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) ≥615 × 10⁹/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.

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 IIE 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 IIC 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-naive.

**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 | 95% CI | P Value | O S | 95% CI | P Value |
|-------------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Total | 22.3 | (16.3-28.3) | 47.2 | (34-60.4) |
| Treatment | 16.5 | (5.2-27.9) | .161 | (47.2) | (31-63.3) | .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) |
| 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) |
| PLR | Without ulceration | 22.3 | (16.4-28.2) | .042 | 51 | (37.2-64.9) | .037 |
| With ulceration | 4.3 | (2-17.1) | 28 | (5.3-34.7) |
| Neutrophil count | <1×10^9 | 22.3 | (16.5-28.1) | .918 | 55 | (36.7-73.2) | .772 |
| ≥1×10^9 | 16.8 | (10.7-21.3) | 42.2 | (28.2-55.7) |
| Neutrophils | <4×10^9 | 25 | (17.9-32.1) | .213 | 51 | (37.9-64.4) | .872 |
| ≥4×10^9 | 18.4 | (11.3-35.5) | 42.2 | (26.4-57.9) |
| MLR | <2.5 | 30.2 | (19.4-41.1) | .05 | 55 | (40.8-69.2) | .047 |
| ≥2.5 | 15 | (9.8-20.1) | 39.4 | (31.8-47) |
| CTII | <129 | 27.4 | (19.4-35.3) | .002 | 62 | (39.6-84.4) | .01 |
| ≥129 | 12 | (8.16) | 40.9 | (30.2-51.5) |
| PNI | <54 | 30.2 | (20.3-40.2) | .029 | 62 | (41.1-82.9) | .006 |
| ≥54 | 14.8 | (11.1-18.4) | 34 | (24.5-43.7) |
| CD4+ Tregs | <6.5 | 22.6 | (13.7-31.7) | .365 | 54.1 | (33.6-74.6) | .461 |
| ≥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 | (50.96-79.9) | .044 |
| ≥0.08 | 22.6 | (10.1-35.2) | 40 | (37.1-42.9) |

*ULN, upper limit of normal.*
(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 × 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.
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, \(P=0.025\)) and OS (HR=2.071, 95% CI=1.204-3.564, \(P=0.009\)). Moreover, a higher AJCC M stage was a strong prognostic factor of RFS (HR=2.848, 95% CI=1.772-4.576, \(P<0.001\)) and OS (HR=3.699, 95% CI=2.128-6.431, \(P<0.001\)) 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 \(P<0.05\)). 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 \(P<0.05\)). 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 \(P<0.05\)). This indicated that SII and CTII may predict melanoma invasiveness and metastatic potential.
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 2. Association between Blood Routine Tests Parameters and RFS and OS of Acral Melanoma Patients in Univariate Cox Regression Analyses

| Variable         | RFS (95% CI) | P Value | OS (95% CI) | P Value |
|------------------|--------------|---------|-------------|---------|
| NLR, per increase of 1 unit | 1.83 (0.81-4.13) | .05 | 1.81 (0.69-4.76) | .47 |
| 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 (0.83-3.79) | .024 |
| Uceteration, 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 |

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

| Variable         | RFS (95% CI) | P Value | OS (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 | 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 | 0.61 (0.507-0.715) | 0.561 | 0.661 | 61.1 | 0.042 |
| SII | 615 | 0.655 (0.533-0.757) | 0.632 | 0.679 | 65.5 | 0.004 |
| CTII | 0.08 | 0.68 (0.58-0.78) | 0.877 | 0.482 | 63.7 | <.001 |

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 | 0.61 (0.507-0.715) | 0.561 | 0.661 | 61.1 | 0.042 |
| SII | 615 | 0.655 (0.533-0.757) | 0.632 | 0.679 | 65.5 | 0.004 |
| CTII | 0.08 | 0.68 (0.58-0.78) | 0.877 | 0.482 | 63.7 | <.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.
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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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.
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