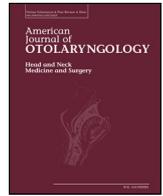




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# The utility of narrow band imaging in endoscopic diagnosis of laryngopharyngeal reflux

Changding He<sup>a,1</sup>, Jinchao Yu<sup>b,1</sup>, Fang Huang<sup>a</sup>, Jun Shao<sup>a,\*</sup>

<sup>a</sup> Department of Otorhinolaryngology Head and Neck Surgery, Eye, Ear, Nose & Throat Hospital, Fudan University, Shanghai, PR China

<sup>b</sup> Department of Facial Plastic and Reconstructive Surgery, Eye & Ear Nose and Throat Hospital, Fudan University, Shanghai, PR China

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## ABSTRACT

**Objective:** This study assessed the utility of narrow band imaging (NBI) in patients with symptoms of laryngopharyngeal reflux (LPR) and tried to quantitatively evaluate the signs found under the NBI Laryngoscope. **Methods:** Patients with and without LPR symptoms completed reflux symptom index (RSI) questionnaires prior to enrolment. The throat was examined by standard white light endoscopy followed by NBI. LPR status was determined using the reflux finding score and the RSI. Laryngoscope images and videos from 70 subjects with LPR and 70 control subjects without LPR were obtained. Features seen only by NBI were compared between the two groups. Then the RGB values of the throat mucosa of the two groups were measured by Photoshop software, and finally statistical analysis was performed.

**Results:** In total, 140 patients were eligible for final analysis (LPR group mean age = 50.0, 47 males; control group mean age = 44.8, 45 males). A significantly higher proportion of patients with LPR had increased vascularity, green spots, contact ulcers and granulomas. Of these, increased vascularity and green spots can only be found under NBI, and the prevalence rates in the LPR group were found to be 92.8% and 88.6% ( $P < 0.05$ ), respectively. In the control group, the prevalence rates of increased vascularity and green spots were 21.4% and 7.1%, respectively ( $P < 0.05$ ). The RGB value of the LPR group was generally higher than that of the control group. The difference is statistically significant ( $P < 0.05$ ).

**Conclusion:** LPR presents vascularity and green spots with high specificity and sensitivity under NBI which can play a role in the auxiliary diagnosis of LPR.

## 1. Introduction

Laryngopharyngeal reflux (LPR) is a common disease in the field of otolaryngology, and approximately 15% [1] of all patients presenting to otolaryngology departments have LPR. Koufman [2] defines LPR as invasion of the upper respiratory tract by the reflux of gastric content. In western countries, 8.7%–27.8% [3] of adults are affected by gastroesophageal reflux disease (GERD), and LPR is often considered to be an extraesophageal symptom of GERD. However, GERD and LPR have pathophysiological differences [4]. For example, LPR often occurs in upright positions during the day while GERD often occurs in supine positions at night. Many patients with LPR do not have typical GERD symptoms, such as heartburn and acid reflux, but present other non-specific symptoms, such as hoarseness, cough, sputum, and foreign body sensation, which can seriously affect their quality of life. LPR has

been associated with otolaryngological disease, for example, Copper et al. [5] found that pathological LPR is common among head and neck cancer patients.

Previous research [6,7] has shown that the gastric content in LPR generally includes gastric acid, pepsin, bile acid, trypsin, and acidic gases, which may cause pathological lesions in the larynx, including pseudosulcus, interarytenoid thickening, Reinke's edema, vocal cord granuloma, and other changes. At present, otolaryngology patients are diagnosed with LPR largely based on their medical history, symptoms, and laryngoscopic manifestations. Clinical diagnosis of LPR is most commonly performed using the reflux symptom index (RSI), the reflux finding score (RFS), and proton pump inhibitor (PPI) diagnostic treatment. These two scores are subjectively influenced by patients and doctors. PPI diagnostic treatment are affected by patient compliance, and many patients with LPR are not sensitive to PPI drugs. As the gold

\* Corresponding author at: Department of Otorhinolaryngology Head and Neck Surgery, Eye, Ear, Nose & Throat Hospital, Fudan University, Building 10, Room 404, 83 Fenyang Road, Shanghai, Xuhui District, PR China.

E-mail address: [eentshao@163.com](mailto:eentshao@163.com) (J. Shao).

<sup>1</sup> The first two authors contributed equally to this paper.

standard for diagnosis of LPR, 24-hour PH monitoring not only has the false positive effect caused by physiological acid reflux, but also has the disadvantages of long examination duration, aggressiveness and unacceptability of patients. Mesallam et al. [8] demonstrate a highly significant correlation between RFS and RSI results. Throat clearing, hoarseness, and globus sensation appear to be the most common RSI symptoms that correlate significantly with laryngeal signs such as interarytenoid thickening, Reinke's edema, vocal cord granuloma and so on.

Narrow band imaging (NBI) is an optical technology that can clearly show the distribution of small lesions and capillaries in superficial mucosa. It has been widely used in the diagnosis of some tumours and precancerous lesions [9,10]. In otolaryngology, NBI is also commonly used in preliminary diagnosis of laryngopharyngeal neoplasm, evaluation of the preoperative surgical margin range, judgment of post-operative recovery, and diagnosis of precancerous lesions such as leukoplakia [10]. NBI is rarely used in the diagnosis and evaluation of inflammatory ENT diseases.

The etiology of LPR is generally considered to be the invasion and damage of the throat mucosa caused by the reflux of gastroesophageal contents [7]. In theory, specific signs of LPR invasion should be observable as damage in the throat. However, these signs, such as edema, erythema, and combined hyperplasia and granuloma, these are not readily discernible in conventional light source laryngoscopy, and some studies [11,12] have found that the same signs are found in normal subjects. Therefore, this study investigates LPR with an NBI laryngoscope to find relatively sensitive and specific signs to assist in clinical diagnosis.

## 2. Materials and methods

### 2.1. Study design

This study was performed in accordance with the guidelines of Declaration of Helsinki and approved by the Institutional Review Board of a hospital. From October 2017 to March 2018, patients with LPR symptoms were recruited from the Laryngoscopy room; symptoms included more than three months of hoarseness, foreign body sensation, cough, or throat clearing. Patients meeting one or more of the following criteria were excluded from the study: those that had taken PPI drugs in three months or those with acute laryngitis, acute epiglottitis, laryngeal cancer, tonsillar inflammation, or allergic disease. All participants were informed and signed informed consent.

### 2.2. Equipment

The NBI system (CLV-180) and endoscope used in the study were produced by Olympus, Japan. This particular system can easily switch between traditional light source and NBI mode.

Statistical analysis was performed using IBM SPSS 20 for Windows. Overall descriptive statistics, including mean and standard deviation for continuous variables and frequencies, were calculated. Image information analysis was performed using Adobe Photoshop 8.0.1.

### 2.3. Instruments and methods

The RSI is a measure of LPR first proposed by Belafsky et al. in 2002 [13]. It is a method of rating patients' symptoms based on their own perspective. There are nine items, and the scale for each ranges from 0 (no problem) to 5 (severe problem) with a maximum total score of 45. If the RSI score is  $> 13$ , the patient is suspected to have LPR. Many studies [14,15] have shown that the RSI is a valid and reliable tool. The RFS is a clinical severity rating of eight items based on fiberoptic laryngoscopy findings presented by Belafsky et al. [16] in 2001. The scale includes the most common laryngeal findings related to LPR, and the total ranges from 0 (no abnormal findings) to a maximum of 26 (worst

possible score). If the RFS is  $> 7$ , LPR is suspected.

To begin, patients were required to complete an RSI questionnaire and undergo electronic fiber laryngoscopy for which laryngopharyngeal anesthesia of 2% tetracaine was administered; the patient then took a sitting position before the laryngoscope was inserted through the mouth. The larynx was imaged in both standard and NBI mode to fully expose the vocal cords, false vocal cords, anterior commissure, posterior commissure, arytenoid cartilage, and pyriform sinus, and the entire process was recorded. All the participants in the study had pictures and videos of the whole process, which doctors could use to rate and evaluate the subjects. Three doctors measured RFS from each patient's standard and NBI images and videos, the first doctor made a diagnostic score, only as a judgment as to whether it could be enrolled, and did not participate in the calculation of the Intraclass Correlation Coefficient (ICC). ICC calculated by the scores of the other two doctors. Subjects with self-reported RSI  $> 13$  and RFS  $> 7$  were selected as the LPR group, and those with RSI  $\leq 13$  and RFS  $\leq 7$  were selected as the control group. In order to reduce errors caused by subjectivity, three doctors were trained in the RFS evaluation criteria, and each patient's laryngoscopic images and videos were then graded. These were re-evaluated three days later and the final score determined if both grading values were the same.

The endoscopic findings of NBI include increased vascularity, green spots, erythema, and hyperplastic changes, and these are similar to NBI findings in patients with GERD [17,18]. NBI can reveal differences between increased vascularity that occurs outside of the epithelial layer and that which occurs within it. Erythema is caused by micro-erosions in the mucous layer, and these mucosal changes are not visible under traditional light sources [19]. Some mucosal lesions, such as contact ulcers and granuloma, can be observed by both traditional and NBI laryngoscopes but the characteristics of contact ulcers in particular are more obvious using NBI.

We used RGB to determine mucosal properties. RGB color mode is a commonly used color standard, which is obtained by changing the three color channels of red (R), green (G), and blue (B) and superimposing them on each other. RGB is the color of the three channels of red, green and blue. This standard includes almost all colors that human vision can perceive. In other words, any color is a R, G, B three colors with different values. (0–255), so we can use RGB values to quantitatively compare mucosal properties in different populations. In terms of detection area selection, since the anatomical division of the throat is large, it is impossible to measure all areas. We finally chose a relatively flat and smooth cartilage zone (arytenoid interchondral area). As shown in the Fig. 2, the area of the fixed area (100\*100 pixels) was selected and taken out. The average value of R, G, and B in the area was measured by Photoshop software.

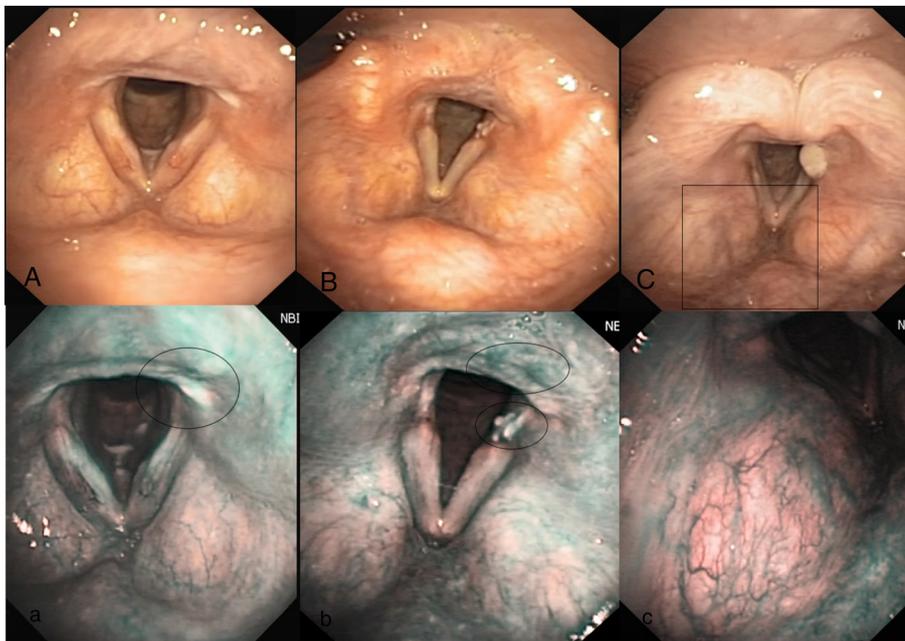
## 3. Results

### 3.1. Patient characteristics

As presented in Fig. 1, a total of 100 LPR patients were screened of which 70 were enrolled in the study as 30 patients did not meet the inclusion criteria. The mean age of the LPR study group was 50.0 years (SD = 9.7, range 21–78). A control group of 70 patients was matched according to age and gender with a mean age of 44.8 years (SD = 11.5, range 20–67) (Table 1).

### 3.2. RSI and RFS

The mean RSI and RFS scores of the LPR group were 15.8 and 9.4, respectively. The most common symptoms of the LPR group were foreign body sensation and throat clearing, with prevalence rates of 95.8% and 82.9%, respectively. (Table 2).



**Fig. 1.** Fig. 1 shows the performance of patients with LPR under conventional laryngoscope and NBI electronic laryngoscope. Figs. (A, B, C) are the patient's images under conventional laryngoscope, and figures (a, b, c) are the corresponding patient's performances under NBI. The presence of contact ulcers can be seen from Fig. (a) (shown in the circle in the figure (a)), which is not apparent under conventional laryngoscope. Fig. (b) shows the presence of green spots, which are not visible under conventional laryngoscopy, and we can also see the presence of granulomas. Fig. (c) is an enlarged image of the area in the black box in Fig. (C) under the NBI laryngoscopy, suggesting a marked increase in blood vessels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 1**  
Clinical Characteristics of LPR group Patients Versus Controls group.

	LPR group (70)	Control group (70)	P
Mean age, y	50.0	44.8	0.19
Male: female ratio	47:23	45:25	0.48
RFS, mean $\pm$ SD	9.4 $\pm$ 6.2	1.5 $\pm$ 2.3	P < 0.05
RSI, mean $\pm$ SD	15.8 $\pm$ 8.4	2.5 $\pm$ 3.6	P < 0.05
BMI, median [range]	22.4(16.7–24.6)	21.1(15.9–25.3)	

### 3.3. NBI Endoscopy Patterns

In order to more vividly describe the signs found under the NBI microscope, we defined the green patch-like signs of the pharyngeal mucosa under the NBI mirror as green plaques, which can be patchy or elongated (shown in the circle in the figure(b)). The cause may be due to the increase of submucosal vascular density combined with superficial mucosal injury. Vascular hyperplasia is defined as submucosal capillary hyperplasia (shown in the circle in the figure(c)). In the LPR group, we observed particular morphological manifestations, such as increased vascularity, green spots, contact ulcers, and granulomas, of which increased vascularity and green spots were the most common at 92.9% and 88.6%, respectively. The prevalence rates of these two manifestations in the control group were 21.4% and 7.1%, respectively. The microscopic manifestations of vascular hyperplasia and green spots can be observed with high specificity and sensitivity by NBI in patients with LPR (Table 3).

### 3.4. Interobserver and intraobserver agreement

Interobserver and intraobserver agreements were calculated between 2 investigators. As can be seen from Tables 3 and 5, different doctors have great differences in the laryngeal manifestations of LPR under traditional laryngoscopy, such as erythema, hyperemia and ventricular obliteration. However, the interobserver agreement for the NBI Endoscopy Patterns ranged from moderate to almost perfect. (Tables 2,4).

### 3.5. Comparison of RGB values of laryngopharyngeal mucosa between LPR group and control group under NBI laryngoscopy

The images and statistical results of the study indicate that LPR under NBI laryngoscopy, green spot and vascular proliferation are less objective than granuloma and contact ulcers. Doctors may have many differences in hypervascularity and green spot. So we tried to quantitatively evaluate these two signs with some kind of tool. In the end, we chose Adobe photoshop software, which can detect the corresponding RGB values according to the mucosa color. In this way, we can get the value of LPR group and control group, and then carry out comparative analysis. The selected arytenoid interchondral areas of the two groups were sampled and the numerical analysis statistics were recorded, as shown in the following table (Table 5). It can be seen that there are significant differences in the values of R, G and B between the throat reflux group and the control group under the NBI microscope, and the experimental group has higher values than the control group, and P < 0.05, the difference has Statistical significance.

## 4. Discussion

As a common otorhinolaryngology disease, LPR is often considered to be an external manifestation of GERD. According to reports in the literature [1], about 10% of otorhinolaryngology patients present GERD and, in addition, LPR has been associated with other otolaryngological diseases such as leukoplakia, laryngeal cancer, otitis media, and Reinke's edema. LPR is often accompanied by non-specific symptoms and signs, and the RSI and RFS measures proposed by Belafsky et al. are based on these [4,13]. However, the RSI score is a subjective assessment by patients of their own symptoms which may be affected by the individual's cultural perspective and psychological state. Although Belafsky et al. [16] suggest that 94% of patients with an RFS > 7 have LPR, this score may be also be influenced by subjectivity, both of individual doctors and between them. Elsewhere, Chang [20] shows that a doctor's knowledge of a patient's RSI score can influence the RFS they then provide. The study indicates that a low symptom score is more likely to be rated as low in terms of RFS, and likewise a high RSI value is more likely to be given a high RFS.

Although it has high specificity, 24-hour pH monitoring was not used as an enrolment test because of its low sensitivity to non-acid reflux and its invasiveness that is difficult for patients to accept. False

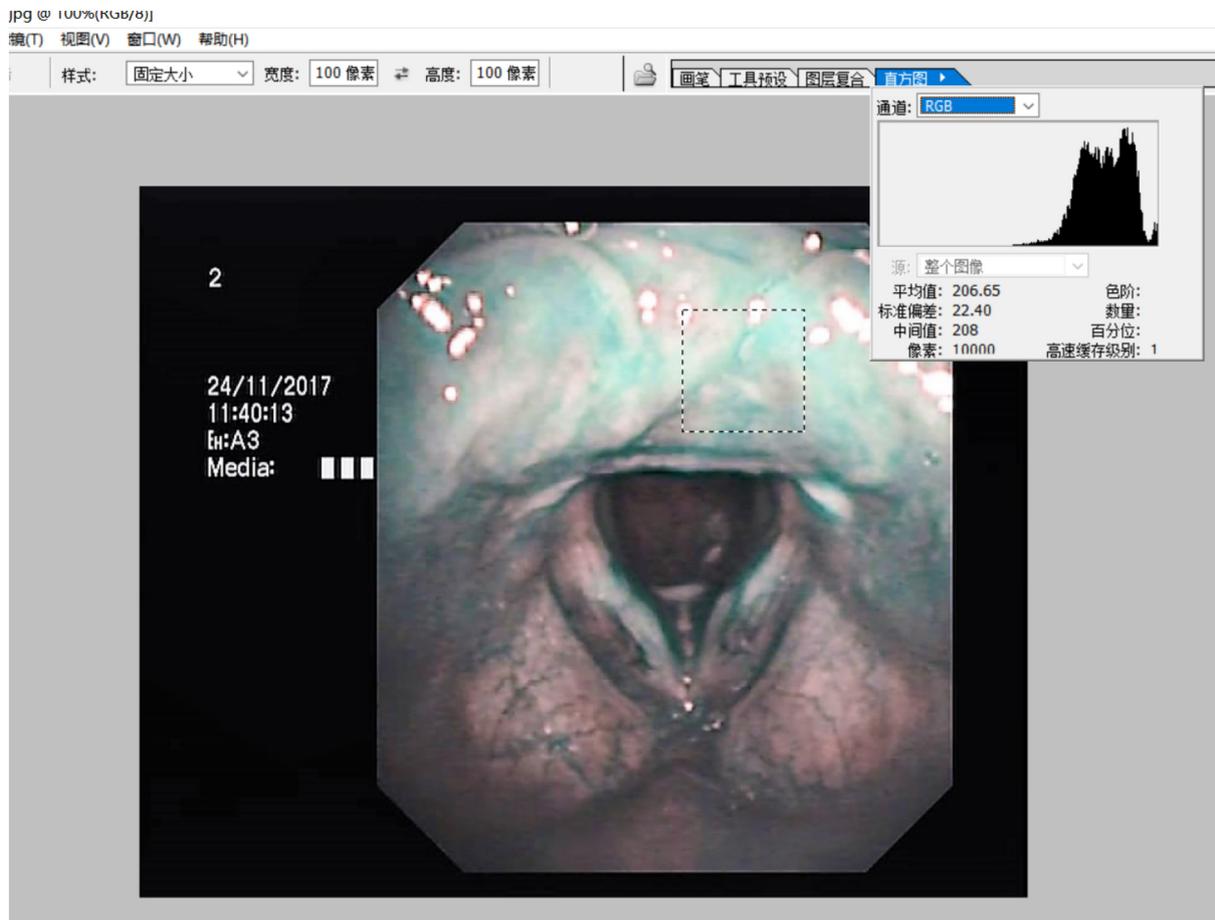


Fig. 2. As shown in the figure, the fixed area (100\*100 pixels) in the arytenoid interchondral area is selected to measure the RGB value.

positives caused by physiological acid reflux could not, however, be ruled out. Ultimately, the LPR group was defined to include patients with RFS > 7 and RSI > 13.

Using traditional laryngoscopy, evidence of LPR is generally observed as interarytenoid thickening, granuloma, and other non-specific signs; some studies have found that many healthy people present the same signs and so their specific cause is not always clear by traditional laryngoscopy [11]. Changes in microvessels and mucosa of the throat can be seen more clearly under an NBI microscope which may make distinguishing between LPR and control patients more straightforward [17]. In this way, our study found that NBI revealed particular LPR manifestations such as increased vascularity and green spots; specificity and sensitivity were relatively high and this performance is more objective than findings using traditional laryngoscopy.

Wood et al. [21] confirm significant differences, both histologically and in gene expression, between LPR and control patients, suggesting that it is possible to identify mucosal changes that are a direct result of LPR in a clinically diagnosed population. In particular, the study suggests that the medial arytenoid region could be more sensitive to these changes than the posterior commissure, and this coincides with our findings that particular mucosal changes, such as green spots and contact ulcers, are mostly distributed in the posterior commissure.

Table 2

Intraclass Correlation Coefficient (ICC) for RFS comparing videos and pictures with LPR group and control group (P < 0.05).

	Diffuse laryngeal edema	Posterior commissure hypertrophy	Erythema/hyperemia	Ventricular obliteration	Vocal fold edema	Granuloma	Total RFS score
LPR group	0.52	0.70	0.43	0.57	0.76	0.93	0.64
Control group	0.62	0.63	0.36	0.42	0.69	0.91	0.61

Table 3

Comparison of LPR group and control group under NBI.

NBI Endoscopy Patterns	LPR group	Control group	Sensitivity	Specificity	P
Increased vascularity	65(92.9%)	15(21.4%)	92.9%	78.6%	< 0.05
Green spots	65(88.6%)	5(7.1%)	88.6%	92.9%	< 0.05
Contact ulcers	44(62.9%)	11(15.7%)	62.9%	84.3%	< 0.05
Granuloma	24(34.3%)	0(0%)	34.3%	100%	< 0.05

Table 4

Intraclass Correlation Coefficient (ICC) for NBI Endoscopy Patterns comparing videos With LPR group and control group (P < 0.05).

NBI Endoscopy Patterns	Increased Vascularity	Green Spots	Contact ulcers	Granuloma
LPR group	0.81	0.86	0.91	0.93
Control group	0.75	0.82	0.64	0.91

**Table 5**  
Statistical analysis of RGB values in LPR group and control group (P < 0.05).

Color	Mean of LPR group (SD)	Mean of control group (SD)	t-Test	P value
R	158.6(13.8)	114.2(18.4)	-15.3	< 0.05
G	175.5(17.4)	93.4(21.3)	-17.9	< 0.05
B	169.1(14.6)	99.1(31.2)	-15.7	< 0.05

This study has some shortcomings. First, while we could have used clearer rigid endoscopic images, we chose to use flexible endoscopic videos to better replicate real-life settings. Because rigid laryngoscope cannot observe the situation of each part of larynx flexibly. Secondly we used the Olympus Evis Exera II imaging system rather than the more advanced Evis Lucera and could therefore only perform digital and not optical magnification. Secondly, participants that were selected for the LPR group may not all have had true LPR, and, similarly, the control group may not all have been healthy people without reflux; this error can only be minimized. This study can be viewed as reporting the shared and different characteristics between patients with LPR symptoms and those without as observed using NBI. Finally, although we found that the difference of RGB value under NBI laryngoscope between the LPR group and the control group was statistically significant, it is difficult to calculate the critical value and range of RGB abnormalities in the LPR group because of the small number of cases, and the standard diagnosis cannot be determined.

## 5. Conclusion

This preliminary study suggests that NBI laryngoscopy can be used to detect the presence of LPR and not just for tumour detection. As the results show, LPR presents vascularity and green spots with high specificity and sensitivity under NBI which can play a role in the auxiliary diagnosis of LPR.

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