ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.24179/kbbbbc.2021-82505

Can We Use Neutrophil: Lymphocyte Ratio, Platelet: Lymphocyte Ratio, and Systemic Immune-Inflammation Index Values to Differentiate Larynx Carcinoma from Benign and Premalignant Laryngeal Diseases in the Elderly?

Yaşlılarda Laringeal Skuamoz Hücreli Karsinomla Benign ve Premalign Laringeal Hastalıkların Ayrımında Nötrofil: Lenfosit Oranı, Trombosit: Lenfosit Oranı ve Sistemik İmmün-İnflamasyon İndeksi Değerlerini Kullanabilir miyiz?

Mehmet Emre SİVRİCE[a], Yusuf Çağdaş KUMBUL[a], Hasan YASAN[a], Mustafa TÜZ[a], Erdoğan OKUR[a], Vural AKIN[a]

[a]Department of Oto-Rhino-Laryngology and Head&Neck Surgery, Süleyman Demirel University Faculty of Medicine, Isparta, TURKEY

ABSTRACT Objective: Timing for laryngeal biopsy is challenging for geriatric patients due to their comorbidities and anesthetic risks. The aim of this study is to find an indicator that would both allow surgeons to predict the need for laryngeal biopsy, and to diagnose the malignancy at an early stage. **Material and Methods:** This is a retrospective cohort study of 103 participants. Three groups were constituted according to the results of laryngeal biopsy (benign-Group 1, premalignant-Group 2, and malignant-Group 3). The neutrophil: lymphocyte ratio, the platelet: lymphocyte ratio, and the systemic immune-inflammation index (neutrophil count × platelet count) / lymphocyte count) values of the three groups were compared between groups. **Results:** The male: female ratio was 100:3, and the mean age was 70.87 (±6.38) years, with no significant differences among the three groups [Group 1: 70.40 (±5.94), Group 2: 70.44 (±5.09), Group 3: 71.15 (±6.91)] (p=0.88). There were no statistically significant differences among the three groups in neutrophil: lymphocyte ratio (p=0.84), platelet: lymphocyte ratio (p=0.36), or systemic immune-inflammation index values (p=0.67). **Conclusion:** Indices calculated from haematological parameters and showing systemic inflammation may not be reliable in the geriatric population due to immunosenescence. For this reason, indices calculated from haematological parameters should be studied distinctly in the geriatric population without including other age groups. Other methods are needed to help predict the timing of laryngeal biopsy in geriatric patients.

Keywords: Aged; carcinoma; squamous cell; larynx; inflammation; immunosenescence

ÖZET Amaç: Laringeal biyopsi için zamanlamanın planlanması, komorbiditeleri ve anestezi riskleri nedeniyle geriatrik hastalar için zordur. Bu çalışmanın amacı, hem laringeal biyopsi ihtiyacını tahmin etmemize hem de maligniteyi erken dönemde teşhis etmemize olanak sağlayacak bir indeks tespit etmektir. **Gereç ve Yöntemler:** Bu çalışma, 103 hastayı içeren retrospektif bir kohort çalışmasıdır. Laringeal biyopsi sonuçlarına göre 3 grup oluşturuldu (benign-Grup 1, premalign-Grup 2 ve malign-Grup 3). Üç grubun nötrofil: lenfosit oranı, trombosit: lenfosit oranı ve sistemik immün-inflamasyon indeksi (nötrofil sayısı × platelet sayısı)/lenfosit sayısı) değerleri karşılaştırıldı. **Bulgular:** Çalışma grubunun erkek: kadın oranı 100: 3 ve ortalama yaşı 70.87 (±6.38) yıl olup, gruplar kıyaslandığında anlamlı bir fark yoktu [Grup 1: 70.40 (±5.94), Grup 2: 70.44 (±5.09), Grup 3: 71.15 (±6.91)] (p=0.88). Üç grup arasında nötrofil: lenfosit oranı (p=0.84), trombosit: lenfosit oranı (p=0.36) ve sistemik immün-inflamasyon indeksi değerleri (p=0.67) arasında istatistiksel olarak anlamlı fark yoktu. **Sonuç:** Hematolojik parametrelerden hesaplanan ve sistemik inflamasyonu gösteren indeksler immün yaşlanma nedeniyle geriatrik popülasyonda güvenilir olmayabilir. Bu nedenle hematolojik parametrelerden hesaplanan indeksler, geriatrik popülasyonda diğer yaş grupları dâhil edilmeden çalışılmalıdır. Geriatrik hastalarda, laringeal biyopsinin zamanlamasını tahmin etmeye yardımcı olmak için başka yöntemlere ihtiyaç vardır.

Anahtar Kelimeler: Yaşlı; karsinom; skuamöz hücre; larinks; inflamasyon; immün yaşlanma

Correspondence: Mehmet Emre SİVRİCE
Department of Oto-Rhino-Laryngology and Head&Neck Surgery, Süleyman Demirel University Faculty of Medicine, Isparta, TURKEY/TÜRKİYE
E-mail: emresivrice@gmail.com

Peer review under responsibility of Journal of Ear Nose Throat and Head Neck Surgery.

Received: 22 Feb 2021 ***Received in revised form:*** 12 Mar 2021 ***Accepted:*** 14 Mar 2021 ***Available online:*** 18 Mar 2021

The World Health Organization has defined geriatric age as 65 years and above. With the aging process, some anatomical and physiological changes in the larynx may appear, such as connective tissue changes, vocal fold atrophy, oedema, cartilage ossification, increased laryngeal tension, and disruption of vocal fold vibration.[1-3]

Head and neck cancers like laryngeal squamous cell carcinoma (LSCC) occur mainly in the elderly and constitutes a major health problem in geriatrics patients. Laryngeal cancer aetiology and prognosis are affected by the age of admission. Age includes a critical affect on the development and progression of cancer. Aging also creates changes in the hormonal, circulatory, skeletal and neuromuscular systems in the human body.[4-5] For these reasons, malignancies in geriatric patients should be evaluated distintcly.

The relationship between inflammatory processes and neoplasms was first demonstrated many years ago. Previous studies that have found a correlation between cancer and inflammation biomarkers like the neutrophil: lymphocyte ratio (NLR) and the monocyte: lymphocyte ratio (MLR) have been published.[6-9] Systemic immune inflammation index (SII) has also been found to be correlated with poor prognosis in various malignancies such as nasopharynx cancer., renal cell cancer, small cell lung cancer, colorectal carsinoma, oesophageal squamous cell cancer, and hepatocellular carcinoma.[11-16] But aging of the immune system (immunosenescence) may led to some changes in inflammatory parameters. To our knowledge there has been no study evaluating NLR, PLR, or SII in geriatric patients with laryngeal carcinoma.

MATERIAL AND METHODS

We conducted this study in our tertiary clinic between January 2012 and January 2019. The study was carried out in accordance with the Helsinki Declaration. The ethical committee of Süleyman Demirel University approved the study protocol (date: 21.03.2020, number: 76). Informed consent was obtained from all participants.

Laryngeal biopsy was performed on 348 patients in our clinic between January 2012 and January 2019. One hundred twenty one of these patients were over 65 years old. After review, 103 patients met the inclusion criteria, namely: geriatric age (65 years and above); patients who were evaluated for complete blood count (CBC) before laryngeal biopsy. Exclusion criteria were: acute or chronic infections; autoimmune diseases; chronic inflammatory diseases; chronic liver disease; connective tissue diseases; inflammatory bowel diseases; cardiac diseases; obstructive sleep apnoea; patients receiving drugs that may affect CBC parameters; haematological disorders; and coagulation disorders.

Laryngeal lesions are classified into three groups histopathologically due to differences in follow-up and treatment methods. Three groups were constituted according to the results of the laryngeal biopsy: benign pathology (Group 1), such as vocal nodules, vocal polyps, vocal cysts, granuloma, Reinke's oedema, and non-specific-chronic laryngitis; premalignant lesions (Group 2), such as laryngeal dysplasia and laryngeal keratosis; and malignant lesions (Group 3), namely every stage of LSCC.

CBC was obtained from all participants prior to surgery and NLR, PLR, and SII values were calculated from the CBC.

STATİSTİCAL ANALYSİS

SPSS 20.0 (IBM Inc, Chicago, IL, USA) software was used for statistical analysis. The descriptive variables are presented as mean±SD for numerical and frequency (percentage) for categorical variables. The Chi-square test was used to assess the relationships between the categorical variables. One-way Anova test was used to compare the NLR, platelet:lymphocyte ratio (PLR) and SII values of the three groups. The null hypothesis was rejected if the p value was < 0.05.

RESULTS

A total of 103 patients were included in the study. The male: female ratio was 100:3, and the mean age was 70.87 years (6.38), with no significant differences among the three groups (Group 1: 70.40 (5.94), Group 2: 70.44(5.09), Group 3: 71.15(6.91)) (p=0.88). There were 22 patients in Group 1, 19 in Group 2, and 62 in Group 3, of whom 72.73%,

94.45%, and 100% had a history of smoking for at least 10 years, respectively.

There were no statistically significant differences among the three groups in neutrophil, lymphocyte, or platelet counts (p=0.77, p=0.48 and p=0.60, respectively) (Table 1) and in NLR, PLR, or SII values (p=0.84, p=0.36 and p=0.67, respectively) (Table 2).

DISCUSSION

Studies focusing on inflammation indices calculated using haematological parameters have been published over the last 10 years. These indices have shown promising results in determining the prognosis of cancers. These indexes are simple, inexpensive, and easy-to-calculate using existing data from routine CBC values without additional patient intervention. NLR, PLR, and similar indices for larynx cancer and precancerous lesions have been used in many studies, but not particularly in the elderly. Deveci et al. studied NLR, MLR and SII biomarkers in patients diagnosed with LSCC, and found that all three biomarkers were higher in the LSCC group than the control group.[17] In that study, the mean age was 59 years in those with LSCC, and 57 years in the control group. Kum et al. compared the NLR values in benign laryngeal lesions, precancerous laryngeal lesions, and LSCC, and found that NLR was lowest in the benign group and highest in the LSCC group. Also, they did not find a correlation between dysplasia grade and NLR. In this study, the mean age of benign, precancerous, and LSCC groups were 47, 57, and 63, respectively.[6]

There is a negative correlation between aging and the inflammatory response. A study in rats demonstrated a decrease in cell-mediated response in chronic inflammation, and an increase in Th2-induced humoral immunity during the aging process. According to this study, there is a significant decrease in the number of neutrophils, lymphocytes, monocytes, and a smaller decrease in platelets comprising the cellular immune response in elderly people, while antibody levels increase as a result of exacerbation of the humoral immune response.[18] Major problems may arise due to the susceptibility to infectious diseases during the aging process. Moreover, the loss in immune capacity may have lots of effects. Cancer prevalence increases with aging as a decline in effective immunity.[19] Finally, aging declines the immunity and its regulation. Autoimmune and inflammatory diseases also increase with aging.[20] The decline in thymus productivity with age causes insufficient replacement of the daily T cell loss occurring in the peripheral blood, and this results in a constant decrease in T cell levels.[21]

Unlike other studies, we did not find significant differences in NLR, PLR, and SII parameters among patients with benign lesions, premalignant lesions and LSCC. Our geriatric patient cohort had a higher mean age of 70 years. Aging of the immune system is called "immunosenescence". One of the main reasons for cancer developing is the accumulation of genetic injury during life and reduced immunity in the elderly increases the risk.[22] Tumours are no longer effectively re-

TABLE 1: Comparison of groups for neutrophil, lymphocyte, or platelet counts.

	Group 1	Group 2	Group 3	p value
Neutrophil	5.32±2.53	5.02±2.24	5.39±1.91	0.77
Lymphocyte	1.8±0.58	1.98±0.66	1.91±0.78	0.48
Platelet	262.5±88.21	220.38±62.45	225.85±52.64	0.60

TABLE 2: Comparison of groups for NLR, PLR and SII results.

	Group 1	Group 2	Group 3	p value
NLR	3.19±1.72	3.16±3.21	3.53±3.21	0.84
PLR	162.00±72.30	129.22±90.81	140.35±73.46	0.36
SII	909.81±813.75	721.87±864.29	789.48±589.16	0.67

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

jected and increased inflammation found with age elevates the frequency of the cancer.[23] We concluded that indices showing inflammation such as NLR, PLR and SII do not increase due to cancer in old age because chronic inflammation and immune responses decrease in geriatric patients. We conclude that the use of biomarkers containing neutrophil, lymphocyte, and platelet values in geriatric patients will not provide reliable results since there is a decrease in all cell types due to "immunosenence" in the elderly.

The limitations of our study are the small number of our patients, retrospective design and we can only investigated three inflammatory indices. Also another important limitation is that we do not have a healthy control group to compare with larynx carcinoma group. There is a need for wider studies which investigate more inflamatuar indices.

CONCLUSION

We determined that the indices of inflammation may not be reliable in the geriatric population due to immunosenescence. For this reason, indices calculated from haematological parameters should be studied separately in the geriatric population without including other age groups. Different methods are needed to help predict the timing of laryngeal biopsy in geriatric patients. In addition, we believe that prognostic studies with inflammatory index should be done separately for laryngeal cancer in geriatric patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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: *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur, Vural Akın;* ***Design:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur, Vural Akın;* ***Control/Supervision:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur, Vural Akın;* ***Data Collection and/or Processing:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Vural Akın;* ***Analysis and/or Interpretation:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur;* ***Literature Review:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur, Vural Akın;* ***Writing the Article:*** *Mehmet Emre Sivrice, Yusuf Çağdaş Kumbul, Hasan Yasan, Mustafa Tüz, Erdoğan Okur, Vural Akın;* ***Critical Review:*** *Hasan Yasan, Mustafa Tüz, Erdoğan Okur;* ***References and Fundings:*** *Mehmet Emre Sivrice;* ***Materials:****Mehmet Emre Sivrice.*

REFERENCES

1. Honjo I, Isshiki N. Laryngoscopic and voice characteristics of aged persons. Arch Otolaryngol. 1980;106(3):149-50. [Crossref] [PubMed]
2. Kahane JC. Connective tissue changes in the larynx and their effects on voice. J Voice. 1987;1(1):27-30. [Crossref]
3. Casiano RR, Ruiz PJ, Goldstein W. Histopathologic changes in the aging human cricoarytenoid joint. Laryngoscope. 1994;104:533-8. [Crossref] [PubMed]
4. Crawford J, Cohen HJ. Relationship of cancer and aging. Clin Geriatr Med. 1987;3(3):419-32. [Crossref] [PubMed]
5. Hutchins LF, Lipschitz DA. Cancer, clinical pharmacology, and aging. Clin Geriatr Med. 1987;3(3):483-503. [Crossref] [PubMed]
6. Kum RO, Ozcan M, Baklaci D, Kum NY, Yilmaz YF, Gungor V, et al. Elevated neutrophil-to-lymphocyte ratio in squamous cell carcinoma of larynx compared to benign and precancerous laryngeal lesions. Asian Pac J Cancer Prev. 2014;15(17):7351-5. [Crossref] [PubMed]
7. Mascarella MA, Mannard E, Silva SD, Zeitouni A. Neutrophil-to-lymphocyte ratio in head and neck cancer prognosis: A systematic review and meta-analysis. Head Neck. 2018;40(5):1091-1100. [Crossref] [PubMed]
8. Kara M, Uysal S, Altinişik U, Cevizci S, Güçlü O, Dereköy FS. The pre-treatment neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and red cell distribution width predict prognosis in patients with laryngeal carcinoma. Eur Arch Otorhinolaryngol. 2017;274(1):535-42. [Crossref] [PubMed]
9. Nishijima TF, Muss HB, Shachar SS, Tamura K, Takamatsu Y. Prognostic value of lymphocyte-to-monocyte ratio in patients with solid tumors: A systematic review and meta-analysis. Cancer Treat Rev. 2015;41(10):971-8. [Crossref] [PubMed]
10. Eltohami YI, Kao HK, Lao WW, Huang Y, Abdelrahman M, Liao CT, et al. The prediction value of the systemic ınflammation score for oral cavity squamous cell carcinoma. Otolaryngol Head Neck Surg. 2018;158(6):1042-50. [Crossref] [PubMed]

11. Jiang W, Chen Y, Huang J, Xi D, Chen J, Shao Y, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with nasopharyngeal carcinoma: a propensity score-matched analysis. Oncotarget. 2017;8(39):66075-086. [Crossref] [PubMed] [PMC]
12. Lolli C, Basso U, Derosa L, Scarpi E, Sava T, Santoni M, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Oncotarget. 2016;7(34):54564-71. [Crossref] [PubMed] [PMC]
13. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer. Tohoku J Exp Med. 2015;236(4):297-304. [Crossref] [PubMed]
14. Passardi A, Scarpi E, Cavanna L, Dall'Agata M, Tassinari D, Leo S, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. Oncotarget. 2016;7(22): 33210-9. [Crossref] [PubMed] [PMC]
15. Geng Y, Shao Y, Zhu D, Zheng X, Zhou Q, Zhou W, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients with Esophageal Squamous Cell Carcinoma: A Propensity Score-matched Analysis. Sci Rep. 2016;6:39482. [Crossref] [PubMed] [PMC]
16. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-22. [Crossref] [PubMed]
17. Deveci I, Surmeli M, Onder S, Karabulut B, Deveci HS, Oysu C. Correlation of Histopathological Findings in Laryngeal Squamous Cell Carcinoma with Inflammatory Biomarkers. ENT Updates. 2019;9(1):44-52. [Link]
18. Sharma R, Kapila R, Haq MR, Salingati V, Kapasiya M, Kapila S. Age-associated aberrations in mouse cellular and humoral immune responses. Aging Clin Exp Res. 2014;26(4): 353-62. [Crossref] [PubMed]
19. Zhang HG, Grizzle WE. Aging, immunity, and tumor susceptibility. Immunol Allergy Clin North Am. 2003;23(1):83-102, vi. [Crossref] [PubMed]
20. Johnson SA, Cambier JC. Ageing, autoimmunity and arthritis: senescence of the B cell compartment - implications for humoral immunity. Arthritis Res Ther. 2004;6(4):131-9. [Crossref] [PubMed] [PMC]
21. Hakim FT, Gress RE. Immunosenescence: Deficits in adaptive immunity in the elderly. Tissue Antigens. 2007;70(3):179-89. [Crossref] [PubMed]
22. Derhovanessian E, Solana R, Larbi A, Pawelec G. Immunity, ageing and cancer. Immun Ageing. 2008;5:11. [Crossref] [PubMed] [PMC]
23. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015;282(1821):20143085. [Crossref] [PubMed] [PMC]