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ORIGINAL ARTICLE

Evaluation of Systemic Inflammatory Marker in Patients with Laryngopharyngeal Reflux

Larengofaringeal Reflüsü Olan Hastalarda Sistemik İnflamatuar Belirteçlerin Değerlendirilmesi

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ABSTRACT

Aim: It was aimed to investigate whether systemic inflammation markers have diagnostic value in laryngopharyngeal reflux disease.
Materials and Methods: This retrospective study was conducted including 32 patients with laryngopharyngeal reflux and 27 subjects with vocal cord nodules. Patients with laryngopharyngeal reflux were evaluated as Group 1, and subjects with vocal cord nodules as Group 2. Patient files were scanned. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values were calculated. In addition, the previously filled Reflux symptom index and the Reflux sign scores performed by videoendoscopic examination were noted.
Results: While the mean age was 43.21±13.26 years in Group 1, it was 38.04±10.39 years in Group 2. While there were 12 male and 20 female patients in Group 1, there were 12 male and 15 female patients in Group 2. When Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values were examined, no statistically significant difference was found between Group 1 and Group 2 ($p>0.05$). Reflux symptom index and Reflux sign scores were significantly higher in Group 1 ($p<0.05$). There was a significant positive correlation between the Reflux symptom index and Reflux sign scores.
Conclusion: In our study, no significant difference was found in the Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values used in the follow-up of many diseases compared to the control group in laryngopharyngeal reflux patients and had no diagnostic value. While the Reflux symptom index and Reflux sign scores were found to be significantly higher in laryngopharyngeal reflux patients compared to the control group, they were significantly positively correlated with each other.

Keywords: Laryngopharyngeal Reflux, Lymphocyte, Neutrophil, Reflux Symptom Index, Reflux Finding Score

ÖZ

Amaç: Laringofaringeal reflü hastalığında sistemik inflamasyon belirteçlerinin tanısal değeri olup olmadığının araştırılması amaçlandı.
Gereç ve Yöntemler: Bu retrospektif çalışma laringofaringeal reflüsü olan 32 hasta ve vokal kord nodülü olan 27 olgu dahil edilerek yapıldı. Laringofaringeal reflü hastaları Grup 1, vokal kord nodülü olan olgular Grup 2 olarak değerlendirildi. Hasta dosyaları tarandı. Nötrofil/lenfosit oranı, trombosit/lenfosit oranı ve sistemik inflamasyon indeksi değerleri hesaplandı. Ayrıca daha önce doldurulmuş olan Reflü semptom indeksi ve videoendoskopik muayene ile yapılan Reflü belirti skorları not edildi.
Bulgular: Grup 1'de yaş ortalaması 43.21±13.26 iken, Grup 2'de 38.04±10.39 bulundu. Grup 1'de 12 erkek ve 20 kadın hasta bulunurken, Grup 2'de ise 12 erkek ve 15 kadın hasta mevcuttu. Nötrofil/lenfosit oranı, platelet/ lenfosit oranı ve sistemik inflamasyon indeksi değerleri incelendiğinde Grup 1 ve Grup 2 arasında istatistiksel olarak anlamlı fark saptanmadı ($p>0.05$). Reflü semptom indeksi ve Reflü bulgu skorları Grup-1'de anlamlı olarak daha yüksek bulundu ($p<0.05$). Reflü semptom indeksi ve Reflü bulgu skorları arasında önemli ölçüde pozitif korelasyon mevcuttu.
Sonuç: Bizim çalışmamızda Laringofaringeal reflü hastalarında, birçok hastalığın takibinde kullanılan nötrofil/lenfosit oranı, platelet/lenfosit oranı ve sistemik inflamasyon indeksi değerlerinde kontrol grubuna göre anlamlı fark saptanmadı ve tanısal değeri yoktu. Reflü semptom indeksi ve Reflü bulgu skorları, laringofaringeal reflü hastalarında kontrol grubuna göre anlamlı yüksek bulunurken, birbirleri ile önemli ölçüde pozitif korele bulundular.

Anahtar Kelimeler: Laryngopharyngeal Reflux, Lymphocyte, Neutrophil, Reflux Symptom Index, Reflux Finding Score

Introduction

The inflammatory state caused by the reflux of gastric contents into laryngeal and pharyngeal tissue is known as laryngopharyngeal reflux (LPR). Although the prevalence of LPR is still unclear, it is a frequently encountered entity in ear, nose, and throat (ENT) clinical practice. It causes symptoms of a tickling sensation in the throat, voice disorders, difficulty in swallowing, chronic cough, and globus pharyngeus. These symptoms result from laryngeal epithelial damage caused by the reflux content or vagal nerve-mediated stimulation of laryngeal reflexes (1). The laryngopharynx has been reported to be potentially more sensitive to reflux content than the esophagus (2).

The diagnosis of LPR was difficult. The methods employed in diagnosis included the Reflux Finding Score (RFS) (Table 1) and were evaluated using the video laryngoscopic examination and the Reflux Symptom

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Index (RSI) (Table 2) (3,4). The RSI scores over 13 are regarded as pathological, and the RFS scores over 7 were interpreted in favor of LPR.

Table 1. Reflux Finding Scores

Reflux Finding Scores	
Subglottic edema	0 Absent
	2 Present
Ventricular Obliteration	0 Absent
	2 Partial
	4 Complete
Erythema/hyperemia	0 Absent
	2 Arytenoids
	4 Diffuse
Vocal fold edema	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Polypoid
Diffuse laryngeal edema	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Obstructing
Posterior commissure hypertrophy	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Obstructing
Granuloma/granulation tissue	0 Absent
	2 Present
Thick endolaryngeal mucus	0 Absent
	2 Present

RSF >7 = Laryngopharyngeal Reflux

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic inflammation index (SII) can be easily calculated by peripheral complete blood count. NLR and PLR have been identified as potential markers of systemic inflammation (5-7). It is known that NLR, PLR, and SII, which are widely studied especially in cardiovascular diseases, can be used as classical inflammatory markers (8,9). The prognostic value of the systemic inflammation index (SII), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) have been demonstrated in many inflammatory diseases, particularly cancer (10,11).

Based on the literature, we encountered no studies investigating the relationship between LPR and SII in the literature search. This study aimed to examine the relationship between LPR, a disease frequently encountered in ENT medicine, and systemic inflammatory markers.

Table 2. Reflux Symptom Index

Within the last Month, how did the following problems affect you?	**(0=No problem-5=Severe problem)**					
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucus or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensation of something sticking in your throat, or a lump in your throat	0	1	2	3	4	5
Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

RSI>13=Abnormal

Material And Method

The study was carried out under the Declaration of Helsinki and with the approval of the Non-Interventional Ethical Committee of xxx University (Date:19.03.2021, Decision 2021-KAEK-6934). Since the data in the research was obtained from electronic records of the patients, consent from the patients was not obtained.

The study was planned retrospectively. Thirty-two patients presenting to the ENT clinic between 1st October 2020 and 1st March 2021, diagnosed with LPR, and with no additional systemic disease were included in the study. These were assigned to Group 1, while 27 subjects with vocal cord nodules constituted Group 2.

Once the patient's age and sex distributions had been determined, RFS and RSI forms routinely applied in ENT clinics to assist in the diagnosis of LPR were scanned from the files. The Turkish language versions of both forms had previously been validated (12,13).

Hemoglobin values and neutrophil, platelet, and lymphocyte counts were retrieved from complete blood counts (CBC) performed for other reasons during the previous three months. CBC parameters were calculated with an automated hematologic analyzer (XN-1000-Hematology-analyzer-Sysmex Corporation,

Japan). NLR, PLR, and SII values were calculated by formula. SII (platelet×neutrophil/lymphocyte), NLR, and PLR analyses were also performed. The groups were then compared based on these values.

The study assessed patients aged 18 to 60 diagnosed with gastroesophageal reflux who followed a reflux diet for at least one month without taking medication. An ENT physician then examined these patients. A single otolaryngologist with ten years of experience obtained a thorough medical history from the study participants, and a flexible endoscopic examination of the larynx revealed laryngopharyngeal reflux. The control group consisted of subjects with vocal cord nodules with similar age and gender characteristics as the study group. This study group presented to the ENT outpatient clinic with a complaint of dysphonia but no complaints or symptoms of reflux.

Patients at the age of <18 years or >60 years, those consistently taking medications for any reason, those with blocked nasal air passages such as septum deviation, allergic rhinitis, and turbinate hypertrophy, those with postnasal purulent discharge, those smoking and consuming alcohol, those with such disorders as coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic liver disease, acute and chronic renal diseases, and those with previous interventional procedures or surgery in the laryngopharyngeal area, and those choosing not to participate in the study were excluded from the study.

Statistical Analysis

Statistical analyses were performed on the Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 software (IBM SPSS Inc., Chicago, IL, USA). Mean±standard deviation and descriptive statistics were employed. The normality of distribution was evaluated using the Kolmogorov–Smirnov test. NLR and PLR values were not normally distributed in Group 1, and NLR, PLR, RSI, and RFS values were not normally distributed in Group 2. Normally distributed data were compared between the groups using the independent samples t-test. The Mann–Whitney U test was applied in the comparison of non-normally distributed variables between the groups. The correlation between RSI and RFS was investigated using Spearman's correlation test. A p-value of <0.05 was considered statistically significant. The Cronbach's alpha test was used to assess the intra-rater reliability. The value is 0.731.

Results

Group 1 consisted of 20 (62.5%) women and 12 (37.5%) men, and Group 2 of 15 (55.6%) women and 12 (44.4%) men. Mean ages were 43.21±13.26 years in Group 1 and 38.04±10.39 in Group 2. No significant differences were observed between the groups in terms of age (p=0.178) or sex (p=0.783).

Platelet counts, hemoglobin values, lymphocyte counts, neutrophil counts, and NLR, PLR, and SII values in groups 1 and 2 are shown in Table 3. No significant differences were observed between the groups in terms of the values shown in Table 3 (p>0.05).

Table 3. Age, platelet count, hemoglobin, lymphocyte count, neutrophil count and NLR, PLR and SII values of the groups

	Group 1	Group 2	P value
Age (years) (mean±SD)	43.21±13.26	38.92±10.39	0.178*
Platelet Count (x1000 uL) (mean±SD)	244.78±51.40	265.29±48.07	0.121*
Hemoglobin (mean±SD)	14.59±1.59	15.15±1.77	0.205*
Lymphocyte Count (mean±SD)	2.30±0.73	2.54±0.81	0.236*
Neutrophil Count (mean±SD)	5.06±1.95	4.83±1.73	0.627*
NLR [median (IQR)]	1.94 (1.38-2.32)	2.10 (1.40-3.07)	0.338¥
PLR [median (IQR)]	105.93 (80.00-139.52)	109.19 (86.33-138.91)	0.831¥
SII (mean±SD)	579.83±293.15	549.17±263.76	0.677*

*: Independent Sample t test was used. ¥: Mann-Whitney U test was used. NLR: Neutrophil/Lymphocyte ratio,

PLR: Platelet/ Lymphocyte ratio, SII: Systemic Inflammation Index, IQR: Interquartile Range

RSI and RFS values in groups 1 and 2 are shown in Table 4. RSI and RFS values were significantly higher in the LPR group than in the control group (Table 4) (p<0.05). A significant positive correlation was observed between RSI and RFS (p=0.000).

Table 4. RSI and RFS values of groups.

	Group 1 [median (IQR)]	Group 2 [median (IQR)]	***p*-value**
RSI	1.00 (0.00-6.00)	15.50 (12.25-19.50)	0.000¥
RFS	0.00 (0.00-2.00)	7.00 (4.00-9.00)	0.000¥

¥: Mann-Whitney U test was used. RSI: Reflux Symptom Index, RFS: Reflux Finding Scores,

IQR: Interquartile Range

Discussion

LPR is an inflammatory disease caused by the reflux of gastroduodenal contents. It causes non-specific symptoms such as a tickling sensation in the throat and voice disorders. Its association with chronic pharyngitis,

premalignant lesions of the larynx, and squamous cell carcinoma has also been reported (14,15). Gastroesophageal reflux disease is observed in 57-80% of patients with clinical symptoms of LPR (16). However, LPR patients may not have gastroesophageal reflux findings.

Although the main diagnostic test for LPR is 24-hour pH monitoring, more rapid tests have begun entering into use. Belafsky et al. defined the RSI and RFS forms (3,4). RSI exceeding 13 is compatible with LFR, while RFS above seven indicates LPR with a likelihood of 95% (3,4). RFS in the LPR group in the present study was 15.65±5.82, while RSI was 7.03±3.37.

The RSI and RFS forms are practical for the diagnosis of LPR and observing the response to treatment (3). Karakaya et al. showed that RSI and individual variables in RFI were correlated in LPR, except for posterior commissure hypertrophy (12). In agreement with the previous literature, a significant correlation was observed between RSI and RFS in the present study, and both were significantly higher in the LPR group than in the control group.

Increasing platelet and decreasing lymphocyte counts during inflammation allows the PLR to be employed as an inflammatory marker. The NLR and PLR can be used to predict prognosis in several cancers and in the evaluation of inflammation in diseases such as diabetes, hypertension, rheumatoid arthritis, and acute coronary syndrome (17,18). Ateş et al. showed that NLR values may rise in gastroesophageal reflux-related erosive esophagitis and non-erosive esophagitis (19). Arslan et al. found that PLR was significantly higher in patients with LPR than in the control group, but NLR did not differ significantly. They also suggested that the mean platelet volume value has prognostic significance in treating LPR (8). No significant difference in PLR and NLR values was observed between the LPR and control groups in the present study.

The systemic inflammation index (SII), consisting of three cell types (neutrophils, platelets, and lymphocytes), was developed by Hu et al. in 2014 (20). The SII can provide a clearer picture of immune and inflammatory conditions (21,22). It has also been shown to be a useful marker in predicting clinical outcomes in tumors and several inflammatory diseases (21-23). Our search of the literature revealed no studies investigating the relationship between LPR and the SII. In the present study, SII values were lower in the control group than in the LPR group, although no significant difference was found between the two groups.

The principal limitations of this study are its retrospective nature and the low case number. The fact that more objective tests for LPR were not used is another limitation.

LPR is a common condition frequently encountered in otolaryngology practice. Regarding the prevalence of LPR, it is clear that it is impractical to perform objective diagnostic tests on every patient. The RSI and RFS forms are practical and valuable for the initial assessment and subsequent evaluation of treatment. SII, NLR, and PLR are biomarkers that can be used to assess inflammation.

Conclusion

Our study indicated that patients with LPR exhibited significantly elevated levels of RSI and RBS, diagnostic markers for LPR. The analysis found no significant correlation between the markers SII, NLR, and PLR, extensively studied in recent years, and LFR. Prospective studies can be designed to include more patients and assess these markers before and after treatment.

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