Acoustic voice analysis in patients with laryngopharyngeal reflux

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Abstract. Exposure of laryngeal mucosa to gastric juice causes trauma either directly or through a secondary mechanism, which causes chronic cough. Laryngeal mucosal trauma can cause voice problems, which is a frequent complaint in patients with laryngopharyngeal reflux (LPR). Acoustic voice analysis using Multi-Dimensional Voice Program (MDVP) is a relatively convenient and objective method for the assessment of voice disorders. This study assessed the differences between the values of acoustic voice parameters in patients with LPR and those without LPR. A comparative cross-sectional study was conducted in the outpatient Clinic at the Cipto Mangunkusumo Hospital between May and November 2016 (LPR group, n = 40; non-LPR group, n = 20). Some acoustic voice parameters in the LPR group were higher than those in the non-LPR group. Male patients exhibited significantly higher jitter, Pitch Perturbation Quotient (PPQ), and Noise/Harmony noise (NHR) values, whereas female patients exhibited significantly higher shimmer and Amplitude Perturbation Quotient (APQ) values. Significant differences were observed with respect to jitter, PPQ, APQ, and NHR values between male patients in the mild-LPR group and those in the moderate–severe LPR group.

1. Introduction
The term laryngopharyngeal reflux (LPR) was adopted in 2002 by the American Academy of Otolaryngology and Head and Neck Surgery. It refers to the clinical manifestations of reflux of gastric juice into the upper airway. Association of LPR with various abnormalities of the larynx has been reported, presumably because the larynx is susceptible to injury from gastric juices because of the lack of intrinsic and extrinsic defense mechanisms in the laryngeal epithelium. LPR can induce laryngeal abnormalities owing to direct irritation of laryngeal mucosa by the gastric juice or through a secondary mechanism that causes chronic cough and eventually leads to laryngeal trauma [1–15].

Subjective assessment of the quality of voice is liable to be affected by the experience and expertise of the examiner. Several computer programs for voice acoustic analysis are currently available and the most commonly used is the Multi-Dimensional Voice Program (MDVP). It is an objective and relatively straightforward method that is safe and comfortable for the patient. Several studies have assessed the relationship between dysphonia and LPR; however, there is little research on sound acoustic analysis in patients with LPR. In a study by Pavlidou et al., there was no reported significant difference in baseline mean frequency between patients with LPR and healthy controls; however, jitter and shimmer acoustic parameters values in patients with LPR were significantly higher than those in the healthy control group.
In a study by Dalgic et al., jitter and shimmer acoustic parameter values of functional dysphonia in patients with LPR were higher than those of functional dysphonia in patients without LPR [5, 10–13]. Currently, there is no data on the value of acoustic voice in patients with LPR examined using MDVP in the Department of Ear, Nose, and Throat (ENT)- Head and Neck Surgery, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo Hospital. Therefore, it was necessary to study this case considering the case of LPR was one of the many cases that founded in the field of ENT. Besides the voice quality assessment in patients with LPR currently was only subjectively perceptual.

2. Methods
This cross-sectional study compared the acoustic voice parameters between patients with LPR (LPR group) and patients without LPR (non-LPR group). The study protocol had been approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital. The study was conducted in the outpatient clinic of Department of ENT- Head and Neck Surgery, Cipto Mangunkusumo Hospital. Diagnosis of LPR was based on values of RSI > 13 and reflux finding score (RFS) value >7. Patients in the non-LPR group showed no significant laryngeal abnormality on nasopharyngeal laryngoscopy examination, exhibited no subjective or objective signs of LPR (RSI ≤13 and RFS value ≤7), and had no obvious voice disorder.

Exclusion criteria were impaired lung function or lung abnormalities (maximum phonation time less than normal), thyroid disease, tumor/history of trauma/surgery in the neck and laryngeal areas, neurologic abnormalities, immune disorders, cardiorespiratory or endocrine disorders that are associated with laryngeal mucosal abnormalities or impaired voice quality, lesions in the vocal cords other than the lesions mentioned in the RFS value. Written informed consent was obtained from all patients prior to their enrolment. All patients were capable of participation in the study and filling the RSI questionnaires. Next, physical examination of ENT and flexible nasopharyngeal laryngoscopy for RFS replenishment based on clinical findings on the larynx. At the time of voice sampling, all patients were educated about the use of pitch and voice intensity. Voice sampling was recorded by a microphone connected to a computer with pre-installed MDVP program. The voice was recorded for a minimum of 3 seconds with the microphone held 10 cm from the patient’s mouth in a quiet room. Patients were instructed not to drink coffee or tea or smoke for at least 2 h prior to the examination. Voice recording was performed 3–5 times, and the best record on the basis of acoustic voice analysis was used for the research.

Data was analyzed with SPSS (Statistical Package for Social Sciences; IBM Corp.) 20.0. The analysis started with univariate analysis of patient characteristics. Between-group differences with respect to normally distributed variables were assessed using unpaired t-test and those with respect to non-normally distributed variables were assessed with nonparametric Mann–Whitney test.

3. Results
The study population comprised 60 patients: 40 in the LPR group and 20 in the non-LPR group. All patients had a maximum phonation time of >11 seconds, which indicated no lung function abnormalities. Age distribution was comparable between the two groups. In the LPR group, the RFS values were similar in male and female patients (Table 1).

| Variable     | LPR group (n = 40) | Non-LPR group (n = 20) |
|--------------|--------------------|------------------------|
| **Age (years)** |                    |                        |
| Male         | 32.5 (28–60)**     | 30.5 (28–53)**         |
| Female       | 45.5 (29–60)**     | 36.5 (25–56)**         |
| **RFS value** |                    |                        |
| Male         | 12.5 (8–15)**      | 6.5 (3–7)**            |
| Female       | 12.31 ± 2.15*      | 4.5 ± 1.99*            |

* Mean and standard deviation values
** Median value and min–max value
The number of female patients was greater than the number of male patients in both groups; the proportion of male and female patients was comparable in the two groups. The patients showed no risk of vocal abuse. The proportion of smokers was also comparable in the two groups (Table 2).

### Table 2. Gender, voice usage pattern, and smoking history in the LPR and non-LPR groups.

| Variable                   | LPR group (n = 40) | Non-LPR group (n = 20) |
|----------------------------|--------------------|------------------------|
| Gender                     | Male               | 14                     | 6                      |
|                            | Female             | 26                     | 14                     |
| Voice Usage Pattern        | Risk of vocal abuse| 40                     | 20                     |
|                            | No risk of vocal abuse| 0                     | 0                      |
| Smoke                      | Nonsmokers         | 34                     | 17                     |
|                            | Smokers            | 6                      | 3                      |

The most common complaint (based on the reflux symptoms index questionnaire) of patients in the LPR group was the flow of mucus into the throat (Table 3).

### Table 3. Main complaints of patients with LPR (based on RSI).

| Variable                          | Number of patients (n = 40) | (%)   |
|-----------------------------------|-----------------------------|-------|
| Main complaint (RSI)              |                             |       |
| Hoarseness/noise                  | 3                           | 7.5   |
| Clearing throat                   | 4                           | 10    |
| Mucus flows into the throat       | 12                          | 30    |
| (post-nasal drip)                 |                             |       |
| Difficulty swallowing             | 0                           | 0     |
| Coughing after eating or lying    | 2                           | 5     |
| down                              |                             |       |
| Difficulty breathing or choking   | 0                           | 0     |
| A disturbing cough                | 7                           | 17.5  |
| Lump-in-the-throat sensation      | 8                           | 20    |
| Heartburn/chant pain/gastric reflux juice sensation | 4 | 10 |

### Table 4. Acoustic voice parameters in the LPR and non-LPR groups.

| Variable | LPR group (n = 40) | Non-LPR group (n = 20) | p     |
|----------|--------------------|------------------------|-------|
| F0       |                    |                        |       |
| Male     | 132.46 ± 13.61*    | 126.67 ± 5.90*         | 0.335*** |
| Female   | 208.68 ± 34.36*    | 215.27 ± 24.6*         | 0.457**   |
| Jitter   |                    |                        |       |
| Male     | 0.71 (0.30–2.81)** | 0.36 (0.27–0.69)**     | 0.021*** |
| Female   | 0.50 (0.24–2.15)** | 0.39 (0.13–0.86)**     | 0.084*** |
| PPQ      |                    |                        |       |
| Male     | 0.44 (0.17–1.90)** | 0.21 (0.17–0.41)**     | 0.032*** |
| Female   | 0.31 (0.13–1.27)** | 0.23 (0.07–0.5)**      | 0.122*** |
| Shimmer  |                    |                        |       |
| Male     | 4.61 ± 2.49*       | 3.29 ± 0.99*           | 0.230*** |
| Female   | 3.67 ± 1.29*       | 2.59 ± 1.00*           | 0.010*** |
| APQ      |                    |                        |       |
| Male     | 3.55 ± 1.69*       | 3.10 ± 1.08*           | 0.565*** |
| Female   | 2.85 ± 1.04*       | 2.05 ± 0.64*           | 0.013*** |
| NHR      |                    |                        |       |
| Male     | 0.16 ± 0.03*       | 0.13 ± 0.02*           | 0.03***  |
| Female   | 0.13 (0.10–0.18)** | 0.13 (0.12–0.16)**     | 0.469*** |
| SPI      |                    |                        |       |
| Male     | 11.20 (5.50–13.64)**| 8.36 (5.32–14.58)**   | 0.680*** |
| Female   | 8.13 (2.41–57.62)**| 7.64 (2.88–26.20)**   | 0.887*** |
| FTRI     |                    |                        |       |
| Male     | 0.20 (0.00–1.159)**| 0.21 (0.00–0.28)**    | 0.650*** |
| Female   | 0.29 (0.00–0.583)**| 0.15 (0.00–0.37)**    | 0.064*** |
| ATRI     |                    |                        |       |
| Male     | 1.01 (0.00–8.66)** | 1.60 (0.00–4.61)**    | 0.932*** |
| Female   | 3.59 (0.00–17.15)**| 1.43 (0.00–5.95)**    | 0.083*** |

* Mean and standard deviation values
** median value and min–max value
*** Results of data analysis with unpaired t-test
**** Results of data analysis with nonparametric Mann–Whitney test
The F0 values in male patients were higher in the LPR group, whereas the F0 values of the female patients were higher in the non-LPR group. There was no significant difference with respect to mean F0 values between the two groups. The between-group differences with respect to frequency perturbation parameters (jitter and PPQ) and amplitude perturbation parameters (shimmer and APQ) showed a similar pattern in both male and female patients. All acoustic parameters in the LPR group were higher than those in the non-LPR group; however, the differences with respect to frequency perturbation parameters were statistically significant only among the male patients, whereas those with respect to amplitude perturbation parameters were statistically significant only among the female patients. Both noise parameters (NHR and SPI) in male patients in the LPR group were higher than those in male patients in the non-LPR group; however, only the difference with respect to NHR was statistically significant. Noise parameters in female patients were comparable between the LPR and non-LPR groups. With respect to the tremor parameters, FTRI and ATRI in male patients were comparable between the two groups, whereas FTRI and ATRI in female patients in the LPR group were higher than those in the female patients in the non-LPR group; however, the differences were not statistically significant (Table 4).

In this study, we also sought to assess potential correlation between the degree of LPR (severity) and the acoustic voice parameter values. Because there is no published method for the classification of LPR severity, we classified the degree of LPR severity based on the RFS value. The RFS value of 7–13 was defined as mild LPR, and the RFS value of 14–26 was defined as moderate–severe LPR. No significant difference was observed with respect to age in patients with mild LPR and with moderate–severe LPR (Table 5).

| Variable       | Mild-LPR group (n = 29) | Moderate–severe-LPR group (n = 11) |
|----------------|------------------------|-----------------------------------|
| Age (Years)    | Male 39.9 ± 12.46*     | 33 ± 5.099*                       |
|                | Female 44 (29–59)***   | 46 (39–60)***                     |
| RFS Value      | Male 10.50 (8–13)***   | 14.50 (14–15)***                  |
|                | Female 11.32 ± 1.45*   | 15 ± 1.15*                       |

* Mean and standard deviation values  
** Median value and min–max value

The proportion of male and female patients in the mild-LPR group was comparable with that in the moderate–severe LPR group. The proportion of male smokers in the moderate–severe LPR group was slightly higher than that in the mild-LPR group (Table 6).

| Variable            | Mild-LPR group (n = 29) | Moderate–severe-LPR group (n = 11) |
|---------------------|------------------------|-----------------------------------|
| Gender              | Male 10                | 4                                 |
|                     | Female 19              | 7                                 |
| Smoking habit       | Male 4                 | 2                                 |
|                     | Female 0               | 0                                 |

Laryngeal hyperemia, moderate–severe vocal cord edema, and mild hypertrophy of posterior comissura were found in all patients. Granulation tissue was observed only in one female patient with moderate–severe LPR (Table 7).
Table 7. Characteristics of laryngeal disorders based on reflux finding score in patients with LPR.

| Variable                  | Mild-LPR group | Moderate–severe-LPR group |
|---------------------------|----------------|---------------------------|
|                           | Male (n = 10)  | Female (n = 19)           | Male (n = 4)  | Female (n = 7) |
| Subglottic edema          |                |                          |              |
| Found                     | 0              | 3                        | 0            | 0             |
| Not found                 | 10             | 16                       | 4            | 7             |
| Hyperemic                 |                |                          |              |
| Not found                 | 1              | 3                        | 0            | 0             |
| Ventricular Obliteration  |                |                          |              |
| Partial                   | 9              | 15                       | 4            | 6             |
| Complete                  | 0              | 1                        | 0            | 1             |
| Not found                 | 0              | 0                        | 0            | 0             |
| Only arytenoid            | 10             | 17                       | 1            | 4             |
| Diffuse                   | 0              | 2                        | 3            | 3             |
| Moderate                  | 2              | 7                        | 3            | 4             |
| Severe                    | 0              | 0                        | 0            | 3             |
| Obstructing               | 0              | 0                        | 0            | 0             |
| Posterior Comissura       |                |                          |              |
| Not found                 | 0              | 0                        | 0            | 0             |
| Hypertrophy               |                |                          |              |
| Mild                      | 5              | 5                        | 0            | 0             |
| Moderate                  | 5              | 14                       | 4            | 7             |
| Severe                    | 0              | 0                        | 0            | 0             |
| Obstructing               | 0              | 0                        | 0            | 0             |
| Granulation tissue        |                |                          |              |
| Not found                 | 10             | 19                       | 4            | 6             |
| Found                     | 0              | 0                        | 0            | 1             |
| Thick endolaryngeal       |                |                          |              |
| Not found                 | 5              | 9                        | 1            | 3             |
| Mucus                     |                |                          |              |
| Found                     | 5              | 10                       | 3            | 4             |

Table 8. Acoustic voice parameters of patients in the mild-LPR and moderate–severe LPR groups.

| Variable | Mild-LPR group (n = 29) | Moderate–severe-LPR group (n = 11) | p    |
|----------|-------------------------|------------------------------------|------|
| F0       |                         |                                    |      |
| Male     | 131.35 ± 15.38*         | 135.22 ± 8.903*                    | 0.650***|
| Female   | 214.44 ± 29.66*         | 193.28 ± 23.36*                    | 0.100***|
| Jitter   |                         |                                    |      |
| Male     | 0.72 ± 0.46*            | 1.81 ± 0.88*                       | 0.009***|
| Female   | 0.49 (0.24–1.25)**      | 0.88 (0.24–2.15)**                 | 0.470***|
| PPQ      |                         |                                    |      |
| Male     | 0.42 ± 0.27*            | 1.11 ± 0.61*                       | 0.010***|
| Female   | 0.30 (0.14–0.73)**      | 0.51 (0.13–1.27)**                 | 0.583***|
| Shimmer  |                         |                                    |      |
| Male     | 3.88 ± 2.24*            | 6.44 ± 2.35*                       | 0.080***|
| Female   | 3.77 ± 1.38*            | 3.40 ± 1.05*                       | 0.526***|
| APQ      |                         |                                    |      |
| Male     | 2.69 (1.34–7.60)**      | 4.20 (3.58–6.27)**                 | 0.048****|
| Female   | 2.95 ± 1.15*            | 2.60 ± 0.67*                       | 0.464***|
| NHR      |                         |                                    |      |
| Male     | 0.14 (0.13–0.18)**      | 0.18 (0.17–0.23)**                 | 0.023***|
| Female   | 0.135 ± 0.022*          | 0.132 ± 0.018*                     | 0.746***|
| SPI      |                         |                                    |      |
| Male     | 12.47 (5.67–13.640)**   | 10.63 (5.50–11.69)**               | 0.120***|
| Female   | 7.56 (2.41–57.62)**     | 10.11 (5.15–21.79)**               | 0.435***|
| FTRI     |                         |                                    |      |
| Male     | 0.24 (0.13–1.16)**      | 0.01 (0.00–0.29)**                 | 0.066***|
| Female   | 0.28 ± 0.14*            | 0.34 ± 0.14*                       | 0.341***|
| ATRI     |                         |                                    |      |
| Male     | 0.43 (0.00–8.66)**      | 4.57 (0.00–8.23)**                 | 0.339***|
| Female   | 3.85 (0.00–15.15)**     | 3.33 (0.00–6.17)**                 | 0.540****|

* Mean and standard deviation values
** Median value and min–max value
*** Results of data analysis with unpaired t-test
**** Results of data analysis with nonparametric Mann–Whitney test
F0 values in male patients were higher in the moderate–severe-LPR group, whereas F0 values in female patients were higher in the mild-LPR group. However, the between-group differences were not statistically significant for both male and female patients. The frequency perturbation parameter values (jitter and PPQ) in both male and female patients in the moderate–severe-LPR group were higher than those in their counterparts in the mild-LPR group; however, the differences were statistically significant only in male patients. The amplitude perturbation parameter values (shimmer and APQ) in male patients were higher in the moderate-to-moderate LPR group; however, a significant between-group difference was observed only with respect to median APQ values in male patients. The amplitude perturbation parameter values in female patients in the mild-LPR group were slightly higher than those of their counterparts in the moderate–severe-LPR group; however, the differences were not statistically significant (Table 8).

The NHR values in male patients in the moderate–severe LPR group were significantly higher than those of their counterparts in the mild-LPR group. The SPI values in male patients in the mild-LPR group were higher than those of their counterparts in the moderate–severe group; however, the difference was not statistically significant. The NHR values in female patients were higher in the mild-LPR group, while the SPI values in female patients were higher in the moderate–severe LPR group. However, the between-group differences were not statistically significant. FTRI values in male patients were higher in the mild-LPR group, whereas the ATRI values in male patients were higher in the moderate–severe LPR group. In contrast, the FTRI values in female patients were higher in the moderate–severe LPR group, while the ATRI values in female patients tended to be equal (Table 8).

4. Discussion
In the present study, the acoustic voice parameters in the non-LPR group were representative of the normal values of acoustic voice parameters. Voice characteristics are influenced by many factors, such as the anatomy of the head and neck (particularly the shape and size of the larynx) and cultural, psychological, environmental, and genetic factors. Therefore, normal reference values of acoustic voice parameters consistent with the characteristics of the study population are required, although the normal sound acoustic parameters are programmed in the MDVP software. The number of patients in the LPR group were higher than that in the non-LPR group. This is attributable to the higher case load of patients with LPR seen at the URJT Department of ENT FKUI-RSCM. Therefore, the study population is representative of the population with LPR visiting our department. In this study, the voice samples for acoustic voice analysis were in the form of the pronunciation of the vowel “a”. This vowel was selected to avoid bias associated with voice resonance. The sound produced on pronunciation of vowels originates purely from the vocal cords and is not influenced by noise produced by contractions or closure of the vocal tract at one or more points. Moreover, among all vowels, the tongue position is the most relaxed during the pronunciation of “a.”

In the present study, the patient age was 18–60 years to avoid bias due to age factor. Campisi et al. [16] found no significant difference in F0 value in boys and girls under 12 years of age; however, the F0 value in boys showed a sharp decrease after the age of 12 years and approximated the F0 values of adult males. Abo-Ras et al. [17] reported that the F0 value in pre-pubertal children decreased and that the F0 values decreased with increase in age, particularly in boys. This phenomenon is attributable to the development of the laryngeal structure as part of the child’s growth. The values of jitter and shimmer parameters also decrease with age as the stability of the laryngeal movement increases with increase in age [13,16,17].

Elderly people develop changes in the respiratory system, which may affect phonation. In a study conducted by Dehqan et al. [18] on subjects aged 70–90 years, F0 values in elderly males were predicted to increase, whereas those in elderly females were lower or comparable to those in young adult females. This phenomenon is believed to be related to degenerative changes and changes in hormonal levels. Some studies have also found that the jitter, shimmer, and NHR values in elderly men and women are
higher than those in young adults. This is likely attributable to impaired voice control owing to degenerative changes [18–21].

The differences in the characteristics of laryngeal structure as well as the length, mass, and distribution of extracellular matrix of vocal cords between males and females may account for the sex-related differences in acoustic parameters. Moreover, the differences with respect to lungs, hormone levels, hydration, and psychological capacity may all contribute to acoustic variations between men and women [22,23]. In present study, the data analysis was disaggregated by sex to minimize bias attributable to these factors.

In this study, the proportion of females in both LPR and non-LPR groups was higher than that of males. According to Kadakia et al. [24], at the beginning of the menstrual cycle, there is an increase in estrogen hormone and a decrease in progesterone hormone; this may induce a decrease in gastric motility which increases the risk of gastric juice reflux. According to Hunter et al. [22], the increased risk of LPR in females is associated with the longer transit time of food in the stomach (the average ambulatory gastric residence time) in females than in males; moreover, females are also more susceptible to eating disorders (such as anorexia and bulimia). Some studies have investigated the direct effects of eating disorders on voice disorders; increase in vomiting frequency in subjects with eating disorders was shown to increase the risk of gastric juice reflux [24-26].

Smoking induces various changes in the larynx, such as chronic inflammation, erythema, and dryness of laryngeal mucosa, all of which can lead to phonation disorders. In a study by Chai et al. [27], the mean value of jitter and shimmer in smokers was significantly higher than that in nonsmokers. Gonzalez et al. [28] reported lower F0 values in nonsmokers and higher frequency and tremor perturbation parameter values among smokers than among nonsmokers. In this study, although the number of smokers varied between the two groups, the ratio of smokers and nonsmokers was the same in both groups. This is expected to reduce the bias due to smoking habit [27,28].

In this study, the most common complaint of the patients in the LPR group was the feeling of excessive mucus or mucus flow into the throat and a sense of sore throat. Silva et al. [4] reported a significant correlation between the sensation of lump (foreign body sensation) in the throat and posterior komisura hypertrophy. Inflammation of the larynx and pharynx, accumulation of secretions in the throat, and disordered relaxation of muscles of deglutition due to irritation caused by regurgitated gastric fluid can also induce foreign body sensation in the throat. According to Blumin et al. [8], the sensation of excessive mucus in the throat is associated with mucociliary disorders and inflammation of the laryngeal mucosa due to irritation caused by gastric fluid, whereas post-nasal drip was associated with rhinosinusitis induced directly by gastric juice reflux or via vagal reflex mechanism [4,8,29,30].

Most studies have suggested that pathological abnormalities in the larynx did not have a significant effect on the F0 values, except in the case of vocal cord paralysis. The difference in the F0 values in this study is likely attributable to differences with respect to the degree of laryngeal inflammation. Gastric irritation may cause laryngeal inflammation and result in increased mass and decreased vocal cord tension, which in turn causes a decrease in the F0 values. However, in more severe laryngeal inflammatory conditions, vocal cord edema would lead to increased glottic resistance. Under these circumstances, greater subglottic air pressure is required to initiate and maintain phonation. Greater subglottic air pressure increases the tension of the vocal cords that would ultimately increase the voice frequency; on the other hand, increase in subglottic air pressure would also increase the intensity and decrease the quality of voice. In addition to gastric reflux, the smoking factor likely exacerbated laryngeal inflammation in male patients. In addition, the difference between male and female patients with respect to F0 values may also be attributable to differences in voice intensity as well as to the anatomical, hormonal, psychological, and cultural differences (including language dialects), all of which are known to affect the F0 value [10,11,13,31].

Inflammation in the laryngeal area due to gastric irritation would lead to increased mass (edema) of the vocal cords and changes in vocal cord tension and laryngeal secretions (due to mucociliary clearance disorders) that would disturb the pattern and periodicity of vocal cords. The jitter parameter was used to evaluate the short-term frequency perturbation of the voice signal, whereas the PPQ parameter was used
to evaluate the voice frequency perturbation. Both these parameters reflect the instability of vibration of the vocal cords that may be caused by pathological conditions of the vocal cords. In this study, the jitter and PPQ parameters in both male and female patients in the LPR group were higher than those in the non-LPR group; however, the between-group difference was statistically significant only in male patients. In a study by Dalgiç et al., a significant increase in jitter value was observed in patients with LPR. Similarly, Pavlidou et al. [10] also reported significantly higher jitter values in the LPR group (in both male and female patients) [10,11,13,31,32].

Shimmer parameters are often used for the relative evaluation of short-term amplitude perturbation in a sample of voice. The best voice amplitude perturbation measurements with APQ parameters are obtained from variations of peak amplitude in 11 iterations. Changes in shimmer values are influenced by glottic resistance, and the state of adduction of the vocal cords is associated with noise and breathiness. These parameters increase because of inadequate or inconsistent vocal cord adduction. In this study, the shimmer and APQ values in male and female patients were relatively higher in the LPR group; however, a significant between-group difference was observed only in female patients (Table 4.4), which is consistent with the research results of Pribuisine [10,11,31−33,42].

NHR is a measure of the quantity of noise in the voice sample. Inadequate closure of the vocal cords and vibration of the aperiodic vocal cords cause excessive airflow turbulence and noise. SPI is a noise parameter component of acoustic voice analysis associated with vocal cord adduction; the value of this parameter increases with increase in the breathiness component. In this study, the NHR and SPI values in male patients were higher in the LPR group, although only NHR showed a significant between-group difference (Table 4). This is likely attributable to impaired vocal cord adduction due to turbulence and noise induced by inflammation of the vocal cords. Female patients in the LPR group showed higher NHR and SPI values than their counterparts in the non-LPR group, although the values were relatively similar (Table 4). This is possibly because most of the female patients in the LPR group suffered from mild degrees of LPR and because the laryngeal inflammation was not severe enough to affect the adduction of the vocal cords. Our results are consistent with those of Oguz et al. [34], who reported higher NHR values in the LPR group than in the non-LPR group; however, the difference was not statistically significant [35-38].

Some studies have examined the characteristics of tremor parameters in patients with LPR. In a study by Domerecka-Kołodziej et al. [39], patients with LPR showed improvement in FTRI and ATRI values after treatment, although the pre- and post-treatment values were not significantly different. Physiological voice tremors may occur in normal people, particularly during low-amplitude, high-frequency phonation. Pathological voice tremors commonly occur in patients with Parkinson’s disease and vocal cord polyps. Patients with Parkinson’s disease have rigid vocal cords due to which there is inadequate vocal cord adduction and changes in the mass and tension of the vocal cords. This is accompanied by progressive motor disorder, resulting in voice tremors. In patients with vocal cord polyps, the presence of polyps disrupts the symmetry of vocal cord adduction and induces vibration of vocal cords. Laryngeal inflammation due to regurgitated gastric juice also causes changes in vocal cord tension, as described previously. It induces instability and irregularity of the vibration of the vocal cords, thereby causing voice tremor. In this study, the FTRI and ATRI values in male patients was comparable between the two groups, whereas female patients in the LPR group tended to show higher FTRI and ATRI values than those in the non-LPR group. However, the between-group difference with respect to FTRI and ATRI values in both female and male patients were not statistically significant (Table 4). This is likely attributable to the fact that irregularity of vocal cord vibration due to inflammatory changes was not as severe as that caused by the vocal cord polyps or Parkinson’s disease; therefore, the voice tremor was not too different from that in non-LPR patients. In addition, although FTRI and ATRI are specific parameters of tremor, these typically have a low consistency. This likely played a role in the observed inconsistency between FTRI and ATRI values in this study [39-41].

The determination of LPR degree in this study was only based on RFS value, assuming that the more severe the laryngeal abnormality, the more impaired will be the voice quality (related to the pattern of disturbance and the period of vibration of the vocal cords). All patients in this study showed mild–
in our study, the jitter and PPQ values in male and female patients tended to be higher in the moderate–severe LPR group; however, the between-group difference was only significant in male patients (Table 8). This is presumably because the inflammation in male patients in the moderate–severe-LPR group was more heavily linked to smoking, as described previously [34].

Domeracka et al. [39] stated that edema and excessive mucus in the larynx associated with LPR caused irregularity of the vocal cords; after LPR treatment, a decrease in laryngeal edema was observed along with more regular vocal cords. This implies that the severity of laryngeal abnormalities affect the pattern and periodicity of the vocal cords. The more severe the laryngeal abnormalities, the more irregular are the vibrations of the vocal cords. These findings are consistent with our results, wherein the shimmer and APQ values in male patients were higher in the moderate–severe LPR group, although the between-group difference was only significant with respect to APQ values (Table 8). The shimmer and APQ values shimmer and APQ among the female patients in the two groups (Table 8). The observed lack of significant between-group differences with respect to shimmer and APQ values is likely attributable to the lack of significant difference with respect to laryngeal abnormalities (as reflected in the RFS values) between the mild and moderate–severe LPR groups [39].

The NHR values in male patients and SPI value in female patients were higher in the moderate–severe LPR group, whereas the NHR values of female patients and the SPI value in male patients was slightly higher in the mild-LPR group. However, on further evaluation, the SPI parameter range in male patients in the mild-LPR group did not differ greatly from that in the moderate–severe-LPR group (Table 8). As already noted, patients in the LPR group already had a voice disorder. This was reflected in the higher acoustic parameter values in the LPR group than in the non-LPR group. In this study, the LPR severity was determined based on RFS value alone without looking at other factors, such as the onset and duration of LPR symptoms and LPR treatment history. Further research is required to determine if this affected the voice quality of patients with LPR.

In this study, only a few confounding factors were matched, including age, the risk of vocal abuse, and smoking. However, several other confounding factors that may also affect the voice quality, such as body mass index, ethnicity, allergic status, comorbidities, psychological conditions, and menstrual cycle, were not accounted for in the analysis.

5. Conclusion
In this study, the main complaints of patients with LPR were excessive mucus or mucus flow into the throat and lump-in-the-throat sensation. Some acoustic voice parameters in the LPR group were significantly higher than those in the non-LPR group. For male patients, they were the parameters of frequency perturbation (jitter and PPQ) and noise (NHR) parameters, whereas for the female patients were the amplitude perturbation parameters (shimmer and APQ). There were significant differences...
between the male patients in the mild-LPR and those in the moderate–severe-LPR group with respect to frequency perturbation parameters (jitter and PPQ), amplitude perturbation (APQ) and noise (NHR).

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