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Sensitivity, Specificity, and Predictive Values of Laryngopharyngeal Reflux Symptoms and Signs in Clinical Practice

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Abstract

Objective. To investigate the sensitivity (SE), specificity (SP), and positive and negative predictive value (PPV and NPV) of symptoms and signs of laryngopharyngeal reflux (LPR).

Study Design. Prospective controlled.

Setting. University medical center.

Methods. Patients presenting with LPR symptoms and signs were consecutively included after diagnosis confirmation through 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance–pH monitoring. Healthy individuals were recruited to compose a control group. Symptoms and signs were evaluated with the reflux symptom score and reflux sign assessment. The SE, SP, PPV, and NPV of symptoms and signs were assessed.

Results. The study included 403 patients with LPR and 144 healthy individuals. Throat clearing, globus sensation, heartburn, and excess throat mucus were symptoms with the highest SE (67.5%-69.7%), SP (12.5%-20.8%), and NPV (48.3%-49.2%). The combination of throat clearing, heartburn, globus sensation, and excess throat mucus led to a high SE (96.0%) and NPV (85.2%). Anterior pillar erythema, tongue tonsil hypertrophy, and posterior commissure hypertrophy resulted in the highest SE (75.5%-83.5%). The highest SP was found for uvula erythema/edema, epiglottis erythema, and interarytenoid granulatory tissue (97.1%-97.2%). The association of nonendoscopic signs (anterior pillar erythema, uvula erythema/edema, and coated tongue) had an SE and SP of 80.1% and 47.2%, respectively. The association of throat clearing, heartburn, globus, anterior pillar erythema, and uvula erythema/edema had the highest SE (98.8%), SP (33.3%), PPV (94.3%), and NPV (70.6%).

Conclusion. LPR symptoms and signs reported low SP and NPV. The SE, SP, PPV, and NPV may be maximized with the association of throat clearing, heartburn, globus sensation, anterior pillar erythema, and uvula erythema/edema.

Keywords

laryngeal, laryngopharyngeal, reflux, gastroesophageal, symptoms, signs, voice, diagnosis, otolaryngology, laryngology, head neck

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Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effect of gastroduodenal content reflux, which induces morphologic changes in the upper aerodigestive tract.[1] The main symptoms of reflux consist of globus sensation, throat clearing, pharyngeal sticky mucus, dysphonia, and throat pain.[1-3] The findings associated with LPR include arytenoid erythema, posterior commissure hypertrophy, oropharyngeal erythema, or coated tongue.[1-3] LPR symptoms concern 1% to 10% of the general population of Western countries and up to 30% of outpatients consulting in ear, nose, and throat departments.[4,5] The LPR diagnosis remains clinically difficult because gastroesophageal reflux disease (GERD) symptoms are often lacking.[1,2] Moreover, LPR symptoms and signs are nonspecific and may be encountered in many common otolaryngologic conditions, such as chronic rhinosinusitis,[6] allergy,[7] tobacco laryngopharyngitis,[8] or vocal fold benign lesions.[9] The recent development of the 22-item reflux symptom score (RSS) may lead to the study of most LPR symptoms, which were previously not considered in patient-reported outcome questionnaires (eg, throat pain, halitosis, odynophagia, regurgitation).[1,10]

The best LPR diagnosis approach remains the use of hypopharyngeal-esophageal multichannel intraluminal impedance–pH monitoring (HEMII-pH), but to date, this costly approach is not available in all centers, making the clinical presentation the more practical diagnostic way.[11]

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The aim of this study was to assess the sensitivity (SE), specificity (SP), and predictive values of the symptoms and signs associated with LPR.

Methods

Subjects and Setting

From September 2017 to January 2022, patients with LPR symptoms (ie, globus sensation, throat clearing, dysphagia, cough, or burning mouth) and a diagnostic confirmation at the 24-hour HEMII-pH were prospectively recruited from the European Reflux Clinic. According to findings of the literature,[12] the LPR diagnosis was based on the occurrence of >1 acid, weakly acid, or nonacid hypopharyngeal reflux event. All patients underwent HEMII-pH irrespective of their history (acute, recurrent, or chronic reflux symptoms). Gastrointestinal (GI) endoscopy was proposed to patients with GI symptoms or elderly persons (age >55 years). Indeed, according to the aging process, elderly patients may have esophageal lesions without symptoms.[13]

Healthy volunteers were recruited by advertisement and did not have any esophageal or laryngeal symptoms over the past 12 months. Patients and controls with the following outcomes were excluded: active smoking with laryngopharyngitis, alcoholism (>3 glasses/d), an upper respiratory tract infection within the 3 last months, neurologic or psychiatric illness, head and neck malignancy, head and neck radiotherapy, inhaled corticosteroid intake, active seasonal allergies, asthma, or intake of inhaled corticosteroids or antireflux medication at the time of inclusion. Patients had to consent to participate to the study, and the ethics committee approved the protocol (CHU Saint-Pierre; BE076201837630). The STROBE statement was followed for the present study.

Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance–pH Monitoring

The HEMII-pH probe placement and composition were reported in previous studies[10] and respect some recent recommendations.[11] The catheter was composed of 8 impedance ring pairs and 2 pH electrodes (Versaflex Z, LPR ZNID22+8R FGS 9000-17, Digitrapper pH-Z Testing System; Medtronic). Six impedance segments were placed along the esophagus zones (Z1-Z6) below the upper esophagus sphincter. The 2 additional impedance segments were placed 1 and 2 cm above the upper esophagus sphincter in the hypopharyngeal cavity. The LPR diagnosis was confirmed in patients with >1 hypopharyngeal reflux event.[11] A hypopharyngeal reflux event was defined as an episode that reached 2 hypopharyngeal impedance sensors. Acid reflux event was defined as an episode with pH ≤4.0. Nonacid reflux consisted of a pharyngeal reflux event with pH >4.0. HEMII-pH tracing was electronically analyzed by the software, and the result was verified by 2 senior physicians. Acid LPR was defined when the ratio of the number of acid pharyngeal events to the number of nonacid events was >2. LPR was defined as nonacid or alkaline when the ratio of the number of acid events to the number of nonacid events was <0.5. Mixed or weakly acid reflux consisted of a ratio ranging from 0.51 to 2.0. GERD diagnosis was made per the Lyon guidelines.[14] Importantly, HEMII-pH was performed after patients stopped taking a proton pump inhibitor and alginate (Gaviscon) for 1 to 2 weeks. The Lyon guidelines proposed conclusive evidence for reflux in case of advanced-grade erosive esophagitis (Los Angeles grades C and D), long-segment Barrett mucosa, or peptic strictures on GI endoscopy. Distal esophageal acid exposure time >6% may be consistent with a GERD diagnosis.[14]

Symptoms and Findings

Because LPR may be associated with otolaryngologic, digestive, or respiratory symptoms, LPR symptoms were evaluated with the full version of the RSS.[10] Findings were rated with the reflux sign assessment (RSA) considering oral signs (anterior pillar/uvula erythema, coated tongue), laryngeal signs (endolaryngeal sticky mucus; edema/erythema of posterior commissure, retrocricoid epiglottis, ventricular band, and vocal fold regions), and pharyngeal signs (erythema of oropharyngeal wall, edema of base of tongue, and pharyngeal sticky mucus).[15] At the time of the finding assessment, patients were not being treated with a proton pump inhibitor and alginate for 4 to 5 weeks. The assessment of signs was performed by 2 laryngologists in a blind manner with videolaryngostroboscopy (StrobeLED-CLL-S1; Olympus Corporation). According to a recent study, the 2 laryngologists reported an adequate interclass coefficient ($r = 0.663$).[15] The same material and methods were used for the healthy evaluations.

Statistical Methods

Statistical analyses were performed with SPSS for Windows (version 24.0; IBM Corp). The SE, SP, positive and negative predictive value (PPV and NPV) of symptom and finding were evaluated considering the LPR definition (HEMII-pH). Cumulative SE, SP, PPV, and NPV were assessed with a combination of symptoms and findings with the highest SE.

A multivariate linear model was performed to predict the RSS by using the signs and RSA total score and subscores as predictor variables. We assessed multicollinear variables and excluded vocal fold lesions from the model (last item of the RSA). Furthermore, a Spearman correlation coefficient was computed to test for the magnitude of the relationship between the RSS and RSA after a Shapiro-Wilk evaluation. A level of significance of $P < .05$ was used.

Results

A total of 403 patients with positive HEMII-pH results were prospectively recruited (age, 18-90 years). A control group of 144 healthy subjects with an RSS <13 and RSA <14 was composed (age, 18-73 years). There were 103 (57%) women in the LPR group and 102 (71%) in the control group. The mean ± SD body mass index was 22.2 ± 2.7 and 21.0 ± 3.1 for patients with LPR and healthy individuals, respectively. The LPR and control groups were comparable. The epidemiologic and clinical features of patients are available in **Table I**.

Table 1. Epidemiologic and Clinical Features of 403 Patients With Laryngopharyngeal Reflux.[a]

Characteristic	Mean ± SD or No. (%)
Body mass index	25.2 ± 5.0
Sex	
Male	174 (43)
Female	228 (57)
Gastrointestinal endoscopy (n = 165)	
Normal	62 (38)
Esophagitis	97 (59)
Hiatal hernia	60 (36)
Lower esophageal sphincter insufficiency	90 (55)
Gastritis	77 (47)
Helicobacter pylori infection	16 (10)
HEMII-pH feature	
Pharyngeal acid reflux episodes	12.4 ± 16.5
Pharyngeal nonacid reflux episodes	21.9 ± 42.8
Pharyngeal reflux episodes upright	33.5 ± 46.3
Pharyngeal reflux episodes supine	5.5 ± 11.9
Pharyngeal reflux episodes (total)	34.5 ± 47.9
GERD	
Patients	180 (45)
Percentage of time with distal pH <4	5.3 ± 9.2
DeMeester score	18.9 ± 31.0

Abbreviations: GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance–pH monitoring.
[a]Age range, 18-90 years.

GI endoscopy was performed in 165 patients and had the following outcomes: esophagitis (59%), lower esophageal sphincter insufficiency (55%), gastritis (47%), and hiatal hernia (36%). The GI endoscopy outcome was unremarkable in 38% of cases. GERD was found in 180 (45%) patients. The HEMII-pH findings are described in **Table 1**. Hypopharyngeal reflux events mainly occurred upright and were nonacid events. Symptoms and findings of LPR were available in 403 and 357 patients, respectively (**Tables 2** and **3**). The most prevalent symptoms associated with LPR were throat clearing (70%), heartburn (69%), globus pharyngeus sensation (68%), and excess throat mucus (67%). The most prevalent findings were anterior pillar erythema (84%), tongue tonsil hypertrophy (78%), and posterior commissure hypertrophy (76%; **Table 3**). There were no significant differences in symptom and sign prevalence according to the presence of GI findings (esophagitis) or the performance of GI endoscopy.

Epidemiologic Outcomes of Symptoms and Signs

Epidemiologic data (SE, SP, PPV, and NPV) of RSS symptoms are presented in **Table 4**. The highest SE and SP were found for throat clearing, globus sensation, heartburn, and excess throat mucus. Most LPR-associated symptoms had a high PPV but low NPV. Throat clearing, globus sensation, heartburn, and excess throat mucus had the highest NPV.

Table 2. Prevalence of Symptoms in Reflux Cases and Controls.[a]

Symptoms	LPR (n = 403)	Controls (n = 144)
Ear, nose, and throat		
1. Voice disorder	232 (58)	10 (7)
2. Throat pain	240 (60)	12 (8)
3. Pain during swallowing time	173 (43)	12 (8)
4. Dysphagia	181 (45)	8 (6)
5. Throat clearing	281 (70)	30 (21)
6. Globus sensation	275 (68)	19 (13)
7. Excess throat mucus	272 (67)	18 (13)
8. Ear pressure/pain	189 (47)	18 (13)
9. Tongue burning	118 (29)	1 (1)
Digestive		
1. Heartburn	278 (69)	23 (16)
2. Regurgitations or burps	223 (55)	13 (9)
3. Abdominal pain	187 (46)	14 (10)
4. Diarrhea	147 (36)	13 (9)
5. Constipation	155 (38)	14 (10)
6. Indigestion	147 (36)	7 (5)
7. Abdominal distension/flatus	243 (60)	16 (11)
8. Halitosis	210 (52)	12 (8)
9. Nausea	165 (41)	13 (9)
Respiratory		
1. Cough after eating/lying down	205 (51)	9 (6)
2. Cough	227 (56)	17 (12)
3. Breathing difficulties	153 (38)	3 (2)
4. Chest pain	218 (54)	8 (6)

Abbreviation: LPR, laryngopharyngeal reflux.
[a]Symptoms consisted of the items of the reflux symptom score. Data are presented as No. (%).

Statistical analysis revealed that the combination of throat clearing, heartburn, globus sensation, and excess throat mucus led to high SE and NPV (**Table 5**).

Anterior pillar erythema, tongue tonsil hypertrophy, contact between the base of tongue and epiglottis, and posterior commissure hypertrophy had the highest SE (**Table 6**). The highest SP values were for uvula erythema/edema, epiglottis erythema, and interarytenoid granulatory tissue. Some of these findings are described in **Figure 1**. The PPVs of most signs were high, while the highest NPV concerned tongue tonsil hypertrophy, contact between epiglottis and base of tongue, posterior commissure hypertrophy, and anterior pillar erythema. The combinations of various sensitive signs are available in **Table 5**. Associations of anterior pillar erythema, tongue tonsil hypertrophy, and posterior commissure hypertrophy with or without contact between the epiglottis and base of tongue resulted in the highest SE. According to the epidemiologic features of nonendoscopic signs (anterior pillar erythema, uvula erythema/edema, and coated tongue), the association of oral findings was 80.1% SE and 47.2% SP. As shown in the receiver operating characteristic curve, the value

Table 3. Prevalence of Findings: Reflux Sign Assessment.[a]

Item	No. (%)
Oral findings	
1. Anterior pillar erythema	298 (84)
2. Uvula erythema/edema	130 (36)
3. Coated tongue	198 (56)
Pharyngeal findings	
1. Posterior oro- or hypopharyngeal wall erythema	136 (38)
2. Posterior oro- or hypopharyngeal wall inflammatory granulations	103 (29)
3. Tongue tonsil hypertrophy	280 (78)
4. Contact between epiglottis and tongue tonsils	258 (72)
5. Pharyngeal sticky mucus	186 (52)
Laryngeal findings	
1. Epiglottis erythema	222 (62)
2. Ventricular band erythema/edema	230 (64)
3. Commissure posterior/arytenoid erythema	244 (68)
4. Interarytenoid granulatory tissue	60 (17)
5. Posterior commissure hypertrophy	270 (76)
6. Retrocricoid erythema	69 (19)
7. Retrocricoid edema	208 (58)
8. Endolaryngeal sticky mucus deposit	153 (43)

[a]Data are presented as No. (%).

of SP may be improved by combining some items but not all. More details are described in Appendix 1 (available online).

Associations of Symptoms and Findings

The associations between the aforementioned symptoms and signs are available in **Table 5**. The association among throat clearing, heartburn, anterior pillar erythema, and tongue tonsil hypertrophy had a high SE (98.3%), moderate NPV (56.3%), and low SP (25.0%). The highest SE, SP, PPV, and NPV were found for the association of throat clearing, heartburn, globus, anterior pillar erythema, and uvula erythema/edema.

Multivariate analysis revealed a significant positive association between throat clearing and posterior commissure hypertrophy scores ($r_s = 0.111$, $P = .037$). There were no other significant associations among symptoms, signs, or clinical subscores and total scores.

Discussion

The best diagnostic approach for LPR remains the use of HEMII-pH and the demonstration of hypopharyngeal reflux events. Currently, there are many barriers for the use of HEMII-pH in otolaryngologic practice, such as cost,[10] interpretation difficulties,[16] and poor patient tolerance.[17] Awareness of HEMII-pH is an additional barrier because only 5% of otolaryngologists reported adequate knowledge about the indication and usefulness of pH testing for LPR.[16] For these reasons, the LPR diagnosis continues to be mainly based on symptoms and findings and response to empirical therapeutic trial, which is challenging regarding the non-SP of symptoms and findings. Many patient-reported outcome questionnaires[18] and finding instruments[19] were developed to improve the clinical approach. The items were based on physician experience and the prevalence of symptoms and signs in large cohort studies.[18,19] These clinical tools are associated with various values of reliability and validity, but to date, no study has evaluated the epidemiologic parameters (SE, SP, PPV, and NPV) of symptoms, findings, or associations. In the present study, based on a cohort of 403 patients with LPR, we observed that the association of throat clearing, heartburn, globus, anterior pillar erythema, and uvula erythema/edema had the highest SE (98.8%), SP (33.3%), PPV (94.3%), and NPV (70.6%). The importance of these symptoms was supported in the largest cohort studies.[20-22] Lee et al observed that the most prevalent symptoms associated with LPR were globus sensation (89%), throat clearing (82%), and hoarseness (79%).[20] Andersson et al reported significant prevalence of cough (91%), throat clearing (89%), and globus sensation (88%) in their patients with positive pH monitoring.[21] Globus sensation (70%) and throat clearing (47%) were also the most prevalent symptoms in the study of Chappity et al.[22] The data of these studies may support the need to consider globus sensation, throat clearing, and excess throat mucus as the most sensitive symptoms in the clinical diagnostic approach of LPR, but there were substantial methodological differences with the present study. Indeed, these authors did not consider all symptoms of LPR. For example, the prevalence of throat pain, odynophagia, and halitosis was not evaluated in the studies of Lee et al and Chappity et al[20,22] because the authors used incomplete validated or unvalidated patient-reported outcome questionnaires. Moreover, they included patients with a clinical diagnosis of LPR,[20,22] while Andersson et al considered only patients with acid LPR at the pH monitoring.[21] The originality of the present study is the consideration of a large panel of LPR symptoms in patients with a confirmed LPR diagnosis at the HEMII-pH.

Interestingly, we observed that the association of these symptoms with oral findings such as anterior pillar erythema and uvula erythema/edema maximized the SE, SP, and predictive values. These signs are easy to evaluate in clinical practice. The comparison of this observation with the literature is limited because most authors used the reflux finding score,[19,23] which considers only laryngeal findings. In the literature, most studies reported that posterior commissure hypertrophy (43%-89%) and laryngeal erythema (44%-79%) were the most prevalent findings in patients with suspected or confirmed LPR.[1,20,22,24] In this study, laryngeal signs such as posterior commissure hypertrophy or laryngeal erythema had a high but comparable SE than pharyngeal (tongue tonsil hypertrophy) or oral (anterior pillar erythema) findings. In this study, the evaluation of findings was performed by 2 laryngologists exhibiting an adequate interclass coefficient, which is a strength regarding the overall low interrater reliability outcome in previous reflux studies using the reflux finding score.[25,26]

The key role of oral findings is particularly interesting for nonotolaryngologic specialists. Indeed, laryngopharyngeal

Table 4. Sensitivity, Specificity, and Positive and Negative Predictive Values of Symptoms.

	Epidemiologic outcome, %			
Symptom	Sensitivity	Specificity	PPV	NPV
Ear, nose, and throat				
1. Voice disorder	57.6	6.9	95.9	45.7
2. Throat pain	59.6	8.3	89.2	41.3
3. Pain during swallowing time	42.9	8.3	93.5	36.5
4. Dysphagia	44.9	5.6	95.3	38.0
5. Throat clearing	69.7	20.8	90.4	48.3
6. Globus sensation	68.2	13.2	93.5	49.4
7. Excess throat mucus	67.5	12.5	93.8	49.2
8. Ear pressure/pain	46.9	12.5	90.9	37.1
9. Tongue burning	29.3	0.7	99.2	33.4
Digestive				
1. Heartburn	69.0	16.0	92.4	49.2
2. Regurgitations or burps	55.3	9.0	94.9	42.1
3. Abdominal pain	46.4	9.7	93.0	37.6
4. Diarrhea	36.5	9.0	91.9	33.9
5. Constipation	38.5	9.7	91.7	34.9
6. Indigestion	36.5	4.9	95.5	34.9
7. Abdominal distension/flatus	60.3	11.1	93.8	44.4
8. Halitosis	52.1	8.3	94.6	40.1
9. Nausea	40.9	9.0	92.7	35.5
Respiratory				
1. Cough after eating/lying down	50.9	6.3	95.8	40.4
2. Cough	56.3	11.8	93.0	41.9
3. Breathing difficulties	38.0	2.1	98.1	36.1
4. Chest pain	54.1	5.6	96.5	42.4

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 5. Sensitivity, Specificity, and Positive and Negative Predictive Values of Associations of Symptoms and Findings.

	Epidemiologic outcome, %			
Association	Sensitivity	Specificity	PPV	NPV
Symptoms				
Throat clearing + heartburn	91.6	69.4	89.3	74.6
Throat clearing + heartburn + globus	95.3	67.4	89.1	83.6
Throat clearing + heartburn + globus + throat mucus	96.0	63.9	88.2	85.2
Signs				
Pillar erythema + TTH	84.4	30.6	93.2	14.9
Pillar erythema + TTH + PCH	86.4	27.8	93.0	15.4
Pillar erythema + TTH + PCH + tongue tonsil and epiglottis contact	86.8	25.0	92.8	14.5
Pillar erythema + uvula + coated tongue	80.1	47.2	94.4	17.5
Symptoms and signs				
Throat clearing + heartburn + pillar erythema + TTH	98.3	25.0	93.6	56.3
Throat clearing + heartburn + globus + pillar erythema	98.5	33.3	94.2	66.7
Throat clearing + heartburn + globus + pillar erythema + uvula	98.8	33.3	94.3	70.6

Abbreviations: NPV, negative predictive value; PCH, posterior commissure hypertrophy; PPV, positive predictive value; TTH, tongue tonsil hypertrophy.

disease and GERD are prevalent in gastroenterology, pulmonology, and general and internal medicine.[4,27,28] An estimated 1% of general medicine consultations and 10% to 30% otolaryngologic consultations are dedicated to LPR, which supports the need of development of a more cost-effective approach.[1,5,27,28] Thus, the results of the present study may be

Table 6. Sensitivity, Specificity, and Positive and Negative Predictive Values of Reflux Sign Assessment Findings.

Finding: item	Epidemiologic outcome, %			
	Sensitivity	Specificity	PPV	NPV
Oral				
1. Anterior pillar erythema	83.5	50.0	94.3	23.4
2. Uvula erythema/edema	36.4	97.2	99.2	13.4
3. Coated tongue	55.5	88.9	97.0	16.8
Pharyngeal				
1. Posterior oro- or hypopharyngeal wall erythema	38.1	94.4	98.6	13.3
2. Posterior oro- or hypopharyngeal wall inflammatory granulations	28.9	91.7	98.8	11.5
3. Tongue tonsil hypertrophy	78.4	88.9	98.6	29.4
4. Contact between epiglottis and tongue tonsils	72.3	52.8	93.8	16.1
5. Pharyngeal sticky mucus	52.1	75.0	95.4	13.6
Laryngeal				
1. Epiglottis erythema	62.2	97.2	99.6	20.6
2. Ventricular band erythema/edema	64.4	91.7	98.7	20.6
3. Commissure posterior/arytenoid erythema	68.3	83.3	97.6	21.0
4. Interarytenoid granulatory tissue	16.8	97.1	98.4	10.5
5. Posterior commissure hypertrophy	75.6	94.4	99.3	28.1
6. Retrocricoid erythema	19.3	97.1	98.6	10.8
7. Retrocricoid edema	58.3	88.9	98.1	17.7
8. Endolaryngeal sticky mucus deposit	42.9	72.2	93.9	11.3

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

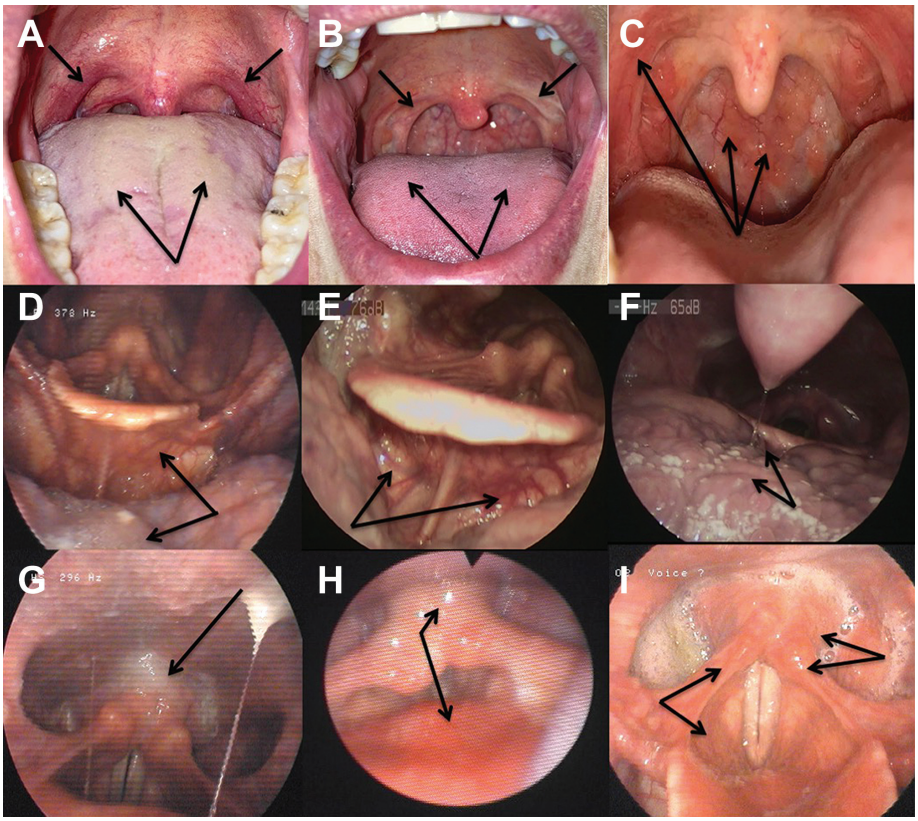

Figure 1. Oral, pharyngeal, and laryngeal findings associated with reflux: (A, C) anterior pillar erythema, (A) coated tongue, (B) lack of coated tongue and pillar erythema, (D) lack of tongue tonsil hypertrophy (nonsticky tongue), (E) visualized vallecula with mild to moderate tongue tonsil hypertrophy (only when tongue was sticky), (F) severe tongue tonsil hypertrophy, (G) retrocricoid edema, (H) posterior commissure hypertrophy, (H, I) epiglottis erythema, and (I) laryngeal erythema.

useful for nonotolaryngologic physicians who have front-line medical consultations.

The low number of healthy participants in the control group is the primary limitation of the study. The recruitment of healthy individuals without otolaryngologic conditions associated with similar symptoms/findings than reflux as the inclusion criteria (RSS <13 and RSA <14) made it difficult to create the control group. Future study needs a power analysis and sample size calculation. Moreover, it was difficult to perform 24-hour pH testing in healthy individuals because of cost and poor tolerance. To limit the risk of inclusion bias in the control group, we selected subjects without comorbidities or clinical conditions that may be associated with laryngopharyngeal symptoms or a high risk of reflux. Moreover, controls were recruited by advertisement, which may involve an inclusion bias related to the individual motivation. The second weakness of the study is the lack of consideration of types of LPR (ie, acid, nonacid, or weakly acid) in the evaluation of epidemiologic parameters.

The main strength of the study is the high number of patients with LPR diagnosed with HEMII-pH. To the best of our knowledge, this is the largest cohort study dedicated to symptoms and findings of patients with LPR. The use of the RSS and RSA is another strength because they are valid and reliable clinical tools including the most prevalent symptoms and findings in previous large cohort studies.[13,15,27]

Conclusion

The clinical diagnosis of LPR is the most widely used approach for the LPR diagnosis. LPR symptoms and signs had low SP and NPV. Based on the symptoms and findings of 403 patients with LPR, SE, SP, PPV, and NPV may be maximized with the association of throat clearing, heartburn, globus sensation, anterior pillar erythema, and uvula erythema/edema.

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Author Contribution

Jerome R. Lechien, design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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