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Systemic Inflammation Response Index and Pan-Immune-Inflammation Value: Prognostic Significance in Metastatic Melanoma

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ABSTRACT Objective: Melanoma is an aggressive form of skin cancer. The growing incidence of cancer has been associated with systemic inflammation, and novel indicators such as the pan-immune inflammation value (PIV) and Systemic Inflammation Response Index (SIRI) may be used as prognostic markers for cancer. In this context, the prognostic significance of SIRI and PIV was evaluated in patients with metastatic melanoma. **Material and Methods:** A retrospective analysis involving 58 patients diagnosed with metastatic melanoma at Marmara University was conducted. SIRI and PIV were calculated using baseline neutrophil, monocyte, platelet, and lymphocyte counts. **Results:** Patients with SIRI≥1.5 had significantly shorter progression-free survival (PFS) (mean 29.7 vs. 55.6 months, p=0.022) and overall survival (OS) (mean 38.9 vs. 78.8 months, p=0.006) compared to those with SIRI<1.5. Similarly, PIV≥390 was associated with shorter PFS (mean 28.3 vs. 57.4 months, p=0.007) and OS (mean 39.2 vs. 78.8 months, p=0.007). The multivariate analysis, revealed SIRI as an independent prognostic factor for OS (HR: 2.2; 95% CI: 1.16-4.26, p=0.01), while PIV did not reach significance (HR: 1.2; 95% CI: 0.25-5.97, p=0.78). **Conclusion:** SIRI is an important independent prognostic marker for OS in patients with metastatic melanoma and should, therefore, be incorporated into clinical practice for risk stratification. Although PIV is associated with survival outcomes of patients, as revealed in the univariate analysis, it did not reach significance in the multivariate analysis. Further studies are necessary to confirm these findings, increase the prognostic significance of SIRI, and evaluate the efficacy of using SIRI in combination with other biomarkers.

Keywords: Systemic Inflammation Response Index; pan-immune inflammation value; prognostic markers; melanoma; survival analysis

Melanoma is one of the most aggressive forms of skin cancer and is characterized by rapid progression and high potential for metastasis.[1,2] The prognosis for patients with advanced stages of melanoma remains poor despite advances in targeted therapies and immunotherapies, and survival outcomes vary significantly among these patients.[3,4] Therefore, it is imperative to search for reliable prognostic biomarkers for predicting survival and guiding treatment decisions for melanoma patients.

Inflammation plays an important role in the pathogenesis of melanoma, as it does in several other types of cancer.[5-7] Chronic inflammation creates a pro-tumorigenic environment, leading to tumor initiation and progression. Systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been studied for their potential as prognostic indicators in various malignancies.[8,9] However, these markers provide a limited view of the complex interplay between the different components of the immune system.

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Systemic Inflammation Response Index (SIRI) and pan-immune inflammation value (PIV) are two emerging biomarkers that offer a further comprehensive assessment of the systemic inflammatory response. PIV includes the assessment of neutrophils, monocytes, platelets, and lymphocytes, while SIRI includes the assessment of neutrophils, monocytes, and lymphocytes.[10-13] SIRI and PIV reflect the balance between pro-tumorigenic and anti-tumorigenic factors in the immune system, thereby facilitating prognosis prediction for patients with malignancy.

In the above context, the present study aimed to evaluate the prognostic significance of PIV and SIRI in patients with metastatic melanoma. The relationship of these two systemic inflammatory markers with the survival outcomes in patients was determined to evaluate the potential of these markers as novel prognostic factors that would facilitate risk stratification of patients and guide clinical decision-making. The present study is, to the best of the author's knowledge, one of the first ones to comprehensively evaluate the prognostic value of PIV and SIRI in metastatic melanoma. The findings of the study might be useful for designing and developing personalized treatment strategies.

MATERIAL AND METHODS

A total of 58 patients with metastatic melanoma who were followed and treated at Marmara University between the years 2006 and 2023 were analyzed retrospectively.

The study followed the principles of the Declaration of Helsinki and was approved by the Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Marmara University (date: December 8, 2023, no: 09.2023.1555).

The inclusion criteria were a confirmed diagnosis of melanoma, having received the systemic treatment, and the availability of laboratory data for the patients. Patients with a history of other malignancies, active infection, or autoimmune diseases and those with missing clinical data or follow-up data were excluded from the study.

Data were collected from patient files and the electronic information system. The demographic and clinical characteristics of the patients, including their age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, Breslow thickness, ulceration status, metastatic sites, and treatment history, were recorded.

The systemic inflammatory markers SIRI and PIV at the time of diagnosis were calculated as follows: SIRI=(neutrophil count×monocytes count)/lymphocyte count; PIV=(neutrophil count× platelet count×monocyte count)/lymphocyte count.

In the patients analyzed retrospectively, an optimal value with appropriate sensitivity and specificity could not be determined from the ROC curves. The optimal threshold values of SIRI (low, <1.5; high, ≥1.5) and PIV (low, <390; high, ≥390) were determined according to the previous studies.[13-16]

Progression-free survival (PFS) was defined as the duration between the time of diagnosis and disease progression or death. OS was defined as the duration between the time of diagnosis and death due to any cause.

Kaplan-Meier survival curves were generated to estimate PFS and overall survival (OS), and the differences between groups were compared using the Log-rank test. Univariate and multivariate Cox proportional hazard regression models were employed to determine the prognostic factors for OS. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to reflect the strength of associations. A p-value of <0.05 was considered statistically significant.

RESULTS

The 58 patients analyzed retrospectively in the present study had a mean age of 61 years (IQR: 21-83 years), and 35 (60.3%) of these patients were male. Most of the patients (89.7%) had ECOG 0. The *de novo* metastatic disease was observed in 29.3% of the patients. Breslow thickness was 1-2 mm in 18.9% of patients, 3 mm in 22.4% of patients, and 4 mm in 58.6% of patients. Ulceration was present in 32.7% of the patients (Table 1).

PFS and OS were stratified based on SIRI and PIV. The mean PFS (55.6 months) of patients with SIRI<1.5 was significantly longer compared to the PFS (29.7 months) of patients with SIRI≥1.5

TABLE 1: Demographic and clinical charateristics of the patients.

Age, year	
Median (Interquartile range)	61 (21-83)
Gender, n (%)	
Female	23 (39.7)
Male	35 (60.3)
ECOG-performance score, n (%)	
0	52 (89.7)
1	6 (10.3)
De novo metastatic stage, n (%)	17 (29.3)
Breslow Thickness, n (%)	
1-2	11 (18.9)
3	13 (22.4)
4	34 (58.6)
Ulceration status, n (%)	18 (32.7)
Metastatic site, n (%)	
Lymph node	25 (43.1)
Bone	13 (22.4)
Lung	26 (44.8)
Brain	11 (19.0)
Liver	10 (17.2)
Metastatic site number, (%)	
0-1	42 (72.4)
2	8 (13.8)
≥3	8 (13.8)
First-line treatment option, n (%)	
Temozolomide	38 (65.5)
Dabrafenib+trametinib	11 (19)
Nivolumab	9 (15.5)
BRAF mutation, n (%)	18 (31)
Cutaneous malign melanoma, n (%)	39 (67.2)
Mucosal malign melanoma	8 (13.8)
Acral malign melanoma	6 (10.3)
Uveal malign melanoma	5 (8.6)
Progression, n (%)	
Yes	50 (86.2)
No	8 (13.8)
Second-line treatment option, n (%)	
Nivolumab	15 (50)
Dabrafenib+trametinib	3 (10)
Temozolomide	4 (13)
Others	8 (27)
Status, n (%)	
Alive	17 (29.3)
Death	41 (70.7)

ECOG: Eastern Cooperative Oncology Group performance status.

(p=0.022). Similarly, OS (78.8 months) was significantly higher in the SIRI<1.5 group compared to the mean OS (38.9 months) in the SIRI≥1.5 group (p=0.006). In regard to PIV, the median PFS of patients with PIV<390 was 57.4 months, which was significantly longer (p=0.007) than the median PFS of patients with PIV≥390 (28.3 months). OS followed a similar trend (Table 2), and the median OS of patients with PIV<390 was 78.8 months compared to 39.2 months for patients with PIV≥390 (p=0.007).

The univariate analysis revealed SIRI and PIV as the significant predictors of OS. In particular, SIRI≥1.5 (HR: 2.38; 95% CI: 1.25-4.53; p=0.008) and PIV≥390 (HR: 2.37; 95% CI: 1.24-4.51; p=0.009) presented significant associations with the OS of patients. In multivariate analysis (Table 3), while SIRI remained an important independent prognostic factor for OS (HR: 2.22, 95% CI: 1.16-4.26, p=0.01), PIV could not reach significance (HR: 1.24, 95% CI: 0.25-5.97, p=0.78).

The Kaplan-Meier curves generated are depicted in Figure 1 and Figure 2. Progression-free and OS times determined based on SIRI and PIV may be observed from the curves. The survival curves further emphasized the significant differences in the survival outcomes between the low and high groups for both SIRI and PIV.

DISCUSSION

The present study evaluated the prognostic significance of two systemic inflammatory markers, namely, SIRI and PIV, in metastatic melanoma. The findings revealed both SIRI and PIV as important predictors of survival, with SIRI revealed as an independent prognostic factor in the multivariate analysis.

Inflammation is known to play an important role in cancer progression. An increase in systemic inflammatory responses is associated with the creation of a pro-tumorigenic environment that induces angiogenesis, tumor growth, and metastasis. In the present study, patients with high SIRI (≥1.5) had significantly worse PFS and OS compared to patients with low SIRI (<1.5). These results were consistent with previous reports that have stated the predictive significance of SIRI in several malignancies, including gastrointestinal and lung tumors.[10,13,17,18]

Similarly, high PIV (≥390) was linked to lower PFS and OS in the evaluated patients. The results of the univariate analysis revealed the significance of

TABLE 2: PFS and OS times according to infammatory markers.

			PFS			OS		
	Total (n)	Total (%)	Mean	Median	p value	Mean	Median	p value
SIRI								
<1.5	34	59	55.6	45.4	**0.022**	78.8	58.3	**0.006**
≥1.5	24	41	29.7	21.0		38.9	27.6	
PIV								
<390	33	57	57.4	45.4		78.8	58.3	
≥390	25	43	28.3	19.9	**0.007**	39.2	30.1	**0.007**
Overall	58	100	45.8	31.4		64.5	42.4	

PFS: Progression-free survival; OS: Overall survival; SIRI: Systemic inflammation response index; PIV: Pan-immune inflammation value

TABLE 3: Univariate and multivariate analysis of potential prognostic factors for overall survival.

	Univariate		Multivariate	
Parametres	**HR (95% CI)**	**p value**	**HR**	**p value**
Age (<65 vs ≥65)	1.48 (0.77-2.81)	0.230	1.67 (0.86-3.21)	0.12
Gender (female vs male)	1.17 (0.62-2.20)	0.620	-	-
ECOG-PS (0 vs 1)	0.59 (0.18-1.97)	0.390	-	-
De novo metastatic (no vs yes)	2.1 (1.09-4.25)	**0.020**	1.95 (0.99-3.84)	**0.05**
Ulceration status (no vs yes)	1.36 (0.69-2.67)	0.370	-	-
SIRI (<1.5 vs ≥1.5)	2.38 (1.25-4.53)	**0.008**	2.22 (1.16-4.26)	**0.01**
PIV (<390 vs ≥390)	2.37 (1.24-4.51)	**0.009**	1.24 (0.25-5.97)	0.78

ECOG-PS: Eastern Cooperative Oncology Group performance status; SIRI: Systemic inflammation response index; PIV: Pan-immune inflammation value; HR: Hazard ratio; CI: Confidence interval.

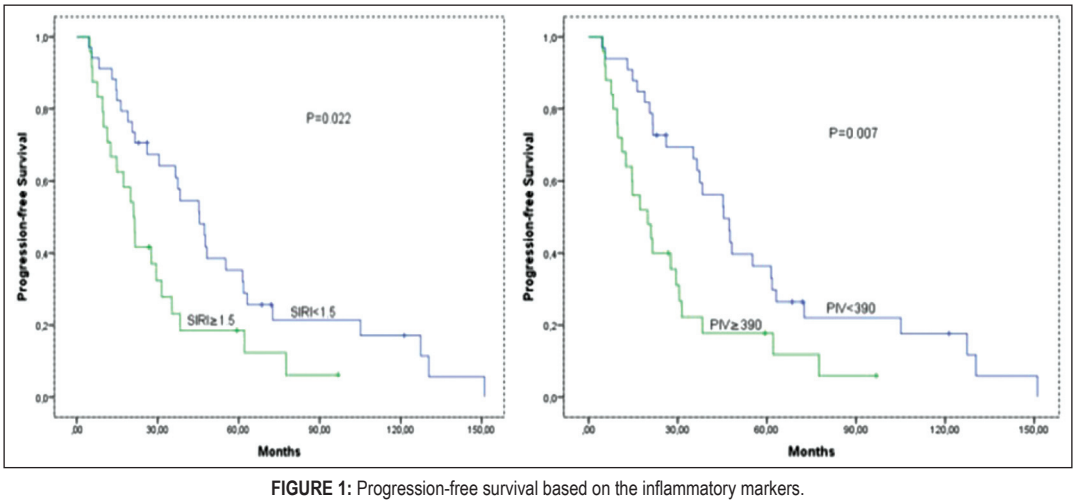

FIGURE 1: Progression-free survival based on the inflammatory markers.

PIV as a predictive marker, demonstrating the usefulness of this marker in risk stratification. However, PIV was revealed to be non-significant in the subsequent multivariate analysis, which could be attributed to the associations between several inflammatory indicators or the small sample size of the present study.

The above findings are consistent with the growing evidence that highlights the significance of systemic inflammation as a prognostic factor in cancer. Certain indicators, such as NLR and PLR, have, for instance, been linked to unfavorable outcomes in melanoma and other malignancies in previous re-

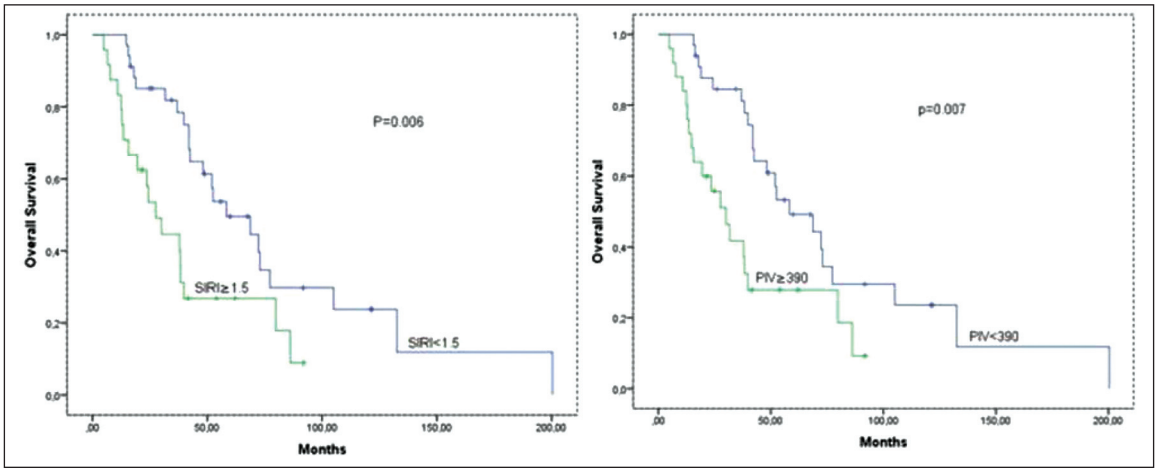

FIGURE 2: Overall survival based on the inflammatory markers.

ports.[5,19,20] SIRI and PIV, which include multiple laboratory parameters, may offer superior prognostic value and provide a further comprehensive evaluation of the inflammatory status of patients.

Remarkably, SIRI was revealed as an independent prognostic factor, without reliance on other clinical factors such as age, gender, ECOG performance status, and *de novo* metastatic status. This finding suggests that SIRI could serve as a robust marker for the identification of high-risk patients who could benefit from a more aggressive treatment or closer monitoring.

The identification of reliable prognostic markers is crucial for undertaking important treatment decisions for patients and determining their survival outcomes. The incorporation of SIRI as an independent prognostic factor in clinical practice is convenient and preferable due to the simplicity and cost-effectiveness of this indicator. Monitoring SIRI in patients with metastatic melanoma would assist in identifying the patients at higher risk for disease progression, and accordingly, design and develop tailored treatment strategies for specific patients.

Further, the incorporation of the markers of systemic inflammation in prognostic models would play an important role in predicting survival outcomes, leading to better stratification of patients and improved personalized treatment strategies.

It is important to state that, despite the favorable results, the present study also has a few limitations. The results of the study may, for instance, not be widely applicable due to the relatively small sample size and the retrospective nature of the study. Moreover, while SIRI was revealed as an independent prognostic predictor, the importance of PIV remained uncertain as this indicator could not reach significance in the multivariate analysis. Consequently, studies with larger sample sizes and a prospective design are warranted to confirm the results of the present study and further investigate the underlying processes involved in the association between systemic inflammation and melanoma progression.

CONCLUSION

SIRI is an important independent prognostic factor for patients with metastatic melanoma. The incorporation of SIRI into standard clinical practice could facilitate personalized treatment for patients, guide clinical decision-making, and provide insights into patient prognosis. Further studies are nonetheless warranted to confirm these findings and explore the opportunities of using SIRI in combination with other biomarkers to achieve improved prognosis prediction.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

nection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nargis Majidov, Muhammed Fatih Kırcalı;* ***Design:*** *Ali Kaan Güren, Nargiz Majidov****; Control/Supervision:*** *Nadiye Sever, Erkam Kocaaslan;* ***Data Collection and/or Processing:*** *Yeşim Ağyol, Pınar Erel;* ***Analysis and/or Interpretation:*** *Burak Paçacı, Mustafa Alperen Tunç;* ***Literature Review:*** *Abdussamet Çelebi, Selver Işık;* ***Writing the Article:*** *Rukiye Arıkan;* ***Critical Review:*** *İbrahim Vedat Bayoğlu;* ***References and Fundings:*** *Osman Köstek, Murat Sarı;* ***Materials:*** *Nargiz Majidov.*

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