

ORIGINAL RESEARCH

Clinical Evaluation of Laryngopharyngeal Reflux and Its Response to Anti-Reflux Therapy

¹Dr. Panchanan Sahoo, ²Dr. Subhalaxmi Rautray, ³Dr. Monalisa Patsani,
⁴Dr. Gaveshani Mantri, ⁵Dr. Subrat Kumar Behera

¹LTRMO, Department of ENT & HNS, DHH, Balangir, Odisha, India.

²Associate Professor, ³Assistant Professor, ⁴Senior Resident, ⁵Professor & HOD, Department of ENT and HNS, SCB Medical College and Hospital, Cuttack, Odisha, India.

Corresponding Author

Dr. Monalisa Patsani

Assistant Professor, Department of ENT and HNS, SCB Medical College and Hospital, Cuttack, Odisha, India.

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Abstract

Background: Laryngopharyngeal reflux disease (LPRD) is a very common presenting condition in otorhinolaryngology departments nowadays, it is very important to diagnose promptly and treat these patients efficiently. The aim of our study is to evaluate symptoms of LPR, laryngeal endoscopic findings, and treatment outcomes of anti-reflux therapy.

Methods: This was a prospective study carried out from February 2018 to November 2019. A total number of 140 patients, aged 8 to 65 years, with symptoms of LPR, Reflux Symptom Index (RSI) of more than 13, and Reflux Finding Score (RFS) of more than 7, were included in this study.

Result: After recommending dietary and lifestyle changes to all patients, Rabeprazole 20 mg tablets were administered twice daily orally for three months. In our study, it has been seen that there is a significant improvement in RSI and RFS scores after 12 weeks of Proton Pump Inhibitor therapy.

Conclusion: We conclude that a combination of RSI and RFS are very useful method in diagnosing LPR patients, treating with twice daily dose of PPI for a duration of 12 weeks shows significant improvement in both symptoms and endoscopic findings of LPR.

Keywords: Laryngopharyngeal reflux (LPR), Reflux Symptoms Index (RSI), Reflux Finding Score (RFS), Proton Pump Inhibitor (PPI).

Introduction

The spillover of stomach acid into the hypopharynx is known as laryngopharyngeal reflux (LPR), a term that was coined by James in 1980 and approved by the American Academy of Otolaryngology.⁽¹⁾ In his article, he mentioned that 40-60% of people presenting to otolaryngologists with voice disorders are because of LPR. There are so many other terminologies for LPR, out of which extra-esophageal reflux is a very commonly used one.⁽²⁾ In 1996, Koufman proposed that LPR and GERD are two distinct diseases. In LPR acid and pepsin content of the refluxed material from the stomach leads to chemical injuries and inflammation of the laryngopharyngeal mucosa and it may stimulate afferent nerves endings of vagus nerve leading to cough, change in voice, foreign body sensation of throat, as well as signs of laryngeal irritation on video- laryngoscopic examination.⁽³⁾ Whereas in GERD there is the backflow of gastric contents into the oesophagus, which leads to tissue damage or leads

to esophagitis and symptoms like heartburn. From this, it is known that LPR and GERD are two different diseases.

LPR is not commonly postprandial. Patients with LPR are commonly daytime refluxers. In LPR prolonged periods of acid exposure, dysmotility, and prolonged oesophageal acid clearance is not seen.

History taking, video-laryngoscopic examination of the larynx, double probe pH monitoring, are very sensitive and specific for diagnosis of LPR. Due to wide unavailability in clinical practice and the cost of the double probe pH monitoring, the laryngoscopic examination is the most preferred one.

Belafsky et al developed more easy and economical instruments for the diagnosis of LPR that as RSI (reflux symptoms index)⁽³⁾, and RFS (reflux finding score)⁽⁴⁾, which are mostly based on history taking and video-laryngoscopic examination. RSI is an instrument that is based on 9 symptoms. The total score ranges between 0-45 and >13 indicates LPR. Similarly, RFS is an assessment that is based on 8 signs on laryngoscopic examination and it has been concluded that any individual with a RFS score of >7 indicates the probability of LPR is > 95%.

Five PPIs are widely available nowadays like Omeprazole, Rabeprazole, Pantoprazole, Lansoprazole, and Esomoprazole. We have tried Rabeprazole twice daily dose to patients to study the effect of PPIs in LPR.

Materials and methods

The study is a prospective study conducted at S.C.B. Medical College & Hospital, Cuttack from February 2018 to November 2019 (22 months), after taking ethical committee clearance. It includes 140 patients.

Inclusion Criteria

Patients between the ages 18 to 65 years, with symptoms of LPR for at least 3 months, having RSI greater than 13 (table number 1) and RFS greater than 7 (table number 2).

Sl. no.	Symptoms	No Problem					Severe Problem
1	Hoarseness or problem with your voice	0	1	2	3	4	5
2	Clearing your throat	0	1	2	3	4	5
3	Excess throat mucous or post-nasal drip	0	1	2	3	4	5
4	Difficulty in swallowing food, liquid, or pills	0	1	2	3	4	5
5	Coughing after you ate or after lying down	0	1	2	3	4	5
6	Breathing difficulties or choking episodes	0	1	2	3	4	5
7	Troublesome or annoying cough	0	1	2	3	4	5
8	throat	0	1	2	3	4	5
9	Heartburn, chest pain, indigestion, stomach acid coming up	0	1	2	3	4	5

Sl. no.	Finding	Score
1	Infraglottic oedema (PseudosulcusVocalis)	0= absent, 2= present
2	Ventricular Obliteration	2= partial, 4 complete
3	Erythema or Hyperemia	2= arytenoids only, 4= diffuse

4	Vocal fold edema	1=mild, 2= moderate, 3= severe, 4= polypoid
5	Diffused laryngeal edema	1= mild, 2= moderate, 3= severe, 4=obstructing
6	Posterior commissure hypertrophy	1= mild, 2= moderate, 3= severe, 4=obstructing
7	Granuloma or Granulation	0= absent, 2= present
8	Thick endolaryngeal mucous	0= absent, 2= present

Exclusion Criteria

Patients who did not give consent, Patients with ages <18 years &>65 years, Patient has a history of anti-reflux medication in the last 3 months, those whose RSI score is less than 13 and/or score of RFS is less than 7, or hypersensitivity to any PPI, Patient with voice abuse, trauma, acute laryngitis, acute epiglottitis, tonsillar inflammation, or allergic diseases and Laryngeal malignancy, Hepatic functional impairment, and patients who were lost to follow-up, are excluded from the study.

Procedure

Each patient got a thorough physical examination, complete history taking, and laryngeal endoscopy. On the basis of presenting symptoms by patient (reflux symptom index) and video-laryngoscopic examination features of larynx and hypopharynx known as the reflux finding score (RFS), LPR was diagnosed on the initial visit.

All patients with the above symptoms were given a questionnaire at the start of the study and calibrated each symptom from no problem to severe problem, based on the reflux symptom index (RSI)⁽³⁾. Patients with RSI greater than 13 were undergone laryngeal endoscopy.

After administering 10% xylocaine spray, larynx and hypopharynx was examined by inserting a 70-degree rigid laryngoscope through oral cavity. The larynx was examined after inspecting two vocal cords, false vocal cords, both anterior commissure and posterior commissure, ventricle, inter-arytenoid area, and pyriform sinus, and the laryngeal finding of each patient was recorded. The laryngeal endoscopic finding will be graded based on reflux finding score (RFS) and patients with RFS greater than 7 are included in the study, and have undergone further management.

Every patient received dietary and lifestyle counselling before using PPI medication.

Diet & lifestyle advice

As given below along with the medication. They were advised to reduce alcohol and caffeine intake, to decrease smoking and to decrease intake of fatty diet like cheese, fried dish, chocolate and pastries etc. They were also instructed to use voice as less as possible.

Medication: T. Rabeprazole (20 mg), 1 Tab, twice daily, 1 hour before food, for 12 weeks. We didn't advise anyprokinetic in our study due to adverse effects like hyperprolactinemia and galactorrhoea.

Follow-up

Patients were followed up after 4 weeks, 8 weeks, and 12 weeks, and RSI & RFS were noted and compared at each visit.

Statistical analysis

Microsoft Excel was used to tabulate the observations. MedCalc 18.2.1 program version (MedCalc Software, Ostend, Belgium) was used for statistical analysis. Statistical significance ($P < 0.05$) was set to analyse the data sets.

Result

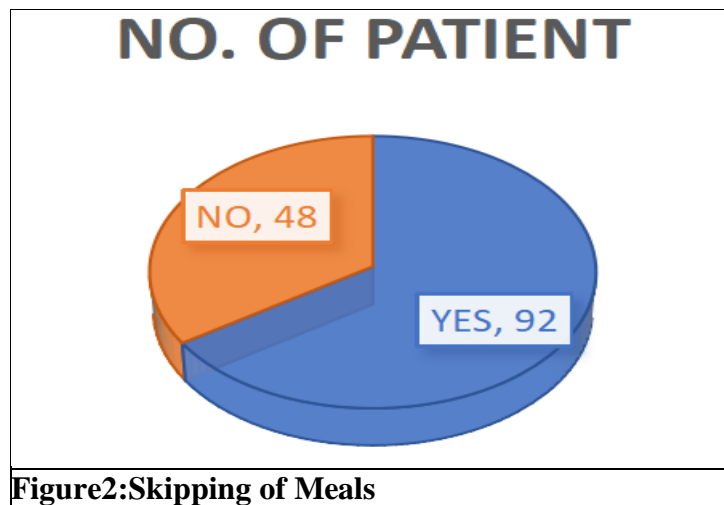
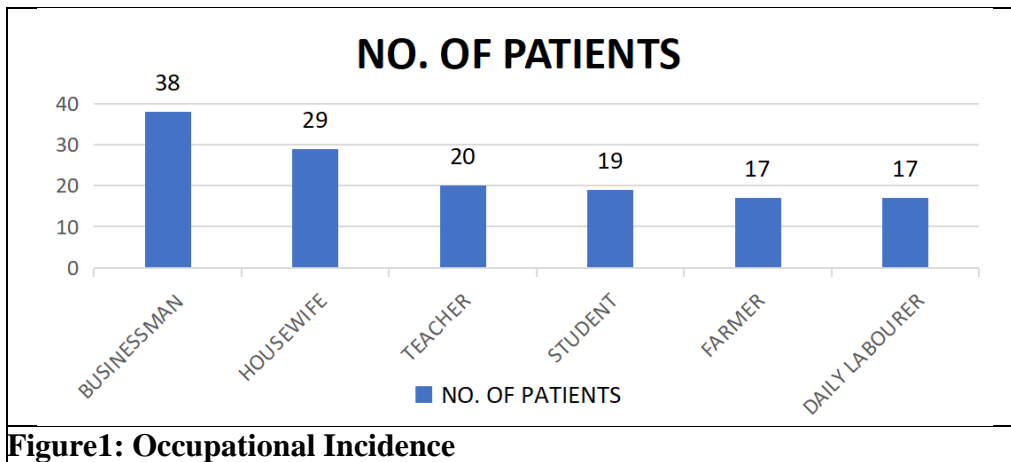
A total of 140 patients were included in our study out of which 62 were male and 78 were females (Table-3). The mean age is 37.46 years and the majority of patients are from urban areas which is 86 (61%). In our study, we found the maximum number of patients were businessmen 27.14% followed by housewives 20.7% (Fig-1). Here we found 21% of people have only tobacco chewing habits, 12% have both tobacco and smoking habits and 8% of patients have tobacco, smoking, and alcohol habit (Table-4). About 92% of patients have a skipping meal habit (Fig-2).

The most frequent presenting symptom in our study was a feeling of a foreign body in the throat or something sticking in the throat (78%) followed by frequent throat cleaning (58%) (Table -5). On 70-degree video-endoscopic laryngeal examination erythema or hyperemia of the inter arytenoid area is most commonly found at 82% followed by hypertrophy of posterior commissure in 69% of patients (Table-7).

After starting the 20mg twice a daily dose of Rabeprazole (proton pump inhibitor), RSI values were compared before and after starting the treatment. The mean RSI value before treatment was 24.26 (SD=0.95%) whereas the score of RSI after 8wk treatments was 13.46 (SD=0.50%) which is significant (Table 6A & 6B). Again, after a further 4wk of the same treatment, there is no significant change. Similarly mean RFS score before treatment was 11.78(SD=0.80). After 8wk of Rabeprazole twice daily therapy there is no significant change in laryngeal examination findings, but after 12 weeks of the same treatment, there is quite a significant drop in RFS score to 6.47(SD=0.50) (Table 8A & 8B).

Age Group(Years)	Male	Female	Percentage
18-20	1	3	2.85%
21-30	12	14	18.57%
31-40	29	37	47.14%
41-50	14	16	21.42%
51-60	5	7	8.57%
61-65	1	1	1.43%
	62(44.29%)	78(55.71%)	

Addiction	No. of Patients	Percentage
Tobacco	29	21%
Tobacco & Smoking	17	12%
Tobacco, Smoking & Alcohol	11	8%
No Addiction	83	59%



Symptoms	Total No. of Patients	Percentage
Sensation of something sticking in your throat/ a lump in your throat	109	78%
Frequent clearing of the throat	92	66%
Troublesome or annoying cough	81	58%
Difficulty in swallowing foods, liquids, or pills	66	47%
Heartburn, Chest Pain, Indigestion, or Stomach Acid Coming Up	64	46%
Excess throat mucus	50	36%
Cough after eating or after lying down	45	32%
Hoarseness	43	31%
Breathing difficulties	36	26%

	Number	Mean	Std. deviation
Pre-treatment	140	24.26	0.95
After 1 month	140	24.22	0.95
After 2 months	140	13.46	0.54
After 3 months	140	13.44	0.50

	Std. Error	95% Confidence Interval of the Difference		t	DF	Significance
		Lower	Upper			
1 Month Vs PRE-T/T	0.114	-0.2635	-0.1835	-0.352	278	P=0.7249
2 Month Vs PRE-T/T	0.092	-10.9818	-10.6182	-116.941	278	P<0.0001
3 Month Vs PRE-T/T	0.091	-10.9986	-10.6414	-119.253	278	P<0.0001

Findings	No. of Patients	Percentage
Erythema / Hyperemia	115	82%
Posterior commissure hypertrophy	97	69%
Ventricular obliteration	88	63%
Diffuse laryngeal edema	78	56%
Vocal fold edema	71	51%
Granuloma	59	42%
Pseudosulcus	59	42%
Thick endolaryngeal mucus	53	38%

	Number	Mean	Std. deviation
PRE-treatment	140	11.78	0.80
After 1 month	140	11.62	0.75
After 2 months	140	11.61	0.73
After 3 months	140	6.47	0.50

	Std. Error	95% Confidence interval of the difference		t	DF	Significance
		Lower	Upper			
1 Month vs. PRE-T/T	0.093	-0.3424	-0.0224	-1.726	278	P=0.0854
2 Month vs. PRE-T/T	0.092	-0.3502	-0.0102	-1.857	278	P=0.0643
3 Month vs. PRE-T/T	0.080	-5.4670	-5.1530	-66.598	278	P<0.0001

Discussion

LPR is a very frequently encountered disease in otolaryngology clinics nowadays because of changing lifestyle and food habits of modern people. For it is seen that there are several medical research articles regarding the standardization of different methods for the assessment of symptoms, signs, and treatment of LPR. But still, there is the existence of so many controversies.

LPR is caused by mucosal damage of the pharynx, larynx, and upper aero-digestive tract area by the acid and pepsin content of gastric reflux fluid. Different signs and symptoms of LPR are due to mucosal damage of the larynx and pharynx.

Though 24-hour dual-channel pH monitoring is the gold standard for the diagnosis of LPR, still it is not done routinely due to its unavailability, invasiveness & cost. Mostly LPR is diagnosed on clinical grounds, which includes history taking and examination with the flexible or rigid laryngeal endoscope. The RSI and RFS are very useful methods to be followed for the assessment of LPR before and after treatment. Similar to the work of Belafsky et al., RSI and RFS were used in our investigation to diagnose LPR.^(3, 4) Feng et al. demonstrated that RSI scoring and laryngopharyngeal pH monitoring are equally effective for detecting LPR sickness.⁽⁵⁾ According to a study by Yichen Wan et al., the 24-hour pH monitoring and a combination of RSI and RFS bear equal competence in choosing LPR patients.⁽⁶⁾

Along with advice on lifestyle and dietary modification patients require medical therapy. Proton pump inhibitors are required to neutralize the acidity of gastric juice. After absorption into the circulation and subsequent diffusion into the parietal cell, it gets concentrated in the acidic pH of the canaliculi because the charged forms formed there are unable to diffuse back. Furthermore, covalent connections firmly bind it to the enzyme. All PPIs have a high degree of action selectivity due to these characteristics and the particular localization of H+K+ATPase to the apical membrane of the parietal cells. Only after the synthesis of fresh H+K+ATPase molecules, which takes 18 hours, does acid secretion begin again.

In our study, the total number of patients included was 140, out of which 62 were males and 78 were females. The age group of patients taken in my study was 18-65 years. The maximum number of patients belongs to the age group of 31-40 years, constituting about 47%. Followed by 21% in the 41-50 age group. The mean age was 37.46 years with an SD of 9.66 years. Male to female ratio was 6:8 (44.29% male and 55.71% female). According to the study done by S A Patigaroo, and S. F. Hashmi, the maximum number of patients was in the age group 31–40 yrs. forming about 40% of the study group, similar to our study.⁽⁷⁾ The mean patient age was 38.7 (SD =10.2 years) in Murat Saruç et al study in 2011, which matches with our study.⁽⁸⁾ In another study by Mesallam and Stemple in 2007, females (65%) were more than males with a mean \pm SD age of 41.7 ± 10.7 years.⁽⁹⁾ The majority of the patients were from urban areas, 61% (86), Whereas, 38% (54), were from rural. The rural-to-urban ratio was 6:9. This may be due to their modern lifestyle, dietary pattern, and more awareness about the disease. In our study, the maximum incidence was among businessmen (27.14%) followed by housewives (20.71%). 14.28% were teachers while students comprise 13.57% of the study population. 12% were farmers and daily laborers each. The more prevalent amongst businessmen could be due to irregularity in taking meals.

In our study, we found 21% of tobacco chewers, and 12% of patients were addicted to both tobacco and smoking, while 8% have a history of addiction to tobacco, smoking, and alcohol. The majority of patients (59%) have no addiction. In another study by A. Bhargava et al in the year 2019 they also found 22% of tobacco chewers, 12% of smokers, and 10% of alcoholics.⁽¹⁰⁾

In our study, the most common presenting symptom was the sensation of something sticking in the throat or foreign body sensation of the throat which constitute 78% of cases, with Mean \pm SD (0.69 ± 0.46) $p < 0.0001$. Followed by frequent clearing of the throat in 66% and cough in 58% of cases. The most prevalent symptom in our study, which is identical to the study by SA Patigaroo, was the sense of a foreign body in 74% of patients. This was followed by frequent throat clearing in 64% of patients and a bothersome or irritating cough in 56% of the study population. Other studies like Mesallam and Stemple⁽⁹⁾, Jerome R. Lechien et al⁽¹¹⁾,

Karkos, and Yates⁽¹²⁾ have also found something sticking to the throat is the most common symptom.

Erythema/hyperemia of inter arytenoid area (82%), is the most common laryngeal finding in our study, followed by posterior commissure hypertrophy (69%) and ventricular obliteration (63%). This is similar to the study by Book, Rhee⁽¹³⁾ and Toros, Toros⁽¹⁴⁾. The most frequently found sign on laryngoscopic examination was erythema (85%)⁽⁹⁾. Similar to our study, S.A. Patigaroo's other study found that erythema/hyperemia was the most prevalent laryngoscopic sign in 88% of patients, followed by ventricular obliteration in 76% of patients and posterior commissure hypertrophy in 60% of the study population.

On comparing the pre and post-treatment RSI the mean RSI of all patients was found 24.26 (SD \pm 0.95) before treatment. After 4 weeks of PPI medication, the mean RSI fell to 24.22; after 8 weeks, it fell to 13.46; and after 12 weeks, it fell to 13.44 (SD 0.50). After the first eight weeks of therapy, there was a significant change in RSI (p0.0001), and for the next four weeks, there was no further significant change. This was similar to the study by SA Patigaroo et al, 2011.⁽⁷⁾ Myung-Hee Shin found that significant improvement in RSI was seen after 8 weeks of PPI therapy which is similar to our study.⁽¹⁵⁾ According to Ford CN et al, Empirical therapy should use the full dose of PPIs for a minimum period of 2 to 3 months.⁽¹⁶⁾

On comparison of pre and post-treatment values of RFS, it is found that the mean RFS of the patients was 11.78(SD: \pm 0.80) before treatment. Following 8 weeks of PPI therapy, the mean RFS dropped to 11.61 (SD 0.73), and following 12 weeks, the mean RFS fell to 6.47 (SD 0.50), which was statistically significant, p0.0001. Physical findings in all age groups showed a modest improvement after 8 weeks of therapy and a substantial improvement after 12 weeks of therapy overall. Similar to our work, Myung-Hee Shin discovered that RFS significantly improved following 12 weeks of PPI treatment.⁽¹⁵⁾ According to Cathal Coyle, a period of 2 to 3 months of twice-daily PPI therapy is necessary to establish benefit from the medication with, a similar treatment duration as our study.⁽¹⁷⁾ We found proton pump inhibitors are the mainstay of therapy which is also similar to other studies like Mosca F et al in 2006, Abou-Ismael A et al in 2011, and Ford CN et al in 2005.^(16, 18, 19)

According to the study conducted by Koufman JA et al., the current care recommendation for patients with LPR is empiric therapy with twice-daily proton pump inhibitors for 3 months⁽²⁰⁾, as we found in our study.

Summary

About 10-15% of all patients who visit otolaryngology departments have laryngopharyngeal reflux (LPR), which is a frequent condition in the area. The reflux symptom index (RSI) and reflux finding score (RFS) are most frequently used in the clinical diagnosis of LPR. Patients received dietary and lifestyle recommendations before receiving medication, for 12 weeks, take one tablet of T. Rabeprazole (20 mg) twice daily, one hour before eating. Follow-up was done after 4 weeks, 8 weeks, and 12 weeks and RSI & RFS were noted and compared at each visit. The most common symptom of the LPR group was foreign bod Patients received dietary and lifestyle recommendations before receiving medication. For 12 weeks, take one tablet of T. Rabeprazole (20 mg) twice daily, one hour before eating y sensation and the most common laryngeal sign was erythema of inter arytenoid area with prevalence rates of 78% and 82%, respectively. The mean RSI and RFS scores of the LPR group were 24.26 and 11.78, respectively before starting the treatment. After 12 weeks of PPI therapy, the mean RSI and RFS became 13.44 and 6.47 respectively.

Conclusion

Despite the fact that LPR is a disorder that frequently manifests in ENT settings, the symptoms and diagnostic results are subjective. The mainstay of management is changing

one's lifestyle and taking anti-reflux medication. As utilised in our study, the reflux finding score and reflux symptom index are useful diagnostic tools for LPR. Only a minor amount of acid reflux into the upper aero-digestive tract may be capable of creating no. Despite the fact that LPR is a disorder that frequently manifests in ENT settings, the symptoms and diagnostic results are subjective. The mainstay of management is changing one's lifestyle and taking anti-reflux medication. So, the treatment of LPR requires more complete and aggressive treatment than GERD. Our patients of LPR showed complete (100%), symptom-free healing after 8 weeks of treatment with Tab. Rabeprazole-20mg twice daily, however, laryngeal signs took 3 months to resolve. Overall, we observed that for treatment of LPR, we should continue the twice-daily dose of proton pump inhibitor for at least 3 months.

Bibliography

1. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R, Group GC. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Official journal of the American College of Gastroenterology| ACG.* 2006;101(8):1900-20.
2. Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngology—Head and Neck Surgery.* 2002;127(1):32-5.
3. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *Journal of voice.* 2002;16(2):274-7.
4. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *The laryngoscope.* 2001;111(8):1313-7.
5. Feng G-J, Zhang L-H, Zhao L-L, Liu Y-L. A pilot study on diagnosing laryngopharyngeal reflux disease by pH monitoring in laryngopharynx. *Zhonghua Yi Xue Za Zhi.* 2008;88(12):805-8.
6. Wan Y, Yan Y, Ma F, Wang L, Lu P, Maytag A, et al. LPR: how different diagnostic tools shape the outcomes of treatment. *Journal of Voice.* 2014;28(3):362-8.
7. Patigaroo SA, Hashmi S, Hasan SA, Ajmal M, Mehfooz N. Clinical manifestations and role of proton pump inhibitors in the management of laryngopharyngeal reflux. *Indian Journal of Otolaryngology and Head & Neck Surgery.* 2011;63:182-9.
8. Saruç M, Aksoy EA, Vardereleli E, Karaaslan M, Çiçek B, İnce Ü, et al. Risk factors for laryngopharyngeal reflux. *European Archives of Oto-Rhino-Laryngology.* 2012;269:1189-94.
9. Mesallam TA, Stemple JC, Sobeih TM, Elluru RG. Reflux symptom index versus reflux finding score. *Annals of Otolaryngology, Rhinology & Laryngology.* 2007;116(6):436-40.
10. Bhargava A, Faiz S, Srivastava MR, Shakeel M, Singh NJ. Role of Proton Pump Inhibitors in Laryngopharyngeal Reflux: Clinical Evaluation in a North Indian Population. *Indian Journal of Otolaryngology and Head & Neck Surgery.* 2019;71:371-7.
11. Lechien JR, Finck C, Huet K, Khalife M, Fourneau A-F, Delvaux V, et al. Impact of age on laryngopharyngeal reflux disease presentation: a multi-center prospective study. *European Archives of Oto-Rhino-Laryngology.* 2017;274:3687-96.
12. Karkos PD, Yates PD, Carding PN, Wilson JA. Is laryngopharyngeal reflux related to functional dysphonia? *Annals of Otolaryngology, Rhinology & Laryngology.* 2007;116(1):24-9.
13. Book DT, Rhee JS, Toohill RJ, Smith TL. Perspectives in laryngopharyngeal reflux: an international survey. *Laryngoscope.* 2002;112(8 Pt 1):1399-406.
14. Toros SZ, Toros AB, Yuksel OD, Ozel L, Akkaynak C, Naiboglu B. Association of laryngopharyngeal manifestations and gastroesophageal reflux. *Eur Arch Otorhinolaryngol.* 2009;266(3):403-9.

15. Shin M-H, Nam SY, Park Y-H, Son Y-I. Open-label observational study for evaluating the short-term benefits of rabeprazole medication on laryngopharyngeal reflux. *Clinical and Experimental Otorhinolaryngology*. 2012;5(1):28-33.
16. Ford CN. Evaluation and management of laryngopharyngeal reflux. *Jama*. 2005;294(12):1534-40.
17. Laryngopharyngeal Reflux—Reflux beyond the Esophagus: Pathophysiology, Diagnosis, and Treatment. 2014 2014/11/19. In: *Laryngology* [Internet]. Stuttgart: Georg Thieme Verlag KG. Available from: <http://www.thieme-connect.de/products/ebooks/lookinside/10.1055/b-0034-97955>.
18. Mosca F, Rossillo V, Leone C. Manifestations of gastro-pharyngo-laryngeal reflux disease. *Acta otorhinolaryngologica italica*. 2006;26(5):247.
19. Abou-Ismaïl A, Vaezi MF. Evaluation of patients with suspected laryngopharyngeal reflux: a practical approach. *Current gastroenterology reports*. 2011;13:213-8.
20. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24- hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *The Laryngoscope*. 1991;101:1-78.