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ORIGINAL ARTICLE

Asthma and Rhinitis

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Diagnosis of concomitant inducible laryngeal obstruction and asthma

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Summary

Background: Inducible laryngeal obstruction, an induced, inappropriate narrowing of the larynx, leading to symptomatic upper airway obstruction, can coexist with asthma. Accurate classification has been challenging because of overlapping symptoms and the absence of sensitive diagnostic criteria for either condition.

Objective: To evaluate patients with concomitant clinical suspicion for inducible laryngeal obstruction and asthma. We used a multidisciplinary protocol incorporating objective diagnostic criteria to determine whether asthma, inducible laryngeal obstruction, both, or neither diagnosis was present.

Methods: Consecutive patients were prospectively assessed by a laryngologist, speech pathologist and respiratory physician. Inducible laryngeal obstruction was diagnosed by visualizing paradoxical vocal fold motion either at baseline or following mannitol provocation. Asthma was diagnosed by physician assessment with objective variable airflow obstruction. Validated questionnaires for laryngeal dysfunction and relevant comorbidities were administered.

Results: Of 69 patients, 15 had asthma alone, 11 had inducible laryngeal obstruction alone and 14 had neither objectively demonstrated. Twenty-nine patients had both diagnoses. In 19 patients, inducible laryngeal obstruction was only seen following provocation. Among patients with inducible laryngeal obstruction, chest tightness was more frequent with concurrent asthma. Among patients with asthma, stridor was more frequent with concurrent inducible laryngeal obstruction. Cough was more frequently found in asthma alone, whereas difficulty with inspiration and symptoms triggered by psychological stress were more frequently found in inducible laryngeal obstruction alone. Patients with asthma alone had greater airflow obstruction. Relevant comorbidities were frequent (rhinitis in 85%, gastro-oesophageal reflux in 65%), and questionnaire scores for laryngeal dysfunction were abnormal. However, neither comorbidities nor questionnaires differentiated patients with or without inducible laryngeal obstruction.

Conclusions and clinical relevance: In this cohort with suspected inducible laryngeal obstruction and asthma, 42% had objective evidence of both conditions. Clinical

assessment, questionnaire scores and comorbidity burden were not sufficiently discriminatory for diagnosis, highlighting the necessity of objective diagnostic testing.

KEYWORDS
asthma, inducible laryngeal obstruction, larynx, mannitol, paradoxical vocal fold motion

1 | INTRODUCTION

Inducible laryngeal obstruction (ILO) is characterized by recurrent variable airflow obstruction in the larynx. It is an umbrella term for any triggered laryngeal obstruction occurring at either the supraglottic (arytenoid region, epiglottis or false vocal folds) and/or glottic (true vocal folds) level of the larynx and includes the condition also known as paradoxical vocal fold motion disorder (PVFM), or vocal cord dysfunction (VCD).[1,2] Traditionally, the gold standard for diagnosis has been the demonstration on direct laryngoscopy of abnormal (hence paradoxical) adduction of the vocal folds during the respiratory cycle accompanying a symptomatic episode.[3]

Although patients with symptoms and signs suggestive of ILO were described as early as 1885[4] advances in this field may have been hindered in part by a belief that the condition was psychosomatic in origin.[1] More recently, ILO has been considered as part of a spectrum of laryngeal dysfunction, which also includes chronic cough, globus pharyngeus and muscle tension dysphonia. All are thought to share a common pathophysiological pathway of laryngeal hypersensitivity, or "irritable larynx."[5,6]

Confusingly, ILO and asthma share many common symptoms, such as dyspnoea, chest tightness and wheeze. Distinguishing between the two conditions may be challenging and validated diagnostic and treatment algorithms have not yet been established.

Compounding this difficulty, asthma and ILO are not mutually exclusive. A high proportion of patients with difficult-to-treat asthma may have comorbid ILO,[7] with a reported prevalence of ILO in this population of between 30% and 50%.[8,9] Patients with asthma and concurrent ILO are more likely to have poor quality of life and increased healthcare utilization.[10] Importantly, the treatment modalities for asthma and ILO are vastly different.

Our centre provides a difficult asthma service which focuses heavily on comorbidity assessment, including ILO.[11,12] As an extension of this service, we developed a multidisciplinary Middle Airway Clinic to systematically assess and manage patients with suspected concurrent asthma and ILO. We report the clinical characteristics and objectively determined diagnoses of a consecutive series of patients undergoing systematic evaluation.

2 | METHODS

Our centre is a 600 bed tertiary hospital in Melbourne, Australia. The Middle Airway Clinic was established in May 2015 specifically for the diagnosis and management of patients with concurrent suspected diagnoses of inducible laryngeal obstruction and asthma. Patients were referred by specialists, either from the respiratory and allergy units, or from the Ear, Nose and Throat surgical unit. All patients underwent systematic assessment by a laryngologist, speech pathologist and respiratory physician. This report was approved by the Alfred Health Ethics committee (Reference number 37/16).

2.1 | Multidisciplinary assessment

Baseline characteristics and presenting symptoms were documented by the respiratory specialist (RH, TT, JL) using a standardized clinic template. We assessed for the presence of all forms of laryngeal dysfunction: ILO, chronic cough, muscle tension dysphonia and globus pharyngeus. Triggers or "inducers" of symptoms were classified as inhalational (odours or perfume, chemical or cleaning solutions, smoke and exhaust fumes), physiological (exercise) or psychological. Patients completed validated questionnaires for laryngeal dysfunction: Pittsburgh Vocal Cord Dysfunction Index,,[13] VCD-Questionnaire,[14] and the Newcastle Laryngeal Hypersensitivity Questionnaire,[15] as well as the Chemical Sensitivity Scale for Sensory Hyper-reactivity[16] and the Dyspnoea Index.[17] (See Table S1).

Laryngologist evaluation (PP, AR) comprised an ENT history and examination followed by flexible laryngoscopy to assess for paradoxical vocal fold motion, both at rest and following provocation manoeuvres. Any inducible laryngeal obstruction was classified, when possible, by location (supraglottic, glottic or both) and phase of respiratory cycle (inspiratory, expiratory or both) as described in recent consensus statements.[1,2] We also examined for laryngoscopic evidence of exacerbating conditions such as laryngopharyngeal reflux, chronic rhinosinusitis and oral candidiasis. Video stroboscopy was performed when clinically relevant and available.

A comprehensive asthma history was elicited. Variable airflow obstruction was sought in a stepwise fashion based on bronchodilator reversibility, peak flow variability and bronchoprovocation with mannitol. Spirometry was scheduled for all patients (Medgraphics Platinum, MGC Diagnostics, Minnesota, USA). Patients were asked to withhold medications that may affect bronchial hyperresponsiveness as per the Aridol protocol.[18] All inhaled corticosteroids with long acting beta2 agonists were withheld for at least 24 hours. Patients were assessed for allergy and designated atopic if they had at least one wheal $\geq$3 mm on skin prick testing to twenty aeroallergens (Stallergenes-Greer®, Antony, France) or a serum allergen-specific IgE >0.34 kUA/L (ImmunoCap® Abacus ALS, Brisbane, Australia) to at least one of: Ryegrass pollen, house dust mite or *Aspergillus*.

Speech pathologist review (LP, MV) included a comprehensive voice assessment with auditory-perceptual evaluation using the GRBAS (Grade, Roughness, Breathiness, Asthenia and Strain) scale

and where appropriate, measurement of the maximum phonation time (MPT). Posturing, vocal hygiene and swallow were also clinically assessed.

2.2 | Diagnosis of asthma and inducible laryngeal obstruction

A diagnosis of definite ILO was made by the demonstration of any vocal cord adduction during inspiration, or >50% vocal cord adduction on expiration, either at baseline laryngoscopy, or on laryngoscopy following provocation with dry powder mannitol (Aridol™, Pharmaxis, NSW, Australia) as previously described.[19] Inappropriate adduction of the vocal folds in expiration was determined by the observer as more than 50% reduction in the area of the rima glottidis, or laryngeal inlet airspace between the edges of the true vocal cords. If laryngoscopy was performed by respiratory physician, confirmation was sought from blinded laryngologist review. The angle at the anterior commissure from the position of the vocal processes was observed and was also considered positive if there was more than 50% reduction in the angle.

A diagnosis of definite asthma was confirmed by demonstrating variable airflow obstruction based on bronchodilator response (Increase in ≥200 mL and 12% from baseline FEV_1 or FVC),[20] peak flow variability >15%, or positive bronchial provocation challenge (≥15% drop in FEV_1 with cumulative mannitol dose <635 mg).

Although many patients had a clinical history suggestive of ILO and asthma and were eventually treated as such, for the current study analysis, the "ILO" group comprised only patients with objective findings of paradoxical vocal cord movement confirming definite ILO. Similarly the "asthma" group comprised only patients with demonstrable variable airflow obstruction confirming definite asthma.

2.3 | Comorbidity assessment

Patients were assessed for the presence of eight comorbidities: obesity, allergic rhinitis, chronic rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnoea, anxiety, depression and dysfunctional breathing. Comorbidity diagnosis was assisted by a battery of validated questionnaires (Table S2**). These were the Score for Allergic Rhinitis,[21] Rhinitis Control Assessment Test,[22] Gastroesophageal reflux disease Questionnaire,[23] Hospital Anxiety and Depression Scale,[24] Berlin[25] and Nijmegen questionnaires.[26]

2.4 | Statistical analysis

Data analysis was performed using SPSS version 22 (IBM, Armonk, NY). Categorical variables are presented as percentages (frequency) and continuous variables as mean or median values with standard deviations. Student's *t* tests or one-way ANOVA were performed for comparison of means, and Kruskal-Wallis tests followed by post hoc Mann-Whitney tests were performed for comparison of non-parametrically distributed continuous data. Fisher's exact or *chi*-square tests were performed for comparison of proportions as appropriate.

3 | RESULTS

3.1 | Patients included

Sixty-nine consecutive patients were assessed between 1 May 2015 and 1 February 2017 with the suspicion of co-existing inducible laryngeal obstruction and asthma. Thirty-one patients (45%) were referred from the difficult asthma service, 35 (51%) from general respiratory/allergy clinics and three (5%) from the general ear, nose and throat clinic. Baseline demographics are presented in Table 1.

3.2 | Assessment procedures

All 69 patients underwent clinical assessment. All but one patient (who declined) completed the questionnaire battery. All but one (who declined) underwent spirometry. Sixty-seven patients underwent flexible nasoendoscopy ± stroboscopy, of whom 42 patients had nasoendoscopy performed as part of a mannitol challenge test. Two patients did not undergo nasoendoscopy; one patient declined

TABLE 1 Baseline demographics of patients

Age, mean (SD) y	47 (15), range 18-72
Gender, n (%)	
Female	55 (80%)
BMI, mean (SD), kg/m^2	29.6 (5.6)
BMI ≥30, n (%)	28 (40%)
Smoking status, n (%)	
Never	45 (65%)
Ex-smoker	22 (32%)
Current smoker	2 (3%)
Pre bronchodilator FEV_1(%predicted), mean (SD)	81.7% (21)
Pre bronchodilator FVC (%predicted), mean (SD)	87.8% (19)
Pre bronchodilator FER, mean (SD)	73.4% (12.5)
Pre bronchodilator FER <70% (airflow obstruction), n (%)	24 (35)
Medication use, n (%)	
Inhaled corticosteroids	50 (73%)
Intranasal corticosteroids	38 (55%)
Antihistamines	24 (35%)
Proton pump inhibitors	31 (45%)
Atopic[a], n (%)	36 (52%)
Occupation, n (%)	
Unemployed	15 (22%)
Cleaner	7 (12.3%)
Healthcare professional	13 (19%)
Professional voice user, including teachers	12 (17.4%)

FEV_1, Forced expiratory volume in one-second; FVC, forced expiratory volume; FER, forced expiratory ratio.
[a]Defined in text.

the procedure while the other had severe airflow obstruction and a clinical history inconsistent with ILO and was therefore not tested.

Forty of 69 patients (58%) had definite ILO with objectively visualized paradoxical vocal fold motion. Of these patients, 18 (45%) were diagnosed at baseline laryngoscopy, 19 (47.5%) following mannitol challenge, and three (7.5%) underwent laryngoscopy under both conditions. Of the 40 patients with ILO, 10 (24.4%) patients had inspiratory, 14 (34.1%) had expiratory and 10 (24.4%) had both inspiratory and expiratory ILO identified. Only two patients (5%) had obstruction documented at the level of the supraglottis. Six patients with laryngologist-visualized ILO did not have the type of ILO specified.

In patients with ILO, the median time to diagnosis was 5.5 years. Eleven patients (27.5%) described an incident at onset, including nine triggered by respiratory infection (22.5%), one (2.5%) with environmental irritant exposure and one reportedly triggered following a general anaesthetic. Over half of all patients had presented to the emergency department with symptoms (62.5%). Inhaled odours (55%), exercise (57.5%) and psychological stress (57.5%) were common triggers for symptoms. An additional third of patients described triggers in their workplace including: cleaning products, chlorine, chalk dust, dust, singing, voice use and work-related stress.

Forty-four of 69 patients (64%) were diagnosed with definite asthma, with proven variable airflow obstruction. Of these, 19 (43%) patients had reversibility on spirometry, 6 (13.6%) patients had peak flow variability and 19 (43%) had positive bronchial provocation challenges.

3.3 | Co-existence of ILO and asthma

The total numbers of patients with or without ILO and asthma are shown in Table 2.

3.3.1 | Patients without asthma or ILO (A−I−)

Of the 14 patients with neither objectively demonstrable ILO nor asthma, one had globus pharyngeus and vocal cord paresis, two had chronic cough with laryngeal hypersensitivity, one had post-nasal drip due to chronic rhinitis and one had laryngeal hypersensitivity associated with recurrent upper airway angioedema. The remaining nine patients were still thought to have either probable ILO or asthma based on clinical assessment, but neither could be proven objectively. Of these 14 patients, nine were on inhaled corticosteroids for suspected asthma. Following evaluation, six of these nine patients had their inhaled corticosteroids ceased and an additional patient had the dose of inhaled corticosteroids reduced. Two patients were thought to have well-controlled asthma and thus were continued on their prescribed treatment.

TABLE 2 Asthma and ILO diagnoses

		ILO	
		No	**Yes**
Asthma	No	14 (20.3%)	11 (15.9%)
	Yes	15 (21.7%)	**29 (42%)**

ILO, inducible laryngeal obstruction.
Bold - patients diagnosed with concomitant asthma and ILO.

3.3.2 | Patients with asthma only (A+I-)

Of the 15 patients with asthma but not ILO, five were thought to have symptoms attributable only to asthma. Another six patients had additional contributors to symptoms; two had dysfunctional breathing, one had angioedema and three had an irritable larynx in the context of high-dose inhaled corticosteroid treatment for asthma. The remaining four patients were treated for symptoms of ILO based on clinical assessment. As a direct result of the clinic evaluation, three patients were commenced on inhaled corticosteroids for uncontrolled asthma, while the other patients had their existing asthma treatment adjusted as per treatment guidelines.

3.3.3 | Patients with ILO only (A−I+)

Eleven patients were classified as having ILO only. Six of these patients had been on high dose inhaled corticosteroids or combination therapy for asthma. One patient was found to have COPD. The remaining four patients were using intermittent short acting bronchodilators. Following clinical evaluation, three of the six patients had their inhaled corticosteroids ceased and the remaining three had their cumulative steroid dose reduced with aim to wean. The remaining four patients were encouraged to use speech pathology techniques for management of their symptoms rather than short acting bronchodilators.

3.3.4 | Patients with both asthma and ILO (A+I+)

Of the 29 patients with both ILO and asthma, the managing clinician's impression was that ILO predominantly contributed to symptoms in 41%, while asthma predominantly contributed to symptoms in 24%; dual contribution occurred in 14% (Figure 1). Management of these patients included speech therapy and/or titration of asthma treatment according to recognized guidelines (GINA).

3.3.5 | Comparison between groups

When patients with both ILO and asthma (A+I+) were compared to patients with only ILO (A−I+), chest tightness was significantly more common in patients with both ILO and asthma ($P = .01$) than in those with ILO alone. Forced expiratory ratio was also significantly higher in patients with ILO alone when compared to patients with both asthma and ILO ($P = .009$) (Figures 2 and 3).

There was a statistically significant difference in forced expiratory ratio between the four different patient groups (Kruskal–Wallis test χ^2 (3) = 21.17, $P < .0001$), with a mean rank FER of 46.5 for patients without A−I−, 30.19 for A+I+, 48.68 for A−I+ and 19.2 for A+I−. Post hoc analyses demonstrated that the significant differences were between patients with and without asthma, regardless of the presence of ILO (Figure 3).

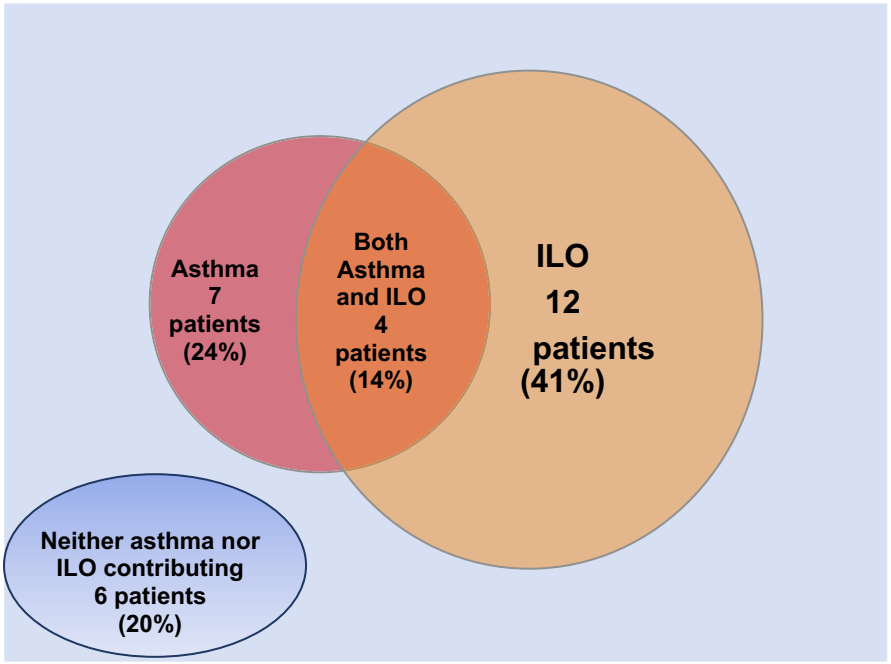

FIGURE 1 Contribution of Asthma and ILO to symptoms in patients with both conditions. ILO, inducible laryngeal obstruction

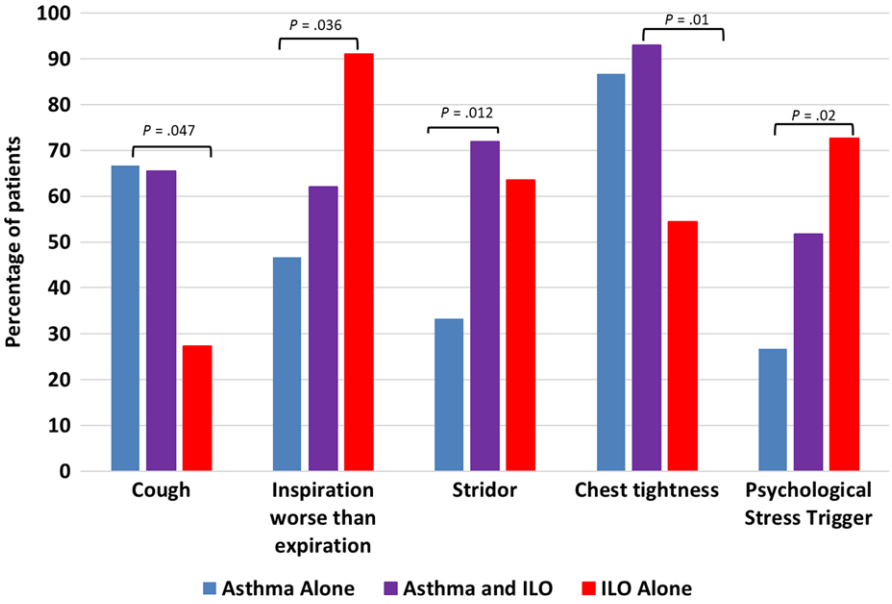

FIGURE 2 Clinical Features in patients with ILO, Asthma and both ILO and Asthma. ILO, inducible laryngeal obstruction

When patients with both ILO and asthma (A+I+) were compared to patients with asthma alone (A+I−), patients with asthma alone had a lower FEV_1 (mean 81% vs 67%, $P = .05$), (Figure 4), while those with both ILO and asthma reported stridor more frequently ($P = .012$) (Figure 2).

When patients with asthma alone were compared to patients with ILO alone, FEV_1 was significantly lower in those with asthma (mean 94.3% vs 66.9%, $P = .003$). Similarly, the forced expiratory ratio was significantly lower in patients with asthma alone (mean 83% vs 64%, $P < .001$). Cough was found to be a more prominent feature in patients with asthma rather than ILO ($P = .047$). Difficulty with inspiration rather than expiration was more commonly seen in the ILO only group ($P = .036$). The presence of psychological stress as a trigger for symptoms was also more commonly seen in the ILO only patient group ($P = .02$). There were no significant differences in frequency of throat symptoms, voice change or vocally traumatic behaviours. (See Table 3 and Figure 2).

Laryngeal dysfunction questionnaire results were not discriminatory in our sample of patients, with abnormal scores seen in patients who had asthma and ILO, as well as patients who had asthma alone (Table S1).

3.4 | Comorbidities accompanying ILO and asthma

In addition to asthma, rhinitis (85%) and gastroesophageal reflux disease (75%) were common comorbidities in the overall cohort. On

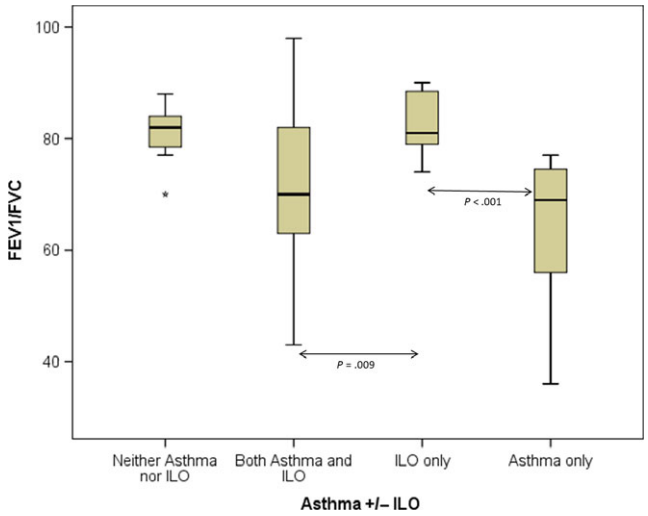

FIGURE 3 Forced Expiratory Ratio (FEV_1/FVC) in patients with asthma, ILO and comorbid asthma and ILO. Hinge: median value, boxes: interquartile range, whiskers: minimum and maximum value. FEV_1, Forced expiratory volume in one-second; FVC, forced expiratory volume; ILO, inducible laryngeal obstruction

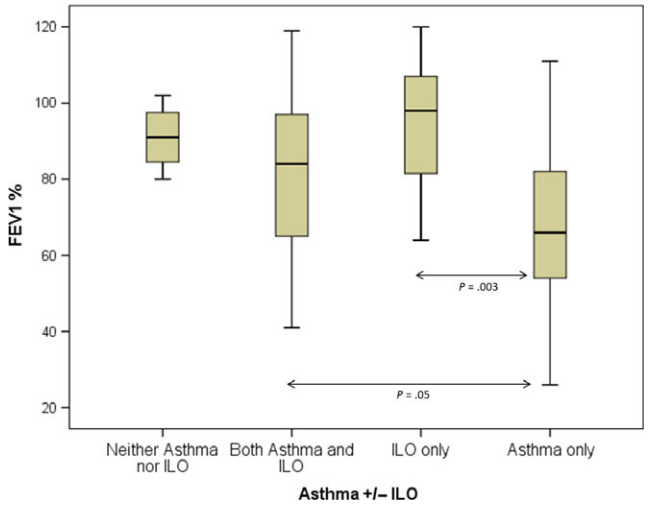

FIGURE 4 FEV_1 in patients with Asthma, ILO and comorbid Asthma and ILO. Hinge: median value, boxes: interquartile range, whiskers: minimum and maximum value. FEV_1, Forced expiratory volume in one-second; ILO, inducible laryngeal obstruction

TABLE 3 Clinical features

	Asthma and ILO (A+I+) n = 29	Asthma alone (A+I−) n = 15	ILO alone (A−I+) n = 11
Respiratory symptoms, n (%)			
Cough*	19 (65.5%)	10 (66.7%)	3 (27.3%)
Unable to breathe beyond a point in the throat	21 (72.4%)	8 (53.3%)	10 (91%)
Inspiration worse than expiration*	18 (62%)	7 (46.7%)	10 (91%)
Choking	18 (62%)	6 (40%)	7 (63.6%)
Stridor*	21 (72%)	5 (33.3%)	7 (63.6%)
Wheeze	23 (79%)	11 (73.3%)	5 (45.4%)
Chest tightness*	27 (93%)	13 (86.7%)	6 (54.5%)
Numbness/dizziness	13 (44.8%)	8 (53.3%)	7 (63.6%)
Rapid onset of symptoms	24 (82.8%)	12 (80%)	10 (91%)
Rapid resolution of symptoms	12 (41.4%)	8 (53.3%)	6 (54.5%)
Relieved by bronchodilators	15 (51.7%)	11 (73.3%)	4 (36.4%)
Emergency department presentation with symptoms, n (%)	19 (65.5%)	11 (73.3%)	6 (54.5%)
Pre-bronchodilator FEV_1%, mean (SD)*	81% (21)	67% (17.1)	94% (17.1)
Pre-bronchodilator FVC %, mean (SD)	88% (19)	81% (21.9)	93% (21)
Forced Expiratory Ratio, mean (SD)**	72% (12.8)	64% (12.3)	83% (6)
Triggers for symptoms			
Odours	17 (56.8%)	6 (40%)	5 (45.5%)
Chemical smell	15 (51.7%)	10 (66.7%)	5 (45.5%)
Smoke	13 (44.8%)	10 (66.7%)	4 (36.4%)
Exercise	18 (62.1%)	8 (53.3%)	5 (45.5%)
Psychological stress*	15 (51.7%)	4 (26.7%)	8 (72.7%)
Workplace trigger	10 (34.5%)	3 (21.4%)	3 (27.3%)

FEV_1, Forced expiratory volume in one-second; FVC, forced expiratory volume.
*$P < .05$, **$P < .001$.

average, each patient had at least 3 comorbid conditions. Validated questionnaires also suggested a high prevalence of dysfunctional breathing. A third of patients described a history of anxiety or depression. However, comorbidities were not significantly different between patients with or without asthma and/or ILO (Table S2).

4 | DISCUSSION

In our patients suspected to have asthma, inducible laryngeal obstruction, or both, almost half had objective evidence of both conditions. Achieving accurate diagnosis was extremely challenging. While a handful of clinical features were statistically more common in one or other condition, none was sufficiently distinctive to guide diagnosis. Furthermore, the frequency of comorbidities and abnormal laryngeal questionnaires could not reliably distinguish patients with each condition. This highlights the necessity of objective testing for both conditions in this clinical scenario. The diagnostic difficulty in our cohort is demonstrated by the mean delay of 5.5 years before achieving an ILO diagnosis.

Although challenging, accurate classification of patients is vitally important. In our 29 patients with both asthma and ILO, 40% were thought to have their symptoms directly attributable to ILO, that is

with stable asthma. As a direct result of our evaluation process, 16 patients had a change to prescribed asthma treatment, either commencing inhaled corticosteroids for uncontrolled asthma or weaning and ceasing inappropriate treatment, often with significant improvements to laryngeal symptoms. These outcomes illustrate the importance of clarifying these two diagnoses.

Our data suggest that many patients with ILO do not fit the previously reported typical profile. Firstly, previous investigators[27,28] have suggested the typical patient with ILO is a female between the second and fourth decades of life with or without a psychological disorder.[29] While our patients were predominantly female, we found a much wider age range. It is true that psychological stress was identified as a trigger for symptoms more commonly in the patients with ILO, but anxiety, depression and dysfunctional breathing were seen with similar prevalence across all our patient groups. Secondly, ILO has been reported to have a higher prevalence among healthcare workers and other occupations where exposure to a variety of irritant chemicals, dusts, mists and fumes may increase risk.[28,30-32] Although some of our patients had identifiable occupational risk factors, the majority of patients did not. We therefore believe that clinicians should be alert to the possibility of ILO even in patients who do not fit the "typical" demographic and clinical profile.

Clinical symptoms of ILO and asthma overlap significantly, and although some clinical features may be more associated with ILO, none have been shown to be specific.[27,33] In our sample, a few key clinical features occurred with a different frequency between patient groups. Stridor and difficulty with inspiration (as compared to expiration) were more prominent in the patients with ILO. Both of these symptoms emphasize the "misbehaving" larynx[5] as the focus of the underlying pathophysiology. Morris and colleagues also previously identified dyspnoea, wheeze, stridor, cough, throat and chest tightness and change in voice as key symptoms. Nevertheless, no single clinical feature in our study was sufficiently accurate to discriminate between ILO and asthma.

To our knowledge, we are the first to report the use a battery of questionnaires, designed to identify and evaluate laryngeal dysfunction as well as to identify relevant comorbidities. However, questionnaire results for laryngeal dysfunction were similarly abnormal in patients (with and without ILO), probably because all patients evaluated in this cohort had already been preselected to have a high clinical probability for ILO. Furthermore, the questionnaires employed had a limited applicability to our particular clinical question. Although the Pittsburgh questionnaire has a high specificity for the diagnosis of ILO, patients with concomitant ILO and asthma were deliberately excluded during its development.[13] The VCD-Q was designed to be a symptom monitoring rather than a diagnostic tool. The dyspnoea index and Newcastle laryngeal hypersensitivity questionnaire were not developed specifically for ILO. Future longitudinal research comparing questionnaire results before and after interventions such as speech pathology, use of neuromodulator agents and treatment of comorbidities may help to validate the utility of these questionnaires.

Specific comorbidities such as chronic rhinitis and gastroesophageal reflux were highly prevalent in our cohort. While they did not distinguish between asthma and ILO, they may serve to trigger both conditions and if detected, should be treated aggressively.[9,27,34,35]

Most authors suggest that formal diagnosis of ILO should be supported where possible by direct visualization of paradoxical vocal fold movement[3,6] as well as the exclusion of alternative diagnoses. Our data show the unreliability of clinical evaluation and support the need for objective testing with direct visualization of ILO in all patients. Fibreoptic laryngoscopy has been criticized as being operator dependent and subjective[36] with a reduced sensitivity if the patient is not experiencing symptoms at the time of examination. Nevertheless at this time, laryngoscopy remains the gold standard for diagnosis. Other methods such as impulse oscillometry[37] and 320 slice CT[38] have considerable drawbacks, due to their limited availability and radiation exposure required, respectively.

Numerous provocation techniques have been used to elicit ILO for diagnosis. Agents have included methacholine, exercise, cold air and irritant challenges, although the sensitivity of these challenges are <50%.[39] Over half of our patients reported exercise as a trigger for their symptoms, but we were unable to undertake exercise provocation at our centre.

We used mannitol, a dry powder inhalant, and have previously reported the ability of mannitol to induce ILO.[19] Direct provocation challenge with histamine or methacholine has traditionally been considered to be more sensitive but less specific for asthma diagnosis.[40,41] We hypothesize that mannitol may be more effective as a laryngeal provoking agent due to its direct irritant effects on the upper airway, although we acknowledge its ability to induce laryngoscopically visualized ILO has not been compared to direct challenge agents. Other measurements obtained during bronchial provocation challenge testing, such as the mean decrease in forced inspiratory flow (%FIF_{50}) has not been found to be a reliable method of detecting (exercise induced) ILO.[42] The inclusion of mannitol provocation testing combined with laryngoscopy in our protocol doubled the detection rate for ILO. We therefore believe provocation testing to form an essential tool in the diagnostic work-up of suspected ILO.

The question as to whether ILO is a physiological consequence of severe asthma or a distinct clinical entity unto itself remains unresolved.[33,36] Uniting mechanisms of airway inflammation and hyperresponsiveness have been suggested[8] as well as an observation of expiratory glottic closure during bronchoconstriction. This may be a compensatory mechanism to increase intrinsic positive end-expiratory pressure and improving alveolar gas exchange.[43,44] However, in our sample, patients with ILO tended to have better lung function, less severe airflow obstruction; and both expiratory and inspiratory ILO were observed, suggesting that ILO was not solely due to airflow limitation or severe asthma.

In normal respiration, the glottic aperture should remain mostly open. Closure of the glottis is mediated by a neuronal reflex arc which may be triggered by proprioceptive, chemical or thermal stimuli.[6] We elected to use the definition of more than 50% adduction

of the vocal folds during expiration in addition to any adduction during inspiration as an indicator of paradoxical movement as has been previously described.[27] We suggest this represents a hypersensitive response, especially as it only occurred in a subset of our cohort. However, we acknowledge there is currently no validated measurement guideline to differentiate normal from abnormal laryngeal responses and the area requires further research.[2]

Two patients in our series demonstrated supraglottic closure, which has been usually described in association with exercise provocation. As we did not undertake exercise provocation, supraglottic laryngeal obstruction may have been underdiagnosed in our cohort.

We recognize several limitations in our study. There was no control group to our observational series. Included patients were highly selected and had a high pre-test probability of some form of laryngeal dysfunction (including inducible laryngeal obstruction), limiting the generalizability of our findings. Detection of paradoxical movement of the vocal folds was by observation which may lead to inter-rater observer variability; although our previous work has demonstrated significant inter-rater agreement.[19] The limited statistical power due to our small sample size may have led to some non-significant results.

5 | CONCLUSION

Asthma and ILO commonly co-exist. We describe a systematic, multidisciplinary assessment process for the diagnosis of asthma and ILO when both conditions are suspected. In patients with both diagnoses, ILO appears to be more clinically symptomatic. In this selected series, laryngeal dysfunction questionnaires were non-discriminatory and a high comorbidity burden was seen in all patients; objective diagnostic testing is therefore essential. Further longitudinal studies evaluating patient outcomes following such diagnosis and assessment processes are warranted.

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CONFLICTS OF INTEREST

Joy Lee has delivered educational talks for GlaxoSmithKline and Astra Zeneca. Michael Abramson holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has also received assistance with conference attendance from Sanofi. Mark Hew has undertaken contracted research for AstraZeneca, Sanofi, Novartis, & GlaxoSmithKline; delivered Educational talks for GlaxoSmithKline, AstraZeneca & Novartis; Participated on advisory boards/consultancies for AstraZeneca, GSK & Seqirus; for all of which his employer (Alfred Health) has been reimbursed.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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