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LARYNGOLOGY

# Impact of age on laryngopharyngeal reflux disease presentation: a multi-center prospective study

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**Abstract** The objective is to assess the differences in the severity of symptoms, signs, voice quality, and quality of life before and after treatment according to age in suspected laryngopharyngeal reflux (LPR) patients. The design used in this paper is prospective multi-center study. Eighty clinically diagnosed LPR patients with a reflux finding score (RFS) >7 and a reflux symptom index (RSI) >13 were treated with pantoprazole and diet recommendations for 3 months. Patients were subdivided into three groups according their age: group 1 (18–39 years, $N = 21$), group 2 (40–59 years, $N = 31$), and group 3 (≥60 years, $N = 28$). RSI, RFS, Voice Handicap Index (VHI), Short Form 36 questionnaire (SF36), aerodynamic, and acoustic measurements were evaluated at baseline and after treatment. The response to the empiric treatment was also assessed. Significant improvements in RSI, RFS, and VHI were found in all patient groups. The elderly patients showed a significantly lower RSI score than younger subjects ($p = 0.035$) without RFS difference among groups. At baseline, the SF36 score was better in group 3 with respect to social functioning ($p = 0.049$). At the 3-month follow-up, we found significant improvement of acoustic parameters only in the younger age groups (group 1 and group 2). The rate of resistant patients to the empiric treatment was higher in the younger group than in the elderly patient group (42.9 versus 28.6%). Age appears to reduce the subjective LPR symptom perception, leading to a lower rate of uncured patients. The utilization of acoustic parameters as an indicator of treatment effectiveness seems less useful for elderly subjects, probably due to an overlap between an aging voice and LPR.

**Keywords** Laryngopharyngeal · Reflux · Laryngitis · Voice

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## Introduction

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition defined as the back flow of gastric contents into the laryngopharynx which comes in contact with the tissues of the upper aerodigestive tract [1]. In otolaryngologic practice, LPRD afflicts 4–30% of outpatients who visit otolaryngology and head and neck surgery departments and up to 50% of subjects in the voice departments [2, 3]. This pathology typically affects the patients' quality of life via the development of a myriad of symptoms including hoarseness, throat clearing, excess throat mucus, dysphagia, coughing, globus sensation, and, in less than 50%, heartburn or stomach acid reflux [4–6]. The usual laryngostroboscopic signs

suggesting the LPRD diagnosis involve posterior commissure hypertrophy, posterior granulations, hyperemia, diffuse laryngeal edema, sticky mucus, and, in several cases, vocal fold edema [5, 7]. All of these symptoms and signs have been previously described and are easily assessed using the reflux symptom index (RSI >13) and reflux finding score (RFS >7); both clinical scales are used for evaluation of the treatment efficiency, but are also used as a cost-effective method for LPRD diagnosis. Indeed, regarding the many critics of the pH meter (i.e., high false-positive and false-negative rates, interpretation difficulties, inconsistency between pH findings, signs, and symptoms) [8, 9], many authors consider the empirical therapy approach [using a proton pump inhibitor (PPI) twice daily, 12 weeks] as an alternative reliable approach and report similar management than the diagnosis approach based on measurements using a pH meter [10, 11].

To date, it has been long established that the clinical expression of many diseases, such as heart or endocrinal disorders, substantially varies according to the age with unusual symptoms occurring in elderly patients [12, 13]. Thus, the sensation of clinical complaints related to gastroesophageal reflux disease (GERD) may decrease with the elderly [14]. Concerning LPRD, only one study conducted within a Korean population has suggested differences in the clinical presentation of LPRD between age groups, and since elderly patients could present with more symptoms than young patients, this may impact the LPRD-related quality of life [15]. Notwithstanding the results of this paper, the influence of age in LPRD clinical presentation and in the treatment efficiency still remains unclear.

The aim of this study is to assess the differences in the severity of symptoms, signs, voice quality, and quality of life according to the age of the suspected LPRD patients. In addition, we aimed to assess the usefulness of RSI, RFS, and voice quality as outcomes of the empirical treatment efficiency according to the age.

## Materials and methods

### Subject characteristics

One hundred and twenty-two outpatients with LPRD-related symptoms were recruited at three otolaryngology departments (EpiCURA Baudour & Ath Hospitals, and Liege University Hospital) from September 2013 to April 2016. To be included, patients should have an RSI >13 and an RFS >7; these two thresholds being significantly correlated with a positive double-probe pH monitoring result [16]. To reduce the risk to include subjects with cofactors able to bias the study of the voice quality and the LPRD diagnosis, we adopted strict exclusion criteria's available in Fig. 1. From these 122 patients, 80 completed the study. We studied three groups of these patients according to their age: these groups included patients from 18 to 39 (Gr1, $N = 21$), 40 to 59 (Gr2, $N = 31$), and more than 60 (Gr3, $N = 28$) years. The choice of these age limits was made according those of the previous studies [15].

The patient characteristics are described in Table 1. All patients were treated using diet and lifestyle behavioral recommendations based on Koufman's work [17] and were prescribed a twice daily pantoprazole (20 mg, 12 weeks). The adherence of diet and behavioral changes was assessed using a point scale with results between 0 (non-adherent) and 10 (fully adherent to the recommendations). At 12 weeks, the patients exhibiting both an RSI ≤13 and RFS ≤7 were considered to be responder. Following 12 weeks of uncompleted improvement (RSI >13 and/or RFS >7), the twice daily pantoprazole dose was increased (40 mg) for 12 additional weeks. At this time, the uncured patients received a complementary examination [i.e., 24-h pH/impedance monitoring, esophagoduodenoscopy (patients with heartburn), etc.] and were considered as resistant to the empiric treatment. To improve patient care [11], we used a clinically validated protocol [10, 11] for the management of the LPRD patients (Fig. 1). This study was approved by the local ethics committee (Ref.2015/99-B707201524621).

### Clinical evaluations, subjective voice assessments, and quality of life

All patients fulfilled the French version of the RSI score [18] at baseline and at the end of the empiric treatment. The RFS evaluation was made using video laryngostroboscopy (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) in a blind manner with regard to the patient complaints (RSI). Specifically, particular attention was given when evaluating the vocal fold edema and trophicity regarding the risk of aging voice occurrence in elderly patients. Subjects also completed the Voice Handicap Index (VHI) [19] and the Short Form 36 Health Survey (SF-36) at baseline and after treatment.

### Objective voice quality measurements

Currently, two main approaches exist to objectively assess voice quality: aerodynamic and acoustic measurements. Aerodynamic measurements provide useful information about both the subglottic blowing and the laryngeal functioning. They include many measurements, i.e., maximum phonation time (MPT), the phonatory quotient (PQ), estimated subglottic pressure, and the S/Z ratio. In this paper, we assessed the MPT, PQ, and S/Z ratio using a calibrated spirometer

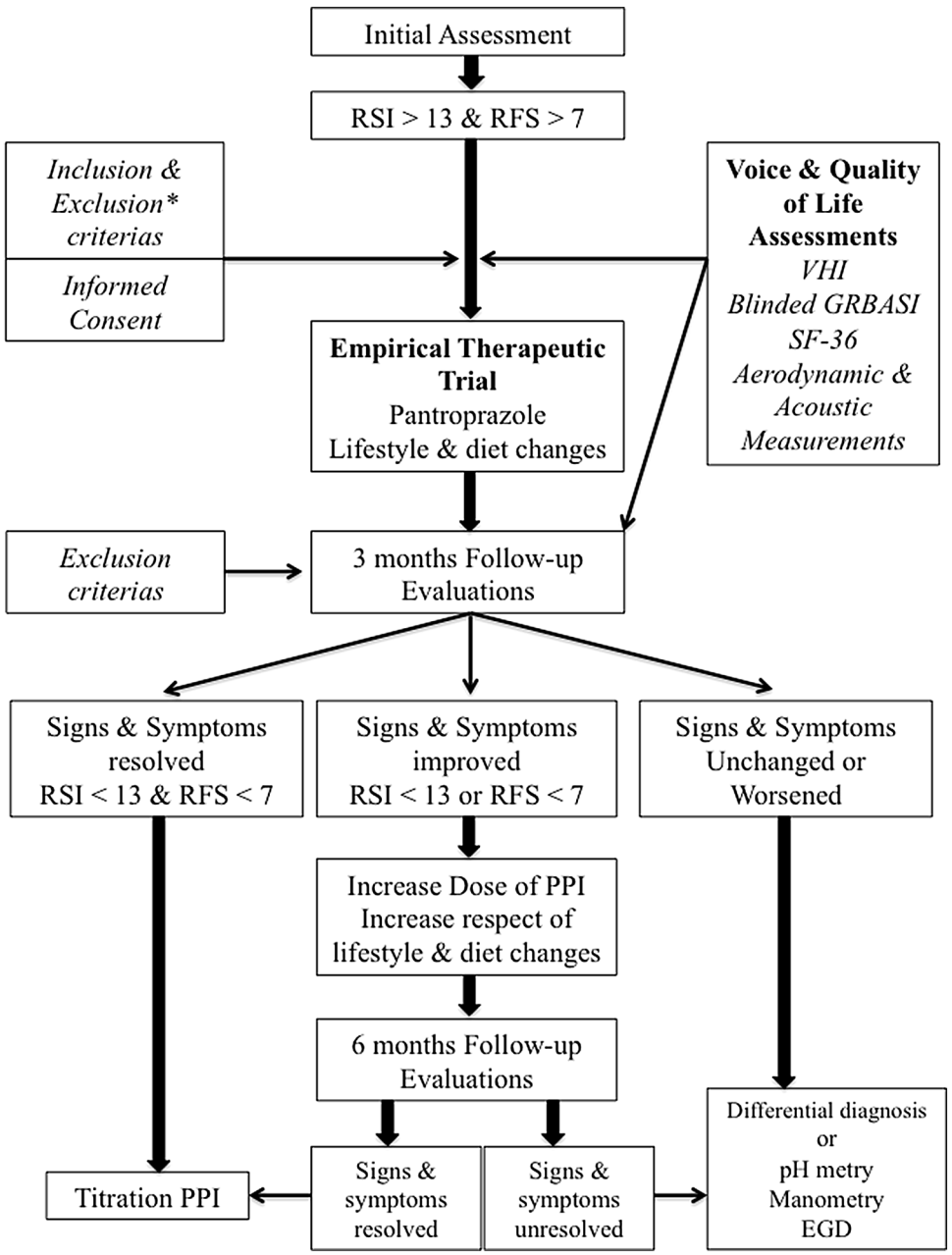


**Fig. 1** Flow chart describing the algorithm for assessment and management of patients. *Asterisk* Patients were excluded if they had infectious, functional, or neurological diseases, history of cervical surgery/radiotherapy, vocal cord paralysis/paresis, malignancy, allergies, or any causes of laryngitis. Active smokers and alcoholics were also excluded

(Spiro-USB100; Medical Electronic Construction, Brussels, Belgium).

Acoustic parameters also assess the vibratory function of the margin of the vocal folds and partially reflect the stability of the vibratory process. Thus, patients were asked to produce the/a/vowel several times, holding the utterance as long as possible. We used the second sample to measure the acoustic assessment including the Jitter percent (Jitt), relative average perturbation (RAP), smoothed pitch perturbation quotient (sPPQ), standard deviation of F0 (STD), shimmer percent (Shim), amplitude perturbation quotient (APQ), smoothed amplitude perturbation quotient (sAPQ), and the noise harmonic ratio (NHR). Measurements of the acoustic parameters were made on the most stable time interval, 1 s, as defined by the exhibition of the lowest Jitt, Shim, and NHR values (MDVP®, KayPentax, NJ, USA) [20].

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS; IBM Corporation, NY, USA). To compare age differences in RSI, RFS, VHI, SF-36, aerodynamic, acoustic measurements, and the proportion of responders at baseline and throughout the treatment period, we used both the median and the

**Table 1** Clinical characteristics of patients

| | Score, mean (SD) | | | *p* value |
|---|---|---|---|---|
| | 18–39 y | 40–59 y | >60 y | |
| | *N* = 21 | *N* = 31 | *N* = 28 | |
| Mean age (y) | 28.43 | 50.48 | 69.11 | – |
| BMI (kg/m$^2$) | 24.57 | 27.68 | 26.23 | 0.039 |
| Gender (F/M) | 7/14 | 16/15 | 10/18 | 0.509 |
| Treatment respect | 6.36 | 6.57 | 6.32 | 0.813 |
| Adverse reactions | 0 | 0 | 0 | 1.00 |
| Cured/uncured | 12/9 | 27/4 | 20/8 | 0.054 |
| Main complaints | | | | |
| Globus sensation | 5 (23%) | 5 (16%) | 6 (21%) | |
| Dysphonia | 5 (23%) | 4 (13%) | 7 (25%) | |
| Cough | 1 (5%) | 6 (19%) | 4 (14%) | |
| Odynophagia | 4 (19%) | 5 (16%) | 0 | |
| Heartburn | 1 (5%) | 3 (10%) | 3 (11%) | |
| Throat clearing | 1 (5%) | 2 (6%) | 4 (14%) | |
| Dysphagia | 1 (5%) | 3 (10%) | 1 (4%) | |
| Sticky expectorations/ | 1 (5%) | 1 (3%) | 2 (7%) | |
| Xerostomia | 0 | 0 | 0 | |
| Postnasal drip | 1 (5%) | 2 (6%) | 0 | |
| Otalgia | 1 (5%) | 0 | 0 | |
| Dyspepsia | 0 | 0 | 1 (4%) | |
| Breathing difficulties | 0 | 0 | 0 | |

*F/M* female/male, *N* number of subjects, *y* years

Kruskal–Wallis tests. The improvement of these items throughout the treatment was assessed with the Wilcoxon signed-rank test (within group). A level of significance of 0.05 was adopted.

## Results

### Differences in RSI, RFS, and SF-36 in accordance with age (baseline and after treatment)

Older patients (gr3: more than 60 years) had a significantly lower RSI score at baseline than younger subjects (gr1 and gr2). Among the RSI items, the GERD items were significantly different between groups (Table 2). Our RFS analysis did not reveal a significant difference according to age (Table 2). Within each group, both RSI and RFS significantly improved after treatment without substantial differences among groups (Table 3). Moreover, according to the Kruskal–Wallis test, we found a trend for younger patients to have higher rate of resistant patients than other groups (Table 1).

Concerning the general quality of life, only the social functioning item of SF-36 revealed a significant difference between groups. Thus, similar to RSI, the oldest subjects had significantly better scores than younger patients (Table 2). The mental health score improved in each group after the treatment period, while the physical score only improved in gr2 (Table 3). The improvement of both physical and mental health scores of SF-36 did not show significant differences between groups (Table 3).

### Difference of VHI according to age (baseline and after treatment)

At baseline, we did not find significant differences in the VHI total and item scores between groups according to age. Prospectively, the VHI total score significantly improved in each group without showing a significant difference in accordance with age (Table 4).

### Objective voice quality difference in accordance with age at baseline and throughout treatment

At diagnosis, older patients presented lower values of PQ than younger subjects. Simultaneously, the older patient cohort exhibited a lower vital capacity (Table 5). No aerodynamic measurements improved after treatment in all groups.

Concerning the acoustic measurements, at baseline, we found higher values of sAPQ in older patients than in younger patients ($p = 0.039$). However, the other short-term perturbation cues (Shim, APQ, and sAPQ) reported significant improvement after treatment only within the younger groups. We found similar enhancements with the values of Jitt, RAP, sPPQ, and STD (Table 6).

## Discussion

LPRD is a causative factor of chronic laryngitis and complaints affecting the quality of life of patients. Since the first work of Koufman et al. [21], only one study investigated the impact of LPRD on the severity of symptoms, signs, voice quality, and quality of life according to age [15]. The main result of our study highlighted that older patients complained less than younger patients at baseline even if they had similar laryngeal signs of chronic laryngitis. This difference was strengthened between the groups on the assessment of heartburn, dyspepsia, and chest pain (GERD complaints). In GERD, the unusual expression of symptoms by elderly patients has already been the subject of previous studies, which showed similar findings compared to ours [14]. Furthermore, several studies reported that the frequency of GERD complications (i.e., esophagitis, stricture, and Barrett esophagus) was substantially higher in elderly than in younger patients [22–25]. A possible explanation

**Table 2** Initial RSI, RFS, and SF-36 scores according to age

| Scales, items | Score, mean (SD) | | | |
|---|---|---|---|---|
| | 18–39 years | 40–59 years | >60 years | *p* value |
| | *N* = 21 | *N* = 31 | *N* = 28 | |
| RSI | 23.94 ± 1.71 | 23.78 ± 1.50 | 19.19 ± 1.26 | 0.035 |
| Voice problem | 2.75 ± 0.45 | 2.74 ± 0.39 | 2.81 ± 0.38 | 0.641 |
| Throat clearing | 3.44 ± 0.48 | 4.11 ± 0.28 | 3.13 ± 0.50 | 0.193 |
| Postnasal drip | 2.94 ± 0.50 | 3.04 ± 0.37 | 2.69 ± 0.44 | 0.734 |
| Dysphagia | 2.00 ± 0.49 | 1.78 ± 0.33 | 0.94 ± 0.31 | 0.385 |
| Coughing post-eating and lying down | 1.75 ± 0.49 | 2.30 ± 0.47 | 1.44 ± 0.34 | 0.698 |
| Breathing difficulties | 1.50 ± 0.42 | 1.59 ± 0.35 | 1.38 ± 0.35 | 0.969 |
| Troublesome cough | 2.56 ± 0.46 | 2.44 ± 0.41 | 1.94 ± 0.46 | 0.895 |
| Globus pharyngeus | 3.25 ± 0.49 | 2.89 ± 0.41 | 2.38 ± 0.50 | 0.590 |
| Pyrosis, heartburn and chest pain | 4.06 ± 0.34 | 2.78 ± 0.38 | 2.44 ± 0.47 | 0.006 |
| RFS | 10.00 ± 0.40 | 11.04 ± 0.46 | 10.59 ± 0.48 | 0.195 |
| Subglottic edema | 0.04 ± 0.04 | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.485 |
| Ventricular obliteration | 1.00 ± 0.32 | 1.41 ± 0.30 | 0.75 ± 0.31 | 0.879 |
| Arytenoid/diffuse redness | 3.00 ± 0.26 | 3.33 ± 0.18 | 3.25 ± 0.25 | 0.510 |
| Vocal folds edema | 1.13 ± 0.18 | 1.56 ± 0.13 | 1.38 ± 0.22 | 0.357 |
| Diffuse laryngeal edema | 1.13 ± 0.22 | 1.19 ± 0.20 | 1.06 ± 0.28 | 0.795 |
| Posterior commissure hypertrophy | 2.00 ± 0.16 | 2.26 ± 0.11 | 2.13 ± 0.18 | 0.287 |
| Granuloma/granulation | 0.38 ± 0.20 | 0.30 ± 0.14 | 0.56 ± 0.22 | 0.240 |
| Endolaryngeal mucous | 1.37 ± 0.24 | 0.96 ± 0.20 | 1.50 ± 0.22 | 0.220 |
| SF36 | | | | |
| Physical functioning | 89.69 ± 3.37 | 80.56 ± 3.00 | 75.94 ± 6.56 | 0.127 |
| Role-physical | 68.75 ± 8.99 | 62.04 ± 7.11 | 56.25 ± 11.52 | 0.881 |
| Bodily pain | 75.19 ± 7.48 | 68.63 ± 5.86 | 64.81 ± 6.81 | 0.329 |
| General health | 54.88 ± 4.97 | 58.81 ± 3.76 | 63.38 ± 3.67 | 0.853 |
| Vitality | 47.06 ± 5.77 | 52.52 ± 3.59 | 57.13 ± 5.23 | 0.702 |
| Social functioning | 72.00 ± 8.34 | 67.63 ± 4.75 | 88.38 ± 4.90 | 0.049 |
| Role-emotional | 62.50 ± 10.49 | 77.70 ± 7.13 | 77.00 ± 9.01 | 1.00 |
| Mental health | 54.25 ± 4.88 | 59.44 ± 4.07 | 63.19 ± 4.91 | 0.351 |
| Physical health | 70.34 ± 20.24 | 68.11 ± 19.40 | 65.78 ± 22.82 | 0.755 |
| Mental health | 60.17 ± 26.48 | 63.49 ± 19.59 | 70.73 ± 18.80 | 0.559 |

*RFS* reflux finding score, *RSI* reflux symptom index, *SD* standard deviation, *SF-36* Short Form 36 Health Survey

for this result may consist of neurological deterioration of the terminal sensitive nerve ending, especially in the upper aerodigestive tract, leading to a reduction of the symptom's perception. This observation is critical, since, as shown in GERD studies [14], the reduction of the symptom perception encountered in older people suggests that the subjective complaints of this category of patients could be an incorrect indicator of LPRD presence and severity, and may bias the response to PPI treatment. However, our data, which exhibit a higher rate of non-responder patients in younger (42.9%) than in older patients (28.6%), tend to support this hypothesis. These observations may raise questions about the similar application of the current RSI threshold (RSI > 13) in all age groups for selecting patients with a high probability of LPRD diagnosis.

To the best of our knowledge, only the study by Lee et al. investigated the effect of age on LPRD signs, symptoms, and quality of life [15]. These authors found that elderly persons could have a higher RSI at baseline than younger subjects, which conflicts with the results of the present study [15]. Various factors may explain the inconsistencies between our results. First, the inclusion process of patients varies between our two studies, since we included patients with both RSI >13 and RFS >7 scores, fully respecting the initial thresholds of Belafsky et al. that suggest a high probability of LPRD [16]. The selection of patients in the study by Lee et al. was based on a physician's diagnosis, irrespective of the well-validated thresholds of both the RSI and RFS scores. This difference represents a potential bias regarding the recruited population

**Table 3** Improvement in RSI, RFS, and SF-36 scores after treatment

| Test | Score, mean (SD) | | *p* value | |
|---|---|---|---|---|
| | Baseline | 3 months | Within group | Among Groups |
| RSI | | | | |
| 18–39 years | 23.94 ± 1.71 | 12.05 ± 6.37 | <0.001 | |
| 40–59 years | 23.78 ± 1.50 | 8.39 ± 6.28 | <0.001 | 0.115 |
| 60–79 years | 19.19 ± 1.26 | 7.18 ± 5.00 | <0.001 | |
| RFS | | | | |
| 18–39 years | 10.00 ± 0.40 | 4.24 ± 3.00 | <0.001 | |
| 40–59 years | 11.04 ± 0.46 | 5.26 ± 3.01 | <0.001 | 0.903 |
| 60–79 years | 10.59 ± 0.48 | 4.93 ± 3.47 | <0.001 | |
| SF-36 | | | | |
| Physical health | | | | |
| 18–39 years | 70.34 ± 20.24 | 77.97 ± 18.43 | 0.061 | |
| 40–59 years | 68.11 ± 19.40 | 78.53 ± 15.45 | 0.001 | 0.615 |
| 60–79 years | 65.78 ± 22.82 | 72.25 ± 20.16 | 0.061 | |
| Mental health | | | | |
| 18–39 years | 60.17 ± 26.48 | 72.75 ± 20.79 | 0.003 | |
| 40–59 years | 63.49 ± 19.59 | 76.19 ± 17.26 | <0.001 | 0.465 |
| 60–79 years | 70.73 ± 18.80 | 78.83 ± 13.60 | 0.024 | |

*RFS* reflux finding score, *RSI* reflux symptom index, *SD* standard deviation, *SF-36* Short Form 36 Health Survey

**Table 4** Improvement in VHI scores after treatment

| Test | Score, mean (SD) | | *p* value | |
|---|---|---|---|---|
| | Baseline | 3 months | Within group | Among groups |
| VHI | | | | |
| 18−39 years | 17.86 ± 12.31 | 10.67 ± 9.05 | 0.002 | |
| 40–59 years | 16.66 ± 13.70 | 10.63 ± 10.28 | 0.007 | 0.313 |
| 60–79 years | 20.50 ± 17.37 | 9.77 ± 10.67 | <0.001 | |

*SD* standard deviation, *VHI* voice handicap index

**Table 5** Initial aerodynamic measures according to age

| Aerodynamic measurements | Values, mean (SD) | | | |
|---|---|---|---|---|
| | 18–39 years | 40–59 years | >60 years | *p* value |
| | *N* = 21 | *N* = 31 | *N* = 28 | |
| MPT | 15.84 ± 2.21 | 14.58 ± 1.05 | 16.66 ± 2.24 | 0.194 |
| PQ | 283.75 ± 24.86 | 283.33 ± 20.79 | 227.38 ± 22.68 | 0.021[a] |
| S/Z | 1.08 ± 0.07 | 1.17 ± 0.14 | 0.81 ± 0.07 | 0.177 |

*MPT* maximum phonation time, *PQ* phonatory quotient, *S/Z* S/Z ratio, *SD* standard deviation

[a]The vital capacity of each group in the present study was, respectively, 3895.63 ± 291.26 (gr1), 3706.30 ± 165.95 (gr2), and 3167.62 ± 147.46 (gr3), showing a trend to significant difference between groups ($p = 0.08$; Kruskall–Wallis test)

for the study, limiting our inter-study comparison. Second, it has been suggested in the previous studies that the variation of diet according to the world region also impacts the reflux presentation and the values of the RSI at baseline with higher scores in Western areas [16, 18] than in Asian populations [26]. Third, it is possible that other extrinsic factors may have impacted the laryngeal complaints particularly in the elderly Korean people. Thus, an existing difference between Korea and Belgium (Western Europe) still remains with regard to exposure to fine particles, since the level of fine particles seems to be lower in Belgium than in Korea [27, 28], where the air quality is impacted

**Table 6** Improvement of acoustic measurements after treatment

| Test | Score, mean (SD) | | *p* value | |
|---|---|---|---|---|
| | Baseline | 3 months | Within group | Among groups |
| F0 perturbation cues | | | | |
| Jitt | | | | |
| 18–39 years | 1.31 ± 0.75 | 1.23 ± 0.93 | 0.002 | |
| 40–59 years | 1.48 ± 0.15 | 1.05 ± 0.63 | 0.033 | 0.409 |
| 60–79 years | 1.54 ± 0.31 | 1.98 ± 3.91 | 0.790 | |
| RAP | | | | |
| 18–39 years | 0.72 ± 0.48 | 0.74 ± 0.57 | 0.054 | |
| 40–59 years | 0.83 ± 0.44 | 0.62 ± 0.39 | 0.031 | 0.386 |
| 60–79 years | 0.89 ± 0.74 | 1.20 ± 2.36 | 0.946 | |
| sPPQ | | | | |
| 18–39 years | 0.89 ± 0.43 | 0.91 ± 0.51 | 0.520 | |
| 40–59 years | 1.16 ± 0.11 | 0.89 ± 0.44 | 0.027 | 0.375 |
| 60–79 years | 1.60 ± 0.26 | 2.41 ± 5.86 | 0.853 | |
| STD | | | | |
| 18–39 years | 2.31 ± 1.39 | 2.52 ± 1.75 | 0.054 | |
| 40–59 years | 2.60 ± 0.34 | 1.96 ± 1.02 | 0.033 | 0.860 |
| 60–79 years | 5.53 ± 1.49 | 4.87 ± 10.12 | 0.238 | |
| Intensity perturbation cues | | | | |
| Shim | | | | |
| 18–39 years | 4.26 ± 1.83 | 4.01 ± 1.17 | 0.520 | |
| 40–59 years | 5.26 ± 0.43 | 4.02 ± 1.64 | 0.001 | 0.230 |
| 60–79 years | 4.42 ± 0.51 | 5.51 ± 4.78 | 0.258 | |
| APQ | | | | |
| 18–39 years | 3.41 ± 1.35 | 3.33 ± 1.11 | 0.002 | |
| 40–59 years | 4.35 ± 0.33 | 3.18 ± 1.33 | <0.001 | 0.219 |
| 60–79 years | 5.03 ± 0.48 | 4.56 ± 3.67 | 0.191 | |
| sAPQ | | | | |
| 18–39 years | 6.36 ± 2.49 | 6.42 ± 2.65 | 0.054 | |
| 40–59 years | 8.59 ± 0.55 | 6.27 ± 3.89 | 0.002 | 0.051 |
| 60–79 years | 9.20 ± 0.83 | 9.15 ± 5.44 | 0.949 | |
| Noise-related measurements | | | | |
| NHR | | | | |
| 18–39 years | 0.13 ± 0.04 | 0.13 ± 0.02 | 0.520 | |
| 40–59 years | 0.14 ± 0.01 | 0.13 ± 0.02 | 0.183 | 0.520 |
| 60–79 years | 0.14 ± 0.05 | 0.17 ± 0.16 | 0.339 | |

*SD* standard deviation

by China's pollution [29]. Regarding scientific evidence that suggests an epidemiological relationship between the exposure to fine particles and the development of chronic laryngitis [30], particularly in Korea [31], it is possible that the complaints of elderly subjects reported in the study of Lee et al. may be related to both LPRD and lifelong pollution exposure [30, 31]. Concerning the improvement of RSI and RFS throughout the treatment period, all patient groups reported significant improvement of both signs and symptoms in a similar manner that corroborates the results of Lee et al. [15] and those of many single cohort studies [16, 20, 26]. Thus, age seems to have no effect on the improvement of symptoms (RSI) and signs (RFS) throughout the treatment period.

The various clinical complaints of LPRD patients are well known to negatively impact the quality of life [4, 5, 32, 33]. In this paper, we observed that elderly patients, who had less laryngeal symptoms, have better scores in social functioning quality of life. However, this discrete result, which only concerns one item on the SF-36 scale, could be reflected by the lower complaints of LPRD (RSI total score) and/or heartburn in the elderly group. These results are in line with other studies demonstrating that laryngeal symptoms related to LPRD significantly impact the social functioning

quality of life of patients [4, 32, 34]. Among them, Lee et al. also observed that the patients with higher RSI scores had lower LPR health-related quality of life scores [15]. Prospectively, the mental health score significantly improved in all groups, while the physical health score only improved in the second group (40–59 years). However, among groups, we did not find significant differences in the improvement of these two scores according to age. Our data reflect those of the current literature since it is well established that LPRD treatment improves the quality of life for LPRD patients [4, 32]. Concerning the improvement of quality of life among groups according to age, Lee et al. observed similar findings, namely, a significant impact of age on the improvement of the quality of life [15].

In addition, regarding the evidences reporting a significant impact of LPRD on voice quality, we aimed to investigate the usefulness of objective voice quality as an outcome of treatment efficiency according to the age. The motivation for this part of study was embodied by the occurrences reporting that older patients have micro- and macrostructural changes in the composition of the vocal fold [35], which may lead to a higher sensitivity to voice disorders, that may also impact the utilization of voice quality as outcome [36, 37]. Moreover, it has recently been suggested that wound healing and inflammation within the vocal fold tissue presumably underlie physiological aging influences [38, 39]. Regarding these recent data, we postulated that elderly patients have a high negative impact of LPRD on voice quality compared to younger subjects. Our study of voice quality reported no difference between groups at the moment of the diagnosis and throughout treatment, concerning both the VHI scores and the improvement of these scores. Concerning the initial aerodynamic evaluations, the lower value of vital capacity in the older group limits the interpretation of the PQ results, since that measure may significantly impact and bias the final results. Acoustically, older patients had higher values of sAPQ, which is an acoustic parameter reflecting the short-term perturbation of the voice intensity. This small difference related to age makes sense prospectively, since we observed better improvement in several acoustic cues (Jitt, RAP, sPPQ, STD, Shim, APQ, and sAPQ) within younger groups (gr1 and gr2) but not in elderly patients (gr3). Several hypotheses may explain these results.

First, we must keep in mind that the RFS score does not take into consideration all signs of LPRD that have a substantial impact on voice quality, especially several chronic signs including vocal fold keratosis, epithelium thickening, and mucosa microtraumatisms [5]. In their older age, the elderly patients could present with more of these chronic signs than younger patients who may significantly impact their voice quality. However, several of these signs (keratosis or microtraumatisms and the microscars) are known to need more time to disappear, especially in a context of a slower wound healing process related to age [5]. In addition, in light of the studies supporting that the mucosa of the margin of the vocal folds of the older patients is less resistant to vocal aggression [38, 39], we may suspect that the irritation related to the refluxed content of the stomach (pepsin, trypsin, and other gastroduodenal proteins) could rapidly lead to vocal fold lesions and biomolecular alterations, both decreasing the vibratory biomechanical properties of the vocal folds.

Second, it is probable that many of our older patients have both LPRD and presbyphonia which is more prevalent in people older than 65 years of age [40]. Skeletal, pharmaceutical, hormonal, circulatory, and neuromuscular changes usually occurred in elderly patients and may insidiously impact voice quality [41]. These modifications result in expected age-related acoustic variability, which remains difficult to distinguish from a true voice disorder such as LPRD [41]. In the present study, according to the RFS (vocal fold trophicity and the endolaryngeal mucus thickening items), we determined that the most common video laryngostroboscopic sign found in presbyphonia (i.e., vocal fold atrophy with incomplete glottal closure and dryness of the mucosa) are no more prevalent in older patients than in younger patients [40, 41]. Moreover, our older patients did not have a significantly lower MPT, which is a usual aerodynamic alteration related to incomplete glottal closure observed in aging voice patients [42]. The lack of these differences between our older group and the other groups may support a low rate of presbyphonic patients in our cohort, but it does not exclude the occurrence of both symptoms and signs related to aging voice in our older population. Indeed, beyond the usual signs, aging voice is characterized by laryngeal symptoms, such as dysphonia, throat clearing, and globus sensation that can be misattributed to LPRD [41]. Currently, we cannot say that these two main hypotheses are true; thus, biomolecular studies are needed to investigate these hypotheses.

In this study, we did not record the LPRD events using a multichannel pH monitoring study, since this method still remains controversial and expansive. Moreover, it has been demonstrated that 24-h MII pH monitoring and a combination of RSI and RFS are quite competitive with each other in selecting LPRD patients [43]. Largely for these reasons, the increased management strategy for LPRD patients is based on the clinical response to diet and empirical medical treatment to confirm the diagnosis [10, 11], which is usually very explicit and recommended by both gastroenterology and otolaryngology experts and guidelines. However, our observations raise the question of the utilization of this approach both in the evaluation of the symptoms related to LPRD in elderly patients who often have LPR-like symptoms due to

aging voice. At the end of the empirical period of 3 months, the proportion of responder patients varied, ranging from 41 to 100% according to the previous studies [6, 44]. Our lower rate of non-responders in the older group tends to support the notion that the reliability of the clinical complaints of the elderly patients could be lower than younger patients, ultimately reducing the ability to detect resistant patients. To date, there are three main causes explaining the treatment resistance. The first concerns the poor treatment compliance. Indeed, as showed in the study of Pisenga et al., 62.7% of patients reported an incorrect routine in taking their PPI, since they take it with other pills, with food/drink, and many patients often forget the PPI taking [45]. The second cause involves the biliary LPRD that cannot improve with high doses of PPI, because the increase of pH in the laryngopharyngeal space may improve the destructive activity of trypsin and strengthen the mucosa damage [46, 47]. The third cause is the misdiagnosis of LPRD. Regarding these main causes, the management of resistant patients must at least include a verification of the treatment compliance, the realization of pH impedance monitoring, and the exploration of both differential diagnoses and laryngeal cofactors that could explain the persistence of signs and symptoms (i.e., allergy, exposition of toxic particles, etc.).

Regarding the higher risk of elderly subjects to develop laryngeal cancer favored by LPRD, we need to improve the detection of LPRD resistance to effectively treat the illness. Finally, our report suggests that the usefulness of voice quality as outcome of the treatment efficiency should be done carefully, since many patients have aging voice that may bias the voice quality evaluations.

## Conclusion

Elderly patients with LPRD had lower symptom score and better quality of life score than younger patients. These observations, and the lower rate of uncured older patients, put into question the reliability of the symptom's evaluation of elderly patients for both the LPRD diagnosis and the judgment of the treatment efficiency. Moreover, our results suggest that the utilization of voice quality as outcome of the treatment efficiency is less reliable in elderly patients who often suffer from presbyphonia. Further studies with a higher number of patients and precise evaluations of all signs and symptoms of both LPRD and presbyphonia are needed to confirm our results.

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