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### ARTICLE DETAILS

| TITLE (PROVISIONAL) | Awareness about Laryngopharyngeal Reflux Disease among Chinese Otolaryngologists: A Nationwide Survey |
|---------------------|----------------------------------------------------------------------------------------------------|
| AUTHORS             | Xiao, Shuifang; Li, Jinrang; Zheng, Hongliang; Li, Xiangping; Yang, H; Junbo, Zhang; Peng, Xiaoxia; Zhou, Shuihong; Zhao, Chen; Chen, Donghui; Xiao, Xuping; Shi, Li; Huangfu, Hui; Tao, Zhenfeng; Chen, Xiong; Liu, Yehai; Qu, Shenhong; Wang, Guangke; Chen, Ting; Cui, Xiaobo; Tian, Linli; Zhou, Wensheng; Hongyan, Fang; Huang, Yongwang; Yu, Guodong; Lin, Zhenqun; Tang, Liang; He, Jian; Ma, Ruixia; Yu, Zhaoyan |

### VERSION 1 – REVIEW

| REVIEWER | Dhyanesh Patel  
Vanderbilt University Medical Center, Division of Gastroenterology, Hepatology and Nutrition |
|----------|------------------------------------------------------------------------------------------------|
| REVIEW RETURNED | 08-Dec-2021 |

| GENERAL COMMENTS | This is a nationwide survey study of ENT providers in China evaluating knowledge of LPR as an entity and about its risk factors, laryngoscopy signs, diagnostic methods and treatments. The manuscript is primarily descriptive, which reduces impact in clinical practice, but here are my concerns:  

Major concerns:  
1) The manuscript has multiple grammatical errors or spelling errors, which significantly reduce the readability. For instance, in abstract, results. "The most common knew risk factor, symptom, laryngoscope sign." Or conclusion saying "Although the majorities of Chinese otolaryngologists had head of LPRD."  
2) Given LPR is a debated diagnosis, probably the most important result might be that only 28% of participants knew about the use of pH testing as diagnostic test. I.e. majority of ENT providers diagnose LPR based on non-specific laryngoscopy findings or throat symptoms, which is a major knowledge gap. However, in figure 2 (panel A), it shows different information with 47.6% awareness of pH testing.  
3) The authors hypothesize that insufficient physician's knowledge about the disease might contribute to low diagnosis rate, but in the introduction note high prevalence of nearly 10%. In fact, LPR is falsely over diagnosed based on symptoms and laryngoscopy. The focus of the manuscript should be on how lack of knowledge about the disease leads to false misdiagnoses of LPR. This is clearly shown now by multiple RCTs including most recent multicenter trial in Eruope (O'Hare et al. BMJ 2021), which showed that use of empiric PPI therapy (based on throat symptoms, RSI or laryngoscopy) compared to placebo did not lead to any improvement in symptoms at 16 weeks or 12 months. |
4) Diagnosis of LPR now should require symptoms + moderate to severe AET (on objective pH testing such as 24 hour pH, 96 hour wireless pH monitoring).

5) In discussion, it is noted that “LPRD is considered to be an independent disease in the absence of GERD,” which is not true. Yes, most do not have typical symptoms of GERD, but having just throat symptoms without abnormal acid refluxing into esophagus (GERD) is not consistent with LPRD, but more consistent with laryngeal hypersensitivity or functional laryngeal disorder. The authors cite 26-28 references, which clearly show the opposite of how a true diagnosis of LPR needs reflux of acid.

6) The survey itself is a bit confusing. In the educational background, options are “Postgraduate or above” or “undergraduate or below.” Shouldn’t all otolaryngologists be postgraduate or above? How is that only in 51% of the country (unless the education structure is different)?

REVIEWER
Giannicola Iannella
University of Rome La Sapienza

REVIEW RETURNED
07-Jan-2022

GENERAL COMMENTS
Very interesting study that clearly shows the awareness overview of otolaryngologists regarding LPRD disease in a specific Chinese region. This field of study is interesting and poor similar studies has been published. Besides, the study is well conducted without major limitations. I suggest only minor revisions:

MATERIAL AND METHODS
- a flow chart of the study would be useful to better understand the design of the study

RESULTS
- consider a geo chart that could better represent the distribution of the survey in the region

DISCUSSION
Recently the salivary pep test has been validated in the diagnosis of LPRD (see and cite DOI 10.1016/j.ijporl.2015.10.034 and DOI 10.23812/19-437-L-26) it would have been useful to ask how many ENTs are familiar with this method of reflux diagnosis. in case it is not possible to know this data please describe this aspect in the discussion section.

diet is one of the most important behavioral aspects. this should be discussed (doi: 10.1002/lary.29890)

VERSION 1 – AUTHOR RESPONSE
Reviewer 1:
This is a nationwide survey study of ENT providers in China evaluating knowledge of LPR as an entity and about its risk factors, laryngoscopy signs, diagnostic methods and treatments. The manuscript is primarily descriptive, which reduces impact in clinical practice, but here are my concerns:

Major concerns:
1) The manuscript has multiple grammatical errors or spelling errors, which significantly reduce the readability. For instance, in abstract, results, "The most common knew risk factor, symptom,
laryngoscope sign.” Or conclusion saying “Although the majorities of Chinese otolaryngologists had head of LPRD.”

Response: Thank you very much for this valuable advice. The paper has been checked and revised by a native English speaker for language and grammatical editing.

2) Given LPR is a debated diagnosis, probably the most important result might be that only 28% of participants knew about the use of pH testing as diagnostic test. I.e. majority of ENT providers diagnose LPR based on non-specific laryngoscopy findings or throat symptoms, which is a major knowledge gap. However, in figure 2 (panel A), it shows different information with 47.6% awareness of pH testing.

Response: Thank you very much for this reminding. These clinical implicating of these two data were not entirely the same: a total of 47.6% of our participants knew about the use of pH testing in diagnosing LPR. However, only 28.3% of our participants knew about the use of 24-hour pH testing, not just pH testing, in diagnosing this disease. A great percentage of our participants did not know the time period demand of pH testing for diagnosing of LPRD.

3) The authors hypothesize that insufficient physician’s knowledge about the disease might contribute to low diagnosis rate, but in the introduction note high prevalence of nearly 10%. In fact, LPR is falsely over diagnosed based on symptoms and laryngoscopy. The focus of the manuscript should be on how lack of knowledge about the disease leads to false misdiagnoses of LPR. This is clearly shown now by multiple RCTs including most recent multicenter trial in Europe (O’Hare et al. BMJ 2021), which showed that use of empiric PPI therapy (based on throat symptoms, RSI or laryngoscopy) compared to placebo did not lead to any improvement in symptoms at 16 weeks or 12 months.

Response: Thank you very much for this valuable advice. In the introduction part, the data of 10% is come from one our previous research (PMID: 32449029). In that research, we surveyed and found that the incidence of LPRD-related symptoms in Chinese ENT departments could reach to 10%. However, only 14% of those with positive symptoms had previous diagnosis of LPRD, suggesting that as high as 86% of patients with possible LPRD had never been advised for LPRD related examinations or treatments. We speculated that the LPRD knowledge among our physicians are not good and may contribute to this phenomenon. Therefore, we surveyed the awareness of LPRD knowledge and proved that lack of such knowledge is common in Chinese otolaryngologists. We surely think that lack of knowledge may lead to not only missed diagnosis, but also false misdiagnoses of LPR. We had added this into the discussion part of this paper and had added the valuable reference you provided (Page 11, line 33-36).

4) Diagnosis of LPR now should require symptoms + moderate to severe AET (on objective pH testing such as 24 hour pH, 96 hour wireless pH monitoring).

Response: Thank you very much for this valuable advice. We also think that the diagnose of this disease should require both subjective symptoms and objective examinations. Regrettably, we did not include a question about the diagnostic criteria of this disease. We think that the awareness result about this maybe not good as the poor awareness of diagnostic methods.

5) In discussion, it is noted that "LPRD is considered to be an independent disease in the absence of GERD," which is not true. Yes, most do not have typical symptoms of GERD, but having just throat symptoms without abnormal acid refluxing into esophagus (GERD) is not consistent with LPRD, but more consistent with laryngeal hypersensitivity or functional laryngeal disorder. The authors cite 26-28 references, which clearly show the opposite of how a true diagnosis of LPR needs reflux of acid.

Response: Thank you very much for this reminding. This is surely our mistake, what we want to say is that LPRD symptoms could existed in the absence of GERD symptoms, as the pharyngeal mucosa is more sensitive to acid reflux. Some reflux events could cause severe damage to pharyngeal mucosa, but at same time cause even no damage to esophageal mucosa. We had corrected this mistake in discussion which was highlighted in yellow (Page 10, line 55-58).
6) The survey itself is a bit confusing. In the educational background, options are "Postgraduate or above" or "undergraduate or below." Shouldn't all otolaryngologists be postgraduate or above? How is that only in 51% of the country (unless the education structure is different)?
Response: Thank you very much for this reminding. I think that this is due to the different education structures. In our country, a great percentage of physicians had just completed the undergraduate education before starting work. Such phenomenon is much more common in physicians who had graduated a long time ago and in physicians who worked at small scale hospitals. However, such physicians will still receive specialized training after work. Currently, nearly all physicians graduating to work in big hospitals have completed postgraduate education.

Reviewer: 2
Dr. Giannicola Iannella, University of Rome La Sapienza
Comments to the Author:
Very interesting study that clearly shows the awareness overview of otolaryngologists regarding LPRD disease in a specific Chinese region. This field of study is interesting and poor similar studies has been published. Besides, the study is well conducted without major limitations. I suggest only minor revisions:
MATERIAL AND METHODS- a flow chart of the study would be useful to better understand the design of the study
Response: Thank you very much for this valuable advice. We had added a flow chart (the new Figure 1) into method part of this study.

RESULTS - consider a geo chart that could better represent the distribution of the survey in the region
Response: Thank you very much for this reminding. We had added a geo chart (the new Figure 2) to show the provincial administrative districts where this survey had been carried out in China.

DISCUSSION Recently the salivary pep test has been validated in the diagnosis of LPRD (see and cite DOI 10.1016/j.ijporl.2015.10.034 and DOI 10.23812/19-437-L-26) it would have been useful to ask how many ENTs are familiar with this method of reflux diagnosis. in case it is not possible to know this data please describe this aspect in the discussion section.
Response: Thank you very much for this reminding. In fact, there were some of our participants knew the use of salivary pepsin test for diagnosing LPRD. However, the proportion of such participants was very low, only accounts for 6.1% (138/2254). We think that this may be due to the extremely low penetration of this test in China. We had added such data into results part (Page 10, line 5) and corresponding Figure (the new Figure 4). We also had cited the two references you suggested in the method part (references 22-23).

diet is one of the most important behavioral aspects. this should be discussed (doi: 10.1002/lary.29890)
Response: Thank you very much for this reminding. We also think that diet change is so important in treating LPRD, and we had added related content into the discussion part which was highlighted in yellow (Page 11, line 54-60).

VERSION 2 – REVIEW

| REVIEWER       | Dhyanesh Patel |
|----------------|---------------|
|                | Vanderbilt University Medical Center, Division of Gastroenterology, Hepatology and Nutrition |
| REVIEW RETURNED| 05-Apr-2022   |
| GENERAL COMMENTS| The authors have addressed my concerns from prior review. |