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Classical reflux symptoms, hiatus hernia and overweight independently predict pharyngeal acid exposure in patients with suspected reflux laryngitis

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SUMMARY

Background
Gastro-oesophageal reflux disease (GERD) has been associated with reflux laryngitis.

Aims
To investigate the risk factors and the predictors of pharyngeal acid reflux (PAR) in Taiwanese patients with suspected reflux laryngitis.

Methods
With referral from ENT physicians, 104 patients with symptoms and signs suggestive of reflux laryngitis completed a validated symptom questionnaire, an upper endoscopy exam and ambulatory 24-h pH tests with three sensors located at the hypopharynx, proximal and distal oesophagus. Patients with one or more episodes of PAR were considered abnormal.

Results
Pharyngeal acid reflux was identified in 17% (18/104) of patients. In multivariate logistic regression analysis, PAR was independently associated with classical reflux symptoms [adjusted odds ratio (aOR) = 3.5, 95% confidence interval (CI): 1.0–12.8], hiatus hernia (aOR = 6.7, 95% CI: 1.5–30.2) and overweight (aOR = 3.4, 95% CI: 1.0–11.0). In predicting PAR, classical reflux symptoms had a sensitivity of 78% and hiatus hernia had a specificity of 95%. With all three factors, the positive predictive value for PAR was 80%. Classical reflux symptoms included heartburn, chest pain, dyspepsia and acid regurgitation.

Conclusions
Classical reflux symptoms, hiatus hernia and overweight are independent risk factors that may predict pharyngeal acid reflux in patients with suspected reflux laryngitis.

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INTRODUCTION

The association between reflux laryngitis and gastro-oesophageal reflux disease (GERD) has been established. However, the causality between them remains controversial.[1] Conversely, some investigators have proposed that reflux laryngitis and GERD are two different disease identities, because heartburn and erosive oesophagitis are relatively uncommon in patients with pH-documented reflux laryngitis.[2] It remains unclear whether the risk factors of GERD such as obesity and hiatus hernia are also associated with pH-documented reflux laryngitis.[3–5]

The pH-documented reflux laryngitis is defined by the presence of pharyngeal acid reflux (PAR) detected by double- or multiple-sensor ambulatory pH-metry in patients with suspected reflux laryngitis. In a meta-analysis involving over 790 pharyngeal pH reports in 16 studies, Merati *et al.*[6] found that PAR appears to be able to discriminate patients with reflux laryngitis from normal controls. Both laryngeal symptoms and signs are nonspecific in diagnosing reflux laryngitis.[7] The ambulatory pH test is often the choice for the diagnosis of reflux laryngitis in question, even though its role in prediction of therapeutic response remains unproven. The test is costly, invasive and inconvenient. To the best of our knowledge, little is known about the predictors of PAR in patients with suspected reflux laryngitis. Identifying possible risk factors could help predict the presence of PAR in clinical settings.

Unlike distal oesophageal pH monitoring in diagnosing pathological GERD, there are no uniform or accepted criteria for diagnosing pathological PAR.[8] Although both Noordzij *et al.*[9] and Eubanks *et al.*[10] have adopted different criteria, they both found that heartburn and abnormal oesophageal acid exposure were associated with abnormal PAR in patients with suspected reflux laryngitis. Thus, we hypothesised that pH-documented reflux laryngitis and GERD may share some common risk factors.

In this study, we evaluated the risk factors for PAR. We also investigated the predictors of PAR based on demographic data, clinical symptoms as well as endoscopic findings in Taiwanese patients with suspected reflux laryngitis who were unselectively referred from otolaryngology outpatient clinic.

MATERIALS AND METHODS

Study design

This study was prospectively designed to investigate PAR in patients with suspected reflux laryngitis at the Taichung Veterans General Hospital in central Taiwan. Consecutive patients with chronic laryngeal symptoms and signs suspected to be reflux-related referred from the Department of Otolaryngology clinic, from January 2007 to December 2008, were assessed for study eligibility. All patients provided written informed consent. The protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital.

Inclusion and exclusion criteria

Patients (aged >18 years) were eligible for inclusion if they had one or more of symptoms as the major complaint, including throat clearing, cough, globus, sore throat, or hoarseness, for three or more consecutive months before screening. In addition, all enrolled patients were required to have laryngoscopic signs consistent with reflux, such as posterior laryngitis, interarytenoid bar, granuloma, erythema or oedema of the larynx.

Patients were excluded if they had any of the following conditions that might account for their symptoms, or put them at risk: (i) respiratory or gastrointestinal (GI) malignancy; (ii) radiation therapy or surgery to the head, neck, lung, or GI tract; (iii) traumatic event or surgery near the larynx; (iv) past or present smoking, substance or alcohol abuse history; (v) presence of an infectious cause of laryngitis in the last 3 months; (vi) referral from gastroenterologists for their laryngeal symptoms; (vii) exposure to environmental irritants in the last 3 months; (viii) vocal cord papilloma, enlarged lingual or palatine tonsils, or goitres; (ix) excessive voice use; (x) bronchial asthma; (xi) chronic cough attributable to angiotensin-converting enzyme inhibitor, or known chronic pulmonary or tracheobronchial aetiologies, such as eosinophilic bronchitis, positive methacholine provocative test, or response to inhaled or systemic steroid; (xii) acid suppressive therapy within 4 weeks prior to recruitment; (xiii) pharyngeal (Zenker's) diverticulum, or oesophageal stasis syndrome such as achalasia; (xiv) chronic rhinitis, nasal polyposis, or sinusitis defined by nasal endoscopy or CT scan; and (xv) postnasal drip with response to at least 1 month of medical therapy with first-generation antihistamine, topical steroid spray, and antibiotics,[11, 12] and (xvi) pregnancy.

Each patient underwent assessment of demography, medical history, upper GI endoscopy, 24-h triple-sensor ambulatory pH monitoring and completed a self-reported questionnaire, and the laryngeal reflux symptom index (RSI).[13]

Assessment of demography and clinical presentations

Patients were interviewed for demographic data including age, gender, weight and height (body mass index),

medical history including diabetes mellitus and hypertension, occupation, alcohol consumption, smoking, drug, and allergy history. The presence and the duration of five laryngeal symptoms (hoarseness, throat clearing, sore throat, globus and cough) were also assessed. We also collected other information, such as the date of first visit to an otolaryngologist or a gastroenterologist for their laryngeal complaints, a history of suspected GERD, use of anti-secretory agents and response to laryngeal symptoms, rhinosinusitis/postnasal drip and response to anti-allergic treatment, excessive voice use, pulmonary evaluations such as methacholine inhalation challenge test, chest X-ray, and exhaled nitric oxide, and laryngoscopic findings in the otolaryngology clinic.

Upper GI endoscopy

Each patient underwent diagnostic upper GI endoscopy to evaluate the presence of erosive oesophagitis, hiatus hernia, peptic ulcer, *Helicobacter pylori* and other upper GI mucosal lesions. Erosive oesophagitis was defined using Los Angeles classification Grade B or higher, as Grade A may contain heterogeneous factors.[14] Hiatus hernia was diagnosed by the presence of the gastric wall 2 cm above the diaphragmatic hiatus, as previously described.[15] *Helicobacter pylori* status was assessed by histology (haematoxylin and eosin staining or Giemsa staining) and rapid urease test on biopsies with Pronto Dry (Medical Institute Corp., Solothurn, Switzerland). A patient was considered *H. pylori*-positive if any of the diagnostic methods applied was positive, and otherwise *H. pylori*-negative if both the applied methods were negative.

Reflux symptom index questionnaire

We used a validated self-administered instrument, the RSI questionnaire, which was specifically designed to evaluate the symptom severity of reflux laryngitis.[13] The RSI contains eight items with various throat symptoms and one item with classical reflux symptoms i.e. heartburn, chest pain, dyspepsia or acid regurgitation (Table S1). Each item was scored from 0 (no problem) to 5 (severe problem). The questionnaire was translated into the Chinese language. The patients were dichotomized into abnormal and normal groups with a cut-off value of either two or three for each item.

Twenty-four-hour ambulatory pharyngeal pH monitoring

Water-perfused oesophageal manometry with station pull-through method was performed for each patient, to determine the locations of the upper border and resting pressures of both the upper oesophageal sphincter (UES) and the lower oesophageal sphincter (LES) before the pH study. An ambulatory 24-h pH catheter incorporating three antimony sensors into a bifurcated probe with a single connector and recording box was used (Sandhill Scientific, Highlands Ranch, CO, USA). The pH values were measured at 5-s intervals. Following calibration of the probe with pH 7.0 and pH 4.0 buffers, one arm of the probe, equipped with a single sensor at the tip, was positioned 5 cm above the upper border of the LES. The second arm of the probe containing two sensors spaced at a 10-cm interval was positioned with its proximal sensor 1 cm above the upper border of the UES. This setup provided a probe adjustable to the individual patient and capable of recording the distal oesophageal and pharyngeal reflux at a standard location. The third sensor provided a proximal oesophageal recording located approximately 6 cm below the distal border of the UES.[16] The probe was secured to the nose for 24-h recording. Patients were instructed to continue their daily activities during recordings except bathing. They had their usual diet except citrus fruit, acidic beverages or drinks, carbonated beverages, and caffeinated beverages. Patients also kept a detailed diary to record the meal times, the times of body position (upright or recumbent), and the times and content of liquid swallowed other than meals.

Definition of PAR

Pharyngeal acid reflux was defined according to the criteria derived from Williams' study with slight modifications, as follows: (i) a pH decrease that occurred during oesophageal acidification with pH <4; (ii) a pH decrease of greater than two units; and (iii) a pH decrease reaching a nadir of less than pH 4 or pH 5 in less than 30 s.[17] Using the above criteria, an inter-observer agreement of PAR was reached for 98% of 56 events (55/56) between two experienced independent interpreters (H.C. Lien & C.S. Chang). Potential pH artefacts of PAR including meal periods, liquid swallows outside of meals, out of range (pH = 0 or pH >8), pH drift (drop to nadir >30 s), isolated pharyngeal pH drop (no oesophageal acidification) and short pH drop (duration <5 s) were excluded.[18] Data analysis was also performed by a software program, which reported the number of oesophageal reflux episodes and calculated acid exposure times of both the oesophagus and pharynx over the course of the study. Data collected during meals or liquid swallows outside of meals were not analysed. Patients

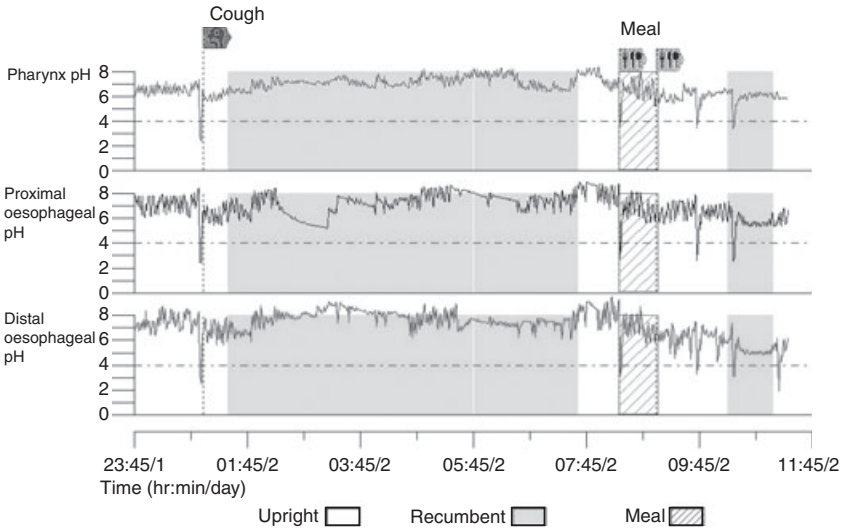

Figure 1 | An example of pharyngeal acid reflux demonstrating four events of acid reflux, which reached the pharynx. From the left side to the right side: the first event was temporally associated with cough; the second event was excluded for analysis because it occurred during meal time; the third event occurred with the patient in the upright position; and the fourth event occurred with the patient in the supine position. The 24-h acid exposure in the distal oesophagus was within the normal limit in this particular patient.

with one or more episodes of PAR were labelled as having PAR (Figure 1). Abnormal distal oesophageal acid exposure was defined as the total fraction time pH <4 at 5 cm above the upper border of the LES for more than 5% of a 24-h period based on data derived from Asian patients.[19] An oesophageal reflux episode was defined as a drop in oesophageal pH <4 lasting longer than 5 s, or an additional decrease in pH of $\geqq$1 unit if baseline pH was <4.[20]

Statistical analysis

All data including demographic data, medical history, clinical symptoms, self-reported symptoms and upper GI endoscopic findings were compared between patients with PAR and without PAR. All formal statistical tests were performed using a two-sided test at a significance level of 0.05. Numerical data such as mean ages and body mass indexes (BMI) were analysed using an independent *t*-test, while percentage time of acid exposure in 24-h ph monitoring, and total RSI scores were analysed using the Mann–Whitney *U*-test. Categorical data such as gender, presence of erosive oesophagitis, hiatus hernia, *H. pylori* and presence of individual symptoms in the RSI questionnaire were analysed using the univariate logistic regression analysis. BMI was assessed both as a continuous and a categorical variable. BMI $\geqq$24 kg/m^2 was considered as overweight based on Taiwan's criteria.[21]

Variables having a *P*-value <0.20 in the univariate analysis were entered as candidate risk factors in the multivariate logistic regression analyses, including models for differentiating the effect on the presence and absence of PAR. A multivariate logistic regression model was selected to identify independent risk factors associated with PAR. Predictors of PAR were further calculated for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) based on the individual as well as the combinations of these risk factors.

RESULTS

A total of 118 patients eligible for 24-h pH test enrolled initially, and then 104 patients were included for analysis after exclusion. Eighteen patients had one or more episodes of PAR. The remaining 86 patients with no evidence of PAR that fulfilled the previously defined criteria served as controls (Figure 2). The baseline characteristics, clinical presentations and upper GI endoscopic findings of the PAR patients and the controls are shown in Table 1. There were no differences in distributions of age, gender and the five primary laryngeal symptoms, and the presence of *H. pylori* or peptic ulcer between patients with and without PAR. However, both BMI and the percentage of BMI $\geqq$24 kg/m^2 were higher in patients with PAR than in those in patients without PAR (P = 0.09 and P = 0.04). Erosive oesophagitis was evident

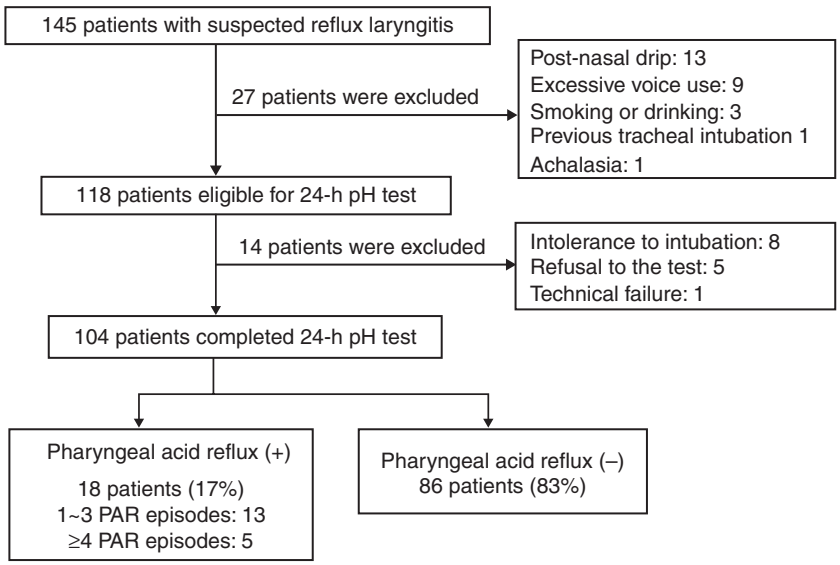

Figure 2 | Algorithm of inclusion and exclusion.

in 20 (19%) patients with suspected reflux laryngitis. Patients with PAR were more common than patients without PAR for both erosive oesophagitis (44% vs. 14%, $P = 0.005$) and hiatus hernia (33% vs. 5%, $P = 0.001$) (Table 1).

RSI questionnaire

There were no differences between PAR cases and controls for total RSI scores and for individual RSI scores, except that for the question 'Do you have heartburn, chest pain, dyspepsia, or acid regurgitation? (i.e. classical reflux symptoms)' patients with PAR had a higher score than patients without PAR (3.3 ± 1.0 vs. 2.4 ± 1.6, $P = 0.004$; Table S1). Using symptom severity scores dichotomized by a cut-off value of either 2 or 3, the classical reflux symptoms were also more common in patients with PAR than in patients without PAR (100% vs. 65%, $P = 0.002$; or 78% vs. 48%, $P = 0.03$; respectively).

Twenty-four-hour ambulatory pH test

A total of 56 episodes of PAR were identified in the 18 patients with PAR (median = 2, IQR = 3.5). Fifteen patients were classified as having PAR due to pH nadir dropping to 4, while the remaining three patients fulfilled the criteria of pH nadir dropping to 5. Of the 56 PAR episodes, 10 (18%) were temporally associated with symptoms of either acid regurgitation or cough. Majority (91%) of PAR episodes occurred in the upright position except for five (9%) in the supine position. Potential artefacts mimicking PAR were excluded, including 48 episodes during meal times, 21 episodes of liquid swallows outside meals, one episode of isolated PAR without oesophageal acidification, one episode during vomiting, and five episodes of slow pH drift, based on the criteria mentioned above.

Concurrent abnormal distal oesophageal acid exposure was found in 7 of the 18 patients with PAR, which was more common than that in patients without PAR (39% vs. 20%, $P = 0.09$). The total percentage time of pH <4 in the distal oesophagus was also higher in patients with PAR than in patients without PAR [median: 1% (IQR: 5%) vs. median: 0.6% (IQR: 2%), $P = 0.03$].

Multivariate logistic regression analysis and predictors of PAR

The stepwise logistic regression analysis showed that classical reflux symptoms, hiatus hernia and BMI $\geqq 24$ kg/m^2 were significantly independently associated with the presence of PAR after adjustment age and gender (Table 2). For individual independent risk factor, the sensitivity of classical reflux symptoms was 78% (14/18) and the specificity of hiatus hernia was 95% (82/86) (Table 3). When any combinations of these three independent risk factors were applied in the prediction model, the positive predictive values increased as the number of risk factors increased (P for trend, 0.002), while the negative predictive values were high in all circumstances (Figure 3). The prevalence of hiatus hernia and classical reflux symptoms also increased as the PAR episodes increased from 0, to 1–3, and $\geqq 4$: from 5% (4/86), to 31% (4/13), and 40% (2/5) respectively, for hiatus hernia; and from 48% (37/77), to 69% (9/13), and 100% (5/5), respectively, for classical reflux symptoms (Table 4).

Table 1 | Comparisons between patients with and without pharyngeal acid reflux by demography, clinical presentations, and endoscopic findings

	Pharyngeal acid reflux		
	Yes (*N* = 18)	No (*N* = 86)	*P*-value*
Demography			
Age (years) (mean ± s.d.)	46.2 ± 16.4	48.8 ± 10.7	0.4
Gender (Male), % (*n*/*N*)	38.9 (7/18)	57.0 (49/86)	0.2
BMI (kg/m^2) (mean ± s.d.)	25.0 ± 4.4	23.3 ± 3.6	0.09
BMI ≧24 (kg/m^2), % (*n*/*N*)	66.7 (12/18)	39.5 (34/86)	0.04
Clinical presentations			
Major complaint of laryngeal symptoms, % (*n*/*N*)			
Globus sensation	72.2 (13/18)	65.1 (56/86)	0.6
Sore throat	33.3 (6/18)	36.0 (31/86)	0.8
Hoarseness	55.6 (10/18)	53.5 (46/86)	0.9
Cough	33.3 (6/18)	27.9 (24/86)	0.6
Throat clearing	50.0 (9/18)	44.2 (38/86)	0.7
Duration of laryngeal symptoms, % (*n*/*N*)			
3–6 months	33.3 (6/18)	28.0 (23/82)	0.9
7–12	16.7 (3/18)	20.7 (17/82)	0.6
13–24	16.7 (3/18)	19.5 (16/82)	0.7
>24	33.3 (6/18)	31.7 (26/82)	0.8
Refractory postnasal drip, % (*n*/*N*)	44.4 (8/18)	42.9 (36/84)	0.9
History of taking anti-reflux medications, % (*n*/*N*)	44.4 (8/18)	48.1 (37/77)	0.8
Anti-reflux medication response, % (*n*/*N*)	75.0 (6/8)	48.6 (18/37)	0.2
Diabetes mellitus, % (*n*/*N*)	11.1 (2/18)	1.2 (1/86)	0.06
Hypertension, % (*n*/*N*)	11.1 (2/18)	18.6 (16/86)	0.5
Endoscopic findings			
Erosive oesophagitis, % (*n*/*N*)	44.4 (8/18)	14.0 (12/86)	0.005
Hiatus hernia, % (*n*/*N*)	33.3 (6/18)	4.7 (4/86)	0.001
Peptic ulcer, % (*n*/*N*)	22.2 (4/18)	20.9 (18/86)	0.9
Helicobacter pylori, % (*n*/*N*)	28.4 (4/14)	26.9 (18/67)	0.9

BMI, body mass index; s.d., standard deviation.

* *t*-test for continuous variables; Chi-squared test for categorical variables.

DISCUSSION

We performed the 24-h ambulatory pH tests for Taiwanese patients with suspected reflux laryngitis and found that the prevalence of PAR was 17%. In addition, classical reflux symptoms, hiatus hernia, and overweight were independent risk factors and predictors of PAR.

In Western countries, the prevalence of PAR has been ranged from 40% to 95% among patients with suspected reflux laryngitis,[6] whereas data are scant in Asia. Similar to our findings, the results of a small-scale study in Hong Kong showed that the frequency of PAR was 21%.[22] However, comparability among studies may be compromised by differences in methodologies, study populations, and, in most, small sample sizes.[8] Nevertheless, the low PAR prevalence found in our study may be attributable to the low GERD prevalence in Asia,[23] a heterogeneous study population, such as patients with refractory postnasal drip, which has been attributed to GERD,[12, 24–26] or an overestimation of reflux laryngitis in ENT clinics.

Table 2 | Independent risk factors for pharyngeal acid reflux in multivariate logistic regression models controlling for gender and age

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
BMI ≧24 (kg/m^2)	3.0 (0.9–10.1)	0.07	3.4 (1.0–11.0)	0.05
Hiatus hernia	5.4 (1.2–25.0)	0.03	6.7 (1.5–30.2)	0.01
Erosive oesophagitis	2.5 (0.7–8.7)	0.2		
Classical reflux symptoms	3.2 (0.9–11.9)	0.08	3.5 (1.0–12.8)	0.05

BMI, body mass index; Classical reflux symptoms = heartburn, chest pain, dyspepsia, or acid regurgitation, RSI score ≧3 (RSI score 0 = No problem, RSI score 5 = Severe problem); OR, odds ratio; CI, confidence interval.

Table 3 | Univariate logistic regression in the predictions of presence of pharyngeal acid reflux

	PPV	NPV	Sensitivity	Specificity	OR (95% CI)
Individual risk factors					
BMI ≧24 (kg/m^2)	0.26 (12/46)	0.90 (52/58)	0.67 (12/18)	0.60 (52/86)	3.1 (1.0–8.9)
Hiatus hernia	0.60 (6/10)	0.87 (82/94)	0.33 (6/18)	0.95 (82/86)	10.3 (2.5–41.7)
Classical reflux symptoms	0.27 (14/51)	0.91 (40/44)	0.78 (14/18)	0.52 (40/77)	3.8 (1.1–12.5)
Combinations of risk factors					
Any one or more risk factors	0.23 (17/73)	0.95 (21/22)	0.94 (17/18)	0.27 (21/77)	6.4 (0.8–50.9)
Any two or more risk factors	0.44 (11/25)	0.90 (63/70)	0.61 (11/18)	0.82 (63/77)	7.1 (2.3–21.5)
All three risk factors	0.80 (4/5)	0.84 (76/90)	0.22 (4/18)	0.99 (76/77)	21.7 (2.3–209.0)

BMI, body mass index; Classical reflux symptoms = heartburn, chest pain, dyspepsia, or acid regurgitation, RSI score ≧3 (RSI score 0 = No problem, RSI score 5 = Severe problem); PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; CI, confidence interval.

The pathophysiology of reflux laryngitis has been poorly understood, while the risk factors for PAR have been explored. Despite utilising different criteria of pathological PAR, both Noordzij *et al.*[9] and Eubanks *et al.*[10] found that heartburn and abnormal oesophageal reflux were associated with PAR. In addition to their findings, we found that overweight, hiatus hernia and erosive oesophagitis were associated with PAR, which are in common with the risk factors of oesophageal GERD syndrome, suggesting that pH-documented reflux laryngitis is a subgroup of GERD, instead of a different disease entity.[1, 2]

In a study on the prevalence of oesophagitis and heartburn in 58 patients with pH-documented reflux laryngitis, Koufman *et al.*[27] found 19% of patients had oesophagitis or Barrett's oesophagus and 40% had heartburn. In contrast, we found that 44% had oesophagitis, and 78% had moderate classical reflux symptoms (100% had mild classical reflux symptoms). The reasons for these discrepancies may be attributable to a broad definition of classical reflux symptoms adopted from the RSI questionnaire, including heartburn, chest pain, acid regurgitation, dyspepsia. A high sensitivity of classical reflux symptoms in the prediction of PAR may have clinical implication. In addition, a high prevalence of oesophagitis in our patients with PAR may be attributable to a high prevalence of hiatus hernia (33%) (Table 1).

Hiatus hernia can disrupt the anti-reflux mechanism and may potentiate acid reflux up to the pharynx during transient relaxation or in case of dysfunction of the upper oesophageal sphincter.[4, 28] However, little is known about the role of hiatus hernia in patients with reflux laryngitis. Unlike Western countries, the prevalence of hiatus hernia was estimated as low as 4% in Taiwanese adults undergoing gastroscopy for health check-up.[29, 30] In accordance with our findings, a recent Taiwanese study by Lai *et al.*[31] found hiatus hernia in

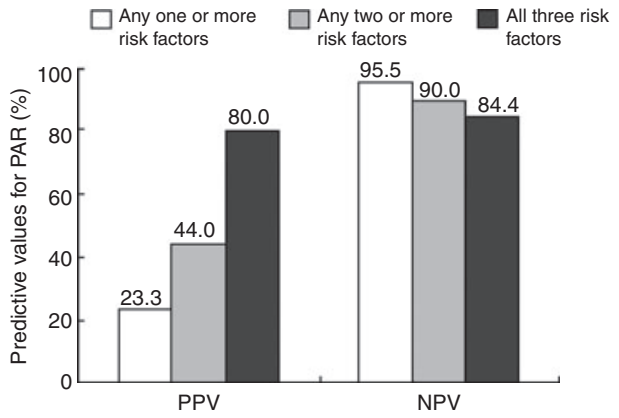

Figure 3 | Positive predictive values (PPV) and negative predictive values (NPV) for pharyngeal acid reflux based on any combinations of three risk factors including classical reflux symptoms, hiatus hernia and overweight, where clinical reflux symptoms were defined as RSI score ≧3 for the symptoms of heartburn, chest pain, dyspepsia, or acid regurgitation (RSI score 0 = no problem, RSI score 5 = severe problem), and overweight was defined as BMI ≧24 kg/m^2 based on Taiwan's criteria. The positive predictive values increased by increasing the number of risk factors (*P** = 0.002 for trend), whereas the negative predictive values were high in all circumstances. *Cochran-Armitage Trend Test.

28% of patients with reflux laryngitis, as an independent risk factor for reflux laryngitis. In addition, a high specificity (95%) of hiatus hernia for PAR in our study is helpful in screening patients at the clinical settings.

Obesity is a well-known risk factor for oesophageal GERD syndrome,[3] but little is known about its association with reflux laryngitis. To the best of our knowledge, we are the first to report an association between overweight and pH-documented reflux laryngitis. It seems to contradict the finding reported by Halum *et al.*[5] who reviewed 285 patients undergoing double probe pH and found obesity was not associated with isolated PAR. However, most (67%) of their study subjects were with both PAR and abnormal oesophageal acid exposure, and were associated with a higher BMI. In our study, we did not correlate isolated PAR with BMI because of small sample size. Instead, overweight (BMI ≧24 based on Taiwan's criteria) was associated with PAR in both univariate and multivariate logistic regression models. Further large studies are needed to clarify whether obesity or overweight is a true risk factor for pH-documented reflux laryngitis.

Several laryngeal signs have been proposed to diagnose reflux laryngitis. However, most of these signs are nonspecific for reflux.[32] In the literature, no correlation has been found between laryngeal injury and PAR.[9, 10] In this study, we did not adopt laryngeal signs as a predictor for PAR because the inter- and intra-observer agreements remain controversial.[33] We adopted a validated RSI questionnaire for symptoms evaluation to differentiate patients with and without PAR using the classical reflux symptoms instead of laryngeal symptoms (Table S1). In addition, we categorised the patients into five subgroups based on their primary laryngeal symptoms (Table 1) and found no difference in symptom distribution between patients with and without PAR. The explanation for no association between various laryngeal symptoms and PAR may, in part, because they were all recruited based on laryngeal symptoms. However, with the combinations of three risk factors found in our study, an 80% of positive predictive values for PAR may be clinically useful for population with the low prevalence of PAR such as Taiwan (Figure 3).

Another important issue is the clinical role of PAR in relation to reflux-induced laryngitis. PAR has been proposed as the gold standard in the diagnosis of reflux laryngitis.[34] Unfortunately, the evidence to prove or

Table 4 | The associations between number of PAR episodes and independent risk factors for PAR

	Number of PAR episodes			
	0 (*n* = 86)	1-3 (*n* = 13)	≧4 (*n* = 5)	*P*-value*
BMI ≧24 (kg/m^2), % (*n*/*N*)	39.5 (34/86)	61.5 (8/13)	80.0 (4/5)	0.03
Hiatus Hernia, % (*n*/*N*)	4.7 (4/86)	30.8 (4/13)	40.0 (2/5)	0.0002
Classical reflux symptoms, % (*n*/*N*)	48.1 (37/77)	69.2 (9/13)	100.0 (5/5)	0.01

BMI, body mass index; Classical reflux symptoms = heartburn, chest pain, dyspepsia, or acid regurgitation, RSI score ≧3 (RSI score 0 = no problem, RSI score 5 = severe problem); PAR, pharyngeal acid reflux.

* Cochran-Armitage Trend Test.

disprove the association between PAR and response to anti-reflux therapy is weak, because of small-scale studies and/or a high placebo effect.[35–38] Moreover, both microaspiration and vagal-mediated oesophago-bronchial reflex have been proposed as the mechanisms of reflux laryngitis, while PAR can only reflect the former. Future research to establish the predictors of reflux laryngitis may need to include surrogate markers representing both mechanisms. The factors predicting PAR are capable of pretesting patients with suspected reflux laryngitis using a 24-h pH testing.

The strengths of this study included using the stringent criteria for diagnosing PAR, applying a validated questionnaire for symptom identification, analysing risk factors for PAR in a multivariate logistic regression model, and establishing a prediction model based on independent risk factors. The limitations in this study involved relatively small sample size, lack of normal controls and lack of uniform criteria for diagnosing pathological PAR. The last mentioned limitation is due to lack of gold standard in the diagnosis of reflux laryngitis among current technologies.

In conclusion, PAR in Taiwanese patients is not as prevalent as that in the Western patients with suspected reflux laryngitis. Classical reflux symptoms, hiatus hernia and overweight are independent risk factors and predictors of PAR in patients with suspected reflux laryngitis. Our preliminary data support that both reflux laryngitis and oesophageal GERD syndrome share some common risk factors. Further large studies are needed to confirm these findings, more importantly, to define the role of PAR in relation to anti-reflux therapy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparisons between patients with and without pharyngeal acid reflux for the reflux symptom index scores.

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