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The Prognostic Importance of the Systemic Inflammatory Index in Pathologies of the Larynx

Larinks Patolojilerinde Sistemik İnflamatuar İndeksin Prognostik Önemi

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ABSTRACT Objective: This study aimed to determine the prognostic importance of the preoperative systemic immune-inflammatory index (SII) in laryngeal lesions and to investigate its predictive importance compared to the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). **Material and Methods:** Retrospective comparisons were made between the preoperative blood parameters (NLR, PLR, and SII) and clinicopathological features of 133 patients who underwent surgery for a localized laryngeal lesions between March 01, 2010 and June 31, 2021. Receiver-operating characteristic analysis was used to calculate the cut-off value of the SII. **Results:** Of the 133 patients with laryngeal lesions, 81 (60.9%) had benign lesions, 20 (15%) had premalignant lesions, and 32 (24.1%) had malignant pathology results. The mean SII value was determined to gradually increase in the order of benign, premalignant, and malignant pathology (444.36; 525.69; 738.07, respectively). A statistically significant difference was found between the SII values of the groups classified as benign, premalignant, and malignant according to laryngeal pathologies ($p<0.001$). A statistically significant moderate-level correlation of approximately 35% was determined between the benign, premalignant, and malignant pathology results and SII, between the pathology results and NLR at 36%, and with PLR at 29%. **Conclusion:** A significant relationship was observed between the tendency of the disease and malignancy in laryngeal pathologies and the SII. This significant relationship was also determined by NLR and PLR. In this context, the SII was evaluated as an inexpensive, routine screening test that can be used to evaluate the prognosis of patients with laryngeal pathology.

Keywords: Laryngeal pathology; laryngeal cancer; systemic inflammatory index

ÖZET Amaç: Bu çalışmanın amacı, larenks lezyonlarında preoperatif sistemik inflamatuar indeksin [systemic immune-inflammatory index (SII)] prognostik önemini belirlemek ve nötrofil-lenfosit oranı [neutrophil-lymphocyte ratio (NLR)] ve trombosit-lenfosit oranına [platelet-lymphocyte ratio (PLR)] göre prediktif önemini araştırmaktır. **Gereç ve Yöntemler:** 01 Mart 2010 ve 31 Haziran 2021 tarihleri arasında, lokalize laringeal lezyon nedeniyle ameliyat edilen 133 hastanın ameliyat öncesi kan parametreleri (NLR, PLR ve SII) ve klinikopatolojik özellikleri retrospektif olarak karşılaştırıldı. Alıcı-işlem karakteristiği analizi SII'nın cut-off değerini hesaplamak için kullanılmıştır. **Bulgular:** Larenks lezyonu olan 133 hastada yapılan çalışmada 81 (%60,9) hastada benign, 20 (%15) hastada premalign ve 32 (%24,1) hastada malign patoloji sonucu saptandı. Ortalama SII değerinin benign, premalign ve malign patoloji sırasına göre giderek arttığı gözlenmiştir (sırasıyla 444,36; 525,69; 738,07). Laringeal patolojilere göre benign, premalign ve malign olarak sınıflandırılan grupların SII değerleri arasında istatistiksel olarak anlamlı bir fark bulundu ($p<0,001$). Benign, premalign ve malign patoloji sonuçları ile SII arasında pozitif yönde yaklaşık %35 (orta); NLR arasında yaklaşık %36 (orta) ve PLR ile %29 (orta) oranında istatistiksel olarak anlamlı bir korelasyon vardı. **Sonuç:** Larenks patolojilerinde hastalığın maligniteye eğilimi ile SII arasında anlamlı bir ilişki olduğu gözlendi. Bu anlamlı ilişki NLR ve PLR arasında da vardı. Bu bağlamda SII, larenks patolojisi olan hastaların prognozunu değerlendirmek için kullanılabilecek ucuz, rutin bir tarama testi olarak değerlendirildi.

Anahtar Kelimeler: Larenks patolojisi; larenks kanseri; sistemik inflamatuar indeks

Laryngeal cancer comprises 2.4% of all new diagnoses of malignancies worldwide.[1] In 2016, an estimated 13,430 new laryngeal cancers were diagnosed, and 3,620 patients died worldwide.[2] Among the most critical risk factors are smoking, tobacco, and excessive alcohol use.[3,4] Ciolofan et al. reported

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that the histopathological subtype of 98% of laryngeal cancers is squamous cell carcinoma (SCC).[5]

The tumor, node, metastasis (TNM) staging system classification and histopathological grading guide the treatment method for laryngeal cancer. However, despite the decline in overall incidence, the 5-year survival rate for laryngeal cancer has fallen from 66-63% in the last 40 years.[1] Therefore, further research and innovation are needed. Even when the same treatment method is used in patients with similar characteristics, the fact that different results are obtained indicates the need to investigate different prognostic factors.

It is well known that there is a relationship between inflammation and cancer.[6] DNA damage is exacerbated by inflammatory cells which produce cytokines and chemokines in the early stages of the neoplastic process, and these cells are thus strong tumour promoters.[7] Recent studies have also shown that peripheral leukocytes (neutrophils, lymphocyte monocytes) and platelet levels before treatment are associated with prognosis in various cancers.[8] There are studies in literature which have investigated the prognostic importance of some blood parameters in laryngeal SCC, especially platelet/lymphocyte ratio (PLR), and neutrophil/lymphocyte ratio (NLR).[7,8]

A previous study reported that the systemic immune-inflammatory index (SII) is a new marker with predictive value for the assessment of the systemic inflammatory state.[9] SII (platelet count×neutrophil count/lymphocyte count) reflects the overall immune system and inflammatory status of the body as it is calculated from platelets, lymphocytes, and neutrophils counts.[10] It has been shown that SII can be an independent prognostic parameter in various cancers.[11-13]

The aim of this study was to determine the preoperative prognostic importance of SII, an inflammatory marker in laryngeal lesions and compare it with other haematological inflammatory markers (NLR, PLR).

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the Kütahya Health Sciences University Faculty of Medicine (KSBU) and conducted in accordance with the 1964 Declaration of Helsinki (date: June 30, 2021, no: 2021/11-19).

A total of 133 patients who underwent surgery due to laryngeal pathology in the KSBU Ear Nose and Throat Clinic between March 01, 2010 and June 31, 2021 met the study inclusion criteria. A retrospective analysis of medical history, age, sex, alcohol and smoking history, preoperative hematological tests (lymphocytes, neutrophils, and thrombocytes), and histopathological results (tumor stage and lymph node metastasis) obtained from the patient files was performed. As recommended by the American Joint Committee on Cancer (AJCC 2017, 8th edition), the TNM staging system was used to determine prognosis.[14] The study exclusion criteria were defined as the presence of haematological disease, second primary cancer, chronic inflammatory disease, active infection (>12,000/mL, neutrophil >70%) at the time of laryngeal pathology diagnosis, or the use of anti-inflammatory drugs. Patients diagnosed with malignancies other than laryngeal SCC based on histopathological examination were not included in the study.

PERIPHERAL BLOOD ANALYSIS

Antecubital vein blood samples were collected the day before the polysomnography test, following an overnight fast of 8-12 hours. The blood samples obtained from all patients did not reveal any signs of infection. An automated blood count device (LH780, Beckman Coulter Inc., Miami, FL, USA) was utilized in the Bio- chemistry Department of KSBU Faculty of Medicine to analyze the blood samples withdrawn in tubes containing ethylenediaminetetraacetic acid.

SII was calculated by dividing the lymphocyte count (lymphocyte count/μL) by the sum of the neutrophil count (neutrophil count/μL) and platelet count (platelet count/μL).

STATISTICAL ANALYSES

The data obtained in this study were statistically analyzed using IBM SPSS vn. 20 software (Statistical Package, IL, USA). The analyses were performed using frequency tables, descriptive statistics, his-

tograms and box plots, and one-way analysis of variance (ANOVA). The Eta Correlation Coefficient was applied when one parameter was quantitative and the other was qualitative. To determine the cutoff values, receiver operating characteristic (ROC) analysis was performed. The level of statistical significance was set at $p<0.05$.

RESULTS

The 133 patients were divided into 3 groups according to histopathology results: benign, premalignant, and malignant. The demographic data of the patients are summarised in Table 1. There were 133 patients evaluated, with 111 (83.5%) males and 22 (16.5%) females, with a mean age of 52.86±14.33 years (range, 15-85 years).

The mean SII value gradually increased in the order of benign, premalignant, and malignant pathologies (444.36, 525.69, and 738.07, respectively).

A statistically significant positive correlation of approximately 35% (moderate) was observed between the SII and laryngeal pathology groups ($p<0.05$).

In the ROC analysis, the SII cutoff value was determined to be 466.097, with 71% sensitivity and 63% specificity. In this analysis, the p-value was 0.001 (Figure 1).

A statistically significant difference was observed between the benign, premalignant, and malignant groups with respect to the NLR values ($p<0.002$). NLR increased in the sequence of benign, premalignant, and malignant pathologies (1.804, 2.147, and 2.714, respectively).

A statistically significant difference was determined between the benign, premalignant, and malignant groups with respect to PLR values ($^{*}p<0.017$). The PLR value was observed to increase in the sequence of benign, premalignant, and malignant pathologies (105.107, 123.069, 149.108, respectively).

A statistically significant positive correlation of approximately 35% (moderate) was determined between the benign, premalignant, and malignant pathology results and the SII. A positive correlation of approximately 36% (moderate) was determined between the pathology results and NLR, and a slightly lower relationship of 29% (moderate) with PLR. Thus, the correlation between the pathology results and both the SII and NLR was high, and was at a lower level with PLR (Table 2).

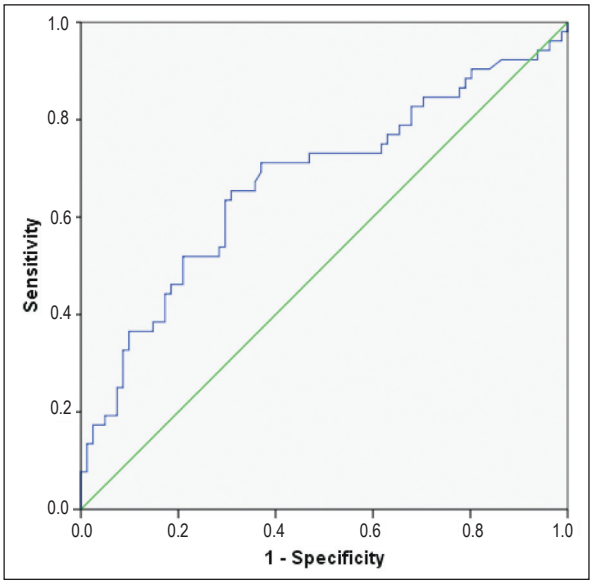

FIGURE 1: ROC curve determining the ideal cut-off point of the SII value.
ROC: Receiver operating characteristic; SII: Systemic immune-inflammatory index.

TABLE 1: Demographic characteristics of the patients.

	Gender		
Larynx lesions	**Male**	**Female**	**Age (years)**
Benign larynx lesions	63	18	47.51±13.25
Premalignant larynx lesions	18	2	59.20±12.82
Malignant larynx lesions	30	2	62.47±11.18

TABLE 2: Examination of the relationship between NLR, PLR, and SII variables, showing a statistically significant relationship between the pathology results and NLR, PLR, and SII variables (*:p<0.05).

	Eta correlation coefficient	**p value**
NLR-larynx pathology	0.360	0.000*
PLR-larynx pathology	0.296	0.001*
SII-larynx pathology	0.352	0.000*

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio;
SII: Systemic immune-inflammatory index.

DISCUSSION

The results of the retrospective comparisons made in this study of the SII values of patients with benign, premalignant, and malignant laryngeal lesions demonstrated a statistically significant difference. The SII and NLR had a higher significant correlation, while the PLR had a lower significant correlation.

The cytokines that occur in the inflammatory process and those that occur in tumor formation serve the same purpose, and there has been a recent increase in studies in this field. The immune system produces the same response to tumour cells and to microorganisms and cells which have been invaded.[15]

Recent studies have reported that the systemic immune-inflammatory response based on the number of neutrophils, platelets, and lymphocytes in the blood is independently associated with oncological outcomes in various cancers.[16] Different tumour markers in laryngeal cancer have been investigated for research into the development of treatments for cancer. In addition, with greater information about the biological behavior of cancer and the host, the prediction of recurrence and secondary cancers will become possible; thus, more effective treatments can be planned for laryngeal cancer. There are studies in the literature that have investigated the prognostic importance of some blood parameters such as NLR and PLR for laryngeal SCC.[7,8]

The SII is an inflammatory marker that has recently gained prominence. It has been reported that it can function as an independent prognostic parameter in different types of cancer, including nasopharyngeal carcinoma, ovarian clear cell carcinoma, gastric carcinoma, hepatocellular cancer, and renal cell carcinoma.[16] It has been reported that SII in laryngeal cancer can have a prognostic significance.[17] However, there is no study that has investigated the difference in SII values between laryngeal lesions (benign-premalignant-malignant). In this study, the prognostic importance of the SII in laryngeal pathologies was evaluated and it was observed that the SII value increased significantly as the tendency for malignancy increased in laryngeal pathologies. To the best of our knowledge, this is the first study of this topic in the literature.

In a study of Demir et al., which investigated the relationship between laryngeal cancer and SII, ROC analysis was applied to determine the appropriate cut-off point of SII for laryngeal cancer; the cut-off point was determined to be 892, with 84% sensitivity and 84% specificity.[18] In the current study, in the ROC analysis applied to all the laryngeal pathologies, the cutoff point was determined to be 466.097 with 71% sensitivity and 63% specificity. The data from these 2 studies support one another. The different cut-off points and different sensitivity and specificity values can be attributed to the fact that the blood parameters were evaluated using different devices.

Yılmaz et al. reported a significant difference between the NLR value and clinical stage ($p=0.003$) in laryngeal cancers.[19] In a study by Wu et al. comparing benign laryngeal, precancerous, and malignant cases, the NLR value in the malignant group was significantly higher than that in the benign and precancerous groups ($p<0.05$), with no significant difference observed between the premalignant and benign groups ($p<0.05$).[20] In another study comparing the NLR ratio between benign, precancerous, and malignant groups, Kum et al. also reported that the mean NLR value was significantly different in the precancerous ($p=0.031$) and malignant ($p=0.001$) groups from the benign group.[21] In the current study, as in previous studies, there was a significant difference in the NLR values between the benign, premalignant, and malignant groups ($p=0.002$).

Chen et al. reported that preoperative PLR value is a more valuable prognostic factor than NLR for laryngeal SCC recurrence.[22] Geng et al. reported that SII was more significant than PLR, and NLR was found to be more valuable than PLR.[23]

The SII is a marker that can be calculated from simple, routine blood tests and can provide clinicians with valuable data about prognosis. However, it would be incorrect to state that this single marker is a diagnostic tool. The SII can be used as a prognostic rather than a diagnostic tool. It can be helpful in developing preventive treatments, predicting secondary problems, and helping more effective treatment management by increasing the knowledge about biological behaviors in the chronic process of cancer. Many studies in the literature reflect different opin-

ions about the SII, NLR, and PLR. The main reason for this difference is that blood parameters can change very quickly for many reasons. Therefore, more extensive studies with a larger series are required to shed more light on these differences.

The modified systemic inflammation score (mSIS), which is based on lymphocyte-monocyte ratios and serum albumin concentrations, has been found to be associated with mortality risk and overall survival in esophageal cancers.[24,25] mSIS is also associated with prognosis of melanoma, lymphoma, breast cancer, and lung cancer.[26-29] However, the value of mSIS, for predicting malignancy remains unclear.[30-32] Further studies evaluating the SII and mSIS together will help to understand the predictive effect.

The most important limitation of this study was its retrospective single-centre design. Moreover, the low number of patients with premalignant and malignant tumors in the groups limited the value of this study.

CONCLUSION

The results of this study demonstrated the prognostic value of SII compared to NLR and PLR in laryngeal lesions. In laryngeal pathologies, SII values increase as the disease progresses to malignancy. The SII should not be considered as a 100% diagnostic criterion, but as valuable data that clinicians can use when evaluating the patient.

The SII can be obtained with simple and routinely used tests, which are performed with non-invasive, inexpensive, and reproducible, routinely used assays.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Muhammet Fatih Topuz, Nurullah Türe;* ***Design:*** *Muhammet Fatih Topuz, Fatih Oğhan;* ***Control/Supervision:*** *Muhammet Fatih Topuz, Fatih Oğhan;* ***Data Collection and/or Processing:*** *Nurullah Türe, Zuhal Zeybek Sivas;* ***Analysis and/or Interpretation:*** *Muhammet Fatih Topuz, Nurullah Türe;* ***Literature Review:*** *Nurullah Türe, Zuhal Zeybek Sivas;* ***Writing the Article:*** *Muhammet Fatih Topuz, Nurullah Türe;* ***Critical Review:*** *Muhammet Fatih Topuz, Fatih Oğhan.*

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