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Systemic Immune-Inflammation Index and Circulating T-Cell Immune Index Predict Outcomes in High-Risk Acral Melanoma Patients Treated with High-Dose Interferon

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Abstract

High-dose interferon alfa-2b (IFN-α-2b) improves the survival of patients with high-risk melanoma. We aimed to identify baseline peripheral blood biomarkers to predict the outcome of acral melanoma patients treated with IFN-α-2b. Pretreatment baseline parameters and clinical data were assessed in 226 patients with acral melanoma. Relapse-free survival (RFS) and overall survival (OS) were assessed using the Kaplan-Meier method, and multivariate Cox regression analyses were applied after adjusting for stage, lactate dehydrogenase (LDH), and ulceration. Univariate analysis showed that neutrophil-to-lymphocyte ratio ≥2.35, platelet-to-lymphocyte ratio ≥129, systemic immune-inflammation index (SII) $\geq 615 \times 10^9$/l, and elevated LDH were significantly associated with poor RFS and OS. The SII is calculated as follows: platelet count × neutrophil count/lymphocyte count. On multivariate analysis, the SII was associated with RFS [hazard ratio (HR)=1.661, 95% confidence interval (CI): 1.066-2.586, P=.025] and OS (HR=2.071, 95% CI: 1.204-3.564, P=.009). Additionally, we developed a novel circulating T-cell immune index (CTII) calculated as follows: cytotoxic T lymphocytes/($CD4^+$ regulatory T cells × $CD8^+$ regulatory T cells). On univariate analysis, the CTII was associated with OS (HR=1.73, 95% CI: 1.01-2.94, P=.044). The SII and CTII might serve as prognostic indicators in acral melanoma patients treated with IFN-α-2b. The indexes are easily obtainable via routine tests in clinical practice.

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Introduction

Malignant melanoma is a highly aggressive skin cancer, and the global incident rate is increasing by 3% to 5% annually [1]. Patients with thick primary lesions, ulcerated lesions, or regional metastases have a high risk of relapse [1]. In particular, patients with stage IIB to IIIC have the highest recurrence risk, with postsurgical relapse rates of 40% to 55% and 40% to 80%, respectively [2]. The clinical characteristics and prognosis of Asian patients show significant variations from those of Caucasian patients [3,4]. Acral melanoma is rarely observed in Caucasians but is the most commonly diagnosed pathological subtype in Asian, accounting for 47.5% to 65% of melanoma cases [5,6]. Furthermore, non-Caucasian melanoma patients exhibit worse prognosis than Caucasian melanoma patients, which is still lack of effective adjuvant treatment strategy [7,8]. Presently, interferon alfa-2b (IFN-α-2b) is the only drug approved by the US Food and Drug Administration for the adjuvant treatment of high-risk postoperative melanoma. A meta-analysis of 14 randomized controlled trials concluded that IFN-α-2b was significantly associated with improved disease-free survival and overall survival (OS) [9].

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Moreover, 1-year administration of IFN-α-2b was clinically beneficial in Asian patients with stage IIIB to IIIC acral melanoma or with ≥3 nodal metastases, which is quite different from Caucasian population [10,11]. However, there remain some controversies to using adjuvant interferon therapy, such as significant toxicities and financial burdens. Therefore, it is crucial to investigate prognostic biomarkers that can identify patients who are more likely to benefit from adjuvant interferon therapy.

It is clear that systemic inflammatory responses are a vital determinant of disease progression and survival in most cancers [12]. Infiltrating inflammatory cells in the immune system are increasingly recognized to be generic constituents of tumors that have opposing functions, as both tumor antagonists and promoters [13,14]. Therefore, several immune-based prognostic scores, such as neutrophil count, lymphocyte count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and circulating $CD4^+$T- and $CD8^+$T-cell counts have been developed to predict the prognosis in several cancers, including melanoma [15–20]. However, such parameters have never been utilized to predict outcome in acral melanoma patients treated with adjuvant interferon therapy. Moreover, the potential effects of peripheral lymphocytes, neutrophils, platelets, $CD4^+$ regulatory T cells ($CD4^+$Tregs), $CD8^+$ regulatory T cells ($CD8^+$Tregs), and cytotoxic T lymphocytes (CTLs) on melanoma recurrence and metastasis have not been explored.

In this study, we developed a novel index, the circulating T-cell immune index (CTII) that is based on $CD4^+CD25^+$regulatory T cells ($CD4^+$Tregs), $CD8^+CD28^-$ regulatory T cells ($CD8^+$Tregs), and $CD8^+CD28^+$cytotoxic T lymphocytes (CTLs). We found that the SII and CTII were promising independent predictive factors of prognosis of the patients with acral melanoma who had undergone adjuvant interferon therapy.

Materials and Methods

Patients

The study was approved by the medical ethics committee of Peking University Cancer Hospital & Institute. Written informed consent was obtained from all participants. We retrospectively reviewed the medical records of 226 patients with high-risk acral melanoma who visited Peking University Cancer Hospital between October, 2010, and October, 2016. All patients diagnosed with melanoma were confirmed histopathologically. All methods were performed in accordance with the relevant guidelines and regulations. To ensure that the whole blood parameters were representative of normal baseline values, none of the patients had lymphatic system disorders or malignant hematologic diseases. Furthermore, all of the patients were treatment-naïve.

Study Design

This was a retrospective, single-center study. Patients were divided into two groups according to IFN-α-2b dose. Cohort A (152 patients) received 4 weeks of intravenous induction therapy of IFN-α-2b (15×10^6 U/m^2/d, 5 days per week); Cohort B (74 patients) received 4 weeks of IFN-α-2b intravenous induction therapy (15×10^6 U/m^2/d, 5 days per week), followed by 48 weeks of subcutaneous maintenance therapy at a dose of 9×10^6 U, 3 times per week. The dosage was based on that used in a previous clinical trial [11] as well as on our own clinical experience in Chinese melanoma patients [10]. The dosage was lower than the standard high-dose IFN dosage applied in the Eastern Cooperative Oncology Group trial [21,22] but was more suitable for Chinese patients since they generally cannot tolerate the standard dosage owing to its toxicity.

The baseline parameters, including demographics, routine hematologic tests results, $CD4^+$Tregs, $CD8^+$Tregs, CTLs, liver function parameters, and clinical history, were all obtained. The following parameters were collected for analysis: age, sex, date of melanoma diagnosis and date of death or last follow-up, American Joint Committee on Cancer (AJCC) M stage, serum lactate dehydrogenase

Table 1. Baseline Characteristics of Acral Melanoma Patients

Variable	R F S (Months)	95% CI	*P* Value	O S (Months)	95% CI	*P* Value
Total	22.3	(16.3-28.3)		47.2	(34-60.4)	
Treatment						
4-week IFN-α-2b	16.5	(5.2-27.9)	.161	47.2	(31.1-63.3)	.731
1-year IFN-α-2b	25.4	(16.3-34.6)		55	(35.6-74.4)	
Gender						
Male	22.9	(10.1-35.8)	.569	51	(30.6-71.5)	.823
Female	20.8	(15.6-26.0)		44.8	(23.2-66.3)	
Age						
<50	21.4	(9.4-23.6)	.642	54.1	(34.8-70.4)	.575
≥50	19	(16.4-29.5)		42.2	(28.7-55.7)	
AJCC M stage						
II	25.8	(11.4-40.1)	<.001	62	(43.9-80.0)	<.001
III	11.9	(6.6-17.2)		28	(18.4-37.8)	
Serum LDH						
<ULN	22.6	(16.9-28.5)	<.001	54.1	(37.9-70.3)	.024
≥ULN	2.5	(2.4-2.6)		26.8	(20.4-33.1)	
Ulceration						
Without ulceration	22.3	(16.4-28.2)	.042	51	(37.2-64.9)	.037
With ulceration	4.3	(2-17.1)		28	(3.7-34.7)	
Lymphocyte cells count						
$<1.8\times10^{10}$	22.3	(16.5-28.1)	.918	55	(36.7-73.2)	.772
$\geq1.8\times10^{10}$	16.8	(10.7-21.3)		42.2	(28.2-55.7)	
Neutrophil cells count						
$<4\times10^9$	25	(17.9-32.1)	.213	51	(37.9-64.4)	.872
$\geq4\times10^9$	18.4	(11.3-25.5)		42.2	(26.4-57.9)	
NLR						
<2.35	30.2	(19.4-41.1)	.05	55	(40.8-69.2)	.047
≥2.35	15	(9.8-20.1)		39.4	(31.8-47)	
PLR						
<129	27.4	(19.4-35.3)	.002	62	(39.6-84.4)	.01
≥129	12	(8-16)		40.9	(30.2-51.5)	
SII						
$<615\times10^9$	30.2	(20.3-40.2)	.029	62	(41.1-82.9)	.006
$\geq615\times10^9$	14.8	(11.1-18.4)		34	(24.5-43.7)	
MLR						
<0.26	22.6	(13.7-31.7)	.365	54.1	(33.6-74.6)	.461
≥0.26	22.3	(13.9-30.7)		47.2	(31.3-63)	
PNI						
<54	18	(9-27)	.649	51	(36.8-65.2)	.759
≥54	23	(17.1-28.8)		47.2	(25.5-68.9)	
CD4+Tregs						
<6.5	22.9	(16.3-29.7)	.917	40	(33-47)	.263
≥6.5	18.4	(8.6-28.3)		55.2	(38.8-41.6)	
CD8+Tregs						
<21	17.9	(8.4-27.5)	.182	40	(35.5-44.5)	.221
≥21	25.4	(16.7-34.2)		55.2	(31.8-78.7)	
CTLs						
<11	17.9	(7.3-28.7)	.33	42.2	(28.6-55.8)	.414
≥11	22.9	(16.9-28.9)		54.1	(33.9-74.4)	
CTII						
<0.08	22.3	(17.1-27.5)	.848	68.4	(50-96.9)	.044
≥0.08	22.6	(10.1-35.2)		40	(37.1-42.9)	

ULN, upper limit of normal.

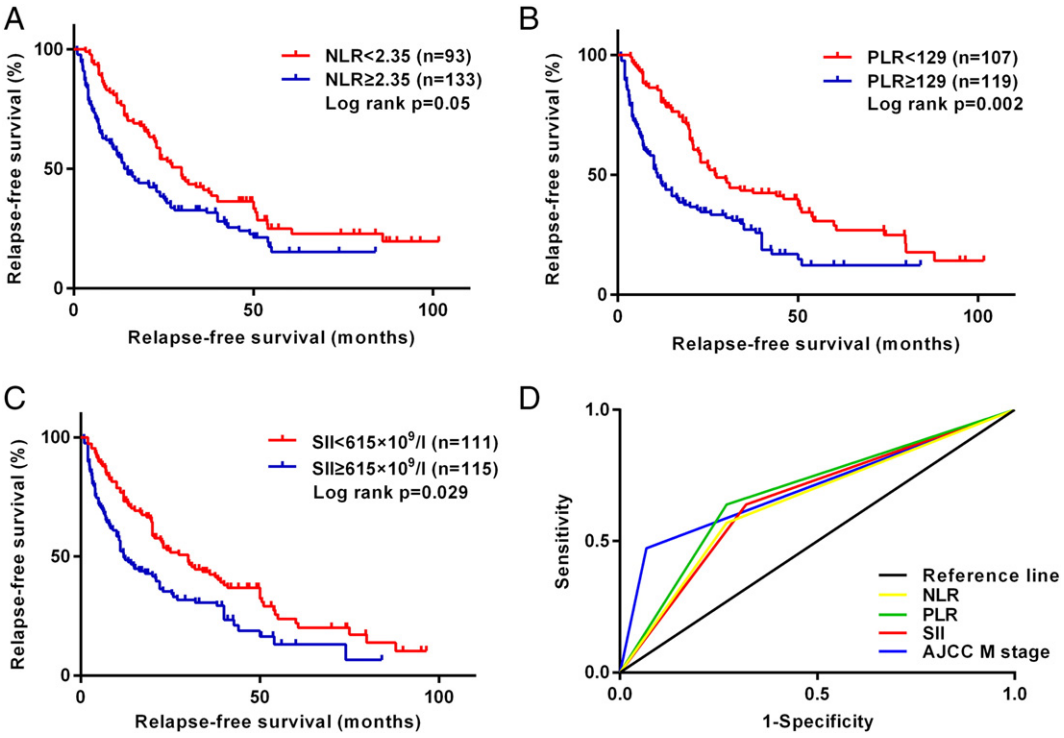

Figure 1. Kaplan-Meier survival curves for RFS according to inflammation-based scores in 226 patients with acral melanoma. (A) Ninety-three patients with NLR ≥2.35 had shorter median RFS than 133 patients with NLR <2.35 (15 vs 30.2 months, P=.005). (B) One hundred seven patients with PLR ≥129 had shorter median RFS than 119 patients with PLR <129 (12 vs 27.4 months, P=.002). (C) One hundred eleven patients with SII ≥615×10^9/l had shorter median RFS than 115 patients with SII <615×10^9/l (14.8 vs 30.2 months, P=.029). (D) ROC curves of NLR, PLR, SII, and AJCC M stage for RFS, with a median survival time of 22.3 months.

(LDH), ulceration, and clinical history. Parameters were collected from data on routine hematologic tests that were performed at the time of initial diagnosis and before the adjuvant high-dose interferon treatments. Six inflammatory factors (NLR, PLR, SII, MLR, PNI, and CTII) were included in this analysis. These inflammatory factors were calculated as follows: NLR = N/L; PLR = P/L; SII = $P \times N/L$; MLR=M/L; PNI = albumin + 5 × L, and CTII= CTLs/($CD4^+$Tregs × $CD8^+$Tregs), where N, L, M, and P are the peripheral neutrophil, lymphocyte, monocyte, and platelet counts, respectively.

Statistical Analysis

Two end points were analyzed: OS and relapse-free survival (RFS). OS was defined as the date of melanoma diagnosis to the time of death due to any cause or until October, 2016, for patients who remained alive (censored). RFS was calculated from the time of initial treatment until the time of disease relapse or death due to any cause, or until October, 2016, for patients who remained alive (censored).

Statistical evaluation was conducted with IBM SPSS statistical software (version 20.0). The t test was used to analyze mean values for normally distributed continuous variables, while the Mann-Whitney U test was used to compare mean values for abnormally distributed continuous variables. OS and RFS curves were estimated with the Kaplan-Meier method. Prognostic parameters associated with OS and RFS were assessed by both Cox univariate and multivariate analyses. Only possible prognostic factors associated with OS and RFS were subjected to Cox multivariable analysis. The R software was used to determine the cutoff values of the parameters associated with OS and RFS. The results are presented as hazard ratio (HR) with 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was used to evaluate predictive values of potential parameters for acral melanoma prognosis. For all statistical tests, P<.05 (two-tailed test) was considered statistically significant.

Results

Patient Characteristics

A total of 226 patients with acral melanoma were enrolled in this study; 152 patients received the 4-week regimen, and 74 patients received the 1-year regimen. The median RFS and OS rates were 22.3 and 47.2 months, respectively. Patient characteristics are summarized in Table 1.

There was no significant difference in OS and RFS rates between treatment arms. Therefore, all patients were subjected to prognostic factor analysis, regardless of their treatment arm.

Association of NLR, PLR, SII, MLR, PNI, and CTII with RFS and OS

We used the R software to determine the cutoff values of lymphocyte cells count, neutrophil cells count, NLR, PLR, SII, MLR, PNI, and CTII for the prediction of RFS and OS based on the data of the 226 melanoma patients. We transformed the continuous data to dichotomous data by employing cutoff values. On univariate Cox analyses, the NLR, PLR, SII, LDH, ulceration, and AJCC M stage were significantly associated with the RFS and OS of patients with acral melanoma (Figures 1 and 2). The CTII was only associated with the OS of patients with acral melanoma (P=.044). The results of the univariate analyses are shown in Table 2.

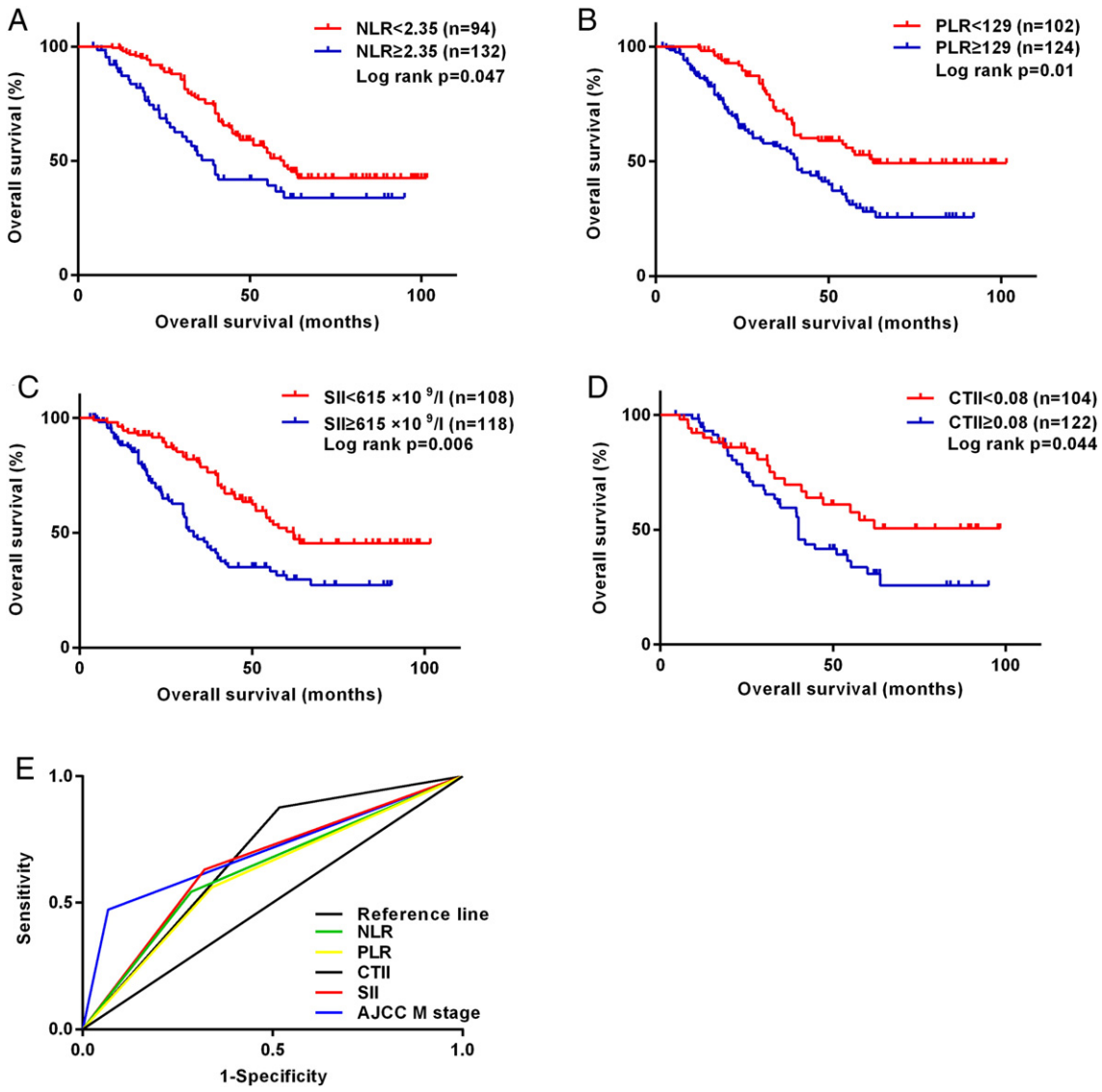

Figure 2. Kaplan-Meier survival curves for OS according to inflammation-based scores in 226 patients with acral melanoma. (A) Ninety-four patients with NLR ≥2.35 had shorter median OS than 132 patients with NLR <2.35 (39.4 vs 55 months, P=.047). (B) One hundred two patients with PLR ≥129 had shorter median OS than 124 patients with PLR <129 (40.9 vs 62 months, P=.01). (C) One hundred eight patients with SII ≥615×10^9/l had shorter median OS than 118 patients with SII <615×10^9/l (34 vs 62 months, P=.006). (D) One hundred four patients with CTII ≥0.08 had shorter median OS than 122 patients with CTII <0.08 (40 vs 68.4 months, P=.044). (E) ROC curves of NLR, PLR, SII, CTII, and AJCC M stage for OS, with a median survival time of 47.2 months.

Factors found significant on univariate analysis were subjected to multivariate Cox proportional hazards analysis. As shown in Table 3, only SII was significantly associated with RFS (HR=1.661, 95% CI=1.066-2.586, P=.025) and OS (HR=2.071, 95% CI=1.204-3.564, P=.009). Moreover, a higher AJCC M stage was a strong prognostic factor of RFS (HR=2.848, 95% CI=1.772-4.576, P<.001) and OS (HR=3.699, 95% CI=2.128-6.431, P<.001) in patients with acral melanoma.

Prognostic Influences of NLR, PLR, SII, and CTII on RFS and OS

We performed ROC analysis to evaluate the accuracy of SII in predicting RFS and OS in patients with acral melanoma. We found that elevated NLR, PLR, and SII predict RFS (area under the curve=0.565, 0.7, and 0.66, respectively; all P<.05). Moreover, elevated NLR, PLR, SII, and CTII values were associated with poor OS (area under the curve=0.629, 0.611, 0.655, and 0.68, respectively; all P<.05). We also performed Spearman's chi-square analysis to test the prognostic values of NLR, PLR, SII, and CTII for RFS and OS in patients with acral melanoma; the data are shown in Tables 4 and 5.

Comparison of SII and CTII in Different Acral Melanoma Subgroups

As AJCC M stage and tumor recurrence were significantly associated with prognosis in patients with acral melanoma, we compared SII and CTII in different patient subgroups that were created based on the clinicopathological features (Figure 3). We found that the SII and CTII in stage III patients as well as those who experienced recurrence were higher than stage II patients and those without recurrence (all P<.05). This indicated that SII and CTII may predict melanoma invasiveness and metastatic potential.

Table 2. Association between Blood Routine Tests Parameters and RFS and OS of Acral Melanoma Patients in Univariate Cox Regression Analyses

	RFS		OS	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
NLR, per increase of 1 unit	1.83 (0.81-4.13)	.05	1.81 (0.69-4.76)	.047
PLR, per increase of 1 unit	1.18 (0.64-2.17)	.002	0.97 (0.46-2.02)	.01
SII, per increase of 1 unit	2.3 (1.02-5.21)	.029	3.7 (1.38-9.88)	.006
AJCC M stage, stage II vs stage III	2.59 (1.5-4.47)	<.001	3.78 (1.95-7.32)	<.001
Serum LDH, <ULN vs ≥ULN	2.33 (0.52-3.37)	<.001	2.96 (0.33-3.79)	.024
Ulceration, without ulceration vs with ulceration	1.04 (0.35-2.8)	.022	1.37 (0.03-3.21)	.017
CTII, per increase of 1 unit	1.41 (0.74-3.67)	.848	1.73 (1.01-2.94)	.044

Discussion

We investigated potential prognostic biomarkers of IFN-α-2b therapy in Asian patients with acral melanoma to evaluate the clinical benefit of the therapy on OS and RFS. Several clinical trials have indicated that the median RFS ranged from 20.4 to 30 months for high-risk melanoma [22,23]. Congruent with these studies, in the present study, the median RFS in acral melanoma patients treated with high-dose interferon was similar to the lower limit of the RFS range in Caucasian population [10], which partly confirms that acral melanoma subtype is associated with significantly inferior prognosis, as previously suggested [24]. Such prognostic differences might arise because of the variations in the genetics, pathogenesis, and immune microenvironment between different ethnic populations [15,25–29].

Several studies have shown that pretreatment NLR, neutrophil counts, and lymphocyte counts in patients with melanoma are valid prognosticators [15,16]. SII, which is based on lymphocyte, neutrophil, and platelet counts, has not been investigated extensively in melanoma patients; we are the first to verify its role in predicting RFS and OS in such patients. The SII prediction value was shown to be higher than that of the NLR, PLR, and other conventional parameters such as serum LDH and ulceration. Moreover, the SII value is based on measures that are easily obtained during routine laboratory tests in clinical practice. Therefore, the SII ought to be a simple, low-cost, and effective biomarker that may assist in the surveillance of patients most likely to relapse or to benefit from adjuvant interferon therapy. This might also contribute to early and accurate decision-making concerning the most effective treatment strategy.

Recent evidence indicates that infiltrating immune system cells present in the tumor microenvironment synergistically promote tumor progression. Tumor-promoting immune cells include macrophages, platelets, neutrophils, and T and B lymphocytes, which produce an attractive tumor microenvironment for tumor growth, metastasis, and facilitate angiogenesis [13,30–33]. Furthermore, some studies showed that immune cells facilitate tumor progression by releasing a series of molecules, such as the proangiogenic vascular endothelial growth factor, the proinvasive matrix degrading enzyme matrix metalloproteinase-9, and other cytokines [32,34]. Meanwhile, activated T cells and other lymphocytes demonstrate potent antitumor effects [35]. The balance between these opposing immune inflammatory responses in tumors is likely to be crucial for accurate prognosis as well as for determining appropriate antitumor treatments [12]. A better understanding of the role of infiltrating immune system cells ought to help clarify the association between cancer, immunity, and inflammation [17].

In our study, Cox univariate and multivariate analyses indicated that the SII was significantly associated with the outcome of melanoma. The CTII was also shown to be a predictive factor for OS. Additionally, we found that elevated SII and CTII values were associated with tumor vascular invasion and recurrence, indicating a more aggressive phenotype [36,37]. A recent study indicated that increased absolute lymphocyte counts concordant with delayed increases in $CD4^+$ and $CD8^+$ T cells are associated with positive outcome in advanced melanoma patients treated with ipilimumab [18]. Patients with metastatic melanoma and a high baseline NLR also appeared to benefit from immunotherapy with agents such as ipilimumab [16]. Therefore, the appropriate predictive biomarkers may help select the appropriate therapies (or sequences). Such predictive biomarkers may also serve to expedite decisions on whether to continue a particular therapy or switch to alternative options.

The limitations of this research include its retrospective nature and small sample size, which could produce selection biases. Moreover, NLR, PLR, SII, and CTII were not of powerful prognostic values in terms of outcome of melanoma patients. A recent study indicated that the underlying mechanism through which elevated SII is associated with poorer a prognosis is an increase in the dissemination of tumor cells into the circulation, allowing such cells to escape immune surveillance and increase peripheral circulating tumor cell levels [17]. Therefore, we hypothesized that additional biomarkers such as circulating tumor cell levels could be combined with SII and CTII in order to improve the prognostic accuracy. Measuring changes in specific immune-related parameters during therapy can improve the real-time assessment of the drug's benefit. Martens et al. found that increases in absolute lymphocyte counts observed 2 to 8 weeks after ipilimumab initiation, combined with delayed increases in CD4+ and CD8+ T cell levels, are indicators of positive outcome in metastatic melanoma patients [18]. Thus, further prospective, well-designed

Table 3. Association between Blood Routine Tests Data and RFS and OS of Acral Melanoma Patients in Multivariate Cox Regression Analyses

Variable	Category	RFS		OS	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
SII	<615 vs ≥615	1.661 (1.066-2.586)	.025	2.071(1.204-3.564)	.009
AJCC M stage	stage II vs stage III	2.848 (1.772-4.576)	<.001	3.699(2.128-6.431)	<.001

Table 4. Predictive Value of NLR, PLR, and SII for RFS of Acral Melanoma Patients

Indexes	Cutoff	AUC (95%CI)	Sensitivity	Specificity	Accuracy	*P*
NLR	2.35	0.565 (0.55-0.76)	0.57	0.74	65.5	.005
PLR	129	0.7 (0.59-0.79)	0.64	0.74	69	<.001
SII	615	0.66 (0.56-0.76)	0.64	0.68	66.4	<.001

AUC, area under curve.

Table 5. Predictive value of NLR, PLR, SII and CTII for OS of acral melanoma patients

Indexes	Cut-off	AUC(95%CI)	Sensitivity	Specificity	Accuracy	P
NLR	2.35	0.629(0.526-0.732)	0.544	0.714	62.8	0.018
PLR	129	0.611(0.507-0.715)	0.561	0.661	61.1	0.042
SII	615	0.655(0.553-0.757)	0.632	0.679	65.5	0.004
CTII	0.08	0.68(0.58-0.78)	0.877	0.482	63.7	<0.001

NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; SII: systemic immune-inflammation index; AUC: area under curve; CI: confidence interval; CTII: circulating T cell immune index.

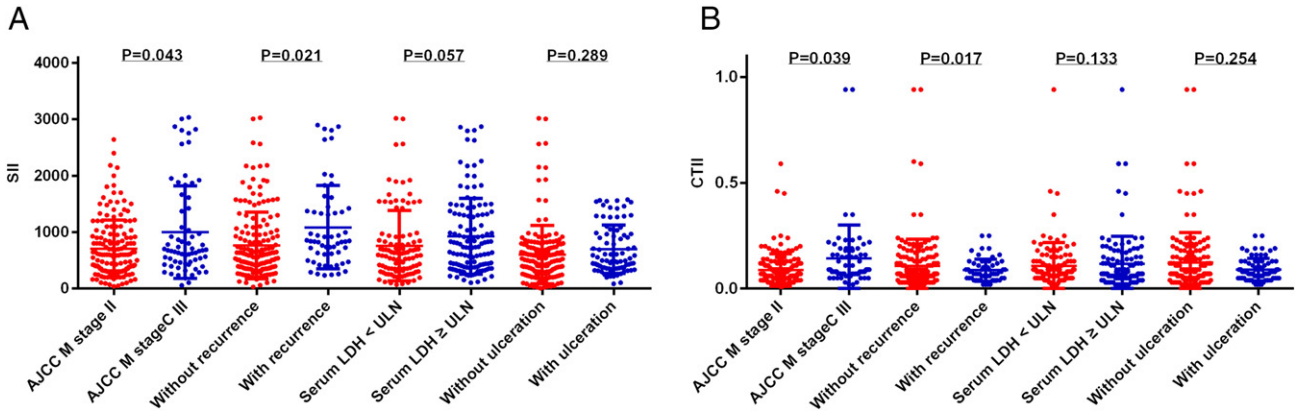

Figure 3. Comparisons of SII (A) and CTII (B) in different subgroups of acral melanoma patients, including AJCC M stage, recurrence, serum LDH, and ulceration.

studies with larger populations focused on changes in SII and CTII during therapy are warranted.

In conclusion, our study is the first to demonstrate the prognostic significance of the SII and CTII in high-risk acral melanoma patients treated with adjuvant IFN-α-2b. Both SII and CTII are easily assessable in clinical practice. Additional studies are required to clarify the mechanisms behind the association between elevated SII and CTII and poorer prognosis in melanoma patients.

Conflict of Interest

None.

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References

[1] Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, and Ding S, et al (2009). Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* **27**, 6199–6206. http://dx.doi.org/10.1200/jco.2009.23.4799.

[2] Tarhini AA and Kirkwood JM (2009). Clinical and immunologic basis of interferon therapy in melanoma. *Ann N Y Acad Sci* **1182**, 47–57. http://dx.doi.org/10.1111/j.1749-6632.2009.05073.x.

[3] Cormier JN, Xing Y, Ding M, Lee JE, Mansfield PF, Gershenwald JE, Ross MI, and Du XL (2006). Ethnic differences among patients with cutaneous melanoma. *Arch Intern Med* **166**, 1907–1914. http://dx.doi.org/10.1001/archinte.166.17.1907.

[4] Bellows CF, Belafsky P, Fortgang IS, and Beech DJ (2001). Melanoma in African-Americans: trends in biological behavior and clinical characteristics over two decades. *J Surg Oncol* **78**, 10–16.

[5] Matsumoto T, Shibata S, Yasue S, Sakakibara A, Yokota K, Sawada M, Kono M, Kato K, Shimoyama Y, and Tomita Y, et al (2010). Interval sentinel lymph nodes in patients with cutaneous melanoma: a single-institution study in Japan. *J Dermatol* **37**, 629–634. http://dx.doi.org/10.1111/j.1346-8138.2010.00856.x.

[6] Roh MR, Kim J, and Chung KY (2010). Treatment and outcomes of melanoma in acral location in Korean patients. *Yonsei Med J* **51**, 562–568. http://dx.doi.org/10.3349/ymj.2010.51.4.562.

[7] Rex J, Paradelo C, Mangas C, Hilari JM, Fernandez-Figueras MT, and Ferrandiz C (2009). Management of primary cutaneous melanoma of the hands and feet: a clinicoprognostic study. *Dermatol Surg* **35**, 1505–1513. http://dx.doi.org/10.1111/j.1524-4725.2009.01265.x.

[8] Chi Z, Li S, Sheng X, Si L, Cui C, Han M, and Guo J (2011). Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases. *BMC Cancer* **11**, 85. http://dx.doi.org/10.1186/1471-2407-11-85.

[9] Mocellin S, Pasquali S, Rossi CR, and Nitti D (2010). Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. *J Natl Cancer Inst* **102**, 493–501. http://dx.doi.org/10.1093/jnci/djq009.

[10] Mao L, Si L, Chi Z, Cui C, Sheng X, Li S, Tang B, and Guo J (2011). A randomised phase II trial of 1 month versus 1 year of adjuvant high-dose interferon alpha-2b in high-risk acral melanoma patients. *Eur J Cancer* **47**, 1498–1503. http://dx.doi.org/10.1016/j.ejca.2011.03.019.

[11] Pectasides D, Dafni U, Bafaloukos D, Skarlos D, Polyzos A, Tsoutsos D, Kalofonos H, Fountzilas G, Panagiotou P, and Kokkalis G, et al (2009). Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. *J Clin Oncol* **27**, 939–944. http://dx.doi.org/10.1200/jco.2008.16.3121.

[12] Hanahan D and Weinberg RA (2011). Hallmarks of cancer: the next generation. *Cell* **144**, 646–674. http://dx.doi.org/10.1016/j.cell.2011.02.013.

[13] DeNardo DG, Andreu P, and Coussens LM (2010). Interactions between lymphocytes and myeloid cells regulate pro- versus anti-tumor immunity. *Cancer Metastasis Rev* **29**, 309–316. http://dx.doi.org/10.1007/s10555-010-9223-6.

[14] de Visser KE, Eichten A, and Coussens LM (2006). Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* **6**, 24–37. http://dx.doi.org/10.1038/nrc1782.

[15] Schmidt H, Suciu S, Punt CJ, Gore M, Kruit W, Patel P, Lienard D, von der Maase H, Eggermont AM, and Keilholz U, et al (2007). Pretreatment levels of peripheral neutrophils and leukocytes as independent predictors of overall survival in patients with American Joint Committee on Cancer Stage IV Melanoma: results of the EORTC 18951 Biochemotherapy Trial. *J Clin Oncol* **25**, 1562–1569. http://dx.doi.org/10.1200/jco.2006.09.0274.

[16] Ferrucci PF, Gandini S, Battaglia A, Alfieri S, Di Giacomo AM, Giannarelli D, Cappellini GC, De Galitiis F, Marchetti P, and Amato G, et al (2015). Baseline neutrophil-to-lymphocyte ratio is associated with outcome of ipilimumab-treated metastatic melanoma patients. *Br J Cancer* **112**, 1904–1910. http://dx.doi.org/10.1038/bjc.2015.180.

[17] Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, and Zhou J, et al (2014). Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res* **20**, 6212–6222. http://dx.doi.org/10.1158/1078-0432.ccr-14-0442.

[18] Martens A, Wistuba-Hamprecht K, Yuan J, Postow MA, Wong P, Capone M, Madonna G, Khammari A, Schilling B, and Sucker A, et al (2016). Increases in absolute lymphocytes and circulating CD4+ and CD8+ T cells are associated with positive clinical outcome of melanoma patients treated with ipilimumab. *Clin Cancer Res* **22**, 4848–4858. http://dx.doi.org/10.1158/1078-0432.ccr-16-0249.

[19] Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, and Clarke SJ (2013). The systemic inflammation-based neutrophil-lymphocyte ratio: experience

in patients with cancer. *Crit Rev Oncol Hematol* **88**, 218–230. http://dx.doi.org/10.1016/j.critrevonc.2013.03.010.

[20] Lolli C, Basso U, Derosa L, Scarpi E, Sava T, Santoni M, Crabb SJ, Massari F, Aieta M, and Conteduca V, et al (2016). Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. *Oncotarget*. http://dx.doi.org/10.18632/oncotarget.10515.

[21] Kirkwood JM, Ibrahim J, Lawson DH, Atkins MB, Agarwala SS, Collins K, Mascari R, Morrissey DM, and Chapman PB (2001). *High-dose interferon alfa-2b does not diminish antibody response to GM2 vaccination in patients with resected melanoma: results of the Multicenter Eastern Cooperative Oncology Group Phase II Trial E2696. J Clin Oncol* **19**, 1430–1436. http://dx.doi.org/10.1200/jco.2001.19.5.1430.

[22] Kirkwood JM, Ibrahim JG, Sosman JA, Sondak VK, Agarwala SS, Ernstoff MS, and Rao U (2001). *High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol* **19**, 2370–2380. http://dx.doi.org/10.1200/jco.2001.19.9.2370.

[23] Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, Smith TJ, Rao U, Steele M, and Blum RH, et al (2000). *High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol* **18**, 2444–2458. http://dx.doi.org/10.1200/jco.2000.18.12.2444.

[24] Bradford PT, Goldstein AM, McMaster ML, and Tucker MA (2009). *Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol* **145**, 427–434. http://dx.doi.org/10.1001/archdermatol.2008.609.

[25] Schmidt H, Bastholt L, Geertsen P, Christensen IJ, Larsen S, Gehl J, and von der Maase H (2005). *Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic model. Br J Cancer* **93**, 273–278. http://dx.doi.org/10.1038/sj.bjc.6602702.

[26] Hanahan D and Weinberg RA (2000). *The hallmarks of cancer. Cell* **100**, 57–70.

[27] Coussens LM and Werb Z (2002). *Inflammation and cancer. Nature* **420**, 860–867. http://dx.doi.org/10.1038/nature01322.

[28] Balkwill F and Mantovani A (2001). *Inflammation and cancer: back to Virchow? Lancet* **357**, 539–545. http://dx.doi.org/10.1016/s0140-6736(00)04046-0.

[29] Furney SJ, Turajlic S, Stamp G, Thomas JM, Hayes A, Strauss D, Gavrielides M, Xing W, Gore M, and Larkin J, et al (2014). *The mutational burden of acral melanoma revealed by whole-genome sequencing and comparative analysis. Pigment Cell Melanoma Res* **27**, 835–838. http://dx.doi.org/10.1111/pcmr.12279.

[30] Coffelt SB, Lewis CE, Naldini L, Brown JM, Ferrara N, and De Palma M (2010). *Elusive identities and overlapping phenotypes of proangiogenic myeloid cells in tumors. Am J Pathol* **176**, 1564–1576. http://dx.doi.org/10.2353/ajpath.2010.090786.

[31] Johansson M, Denardo DG, and Coussens LM (2008). *Polarized immune responses differentially regulate cancer development. Immunol Rev* **222**, 145–154. http://dx.doi.org/10.1111/j.1600-065X.2008.00600.x.

[32] Murdoch C, Muthana M, Coffelt SB, and Lewis CE (2008). *The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer* **8**, 618–631. http://dx.doi.org/10.1038/nrc2444.

[33] De Palma M, Murdoch C, Venneri MA, Naldini L, and Lewis CE (2007). *Tie2-expressing monocytes: regulation of tumor angiogenesis and therapeutic implications. Trends Immunol* **28**, 519–524. http://dx.doi.org/10.1016/j.it.2007.09.004.

[34] Qian BZ and Pollard JW (2010). *Macrophage diversity enhances tumor progression and metastasis. Cell.* **141**, 39–51. http://dx.doi.org/10.1016/j.cell.2010.03.014.

[35] Mantovani A, Allavena P, Sica A, and Balkwill F (2008). *Cancer-related inflammation. Nature* **454**, 436–444. http://dx.doi.org/10.1038/nature07205.

[36] Chaffer CL and Weinberg RA (2011). *A perspective on cancer cell metastasis. Science* **331**, 1559–1564. http://dx.doi.org/10.1126/science.1203543.

[37] Schreiber RD, Old LJ, and Smyth MJ (2011). *Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science* **331**, 1565–1570. http://dx.doi.org/10.1126/science.1203486.