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The Role of Inflammatory Markers in the Differential Diagnosis of Skin Cancers

Cilt Kanserlerinin Ayırıcı Tanısında İnflamatuar Belirteçlerin Yeri

Handan Derebaşınlıoğlu[1], Hande Demir [1], Sanem Nemmezi Karaca[2]

[1]Sivas Cumhuriyet University Medical Faculty Plastic Reconstructive and Aesthetic Surgery Department, Sivas, Turkey
[2]Sivas Cumhuriyet University Medical Faculty Department of Family Medicine, Sivas,Turkey

Abstract

Aim: The purpose of this study was to evaluate the role of WBC count, NLR, LMR, PLR, Systemic immune-inflammation index (SII) [(platelet count X neutrophil count) \ lymphocyte count] and platelet count (Plt)×NLR in the differential diagnosis of basal cell carcinoma, squamous cell carcinoma, and malignant melanoma and to determine the effect of tumor type, prediction of lymph node metastasis at initial diagnosis and location on these inflammatory markers.

Material and Method: Patients who underwent surgery for basal cell carcinoma, squamous cell carcinoma, or malignant melanoma were retrospectively screened. NLR, LMR, PLR, SII and Plt×NLR were calculated. Relationships between tumor type, prediction of lymph node metastasis at initial diagnosis, tumor localization and the inflammatory and hematological parameters of interest were investigated. Tumor location was classified as head and neck and others.

Results: A total of 257 patients were included in the study. No statistically significant differences in WBC, NLR, PLR, LMR, SII or Plt×NLR were detected according to tumor location. The patients with squamous cell carcinoma had higher NLR, PRL, SII and Plt×NLR values than those with basal cell carcinoma. The risk of lymph node metastasis at the time of initial diagnosis was 10.3 times higher in patients with PLR levels of 180.7 and higher. The risk of lymph node metastasis detected at initial diagnosis was 8.9 times higher in patients with Plt×NLR of 747 and higher. The risk of lymph node metastasis detected at initial diagnosis was 7.1 times higher in patients with SII of 414 and higher.

Conclusion: Inflammatory markers seem to be useful in the differential diagnosis of skin cancers and determined the risk of lymph node metastasis. However, it does not differ according to tumor localization.

Keywords: Basal cell carcinoma, squamous cell carcinoma, malignant melanoma, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), Systemic immune-inflammation index (SII), and platelet to lymphocyte ratio (PLR).

Öz

Amaç: Bu çalışmanın amacı, cilt kanserinin ayırıcı tanısında ve ilk tanı anında lenf nodu metastazının öngörülmesinde inflamatuar belirteçlerin rolünün belirlenmesidir.

Gereç ve YÖntem: Bazal hücreli karsinom, skuamöz hücreli karsinom veya malign melanom nedeniyle ameliyat edilen hastalar retrospektif olarak tarandı. NLR, LMR, PLR, SII ve Plt×NLR hesaplandı. Tümör tipi, ilk tanıda lenf nodu metastazının varlığı, tümör lokalizasyonu ile inflamatuvar ve hematolojik parametreler arasındaki ilişkiler araştırıldı. Tümör lokasyonu, baş boyun ve diğerleri olarak sınıflandırıldı.

Bulgular: Çalışmaya toplam 257 hasta dahil edildi. Tümör yerleşimine göre WBC, NLR, PLR, LMR, SII veya Plt×NLR'de istatistiksel olarak anlamlı farklılık saptanmadı. Skuamöz hücreli karsinomalı hastalarda NLR, PRL, SII ve Plt×NLR değerleri bazal hücreli karsinomalı hastalara göre daha yüksekti. PLR düzeyi 180,7 ve üzerinde olan hastalarda ilk tanı anında lenf nodu metastazı riski 10.3 kat daha yüksekti. Plt×NLR 747 ve üzeri olan hastalarda ilk tanıda saptanan lenf nodu metastazı riski 8,9 kat daha fazlaydı. SII 414 ve üzeri olan hastalarda ilk tanıda saptanan lenf nodu metastazı riski 7,1 kat daha yüksekti.

Sonuç: İnflamatuvar belirteçler cilt kanserlerinin ayırıcı tanısında ve lenf nodu metastazı riskinin belirlenmesinde yardımcı olabilir. Ancak tümör lokalizasyonuna göre bir farklılık göstermemektedir.

Anahtar Kelimeler: Bazal hücreli karsinom, skuamöz hücreli karsinom, malign melanom, nötrofil-lenfosit oranı (NLR), lenfosit-monosit oranı (LMR), Sistemik immün-enflamasyon indeksi (SII) trombosit/lenfosit oranı (PLR), Sistemik immün-enflamasyon indeksi (SII) trombosit/lenfosit oranı (PLR).

Corresponding *(İletişim)*: Sanem Nemmezi Karaca, Department of Family Medicine, Sivas Cumhuriyet University Medical Faculty, 58140 Sivas, Turkey
E-mail *(E-posta)*: drsnemmezi@yahoo.com
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INTRODUCTION

Inflammation is regarded as a hallmark feature of cancer development and progression. Cancer-related inflammation is an ongoing and sometimes inappropriate systemic response to malignancy. This inflammation is affected by tumor stage and clinical condition.[1]

There is increasing and consistent evidence that cancer-related inflammation is a main determinant of survival in patients with cancer. Various inflammatory markers for predicting treatment response and survival have been investigated, including white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), all of which can easily be obtained from complete blood count. These parameters have been studied in many types of cancer.[2,3] In addition, systemic inflammatory index (SII) is used to identify high-risk patients.[4,5]

Basal cell carcinoma (BCC) is the most common skin cancer, followed by squamous cell carcinoma (SCC), malignant melanoma (MM), and skin adnexal tumors. Basal cell carcinoma includes subgroups with variable biological behavior. Among skin cancers, basal cell carcinoma has the best prognosis and malignant melanoma has the worst prognosis.[6,7] Another feature that distinguishes basal cell carcinoma from the other two common skin cancers is that although it is locally invasive, it does not metastasize. Tumors with these different biological behaviors can also cause different inflammatory reactions. In a study of inflammatory markers in skin cancers, cancer patients were found to have lower WBC, neutrophil, and monocyte counts and lower NLR compared to a healthy control group, and among all skin cancers, patients with basal cell carcinoma were found to have the lowest NLR.[7]

Our aim in this study was to evaluate the role of WBC count, NLR, LMR, PLR, Systemic immune-inflammation index (SII) [(platelet count X neutrophil count) \ lymphocyte count] and platelet count (Plt)×NLR in the diagnosis of basal cell carcinoma, squamous cell carcinoma, and malignant melanoma and to determine the effect of tumor type and location on these inflammatory markers.

MATERIAL AND METHOD

Patients who underwent surgery for basal cell carcinoma, squamous cell carcinoma, or malignant melanoma in the plastic reconstructive and aesthetic surgery department of the Sivas Cumhuriyet University Faculty of Medicine Hospital between January 1, 2000 and November 30, 2020 were retrospectively screened. The patients were evaluated in terms of age, sex, and tumor type. WBC, neutrophil, monocyte, lymphocyte, and platelet counts and percentages were obtained from preoperative complete blood count analyses performed in an automated system and NLR, LMR, PLR, SII and Plt×NLR were calculated. In addition, the patients' pathology results were screened for tumor dimensions and the largest diameter was accepted as tumor size. Relationships between tumor type, prediction of lymph node metastasis at initial diagnosis, tumor localization and the inflammatory and hematological parameters of interest were investigated. Tumor location was classified as head and neck and others.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 23.00 software (IBM Corp, Armonk, NY). The study data were evaluated using descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum values). Normal distribution of quantitative data was tested using Shapiro–Wilk test and graphical methods. Pairwise comparisons of non-normally distributed quantitative data were made using Mann–Whitney U test. Multiple comparisons of non-normally distributed quantitative data were performed using Kruskal–Wallis test. Pearson chi-square test and Fisher's exact test were used to compare qualitative data. Receiver operating characteristic (ROC) curve analysis and diagnostic screening tests were used to determine optimal cut-off points for the prediction of lymph node metastasis at initial diagnosis. A p value; 0.05 was considered statistically significant.

Sensitivity: Ability of the test to identify patients who had lymph node metastasis at initial diagnosis.

Specificity: Ability of the test to identify patients without lymph node metastasis at initial diagnosis.

PPV: Probability that a patient with a positive result is truly positive (had lymph node metastasis at initial diagnosis).

NPV: Probability that a patient with a negative result is truly negative (did not have lymph node metastasis at initial diagnosis).

RESULTS

A total of 257 patients were included in the study, of whom 38.1% (n=98) were female and 61.9% (n=159) were male. The patients ranged in age from 11 to 95 years, with a mean (SD) age of 66.86 (14.42) years.

Tumor size ranged from 1 to 220 mm, with a mean (SD) of 21.88 (20.66) mm and a median of 15 mm. Tumor type was basal cell carcinoma in 56% (n=144) of the patients, squamous cell carcinoma in 32.7% (n=84), and malignant melanoma in 11.3% (n=29). The tumors were located in the head and neck in 86.4% (n=223), and other regions in 14% (n=36) of the patients. Metastasis was detected in 3.9% (n=10) of the patients at the time of initial diagnosis. Sixty percent (n=6) of metastases were in patients with squamous cell carcinoma and 40% (n=4) were in malignant melanoma patients. The patients' demographic characteristics and laboratory findings are summarized in **Tables 1** and **2**, respectively.

Table 1: Distribution of Demographic Features

		n	%
Age (year)	Min-Max (Median)	11-95 (68)	
	Mean±Sd	66.84±14.44	
Sex	Female	98	38.1
	Male	159	61.9
Tumour size (mm)	Min-Max (Median))	1-220 (15)	
	Mean±Sd	21.88±20.66	
Tumour type	BCC	144	56
	SCC	84	32.7
	MM	29	11.3
Localization	Head-neck	221	86
	Other	36	14
Metastasis at the time of first diagnosis	No	247	95
	Yes	10	5

BCC: Basal cell carsinoma, SCC: Squamous Cell Carsinoma, MM: Malignant Melanoma.

Table 2: Distribution of Laboratory Findings

n=257	Min-Max (Median)	Mean±Sd
WBC	3790-16 770 (7330)	7679±2318
LYMP#	260- 6500(1910)	2028±848
LYMP (%)	1.7-56 (28.3)	27.05±9.42
MONO#	140-1315 (460)	497±188
MONO (%)	0.2-14.30 (6.3)	6.5±1.93
NEU#	2040-14300 (4510)	5004±2050
NEU (%)	41-95(63)	63.53±10.26
PLT (x103)	55-613(234)	243.934±80.25
NLR	0.59-29.8 (2.25)	3.22±3.48
PLR	15.2-974.2 (123.16)	143.46±92.75
LMR	0.61-11.16 (4.41)	4.47±2.03
PLRXNLR	23.63-24951.93 (270.09) (156.66-513.75)*	691.56±1947.72
PLTxNLR (x103)	85.32-7735.01 (539.879)	769.517±820.670

WBC values did not differ significantly according to tumor type (p>0.05). However, there was a significant difference in NLR between tumor types (p=0.003). Pairwise comparisons showed that NLR was significantly higher in patients with squamous cell carcinoma compared to those with basal cell carcinoma (p=0.001). Other pairwise comparisons of NLR were not significant (p>0.05).

LMR also varied significant according to tumor type (p< 0.001). Pairwise comparisons showed that LMR was higher in patients with basal cell carcinoma and malignant melanoma compared to those with squamous cell carcinoma (p<0.001 and p=0.012, respectively). There was no significant difference in LMR between patients with basal cell carcinoma and malignant melanoma (p>0.05).

PRL also varied significant according to tumor type (p=0.045). Pairwise comparisons showed that NLR was significantly higher in patients with squamous cell carcinoma compared to those with basal cell carcinoma (p=0.019). There was no significant difference in LMR between patients with basal cell carcinoma and malignant melanoma (p>0.05).

There was a significant difference in SII according to tumor type (p=0.004). According to pairwise comparisons, SII measurements were higher in patients with squamous cell carcinoma compared to those with basal cell carcinoma (p=0.001).

There was a significant difference in Plt×NLR according to tumor type (p=0.010). According to pairwise comparisons, Plt×NLR measurements were higher in patients with squamous cell carcinoma compared to those with basal cell carcinoma (p=0.002). Other pairwise comparisons of Plt×NLR were not significant (p>0.05; **Table 3**).

No statistically significant differences in WBC, NLR, PLR, LMR, SII or Plt×NLR were detected according to tumor location (p>0.05; **Table 4**).

Patients with metastasis at the time of initial diagnosis did not have significantly different WBC, NLR, or LMR values (p> 0.05) but had significantly higher PLR, SII, and Plt×NLR values (p=0.009, p=0.028 and p=0.007, respectively; **Table 5**).

Based on these significant differences in PLR, SII and Plt×NLR between patients with and without metastasis, ROC curve analysis and diagnostic screening tests were used to identify discriminating cut-off points for these parameters.

Table 3: Evaluations by Tumor Type

		Tumour type			[a]p
		BCC (n=144)	SCC (n=84)	MM (n=29)	
WBC	Min-Max (Median)	3790-14560 (7010)	4240-16770 (7400)	4090-13700 (8300)	0,219
	Mean±Sd	7458±2196	7971±2533	7933±2213	
NLR	Min-Max (Median)	0.59-13.1 (2.1)	0.9-29.8 (2.7)	1.1-14.5 (2.2)	0,003**
	Mean±Sd	2,53±1,54	4.41±5.25	3.25±3.19	
PLR	Min-Max (Median)	15.2-479 (121.1)	58.84-974.2 (134.70)	65.2-518.5 (109.6)	0,045*
	Mean±Sd	134.20±75.00	161.20±116.30	138.15±91.75	
LMR	Min-Max (Median)	0.4-11.2 (4.8)	0,6-8.4 (3.4)	0.08-9.6 (5)	<0,001**
	Mean±Sd	4.81±2.01	3.73±1.81	4.9±2.21	
SII	Min-Max (Median)	23.63-4411.3 (249.2)	57.1-24952 (357.9)	101.5-6866 (245.2)	0,004**
	Mean±Sd	416.5±568.5	1166.5±3179.9	681.9±1412.3	
PLTxNLR (x103)	Mean±Sd	85.319-5028.9 (507.1)	196.3-7735.1 (597.1)	223.1-3707.4 (505.1)	0,010*
	Mean±Sd	638.768±544.893	984,565±1117.652	795.851±843.294	

aKruskal Wallis Test, **p<0,01, *p<0,05, BCC: Basal cell carsinoma, SCC: Squamous Cell Carsinoma, MM: Malignant Melanoma. NLR: neutrophil lymphocyte ratio, LMR: lymphocyte monocytes ratio, PLTxNLR: platelet count x NLR, PLR: platelet lymphocyte ratio, SII: Systemic immune-inflammation index.

Table 4: Evaluations According to Tumor Localization

		Tumour localization		
		Head and neck (n=221)	Other (n=36)	[b]p
WBC	Min-Max (Median)	3790-16770 (7250)	4090-15600 (8215)	0.232
	Mean±Sd	7610±2275	8103±2555	
NLR	Min-Max (Median)	0.6-29.8 (2.2)	0.8-23.4 (2.4)	0.417
	Mean±Sd	3.1±3.3	4.0±4.5	
PLR	Min-Max (Median)	15.2-974.2 (122.8)	65.3-518.5 (133.5)	0.155
	Mean±Sd	140.9±92.7	159.5±92.7	
LMR	Min-Max (Median)	0.6-11.2 (4.4)	1.0-9.6 (4.1)	0.482
	Mean±Sd	4.5±1.98	4.3±2.40	
SII	Min-Max (Median) Mean±Sd	23.6-24952 (269.7) 647.8±1961.1	59.1-8915.9 (380.8) 960.3±1868	0.257
PLTxNLR (x103)	Min-Max (Median)	85.319-7735.1 (520.487)	159.5-5438.7 (668.302)	0.088
	Mean±Sd	733.483±765.362	990.730±1088.9	

bMann Whitney U Test, NLR: neutrophil lymphocyte ratio, LMR: lymphocyte monocytes ratio, PLTxNLR: platelet count x NLR, PLR: platelet lymphocyte ratio, SII: Systemic immune-inflammation index.

Table 5: Evaluations According to prediction of lymph node metastasis at initial diagnosis

		Metastasis at the time of first diagnosis		[a]p
		No (n=103)	Yes (n=10)	
WBC	Min-Max (Median)	4090-16770 (7770)	5240-13690 (8175)	0.374
	Mean±Sd	7877±2388	8828±2981	
NLR	Min-Max (Median)	0.95-29.8 (2.4)	1.5-25.6 (3.7)	0.143
	Mean±Sd	3.9±4.40	6.5±7.7	
PLR	Min-Max (Median)	58.8-518.5 (126.7)	78.4-974.2 (197)	0.009**
	Mean±Sd	144.4±79.1	266.9±257	
LMR	Min-Max (Median)	0.8-9.6 (3.9)	0.6-6.8 (3.3)	0.214
	Mean±Sd	4.1±1.9	3.2±1.9	
SII	Min-Max (Median) Mean±Sd	57.1-12152 (304.9) 823.9±1760	117.9-29952 (547) 3290±7665	0.028*
PLTxNLR (x103)	Min-Max (Median)	196.3-5438.7 (552.245)	327.8-7735.1 (1019)	0.007**
	Mean±Sd	842.452±836.229	1901.05±2181.18	

aMann Whitney U Test, **p<0,01, *p<0,05, NLR: neutrophil lymphocyte ratio, LMR: lymphocyte monocytes ratio, PLTxNLR: platelet count x NLR, PLR: platelet lymphocyte ratio, SII: Systemic immune-inflammation index.

PLR cut-off value for prediction of lymph node metastasis at initial diagnosis

The optimal PLR cut-off point for discrimination of the metastasis and non-metastasis groups was 180.7. At this cut-off, PLR had sensitivity of 70.00%, specificity of 81.6 %, positive predictive value (PPV) of 26.9%, negative predictive value (NPV) of 96.6%, and accuracy of 80.5%. The area under the ROC curve (AUC) was 75.2 with standard error of 8.3% (**Table 6**).

The presence of lymph node metastasis at the time of initial diagnosis was significantly associated with a PLR greater than 180.7 (p=0.009). The risk of lymph node metastasis at the time of initial diagnosis was 10.3 times higher in patients with PLR levels of 180.7 and higher (odds ratio [OR]=10.3, 95% CI: 2.441-43.594) (**Table 7**), (**Graphic 1A**).

SII cut-off value for prediction of lymph node metastasis at initial diagnosis

The optimal cut-off value for SII was determined to be 414. At this value, SII had sensitivity of 80.00%, specificity of 64.4%, PPV of 21.6%, NPV of 97.1%, and accuracy of 65.5 %. The ROC AUC was 71.1% with a standard error of 8.2% (**Table 6**).

SII above the 414 cut-off was significantly associated with the presence of lymph node metastasis at the time of initial diagnosis (p=0.009). The risk of lymph node metastasis detected at initial diagnosis was 7.1 times higher in patients that SII is more than 414 (OR: 7.1, 95% CI: 1.439-35.373) (**Table 7**), (**Graphic 1B**).

Plt×NLR cut-off value for prediction of lymph node metastasis at initial diagnosis

The optimal cut-off value for Plt×NLR was determined to be 747. At this value, Plt×NLR had sensitivity of 80.00%, specificity of 68.9%, PPV of 20%, NPV of 97%, and accuracy of 69.9%. The ROC AUC was 75.8% with a standard error of 8.1% (**Table 6**).

Plt×NLR above the 747 cut-off was significantly associated with the presence of lymph node metastasis at the time of initial diagnosis (p=0.004). The risk of lymph node metastasis detected at initial diagnosis was 8.9 times higher in patients with Plt×NLR of 747 and higher (OR: 8.9, 95% CI: 1.783-44.165) (**Table 7**), (**Graphic 1C**).

Table 6: Diagnostic Screening Tests and ROC Curve Results for PLR and PLTxNLR According to prediction of lymph node metastasis at initial diagnosis

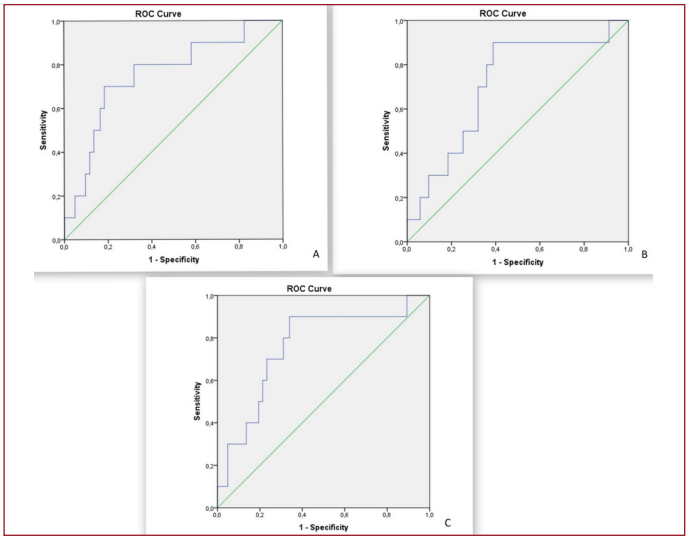
	Diagnostic Scan					ROC Curve		p
	Cut off	Sensitivite	Spesifisite	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
PLR	≥ 180.7	70.0	81.6	26.9	96.6	0.752	0.591-0.914	0.009**
PLTx NLR	≥747x103	80	68.9	20	97	0.758	0.599-0.917	0.007**
SII	≥414	80	64.1	21.6	97.1	0.711	0.549-0.872	0.028*

**p<0.01 , *p<0.05, PLTxNLR: platelet count x NLR, PLR: platelet lymphocyte ratio, SII: Systemic immune-inflammation index.

Table 7: Relationship between PLR and PLTxNLR (Cut-off Values) with prediction of lymph node metastasis at initial diagnosis

		Metastasis at the time of first diagnosis				p
		No		Yes		
		n	%	n	%	
PLR	<180.7	84	81.6	3	30.0	0.001**
	≥180.7	19	18.4	7	70.0	
SII	<414	66	64.1	2	20.0	0.009**
	≥414	37	35.9	8	80.0	
PLT x NLR	<747	71	68.9	2	20.0	0.004**
	≥747	32	31.1	8	80.0	

Fisher Exact Test, **p<0.01, PLTxNLR: platelet countx neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, SII: Systemic immune-inflammation index.



Graphic 1: ROC Curve Results for PLR (A), SII(B) and PltxNLR (C) for prediction of lymph node metastasis at initial diagnosis

DISCUSSION

Inflammation is one of the underlying factors of the six biological abilities acquired during the multi-stage development of oncogenesis (maintaining proliferative signaling, evading growth suppression, resisting cell death, having replicative immortality, inducing angiogenesis, and activating invasion and metastasis).[8]

The interaction between systemic inflammation and the local immune response is regarded as the seventh distinguishing feature of cancer, and its role in the initiation, development, and progression of various cancer types has been demonstrated.[9,10]

Characteristics of cancer-related inflammation include the presence of inflammatory cells and inflammatory mediators in tumor tissue, tissue remodeling, and angiogenesis, as seen in tissue healing and chronic inflammation. These inflammatory cells and mediators are found in the microenvironment of most tumors.[11] In addition, inflammation may cause upregulation of the immune response and allow tumor cells to evade the immune response.[12]

In mice with impaired TGF-β signal transduction, accelerated wound healing and reduced inflammatory response resulted in reduced susceptibility to epithelial skin cancer.[13-15]

Tumor development is induced in animal studies by repeated administration of tumor-inducing agents to animal subjects. The strongest and most commonly used tumor promoter prototype is 12-O-tetradecanoylfrobol 13-acetate (TPA), which activates a series of protein kinase C isoenzymes and induces intense inflammation. This inflammation is similar to the inflammatory response seen in wound healing.[15,16]

One of the earliest descriptions of this phenomenon in humans is Marjolin ulcers, described in 1828, in which a malignant transformation occurs at a chronic inflammatory focus.[15,17] A similar relationship between inflammation and the development of squamous cell carcinoma has also been described in other diseases that cause chronic inflammation, such as leg ulcers, osteomyelitis, and epidermolysis bullosa.[18-20] Not only unhealed wounds but also healing scars are also susceptible to the development of squamous and basal cell carcinomas.[21,22] While inflammation is an important factor in tumor development, it also continues after tumor formation. Recent studies show that cancer is associated with increased and defective myelopoiesis. Several authors have emphasized that both local and systemic inflammation increase tumor formation, promote progression, and influence prognosis.[9,23,24] The typical host response to malignancy includes neutrophilia, monocytosis, thrombophilia, and lymphocytopenia.[25-28] In a study on inflammatory markers for skin cancer, WBC, neutrophil, and monocyte counts and NLR were lower in the cancer group compared to the healthy control group.[7] In the present study, there was no statistical difference in WBC count between cancer types, indicating that this marker is not useful for the differential diagnosis of skin cancers. Relationships between inflammatory markers and various cancers have been investigated. For many solid organ tumors, increased NLR and PLR and decreased LMR have been associated with poor response to treatment, low

survival, and recurrence.[29] In upper urogenital tract cancers, NLR was found to be a prognostic factor for disease-free and progression-free survival.[2] In squamous cell carcinomas of the oral cavity, elevated C-reactive protein values were found to be an independent prognostic factor, while high NLR in patients with high C-reactive protein level was associated with increased risk of recurrence and shorter survival. Therefore, it was reported to have important potential as a biological marker for risk classification in oral squamous cell carcinomas.[30]

Cytokines released from platelets can promote tumor progression by sustaining proliferative signals in tumors, which can contribute to tumor growth and the formation of metastases. Cytokines released from platelets, such as interleukin 6 (IL-6), TNF-α, and platelet-derived growth factor, can protect cancer cells from apoptosis.[31-34] The increase in circulating neutrophils is also associated with the levels of chemokines, growth factors, and proteases that are crucial for angiogenesis.[35] This may help create an appropriate environment for angiogenesis, which is necessary for tumor growth and survival. In addition, enzymatic reactions induced by neutrophils facilitate important stages of metastasis such as the migration of tumor cells to the extracellular space and vascular walls.[36]

Lymphocytes are involved in cellular immunity by cytotoxic cell death. They exert this effect on cancer cells, as well as produce cytokines that inhibit tumor proliferation and metastasis.[37] Increased CD8+ and T lymphocyte counts were found to be associated with longer survival time and delayed metastasis.[38] Therefore, environments with more platelets and neutrophils and/or fewer lymphocytes may help provide suitable conditions for tumor survival and spread. In our study, we used the Plt×NLR formula to evaluate these three parameters together. A previous study showed that among all skin cancers, NLR was lowest in patients with basal cell carcinoma.[7] According to the pairwise comparisons in our study, patients with squamous cell carcinoma had higher NLR, PRL, SII and Plt×NLR values than those with basal cell carcinoma. However, we observed no statistical differences for these two parameters in the other pairwise comparisons. The higher values for these parameters in patients with squamous cell carcinoma may be attributed to it being a more aggressive tumor with more metastasis potential compared to basal cell carcinoma. In that case, however, even higher values would be expected in malignant melanoma.

Abnormal baseline NLR is associated with adverse outcomes in advanced and high-risk melanoma.[29,39-41] Low NLR and PLR detected during definitive treatment for the primary tumor were found to more than double the risk of death from melanoma. It has been reported that patients with positive sentinel lymph node biopsy can be classified according to NLR and PLR, and that this may help clinicians identify patients who could benefit from adjuvant systemic therapy and advanced surveillance imaging. Observations of better survival among patients with high NLR was considered consistent with the evolving hypothesis that host immunity plays a role in the survival of patients with melanoma, and may suppress or eliminate metastasis.[29]

Although NLR value may be effective in predicting the prognosis of malignant melanoma, it does not seem to be effective in the differential diagnosis of malignant melanoma from basal and squamous cell carcinomas.

LMR has been found to be a prognostic indicator of progression-free survival in urogenital cancers [2] and a useful prognostic marker in patients with breast cancer.[42] Low LMR was also reported to be significantly associated with survival in malignant melanoma, independent of other known prognostic factors.[24] In addition, LMR was found to influence the effectiveness of chemotherapeutics in patients with malignant melanoma. Monitoring LMR fluctuations may be used therapeutically to identify the right time point in the immune cycle to administer cytotoxic chemotherapy. It has been suggested that when LMR increases, immunosuppressive monocytes will start multiplying to trigger the next decrease in the anticancer immune response. Patients who received chemotherapy on the day LMR increased were shown to have longer progression-free survival.[43] Although many studies have investigated this parameter in malignant melanoma, there is little information in the literature regarding LMR values in other skin cancers. In the present study, we determined that LMR was higher in patients with basal cell carcinoma and malignant melanoma compared to those with squamous cell carcinoma, while there was no statistically significant difference in LMR between patients with basal cell carcinoma and malignant melanoma.

Low LMR is defined as a poor prognostic factor for many cancers.[2,24,42] In our series, the higher LMR value in basal cell carcinoma than squamous cell carcinoma may be related to the fact that the former is more benign. However, in an aggressive tumor such as malignant melanoma, this value was expected to be lower than the other two tumor types.

The higher LMR values among women than men in this series may be one of the reasons the prognosis for malignant melanoma is better in women.[44,45]

Different types of skin cancers have been reported to have varying densities in different anatomic locations.[46,47] Although skin cancers can originate anywhere on the body, the density of squamous and basal cell carcinomas are 11 and 17 times higher on the face compared to the whole body, respectively.[48] Approximately 20% of malignant melanomas are located in the head and neck region.[49] Anatomic location is an independent prognostic factor for patients with malignant melanoma. The upper arms, neck, and scalp are defined as high-risk areas and the lower trunk, legs, feet, forearms, hands, and face are defined as low-risk areas.[50]

For squamous cell carcinoma, location is not associated with the development of metastasis.[51] In addition, location at the ear, temple, or anogenital region is associated with poor

prognosis.[52] The nodular and morpheiform subtypes of basal cell carcinoma are more frequently located in the head region, while the superficial type is most common on the trunk.[53] Different anatomical areas show varying degrees of susceptibility to different tumor types. In addition, some locations are associated with better prognosis, while other locations are associated with poorer prognosis. However, in the present study, we observed no difference in inflammatory parameters according to tumor location, suggesting that anatomic location did not cause a change in the inflammatory response to the tumor.

Despite the high prevalence of basal cell carcinoma, the rate of metastasis is low, with reported incidence between 0.0028% and 0.55%. Metastases can be lymphatic or hematogenic. Regional lymph nodes are the most common sites, followed by the lungs and bones.[54] Metastasis was not detected in any of the basal cell carcinoma patients in our study. Squamous cell carcinoma metastasizes much more frequently than basal cell carcinomas, with reported incidence rates of 2% to 5%.[55-57] Tumor thickness, immunosuppression, location on the ear, and horizontal size were identified as independent determinants of metastasis risk in cutaneous squamous cell carcinoma.[55]

Malignant melanoma has a greater tendency to spread than the other two types. Approximately 30% of patients develop metastasis in various organs after primary tumor excision.[58] One of the most important independent risk factors for metastasis development is tumor thickness, and the incidence of metastasis can be 5% to 15% even in malignant melanomas less than 1 mm thick.[59-61]

In addition to its role in tumor initiation, the inflammation response is also important in tumor progression and metastasis.[62] High PLR is a result of increased platelets and/or low lymphocyte count. Disruption of the balance between platelets (which are likely to facilitate tumor progression, growth, and metastasis) and lymphocytes (which help eliminate tumor cells by cytotoxic effect and stop metastasis and proliferation) can adversely affect prognosis.[31-34,37] High PLR has been associated with poorer overall survival in melanoma patients, suggesting that PLR may be a promising prognostic marker for melanoma.[34]

SII is used as a potential prognostic marker for various cancers and is an inflammatory marker whose high levels are generally associated with poor prognosis.[63,64]

In the literature Plt×NLR was used for the Hepatocellular Carcinoma as a novel SII. This novel SII has been found to be a powerful prognostic indicator of poor outcome for Hepatocellular Carcinoma and may be associated with elevated levels of circulating tumor cells.[65]

In our series, PLR, SII, and Plt×NLR were found to be significantly higher in patients with metastatic lymph nodes detected at the time of initial diagnosis compared to patients without metastasis at initial diagnosis. At the determined cut-off point of 180.7, PLR had 70.00% sensitivity, 81.6 % specificity, and 80.5% accuracy, and patients with PLR at or above this threshold had a 10.3-fold higher risk of metastasis at initial diagnosis. The cut-off for SII was 414, at which sensitivity was 80.00%, specificity was 64.4%, accuracy was 65.5%, and patients with SII of 414 and above had a 7.1-fold higher risk of detecting metastasis at the time of initial diagnosis. The cut-off for Plt×NLR was 747, at which sensitivity was 80.00%, specificity was 68.9%, accuracy was 69.9%, and patients with Plt×NLR of 747 and above had an 8.9-fold higher risk of detecting metastasis at the time of initial diagnosis.

CONCLUSION

Inflammatory markers seem to be useful in the differential diagnosis of skin cancers. NLR, PRL, SII and Plt×NLR values may help differentiate squamous and basal cell carcinomas, whereas LMR measurements may be helpful in distinguishing squamous cell carcinoma from basal cell carcinoma and malignant melanoma. This study did not include many patients with lymph node metastasis at the time of initial diagnosis, and metastases were not classified according to cancer type. Nevertheless, we believe SII, Plt×NLR and PRL values are promising parameters in the detection of skin cancer metastasis. Separate evaluations of squamous cell carcinoma and malignant melanoma in larger series will yield more information. .

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval for the study was obtained from the local ethics committee of Sivas Cumhuriyet University. (No: 2020-12/26, date: 16.12.2020)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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