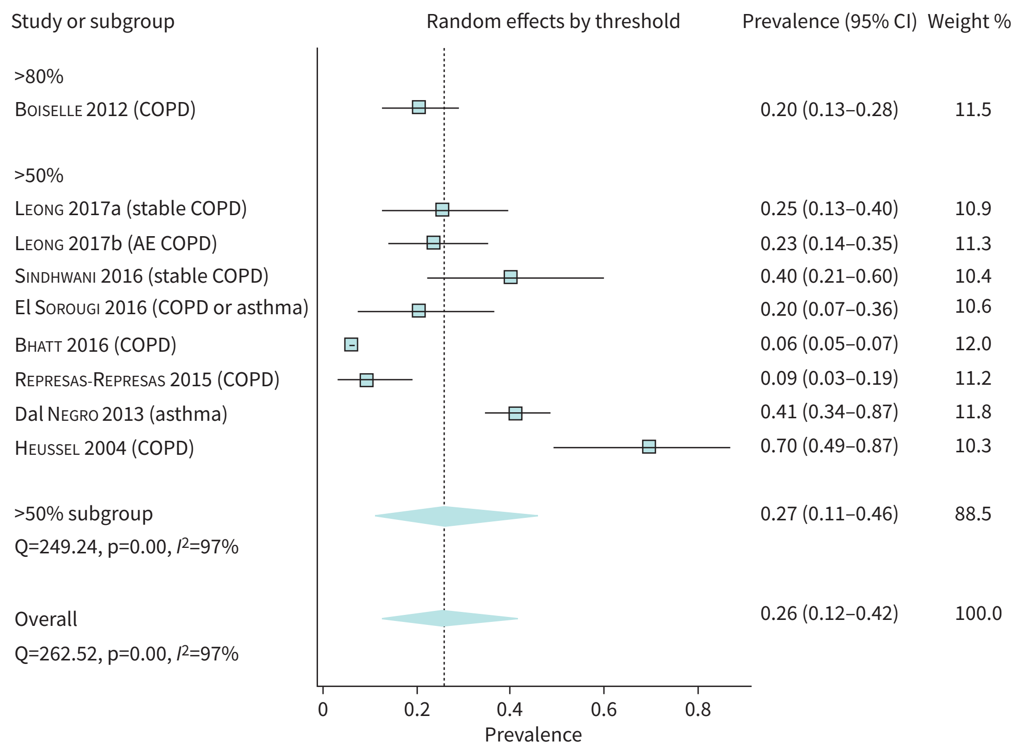

FIGURE 4 Forest plot of the prevalence of large airway collapse in patients with chronic obstructive airway diseases (either COPD or asthma). Random effects meta-analysis was done to estimate the pooled prevalence. Details of included studies, including population, diagnostic modality, and threshold, are summarised in table 2. AE: acute exacerbation.

favourable outcomes with tracheobronchoplasty, and thus it is important that clinicians are able to apply robust and reproducible diagnostic parameters, to reliably detect LAC and consider referral for intervention. A key clinical challenge in this area is the ability to differentiate between physiological and pathological (*i.e.* clinically relevant) collapse. In this respect, the finding that almost one in five healthy individuals appear to have LAC of >50% on CT (figure 3), challenges the notion that collapse of this severity immediately implicates a disease state. The degree of airway collapse does, however, appear to relate to age, certainly in healthy male volunteers, such that the mean collapse in males aged 24–31 years old was 36% [40]. In contrast, very few healthy (2%) individuals demonstrated LAC >70% in the studies reviewed, suggesting a more conservative diagnostic cut-off may be more appropriate. However, even in the context of more marked airway collapse (*e.g.* >70%), it can remain challenging to decipher the relationship between degree of collapse and collapse that induces "clinically relevant" flow limitation and/or symptoms. For example, the degree of LAC observed in patients with COPD appears to relate poorly to pulmonary function and functional capacity (*e.g.* exercise walking test) [24]. These findings should be interpreted with caution due to the considerable heterogeneity that was observed among studies in healthy subjects which could be explained by the variety of methodologies that were employed to assess LAC, such as a broad range of breathing manoeuvres (*e.g.* forced exhalation, breath-hold, coughing) and technical features (*e.g.* spiral or cine CT with single or multi-detectors). Some researchers in this field have sought to extend the diagnostic assessment criteria, proposing a more detailed assessment that incorporates an admixture of clinical and imaging/bronchoscopic findings, to help characterise the relevance and functional implications of LAC. Others have highlighted the importance of determining the location of any flow-limiting segment or choke point (*i.e.* stent insertion at flow-limiting segments has been shown to restore the rigidity of the involved airway segment [49]). Certainly, the relevance of findings arising from a forced dynamic expiratory manoeuvre phase is uncertain from a physiological standpoint [24, 26, 40], especially when compared with more applicable physiological challenges such as exercise or assessment of other symptoms such as cough or recurrent infections.

The interplay and differentiation between pathology and physiology becomes increasingly complex, but clinically relevant, in scenarios whereby the interplay between pleural and intraluminal forces increasingly favours airway closure (*e.g.* in obesity or emphysema). The current review revealed that LAC was present in approximately a third of patients with obstructive airways disease. This was a heterogeneous group but mostly defined by the study authors as patients with COPD. Whilst intervention for LAC in this context may improve QoL, it is not always associated with direct and measurable changes in allied physiological measures. In addition, differentiating obstructive pulmonary function findings from those arising from LAC is not straightforward.

Flexible bronchoscopy is considered the "gold standard" approach to LAC diagnosis by many clinicians since it permits real-time evaluation of the dynamic airway properties, at several sites and with the ability to provide direct instruction. It also permits repeated and sequential assessments during different manoeuvres (*e.g.* tidal breathing, forced dynamic manoeuvres and coughing) and allows airway sampling to be undertaken. This has to be countered by the fact that bronchoscopy is an invasive assessment and in contrast, the latest advances in CT technology have resulted in faster speed, greater breadth and enhanced spatial resolution, facilitating more precise airway luminal measurement [6, 29]. MDCT has the ability to obtain a large amount of data of the entire central airways in only a few seconds compared to bronchoscopy. A few studies have compared dynamic expiratory CT with bronchoscopy (as the diagnostic "gold standard") for the diagnosis of LAC. In the study by Lee *et al*. [50] dynamic expiratory CT (*e.g.* end-inspiratory, and dynamic expiratory imaging) compared well with bronchoscopy in patients with TBM. Namely, CT and bronchoscopic findings showed a good level of agreement with respect to the presence, severity and distribution of TBM in 97% (diffuse TBM in 82%; bronchomalacia in 11%; tracheomalacia in 7%) of patients. Cine-MRI is advantageous in reducing radiation exposure and can improve temporal resolution [31], and it may be useful for therapeutic monitoring (*e.g.* measurement of dynamic luminal diameter change)/evaluating response to treatment.

The reproducibility of any diagnostic technique is important to consider if it has implications for subsequent clinical intervention. In our review, we found that bronchoscopy was associated with a good degree of inter- and intra-observer levels of agreement, irrespective of level of training and experience [19].

Methodological considerations

There are several limitations to consider in the interpretation of our meta-analysis. First, the numbers of included studies in quantitative analyses were small, and they were all conducted at single centres. Thus, our meta-analyses are explorative and may not be an entirely inclusive representation of the findings of the prevalence of LAC in healthy subjects. However, two studies [14, 26] clearly pointed out that the diagnostic criterion of >50% may classify 55–78% of healthy subjects as abnormal. Second, there was a considerable heterogeneity among the studies (I^2>90%; figures 3 and 4), which could not be fully investigated because of the limited number of relevant studies, and thus, our results should be interpreted with caution. In patients with chronic airway diseases, certain clinical factors such as age, disease severity or lung function are likely to underpin heterogeneity[7]. In healthy controls, however, the reason for a difference between the studies could be associated to the variety of investigation protocols and diagnostic criteria that were utilised. However, two studies [40, 42] clearly showed that the diagnostic criterion of >50% may result in false positives in nonsmokers without respiratory symptoms or history. Third, publication bias could not be assessed because of a small number of included studies. Fourth, it should be acknowledged that the results need to be cautiously interpreted; considering the heterogeneity in respiratory pathologies included in this review (*e.g.* COPD, asthma, cystic fibrosis or emphysema), as well as the variety of diagnostic modalities to assess LAC (*e.g.* bronchoscopy, CT, MRI). For example, owing to the heterogeneity in the airway diseases and diagnostic modalities we were only able to estimate the prevalence of LAC in COPD or asthma patients (figure 4).

Conclusion

Our systematic review reveals that, over the past 30 years, a large number of studies (including over 10 500 subjects) have been published evaluating LAC, using a broad variety of investigation protocols and diagnostic criteria. It is likely, however, that the broad range of approaches to assessment and diagnosis has led to the high level of heterogeneity that was observed in our systematic review and, as such, limits robust conclusions being drawn regarding precise cut-off values. Moreover, the varying study methodologies and outcome measures are confusing to interpret for both the clinician and researcher, and whilst a ⩾50% reduction in calibre of the central airway lumen on inspiratory to expiratory CT is the most commonly described diagnostic criterion, this is likely to be confounded by poor diagnostic specificity. Regardless, at this diagnostic threshold, LAC appears to be a frequent comorbidity in patients with COPD or asthma. Overall, these findings highlight the need for improved international consensus regarding the best approach to this condition, agreement regarding diagnostic criteria and further scientific work to establish the physiological and disease implications of LAC.

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