

# Prevalence of Laryngopharyngeal Symptoms in Patients With Gastroesophageal Reflux Disease Refractory to Medical Therapy Undergoing Esophagogastroduodenoscopy

\*Abdul-latif Hamdan, \*Christophe Abi Zeid Daou, †Jerome R. Lechien, \*Anthony Ghanem, ‡Wissam Ghun, and †Fady Daniel, \*‡Beirut, Lebanon, and †Paris, France

**Summary: Objective.** Casting more information on the link between GERD and LPR by investigating the prevalence of laryngopharyngeal symptoms in patients with severe GERD refractory to medical treatment.

**Design.** Prospective Study

**Methods.** Fifty patients with typical GERD symptoms presenting for EGD were recruited. All patients filled the GERD-Health-Related Quality of Life (HRQL) questionnaire and were screened for LPR using the Reflux Symptom Score questionnaire. All patients were also evaluated for the presence of hiatal hernia, esophagitis, inlet patch, gastritis (erosive vs. non erosive), polyps, intestinal metaplasia and or *Helicobacter pylori* infection. Laryngeal images were taken during EGD and evaluated using the Reflux Sign Assessment (RSA).

**Results.** A total of 50 patients were recruited for this study. The prevalence of heartburn was the highest (90%). The mean score of GERD-HRQL was  $30.76 \pm 15.09$ . The mean RSS score was  $70.96 \pm 46.08$ . Laryngeal examination was documented in 49 patients. the most common finding was edema (34.7%) followed by redness (28.6%). The mean RSA score for the total group was  $21.15 \pm 8.04$ . There was a strong correlation between RSS score and GERD-HQRL score. There was no significant correlation between the RSS and any of the EGD findings ( $P > 0.05$ ). There was no significant correlation between RSA and GERD-HRQL scores or any of the EGD findings ( $P > 0.05$ ). However, there was a significant correlation between total RSA and RSS scores ( $\rho = 0.287$ ,  $P = 0.04$ ).

**Conclusion.** The suggested high prevalence of LPRD should alarm the treating physician to the need for a thorough otolaryngologic examination in patients presenting with severe GERD, particularly those in whom the LPR symptoms may be masked by the typical symptoms of GERD.

**Key Words:** Dysphonia—Esophagoscopy—GERD—Laryngology—Laryngopharyngeal reflux—Reflux.

## INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a benign disorder of the upper gastrointestinal tract characterized by the backflow of gastric contents into the esophagus. Exposure of the esophageal mucosa to the refluxate results in a constellation of symptoms, such as heartburn and regurgitation. Patients also may present with dyspepsia, nausea/vomiting, and dysphagia.<sup>1,2</sup> Reflux symptoms are secondary to alterations in the anatomic and physiologic esophageal anti-reflux barriers. These may include anomalies in the gastro-esophageal junction as in patients with hiatal hernia, esophageal motility disorders, and dysfunction in the lower and/or upper esophageal sphincter. Duration and extent of esophageal exposure to the gastro-duodenal refluxate are also important determinants. Symptoms may also occur in the

context of normal reflux burden when there is poor epithelial resistance and/or increased visceral sensitivity.<sup>3</sup>

Extra-esophageal manifestations of GERD are not uncommon. In 1991, *Koufman et al* coined the term laryngopharyngeal reflux to describe the otolaryngologic manifestations in a cohort of 255 patients presenting with atypical GERD.<sup>4</sup> Since then, the term laryngopharyngeal reflux disease (LPRD) is commonly used in reference to an array of laryngo-pharyngeal symptoms and signs due to retrograde movement of gastro-duodenal contents, acidic and non-acidic, into the larynx and pharynx. Reported symptoms in affected patients include globus sensation, cough, exacerbation of asthma, burning sensation in the throat, and change in voice quality among others. The most common laryngeal findings are mucosal edema and redness, inter-arytenoid pachydermia, pseudosulcus vocalis, and supraglottic muscle constriction.<sup>5,6</sup>

To many otolaryngologists, LPRD falls within the spectrum of GERD despite the lack of symptoms of heartburn and regurgitation in affected patients.<sup>1,7</sup> The demarcation of LPRD from GERD is based on the difference in the clinical presentation and response to treatment between the two disease entities. Another important differential construct is the poor diagnostic yield of the conventional methods, namely barium swallow and gastro-esophagoscopy, in patients with LPRD.<sup>8-10</sup> Nevertheless, recent reports substantiate the cross-cutting in the pathophysiology of GERD

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From the \*Department of Otolaryngology and Head & Neck Surgery, American University of Beirut-Medical Center, Beirut, Lebanon; †Laryngopharyngeal Reflux Study Group of Young-Otolaryngologists of the International Federations of Otorhino-laryngological Societies (YO-IFOS), Department of Otolaryngology-Head and Neck Surgery, Foch Hospital, School of Medicine, University Paris Saclay, Paris, France; and the ‡Department of Internal Medicine, Gastroenterology Division, American University of Beirut-Medical Center, Beirut, Lebanon.

Address correspondence and reprint requests to Fady Daniel, American University of Beirut, Department of Gastroenterology, P.O.Box: 11-0236, Beirut, Lebanon. E-mail: fd21@aub.edu.lb

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and LPRD, with a consensus that extra-esophageal symptoms rarely occur in the absence of GERD.<sup>11</sup> To that end, numerous authors reported significant prevalence of LPR symptoms in patients with GERD, with an estimated range of 23% to 80%.<sup>12-21</sup> The variation in prevalence of LPR symptoms in patients with GERD is ascribed to differences in the study groups' demographic characteristics, such as duration and severity of reflux disease, and to the disparity in the outcome measures used, self-reported questionnaires and/or objective testing such pH esophageal and pharyngeal monitoring.

The authors of this manuscript aim at casting more information on the link between GERD and LPR by investigating the prevalence of laryngo-pharyngeal symptoms using the Reflux Symptom Score<sup>22</sup> in patients with severe GERD refractory to medical treatment. The RSS is a comprehensive questionnaire that has been validated in previous studies with a sensitivity and specificity of 94.5 %, and 81.0 %, respectively. The authors of this manuscript also report the correlation between RSS, GERD- Health-related Quality of Life (HRQL) score, and the esophagogastroduodenoscopy (EGD) findings. The authors' hypothesis is that the prevalence of LPR symptoms suggestive of LPRD using the RSS in patients with severe GERD is higher than what has been previously reported. Gastroenterologists treating patients with severe GERD should not hesitate in referring patients for laryngeal examination.

### Subjects and methods

Fifty patients with typical GERD symptoms presenting for EGD were recruited. Inclusion criteria were adults above 18 years of age with symptoms of heartburn, regurgitation, belching, nausea/vomiting, dyspepsia, and/or dysphagia not responding to anti-reflux therapy. Exclusion criteria were patients below 18 years of age, patients with cognitive impairments, and patients with history of head and neck cancer, and radiation. All patients filled the GERD-Health-Related Quality of Life (HRQL) questionnaire which is a self-administered questionnaire that includes two sections, one on regurgitation made of six questions (RS) and another on heartburn made of 10 questions (HB).<sup>23</sup> All patients were also evaluated for the presence of hiatal hernia, esophagitis, inlet patch, gastritis (erosive vs. non-erosive), polyps, intestinal metaplasia and or *Helicobacter pylori* infection.

Patients were screened for LPR using the Reflux Symptom Score (RSS) questionnaire by Lechien *et al.*<sup>22</sup>. RSS is a 22-item patient-reported outcome questionnaire divided into three sections with otolaryngological, digestive and respiratory symptoms. Each item was rated from 0 to 5 for severity, frequency, and interference with quality of life. For each item, the severity score is multiplied by the frequency score to obtain a symptom score (0-25). The sum of these symptom scores is calculated to obtain the RSS final score (0-550). Patients with a RSS>13 were considered suggestive of LPR.<sup>22</sup> Laryngeal images were taken during EGD and evaluated by two otolaryngology physicians. The

oropharyngeal and laryngeal findings were graded using the Reflux Sign Assessment (RSA) by Lechien *et al.*<sup>24</sup>, considering oral, pharyngeal and laryngeal findings. The maximum score is 72 and a RSA>14 is suggestive of LPR.

### Statistical method

Descriptive analysis was used to report the prevalence of heartburn, regurgitation, belching, nausea/vomiting, dyspepsia, and dysphagia. Descriptive analysis and mean scores of GERD-HRQL, RSS and RSA were reported.

Spearman correlation test was done to determine correlations.

## RESULTS

### Demographic data

A total of 50 patients were recruited for this study, 27 males (54%) and 23 females. The mean age was 51.58±14.41 years, 64% were smokers and 36% consumed alcohol. [Table 1](#).

### Clinical presentation and GERD-HRQL score

The prevalence of heartburn was the highest (90%), followed by regurgitation (72%), belching (50%), dyspepsia (42%), nausea/vomiting (40%), and dysphagia (34%). [Table 1](#).

The mean score of GERD-HRQL was 30.76±15.09. Further analysis of the GERD-HRQL showed that the mean heartburn score (HB) was 19.18±9.84 with a minimum score of 0 and maximum of 38. The mean regurgitation score (RS) was 11.58±7.83 with a minimum score of 0 and maximum of 29.

### EGD findings

Hiatal hernia was present in 46% of patients, esophagitis in 20%, and an inlet patch was seen in 6%. Forty-two percent of patients were diagnosed with gastritis on biopsy (erosive

**TABLE 1.**  
**Demographics Information for the Study and Control Groups**

Category	Study Group N = 50 (% of Study group)
Sex	
Male	27 (54%)
Female	23 (46%)
Mean age	51.58 ± 14.41
Smokers	32 (64%)
Alcohol consumption	18 (36%)
Presenting symptoms despite treatment	
Heartburn	45 (90%)
Regurgitation	36 (72%)
Belching	25 (50%)
Dyspepsia	21 (42%)
Nausea/Emesis	20 (40%)
Dysphagia	17 (34%)

**TABLE 2.**  
**EGD Findings for the Study Population**

EGD Finding	Study Group N (% of Study group)
Presence of Hernia	23 (46%)
Hill classification:	22 (96% of hernias)
Class 1	1 (4%)
Class 2	
Presence of Esophagitis	10 (20%)
Grade of Esophagitis:	8 (80% of esophagitis)
Grade A	2 (20%)
Grade B	
Presence of Inlet Patch	3 (6%)

24% and non-erosive 18%). Twenty percent had intestinal polyps, 10% had intestinal metaplasia and 8% had biopsies suggestive of H-pylori infection. [Table 2](#) and [Figure 1](#).

#### Reflux symptom score, laryngeal findings and RSA score

The mean RSS score was  $70.96 \pm 46.08$  with a minimum of 14 and maximum of 227. Forty-eight of the 50 patients in our study group had  $RSS > 13$ . Upon further analysis, the mean score for the ear, nose and throat section was  $22.28 \pm 20.61$ , for the abdomen section was  $38.82 \pm 25.44$  and for the respiratory section  $9.86 \pm 13.36$ .

Laryngeal examination was documented in 49 patients. The most common finding was edema (34.7%) followed by redness (28.6%). Edema and redness were simultaneously present in 16.3% of cases. There were two cases of vocal fold polyps (4.1%), one case of vocal process granuloma (2%), and one case of vocal process ulceration (2%). Notably, one out of seven patients had normal laryngeal examination [Figure 2](#).

The mean RSA score for the total group was  $21.15 \pm 8.04$ . Thirty-eight out of forty-nine (77.5%) examinations had a  $RSA > 14$ . Upon further analysis of the RSA, the mean oral cavity subscore was  $2.69 \pm 2.34$  (out of 9), for the mean pharyngeal cavity sub-score was  $4.17 \pm 3.49$  (out of 21) and for the laryngeal sub-score the mean was  $14.29 \pm 5.59$  (out of 42).

#### Correlation between RSS, GERD-HRQL, GERD symptoms and EGD findings

There was a strong correlation between RSS score and GERD-HQRL score ( $r_s = 0.594$ ,  $P < 0.01$ ).

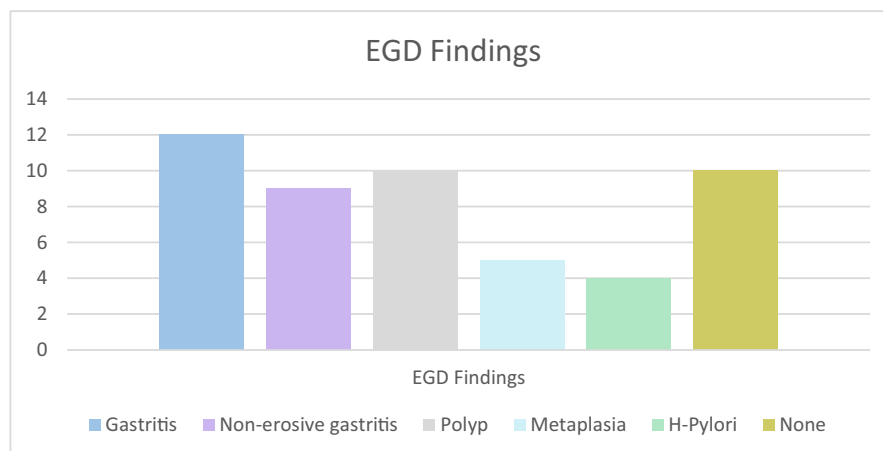
There was also a strong correlation between the RSS score and both the Heartburn and Regurgitation scores ( $\rho = 0.526$ ,  $P < 0.01$  and  $\rho = 0.506$ ,  $P < 0.01$ , respectively).

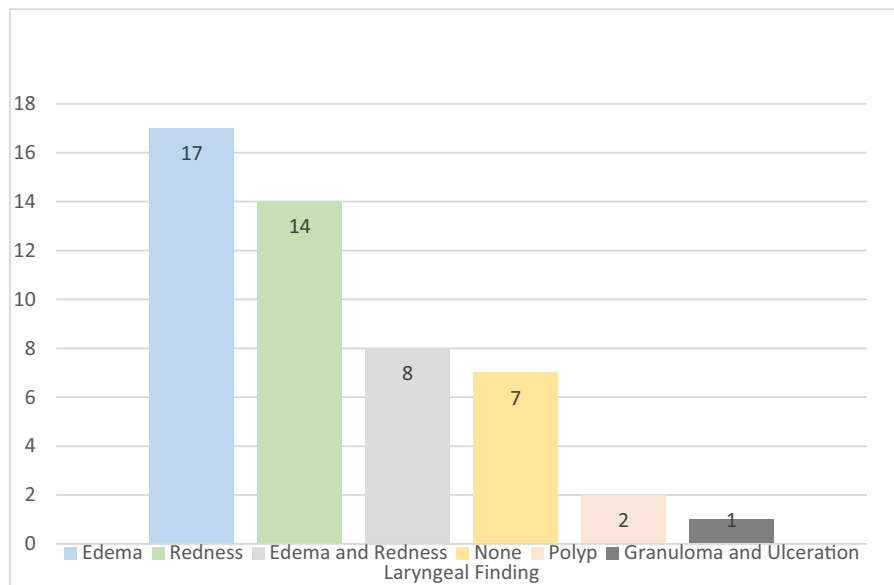
With respect to GERD symptoms, there was a moderate and significant correlation between the total RSS score and regurgitation ( $r = 0.474$ ,  $P = 0.001$ ) and dysphagia ( $r = 0.323$ ,  $P = 0.022$ ). There was no significant correlation between RSS and dyspepsia, nausea/vomiting, heartburn, or belching ( $P > 0.05$ ). There was no significant correlation between the RSS and any of the EGD findings ( $P > 0.05$ ).

#### Correlation between RSA, GERD-HRQL, GERD symptoms, and EGD findings

The RSA score was not significantly correlated with any of the GERD symptom, namely dysphagia, heartburn, regurgitation, dyspepsia, nausea/vomiting, and belching ( $P > 0.05$ ). There was no significant correlation between RSA and GERD-HRQL scores ( $P > 0.05$ ). However, when performing a sub-analysis on the GERD-HRQL sub-sections there was a moderate correlation between the RSA score and the regurgitation score only ( $\rho = 0.363$ ,  $P = 0.011$ ).

Similarly, there was no significant correlation between the RSA and any of the EGD findings, namely hiatal hernia,

**FIGURE 1.** EGD findings of the study population.



**FIGURE 2.** The prevalence of laryngeal findings in the study population.

esophagitis, gastritis, gastric polyp, metaplasia, or H-pylori infections ( $P > 0.05$ ).

On the other hand, there was a significant correlation between total RSA and RSS scores ( $\rho=0.287$ ,  $P = 0.04$ ).

## DISCUSSION

There is no clear consensus in the literature on the prevalence of laryngopharyngeal symptoms in patients with GERD. The results of this investigation indicate that 96% of patients with severe GERD had LPR symptoms suggestive of LPRD, with the mean RSS of the total group being  $70.96 \pm 46.08$ . There was also a significant correlation between the RSS, GERD-HRQL score, and many of the GERD symptoms. The high presence of LPR symptoms suggestive of LPRD was commensurate with abnormal laryngeal findings in 86% of the cases.

Our results substantiate the strong link between LPR symptoms and GERD and indicate a higher prevalence of LPR symptoms in comparison to what has been previously reported. In 2003, Jaspersen *et al.* assessed extra-esophageal disorders in a large cohort of patients with GERD presenting with heartburn and reported a prevalence of **32.8%**. The prevalence was higher in patients with erosive esophagitis in comparison to patients with non-erosive esophagitis.<sup>13</sup> Similarly, in our study, the mean total RSS was higher in patients with erosive gastritis in comparison to patients with non-erosive gastritis (93.56 vs. 67.17, respectively) but the difference was not statistically significant ( $P = 0.304$ ). Dore *et al.* in their evaluation of atypical manifestations of GERD reported the prevalence of globus and cough in **39%** and **24%** of the cases, respectively, almost comparable to the prevalence reported in our study, namely 38% for globus and 46% for cough. The authors also showed that PPI therapy was effective in reducing these atypical symptoms in a

large percentage of patients.<sup>14</sup> In 2007 Groome *et al.* examined the prevalence of LPR symptoms in 1,383 patients with proven GERD admitted for esophagoscopy and reported an association between severity of GERD and LPR score. The mean LPR score using the RSI by Belafsky *et al.*<sup>15</sup> increased from 10.38 in patients with mild GERD to 13.10 and 23.60 in those with moderate to severe GERD, respectively. The stratification of disease severity was based on the Reflux activity Index (RAI) score with less than 94 indicating inactive disease, 94-109 indicating mild disease, 110-124.9 indicating moderate disease, and above 125 indicating severe disease. Although the number of patients with positive LPR was not reported by the authors, careful review of the LPR score against GERD graph shows that the percentage of positive LPR score increased markedly with the severity of the disease. A year later, Lai *et al.* investigated 167 patients diagnosed with reflux esophagitis by endoscopy and reported LPR prevalence (using their own questionnaire) in 23.9% of the cases.<sup>16</sup> The authors also noted that hiatus hernia was a predictive factor of LPR. In 2012, Vardar *et al.* investigated a cohort of 684 patients diagnosed with GERD undergoing esophagoscopy and reported a mean RSI score of  $16.6 + 11.9$ . Unlike our study, there was no correlation between the RSI score and gastroesophageal reflux symptoms. Nevertheless, seventy percent had laryngeal findings suggestive of laryngopharyngeal reflux disease.<sup>17</sup> In 2014, Drinnan *et al.* investigated the prevalence of extra-esophageal reflux in 359 patients undergoing esophagogastroduodenoscopy out of whom 136 had evidence of esophagitis. Each of the items of the 34-item Comprehensive Reflux Symptoms Scale (CReSS)<sup>18</sup> used by the authors was scored above one by more than 28% of their EGD study population. The authors noted the prevalence of throat clearing in 54% of the cases and feelings of things stuck in my throat or and lump sensation in more than 45% of the



cases.<sup>19</sup> Similarly, in 2018, Mosli *et al.* conducted a cross-sectional study looking at the prevalence of LPR in patients with GERD using the RSI. The diagnosis of GERD was confirmed using the GerdQ validated questionnaire.<sup>25</sup> The authors showed that 71% of their study group had RSI>13, with a mean score of  $20 \pm 11$ , irrespective of treatment. Moreover, there was positive correlation between GerdQ, BMI, gender and LPR positive score.<sup>20</sup> In a sample of 101 patients with suspected GERD and symptoms of extra-esophageal involvement who underwent conventional esophageal pH monitoring, Fuchs *et al* reported positive laryngopharyngeal reflux using Restech in 48% of cases. Only 40 patients of 101 had abnormal esophageal PH and an abnormal Restech, and 26 patients had abnormal esophageal Ph and normal Restech. The authors concluded that a positive esophageal pH-metry does not correlate with a positive result on laryngopharyngeal pH-metry.<sup>21</sup>

The prevalence of LPR symptoms in patients with GERD can be attributed to many factors, most important of which are the micro and macro changes in the mucosal lining of the larynx and pharynx as a result of direct exposure to the refluxate contents. The mucosal changes commonly reported vary between edema and hyperemia as described in our study group, to severe inflammatory changes leading to ulceration and granuloma formation. Indirect effect secondary to vagally mediated reflexes also have been documented.<sup>12</sup> Exposure of the esophageal mucosal lining to the gastroduodenal content can elicit or precipitate adductor laryngeal reflexes and cough. This phono-traumatic behavior may cause mucosal injury and precipitate changes in the biomechanical properties of the vocal folds.

The results of this investigation cast more information on the strong link between LPR and GERD. The strong correlation between RSS score and GERD-HQRL suggests that laryngeal examination is warranted in patients with severe GERD refractory to medical treatment. Nevertheless, this study has its limitations. One is the relatively small number of subjects and second is the lack of objective test to diagnose LPR such as hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring. We can definitely conclude that patients with GERD refractory to medical treatment and undergoing EGD have LPR symptoms suggestive of LPRD.

### CONCLUSION

This study shows a very high prevalence of suspected LPR in patients with severe GERD in comparison to the literature. This can be ascribed to the comprehensive nature of the RSS questionnaire that addresses all otolaryngologic manifestations of GERD. The suggested high prevalence of LPRD evidenced by the high mean RSS and large number of patients with a RSS above 13 should alarm the treating physician to the need for a thorough otolaryngologic examination in patients presenting with severe GERD, particularly those in whom the LPR symptoms may be masked by the typical symptoms of GERD such as

heartburn, regurgitation, dyspepsia. Laryngeal findings such as pachydermia of the inter-arytenoid mucosa and pseudosulcus vocalis suggest a change in treatment strategy. Nevertheless, the diagnosis of LPR using the RSS and RSA without objective studies such as hypopharyngeal and esophageal multichannel intraluminal impedance pH-monitoring remains inconclusive.

### CONFLICT OF INTEREST

There is no conflict of Interest or financial support in relation to this paper.

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