Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2026;51(1):293-306
DOI: 10.17826/cumj.1775740

RESEARCH

The role of prognostic factors and inflammatory markers in identifying lymph node metastases of cutaneous malignant melanoma

Kutanöz malign melanom lenf nodu metastazlarinin belirlenmesinde prognostik faktörlerin ve inflamatuar belirteçlerin yeri

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Abstract

Purpose: Malignant melanomas have poor prognosis and comprise a significant part of skin cancer-related mortality. Lymph node metastases significantly reduce survival independent of other factors. This study sought to identify factors associated with lymphatic metastasis in patients with cutaneous malignant melanoma (CMM).

Materials and Methods: Histopathological and clinical prognostic factors, tumor location, inflammatory markers, and Tumor Volume Index (TVI = Breslow thickness × tumor size) were examined in patients operated for CMM in a university hospital between 2012 and 2025.

Results: The study included a total of 56 patients with CMM, 50% (n=28) of whom were female. Of the 33 patients (58.9%) who underwent lymph node sampling, metastasis was detected in 34.4% (n=11). Among patients with lymph node metastasis, CMM was located more frequently in the lower extremities and less frequently in the trunk/upper extremities compared to those without lymph node metastasis. A platelet-to-lymphocyte ratio (PLR) cut-off value of 127 was statistically significant in the prediction of lymph node metastasis risk. A PLR of 127 or higher was associated with 5.3 times higher odds of detecting lymph node metastasis. However, TVI ≥27 was an independent risk factor associated with 11.1 times higher odds of lymph node metastasis (95% CI: 1.123-109.494).

Conclusion: When the Breslow thickness is multiplied by the tumor's largest measured diameter, a TVI value greater than 27 has been found to be an independent risk factor for the development of lymph node metastasis.

Keywords:. Prognostic factor, inflammatory markers, lymph node metastases, cutaneous malignant melanoma

Öz

Amaç: Malign melanomlar kötü prognozları nedeniyle cilt kanserlerine bağlı mortalitenin önemli bir kısmını oluşturur. Lenf nodu metastazları diğer faktörlerden bağımsız olarak sağ kalımın belirgin bir şekilde düşmesine neden olmaktadır. Bu çalışmada kutanöz malign melanom (KMM) hastalarında lenfatik metastazla ilişkili faktörlerin belirlenmesi amaçlandı.

Gereç ve Yöntem: 2012-2025 yılları arasında kliniğimizde KMM nedeniyle ameliyat edilen hastalarda histopatolojik ve klinik prognostik faktörler, tümör yerleşimi, inflamatuvar belirteçler ve Tümör Hacim İndeksi (TVI = Breslow kalınlığı × tümör boyutu) incelendi.

Bulgular: Çalışma %50'si (n=28) kadın olmak üzere toplam 56 KMM tanısı olan hasta ile yapıldı. Hastalarımızın 33 (%58,9)'ünde lenf nodu örneklemesi mevcuttu. Bu hastaların %34,4'ünde (n=11) metastaz mevcuttu. Lenf nodu metastazı olan olgularda lokalizasyonun alt ekstremitede olma oranı yüksek; gövde veya üst ekstremitede olma oranı ise lenf nodu metastazı olmayanlardan düşüktü. Lenf nodu metastazı riskini öngörmede PLR (Platelet Lenfosit Oranı)'nin 127 cut off değeri ile arasında istatistiksel olarak anlamlı ilişki saptandı. PLR değeri 127 ve üzeri olan olgularda lenf nodu metastazı saptanma riski 5,3 kat daha fazladır. Ancak yapılan modellemede TVİ ≥27 olması lenf nodu metastazı riskini 11,086 katına (%95 CI: 1,123-109,494) çıkartmaktadır.

Sonuç: Breslow kalınlığının tümörün ölçülen en büyük çapıyla çarpılmasıyla elde edilen TVİ değerinin 27'den büyük olmasının, lenf nodu metastazı gelişiminde bağımsız risk faktörü olduğu görülmüştür.

Anahtar kelimeler: Prognostik faktör, inflamatuvar markır, lenf nodu metastazı, kutanöz malign melanom.

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Received: 05.09.2025 Accepted: 02.03.2026

INTRODUCTION

Although malignant melanomas are not the most common malignant skin tumors, they are responsible for approximately 75% of skin cancer-related deaths[1]. The presence of lymph node metastasis reduces the 5-year survival rate of patients by approximately 40%, independent of other prognostic factors associated with the primary tumor[2]. Therefore, early diagnosis and treatment are as important for lymph node metastasis as for the primary tumor. The use of positron emission tomography computed tomography (PET-CT) in melanoma has increased since it was shown to detect lymph node metastases of a certain size or volume[3,4]. Unlike conventional imaging methods, PET-CT visualizes not only anatomical relationships but also metabolic activity, and its non-invasive nature is also advantageous. However, it has been reported that tumor volume must be 78 mm^3 for PET to identify regional lymph node involvement with 100% sensitivity[4]. Sensitivity decreases with smaller tumor mass. Because of the low specificity of PET-CT in the initial staging of lymph node metastases in cutaneous malignant melanoma (CMM), its use alone is not recommended[5].

Despite advanced imaging methods such as PET-CT, sentinel lymph node biopsy (SLNB) remains an indispensable method for staging malignant melanoma patients. Histopathological examination of SLNB material enables the diagnosis of microscopic metastases. The most important histopathological predictors of SLN metastases are tumor thickness, ulceration, and mitotic rate. The overall SLNB positivity rate is approximately 5.1% in thin melanoma, but this rate increases to 7% with a Breslow thickness ≥0.8 mm. The presence of mitotic activity further increases the positivity rate to 7.7%. Microsatellites and ulceration were also identified as predictors of SLN positivity[6]. Other parameters associated with SLN metastases are age, sex, Clark level, presence of the radial growth phase, and lymphovascular invasion[7].

Skin tumors, like other neoplasms, have a three-dimensional (3D) structure. Breslow thickness measurements and the Clark staging system provide one-dimensional metrics, which offer limited utility in representing the true volume of a 3D tumor. The size of a 3D structure can only be accurately determined through multiple measurements across different planes. Therefore, this study aimed to evaluate the relationship between lymphatic metastasis at the time of initial diagnosis and Tumor Volume Index (TVI), a metric calculated by multiplying the Breslow value by the maximum tumor diameter.

Although these parameters are used to predict lymph node metastases, they require invasive procedures. In contrast, inflammatory markers can easily be calculated based on the results of complete blood count, a routine test performed in nearly all patients during follow-up and surgical preparation. With mounting and consistent evidence that systemic inflammation plays an important role in cancer development and progression[8] and that cancer-related inflammation is the main determinant of patient survival[9], many studies are being conducted on inflammatory markers in different types of cancer.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used to predict SLN spread of malignant melanoma[10,11]. One study evaluating the relationship between skin cancers and inflammatory markers indicated that PLR and systemic inflammation index (SII) values may be useful in determining lymph node metastasis at the time of initial diagnosis[12]. The present study aimed to examine the relationship between lymph node metastasis and age, sex, malignant melanoma subtype, tumor size, TVI, pathological features, prognostic factors, and inflammatory markers in patients with CMM, as well as the compatibility between PET-CT and ultrasound (US) findings for the detection of lymph node metastasis. Thus, our objective is to contribute to the assessment of lymphatic invasion risk and the identification of candidates for SLNB using values calculated through simple mathematical formulas.

MATERIALS AND METHODS

Study design and sample

This study was designed as a cross-sectional descriptive study. Study power is expressed as $1-\beta$, with 80% conventionally regarded as the minimum requirement. Based on the formula $n=(Nt2pq)/[d2(N-1)+t2pq]$, a sample size of 53 was determined to be necessary to achieve 80% power with a 95% confidence interval and a significance level of $\alpha=0.05$.

We retrospectively reviewed the records of all 61 patients who were operated for CMM in the

Department of Plastic, Aesthetic, and Reconstructive Surgery at Sivas Cumhuriyet University hospital between 01.01.2012 and 01.05.2025. No sample selection was conducted. Five patients were excluded from the study due to missing histopathological records; all others were included in the analyses.

Procedure

Ethical approval was obtained from the Health Sciences Research Ethics Committee of Sivas Cumhuriyet University by its decision date 24.04.2025 and numbered 2025-04/108.

Data collection

The patients' age, sex, whether SLNB and lymph node dissection were performed during surgical excision of the primary tumor, anatomic location and size of the tumor, and histopathological characteristics such as Breslow thickness, Clark stage, lymphovascular invasion and ulceration of the tumor were determined from the hospital information system and patient records of our clinic.

Breslow thickness and maximum tumor diameter measured from pathology specimens following total surgical excision were retrieved from pathology reports. Accordingly, we defined tumor size as the maximum diameter of the lesion.

In addition, we obtained leukocyte, neutrophil, monocyte, and platelet counts and percentages from preoperative complete blood count data and used these values to calculate NLR, PLR, monocyte-to-lymphocyte ratio (MLR), and systemic immune inflammation index (SII; calculated as platelet count × neutrophil count / lymphocyte count). Anatomic locations were classified as head/neck, lower extremities, and trunk/upper extremities.

PET images were evaluated for the presence of lymphadenopathy (LAP). Relationships among these parameters and with lymph node involvement were examined. In our routine procedure, SLNB has been performed in patients with a Breslow thickness of more than 1 mm and those with a Breslow thickness of less than 1 mm but with ulceration and/or Clark level 4 or higher but no signs of LAP on radiological and physical examination.

TVI is a new parameter we created to investigate its potential utility in the prediction of lymph node metastasis at the time of initial diagnosis. It was calculated by multiplying maximum tumor diameter (mm) with Breslow thickness (mm).

Statistical analysis

The study data were analyzed using NCSS (Number Cruncher Statistical System) 2020 statistical software (NCSS LLC, Kaysville, Utah, USA) and IBM SPSS Statistics version 23. Quantitative variables were summarized using mean, standard deviation, median, and range; qualitative variables were summarized using descriptive statistics such as frequency and percentage. Continuous variables were tested for normal distribution using the Shapiro-Wilks test and box plots.

Pearson's chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test were used to compare categorical data according to lymph node metastasis status. For numerical variables, the Mann-Whitney U test was used for comparisons between the two groups, as the data did not exhibit a normal distribution due to the sample size.

Diagnostic screening tests and receiver operating characteristic (ROC) curve analysis were performed to determine the optimal cut-off value of TVI and PLR for predicting the risk of lymph node metastasis. Logistic regression analysis was used to evaluate multivariate risk factors associated with lymph node metastasis. Statistical test results were evaluated within a 95% confidence interval, with p values less than 0.05 considered significant.

RESULTS

The study was conducted with a total of 56 CMM patients (1:1 male-to-female ratio) treated between January 1, 2012 and May 1, 2025. The patients in the study ranged in age from 11 to 95, with a mean age of 62.38±18.82 years.

The distributions of pathological features, subtypes, stages, imaging findings, and anatomic locations of CMM are given in Table 1. Lymph node sampling was performed in 33 (58.9%) of the patients. Of these, metastasis was detected in 34.4% (n=11), while the other 65.6% (n=21) had no lymph node metastasis (Table 1). Composite inflammatory biomarkers based on preoperative blood counts are shown in Table 2.

Table 1. Patient clinical characteristics

Variables	n(%)
Lymph node metastasis, n (%)	11 (34.4)
Breslow (mm)	
Mean ± SD	25.63±23.64
Median (Range)	20 (2-100)
Breslow (mm)	
Mean ± SD	4.30±3.74
Median (Range)	3 (0.1-15)
TVI	
Mean ± SD	137.64±198.66
Median (Range)	40 (2.5-800)
Lymphovascular invasion, n (%)	7 (13)
Ulceration, n (%)	25 (50.0)
Dissection, n (%)	4 (30.8)
SLNB, n (%)	7 (33.3)
T stage, n (%)	
T1	17 (30.4)
T2	4 (7.1)
T3	17 (30.4)
T4	18 (32.1)
Clark, n (%)	
Level 1	4 (7.4)
Level 2	10 (18.5)
Level 3	14 (25.9)
Level 4	17 (31.5)
Level 5	9 (16.7)
Clark	
Mean ± SD	3.31±1.18
Median (Range)	3 (1-5)
Location, n (%)	
Lower extremity	23 (41.1)
Head and neck	18 (32.1)
Trunk & upper extremity	15 (26.8)
Subtype, n (%)	
Acral lentiginous	9 (16.1)
Lentigo malignant	6 (10.7)
Nodular	26 (46.4)
Superficial radiating	11 (19.6)
Other	4 (7.2)
LAP on PET-CT, n (%)	
No	23 (62.2)
Suspected LAP	14 (37.8)
Distant metastasis on PET-CT, n (%)	5 (14.7)
LAP on US, n (%)	
No	25 (92.6)
Suspected LAP	2 (7.4)

SD: Standard deviation, TVI: Tumor volume index, SLNB: Sentinel lymph node biopsy, LAP: Lymphadenopathy, PET-CT: Positron emission tomography-computed tomography, US: Ultrasonography

Table 2. Distribution of patients' preoperative blood count parameters

Parameter	Mean ± SD	Median (Range)
WBC count	7.68±1.99	8 (4.1-13.6)
Lymphocyte count	2.13±0.81	2.1 (0.5-3.9)
Lymphocyte %	28.51±9.79	29.5 (5.9-45.8)
Monocyte count	1.09±3.80	0.5 (0.1-28.3)
Monocyte %	6.24±1.98	5.9 (1.7-14.2)
Neutrophil count	6.08±9.22	4.8 (2-72.8)
Neutrophil %	60.65±14.71	61.5 (5.5-92.1)
Platelet count	253303.57±80040.20	237000 (81000-519000)

SD: Standard deviation, WBC: White blood cell.

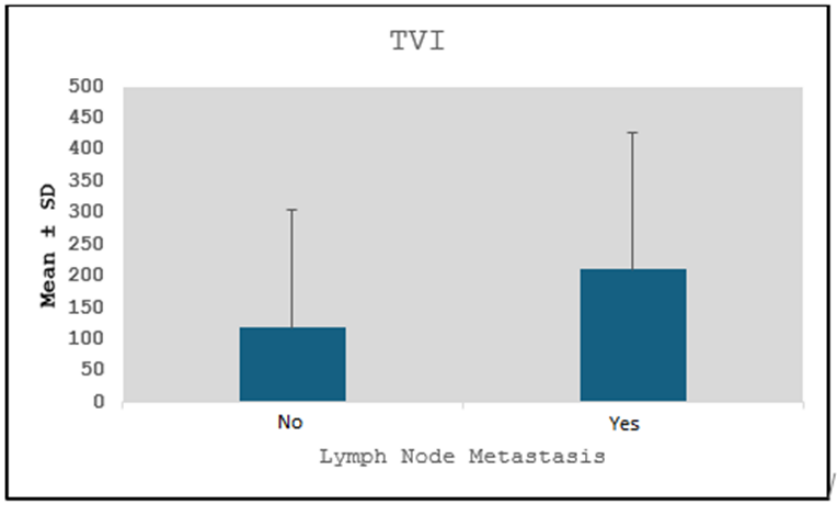

Figure 1. Tumor volume index distribution according to presence of lymph node metastasis

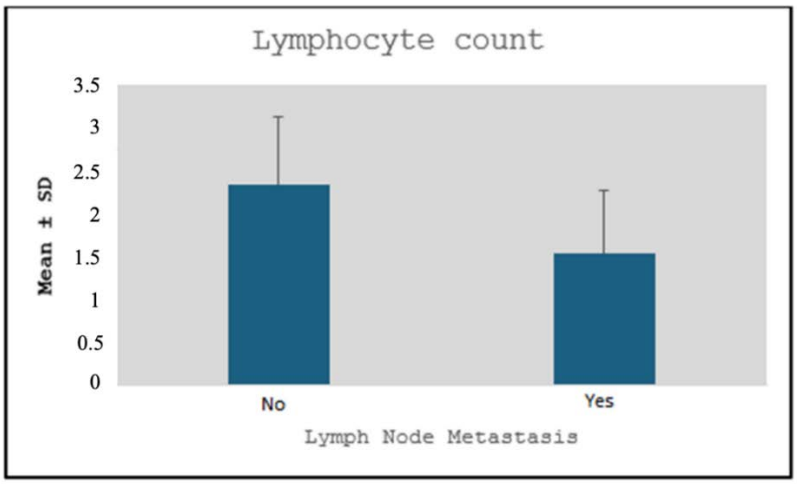

Figure 2. Distribution of lymphocyte counts according to presence of lymph node metastasis.

Table 3. Comparisons according to presence of lymph node metastasis

Variable	Lymph Node Metastasis		p
Sex, n (%)	**No (n=21)**	**Yes (n=11)**	
Female	12 (57.1)	5 (45.5)	[a]0.529
Male	9 (42.9)	6 (54.5)	
Age (years)			
Mean ± SD	61.33±15.77	61.64±23.46	[c]0.725
Median (Range)	64 (36-88)	70 (11-95)	
LVI, n (%)			
No	18 (85.7)	9 (81.8)	[b]1.000
Yes	3 (14.3)	2 (18.2)	
Ulceration, n (%)			
No	11 (52.4)	6 (54.5)	[a]0.907
Yes	10 (47.6)	5 (45.5)	
T stage, n (%)			
T1	6 (28.6)	1 (9.1)	[d]0.497
T2	1 (4.8)	0 (0)	
T3	7 (33.3)	4 (36.4)	
T4	7 (33.3)	6 (54.5)	
Clark, n (%)			
Level 1&2	4 (20.0)	1 (9.1)	[b]0.631
Level 3&4&5	16 (80.0)	10 (90.0)	
Clark			
Mean ± SD	3.45±1.10	4.09±1.04	[c]0.133
Median (Range)	4 (1-5)	4 (2-5)	
Location, n (%)			
Lower extremity	5 (23.8)	8 (72.7)	[d]0.010*
Head and neck	4 (19)	2 (18.2)	
Trunk & upper extremity	12 (57.1)	1 (9.1)	
Subtype, n (%)			
Acral lentiginous	2 (9.5)	2 (18.2)	[d]0.836
Other	1 (4.8)	1 (9.1)	
Lentigo malignant	2 (9.5)	0 (0.0)	
Nodular	11 (52.4)	6 (54.5)	
Superficial radiating	5 (23.8)	2 (18.2)	
LAP on PET-CT, n (%)			
No	11 (73.3)	4 (40)	[b]0.122
Suspected LAP	4 (26.7)	6 (60)	
Distant metastasis on PET-CT, n (%)			
No	14 (93.3)	7 (87.5)	[b]1.000
Yes	1 (6.7)	1 (12.5)	
LAP on US, n (%)			
No	10 (90.9)	5 (100)	[b]1.000
Suspected LAP	1 (9.1)	0 (0)	
Tumor size (mm)			
Mean ± SD	23.05±27.24	30.55±18.68	[c]0.061
Median (Range)	10 (3-100)	25 (7-65)	
Breslow thickness (mm)			
Mean ± SD	4.01±3.30	6.32±4.84	[c]0.155
Median (Range)	3 (0.9-13)	6 (1-15)	
TVI			
Mean ± SD	118.44±187.47	210.33±218.53	[c]0.031*
Median (Range)	27 (4.5-640)	120 (30-675)	

SD: Standard deviation, LVI: Lymphovascular invasion, TVI: Tumor volume index, SLNB: Sentinel lymph node biopsy, LAP: Lymphadenopathy, PET-CT: Positron emission tomography-computed tomography, US: Ultrasonography; [a]Pearson's chi-square test, [b]Fisher exact test, [c]Mann-Whitney U test, [d]Fisher-Freeman-Halton test. *p<0.05.

Table 4. Comparison of blood count parameters and composite inflammatory biomarkers according to presence of lymph node metastasis

Parameter	Lymph Node Metastasis		[c]p
	No (n=21)	Yes (n=11)	
WBC count			
Mean ± SD	7.58±2.19	6.56±1.31	0.180
Median (Range)	7.5 (4.1-13.3)	6.1 (4.2-8.3)	
Lymphocyte count			
Mean ± SD	2.33±0.79	1.53±0.74	0.014*
Median (Range)	2.2 (0.8-3.9)	1.5 (0.5-2.8)	
Lymphocyte %			
Mean ± SD	31.23±7.94	25.24±13.67	0.307
Median (Range)	33.9 (13.3-42.7)	24.7 (5.9-45.8)	
Monocyte count			
Mean ± SD	1.81±6.07	0.36±0.13	0.074
Median (Range)	0.5 (0.3-28.3)	0.4 (0.1-0.5)	
Monocyte %			
Mean ± SD	6.12±1.33	5.72±1.8	0.785
Median (Range)	5.7 (4.4-9.9)	6 (1.7-8.1)	
Neutrophil count			
Mean ± SD	4.51±1.57	4.47±1.82	0.845
Median (Range)	4.5 (2.3-9.2)	3.9 (2-7.6)	
Neutrophil %			
Mean ± SD	60.27±7.93	67.09±15.61	0.367
Median (Range)	57 (46.7-78.8)	68.5 (48.4-92.1)	
Platelet count ($x10^3$)			
Mean ± SD	262.9±87.5	257.2±106.1	0.531
Median (Range)	252 (81-432)	235 (140-519)	
NLR			
Mean ± SD	2.16±1.13	4.76±5.04	0.389
Median (Range)	1.6 (1-5.9)	2.3 (1.1-15.6)	
MLR			
Mean ± SD	1.84±7.49	0.30±0.23	0.223
Median (Range)	0.2 (0.1-34.5)	0.2 (0.1-0.9)	
PLR			
Mean ± SD	120149.70±44186.75	217794.38±156619.36	0.042*
Median (Range)	112000 (48795.2-221538.5)	142173.9 (86231.9-518518.5)	
SII			
Mean ± SD	554698.83±326160.75	1182471.67±1302344.07	0.389
Median (Range)	471410.7 (130771.1-1416880.9)	442160.9 (223125-3707407.4)	

SD: Standard deviation, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic inflammation index.
[c]Mann-Whitney U test. *p<0.05.

Demographic and clinical characteristics are compared between patients with and without lymph node metastasis at initial diagnosis in Table 3. Sex, age, lymphovascular invasion, ulceration, T stage, and Clark level did not differ significantly according to the presence of lymph node metastases (p>0.05). However, CMM tumor location showed a significant difference (p=0.010), with lower extremity tumors being more common and trunk/upper extremity tumors less common in patients with lymph node metastasis compared to those without. There were also no statistically significant differences between patients with and without lymph node metastasis in terms of tumor subtype, LAP on PET-CT, distant metastasis on PET-CT, or LAP on US examination (p>0.05). Additionally, tumor size and Breslow thickness did not differ statistically significantly according to presence of lymph node metastasis (p>0.05), whereas TVI values were significantly higher among patients with lymph node metastasis than in those without (p=0.031) (Table 3) (Figure 1).

Comparisons of inflammatory biomarkers between patients with and without lymph node metastasis are shown in Table 4. White blood cell count, lymphocyte percentage, monocyte count or percentage, neutrophil count or percentage, and platelet count did not differ significantly between the groups (p>0.05). There were also no significant differences in SII, NLR, or MLR according to the presence of lymph node metastases (p>0.05). However, lymphocyte count was significantly lower (p=0.014) (Figure 2) and PLR values were significantly higher (p=0.042) in patients with lymph node metastasis than those without.

According to ROC curve analysis and diagnostic screening tests, a TVI cut-off value of 27 had 100% sensitivity, 47.6% specificity, a positive predictive value of 50%, and negative predictive value of 100% in the prediction of lymph node metastasis in our series (Table 5). The area under the ROC curve was found to be 73.7% with a standard error of 8.7%. A statistically significant relationship was found between a TVI cut-off value of 27 and the risk of lymph node metastasis (p=0.001). A TVI of 27 or higher was associated with two-fold higher odds of lymph node metastasis (OR: 2.000, 95% CI: 1.317-3.037) (Figure 3).

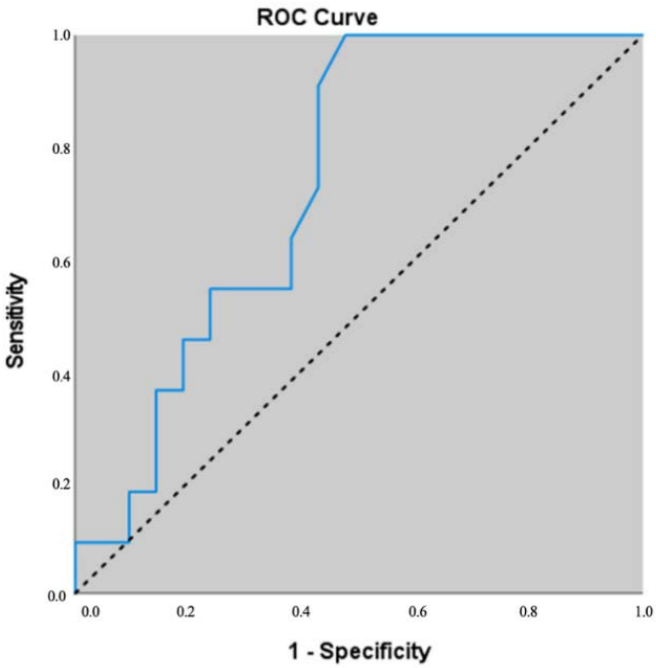

Figure 3. ROC curve for tumor volume index in the prediction of lymph node metastasis risk.

At a cut-off value of 127, PLR had sensitivity of 72.73%, specificity of 66.67%, a positive predictive value of 53.3%, and a negative predictive value of 82.4% in predicting the risk of lymph node metastasis. The area under the ROC curve was 72.3% and the standard error was 9.5%. A PLR cut-off value of 127 was statistically significant in predicting the risk of lymph node metastasis (p=0.021), with a PLR above this cut-off associated with 5.3-fold higher odds of lymph node metastasis (OR: 5.333, 95% CI: 1.069-26.613) (Table 5) (Figure 4).

Table 5. Diagnostic screening tests and ROC curve results for TVI and PLR in the prediction of lymph node metastasis risk

	Diagnostic Scan			ROC Curve				*p*
	Cut-off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	AUC	95% CI	
TVI	*≥27*	100.00	47.62	50.00	100.00	0.737	0.565-0.907	0.001**
PLR	*≥127*	72.73	66.67	53.3	82.4	0.723	0.538-0.908	0.021*

TVI: Tumor volume index, PLR: Platelet-to-lymphocyte ratio, ROC: Receiver operating characteristic, AUC: Area under the ROC curve. *p<0.05, **p<0.01

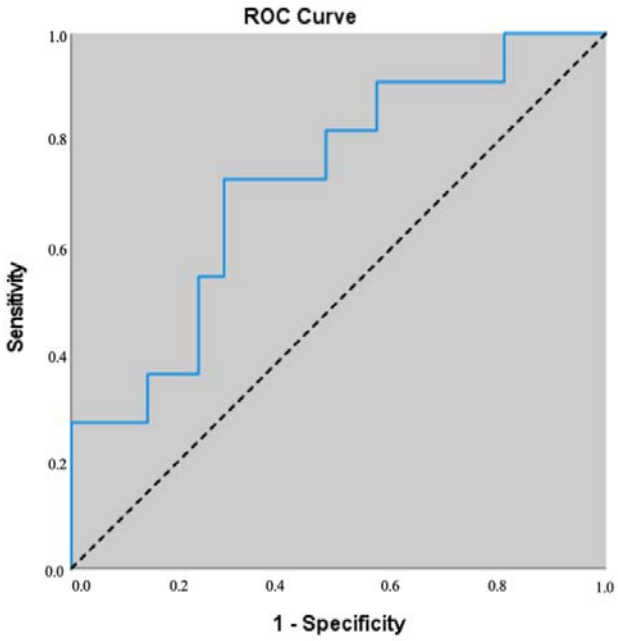

Figure 4. ROC curve for PLR in the prediction of lymph node metastasis risk

Variables that were significant with a p value less than 0.2 in univariate comparisons (tumor location, TVI, lymphocyte count, and PLR) were included in backward logistic regression analysis to identify risk factors associated with lymph node metastasis. The model created in the third step for risk factors associated with lymph node metastasis is shown in Table 6.

The variables included in the study were evaluated by backward stepwise logistic regression analysis. After the third step of the analysis, the model was significant for TVI (X^2: 10.528; p=0.005) with an explanatory coefficient of 75%. According to the model, TVI ≥27 was associated with 11.1 times higher odds of lymph node metastasis (OR: 11.086, 95% CI: 1.123-109.494; p=0.040). Thus, TVI ≥27 was identified as an independent risk factor for lymph node metastasis.

Table 6. Logistic regression analysis of risk factors associated with lymph node metastasis

Parameter			**95% CI**	
	p	OR	Lower	Upper
Tumor location	0.926	1.112	0.117	10.524
TVI (≥27)	0.040*	11.086	1.123	109.494
Lymphocyte count	0.903	0.994	0.904	1.094
PLR (≥127)	0.112	4.182	0.717	24.381

TVI: Tumor volume index, PLR: Platelet-to-lymphocyte ratio, *p<0.05

DISCUSSION

Lymph node metastasis status is the most important determinant of CMM prognosis and recurrence[13,14]. Studies have reported that the most important risk factors for lymph node spread in CMM are Breslow thickness, high Clark level, high mitotic rate, and presence of ulceration[7,15,16]. However, the present study revealed no significant relationship between the detection of lymph node metastasis at initial diagnosis and Breslow thickness, tumor size, and the presence or absence of lymphovascular invasion and tumor ulceration. Differences in our findings from those in the literature may be related to the fact that long-term lymph node metastases were not evaluated in this study.

Melanoma variants represent distinct disease entities. Acral melanoma responds poorly to immunotherapy and is associated with poorer survival. Desmoplastic melanoma, a high-risk cutaneous melanoma, has been reported to have high rates of locoregional recurrence[17].

Additionally, although the nodular or amelanotic subtypes of malignant melanoma have been reported to have worse prognosis[18], studies conducted to date have not demonstrated a relationship between histological subtype and lymph node metastasis[7,15]. Similarly, we detected no significant difference in the rate of lymph node metastasis detected at initial diagnosis according to CMM subtype.

Breslow thickness is a measure of the depth of skin tumors and is calculated by measuring from the surface of the skin to the deepest point of the tumor[19]. As an indicator of tumor invasion and volume, Breslow thickness is considered a quantitative measure of metastasis tendency[20]. However, a single measurement will have low accuracy in describing the size of a three-dimensional structure. As each tumor has a unique three-dimensional profile, a single measurement cannot fully reflect their different shapes and their variable thicknesses at different points. For example, very different shapes can be designed for a tumor with a Breslow thickness of 2 mm. Similarly, tumors defined as having a Breslow thickness of 2 mm will have different combinations of tumor thicknesses at different points in different spatial locations. Although an exact three-dimensional measurement was not made in this study, we used a composite volume index calculated by multiplying the maximum diameter of the tumor by the Breslow thickness. While Breslow thickness and tumor size did not vary according to lymph node metastasis status at initial diagnosis, TVI differed significantly. Upon further analysis, we determined that a TVI of 27 or higher was associated with over 11 times higher odds of lymph node metastasis being detected at initial diagnosis. There is no study in the literature examining the relationship between primary tumor volume and lymph node metastasis in patients with malignant melanoma. Although the specificity was low due to the small number of cases in this series, this volume index is easily calculated from routine pathological parameters and can therefore be used in risk assessment. According to regression modeling, TVI ≥27 was an independent risk factor for lymph node metastasis. These findings suggest that three-

dimensional tumor models and volume calculations can be used in staging instead of Breslow thickness determined from a single point.

Primary lesion location in the scalp or neck is regarded as a clinical poor prognostic factor regardless of tumor thickness[18]. However, different results have been reported regarding the relationship between tumor location and SLN metastasis[21]. Some studies have indicated poorer prognosis for CMM located on the trunk, while others have associated head and neck melanoma with reduced survival[21-23]. The anatomic location of primary melanoma has been reported as an independent predictor of SLN status and survival. Although a low rate of SLN positivity was noted in patients with malignant melanoma of the head and neck region, the risk of recurrence and death was significantly higher compared to other regions[21].

Another study reported that lower extremity melanoma was the most likely to show locoregional nodular spread, while head and neck melanoma was the most likely to present in the most advanced stages of disease. Again, head and neck melanomas were associated with the highest risk of death compared to other sites, independent of other factors. Given these survival differences, it has been recommended that the primary site of melanoma be included in staging to ensure that treatment is as effective as possible[24].

Still, other studies have shown no significant relationship between anatomic location and lymph node metastasis in patients with CMM[7,12,15]. In our study, lower extremity CMM was more common among patients with lymph node metastasis, while CMM located in the trunk or upper extremity was less common.

There is uncertainty about the application of SLNB in patients with CMM located in the head and neck region. Reasons for this include the complex lymphatic drainage of the head and neck region, higher false result rates, higher recurrence rates, significantly lower SLNB positivity, and the risk of nerve injury. It has been reported that 26% of SLNBs in the parotid region are mapped[25,26]. Therefore, the reliability and necessity of SLNB for CMM of the head and neck region are debated. Of the 18 patients with CMM of the head and neck in our series, only 6 underwent lymph node sampling, while the other two-thirds received clinical follow-up.

Identifying prognostic factors is important in selecting the treatment protocol for a patient. According to current guidelines, SLNB is recommended if the risk of nodal metastasis is above 5%[26].

Although the SLNB procedure is reliable, it must be performed by an experienced surgeon. As an invasive procedure, it carries the risk for various surgical complications, including bleeding, infection, seroma, and lymphedema[27,28]. Additionally, lymph node metastasis is detected in less than 20% of all patients requiring SLNB, while the false negative rate is estimated to be 15-20%. False negative results are caused by technical problems, surgeon-related factors, impaired lymphatic drainage resulting from diagnostic biopsies, idiosyncratic lymphatic obstruction, complex lymphatic drainage in the head and neck, insufficient histological analysis, and complex metastatic patterns[26,29].

PET-CT is used in the diagnosis, staging, and treatment response evaluation and monitoring for many cancers. However, when CMM metastasis is limited to the SLNBs, FDG-PET is reported to have low diagnostic performance for the detection of small nodal metastases[30,31]. Skip metastases are also known to occur even in the early stages of CMM. Although PET-CT seems advantageous, especially in patients with skip metastasis, few studies have suggested that PET-CT may be advantageous in early-stage CMM patients[30]. Due to the low sensitivity of PET-CT for small metastases, SLNB remains important for definitive staging of CMMs[31].

In our study, it was observed that there was no statistically significant relationship between the detection of LAP on PET examination and the presence of lymph node metastasis in patients. This demonstrates the importance of lymph node biopsy despite its invasive nature.

In contrast, US is an easily applicable, non-invasive, and inexpensive imaging method. Despite being highly technician-dependent, many previous studies have shown that US is a more sensitive and specific alternative to physical examination in the detection of lymph node metastases[32,33]. However, it has been reported that melanoma metastases smaller than 4.5 mm in diameter cannot be detected by US. As most SLNB metastases are smaller than this at initial staging, US is not effective in these cases[32]. In our study, there was no significant relationship between LAP findings in the preoperative US examination and the detection of lymph node metastasis. Despite the lack of a significant relationship, many clinics use US

for lymph node examination in oncological patients because it is more sensitive and specific than physical examination. We consider the method beneficial in terms of detecting large lymph nodes and planning further examinations.

Most of the studies in the literature on inflammatory markers in CMM patients are related to prognosis. Several studies have shown that high NLR and PLR are inversely proportional to survival rate[33,34]. High NLR and MLR have also been associated with lower recurrence-free survival, while PLR has not. Initial NLR, PLR, and MLR are said to be independent predictors of melanoma prognosis[35].

NLR and PLR were determined to exhibit different patterns in early and advanced malignant melanoma, with high NLR associated with remission of the primary tumor in the early disease stages[10]. In a study examining stage 3 CMM patients with microscopic SLNB metastasis, NLR, LMR, and CRP were found to be strongly associated with relapse-free survival, regardless of other known prognostic parameters. However, the combination of CRP and LMR was reported to have the strongest potential in predicting progression[36]. In another study, high NLR and MLR were also associated with low recurrence-free survival. Baseline NLR, PLR, and MLR have been identified as independent predictors of melanoma prognosis[35].

There are a limited number of studies in the literature examining the relationship between lymph node metastasis and inflammatory markers. In a study including all stages of CMM, it was determined that NLR could help predict microscopic SLNB metastasis[11], although NLR and PLR were independent predictors of microscopic SLNB metastasis only in Stage 2A malignant melanoma patients[37]. The patients in our study were not classified as having microscopic or macroscopic metastasis. As a result, lymphocyte count was significantly lower and PLR significantly higher in patients with lymph node metastasis than in those without. The odds of detecting lymph node metastasis were 5.3 times higher in patients with a PLR value of 127 and above. However, it was not found to be an independent risk factor in the model.

Although malignant melanomas are less common than other skin cancers, they are a serious health problem due to their aggressive behavior. As in other cancers, early diagnosis and treatment are important. Lymph node metastases significantly reduce patient survival and are closely related to prognosis. Diagnosis and treatment at the earliest stage possible are important for survival. Lymph node metastases can be definitively diagnosed by histopathological examination. This requires biopsy, which is an invasive procedure. Therefore, simpler noninvasive methods to predict or detect lymph node metastases are being investigated even if they do not allow definitive diagnosis.

In the present study, we used a previously undescribed composite parameter, TVI (calculated as the product of Breslow thickness and maximum tumor diameter), and determined that a value of 27 or higher was an independent risk factor for lymph node metastasis. However, due to the small number of patients in our study, our findings should be confirmed in larger series. Furthermore, calculating tumor mass through 3D modeling that utilizes multiple measurements across different planes may be more valuable for cancer prognosis and survival studies.

Although PET imaging is a valuable modality in oncological evaluations, we observed no statistically significant correlation between the detection of LAP on PET scans and the actual presence of lymph node metastasis in malignant melanoma patients. This finding underscores the diagnostic necessity and clinical importance of SLNB.

Author Contributions: Concept/Design : HD, İOK; Data acquisition: HD, İOK; Data analysis and interpretation: HD, SNK; Drafting manuscript: HP, İOK; Critical revision of manuscript: HD, SNK; Final approval and accountability: HD, İOK, SNK; Technical or material support: HD; Supervision: HD; Securing funding (if available): n/a.
Ethical Approval: Ethics committee approval for the study was obtained from the local ethics committee of Sivas Cumhuriyet University. (No: 2025-04/108).
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.
Acknowledgement: We would like to thank Emire Bor for her contributions to the statistical analysis of the study.
We would like to thank Jacqueline Gutenkunst-Gözen for her support in translating the article into English.
Informed Consent: All participants were informed about the study and signed written informed consent before enrollment.

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