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ORIGINAL ARTICLE

Clinical significance of prognostic nutritional index (PNI) in malignant melanoma

Cem Mirili[1] · Ali Yılmaz[1] · Serkan Demirkan[2] · Mehmet Bilici[1] · Salim Basol Tekin[1]

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Abstract

Purpose Nutrition and inflammation play a crucial role in the development of cancer. The prognostic value of the prognostic nutritional index (PNI) has been confirmed in some types of human cancers. However, few studies are available indicating its prognostic power in patients with malignant melanoma (MM). Thus, we aimed to identify baseline peripheral blood biomarkers to predict the outcome of MM patients

Material and methods Data of 101 patients with MM were evaluated retrospectively. Associations between clinical and histopathological parameters with overall survival (OS) and progression-free survival (PFS) were analyzed using Kaplan–Meier curves and compared by the log-rank test. The optimal cutoff values were determined by a receiver operating characteristic (ROC) curve analysis. Neutrophil–lymphocyte ratio (NLR), systemic immune-inflammation index (SII) and PNI were grouped based on a cutoff points 2.18, 547.1, and 40.1, respectively. Univariate and multivariate analyses were used to assess their prognostic values for overall survival (OS).

Results Lower NLR (<2.18), SII (<547.1) and higher PNI (≥ 40.1) were linked with a longer PFS and OS in patients with MM, as reflected in the Kaplan–Meier analyses. In univariate analysis, TNM stage, Breslow thickness, Clark stage, ulceration, Ki67 status, LDH, NLR, SII, and PNI were significantly associated with OS. Multivariate analysis identified TNM stage, ulceration, LDH and PNI as an independent predictor of OS in patients with MM.

Conclusion PNI can be regarded as a novel independent prognostic factor for predicting OS in MM.

Keywords Malignant melanoma · Prognostic nutritional index · Neutrophil–lymphocyte ratio · Systemic immune-inflammation index

Introduction

Malignant melanoma (MM) is a skin malignancy characterized by rapid progression, aggressive course, and refractoriness in treatment [1, 2]. It accounts for approximately 4% of all skin malignancies. It is the sixth most common cause of deaths due to malignancy in America [3]. A large number of patients are detected in the local disease period with the chance of curative surgery, but the situation for local advanced or metastatic disease is not good despite immunotherapy or new targeted agents (stage 1–4, 5-year survey rates, 98%, 62%, 40%, and 16%, respectively) [4–6]. Although it is known that various classical factors such as age, gender, Breslow tumor depth, ulceration and mitotic rate are predictive for relapse or short life [7], the clinical course of melanoma may not always be predicted. Therefore, it is always important for clinicians to detect new and effective prognostic markers.

It is now known that systemic inflammation has an important role in tumor development, progression, and metastasis [8]. Protumorigenic cytokines secreted by neutrophil and platelet such as vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNF-α), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10) have been found to contribute to tumorogenesis. Monocytes and lymphocytes were found to have anti-tumoral effects by enhancing the immune response to the tumor [9–11]. In recent years, immune prognostic scores such as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte–monocyte ratio

✉ Cem Mirili
cemirili@gmail.com

[1] Department of Medical Oncology, Ataturk University Faculty of Medicine, 25050 Yakutiye, Erzurum, Turkey

[2] Department of Dermatology, Katip Çelebi University Ataturk Education and Research Hospital, İzmir, Turkey

(LMR) and systemic immune-inflammation index (SII) have been found to be prognostic in many malignancy types including melanoma [12–16]. Prognostic nutritional index (PNI) is a new prognostic score which is calculated by multiplication of albumin and lymphocyte counts and reflecting both inflammatory and nutritional status of patient [17]. Although it was initially aimed at predicting immunogenic status and risks before gastrointestinal surgery, it has been found in recent years that it has a very close relationship with prognosis in many solid tumors such as colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma and pancreatic cancer [18–23]. However, the role of PNI in melanoma is still unclear.

This study aimed to explore associations of the basal NLR, SII, and PNI with clinicopathologic parameters and to identify the prognostic values of individual or combined inflammatory biomarkers using multivariate models.

Materials and methods

Between December 2001 and February 2018, 101 of 120 patients whose data were fully accessible with malignant melanoma diagnosed in Medical Oncology Department of Erzurum Atatürk University were included in the study, retrospectively. Clinical, demographic, and histopathological data such as age, sex, performance status, surgical form, melanoma subtype, pathological features, interferon use and other treatment agents were obtained from the patient archive files. Laboratory data were obtained from the hospital information operating system. At the time of diagnosis leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, LDH, albumin, CEA, vitamin D, and CRP were recorded. NLR value by dividing the number of neutrophils by the number of lymphocytes; 'platelet (P) × neutrophil (N)/lymphocyte (L)' was used to calculate the SII value; PNI values were calculated with the formula '(10 × albumin (g/L) + (0.005 × total lymphocyte count)'.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The participants were informed of the study and they provided written consents and Ethics committee approval was not taken as this is a retrospective study.

Statistics

Overall survival (OS) was calculated from the date of diagnosis to the date of death, and censored at the date of last follow-up for survivors. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of recurrence or death and censored at the date of last follow-up for survivors without recurrence. Associations between clinical and histopathological parameters with OS and PFS were analyzed using Kaplan–Meier curves and compared by the log-rank test. The NLR, SII, and PNI were dichotomized on the basis of a receiver operating characteristic (ROC) curve analysis. NLR, SII, and PNI were grouped based on cutoff points 2.18, 547.1, and 40.1, respectively. Area under curve (AUC) was found over 0.70 for all parameters. The cutoff value for LDH was 247 U/L, which is the upper limit of our hospital laboratory. The Chi-square (X^2) test was used to analyze the relationship between group of NLR, SII, PNI and clinicopathological parameters. Univariate and multivariate cox-regression analyses were performed to determine effects of probable prognostic factors, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, American Joint Committee on Cancer (AJCC) TNM stage, Breslow thickness, Clark stage, ulceration, mitotic rate, Ki67 status for OS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0). $p < 0.05$ was considered as statistically significant.

Results

Detailed clinical and demographic data of 101 patients included in the study are shown in Table 1. 44 (43.6%) of our cases were female; 57 (56.4%) were male. The median age of the patients was 59 years (29–85). 46 (45.5%) of the patients were smokers. When patients are classified according to ECOG performance status; 35 of the patients had score 1, 43 had score 2, 16 had score 3, 7 had score 4. A total of 77 patients underwent curative surgery and 44 had lymph node dissection and 28 had adjuvant interferon therapy. Ipilumumab, one of the immunotherapy agents, was used in 11 patients after the first-line treatment; another agent nivolumab was used in only one patient. The Braf mutation was evaluated in 16 patients, but only one patient was positive, and no patient received anti-BRAF treatment. According to TNM staging system, 9 of the cases were stage 1, 44 were stage 2, 18 were stage 3 and 30 were stage 4. 15 of the patients had superficial spreading, 70 had nodular and 2 had acral type. 14 patients were found to be other histological subtypes. In our study, there were 6, 10, 18, 67 patients from stage 1 to 4, respectively, according to the Breslow depth classification. There were 4, 10, 16, 54, 17 patients from stage 1 to 5, respectively, according to the Clark staging system. 69 of the patients had ulceration in the lesion. In 71 patients more than ten mitosis and ≥ 25 Ki67 were detected. Median follow-up period at the end of 31 months

Table 1 Baseline clinic and demographic characteristics of 101 patients with malignant melanoma

	n (%)
Gender	
Female	44 (43.6)
Male	57 (56.4)
Age	
Median (range)	59 ± 15.3 (29–85)
< 65	67 (66.3)
≥ 65	34 (33.7)
Ecog performance status	
0	35 (34.7)
1	43 (42.6)
2	16 (15.8)
3	7 (6.9)
Cigarette	
Smoker	46 (450.5)
Non-smoker	55 (54.5)
Diagnostic method	
Biopsy	24 (23.8)
Complete resection	77 (76.9
Lymph node dissection	
No	60 (59.4)
Yes	41 (40.6)
AJCC TNM stage	
1	9 (8.9)
2	44 (43.6)
3	18 (17.8)
4	30 (29.79
Histologic subtype	
Superficial spreading	15 (14.9)
Nodular	70 (69.4)
Acral	2 (1.9)
Other	14 (13.8)
Breslow thickness	
1	6 (5.9)
2	10 (9.9)
3	18 (17.8)
4	67 (66.3)
Clark staging	
1	4 (4)
2	10 (9.9)
3	16 (15.8)
4	54 (53.5)
5	17 (16.8)
Ulceration	
No	32 (31.7)
Yes	69 (68.3)
Mitosis	
< 10	30 (29.7)
≥ 10	71 (70.3)
Ki 67	
< %25	30 (29.7)
≥ %25	71 (70.3)
Adjuvant interferon	
No	73 (59.4)
Yes	28 (40.6)
Progression	
No	37 (36.6)
Yes	64 (63.4)
Status	
Alive	42 (41.6)
Death	59 (58.4)

ECOG eastern cooperative oncology group performance status, *AJCC* American joint committee on cancer

(1–203 months), 64 (63.4%) of the cases had progression and 59 (58.4%) had lost their lives.

The ROC curve with the most sensitive and specific cut-off values of NLR, SII and PNI is shown in Fig. 1. Among the prognostic factors, the PNI has the highest AUC (0.73). Median (range/min–max) NLR, SII, and PNI are 2.33 (10.04/0.96–10.1), 628.8 (5664.8/223.2–5888.5), and 40.7 (30.6/18.1–48.7), respectively. The relationship between clinical and pathological parameters with NLR, SII, and PNI groups is shown in Table 2. Low SII score (< 547.1) was associated with female gender, early (< 65) age, low (0–1) ECOG performance score, early (1–2) TNM stage, decreased progression, and death risk. Additionally low

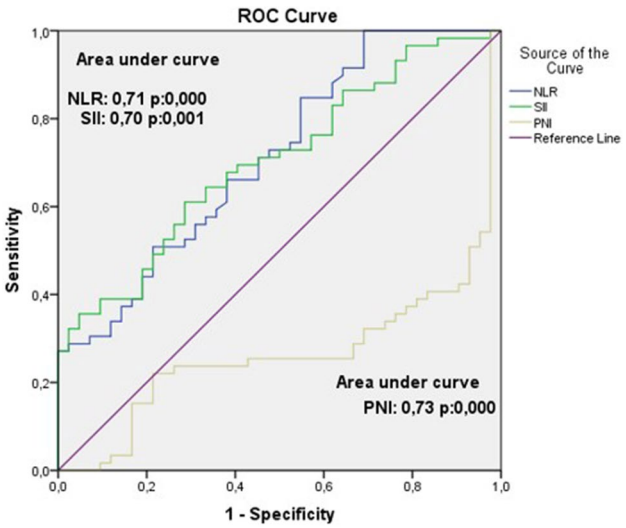

Fig. 1 ROC analysis and AUC for sensitivity and specificity of inflammatory parameters: *NLR* neutrophil–lymphocyte ratio, *SII* systemic immune-inflammation index, *PNI* prognostic nutritional index

NLR (< 2.18) was associated with short (1–2) Breslow depth, early (1–2) Clark stage, low ki67 (< 25%). However, SII and NLR are unrelated to histological subtypes, ulceration and mitosis. High PNI is associated with early (< 65) age, ulceration (negative), low (< 10) mitosis, low (< 25%) Ki67, low progression, risk of death. The high PNI is unrelated to other parameters.

As of the period of analysis, the median PFS and OS periods were 32 and 36 months, respectively. The association of clinicopathological and inflammatory markers with PFS and OS is shown in Table 3. Median PFS durations of female patients was longer than male patients (37 vs 18 months, *p*: 0.030) and similarly median PFS durations were statistically longer than those under 65 years of age (36 vs 16 months, *p*: 0.043) but there was no difference between the duration of OS (*p*: 0.768, *p*: 0.052, respectively) for both these parameters. The PFS duration according to the ECOG performance status 0, 1, 2, 3 were 36, 32, 24, 12 months, respectively. The mean OS time was 37, 44, 34, 12 months, respectively. There was a statistically significant difference between the groups in terms of both PFS and OS (*p*: 0.008, *p*: 0.000, respectively). According to the TNM staging system, the median PFS and OS periods for stage 1 were not reached, but there was a statistically significant difference between the stages for both PFS and OS (*p*: 0.000, *p*: 0.000). The mean PFS/OS duration of the Breslow group 1–2 was 104.7/105.5 months; 52.1/63.3 months of group 3; the group with four was 63.2/72 months. There was a statistical difference in terms of survival (PFS; *p*: 0.006, OS; *p*: 0.016). In the Clark staging system, there were significant differences in PFS and OS duration of the stages (*p*: 0.001, *p*: 0.003, respectively). Patients with ulcerations in the tumor had significantly shorter median PFS (18 vs 132, *p*: 0.001) and OS (26 vs 132, *p*: 0.001) than those without. There was no difference in PFS (40 vs 24 months, *p*: 0.052) nor OS (46 vs 32 months, *p*: 0.058) among patients with low mitosis (< 10) and high mitosis (≥ 10). Median PFS (132 vs. 21, p: 0.000) and OS (132 vs 32, *p*: 0.003) were significantly longer in patients with low Ki67 than in those with high K67.

There was no difference in PFS between patients with LDH values above normal (≥ 247 U/L) and those with normal values(< 247 U/L). Those with LDH above normal had shorter OS (PFS: 24 vs. 34 months, *p*: 0.165, OS: 25 vs 38 months, *p*: 0.012). Patients with low NLR and SII had longer median PFS (132 vs 16, *p*: 0,000, 37 vs 21 months, *p*: 005, respectively) and OS (132 vs 25, *p*: 0.000, 132 vs 25 months, *p*: 0.000 respectively). The median PFS/OS times of those with high PNI were 37/132 months, while those with low PNI were 19/26 months. There was a statistically significant difference (*p*: 0.005, *p*: 0.000) (Fig. 2).

A Cox proportional hazards model was used to evaluate the potential predictors as seen in Table 4, the univariate analysis revealed that OS was significantly associated with AJCC TNM Stage (HR: 1899; 95% CI: 1.445–2.497; *p*: 0.000), Breslow thickness (HR: 1.705; 95% CI: 1.159–2.508, *p*: 0.007), Clark stage (HR: 1.786; 95% CI: 1.297–2.459, *p*: 0.000), ulceration (HR: 2.682; 95% CI: 1.442–4.982, *p*: 0.002), Ki67 (HR: 0.384; 95% CI: 0.199–0.742, *p*: 0.004), LDH (HR: 0.526; 95% CI: 0.314–0.882, *p*: 0.015), NLR (HR: 2522; 95% CI: 1.463–4.346, *p*: 0.001), SII (HR: 2.708; 95% CI: 1.559–4.705, *p*: 0.000) and PNI (HR: 0.344; 95% CI: 0.199–0.597; *p*: 0.000). In multivariate analysis, AJCC TNM stage (HR: 1.773; 95% CI: 1.225–2.450, *p*: 0.002), Ulceration (HR: 2.054; 95% CI: 1.004–4.202, *p*: 0.049), LDH (HR: 1.933; 95% CI: 1.074–3.479, *p*: 0.028) and PNI (HR: 0.417; 95% CI: 0.226–0.770, *p*: 0.005) were still identified as independent prognostic factors for OS.

Discussion

MM is one of the most aggressive cancers [24]. Surgery is the main therapeutic option in cases with localized disease while immune-check point and BRAF inhibitors are main therapeutic agents in cases with metastatic setting [25]. Since clinical progression is not always predictable, it is important for the clinician to detect prognostic or predictive factors. In this study we wanted to explore the prognostic significance of immune-inflammatory indexes in cases with MM. We found that PNI was an independent risk factor in both univariate and multivariate analysis for OS but NLR and SII were only in univariate analysis. This finding is important to understand the association between immunonutritional status and prognosis in MM.

The definition of malignant melanoma (a word derived from the Greek melas, "dark" and oma "tumor") was first made in the fifth century [26]. Since then many studies have been done and continue to be made. As a result of these studies, age, gender, location, Breslow thickness, ulceration, mitotic rate, lymph node involvement, stage and LDH are considered as prognostic factors [27]. Recently, new factors such as BRAF mutation status, circulating melanoma cell presence and serum S-100 protein have also been found to be prognostic [28]. Although in our study, patients under 65 years of age and female patients with longer PFS had no prognostic significance for OS. In accordance with the information in the literature, AJCC TNM stage, Breslow thickness, Clark stage, ulceration, Ki67 status are prognostic in terms of both PFS and OS. Stage and ulceration status were determined as independent prognostic factors according to both univariate and multivariate analyses.

In recent years, studies on the relationship between inflammation and carcinogenesis are increasing. Inflammation has an important role in the onset of tumorigenesis, angiogenesis, inhibition of apoptosis and metastasis [29]. NLR is the most frequently used systemic marker for

Table 2 The association between pretreatment NLR, SII, PNI, and clinicopathological parameters (*n*: 101)

	n	NLR			SII			PNI		
		<2.18	≥2.18	*p*	<547.1	≥ 547.1	*p*	<40.1	≥40.1	*p*
Gender				**0.001**			**0.010**			0.197
Female	44	28	16		26	18		19	25	
Male	57	18	39		19	38		32	25	
Mean Age	101	52.91	61.8	**0.003**	53.5	61.1	**0.014**	61.3	54.1	**0.017**
Age				**0.006**			**0.009**			**0.001**
<65	67	37	30		36	31		26	41	
≥65	34	9	25		9	25		25	9	
Ecog performance status				**0.009**			**0.019**			0.219
0	35	23	12		22	13		17	18	
1	43	18	25		18	25		19	24	
2	16	4	12		4	12		9	7	
3	7	1	6		1	6		6	1	
AJCC TNM stage				**0.04**			**0.001**			0.139
1	9	6	3		4	5		2	7	
2	44	27	17		29	15		20	24	
3	18	6	12		6	12		10	8	
4	30	7	23		6	24		19	11	
Histologic Subtype				0.914			0.421			0.834
Superficial spreading	15	7	8		**9**	**6**		8	7	
Nodular	70	31	39		29	41		34	36	
Other	16	8	8		7	9		9	7	
Breslow thickness				**0.023**			0.276			0.893
1-2	16	12	4		10	6		8	8	
3	18	9	9		8	10		10	8	
4	67	25	42		27	40		33	34	
Clark				**0.008**			0.068			0.131
1-2	14	12	2		10	4		3	11	
3	16	8	8		7	9		9	7	
4	54	19	35		24	30		29	25	
5	17	7	10		4	13		10	7	
Ulceration				0.540			0.749			**0.027**
No	32	16	16		15	17		11	21	
Yes	69	30	39		30	39		40	29	
Mitosis				0.307			0.781			**0.025**
<10	28	16	14		14	16		10	20	
≥10	73	30	41		31	40		41	30	
Ki 67				**0.006**			0.111			**0.007**
<%25	30	20	10		17	13		9	21	
≥%25	71	26	45		28	43		42	29	
Adjuvan interferon				0.147			**0.013**			0.951
No	73	30	43		27	46		37	36	
Yes	28	16	12		18	10		14	14	
Progression				**0.000**			**0.022**			**0.006**
No	37	26	11		22	15		12	25	
Yes	64	20	44		23	41		39	35	
Status				**0.005**			**0.003**			**0.000**
Alive	42	26	16		26	16		11	31	
Death	59	20	39		19	40		40	19	

Statistically significant *p* values are in bold ($p < 0.05$)

ECOG Eastern Cooperative Oncology Group performance status, *AJCC* American Joint Committee on Cancer, *NLR* Neutrophil Lymhocyte Ratio, *SII* Systemic Immune-Inflammation index, *PNI* Prognostic Nutritional Index. Fisher exact test was used in expected minimum is less than 5 with Chi square

Table 3 Overall and progression-free survival times according to clinical parameters and NLR, SII, and PNI

	Total (*n*)	Total (%)	PFS			OS		
			Mean	Median	*p*	Mean	Median	*p*
Gender								
Female	44	43.6	89.3	37	**0.030**	93.8	123.6	0.076
Male	57	56.4	59.1	18		69.2	90.2	
Age								
<65	67	66.3	85.4	36	**0.043**	11.521	5.033	0.727
≥65	34	33.7	53.7	16		10.649	7.200	
Ecog performance status								
0	35	34.7	70.6	36	**0.008**	73.8	37	**0.000**
1	43	42.6	78.4	32		89.2	44	
2	16	15.8	76.4	24		85.5	34	
3	7	6.9	12.7	12		13.8	12	
AJCC TNM stage								
1	9	8.9	77.6	NR	**0.000**	77.6	NR	**0.000**
2	44	43.6	95.2	37		106.4	53	
3	18	17.8	31.9	32		34.2	32	
4	30	29.8	28.1	9		37	15	
Histologic Subtype								
Superficial spreading	15	14.8	56.6	32	0.718	65.7	32	0.692
Nodular	70	69.3	81.9	26		90.3	36	
Other	16	15.9	74.9	32		76.8	36	
Breslow thickness								
1-2	16	15.9	104.7	NR	**0.006**	105.5	NR	**0.016**
3	18	17.8	52.7	26		63.3	36	
4	67	66.3	63.2	22		73	30	
Clark								
1–2	14	13.8	93.8	NR	**0.001**	100.5	NR	**0.003**
3	16	15.9	132	NR		118.48	NR	
4	54	53.4	52.5	24		64.9	31	
5	17	16.8	23.4	21		26.5	25	
Ulceration								
No	32	31.7	103.4	132	**0.001**	107.9	132	**0.001**
Yes	69	68.3	58.2	18		68.8	26	
Mitosis								
<10	30	29.7	86.5	40	0.052	92.6	46	0.058
≥10	71	70.3	67.7	24		76.2	32	
Ki 67								
<%25	30	29.7	121	132	**0.000**	117	132	**0.003**
≥%25	71	70.3	52.3	21		64.6	32	
Adjuvan interferon								
No	73	59.4	65.4	24	0.165	64.7	30	**0.008**
Yes	28	40.6	89	37		124	NR	
LDH					0.145			**0.012**
<247	57	56.4	84.8	34		96.8	38	
≥247	44	43.6	61.8	24		63.5	25	
NLR								
<2.18	46	45.5	110.8	132	**0.000**	108.5	132	**0.000**
≥2.18	55	54.5	43.4	16		57.7	25	

Table 3 (continued)

	Total (*n*)	Total (%)	PFS			OS		
			Mean	Median	*p*	Mean	Median	*p*
SII								
<547.1	45	44.5	96.5	37	**0.005**	111.6	132	**0.000**
≥547.1	56	55.5	54.8	21		55.6	25	
PNI								
<40.8	51	50.4	51.1	19	**0.005**	50.8	26	**0.000**
≥40.8	50	49.6	98	37		117	132	
Overall	101	100	75	32		82.6	36	

Statistically significant *p* values are in bold ($p < 0.05$)

ECOG Eastern Cooperative Oncology Group performance status, *AJCC* American Joint Committee on Cancer, *NLR* Neutrophil Lymhocyte Ratio, *SII* Systemic Immune-Inflammation index, *PNI* Prognostic Nutritional Index

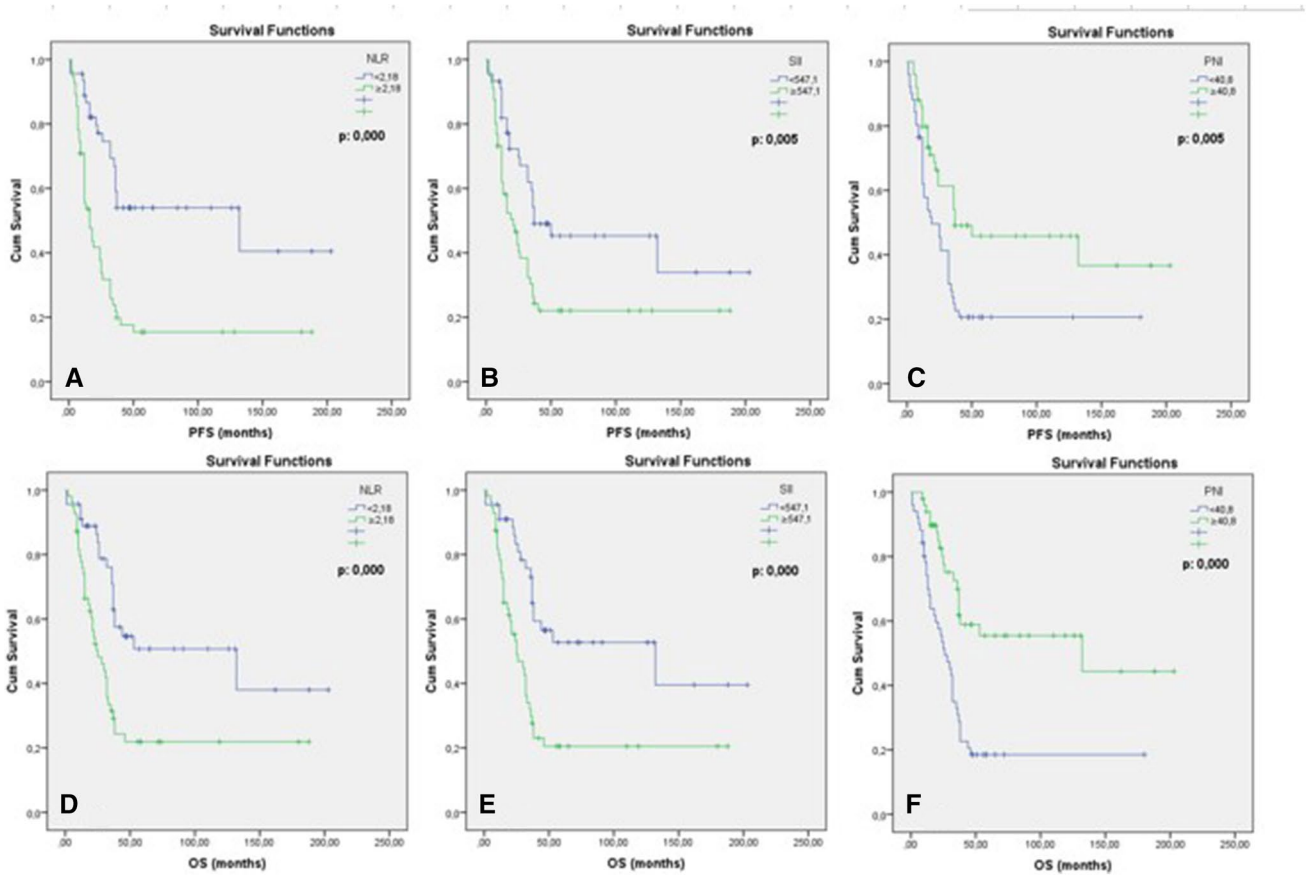

Fig. 2 PFS and OS times according to inflammatory markers. NLR (**a**–**d**), SII (**b**–**e**), PNI (**c**–**f**). *NLR* neutrophil–lymphocyte ratio, *SII* systemic immune-inflammation index, *PNI* prognostic nutritional index

inflammatory status. NLR has proven to be prognostic in many malignancies, including MM. For example, Gandini et al. [30] attempted to determine the prognostic significance of hematological profiles in a 584 MM case. In this study, it was found that high NLR (≥5) was an independent factor in terms of poor prognosis in patients with stage 4. In a study conducted by Lino-Silva et al. [31] 742 MM patients with grade 1–3 had a high NLR (≥2), short OS. In another recently published multicenter study, NLR ≥ 2.5 was associated with a short OS, but unlike other studies, NLR was found to have no independent prognostic significance [32]. In a meta-analysis involving twelve studies and 3207 MM cases, it was concluded that high NLR predicted short PFS and OS. The cutoff value for NLR is not a definite number but values between 2 and 5 are selected [33]. In our study, it was found that high NLR (≥2.18) was associated with

Table 4 Univariate and multivariate analysis of potential prognostic factors for overall survival

Parameters	Univariate		Multivariate	
	HR	*p*	HR	*p*
Age	1.016 (0.999-1.034)	0.066	-	-
Gender (female)	1.597 (0.941-2.711)	0.083	-	-
ECOG performane status	1.321 (0.966-1.807)	0.081	-	-
AJCC TNM Stage	1.899 (1.445-2.497)	**0.000**	1.773 (1.225-2.450)	**0.002**
Breslow Thickness	1.705 (1.159-2.508)	**0.007**	1.693 (0.902-3.179)	0.101
Clark Stage	1.786 (1.297-2.459)	**0.000**	1.099 (0.699-1.728)	0.681
Ulceration	2.682 (1.442-4.982)	**0.002**	2.054 (1.004-4.202)	**0.049**
Ki67 (<%25 vs ≥%25)	0.384 (0.199-0.742)	**0.004**	1.441 (0.722-2.877)	0.301
LDH (<247 vs ≥247)	0.526 (0.314-0.882)	**0.015**	1.933 (1.074-3.479)	**0.028**
NLR (<2.18 vs ≥2.18)	2.522 (1.463-4.346)	**0.001**	1.130 (0.512-2.494)	0.763
SII (<547.1 vs ≥547.1)	2.708 (1.559-4.705)	**0.000**	1.463 (0.663-3.228)	0.347
PNI (<40.8 vs ≥40.8)	0.344 (0.199-0.597)	**0.000**	0.417 (0.226-0.770)	**0.005**

Statistically significant *p* values are in bold ($p < 0.05$)

ECOG eastern cooperative oncology group performance status, *AJCC* American Joint Committee on Cancer, *NLR* neutrophil–lymphocyte ratio, *SII* systemic immune-inflammation index, *PNI* prognostic nutritional index

short PFS and OS in a similar way to OS, although it could not be determined as an independent factor in multivariate examination for OS.

Additionally in recent times it is thought that SII developed with the combination of platelet, neutrophil and lymphocyte numbers reflects the balance between inflammatory and immune status of the patients [34]. SII is a promising index in cancers such as hepatocellular cancer, pancreas, small and non-small cell lung cancer, gastric and esophagial cancers [35–38]. However, there is only one study showing the importance of melanoma patients. In this study, the predictive power of SII was investigated in 226 patients with high-risk acral melanoma patients treated with high-dose interferon. As a result, low SII (< 615) was associated with long relapse-free survival (RFS) (30.2 vs 14.8 months, *p*: 0.029) as well as OS (62 vs 34 months, *p*: 0.006). It has been found that there is only univariate independent factor in terms of RFS [39]. In our study, low SII (< 547) was associated with long PFS and OS; In the cox analysis, it was found to be a univariate independent factor for OS. In the study of Yu et al. only the use of stage 2–3 high-risk acral melanoma cases and the fact that all patients used interferon had differences in our study. However, this situation does not change the prognostic significance of SII in MM cases, but it should be confirmed with studies with high number of patients.

The preoperative conditions of the patients, especially the nutritional and immunological conditions, have been found to be associated with both the post-operative prognosis and the long-term outcomes of malignant tumours [40]. However, the topic of which index shows the nutritional and inflammatory state is the most frequently investigated in recent years. Although various markers have been tried for this purpose, PNI has been the most widely used and accepted marker in many tumors such as non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), pleural mesothelioma and gastric cancer [41]. Low PNI is associated with reduced albumin and/or lymphocyte. Serum albumin is an important indicator that shows both the patient's inflammatory reaction and nutritional status [42]. Serum albumin is prognostic in many types of cancer, either alone or in combination with other factors [43]. Malnutrition is often associated with hypoalbuminemia and is also closely related to inflammatory markers such as NLR, PLR, which are known to be poor prognostic. In fact, pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor α are responsible for the regulation of the production stage of the albumin in hepatocytes. These cytokines are also involved in malignant transformation, neoangiogenesis and cancer progression [44]. This suggests a significant relationship between nutritional status and inflammatory status. Lymphocytes, the other element of PNI, are the most important peripheral blood cell that works against cytotoxic response to cancer cell, proliferation of cancer cell, migration of cancer cell and invasion of cancer cell [45]. Therefore, in the case of lymphocytopenia, the cellular immune system cannot function properly and an appropriate inflammatory reaction cannot be established. Lymphocytopenia is also associated with reduced survival, similar to hypoalbuminemia [46]. In the light of all this information, PNI is an index that reflects chronic inflammation, immune system and nutritional status, and has a prognostic significance in cancer patients [35]. In a meta-analysis of 3414 patients, which included 14 studies, high PNI was

associated with longer OS in malignant pleural mesothelioma, gastric cancer, esophagus cancer, colorectal cancer, pancreatic cancer and hepatocellular cancer. In addition, in colorectal cancer, a relationship was found between the TNM stage and PNI [47]. Although the importance of PNI in malignant melanoma is still not clear, in the study conducted by Yu et al. [39] no relation was found between PNI and PFS and OS. However, in this study, we think that this nonsensitivity could not be generalized for all MM patients because the patient population had only high-risk acral melanoma cases in stage 2–3. In our study, patients with high PNI (≥ 40.8) had longer PFS and OS periods than those with low PNI. Both univariate and multivariate analyses showed that PNI was prognostic for OS. In addition to all these, the highest AUC was 0.73 for PNI, indicating the superiority of this factor relative to NLR and SII predictive factor for survival in MM patients. Currently, the prognostic significance of PNI in MM patients was first shown in this study. These new results show us that the nutritional and immunological status at the time of diagnosis in MM patients have prognostic significance as in other cancers.

There are two important limiting points in this study: one is retrospective nature of the study which limits the comparison with the patient and healthy cohort group. The other limitation is the relatively low number of the patients. Prospective cohort studies are needed to validate the data set forth in the study.

Conclusion

Malignant melanoma, the most deadly form of skin cancer, is a type of tumor strongly related to inflammatory processes. At the same time, as in all malignancies, nutritional status in MM patients has a decisive role in the course of the disease. In our study, it was found that low NLR and SII and high PNI were associated with longer PFS and OS. However, PNI was found to be an independent factor for OS in both univariate and multivariate analyzes. This study shows for the first time that it is more important to evaluate both the nutritional and inflammatory conditions, not only the inflammatory state in the MM prognosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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