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Prognostic Significance of Systemic Inflammatory Markers in Laryngeal Cancer

Abstract

Objective: Systemic inflammatory markers are investigated in many solid cancers, including laryngeal squamous cell carcinoma. Neutrophils, lymphocytes, platelet counts, and red cell distribution width (RDW) are thought to predict survival in patients with cancer.

Methods: Patients included in the study had a diagnosis of laryngeal squamous cell carcinoma and were treated at our hospital. Patients with a metastatic disease, positive margin, insufficient follow-up, treatment before surgery, and hematologic disorders were excluded. This retrospective cohort study included 82 patients. The relationship between inflammatory markers with overall survival (OS) and disease-free survival (DFS) was investigated using Kaplan–Meyer, univariate, and multivariate analyses.

Results: Although pathologic N (pN) status, derived neutrophil to lymphocyte ratio (dNLR), and lymphovascular invasion showed significant correlation with OS in the univariate analysis, dNLR and pN showed significant correlation in the multivariate analysis. DFS was related to perineural invasion, grade, and pN status in the univariate analysis, and perineural invasion and pN were also significantly related in the multivariate analysis.

Conclusion: Platelet to lymphocyte ratio, systemic-immune-inflammation index, RDW, and dNLR correlate to grade, pathologic T, and OS, but not to the neutrophil to lymphocyte ratio.

Keywords: Lyhmphocyte, neutrophil, platelet, recurrence, red cell distribution width, survival

Introduction

Laryngeal carcinoma (LC), one of the most common head and neck cancers, is under investigation to expand our knowledge of its etiopathogenesis, improve the abilities of classification systems, and determine patient-based treatment needs. Improving classification systems will allow us to understand the most appropriate treatment strategies for patients, without under- or over-treating them. Apart from classification systems, other factors that may provide prognostic information in the pretreatment period have also been investigated for some time.

Inflammation is a well-known prognostic factor in patients with cancer. Therefore, systemic inflammatory markers are thought to provide valuable information in the pretreatment period.[1-5] Complete blood counts (CBCs) are examined in nearly all patients with cancer regardless of the treatment modality. CBC parameters are being investigated because they do not result in an extra cost and are easily obtained.

Lymphocytes play a role in anticancer immunotherapy. Neutrophils are stimulated by cytokines, delivered from cancer cells, and may cause tumor growth and angiogenesis.[6] The neutrophil to lymphocyte ratio (NLR) has been investigated in many tumors and head and neck cancers because of this inverse relation. The derived form of NLR (dNLR) is defined as the neutrophil count (white blood cell count - neutrophil count), i.e., NC (WBC-NC), and is investigated in solid tumors. Another systemic inflammatory marker commonly examined is red cell distribution width (RDW), which has been shown to correlate with other systemic markers; however, the exact pathogenesis in tumor development remains unclear.[1-2] A recently published meta-analysis showed that elevated RDWs were negatively

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correlated with survival in upper aerodigestive tract cancers.[2] Platelets are thought to make complexes with tumor cells, rendering the latter "invisible" to the immune system and enabling them to escape.[7] Another recent study showed that a high platelet to lymphocyte ratio (PLR) correlated with a poor outcome in laryngeal squamous cell carcinoma (LSSC).[3] The systemic-immune-inflammation index (SII) is a new parameter, calculated as neutrophil × platelet/lymphocyte, and has been investigated in many cancers; a recent meta-analysis has shown that a high SII can be related to poor survival.[8] To the best of our knowledge, SII has not been investigated in LSSC.

We aimed to identify whether NLR, PLR, RDW, and SII had any predictive value on survival and clinicopathologic parameters in patients with LSSC. However, these inflammatory parameters can be affected by illnesses other than cancer. Therefore, we also analyzed comorbid illnesses.

Methods

Patients diagnosed with operable LSSC and surgically treated between November 2010 and March 2018 at our hospital were included in the study. Ethical approval was obtained from the Bakırköy Dr Sadi Konuk Research and Training Hospital ethical committee (approval number: 2018/346).

This study included 112 patients. The exclusion criteria were previous radiation therapy (n = 1), multiple primary lesions (n = 12), positive surgical margins (n = 5), less than one year of follow-up (n = 12), and hematologic disorders that could affect the CBC results. A total of 82 patients were eligible for the final analysis.

Patients with total laryngectomy were fed orally on postoperative day 10; during this time, the patients were fed via nasogastric tube. Patients with supraglottic and supracricoid laryngectomies were fed orally on postoperative day 7 and were fed via nasogastric tube before then while patients with frontolateral laryngectomies and cordectomies were fed orally on postoperative day 1.

Adjuvant radiotherapy was administered if there was a positive metastatic lymph node, lymphovascular invasion, perineural invasion, and pT3-T4 tumors. Recurrence was detected either pathologically or radiologically. Patients were classified according to the 2010 tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer.

The pathologic parameters of the patients (local or distant metastasis, tumor location, grade, surgical margins, perineural invasion, vascular invasion, and differentiation) and their follow-up information (visit times, presence of recurrence, or death) were recorded. The presence of any comorbid illnesses was recorded. CBCs were performed 7-14 days prior to surgery.

Survival Parameters

Disease-free survival (DFS), defined as the time from the date of curative surgery to the first recurrence date or last follow-up, and overall survival (OS)-defined as the time from the date of curative surgery to the date of the last follow-up or death by any cause—were calculated using Kaplan-Meier analysis.

Statistical Analysis

Receiver operating characteristic (ROC) analysis was performed for NLR, dNLR, RDW, PLR, and SII. The Kruskal-Wallis and Mann-Whitney U tests were used to detect associations between inflammatory and other clinicopathologic parameters. Logistic regression analysis was performed for univariate analysis. Multivariate analysis was performed using a backward method for factors with *P* less than 0.1 ($P < 0.1$). Statistical significance was accepted as $P < .05$.

Results

The study included 77 men (94% of the patients) and 5 women (6% of the patients). Their average age was 59.81 ± 8.25 years. The mean follow-up period, DFS, and OS time were 39.80 ± 21.70, 36 ± 21.26, and 40.51 ± 21.56 months, respectively. During the follow-up period, there were 12 recurrences (14% of the total) and 13 deaths (15% of the total), of which 7 (8% of the total) were caused by a recurrence. Of the patients, 28 (34%) had comorbid illnesses (coronary artery disease [n = 5], hypertension [n = 5], diabetes mellitus [n = 4], chronic obstructive lung disease [n = 16], hypothyroidism [n = 1], and cirrhosis [n = 1]).

There were 40 patients with early-stage LC. We performed 1 type-3 cordectomy, 2 type-4 cordectomies, 4 type-5 cordectomies, 3 frontolateral laryngectomies, 10 supracriocoid laryngectomies, 8 supraglottic laryngectomies, and 12 total laryngectomies; 33 total laryngectomies, 7 supraglottic laryngectomies, and 2 supracroid laryngectomies were performed on 42 patients with advanced stage tumors, with either unilateral or bilateral neck dissection.

The mean neutrophil, mean lymphocyte, mean platelet, and mean RDW counts were 5.95 ± 2.05 (2.39-11.19), 2.65 ± 3.45 (0.63-4.26), 274.3 ± 86.9 (98.3-507), and 13.13 ± 1.85 (9.42-22.34), respectively. The ROC analysis results were NLR 2.75 (sensitivity 69.2%, specificity 63.8%), PLR 132 (sensitivity 61.5%, specificity 65.2%), RDW 13.25 (sensitivity 61.5%, specificity 62.3%), dNLR 1.93 (sensitivity 69.2%, specificity 63.8%), and SII 622 (sensitivity 53.8%, specificity 50.7%).

The relationship among NLR, dNLR, PLR, RDW, SII, comorbid illness status, pT stage, pN status, grade, perineural invasion (PI), lymphovascular invasion, and differentiation with DFS and OS was investigated using univariate analysis; the results are shown in Table 1. Multivariate analysis was performed for pN, grade, PI, lymphovascular invasion, and dNLR for OS; dNLR and pN status were significant, at $P = .042$ and $P = .021$, respectively, at the final step. Survival curves for dNLR and pN are shown in Figures 1 and 2, respectively. Multivariate analysis was performed with grade, PI, pN, lymphovascular invasion, and dNLR for DFS; PI and pN status were significant, at $P = .033$ and $P = .002$, respectively, at the final step. The patients' clinicopathologic characteristics and distributions with inflammatory parameters are shown in Table 2. According to the Kruskal–Wallis test, there was a significant relationship between differentiation and SII status ($P = .042$), N and RDW status ($P = .010$), grade and dNLR ($P = .021$) and SII status ($P = .039$), T and NLR status ($P = .015$), dNLR status ($P < .001$), and SII ($P = .002$). There was no significant relationship between lymphovascular invasion and PI and the investigated inflammatory parameters based on the Mann-Whitney U test.

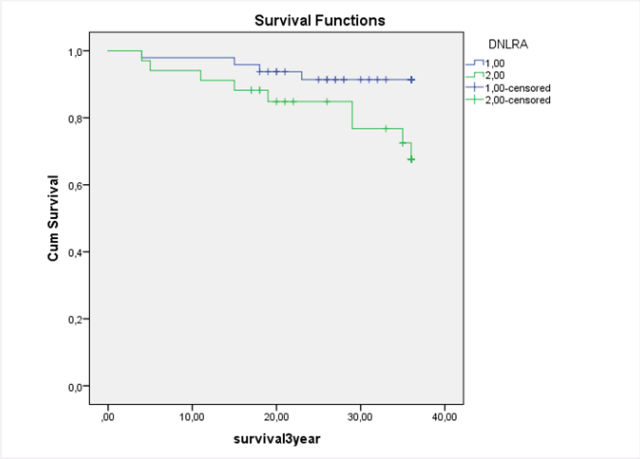

Figure 1. Three-year Survival Analysis Result for Derived Neutrophil to Lymphocyte Ratio

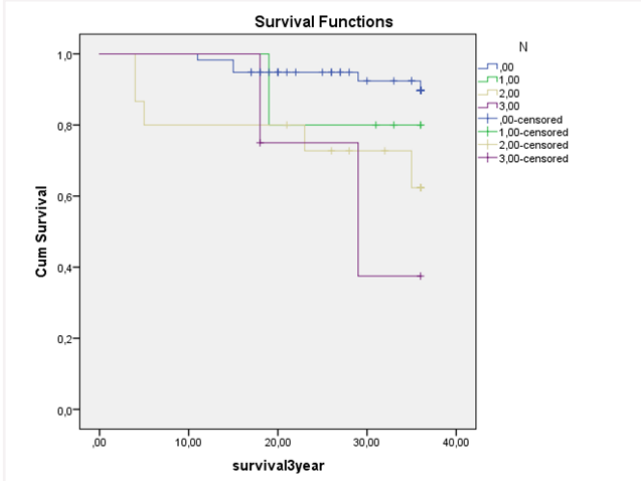

Figure 2. Three-year Survival Analysis Result for pathologic N

Table 1. Univariate Test Results for DFS and OS

			DFS		OS	
		Case	Case	P	Case	P
Grade	Well	19	3	0.372	3	0.475
	Moderate	46	5		6	
	Poor	17	4		4	
Localization	Supraglottic	24	5	0.403	4	0.603
	Glottic	32	3		3	
	Subglottic	2	0		0	
	Transglottic	24	4		6	
T	1	24	1	0.194	1	0.314
	2	23	4		4	
	3	24	6		6	
	4	11	1		2	
N	0	58	5	.002	5	.016
	1	5	1		1	
	2	15	3		5	
	3	4	3		2	
TNM stage	1	22	1	.007	1	.071
	2	18	2		1	
	3	15	3		3	
	4a	23	3		6	
	4b	4	3		2	
LV	0	64	8	0.327	7	.029
	1	18	4		6	
PN	0	67	7	.022	8	.051
	1	15	5		5	
NLR	1	25	1	0.106	3	0.629
	2	57	11		10	
DNLR	1	48	5	.089	4	.025
	2	34	7		9	
PLR	1	37	7	0.286	5	0.679
	2	45	5		8	
RDW	1	48	6	0.485	5	0.117
	2	34	6		8	
SIII	1	41	6	0.890	6	0.842
	2	41	6		7	
Comorbid						
illness	(-)	54	12		9	0.786
	(+)	28	0		4	

DFS: disease-free survival; OS: overall survival; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red cell distribution width; SIII: systemic-immune-inflammation index; TNM: tumor, node, metastasis; LV: Lyhmphovascular invasion, PN: Perineural invasion; Statistically significant values are shown in bold

Table 2. Clinicopathological Characteristics and Distributions with Inflammatory Parameters of the Patients

			NLR		PLR		RDW		dNLR		SIII	
			<2.75	≥2.75	<132	≥132	<13.25	≥13.25	<1.93	≥1.93	<622	≥622
T	1	24	11	13	14	10	15	9	19	5	17	7
	2	23	10	13	11	12	12	11	18	5	15	8
	3	24	3	21	10	14	15	9	9	15	6	18
	4	11	1	10	2	9	6	5	2	9	3	8
N	0	58	20	38	27	31	39	19	37	21	33	25
	1	5	1	4	1	4	3	2	1	4	1	4
	2	15	3	12	7	8	3	12	8	7	6	9
	3	4	1	3	2	2	3	1	2	2	1	3
TNM stage	1	22	11	11	13	9	15	7	17	5	16	6
	2	18	7	11	8	10	11	7	14	4	11	7
	3	15	2	13	6	9	10	5	6	9	5	10
	4a	23	4	19	8	15	9	14	9	14	8	15
	4b	4	1	3	2	2	3	1	2	2	1	3
Grade	Well	19	7	12	10	9	11	8	13	6	12	7
	Mod.	46	15	31	21	25	30	16	28	18	25	21
	Poor	17	3	14	6	12	7	10	7	10	4	13
LV	0	64	20	44	29	35	38	26	41	23	34	30
	1	18	5	13	8	10	10	8	7	11	7	11
PN	0	67	20	47	30	37	39	28	42	25	34	33
	1	15	5	10	7	8	9	6	6	9	7	8
Comorbid	(−)	54	17	37	28	26	32	22	32	22	28	26
Illness	(+)	28	8	20	9	19	16	12	16	12	13	15

NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; RDW: red cell distribution width; dNLR: derived NLR; SIII: systemic-immune-inflammation index; TNM: tumor, node, metastasis; LV: Lyhmphovascular invasion; PN: Perineural invasion

Discussion

In this study, the results of univariate analysis showed a showed significant correlation between OS and N status, dNLR, and lymphovascular invasion. Multivariate analysis showed that dNLR and N were factors that affected OS. PI, grade, and N status showed significant correlation with DFS in the univariate analysis. Multivariate analysis showed that PI and N status were factors that affected DFS. Significant correlations were observed between SII and differentiation, grade, and T; between dNLR, grade, and T; between NLR and T; and between RDW and N from the investigated inflammatory parameters.

The exact pathophysiological mechanism between tumor progression and neutrophils and lymphocytes is still unclear. As is known, lymphocytes are responsible for tumor immunity; thus, lymphopenia is thought to be related to tumor severity.[6] Neutrophils play a role in the microenvironment of the tumor by releasing angiogenetic substances, neutrophil elastases, and interleukins that facilitate tumor invasion and metastases.[4,6] Du et al.[11] showed that patients in a high NLR group had increased levels of IL-6 and IL-8 in the tumor microenvironment. High levels of interleukins also attract neutrophils to the microenvironment of the tumor, resulting in a vicious cycle. Therefore, increased NC with decreased lymphocyte counts are considered a potential inflammatory marker.

The NLR is a well-investigated parameter in LSCC. The NLR values of patients with LC were found to be higher than those in the control group and with benign laryngeal pathologies.[9,10] In most studies, NLR values were correlated with differentiation, T stage, and N stage.[6,10-13] Similarly, our study revealed a significant relationship between NLR and T and N status. It has been shown that NLR has prognostic significance in LC, whether treated with radiotherapy, induction chemotherapy, or surgery.[6,12,14] Du et al.[11] analyzed 654 patients with LC and found that high NLR values correlated with worse OS and PFS. However, Kara et al.[16] found that NLR was correlated with recurrence but not with OS while Wong et al.[17] observed that NLR was correlated with OS but not with DFS. Furthermore, two recent studies revealed that there was no relationship between NLR and survival parameters.[18,19] Our study showed no significant relationship between NLR and survival parameters. The results of aforementioned studies show that although nearly all of them were conducted with similar methodology, there is a controversy regarding the relationship between NLR and survival parameters.

To the best of our knowledge, only one study to date has investigated dNLR status in LC,[6] and it found that dNLR was significantly related to the T, N, M, TNM, and tumoral stage. Unexpectedly, dNLR status was found not to be related with DFS, OS, and disease-specific survival. In our study, dNLR was correlated with grade and T status and OS but not with DFS.

A few studies have investigated the relation of RDW with survival parameters in head and neck tumors. RDW was found to be significantly correlated with OS in esophageal carcinoma; however, it was not correlated with survival in oral cavity and LC.[16,17] Controversially, one study found that RDW was significantly correlated with

OS in LC,[16] whereas another found no correlation.[3] We found that RDW was related with N status but not with survival parameters.

Du et al.[11] have found a significant correlation between PLR and T, N, and TNM status. Two studies observed a significant relationship between PLR and OS,[3,16] while two other studies reported no significant relationship between PLR and survival parameters.[18,19] Zhong et al.[19] found that the preoperative and postoperative change in PLR was related to prognosis; however, we did not observe any significant relationship between PLR and clinicopathologic and survival parameters.

The SII is a recently described parameter, and a recent meta-analysis revealed that high SIIs might be related with poor prognosis in patients with cancer.[8] We found that SII correlated with differentiation, grade, and T but not with survival parameters. We also evaluated the effect of the presence of a comorbid illness on NLR, dNLR, PLR, RDW, and SII and found no significant relationship.

Our study had several limitations similar to other studies in the literature. We could not evaluate smoking and alcohol status as this was a retrospective study, and some information was missing. In addition, this study reflected only the survival of patients who had been treated with surgery because-as is widely accepted-clinical and pathologic N statuses may differ.

Conclusion

Our study revealed that dNLR was correlated with grade, pT, and OS. Furthermore, NLR, PLR, and SII were not correlated with survival parameters although they were correlated with clinicopathologic parameters. Multicentric prospective cohort studies are needed to clarify the relationship between inflammatory markers and LSCC.

Ethics Committee Approval: Ethics Committee Approval was received from the the Ethical Committee of Bakirköy Dr. Sadi Konuk Research and Training Hospital (Approval date: 10.08.2018, Number: 2018/346).

Peer-review: Externally peer-reviewed.

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Author Contributions: Concept - M.A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Design - A.A., ,S.G., F.G., E.A., Z.M.Y., İ.S.; Supervision - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Resource - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Materials - .A.A.,S.G., F.G.,E.A.,Z.M.Y,İ.S.; Data Collection and/or Processing - A.A.,S.G.,Z.M.Y,İ.S.; Analysis and/or Interpretation - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Literature Search - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Writing - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.; Critical Reviews - A.A., S.G., F.G., E.A., Z.M.Y., İ.S.

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References

1. Tham T, Olson C, Wotman M et al. Evaluation of the prognostic utility of the hemoglobin-to-red cell distribution width ratio in head and neck cancer. *Eur Arch Otorhinolaryngol.* 2018; 275(11): 2869-2878. [Crossref]
2. Tham T, Bardash Y, Teegala S, Herman WS, Costantino PD. The red cell distribution width as a prognostic indicator in upper aerodigestive tract (UADT) cancer: A systematic review and meta-analysis. *Am J Otolaryngol.* 2018; 39(4): 453-458. [Crossref]
3. Xun Y, Wang M, Sun H, Shi S, Guan B, Yu C. Prognostic analysis of preoperative inflammatory biomarkers in patients with laryngeal squamous cell carcinoma. *Ear Nose Throat J.* 2020; 96(6): 371-378. [Crossref]
4. Mascarella MA, Mannard E, Daniela SWS, Zeitouni A, Eisele DW. Neutrophil-to-lymphocyte ratio in head and neck cancer prognosis: A systematic review and meta-analysis. *Head & Neck. 2018*; 00: 1-10. [Crossref]
5. Tangthongkum M, Tiyanuchit S, Kirtsreesakul V, Supanimitjaroenporn P, Sinkitjaroenchai W. Platelet to lymphocyte ratio and red cell distribution width as prognostic factors for survival and recurrence in patients with oral cancer. *Eur Arch Otorhinolaryngol*. 2017; 274(11): 3985-3992. [Crossref]
6. Eskiizmir G, Uz U, Onur E et al. The evaluation of pretreatment neutrophil-lymphocyte ratio and derived neutrophil-lymphocyte ratio in patients with laryngeal neoplasms. *Braz J Otorhinolaryngol.* 2019; 85(5): 578-587. [Crossref]
7. Gazi E, Bayram B, Gazi S, et al. Prognostic value of the neutrophil-lymphocyte ratio in patients with ST-elevated acute myocardial infarction. *Clin Appl Thromb Hemost*. 2015; 21(2): 155-159. [Crossref]
8. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: A meta-analysis. *J Cancer*. 2018; 79(18): 3295-3302. [Crossref]
9. Duzlu M, Karamert R, Tutar H, Karaloglu F, Sahin M, Cevizci R. Neutrophil-lymphocyte ratio findings and larynx carcinoma: A preliminary study in Turkey. *Asian Pac J Cancer Prev.* 2015;16(1): 351-4. [Crossref]
10. Yılmaz B, Şengül E, Gül A et al. Neutrophil-lymphocyte ratio as a prognostic factor in laryngeal carcinoma. *Indian J Otolaryngol Head Neck Surg*. 2018; 70(2): 175-179 doi:10.1007/s12070-014-0769-4. [Crossref]
11. Du J, Liu J, Zhang X et al. Pre-treatment neutrophil-to-lymphocyte ratio predicts survival in patients with laryngeal cancer. *Oncol Lett*. 2018; 15(2): 1664-1672. [Crossref]
12. Cho Y, Kim JW, Yoon HI, Lee CG, Keum KC, Lee IJ. The prognostic significance of neutrophil-to-lymphocyte ratio in head and neck cancer patients treated with radiotherapy. *J Clin Med.* 2018; 3: 7(12): E512. [Crossref]
13. Tu XP, Qiu QH, Chen LS, et al. Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma. *BMC Cancer*. 2015; 15: 743. [Crossref]
14. Gorphe P, Bouhir S, Garcia GCTE et al. Anemia and neutrophil-to-lymphocyte ratio in laryngeal cancer treated with induction chemotherapy. *Laryngoscope*. 2020; 130(4): E144-E150. [Crossref]
15. Zeng YC, Chi F, Xing R et al. Pre-treatment neutrophil-to- lymphocyte ratio predicts prognosis in patients with locoregionally advanced laryngeal carcinoma treated with chemoradiotherapy. *Jpn J Clin Oncol.* 2016; 46(2): 126-31. [Crossref]
16. 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): 535-542. [Crossref]
17. 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: E1903-1908. [Crossref]
18. Kucuk U, Ekmekci S, Bozkurt P, Bulgurcu S, Cukurova I. Relationship between local and systemic inflammatory response and prognosis in laryngeal squamous cell carcinoma. *North Clin Istanb*. 2019; 37(2): 180-184. [Crossref]
19. Zhong B, Gu DY, Du JT, Chen F, Liu YF, Liu SX. May the change of platelet to lymphocyte ratio be a prognostic factor for T3-T4 laryngeal squamous cell carcinoma: A retrospective study. *PLoS One*. 2018 Dec 31; 13(12): e0210033. [Crossref]