

# The Ability of Patient-Symptom Questionnaires to Differentiate PVFMD From Asthma

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**Summary: Objectives.** Goals of the current study were to (1) conduct initial validation of a new Paradoxical Vocal Fold Movement Disorder Screening Questionnaire (PVFMD-SQ); (2) determine if symptom-based questionnaires can discriminate between patients with confirmed PVFMD and those with diagnosed uncontrolled asthma without clinical suspicion for PVFMD; and (3) determine if a new questionnaire with diagnostic specificity could be created from a combination of significant items on previously validated questionnaires.

**Methods.** This is a prospective, case-controlled study of patients with PVFMD only and asthma only, who completed five questionnaires: Dyspnea Index, Reflux Symptom Index, Voice Handicap Index-10, Sino-Nasal Questionnaire, and PVFMD-SQ. Factor analysis was completed on the new PVFMD-SQ, and the discrimination ability of selected factors was assessed by receiver operating characteristics curve. The factor with the greatest discriminatory ability was selected to create one diagnostic questionnaire, and scores for each participant were calculated to estimate how well the factor correlated with a PVFMD or asthma diagnosis. Mean scores on all questionnaires were compared to test their discriminatory ability.

**Results.** Patients with PVFMD showed greater voice handicap and reflux symptoms than patients with asthma. A 15-item one-factor questionnaire was developed from the original PVFMD-SQ, with a sensitivity of 89% and specificity of 73% for diagnosing asthma *versus* PVFMD. The combined questionnaires resulted in four factors, none of which showed discriminatory ability between PVFMD and asthma.

**Conclusion.** This study represents the first time that a patient symptom-based screening tool has shown diagnostic sensitivity to differentiate PVFMD from asthma in a cohort of symptomatic patients.

**Key Words:** Voice–Asthma–Paradoxical vocal fold movement disorder–Screening–Vocal cord dysfunction.

## INTRODUCTION

Paradoxical vocal fold movement disorder (PVFMD), also known as vocal cord dysfunction, is a laryngeal-based respiratory disorder characterized by the inappropriate, involuntary closure of the true vocal folds usually during inspiration. This paradoxical movement may result in recurrent episodes of stridor, dyspnea, a choking sensation, and dysphonia.<sup>1–7</sup> PVFMD has been associated with many triggers, including voice use, exercise, psychological conditions, environmental and occupational irritants, rhinosinusitis, gastroesophageal reflux disease, and neuroleptic drugs.<sup>8–14</sup> These symptoms frequently mimic those of asthma.<sup>15</sup> Unlike asthma, the management of PVFMD involves treating underlying comorbid conditions, such as gastroesophageal or laryngopharyngeal reflux disease, in addition to behavioral breathing therapy.<sup>1,10,16</sup> Consequently, individuals with PVFMD misdiagnosed as asthma or other lower airway disorders have persistent symptoms despite aggressive therapy.<sup>2,4,17,18</sup> When PVFMD is misdiagnosed as refractory asthma, patients undergo treatments with high-dose systemic corticosteroids, unnecessary hospitalizations, endotracheal intubations, and

tracheotomies.<sup>7,15,19,20</sup> Additionally, a lack of improvement perpetuates a cycle of symptoms, exacerbations, and additional corticosteroid use, which accumulate into enormous economic and personal costs.<sup>21</sup> As a result, valid, reliable, efficient, and early diagnosis of PVFMD is imperative.

The gold standard for PVFMD diagnosis is flexible laryngoscopy to visualize the abnormal movement of vocal folds and to rule out other causes of upper airway obstruction.<sup>1,4,6,15,22</sup> Signs and symptoms of PVFMD, however, can be difficult to induce in the clinic, and the larynx often functions normally during laryngoscopy. Pulmonary function testing (PFT) is an additional valuable diagnostic test where a flattening of the inspiratory flow-volume loop is considered a positive sign of PVFMD.<sup>4,6,23,24</sup> As with laryngoscopy, however, PFTs are often normal or inconclusive owing to the episodic nature of the disorder. Several studies have suggested inducing an episode with methacholine or exercise.<sup>25–30</sup> Unfortunately, provocation tests along with laryngoscopy and PFTs are not routinely available in primary care clinics where many of these patients initially present.

Because of the symptom overlap between PVFMD and asthma, and the lack of a definitive clinical diagnostic standard for PVFMD, many patients remain inappropriately diagnosed and treated. The time between symptom presentation and accurate diagnosis ranges from 2 to 13 years, with an average of 2.7 years.<sup>2</sup> Further complicating appropriate diagnoses and subsequent treatment, data suggest that 30% of patients have coexisting PVFMD and asthma.<sup>31,32</sup>

The current study had three goals. First, to conduct initial validation of the PVFMD Screening Questionnaire using factor analysis; second, to determine if symptom-based questionnaires can discriminate between patients with confirmed PVFMD

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and those with diagnosed uncontrolled asthma without clinical suspicion for PVFMD; and third, to determine if a new questionnaire with diagnostic specificity could be created from a combination of the significant items on previously validated questionnaires. Such a screening tool has the potential to assist in early identification of PVFMD by primary care and specialist practices alike and prevent unnecessary medication use and hospitalization.

## MATERIALS AND METHODS

All study procedures were approved by the University of Pittsburgh Institutional Review Board.

### Study design

A prospective case-control study of participants determined to have isolated PVFMD and isolated asthma was conducted. Participants were included if they were between 18 and 70 years old. Participants were excluded if they had a known coexistence of PVFMD and asthma or other major illnesses that may impair breathing, including neuromuscular diseases, chronic obstructive pulmonary disease, and restrictive lung diseases.

Participants in the PVFMD-only group were recruited from The University of Pittsburgh Voice Center, an outpatient referral center focused on laryngeal disorders. Participants with newly diagnosed PVFMD, *via* laryngoscopy performed by a fellowship-trained laryngologist, with no evidence of airway obstruction or previous asthma diagnosis, were included. Evidence of airway obstruction was defined as PFT data of forced expiratory volume in 1 second (FEV1) < 80% and FEV1/forced vital capacity (FVC) < lower limit of normal. Additional inclusion criteria were no history of lung diseases, including asthma, and normal vocal fold structure.

The participants in the asthma-only group were recruited from The University of Pittsburgh Comprehensive Lung Center, an outpatient pulmonology center. Asthma-only participants were included if they had been previously diagnosed with asthma, defined as having a history of PFT bronchodilator response >12% or bronchoconstriction on methacholine challenge test (PC20 >20%) or both. Additional inclusion criteria were symptomatic asthma defined as receiving an Asthma Control Questionnaire score  $\geq 1.0$ <sup>33</sup> on enrollment; no clinical evidence of PVFMD; and no evidence of dysphonia, upper airway symptoms, chronic cough, or dyspnea not explained by asthma. All patients with asthma only were evaluated and diagnosed by a fellowship-trained pulmonologist.

Both groups completed two comprehensive respiratory questionnaires to evaluate the ability to discriminate between asthma and PVFMD. The questionnaires used were the PVFMD Screening Questionnaire developed by the senior author and the Dyspnea Index (DI).<sup>34</sup> The PVFMD Screening Questionnaire has 22 symptom-based questions partially derived from items discarded during the validation of the DI, which was conducted in 200 consecutive patients who underwent laryngoscopy for evaluation of vocal fold disorders. Each question was formatted on a four-point Likert scale (eg, "I get hoarse when I cough"; 1 = never; 2 = some of the time; 3 = very frequently; and 4 = all the time). The DI is a validated, widely used, 10-item question-

naire on breathing symptoms.<sup>34</sup> The DI was developed as a way to assess dyspnea symptom severity and as an outcome measure for participants undergoing treatment for PVFMD. It has not been previously assessed for sensitivity of differentiating PVFMD from asthma. Each question is formatted using a five-point Likert scale (eg, "I have trouble getting air in": 0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always).

Participants also completed three previously validated comorbidity questionnaires (Reflux Symptom Index [RSI],<sup>35</sup> Sino-Nasal Questionnaire [SNQ],<sup>36</sup> and Voice Handicap Index-10 [VHI-10]<sup>37</sup>) to compare the rates of comorbidities between groups and to assess if scores on these questionnaires could differentiate between the patient groups. Responses to each item in these questionnaires can be answered using Likert scales as mentioned previously. The RSI assessed the severity of patients' laryngopharyngeal reflux symptoms as well as their variance with treatment, whereas VHI-10 assessed the impact of voice problems and limitations on overall daily function. Higher scores suggested more severe symptoms or higher impact on functionality. SNQ screened for chronic rhinosinusitis. Participants were considered to have laryngopharyngeal reflux if their RSI is >13,<sup>35</sup> rhinosinusitis if SNQ is  $\geq 1$ ,<sup>36</sup> and a voice handicap if VHI-10 is >11.<sup>38</sup>

### Statistical analyses

All analyses were performed in *Stata* 14.0 (StataCorp., College Station, TX). The population was divided into the following two groups: participants with PVFMD only and participants with asthma only. Descriptive statistics were used to summarize participant demographics. The number of participants identified as having any combination of laryngopharyngeal reflux, rhinosinusitis, or a voice handicap as a result of a voice disorder was tabulated based on responses to the RSI, the SNQ, and the VHI-10. Continuous variables (including scores from the questionnaires) were compared with Kruskal-Wallis test and categorical variables with Fisher exact test between two groups.

For initial validation of the PVFMD Screening Questionnaire, comparison of the 22-item responses between the PVFMD-only group and the asthma-only group was performed. Kruskal-Wallis was used to compare the differences in the mean item scores to determine whether the items detected differences between the two groups. After testing for multivariate normal distribution, an exploratory factor analysis with principal factor approach was used to propose a symptom-based scoring system to differentiate PVFMD from asthma. The significant questions were combined to form factors based on how each combination of questions best allocated participants into the correct group. Factors with eigenvalue greater than 1 were selected for further screening because they correlated with more variance in the data than a single item in the questionnaire. The principal factor correlated with the biggest difference between asthma and PVFMD. The unaccounted or residual difference was accounted by the second principal factor. The exploratory factor analysis continued as such until all the difference or variance between asthma and PVFMD was accounted. An orthogonal rotation was used to select the items with factor loading  $\geq 0.3$  and cross-loading  $\leq 0.2$  to avoid factors correlating with each other

**TABLE 1.**  
**Patient Characteristics**

|                                        | PVFMD<br>n = 22  | Asthma<br>n = 28–30 | P Value |
|----------------------------------------|------------------|---------------------|---------|
| <b>Demographics</b>                    |                  |                     |         |
| Female, n (%)                          | 11 (50)          | 22 (73)             | 0.1     |
| Age (y), median (IQR)                  | 50 (33–56)       | 42 (32–51)          | 0.4     |
| White, n (%)                           | 22 (100)         | 15 (50)             | <0.001* |
| BMI (kg/m <sup>2</sup> ), median (IQR) | 28.2 (24.1–34.7) | 31.4 (24.5–40.2)    | 0.2     |
| <b>Comorbidities</b>                   |                  |                     |         |
| Laryngopharyngeal reflux, n (%)        | 17 (77)          | 15 (54)             | 0.1     |
| Rhinosinusitis, n (%)                  | 13 (59)          | 18 (64)             | 0.8     |
| Voice handicap, n (%)                  | 11 (50)          | 8 (29)              | 0.2     |

\*  $P < 0.05$  was considered statistically significant.

Abbreviations: BMI, body mass index; IQR, interquartile range.

and to identify only the questions that have highest reliability in distinguishing PVFMD from asthma.

On the basis of factor analysis, the discrimination ability of selected factors was assessed by receiver operating characteristics (ROC) curve. The factor with the highest area under the curve (AUC), or discriminatory ability, was selected to reduce the items to a one-factor questionnaire. Scores for each study participant were calculated to estimate how well the factor correlated with a PVFMD or asthma diagnosis. This similar procedure was conducted for the DI, the VHI-10, the RSI, and the SNQ.

## RESULTS

### Study population

The study population consisted of two groups: (1) participants with PVFMD only ( $n = 22$ ), and (2) participants with asthma only ( $n = 30$ ). No differences in sex were found, which contrasts with previous data that suggested a predominance of PVFMD in women.<sup>16</sup> Participants in each group were not significantly different in age or body mass index, as summarized in Table 1. PFT values for participants with asthma only are listed in Table 2.

### VALIDATION OF THE PVFMD SCREENING QUESTIONNAIRE

Two rounds of exploratory factor analyses were completed to select 15 out of 22 items from the PVFMD questionnaire. These items formed four different factors as summarized in Table 3. The factor with the highest AUC (0.88 [0.79–0.97]) was used to reduce the 22-item questionnaire to 15 items. These items focus on describing the frequency of characteristic coughs and sensations of breathing. Based on beta coefficients, weights for the final score were assigned to each item to maximize the questionnaire's discriminatory ability between asthma and PVFMD.

Each factor was also used to determine the median scores of each group as summarized in Table 4. Factor 3, the factor with the highest AUC (0.88), also shows statistical significance for distinguishing between PVFMD and asthma ( $P < .001$ ). Participants with a diagnosis of PVFMD only had a median score of  $-1.6$  ( $-2.1$  to  $-0.9$ ), whereas those with asthma only had a median score of  $0.1$  ( $-0.9$  to  $0.8$ ).

The resulting scoring system for distinguishing PVFMD from asthma was tested at different cutoffs, with the results shown in Table 5. A PVFMD Screening Questionnaire cutoff of  $\geq -1.17$  gave a sensitivity of 89% and a specificity of 73% for diagnosing asthma. This cutoff score was considered the most optimal cutoff score to distinguish PVFMD from asthma given the balance of sensitivity and specificity. ROC curves for the PVFMD Screening Questionnaire and DI (AUC = 0.88 and 0.62, respectively) are depicted in Figures 1 and 2. The ROC curve for the PVFMD Screening Questionnaire is above the standard curve, whereas the ROC curve for DI falls below, corresponding to a lower AUC.

### APPLICATION OF THE SCORING SYSTEM

The effectiveness in screening for PVFMD or asthma was tested by applying a cutoff score of  $-1.7$  to the participants in this study using the 15-item PVFMD Questionnaire seen in Table 6. By using our scoring system, 13 out of 22 (59%) participants were correctly screened for PVFMD, whereas 25 out of 28 (90%) participants were correctly screened for asthma.

**TABLE 2.**  
**PFT Value in Patients With Asthma (All Values are Median and IQR)**

|                            | n = 15–30     |
|----------------------------|---------------|
| ACQ                        | 2.0 (1.7–2.7) |
| <b>Pre-challenge test</b>  |               |
| FEV1%                      | 72 (64–87)    |
| FVC%                       | 79 (74–97)    |
| FEV1/FVC%                  | 67 (62–88)    |
| <b>Post-challenge test</b> |               |
| FEV1%                      | 80 (74–97)    |
| FVC%                       | 90 (83–106)   |
| FEV1/FVC%                  | 72 (65–91)    |
| <b>Changes %</b>           |               |
| FEV1                       | 16 (11–21)    |
| FVC                        | 8 (3–13)      |
| FEV1/FVC                   | 5 (3–8)       |

Abbreviations: ACQ, Asthma Control Questionnaire; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

**TABLE 3.**  
Beta Coefficients for the 15 Items of the PVFMD Screening Questionnaire Generated by Exploratory Factor Analysis Orthogonal Rotation

|                                                                                              | Factors             |                     |                     |                     |
|----------------------------------------------------------------------------------------------|---------------------|---------------------|---------------------|---------------------|
|                                                                                              | 1                   | 2                   | 3                   | 4                   |
| <b>Cough Symptoms</b>                                                                        |                     |                     |                     |                     |
| 1. I get hoarse when I cough.                                                                | −0.02               | −0.06               | −0.29               | 0.04                |
| 2. I have tightness in my throat when I cough.                                               | −0.01               | 0.04                | −0.22               | −0.11               |
| 3. My cough is worse when I yell or laugh.                                                   | −0.01               | 0.07                | 0.15                | 0.69                |
| 4. Strong smells (perfumes, cleaning supplies, others) make me cough.                        | 0.51                | −0.07               | −0.02               | −0.36               |
| 5. Second-hand smoke makes me cough.                                                         | −0.12               | −0.23               | −0.20               | −0.17               |
| 6. If I relax, my cough goes away.                                                           | 0.03                | −0.06               | −0.03               | 0.41                |
| <b>Breathing symptoms</b>                                                                    |                     |                     |                     |                     |
| 7. When I am having breathing problems, I feel like I am breathing through a straw.          | −0.27               | −0.27               | −0.12               | −0.06               |
| 8. When I am having breathing problems, I have trouble getting the air in.                   | −0.06               | −0.06               | −0.25               | −0.29               |
| 9. When I am having breathing problems, albuterol spray makes me feel better.                | −0.31               | −0.31               | 0.45                | −0.03               |
| 10. When I am having breathing problems, albuterol nebulizations make me feel better.        | 0.03                | 0.03                | 0.32                | 0                   |
| 11. When I am having breathing problems, stress makes my breathing worse.                    | −0.05               | −0.05               | −0.05               | 0.03                |
| 12. If I relax, my shortness of breath goes away.                                            | −0.27               | −0.27               | −0.18               | 0.39                |
| 13. Strong smells (perfumes, cleaning supplies, others) cause my throat to close or tighten. | 0.04                | 0.04                | 0.08                | 0.13                |
| 14. Strong smells (perfumes, cleaning supplies, others) make me feel out of breath.          | 0.63                | 0.63                | 0.02                | −0.03               |
| 15. Cold air makes me feel out of breath.                                                    | −0.07               | −0.07               | −0.04               | −0.20               |
| <b>AUC (95% CI)</b>                                                                          | 0.64<br>(0.47–0.80) | 0.23<br>(0.10–0.36) | 0.88<br>(0.79–0.97) | 0.30<br>(0.15–0.45) |

**TABLE 4.**  
Median (interquartile range) of factors score in PVFMD and asthma group

|                    | F1                 | F2                | F3                  | F4                |
|--------------------|--------------------|-------------------|---------------------|-------------------|
| Median (IQR) Score |                    |                   |                     |                   |
| PVFMD (n = 22)     | −0.8 (−1.3 to 0.5) | 0.8 (0.3–1.7)     | −1.6 (−2.1 to −0.9) | 0.9 (0.1–1.3)     |
| Asthma (n = 28)    | 0.0 (−0.6 to 0.5)  | 0.0 (−0.6 to 0.6) | 0.1 (−0.9 to 0.8)   | 0.1 (−0.5 to 0.7) |
| P value            | 0.1                | 0.001             | <0.001              | 0.01              |

### COMORBIDITY ANALYSIS

Participants in the PVFMD-only group had higher median RSI, VHI-10, and DI scores than those in the asthma-only group, although these differences were not statistically significant (Table 7).

**TABLE 5.**  
Performance characteristics of the PVFMD Questionnaire at different cutoff points

|                    | Sensitivity | Specificity |
|--------------------|-------------|-------------|
| Score $\geq$ −1.65 | 96          | 45          |
| Score $\geq$ −0.71 | 71          | 86          |
| Score $\geq$ −0.18 | 61          | 95          |
| Score $\geq$ 0.92  | 25          | 95          |

Analysis of ROC curves was applied to the comorbidity questionnaires, RSI, VHI-10, and SNQ, to evaluate their ability to identify PVFMD (Figure 3). These questionnaires' AUCs were 0.62 for RSI, 0.62 for VHI-10, and 0.36 for SNQ. RSI and VHI-10 had AUC similar to that of DI. VHI-10 performed better than DI in identifying PVFMD.

### DISCUSSION

The current study represents the first time patient-symptom questionnaires have shown utility in differentiating PVFMD from asthma. Specifically, results show that 15 questions from the PVFMD Screening Questionnaire represent one factor, with each question in that factor having a different weight. When these weights are applied to a patient's numeric responses on the

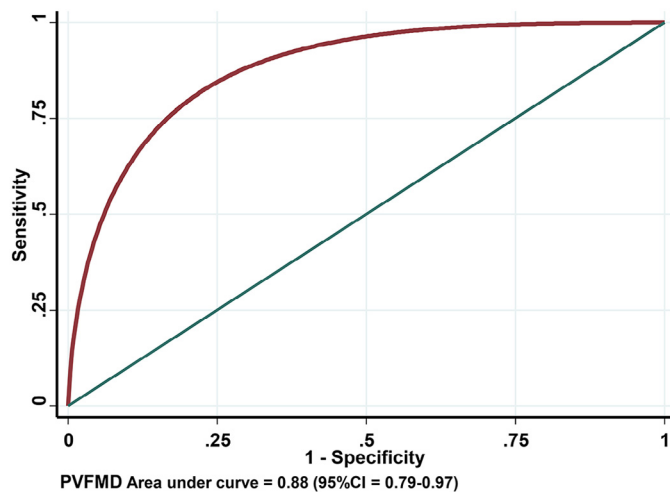


**FIGURE 1.** Receiver operating characteristic curves for the PVFMD Questionnaire.

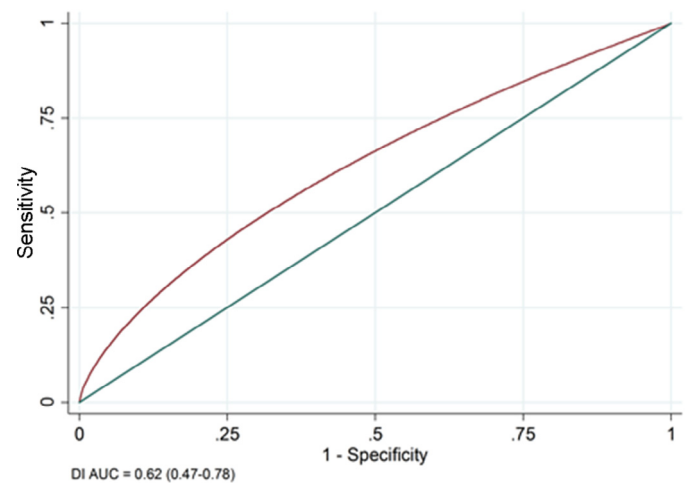


**FIGURE 2.** Receiver operating characteristic curve for the Dyspnea Index to diagnose PVFMD.

questionnaire, the tool can help discriminate between PVFMD and asthma, potentially avoiding the costs of misdiagnosis.

The current study builds upon the work of Traister et al.<sup>39</sup> That author group completed a retrospective review of medical records of patients they had diagnosed with asthma and PVFMD to gather patient-reported symptoms and comorbidities in these groups. They determined that the patient symptoms most associated with

PVFMD were throat tightness, reflux, dysphonia, and the presence of an odor trigger. The current study used validated instruments designed to formally assess the severity of these symptoms (eg, VHI-10, RSI, DI) and applied a new instrument, validated as part of this investigation (PVFMD Screening Questionnaire) to determine the ability of these questionnaires to differentiate patients with PVFMD and asthma. Further, our prospective study using exploratory factor analysis adds

**TABLE 6.**  
**The PVFMD Screening Questionnaire**

Instructions: Each Question Has Four Options That Relate to How Frequently You May Experience the Condition Asked on Each Question. Please Choose the Option That Most Closely Matches What You Feel.

| 1 = Never; 2 = Some of the Time; 3 = Very Frequently; 4 = All the Time |                                                                                          |   |   |   |   | Score                   |
|------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---|---|---|---|-------------------------|
| 1.                                                                     | I get hoarse when I cough.                                                               | 1 | 2 | 3 | 4 | Response * -0.29 = ____ |
| 2.                                                                     | I have tightness in my throat when I cough.                                              | 1 | 2 | 3 | 4 | Response * -0.22 = ____ |
| 3.                                                                     | My cough is worse when I yell or laugh.                                                  | 1 | 2 | 3 | 4 | Response * 0.15 = ____  |
| 4.                                                                     | Strong smells (perfumes, cleaning supplies, others) make me cough.                       | 1 | 2 | 3 | 4 | Response * -0.02 = ____ |
| 5.                                                                     | Second hand smoke makes me cough.                                                        | 1 | 2 | 3 | 4 | Response * -0.2 = ____  |
| 6.                                                                     | If I relax, my cough goes away.                                                          | 1 | 2 | 3 | 4 | Response * -0.03 = ____ |
| 7.                                                                     | When I am having breathing problems, I feel like I am breathing through a straw.         | 1 | 2 | 3 | 4 | Response * -0.12 = ____ |
| 8.                                                                     | When I am having breathing problems, I have trouble getting the air in.                  | 1 | 2 | 3 | 4 | Response * -0.25 = ____ |
| 9.                                                                     | When I am having breathing problems, albuterol spray makes me feel better.               | 1 | 2 | 3 | 4 | Response * 0.45 = ____  |
| 10.                                                                    | When I am having breathing problems, albuterol nebulizations make me feel better.        | 1 | 2 | 3 | 4 | Response * 0.32 = ____  |
| 11.                                                                    | When I am having breathing problems, stress makes my breathing worse.                    | 1 | 2 | 3 | 4 | Response * -0.05 = ____ |
| 12.                                                                    | If I relax, my shortness of breath goes away.                                            | 1 | 2 | 3 | 4 | Response * -0.18 = ____ |
| 13.                                                                    | Strong smells (perfumes, cleaning supplies, others) cause my throat to close or tighten. | 1 | 2 | 3 | 4 | Response * 0.08 = ____  |
| 14.                                                                    | Strong smells (perfumes, cleaning supplies, others) make me feel out of breath.          | 1 | 2 | 3 | 4 | Response * 0.2 = ____   |
| 15.                                                                    | Cold air makes me feel out of breath.                                                    | 1 | 2 | 3 | 4 | Response * -0.04 = ____ |

**Total Score:**

Scores < -1.17 favors PVFMD

Scores ≥ -1.17 favors asthma

**TABLE 7.**  
**Median (Interquartile Range) of Responses to Different Questionnaires by Group**

|                    | RSI        | VHI-10          | SNQ         | DI         | PVFMD |
|--------------------|------------|-----------------|-------------|------------|-------|
| PVFMD (n = 22)     | 23 (16–28) | 13.5 (1.0–24.0) | 1 (0.4–1.2) | 24 (19–32) |       |
| Asthma (n = 29–30) | 14 (5–27)  | 3.5 (0.0–12.0)  | 1 (0.8–1.6) | 22 (18–26) |       |
| <i>P</i> value     | 0.15       | 0.10            | 0.16        | 0.22       |       |

additional cough symptoms, inspiratory symptoms, and alleviating and aggravating factors as significant variables to better characterize the symptoms of PVFMD. These variables used to develop the Pittsburgh PVFMD Questionnaire with the chosen cutoff score of  $-1.7$  improve sensitivity to 85% in exchange for a specificity of 73%. Further, unlike the study by Traister et al, our study enrolled patients with symptomatic asthma and untreated patients with PVFMD. Studying poorly controlled subjects with asthma in contrast with patients with symptomatic PVFMD provides the advantage of discriminating asthma and PVFMD without interference from treatment. Finally, similar to our study, the asthma patients in the study by Traister et al did not undergo laryngoscopy; however, in contrast to our study, although their patients with PVFMD underwent laryngoscopy, they were not evaluated by a laryngologist or speech-language pathologist.

The current gold standard for PVFMD diagnosis, laryngoscopy, is limited in diagnostic utility partly by the transient and intermittent nature of PVFMD. Therefore, it is important to develop a diagnostic tool that does not rely solely on direct visualization of paradoxical vocal fold motion. Recent studies have focused on voice quality impairments<sup>40,41</sup>; vocal fold abduction angle during exercise<sup>42</sup>; dynamic CT<sup>43,44</sup>; lung sound analysis<sup>45</sup>; and scoring systems based on symptoms, comorbidities, PFT data, and physical examination findings<sup>39,46</sup> as possible diagnostic tools.

The 15 items from the PVFMD Screening Questionnaire join the tools in these recent studies to guide the primary care provider, as well as specialists, toward appropriate additional diagnostic work-up and treatment in suspected PVFMD. Early recognition and treatment of PVFMD can avoid the significant economic and personal costs of misdiagnosis and mistreatment as refractory asthma.

### Comorbidity assessment

Patients in the PVFMD-only group scored higher on both the VHI-10 and the RSI compared with the asthma-only group, suggesting that those with PVFMD have more severe voice impairment. The PVFMD-only group's responses also met the threshold for the presence of a voice problem (VHI-10 > 11), whereas the asthma-only group did not. These findings are consistent with previous studies with PVFMD subjects having significant voice impairment compared with healthy subjects.<sup>40,47</sup> Although our findings are not statistically significant, they are clinically significant in their implications for those with PVFMD having poorer voice quality. The lack of statistical significance despite compelling, large descriptive differences may be owing to a small sample size and therefore, a type 2 error. The deterioration of voice quality may be the result of comorbid diseases interfering with phonation or the ability of vocal folds to vibrate.<sup>40</sup>

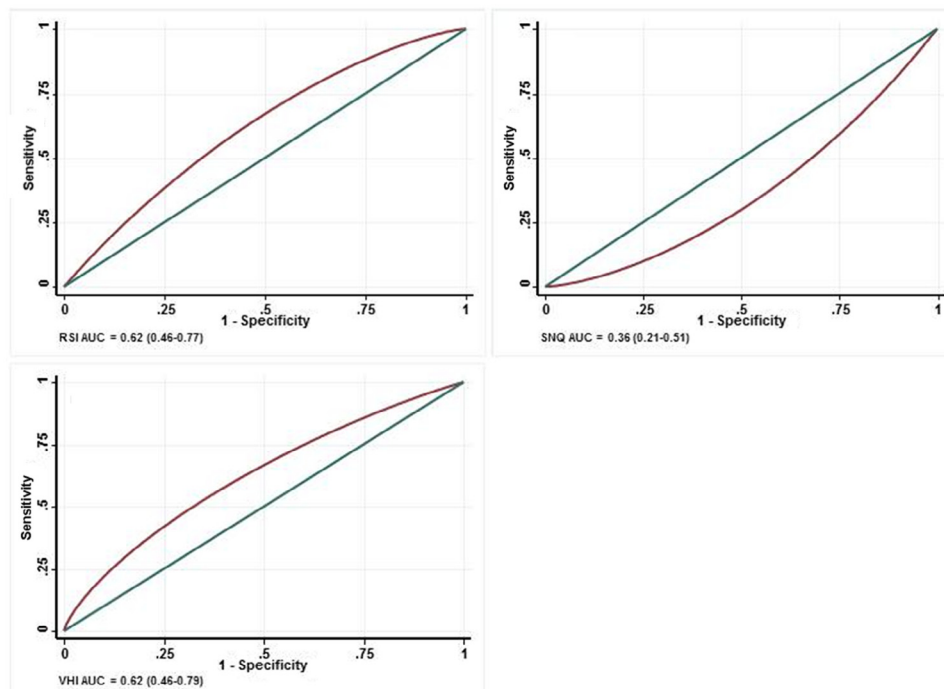


**FIGURE 3.** Receiver operating characteristic curves for three comorbidity questionnaires.

Voice impairment has also been speculated to be a result of vocal fold edema from reflux or the trauma of coughing.<sup>48</sup>

The participants with PVFMD only in this study also had higher RSI scores, suggesting that their laryngopharyngeal reflux symptoms are more severe than that of patients with asthma only and the general population. The proposed laryngeal hyper-responsiveness and laryngeal inflammation in laryngopharyngeal reflux (LPR)<sup>49</sup> may be a contributing factor to the upper airway symptoms of PVFMD. Because both voice handicap and LPR are related to laryngeal or upper airway maladies, it is intuitive that individuals with a laryngeal-based breathing disorder, such as PVFMD, would experience increased voice and LPR-related symptoms than an individual with a lower airway disorder, such as asthma. With these commonalities and comorbidities co-existing, clinicians may be able to use VHI-10 scores with PVFMD Screening Questionnaire scores to guide referrals to a laryngology clinic for further work-up of suspected PVFMD.

### Limitations

The current study has several limitations. First, the gold standard for PVFMD diagnosis remains to be flexible laryngoscopy. The PVFMD Screening Questionnaire currently does not replace flexible laryngoscopy. Instead, its primary purpose is to guide the application of laryngoscopy, or referral to a laryngology clinic in individuals suspected to have PVFMD. Second, although the PVFMD Screening Questionnaire helps distinguish PVFMD from asthma, approximately 30% of patients with PVFMD may have coexisting asthma.<sup>31,32</sup> Consequently, our scoring system may not be able to distinguish isolated PVFMD from PVFMD coexisting with asthma. To that end, further clinical work-up for additional diagnoses, such as asthma, remains an important part of clinical decision-making if patients with suspected PVFMD only do not improve with treatment. Additional studies testing the scoring system in individuals with confirmed coexisting PVFMD and asthma are warranted. In addition, the isolated asthma group did not undergo flexible laryngoscopy to rule out PVFMD. The recruited participants, however, did not have a clinical history or previous data that suggested PVFMD. It will be important for future studies to address this concern by performing laryngoscopies on this population. Lastly, this study is also limited by its study size. Conducting a factor analysis of a questionnaire this size (22 questions) requires approximately 150 participants. As a rule of thumb, the smallest sample size should be at least four or five times the number of items in the questionnaire, preferably a 10 to 1 subject-to-item ratio.<sup>50</sup> Future validation studies will need to address this limitation by having a larger study size for a more robust factor analysis of the PVFMD Screening Questionnaire.

### CONCLUSION

In summary, we attempted to develop a new test aimed at discriminating PVFMD from asthma. First, validation of the PVFMD Screening Questionnaire was completed. Factor analysis was used to identify 15 out of 22 items, selected based on their significant contribution to the summary score, for the final questionnaire. Next, each participant's scores were used to calculate the sensitivity and specificity for each factor to identify asthma compared

with PVFMD. This process is similar to calculating, for example, the diagnostic ability of blood sugar for diabetes. The factor with the best diagnostic ability (area under ROC curve) was proposed as the best test to differentiate between these two conditions. The same process (area under ROC curve) was completed for the VHI-10, the RSI, the DI, and the SNQ; however, these questionnaires had low AUCs and were deemed not diagnostic. The final weighted 15 items of the PVFMD Screening Questionnaire is the first patient symptom-based scoring system developed for distinguishing PVFMD from asthma. It has the potential to guide referrals toward otolaryngology clinics for more detailed PVFMD work-up, or to pulmonology clinics for asthma evaluation. Earlier and more accurate diagnosis could ultimately decrease health-care utilization among those with PVFMD.

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