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Early View

Review

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DETECTION AND DIAGNOSIS OF LARGE AIRWAY COLLAPSE: A SYSTEMATIC REVIEW

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ABBREVIATION LIST

COPD	Chronic Obstructive Pulmonary Disease
CSA	Cross Sectional Area
CT	Computed Tomography
ECAC	Expiratory Central Airway Collapse
EDAC	Excessive Dynamic Airway Collapse
LAC	Large Airway Collapse
MDCT	Multi-detector Computed Tomography
MRI	Magnetic Resonance Imaging
QoL	Quality of Life
TBM	Tracheobronchomalacia

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), and mean (+/- SD) age 59 ± 9 years. Most studies (n=35) reported CT findings and only 3 studies report 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 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 sequalae.

PROPSPERO Registration: CRD42019149347.

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 pathologic weakness of the cartilaginous airway wall[2]. The terms 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 chronic obstructive pulmonary disease (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 co-morbid entity, in the presence of underlying airway disease, rather than representing a primary pathological problem or disease state *per se*. Regardless, the detection and characterization 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 fifty 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 visualize 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 to October 2019 using the following key words (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 summarized in the Online Supplement (e-Table 1). The timeframe for included publications (i.e., only studies within the last thirty 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: i) LAC had to be evaluated using either CT, magnetic resonance imaging (MRI) or flexible fibreoptic bronchoscopy; ii) the anatomic airway sites for evaluation of LAC had to be the trachea, main bronchi or both; iii) 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; iv) studies describing findings in children only were excluded; v) 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 (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).

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 and 47% 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, n=18 respectively)[18,19], and we were unable to find any bronchoscopic studies evaluating LAC in entirely healthy, asymptomatic subjects.

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, the expiratory phase collapse patients was evaluated by instructing subjects to take a deep breath, hold it, and blow it out[19]. In the study by Dal Negro, collapse was assessed spontaneously and following a physician's instruction to perform deep breathing, forced exhalation and coughing[7]. 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 intraobserver 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 10402 participants of which 10244 were patients (age: 58.4 ± 9.3 years; 47% female) with conditions such as COPD, asthma, relapsing polychondritis and sarcoidosis. There was also data available in 158 healthy subjects (age: 50.9 ± 4.1 years; 42% female).

Protocols employed

The majority of the protocols describe utilizing 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.

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 ~20s) 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 vs 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 less than 5 seconds 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 (4 studies; 25%)[35-38]. McDermott et al.[39] instructed the patients to perform a maximal inspiration and forcefully 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[44]. 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 yrs.; 23% female; two studies did not report the age).

Protocols employed

The first study to use MRI for the evaluation of tracheomalacia[40] 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[40]. Moreover, fast acquisition MRI demonstrated excellent temporal resolution, high contrast resolution regardless of imaging plane[40]. A recent study assessed TBM during two 13-second 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 evaluated LAC using cine-MRI[41]; 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[42,43]. 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 refs[14,24,26]), five studies were found to report the prevalence of LAC in healthy volunteers (e-Table 3)[6,7,39,43,44]. In a random effects meta-analysis of the four studies using the criterion of >50% reduction[6,39,43,44], LAC was found in 17% (95% confidence interval [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 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[6,7,24,33,34,41,45,46], asthma[7,34], cystic fibrosis[39], emphysema[47,48], bronchiectasis[49], or pulmonary sarcoidosis[35]. We performed a meta-analysis for LAC prevalence in 8 studies of patients either with COPD or asthma, as the number of studies on other respiratory conditions cystic fibrosis, emphysema, or bronchiectasis was too small. The studies included in the meta-analysis are summarized in e-Table 4 and most of them utilised a >50% reduction[6,7,33,34,43,45,46]. 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 thirty 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 is 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 utilization[50,51]. Recent work has highlighted 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%[44]. 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 characterize 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[52]). Certainly, the relevance of findings arising from a forced dynamic expiratory manoeuvre phase is uncertain from a physiologic standpoint[24,26,44] , 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 heterogenous 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[29,53]. 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.[54] 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 improves temporal resolution[31] and 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%; Figure 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[41,44] clearly showed that the diagnostic criterion of >50% may result in false positives, in non-smokers 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, due to the heterogeneity in the airway diseases and diagnostic modalities we were only able to estimate the prevalence of LAC only in COPD or asthma patients (Figure 4).

Conclusion

Our systematic review reveals that, over the past thirty 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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Authors Contribution

AM, FA and WJS performed the systematic review and meta-analysis. AM, WJS and JH contributed substantially to the study design, data analysis and the writing of the manuscript. MIP and SK contributed to the interpretation of the results. AM takes full responsibility for the integrity of the systematic review as a whole.

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FIGURE LEGENDS

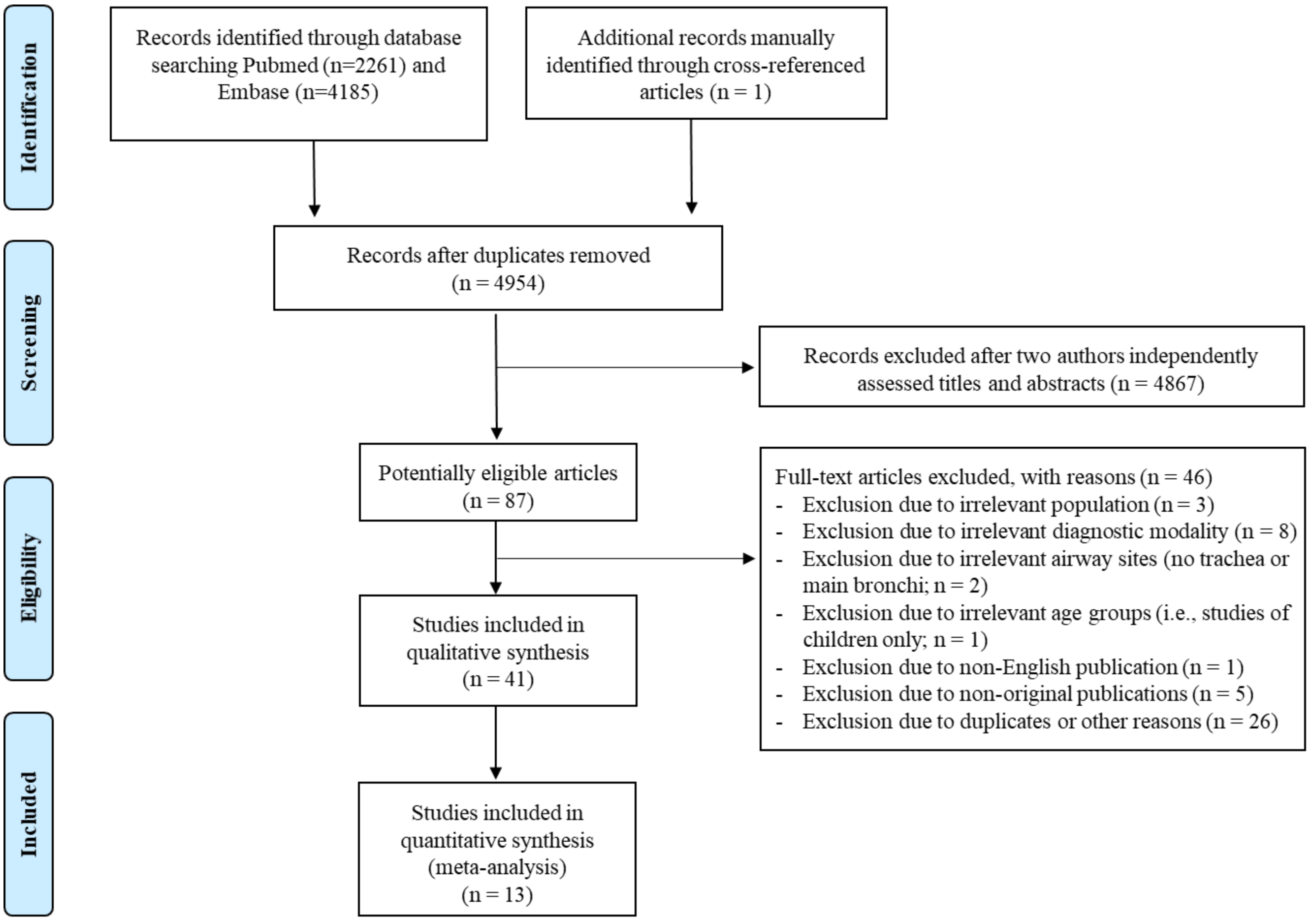

Figure 1. PRISMA flow chart for study selection

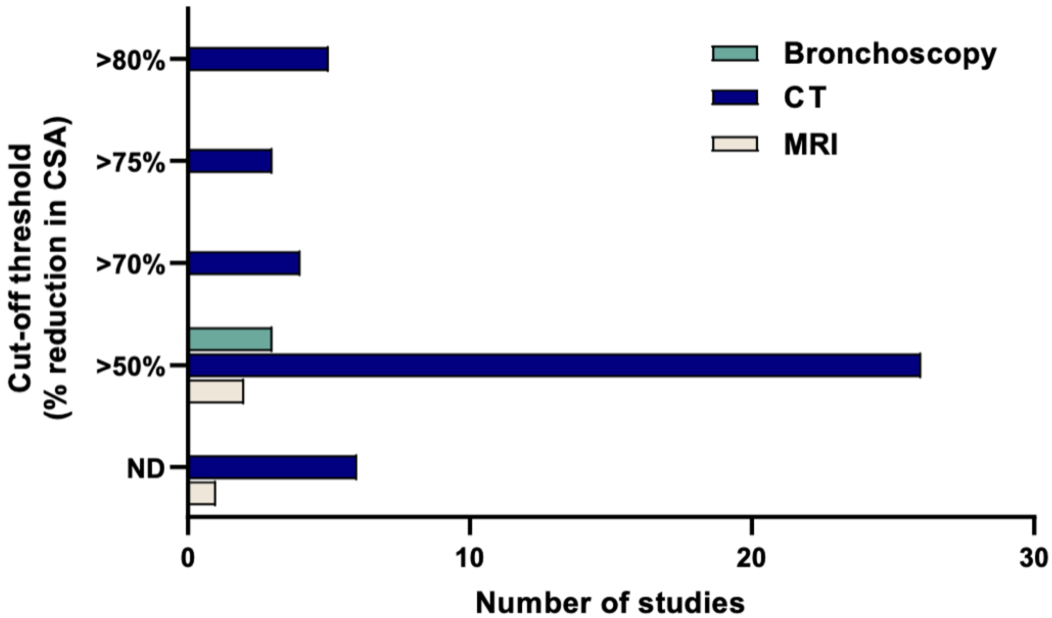

Figure 2. Study cut-off thresholds reported for the diagnosis of large airway collapse, based on diagnostic modality

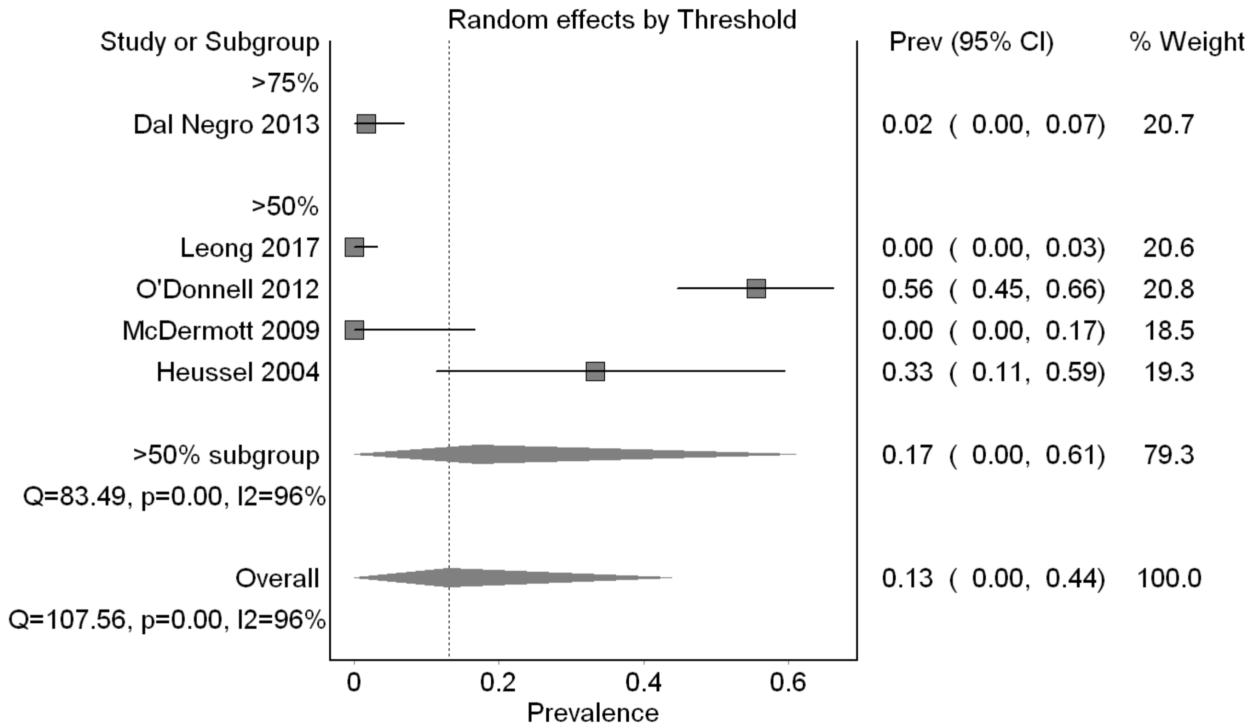

Figure 3. Forest plot of the prevalence of large airway collapse in healthy subjects. Random effects meta-analysis was done to estimate the pooled prevalence. Details of included studies, including population, diagnostic modality, and threshold, are summarized in Table 1.

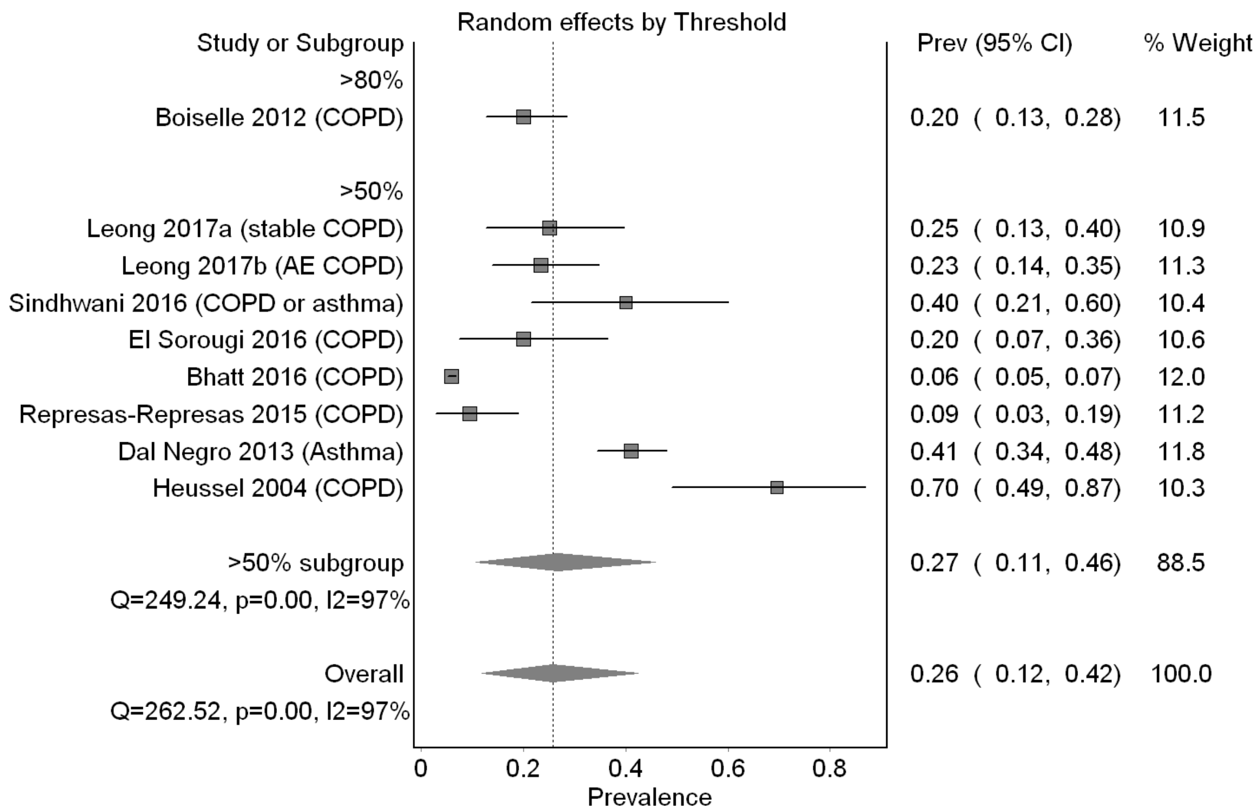

Figure 4. Forest plot of the prevalence of large airway collapse in patients with chronic obstructive airway diseases (either COPD or asthma). Random effects meta-analysis was done to estimate the pooled prevalence. Details of included studies, including population, diagnostic modality, and threshold,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

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 [men (n=4), women (n=6); mean age: 65yrs, age range: 43-74yrs] 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 [men (n=91), women (n=111); age: 47.5 ± 13.3yrs], and 62 subjects without any obstructive disease [men (n=38), women (n=24); age: 38.9 ± 10.4yrs].	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 and Colt, 2007 [18]	• Retrospective single-centre study. • Assessing a multidimensional classification system (FEMOS) for evaluating patients with expiratory LAC.	18 patients [men (n=13), women (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 was 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, extend of disease and severity of airway collapse.

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[55]	• Retrospective single-centre study. • To evaluate patients with TBM after undergoing tracheobronchoplasty.	18 patients [men (n=5), women (n=13); mean age: 65 ±12yrs] with COPD (n=7), GERD (n=14), OSA (n=8), cardiac disease (n=4).	8-, 16- and 64 MDCT scan	LAC ≥70% reduction in the CSA.	Mean tracheal collapsibility improved by 34% in postoperative 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 [men (n=6), women (n=14); mean age: 68yrs].	High resolution MDCT scan	TM ≥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 two years.
Ciet et al. 2017[31]	• Prospective single-centre study. • Comparison of MRI to MDCT in assessing TBM.	12 participants [men (n=5), women (n=7); 9 healthy adults and 3 patients with COPD; mean age: 64.5yrs, age range: 45-77yrs)].	• 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 [men (n=150, women (n=191), mean age: 60yrs, age range: 18-88yrs)] 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 [men (n=19), women (n=21); age: 70.1 ± 8.2yrs]; 64 AECOPD [men (n=40), women (n=24); age: 70.2 ± 11.6yrs]; 53 healthy volunteers [men (n=35), women (n=18); age: 56.6 ± 16.9yrs].	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 up to one third of patients with stable COPD and the abnormality does not seem to be worsened during AECOPD.

Bhatt et al. 2016[46]	• Retrospective multi-centre 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 [men (n=4667), women (n=4153) mean age: 59.7 ±6.9yrs].	CT scan	ECAC ≥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 [men (n=14), women (n=11), mean age: 62.7 ± 7.81yrs] with COPD.	CT scan	TBM/EDAC ≥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.
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 [56]	• Prospective single-centre study. • To describe the imaging characteristics of people presenting exertional dyspnoea.	6 military personnel [men (n=5), women (n=1), mean age: 39.5yrs, age range: 24 to 53yrs] 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[45]	• Prospective single-centre study. • To investigate the prevalence of EDAC in COPD.	53 patients [men (46), women (n=7), mean age: 65±9yrs] 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 [men (n=38), women (n=29); age: 65.1 ± 6.5yrs] 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[57]	• Prospective single-centre study. • To assess the feasibility of low-dose MDCT.	3 patients (3 men; mean age: 63.3yrs) with COPD.	4D MDCT scan	TM criterion was not reported.	EDAC (n=1), saber-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[58]	• Prospective single-centre study. • To assess the tracheal collapse in morbidly obese, non-morbidly obese and normal weight COPD patients.	100 patients [women and 52 men (n=52), women (n=48), mean age: 65 ± 7 yrs.] with COPD.	64-detector CT scan	LAC criterion was not reported.	Expiratory collapse was directly associated with BMI (p=.002).	Obesity is positively correlated with the degree of expiratory tracheal collapse among COPD patients,
*O'Donnell et al. 2012 [44]	• Prospective single-centre study. • To explore the association between forced expiratory tracheal collapse and age or sex.	81 healthy volunteers [men (n=41), women (n=40); age: 47 ± 17yrs.].	64-detector-row CT scan	Tracheal collapse ≥ 80% reduction in CSA.	The mean %collapse was similar for men (55±23%) and women (52±17%). The mean %collapse was correlated to age (r^2 = 0.40, P< .001) in men.	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 [men (n=52), women (n=48); age: 65 ± 7yrs] 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.
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 [men (n=6), women (n=8), mean age: 48.7 ±13.8 yrs.].	64-MDCT scan	TM criterion was not reported.	1st and 2nd year measures of tracheal collapse were strongly associated (r^2 = 0.98, P < .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 [men (n=25), women (n=26); age: 50 ± 15yrs].	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 [men (n=5), women (n=1); mean age: 53yrs, age range: 37 to 70yrs] 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.	51 healthy volunteers [men (n=25), women	64-detector row MDCT scan	Expiratory reduction in	78% of healthy volunteers exceeded the	This study emphasizes the need for a more

	• To assess the tracheal collapsibility in healthy volunteers.	(n=26); age: 50 ± 15yrs].		CSA of >50%.	current diagnostic criterion for TM.	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 [men (n=22), women (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 [47]	• Retrospective single-centre study. • To evaluate the frequency of TBM associated with PE.	56 patients [men (n=55), women (n=1); mean age: 68.9yrs, age range: 49-87yrs] 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 [48]	• Retrospective multi-centre study. • To investigate the prevalence of TM in an emphysema cohort.	431 patients [men (n=267, mean age: 64yrs, range: 41 to 76), women (n=164, mean age: 62yrs, 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 [men (n=43), women (n=27); mean age: 57yrs, age range: 12-79yrs] 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.
Lee et al. 2007[54]	• Retrospective single-centre study. • To compare the dynamic expiratory CT against bronchoscopy for detecting airway malacia.	29 patients [men (n=12), women (n=17), mean age: 60 years, age range: 36 to 79yrs) 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, non-invasive 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 [men (n=6), women (n=11), age range: 62.4yrs] 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 non-invasive diagnosis of TM.

Lee et al. 2006[59]	• Retrospective single-centre study. • To assess the prevalence of expiratory CT abnormalities, including malacia.	18 patients [men (n=3), women (n=15), mean age: 47yrs; age range: 20–71yrs] 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[49]	• Prospective single-centre study. • To evaluate the frequency and severity of BM.	46 patients [men (n=10), women (n=36), mean age: 64yrs, age range: 44-84yrs) 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 [men (n=11), women (n=3), mean age 53yrs old and age range: 19-79yrs] 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 ($P< .004$).	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 [men (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 [men (n=6), women (n=12); mean age: 47yrs, age range: 29-64yrs] with pulmonary sarcoidosis.	High-Resolution CT	LAC >50% reduction in CSA.	BM was found in 61% of patients.	BM is frequently associated with sarcoidosis.
Heussel et al. 2004 [41]	• 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: 59yrs, age range: 41-68yrs) and 15 healthy adults (age: 62yrs, age range: 48 to 74yrs).	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 men (n=73), women (n=90); mean age: 60yrs] with suspected pulmonary embolism.	Single detector CT and MDCT (with four and eight 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 [men (n=5), women (n=5), mean age: 56 ±11yrs] 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[60]	• Retrospective and prospective single-centre study. • To explore the measurements of the trachea between inspiration and end-expiration on CT.	10 TM patients [men (n=6), women (n=4); mean age: 60yrs, age range: 42 to 84yrs] and 23 normal control patients [men (n=15), women (n=8); mean age: 40yrs, age range: 27 to 57yrs].	CT Scan	Diagnostic criterion for TM was not reported.	Collapsibility in tracheal CSA was significantly greater in patients with TM ($1.9\pm0.9cm^2$) compared to controls ($2.4\pm0.6cm^2$) 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 [men (n=7), women (n=6); mean age: 49yrs and age range: 14-88yrs] 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 [men (n=10), women (n=19); mean age: 61yrs, age range: 27-82yrs] 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.
Suto & Tanabe, 1998[40]	• Prospective single-centre study. • To evaluate tracheal collapsibility during coughing in patients with TM who underwent MRI.	6 patients [men (n=4), women (n=2); mean age: 40yrs, age range: 44 to 68yrs] with suspected TBM and 13 healthy volunteers [men (n=10),	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,	Collapsibility during forced expiration-inspiration and collapsibility during coughing was not significant in patients

		women (n=3); mean age: 40yrs, age range: 17 to 63yrs].			respectively.	with TM during MRI.
Stern et al. 1993[61]	• Prospective single centre study. • To define the range of intrathoracic tracheal diameters and CSA during forced respiration.	10 healthy volunteers [men (n=10), age range 24 to 31 yrs.].	CT using the model C-100 scanner.	TM >70% reduction in the CSA.	Trachea significantly decreased (P<.001) from end-inspiration (280mm^2) to end-expiration (178mm^2).	Intrathoracic tracheal shape, sagittal and coronal diameters, and CSA can vary greatly during a forced respiration.

*The studies 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 Boiselle et al 2013 was not analysed as part of the main results as the participants were included in O'Donnell et al., 2014.

Abbreviations: Bronchomalacia (BM), Body mass index (BMI), cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), computed tomography (CT), cross-sectional area (CSA), excessive central airway collapse (ECAC), excessive dynamic airway collapse (EDAC), forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), gastroesophageal reflux disease (GERD), interstitial lung disease (ILD), large airway collapse (LAC), multi-detector CT (MDCT), magnetic resonance imaging (MRI), tracheobronchomalacia (TBM), tracheomalacia (TM), obstructive sleep apnoea (OSA), pulmonary emphysema (PE), pulmonary function testing (PFT).

Online Supplement

Detection and diagnosis of large airway collapse: A systematic review

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e-Table 1. Search strategy

Pubmed
1. "airway collapse"[TIAB] OR "airway collapsibility"[TIAB] OR "bronchial collapse"[TIAB] OR "bronchial collapsibility"[TIAB] OR "tracheal collapse"[TIAB] OR "tracheal collapsibility"[TIAB] OR "expiratory collapse"[TIAB] OR "expiratory tracheal narrowing"[TIAB] OR TM[TIAB] OR tracheobronchomalacia[TIAB] OR bronchomalacia[TIAB] 2. (("Tracheobronchomalacia"[Mesh]) OR "Bronchomalacia"[Mesh]) OR "TM"[Mesh] 3. 1 OR 2 4. 3 Filters: Publication date from 1989/01/01 to 2019/12/31; English
Embase
1. 'airway collapse':ab,ti OR 'airway collapsibility':ab,ti OR 'bronchial collapse':ab,ti OR 'bronchial collapsibility':ab,ti OR 'tracheal collapse':ab,ti OR 'tracheal collapsibility':ab,ti OR 'expiratory collapse':ab,tiOR 'expiratory tracheal narrowing':ab,ti OR TM:ab,ti OR tracheobronchomalacia:ab,ti OR bronchomalacia:ab,ti 2. 'airway collapse'/exp OR 'tracheal collapse'/exp OR 'TM'/exp OR 'TM'/exp OR 'tracheobronchomalacia'/exp 3. 1 OR 2 4. 3 AND [1989-2019]/py AND [english]/lim 5. 4 NOT 'nonhuman'/de

e-Table 2. Quality assessment

Study	**Prospective recruitment** (0: no; 1: yes)	**Sample size justification** (0: no; 1: yes)	**Sample representativeness** (0: recruited at a single centre; 1: recruited at multiple centres; 2: recruited from general populations)	**Risk of selection bias** (0: recruited for suspected large airway collapse; 1: recruited for respiratory symptoms; 2: unselected recruitment; 9: unclear)	**Description of exclusion criteria** (0: no; 1: yes)	**Outcome definition (large airway collapse)** (0: no specific criteria presented; 1: specific criteria)
LAC studies with healthy volunteers						
Leong et al. 2017[1]	1	0	2	9	1	1
Dal Negro et al. 2013[2]	0	0	0	2	0	1
O'Donnell et al. 2012[3]	1	1	2	2	1	0
McDermott et al. 2009[4]	1	0	0	2	1	1
Heussel et al. 2004[5]	1	0	0	2	0	1
LAC studies with COPD patients						
Leong et al. 2017[1]	1	0	0	1	1	1
Sindhwani et al. 2016[6]	1	0	0	0	1	1
El Sorougi et al. 2016[7]	1	0	0	0	0	1
Represas-Represas et al. 2015[8]	1	0	0	0	1	1
O' Donnell et al. 2014[9]	1	0	0	0	1	0
Boiselle et al. 2012[10]	1	0	1	0	1	1
Heussel et al. 2004[5]	1	0	0	1	0	1

e-Table 3. Summary of 5 studies reporting the prevalence of large airway collapse in healthy subjects

Study	Study design	Study subjects	Diagnostic modality	Diagnostic threshold for large airway collapse	Prevalence of large airway collapse
Dal Negro et al. 2013[2]	Prospective, single centre	n=62, non-smokers without any obstructive disease	Bronchoscopy	>75%	1.6%
Leong et al. 2017[1]	Prospective, single centre	n=53, subjects with no respiratory symptoms, no prior diagnosis of chest disease, and not taking any respiratory medications	CT	>50%	0%
O'Donnell et al. 2012[3]	Prospective, single centre	n=81, lifetime non-smokers, no respiratory symptoms or known respiratory disease	CT	>50%	56%
McDermott et al. 2009[4]	Prospective, single centre	n=10, subjects with no smoking history and no respiratory disease	CT	>50%	0%
Heussel et al. 2004[5]	Prospective, single centre	n=15, Life-long non-smokers, FEV1 >70% predicted	MRI	>50%	33.3%

e-Table 4. Summary of 8 studies reporting the prevalence of large airway collapse in patients with chronic obstructive airway diseases (COPD or asthma)

Study	Study design	Study subjects	Diagnostic modality	Diagnostic threshold for large airway collapse	Prevalence of large airway collapse
Leong et al. 2017a[1]	Prospective, single centre	n=40, stable outpatients with COPD	CT	>50%	35%
Leong et al. 2017b[1]	Prospective, single centre	n=64, hospitalized in patients with acute exacerbation of COPD	CT	>50%	39%
Bhatt et al. 2016[11]	Retrospective multi centre	n=8820, ex or active smokers with COPD (43.7%) and asthma (16.6%).	CT	>50%	5%
Sindhwani et al. 2016[6]	Prospective, single centre	n=25, patients with COPD or asthma (stable on medical management but having persistent wheezing)	CT	>50%	40%
El Sorougi et al. 2016[7]	Prospective, single centre	n=30, patients with COPD	CT	>50%	20%
Represas-Represas et al. 2015[8]	Prospective, single centre	n=53, patients with COPD	CT	>50%	9.4%
Dal Negro et al. 2013[2]	Prospective, single centre	n=202, patients with asthma	Bronchoscopy	>50%	41.1%
Boiselle et al. 2012[10]	Prospective, single centre	n=100, patients with COPD	CT	>80%	20%
Heussel et al. 2004[5]	Prospective, single centre	n=38, patients with COPD	MRI	>50%	69.6%

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