Kulak Burun Bogaz Ihtis Derg 2017;27(3):122-127 doi: 10.5606/kbbihtisas.2017.93685

Original Article / Çalışma - Araştırma

Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in malignant and precancerous laryngeal lesions

Malign ve prekanseröz larengeal lezyonlarda nötrofil lenfosit oranı ve trombosit lenfosit oranı

Suphi Bulgurcu, MD.,[1] İlker Burak Arslan, MD.,[2] Bünyamin Dikilitaş, MD.,[2] İbrahim Çukurova, MD.[2]

[1]Department of Otolaryngology, Baskale State Hospital, Van, Turkey
[2]Department of Otolaryngology, Tepecik Training and Research Hospital, Izmir, Turkey

ABSTRACT

Objectives: This study aims to investigate the relationship between neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in patients with precancerous laryngeal lesion or laryngeal squamous cell carcinoma.

Patients and Methods: This retrospective study included 98 patients (92 males, 6 females; mean age 57.4±11.3 years; range 32 to 82 years) who were diagnosed to have precancerous laryngeal lesion or laryngeal squamous cell carcinoma according to histopathology result between January 2011 and June 2016. Patients were divided into two groups as those with precancerous laryngeal lesion or laryngeal squamous cell carcinoma.

Results: There was a statistically significant difference between the two groups in terms of NLR and PLR values (p=0.010, p=0.002, respectively). When patients with laryngeal squamous cell carcinoma were evaluated in terms of lymph node metastasis, primary localization of tumor and differentiation of tumor; there was no statistically significant difference between NLR and PLR values. However, when evaluated in terms of clinical staging, PLR value was statistically different (p=0.047) while NLR value was not statistically different.

Conclusion: To our knowledge, this is the first study to show that PLR can be used to differentiate precancerous laryngeal lesion and laryngeal squamous cell carcinoma.

Keywords: Laryngeal; lymphocyte; neutrophil; platelet.

ÖZ

Amaç: Bu çalışmada, prekanseröz larengeal lezyonu veya larengeal skuamöz hücreli karsinoması olan hastalarda nötrofil lenfosit oranı (NLO) ve trombosit lenfosit oranı (TLO) arasındaki ilişki araştırıldı.

Hastalar ve Yöntemler: Bu retrospektif çalışmaya Ocak 2011 - Haziran 2016 tarihleri arasında histopatoloji sonucuna göre prekanseröz larengeal lezyon veya larengeal skuamöz hücreli karsinoma tanısı konulan 98 hasta (92 erkek, 6 kadın; ort. yaş 57.4±11.3 yıl; dağılım 32-82 yıl) dahil edildi. Hastalar prekanseröz larengeal lezyonlu veya larengeal skuamöz hücreli karsinomalı olmak üzere iki gruba ayrıldı.

Bulgular: İki grup arasında NLO ve TLO değerleri açısından istatistiksel olarak anlamlı farklılık vardı (sırasıyla, p=0.010, p=0.002). Larengeal skuamöz hücreli karsinomalı hastalar lenf nodu metastazı, tümörün primer yerleşimi ve tümörün diferansiasyonu açısından değerlendirildiğinde, NLO ve TLO değerleri arasında istatistiksel olarak anlamlı farklılık yoktu. Ancak klinik evrelendirme açısından değerlendirildiğinde, TLO değeri istatistiksel olarak farklı (p=0.047), NLO değeri ise istatistiksel olarak farklı değildi.

Sonuç: Bildiğimiz kadarıyla, bu çalışma, TLO'nun prekanseröz larengeal lezyon ve larengeal skuamöz hücreli karsinomanın ayrımında kullanabileceğini gösteren ilk çalışmadır.

Anahtar Sözcükler: Larengeal; lenfosit; nötrofil; trombosit.

Available online at
www.kbbihtisas.org
doi: 10.5606/kbbihtisas.2017.93685
QR (Quick Response) Code

Received / *Geliş tarihi:* January 16, 2017 Accepted / *Kabul tarihi:* May 19, 2017

Correspondence / İletişim adresi: Suphi Bulgurcu, MD. Başkale Devlet Hastanesi, Kulak Burun Boğaz Kliniği, 65600 Başkale, Van, Turkey.
Tel: +90 432 - 651 20 37 e-mail *(e-posta):* suphibulg@yahoo.com

Laryngeal squamous cell carcinoma (LSCC) is one of the most common head and neck malignancies and is an important cause of morbidity and mortality. Laryngeal squamous cell carcinoma develops due to structural and cytological differences in the laryngeal squamous epithelium. Transformation of precancerous laryngeal lesions (PLL) to invasive cancer is frequent and includes different degrees of dysplasia and carcinoma in situ.[1]

Recent data have shown that inflammation is a critical constituent of tumor progression and it is related with poor prognosis of various tumors since an oncogenic change proceeds.[2] Studies have indicated that an elevated level of neutrophils is related with angiogenesis that has an important role in the expansion and metastasis of malignancy.[2]

Markers of inflammation such as the neutrophil to lymphocyte ratio (NLR) have been assessed as a prognostic indicator in different types of cancer.[3,4]

Additionally, platelets may also support tumor progression through facilitation of neoangiogenesis, generation of adhesion molecules and rise of early metastatic niches.[5] For this reason, platelet to lymphocyte ratio (PLR) has been proposed as an independent prognostic factor in different solid tumors.[5]

The aim of this study is to investigate the association of histopathologic results with NLR and PLR values in patients with PLL and LSCC.

PATIENTS AND METHODS

The records of 139 patients from whom biopsies were obtained for suspected laryngeal carcinoma between January 2011 and June 2016 at Izmir Tepecik Training and Research Hospital were evaluated. Those whose histopathologic results were PLL (various degrees of dysplasia and carcinoma in situ) were classified under group 1 and those with results of LSCC were classified into group 2. The NLR and PLR values were also obtained from preoperative blood tests. In patients whose histopathological result was LSCC, relations of lymph node metastasis, tumor subsite, pathological differentiation and clinical stage with NLR and PLR values were evaluated. This study was approved by the local ethics committee and was conducted in accordance with the principles of Declaration of Helsinki.

Patients with concurrent infection, chronic inflammatory conditions, those using immunosuppressive medications for a long time, who had synchronous cancer, cancer history, palliative treatment, and patients with no preoperative blood tests were excluded from this study.

Medical records of all patients were evaluated and clinical information (age, gender, clinical stage, smoking status, drinking status, lymph node metastasis, tumor site, pathological differentiation and pre-treatment neutrophil to lymphocyte counts and platelet to lymphocyte counts) was collected. Clinical stage of laryngeal cancer was classified as early (stage 1 and 2) or late (stage 3 and 4) stage in accordance with the 7th Edition Cancer Staging Manual of the American Joint Committee on Cancer.

Hemograms were made using peripheral venous blood samples taken before treatment. These blood samples were tested using an automated blood cell counter (Beckman Coulter analyzer, CA, USA). The NLR and PLR were calculated as a simple ratio between absolute neutrophil and absolute lymphocyte values, and absolute platelet and absolute lymphocyte values, respectively.

Statistical analysis

Statistical analysis of data was made using the IBM SPSS® 20.0 software (IBM Corp., Armonk, NY, USA). For the evaluation of relationships between the study groups, the Pearson chi-square test and Fisher's exact test were used. $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 98 patients were included in the study, (92 males, 6 females; mean age 57.4±11.3 years; range 32 to 82 years). There were 38 patients (4 females, 34 males) in group 1 (PLL) and 60 (2 females, 58 males) in group 2 (LSCC). The mean age of the patients in group 1 was 56.8±12.4, and the mean age of patients in group 2 was 60.2±10.1. There was no statistically significant difference between the two groups in terms of smoking and alcohol status ($p=0.106$, $p=0.68$, respectively). A statistically significant difference was observed between the two groups in terms of NLR and PLR values ($p=0.010$, $p=0.002$, respectively) (Table 1). When evaluated in terms of clinical stage, PLR value was statistically significant

Table 1. Age, gender, smoking and drinking history, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio values of participants in group 1, precancerous laryngeal lesions and group 2, malignant laryngeal lesions

	Premalignant (n=38)			Malignant (n=60)				
	n	%	Mean±SD	n	%	Mean±SD	*p*	χ^2
Age (year)			56.8±12.4			60.1±10.1	0.148	
Neutrophil to lymphocyte ratio			2.4±0.8			2.9±1.5	<0.010	
Platelet to lymphocyte ratio			111.7±36.6			142.2±58.9	<0.002	
Gender							0.146	2.094
Female	4			2				
Male	34			58				
Smoking history	28	73.68		52	86.66		0.106	2.615
Drinking history	0	0		5	8.33		0.068	3.337

SD: Standard deviation.

(p=0.047) but NLR value was not statistically significant (p=0.089), (Table 2). However, no statistically significant difference was found between the NLR and PLR values when the patients in group 2 were evaluated for lymph node metastasis (Table 3), primary tumor location (Table 4) and tumor differentiation (Table 5).

DISCUSSION

Systemic inflammatory responses might facilitate tumor progression in nearly every step including initiation, progression and metastasis.[6] On the other hand, current data shows that platelets can protect tumor cells from immune degradation and are involved in development of aggressive tumor attitudes. Besides, platelets can support tumor-cell transendothelial migration and metastasis by mediating P2Y2 purinergic receptor.[7] Platelets can secrete various growth factors like platelet derived growth factor (PDGF), platelet-activating factor (PAF), and vascular endothelium growth factor (VEGF). These factors can further promote tumor growth, angiogenesis and metastasis.[8,9] Because of this, elevated platelet counts have negative effects on patient survival. On the other hand, lymphocytes play an important role in tumor-derived inflammatory responses. Lymphocytes can induce cytotoxic cell death and inhibit tumor proliferation and because of these effects they have an antitumor activity.

Table 2. Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with clinic stage variables of laryngeal squamous cell carcinoma patients

	Clinical stage 1-2 (n=35)			Clinical stage 3-4 (n=25)				
	n	%	Mean±SD	n	%	Mean±SD	*p*	χ^2
Age (year)			59.11±9.60			61.68±10.80	0.568	
Neutrophil to lymphocyte ratio			2.68±1.38			3.36±1.66	0.089	
Platelet to lymphocyte ratio			129.53±57.58			160.03±57.11	0.047	
Gender							0.808	0.059
Female	1	50		1	50			
Male	34	58.6		24	42.4			
Smoking history							0.199	1.648
Smoker	32	61.5		20	38.5			
Non smoker	3	37.5		5	63.5			
Drinking history							0.937	0.006
Drinker	3	60		2	40			
Non drinker	32	58.2		23	41.8			

SD: Standard deviation.

Table 3. Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with lymph node metastasis variables of laryngeal squamous cell carcinoma patients

	Lymph node metastasis							
	Metastasis negative (n=50)			Metastasis positive (n=10)				
	n	%	Mean±SD	n	%	Mean±SD	*p*	χ^2
Age (year)			60.44±10.44			58.90±8.68	0.664	
Neutrophil to lymphocyte ratio			2.94±1.42			3.07±2.04	0.811	
Platelet to lymphocyte ratio			141.75±59.59			144.69±58.20	0.887	
Gender							0.198	1.655
Female	1	50		1	50			
Male	49	84.5		9	15.5			
Smoking history							0.174	1.846
Smoker	42	80.8		10	19.2			
Non smoker	8	100		8	0			
Drinking history							0.835	0.044
Drinker	4	80		1	20			
Non drinker	46	83.6		9	16.4			

SD: Standard deviation.

[10] Also neutrophils play an important role in cancer development and progression because they can promote tumor cell growth and invasion by production of proangiogenic VEGF and remodeling the extracellular matrix via the release of multiple cytokines and chemokines including interleukin (IL)-1, IL-8, and IL-12.[11,12]

According to recent studies, elevated PLR and NLR values were associated with poor survival in different solid tumors. Kum et al.[13] found statistical significance between the NLR values and the groups in the study conducted with 209 patients by studying three groups of benign, premalignant, and malignant lesions. In their study of 141 patients, Tu et al.[14] found that elevated preoperative NLR was an independent predictor for poor prognosis after surgical resection in patients with LSCC. Gong et al.[15] studied 161 patients and found that increased preoperative

Table 4. Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with tumor localization variables of laryngeal squamous cell carcinoma patients

	Tumor localization										
	Supraglottic (n=17)			Glottic (n=39)			Infraglottic (n=4)				
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*	χ^2
Age (year)			56.6±6.5			60.5±10.8			72.3±5.6	0.057	
Neutrophil to lymphocyte ratio			3.1±1.7			2.9±1.5			3.2±1.9	0.836	
Platelet to lymphocyte ratio			149.3±56			135.2±57.5			180.5±82.1	0.292	
Gender										0.073	5.233
Female	2	100		0	0		0	0			
Male	15	25.9		39	67.2		4	6.9			
Smoking history										0.773	0.516
Smoker	15	28.8		34	65.4		3	5.8			
Non smoker	2	25		5	62.5		1	12.5			
Drinking history										0.724	0.647
Drinker	2	40		3	60		0	0			
Non drinker	15	27.3		36	65.5		4	7.3			

SD: Standard deviation.

Table 5. Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with histological grade variables of laryngeal squamous cell carcinoma patients

	Histological grade										
	Well (n=13)			Moderate (n=43)			Poorly (n=4)				
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*	χ^2
Age (year)			65.2±10.7			59.4±10.3			59±4.1	0.495	
Neutrophil to lymphocyte ratio			3.6±1.6			2.9±1.5			2.1±0.8	0.174	
Platelet to lymphocyte ratio			165.3±47.6			138.3±61.0			110.0±55.2	0.185	
Gender										0.664	0.818
Female	0	0		2	100		0	0			
Male	13	22.4		41	70.7		4	6.9			
Smoking history										0.656	0.843
Smoker	12	23.1		37	71.2		3	5.8			
Non smoker	1	12.5		6	75		1	12.5			
Drinking history										0.457	1.565
Drinker	1	20		3	60		1	20			
Non drinker	12	21.8		40	72.7		3	5.5			

SD: Standard deviation.

NLR could contribute to the advanced tumor node metastasis stage of papillary thyroid carcinoma in patients who were older than 45 years. A study of 140 patients by Li et al.[16] showed that elevated preoperative NLR value was a negative independent prognostic factor in patients undergoing resection for non-metastatic rectal cancer. Liu et al.[17] studied 434 patients and found that increased NLR and PLR values were associated with poor survival in hormone receptor negative breast cancer patients. At the same time, it was also detected that NLR is independently correlated with overall survival and disease free survival, but PLR is not. Han et al.[18] studied 173 patients and found that PLR is an independent prognostic factor for overall survival but NLR is not a prognostic factor. In this study, NLR and PLR value was evaluated in patients with PLL and LSCC. Both NLR and PLR were statistical higher in patients who had LSCC.

We hypothesized that NLR and PLR reflect the systemic inflammatory response created by the laryngeal lesions, and could be used as an inflammatory marker to differentiate patients with LSCC from the ones with benign and precancerous laryngeal lesions.

However, when lymph node metastasis, primary localization of tumor and tumor differentiation were assessed in patients with LSCC, the NLR and PLR values were not statistically significant different. On the other hand, we found that PLR value may be helpful in early stage to late phase discrimination in patients with LSCC, but the NLR value was not significant.

There are publications in the literature where the NLR value was reported as a prognostic marker in laryngeal lesions.[13,14] To the best of our knowledge, this is the first study to suggest that PLR maybe used for PLL and LSCC discrimination. According to the current results PLR may be used for PLL and LSCC discrimination. It should be kept in mind that this study is limited due to its retrospective nature and the relatively small sample size. Multicenter, large prospective studies are needed in the future to confirm these findings.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Ferlito A, Devaney KO, Woolgar JA, Slootweg PJ, Paleri V, Takes RP, et al. Squamous epithelial changes of the larynx: diagnosis and therapy. Head Neck 2012;34:1810-6.
2. Fu Y, Liu W, OuYang D, Yang A, Zhang Q. Preoperative Neutrophil-to-lymphocyte Ratio Predicts Long-term Survival in Patients Undergoing Total Laryngectomy

With Advanced Laryngeal Squamous Cell Carcinoma: A Single-center Retrospective Study. Medicine (Baltimore) 2016;95:2689.
3. Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, et al. Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Cancer 2015;112:1088-97.
4. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015;113:150-8.
5. Ozawa T, Ishihara S, Nishikawa T, Tanaka T, Tanaka J, Kiyomatsu T, et al. The preoperative platelet to lymphocyte ratio is a prognostic marker in patients with stage II colorectal cancer. Int J Colorectal Dis 2015;30:1165-71.
6. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
7. Schumacher D, Strilic B, Sivaraj KK, Wettschureck N, Offermanns S. Platelet-derived nucleotides promote tumor-cell transendothelial migration and metastasis via P2Y2 receptor. Cancer Cell 2013;24:130-7.
8. Goubran HA, Burnouf T, Radosevic M, El-Ekiaby M. The platelet-cancer loop. Eur J Intern Med 2013;24:393-400.
9. Sullivan LA, Brekken RA. The VEGF family in cancer and antibody-based strategies for their inhibition. MAbs 2010;2:165-75.
10. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.
11. Lança T, Silva-Santos B. The split nature of tumor-infiltrating leukocytes: Implications for cancer surveillance and immunotherapy. Oncoimmunology 2012;1:717-725.
12. Wong BY, Stafford ND, Green VL, Greenman J. Prognostic value of the neutrophil-to-lymphocyte ratio in patients with laryngeal squamous cell carcinoma. Head Neck 2016;38:1903-8.
13. 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;15:7351-5.
14. Tu XP, Qiu QH, Chen LS, Luo XN, Lu ZM, Zhang SY, et al. Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma. BMC Cancer 2015;15:743.
15. Gong W, Yang S, Yang X, Guo F. Blood preoperative neutrophil-to-lymphocyte ratio is correlated with TNM stage in patients with papillary thyroid cancer. Clinics (Sao Paulo) 2016;71:311-4.
16. Li H, Song J, Cao M, Wang G, Li L, Zhang B, et al. Preoperative neutrophil-to-lymphocyte ratio is a more valuable prognostic factor than platelet-to-lymphocyte ratio for nonmetastatic rectal cancer. Int Immunopharmacol 2016;40:327-31.
17. Liu C, Huang Z, Wang Q, Sun B, Ding L, Meng X, et al. Usefulness of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in hormone-receptor-negative breast cancer. Onco Targets Ther 2016;9:4653-60.
18. Han Y, Wang J, Hong L, Sun L, Zhuang H, Sun B, et al. Platelet-lymphocyte ratio is an independent prognostic factor in patients with ALK-positive non-small-cell lung cancer. Future Oncol 2017;13:51-61.