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Research Article

Higher Systemic Immune-Inflammation Index (SII) Levels Are Associated With Poorer Survival In Immunotherapy-Treated Melanoma Patients

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Abstract

Objectives: Peripheral blood-based markers like the systemic inflammation index is (SII) could be valuable for melanoma patients treated with immune checkpoint inhibitors (ICIs), although the data is limited. We aimed to evaluate the association between the baseline SII with survival in ICI-treated melanoma patients.

Methods: The data of 44 advanced adult melanoma patients treated with ICIs (ipilimumab or nivolumab) were retrospectively evaluated. The SII was calculated with the platelet*(neutrophil/lymphocyte) formula. The median value of SII as the cut-off point. The association between SII values and survival were evaluated with univariate and multivariate analyses.

Results: The median age was 61 years (IQR 51-68), and 52.3% of the patients were male. During a median follow-up of 7.52 months, 35 patients died (79.5%), and 39 patients (88.6%) had any PFS event. The patients with higher SII values had decreased overall survival (OS) (11.203±2.491 vs. 5.520±2.063 months, p=0.015). In the multivariate analyses, including adjustments according to patient sex, age, and lactate dehydrogenase levels, patients with higher SII values had decreased OS (HR: 2.209, 95% CI: 1.105-4.417, p=0.025).

Conclusion: In our experience, melanoma patients with higher SII values had poorer survival. The SII could be a valuable biomarker for prognosis estimation in ICI-treated melanoma patients.

Keywords: Immunotherapy, melanoma, SII

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Immune checkpoint inhibitors (ICIs) dramatically changed cancer management in the last decade.[1] Melanoma was the first tumor in which a survival advantage was demonstrated with the ICIs.[2] First, the ipilimumab[2] and after nivolumab[3] and pembrolizumab demonstrated improved survivals in the advanced melanoma treatment.[4] Although the ICIs' value is undisputable for melanoma patients, many patients still do not respond to treatment.[5] Besides, toxicities, including class-specific immune-related adverse events and financial toxicity, are important concerns limiting their use.[6, 7] These issues point out the necessity of patient selection with the aid of biomarkers.

Despite the striking velocity of developments in the treatment field, the biomarker research could not catch up, leading to suboptimal outcomes and limited ICI use, especially in the low-resource settings.[8] Other than the programmed death-ligand 1 (PD-L1) expression in tumor tissue for immunotherapy monotherapy for first-line treatment of ad-

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vanced-stage non-small cell lung cancer,[9] and high tumor mutational burden (TMB) and microsatellite instability status in all solid tumor in a tumor agnostic manner,[10] there are no validated biomarkers used in the clinical practice. Additionally, there are no validated biomarkers for ICI use in melanoma patients with limited PD-L1 or TMB based patient selection.[11, 12]

The problems with the tissue-based biomarkers directed the researchers to work on the peripheral blood-based biomarkers, and these simple markers have gained a lot of interest.[13, 14] Among these markers, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are readily available and inexpensive candidate biomarkers. The increased levels of NLR and PLR were reported to be associated with decreased progression-free survival (PFS), and overall survival (OS) in ICI-treated patients.[15, 16] The systemic inflammation index is (SII) could serve in the same manner,[17] although it was not thoroughly investigated in the ICI-treated melanoma patients. From this point, we aimed to evaluate the association between the baseline SII levels with survival outcomes in ICI-treated melanoma patients in our clinic.

Methods

For this single-center study, the data of advanced adult melanoma patients treated with ICIs (ipilimumab or nivolumab) in Hacettepe University Cancer Institute between 09/2014 and 06/2019 were retrospectively evaluated. All patients treated in the prespecified dates were included in the analyses other than patients treated in the context of expanded access programs or clinical trials. Baseline demographics, anthropometric measures (length, height, and body mass index), the site of metastases, baseline lactate dehydrogenase (LDH) levels, regularly used drugs, type of immunotherapy, and best response to immunotherapy were recorded together with survival data. The SII was calculated with the platelet*(neutrophil/lymphocyte) formula as previously proposed in the literature.[17] The NLR was calculated by dividing the neutrophil values into lymphocyte values. The median value of SII and NLR was used as the cut-off points. Patients were dichotomously categorized into the SII low or high groups according to the cut-off.

Descriptive statistics were presented as the median, interquartile range (IQR; 25th-75th percentile), and standard errors for continuous variables and frequency and percentages for categorical variables. The overall survival (OS) time was defined as the period from treatment initiation to the last follow-up and/or death, and progression-free survival (PFS) time was defined as the period between treatment initiation to disease progression and/or death. The univariable analyses for the association of clinical factors with the PFS and OS were analyzed with Kaplan-Meier analyses. A multivariate analysis model was constructed with adjustments according to age, sex, baseline liver metastasis and additional clinical parameters with a significant difference between SII high and low groups. All statistical analyses were performed in SPSS, version 25.0 (IBM Inc., Armonk, NY, USA). P-values below 0.05 were considered statistically significant.

Results

A total of 44 patients were included in the analyses. The cohort's median age was 61 years (IQR 51-68), and 52.3% of the patients were male (23/44). The LDH levels were in the normal range in 62.8%, and the liver metastasis was present in 45.5% of the patients. The study cohort was a rather overweight cohort with a median BMI of 29.39 (IQR 23.91-33.19). The median value for SII was calculated as 924. The baseline characteristics of SII high and low cases were largely similar (Table 1). The median NLR value was 3.21.

Table 1. Baseline Characteristics of the Study Cohort According to SII Values

	SII Low (n=22)	SII High (n=22)	p
Age, median (IQR)	58 (47-65)	64 (54-71)	0.035
IT dose, median (IQR)	4 (3-15)	4 (3-8)	>0.99
Sex			
Female	10 (45.5%)	11 (50%)	0.763
Male	12 (54.5%)	11 (50%)	
BMI Category			
<30	14 (63.6%)	12 (54.5%)	0.540
>30	8 (36.4%)	10 (45.5%)	
IT Type			
Ipilimumab	10 (45.5%)	10 (45.5%)	>0.99
Nivolumab	12 (54.5%)	12 (54.5%)	
Liver Metastasis			
Absent	10 (45.5%)	14 (63.6%)	0.226
Present	12 (54.5%)	8 (36.4%)	
LDH Levels			
Normal	18 (81.8%)	9 (42.9%)	0.008
>ULN	4 (18.2%)	12 (57.1%)	
Polipharmacy			
Absent	21 (95.5%)	21 (95.5%)	>0.99
Present	1 (4.5%)	1 (4.5%)	
IT line			
1st line	4 (18.2%)	4 (18.2%)	>0.99
2nd or later lines	18 (81.8%)	18 (81.8%)	

*IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index; IT: immunotherapy; ULN: upper limit of normal; LDH: lactate dehydrogenase.

During a median follow-up was 7.52 (IQR 4.12-14.13) months, 35 patients died (79.5%), and 39 patients (88.6%) had any PFS event. The patients with higher SII values had decreased overall survival (11.203±2.491 vs. 5.520±2.063 months, p=0.015), while the association with SII and PFS did not reach statistical significance (3.450±0.828 vs. 2.694±0.327, p=0.140) (Figs. 1 and 2). The association between OS and other clinical factors; namely, liver metastasis (p=0.243), BMI category (<30 vs. >30 kg/m^2, p=0.290), LDH levels (normal vs. >ULN, p=0.471), NLR category (<3.21 vs. >3.21, p=0.053), and patient sex (p=0.247) did not reach to statistical significance. The PFS analyses were consistent with OS analyses. In the multivariate analyses, including adjustments according to patient sex, age, baseline liver metastasis and LDH levels, patients with higher SII values had decreased OS (HR: 2.209, 95% CI: 1.105-4.417, p=0.025) (Table 2).

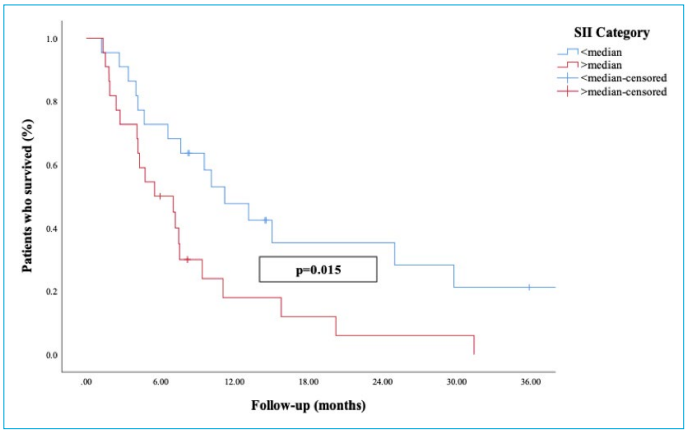

Figure 1. The Association Between SII Category and Overall Survival.

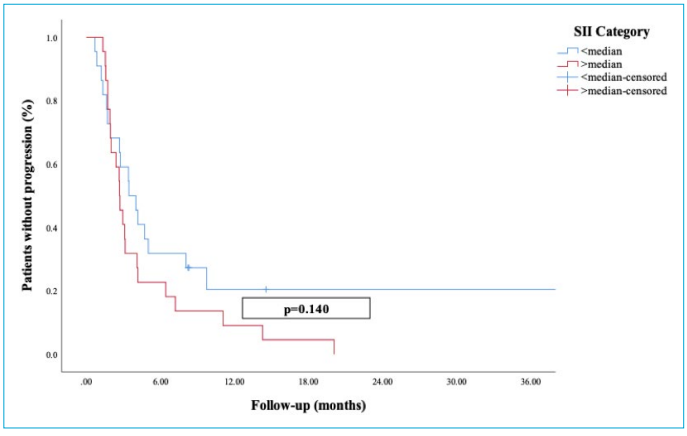

Figure 2. The Association Between SII Category and Progression-Free Survival.

Discussion

In this study, we demonstrated significantly decreased overall survival in ICI-treated melanoma patients with higher SII levels independent of age, sex, and LDH levels in a study cohort consisting of mainly second-line patients. To our knowledge, this study is the first report evaluating the SII as a prognostic biomarker in ICI-treated melanoma patients. Our findings support the further testing of SII in larger datasets and prospective cohorts.

Uncontrolled inflammation is a well-known factor for both cancer development and progression.[18] The platelets[19] and neutrophils[20] are among the main drivers of inflammation in the tumor microenvironment, while the lymphocytes are mainly acting against the cancer development as main effector cells of anti-tumor immunity.[21] So, SII has a strong rationale and could reflect the immune-inflammatory status of the tumor vicinity.

The SII was first developed and validated tested in hepatocellular carcinoma patients who underwent curative resection. In this pioneering study on 256 patients, the SII performed better than survival and recurrence than traditional clinical factors.[17] Later, a study in 916 esophageal squamous cell carcinoma patients demonstrated decreased OS in patients with higher SII scores, and similar to the previous study, SII outperformed other additional indexes in the receptor-operating curve (ROC) analyses.[22] Due to a low number of cases, we did not perform ROC curve comparisons in our study.

Yu and colleagues reported the first study with SII in mela-

Table2. The Results of Multivariate Analyses

	Progression-Free Survival		Overall Survival	
Clinical Factor	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
SII Category (>924 vs. <925)	1.571 (0.824-2.993)	0.170	2.209 (1.105-4.417)	0.025
LDH Levels (normal vs. >ULN)	0.795 (0.366-1.724)	0.561	0.908 (0.391-2.108)	0.822
Sex	1.529 (0.799-2.924)	0.199	1.540 (0.774-3.064)	0.219
Age (<65 vs. >65)	0.665 (0.303-1.458)	0.308	0.721 (0.342-1.520)	0.390
Liver Metastasis (absent vs. present)	0.749 (0.383-1.467)	0.400	0.725 (0.346-1.517)	0.393

*LDH: lactat dehydrogenase; ULN: upper limit of normal.

noma patients in a cohort treated with high-dose interferon. In the study on 226 acral melanoma patients, patients with SII values ≥615 × 109/L had decreased PFS (HR=1.661, p=0.025) and OS (HR=2.071, p=0.009) [23]. While there is a significant body of evidence in patients treated with surgery or chemotherapy, the data on the association of SII and survival is very limited in patients treated with ICIs. In a recent study by Liu et al. in 44 non-small cell lung cancer patients treated with nivolumab, patients with higher SII values had decreased OS and PFS.[24] In contrast, in a recent study on 41 small cell lung cancer patients, no statistically significant difference was present in patients with higher SII levels for PFS.[25] Whether disease-related biologic differences or insufficient study power caused these different results are unknown.

Our study has several limitations. First of all, the study's retrospective design and the modest patient numbers precluded us from conducting extensive multivariable and subgroup analyses. Due to the sample size, we could only make adjustments according to a limited number of factors. Additionally, we evaluated a heterogeneous patient population (both nivolumab or ipilimumab patients), treated with immunotherapy in the later treatment lines rather than the current recommended first-line use due to reimbursement reasons in our country. Although these issues limited our results' generability, we think that we could be able to conduct a hypothesis-generating study using a simple biomarker.

Conclusion

In our experience, melanoma patients with higher SII values had poorer survival with immunotherapy. If additional prospective studies validate our findings, the SII could be a valuable biomarker for patient selection and prognosis estimation in ICI-treated melanoma patients.

Disclosures

Ethics Committee Approval: Hacettepe University Non-interventional Clinical Researches Ethics Board. 2020/19-31.

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Conflict of Interest: None declared.

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