Systemic Immune Inflammation Index as a Key Marker of Survival and Immune-related Adverse Events in Immune Checkpoint Inhibitor Therapy

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ABSTRACT

Objective: To evaluate the prognostic significance of the new index designed by formulating neutrophil, lymphocyte, and platelet counts in patients with metastatic disease receiving immune checkpoint inhibitors (ICI) and its effect on the immune-related adverse events (irAEs).

Study Design: Cohort study.

Place and Duration of Study: Department of Medical Oncology, University of Manisa Celal Bayar, University of Aydin Adnan Menderes, and University of Ege, and Izmir Kent Hospital, Turkey, from January 2016 to April 2020.

Methodology: Patients with metastatic disease receiving ICI sufficient follow-up data were included. Patients, who had received treatment for a minimum of 3 months, were evaluated for the response. Systemic immune-inflammation index (SII) was calculated as neutrophil (/L) × (lymphocyte (/L) / platelet (/L). The cut-off value was determined by examining the area under the receiver operating characteristic (ROC) curve for the SII value. The endpoints of this study included overall survival (OS) and progression-free survival (PFS).

Results: A total of 168, patients who received ICI in the metastatic stage, were evaluated. The OS of the patients with low SII scores was 110.8 months (95% CI, 88.2-133.5), while patients with high SII scores were 36.0 months (95% CI, 28.4-43.6) and reached statistical significance (p <0.001). The results of univariate (HR=3.376, 95% CI, 1.986-5.739, p<0.001 and multivariate (HR=2.792, 95% CI, 1.495-5.215, p=0.011) analyses were statistically significant as well.

Conclusion: The SII score in patients with metastatic disease receiving ICI was closely related to the prognosis. Patients with a high SII score are associated with a worse prognosis, these patients develop fewer irAEs.

Key Words: *Systemic immune inflammation index, Overall survival, Progression-free survival, İmmune checkpoint inhibitor, Pembrolizumab, Nivolumab*.

How to cite this article: Ekinci F, Balcik OY, Demir B, Gursoy P, Ozveren A, Erdogan AP. Systemic Immune Inflammation Index as a Key Marker of Survival and Immune-related Adverse Events in Immune Checkpoint Inhibitor Therapy. *J Coll Physicians Surg Pak* 2022; **32(08)**:996-1003.

INTRODUCTION

Immune checkpoint inhibitors (ICI) are the treatment options that constitute the main treatment for many cancers such as non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and malignant melanoma.[1] Currently, the most commonly used agents are approved for many ICI clinical applications[2] such as ipilimumab, nivolumab, pembrolizumab, and atezolizumab.

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Received: February 14, 2022; Revised: June 02, 2022; Accepted: July 02, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.08.996

The most important problem with these agents, which are highly effective and have fewer irAEs than conventional treatments but at the same time cost more, is which patients will benefit from the treatment. PD-L1 level and microsatellite instability (MSI), circulating T-cell immune index, angiopoietin-2, or tumour mutational burden which are among the markers applied for this purpose not accessible for every patient and have a high cost.[3-7] ICI treatment may be eligible for reimbursement, but MSI or another testing may not be covered due to additional charges. Also, this additional cost limits the repetitive routine use of expensive tests. Therefore, many patients cannot have these tests done.

The use of cost-effective and accessible markers has many clinical implications. It may help uncover mechanisms of interaction between the therapeutic functioning of ICIs and tumour-host immunity. It can also enable decision-making of person-

alised anti-tumour therapy. It can also provide an estimation of which patient may develop irAEs. Thus, recently, searches for markers have been made on the forms of inflammation markers such as leukocytes, neutrophils, lymphocytes, platelets, eosinophils, or monocytes seen in peripheral blood[4,8,9] because inflammation is an important feature of the tumour microenvironment and is associated with poor prognosis of various tumour types.[8]

In many cancer types, some blood cell, count indices such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), which can predict the response of ICIs, have been evaluated, and significant results have been reported.[8,10] Systemic immune-inflammation index (SII) is a new inflammatory marker obtained by the combination of NLR and platelet. It is an independent risk factor for disease progression in some cancer types treated with ICI such as RCC, NSCLC, pancreatic cancer, and melanoma.[11-13] In this study, the aim was to show the power of SII to predict both treatment efficacy and irAEs regardless of the tumour type and the ICI agent used.

METHODOLOGY

The data of the patients with metastatic disease, who received immunotherapy and followed up at three medical oncology clinics of University of Manisa Celal Bayar, University of Aydın Adnan Menderes and University of Ege, Turkey, between June 2014 and March 2021, were reviewed retrospectively. The non-metastatic patients, those with a history of second malignancies, and those without adequate laboratory results were excluded. Those with sufficient follow-up data were included in the study as a retrospective cohort. Patients, who received treatment for at least three months, were included to evaluate the response. Clinicopathological variables such as age, gender, presentation of metastasis (recurrence or de novo), adjuvant therapy status, disease subtypes (RCC, melanoma, lung, and others), BRAF status in melanoma, metastasis status, number of metastasis sites, type of treatment given before ICI, the reason for discontinuation of ICI, and the treatments (nivolumab, atezolizumab, pembrolizumab, and ipilimumab) were recorded. Platelet, lymphocyte, and neutrophil values measured at the time of metastasis, were recorded with an electronic medical record system.

The statistical analysis of the data obtained in this study was performed with the SPSS (Statistical Package for the Social Sciences) 26.0 package program. The SII score was calculated as neutrophil (/L) × (lymphocyte (/L) / platelet (/L). Youden Index was used to find the cut-off value for the SII variable according to the ROC curve, and this value was obtained as 1156.3705. The endpoints of this study included overall survival (OS) and progression-free survival (PFS). PFS was obtained by calculating the difference in months between the onset of immunotherapy and the time of progression. The OS was obtained by calculating the time in months between the date of diagnosis and the date of exitus among those confirmed (data cut-off for non-exitus patients). Tumour response was assessed according to ''Immune-related Response Evaluation Criteria In Solid Tumours'' (irRECIST). The cut-off value was determined by calculating the sensitivity and specificity values for the SII value based on OS and PFS and examining the area under the ROC curve. The SII value was categorised by determining the cut-off value with the ROC curve and then chi-square test was applied and categorical variables were expressed as n(%). SII score and OS-PFS correlations were evaluated using Kaplan-Meier curves with log-rank statistics. The conformity of all the parameters to the normal distribution was then examined. As a result of the examination, it was observed that some variables were normally distributed, and some were not normally distributed. Numerical values were grouped according to the categorical variables to be compared, and then the normality test was applied. The Shapiro-Wilk test was used in those with n <30 group numbers, while the Kolmogorov-Smirnov test was used in those with n >30. Furthermore, univariate and multivariate Cox regression analyses were used to calculate the respective hazard ratios (HRs) and 95% confidence intervals (CIs). Analysis results were presented as median (minimum-maximum), mean and standard deviation. All the statistical assessments were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

A total of 168 patients, who received ICI at the metastatic stage, were evaluated. It was observed that 60.1% of the patients were under the age of 65 years and 70.8% were males and 29.20% were females. While those in the other disease subtypes group constituted the majority with 38.1%, RCC took the second place with 29.2%. When the treatments performed before the initiation of ICI were questioned, it was seen that 44.0% of the patients received chemotherapy (CT) and 19.6% had not received any treatment before. The reasons for the discontinuation of ICI were evaluated, and it was noted that the most common reason was progression with 66.7%, and the second most common reason was hyper-progression with 9.3%. When the ICI agent was questioned, it was reported that nivolumab was the most frequently used with 67.3%, and ipilimumab was the least used with 5.4%. The best response to treatment is seen to be a partial response (PR) in 48.2% of the patients. At the end of the study analysis, it was reported that 36.3% of the patients died.

According to the calculated SII cut-off value, the patients were divided into two groups as <1156.3705 (group 1) and >1156.3705 (group 2, Table I). The number of patients in the first group was calculated as 116 and in the second group was calculated as 52. Those presenting with recurrence were found to be statistically and significantly higher in the first group (43.1%) than in the second group (26.9%, p=0.046). Considering progression to ICI treatment, it was reported that the progression was significantly higher in the second group (61.5%) than in the first group (43.1%, p=0.027). The groups were examined in terms of irAEs and it was found that they were more common in the first group (37.1%) than in the second group (17.3%, p=0.010). This result may suggest that those with lower SII scores will have higher irAEs. The groups were compared in terms of exitus status, and the rate was found to be significantly higher in the second group (55.8%) than in the first group (27.6%, p<0.001).

Table I: Comparison of clinical characteristics and treatment conditions according to the SII cut-off value.

		<1156.370 (n-%)	>1156.3705 (n-%)	Total (n-%)	p-value
Age	<65	74 (63.80)	27 (51.90)	101 (60.10)	0.146
	≥65	42 (36.20)	25 (48.10)	67 (39.90)	
Gender	Male	80 (69.00)	39 (75.00)	119 (70.80)	0.426
	Female	36 (31.00)	13 (25.00)	49 (29.20)	
Presentation of metastasis	Recurrence	50 (43.10)	14 (26.90)	64 (38.10)	0.046
	De novo	66 (56.90)	38 (73.10)	104 (61.90)	
Adjuvant therapy status	No	34 (68.00)	9 (64.30)	43 (67.20)	0.794
	Yes	16 (32.00)	5 (35.70)	21 (32.80)	
Disease subtypes	RCC	36 (31.00)	13 (25.00)	49 (29.20)	0.122
	Malignant melanoma	30 (25.90)	7 (13.50)	37 (22.00)	
	Lung	12 (10.30)	6 (11.50)	18 (10.70)	
	Other	38 (32.80)	26 (50.00)	64 (38.10)	
BRAF status in malignant melanoma	Positive	4 (12.90)	2 (28.60)	6 (15.80)	0.451
	Negative	24 (77.40)	5 (71.40)	29 (76.30)	
Metastasis Status	Lung	63 (54.30)	34 (65.40)	97 (57.70)	0.179
	Liver	33 (28.40)	9 (17.30)	42 (25.00)	0.123
	Brain	16 (13.80)	6 (11.50)	22 (13.10)	0.689
	Bone	35 (30.20)	9 (17.30)	44 (26.20)	0.080
	LN	87 (75.00)	37 (71.20)	124 (73.80)	0.600
	Other	50 (43.10)	26 (50.00)	76 (45.20)	0.406
Number of metastasis sites	<3	65 (56.00)	29 (55.80)	94 (56.00)	0.974
	≥3	51 (44.00)	23 (44.20)	74 (44.00)	
Type of ICI used	Nivolumab	78 (67.20)	35 (67.30)	113 (67.30)	0.565
	Atezolumab	19 (16.40)	12 (23.10)	31 (18.50)	
	Pembrolizumab	12 (10.30)	3 (5.80)	15 (8.90)	
	Ipilimumab	7 (6.00)	2 (3.80)	9 (5.40)	
Type of treatment given prior to ICI	TKI	39 (33.60)	15 (28.80)	54 (32.10)	0.700
	CT	52 (44.80)	22 (42.30)	74 (44.00)	
	TKI and CT	5 (4.30)	2 (3.80)	7 (4.20)	
	No therapy	20 (17.20)	13 (25.00)	33 (19.60)	
Reason for discontinuation of ICI	Progression	46 (67.60)	26 (65.00)	72 (66.70)	0.493
	Hyperprogression	4 (5.90)	6 (15.00)	10 (9.30)	
	irAEs	4 (5.90)	2 (5.00)	6 (5.60)	
	Follow-up after CR	5 (7.40)	1 (2.50)	6 (5.60)	
	Other	9 (13.20)	5 (12.50)	14 (13.00)	
Best response to ICI	PR	63 (54.30)	18 (34.60)	81 (48.20)	0.070
	CR	17 (14.70)	8 (15.40)	25 (14.90)	
	SD	13 (11.20)	7 (13.50)	20 (11.90)	
	PD	23 (19.80)	19 (36.50)	42 (25.00)	
Exitus status	No	84 (72.40)	23 (44.20)	107 (63.70)	<0.001
	Yes	32 (27.60)	29 (55.80)	61 (36.30)	
Progression status under ICI	No	66 (56.90)	20 (38.50)	86 (51.20)	0.027
	Yes	50 (43.10)	32 (61.50)	82 (48.80)	
irAEs	No	73 (62.9)	43 (82.7)	116 (69.1)	0.010
	Yes	43 (37.1)	9 (17.3)	52 (30.9	

The association between the clinicopathological data and the SII score was evaluated using the chi-square test. SII: Systemic immune-inflammation index, ICI: Immune checkpoint inhibitor, RCC: Renal cell carcinoma TKI: Tyrosine kinase inhibitör, CT: Chemotherapy, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease, and irAEs: Immune-related adverse events.

All the patients included in the study were examined, the total median survival was calculated as 91.174 (95% CI, 72.661 - 109.687) months (Table II). The median survival of the patients was analysed in terms of the disease subtypes; it was 112.018 (95% CI, 83.533 - 140.502) months in RCC, 63.624 (95% CI, 45.373-81.876) months in melanoma, 28.161 (95% CI, 22.032 - 34.290) months in lung cancer, and 58.117 (95% CI, 44.965 - 71.269) months in the other cancer group. The longest survival was reported in RCC and the shortest survival in lung cancer (p=0.035). Depending on the type of immunotherapy agent used, the longest survival was 98.82 months (95% CI, 77.664-119.975) and significantly longer in the nivolumab arm (p=0.010). The treatment modalities used before immunotherapy were examined; the survival rate in TKI users was 110.145 months (95% CI, 82.464-137.825), again significantly longer than the others (p=0.002). Survival rates were examined in terms of the reasons for discontinuation of treatment, and the shortest survival, as expected, was observed in those who developed hyperprogression with 22,307 months (95% CI, 13,998-30,617) (p=0.010). Patients were grouped according to the SII score; OS was 110.868 months (95% CI, 88.205-133.531) and PFS was 28.553 months (95% CI, 22.017-35.088) in the group with <1156.3705, whereas OS was 36.069 months (95% CI, 28.473-43.665) and PFS was 13.100 (95% CI, 7.805-18.395) months in the group with >1156.3705 (OS and PFS, p=0.000, p=0.010, respectively). Consistent with the main hypothesis of the study, the SII score appears to predict both OS and PFS in a statistically significant way.

Table II: Comparison of the OS and PFS times according to the characteristics of the patients.

Variables	Categories	Median OS (Month) 95% CI (Min-Max)	p-value	Median PFS (Month) 95% CI (Min-Max)	p-value
Survival	General population	91.174 (72.661-109.687)		24.663 (19.398-29.927)	
Age	<65	97.447 (74.529-120.366)	0.145	26.426 (19.623-33.228)	
	≥65	62.348 (49.477-75.219)		22.005 (13.939-30.072)	0.205
Gender	Male	91.26 (70.144-112.375)	0.797	23.895 (17.878-29.912)	
	Female	63.228 (51.597-74.86)		23.29 (14.41-32.169)	0.479
Presentation of metastasis	Recurrence	117.839 (91.934-143.743)	<0.001	29.557 (20.553-38.561)	
	De novo	50.593 (40.923-60.262)		16.546 (12.357-20.734)	0.133
Adjuvant therapy status	No	113.951 (84.277-143.625)	0.68	24.957 (14.287-35.626)	
	Yes	83.4 (60.574-106.225)		19.527 (13.782-25.271)	0.334
Disease subtypes	RCC	112.018 (83.533-140.502)	0.035	25.442 (16.335-34.549)	
	Malignant melanoma	63.624 (45.373-81.876)		13.393 (9.689-17.098)	
	Lung	28.161 (22.032-34.290)		11.757 (6.000-17.515)	
	Other	58.117 (44.965-71.269)		16.745 (11.356-22.134)	0.547
BRAF status in malignant melanoma	Unknown	31.671 (19.053-44.290)	0.704	5.487 (1.889-9.084)	
	Positive	55.622 (21.842-89.402)		7.326 (2.759-11.894)	
	Negative	47.937 (38.269-57.604)		13.991 (9.748-18.233)	0.490
Lung metastasis	No	61.349 (49.611-73.087)	0.697	20.998 (14.683-27.313)	
	Yes	97.899 (75.035-120.763)		25.948 (18.611-33.284)	0.795
Liver metastasis	No	94.115 (72.79-115.439)	0.249	25.646 (19.358-31.935)	
	Yes	59.586 (44.972-74.200)		21.333 (11.939-30.728)	0.109
Brain metastasis	No	99.692 (78.930-120.454)	0.12	26.289 (20.440-32.137)	
	Yes	49.954 (33.754-66.153)		15.993 (5.590-26.396)	0.091
Bone metastasis	No	104.831(84.196-125.466)	0.363	28.318 (21.892-34.745)	
	Yes	54.904 (43.066-66.743)		12.406 (8.134-16.679)	0.169
LN metastasis	No	85.508 (53.838-117.178)	0.881	11.226 (7.874-14.577)	
	Yes	92.047 (71.091-113.002)		28.168 (21.727-34.609)	0.101
Other metastasis	No	90.286 (65.202-115.37)	0.874	23.822 (17.177-30.466)	
	Yes	92.086 (67.188-116.984)		25.494 (16.836-34.152=	0.780
Number of metastasis sites	<3	96.446 (70.538-122.353)	0.769	18.063 (13.637-22.489)	
	≥3	64.418 (52.361-76.474)		25.774 (17.554-33.994)	0.921
Type of ICI used	Nivolumab	98.82 (77.664-119.975)	0.010	27.305 (20.789-33.821)	
	Atezolumab	36.829 (21.439-52.219)		14.019 (7.220-20.819)	
	Pembrolizumab	64.89 (42.852-86.928)		9.613 (7.224-12.003)	
	Ipilimumab	41.561 (27.707-55.414)		9.055 (3.443-14.667)	0.295
Type of treatment given prior to ICI	TKI	110.145 (82.464-137.825)	0.002	25.585 (16.689-34.481)	
	CT	64.317 (49.898-78.735)		21.236 (15.546-26.925)	
	TKI and CT	33.835 (22.063-45.607)		4.900 (2.351-7.449)	
	No therapy	39.894 (27.480-52.307)		10.854 (6.868-14.84)	0.082
Reason for discontinuation of ICI	Progression	42.21 (33.918-50.503)	0.010		
	Hyperprogression	22.307 (13.998-30.617)			
	irAEs	33.665 (8.134-59.195)			
	Follow-up after CR	46.921 (39.936-53.907)			
	Other	62.65 (48.048-77.253)			
Best response to ICI	PR	107.563 (80.879-134.248)	<0.001	30.633 (22.294-38.973)	
	CR	158.331 (124.43-192.232)		49.555 (38.322-60.788)	
	SD	53.754 (38.225-69.283)		8.416 (6.300-10.531)	
	PD	28.904 (21.394-36.414)		2.874 (2.070-3.677)	<0.001
irAEs	No	77.882 (56.252-99.511)	0.107	12.052 (9.508-14.595)	
	Yes	77.502 (62.713-92.291)		32.326 (23.387-41.266)	0.018
irAEs grade	Grade 1	61.671 (39.868-83.474)	0.052	22.656 (11.537-33.776)	
	Grade 2	92.157 (73.691-110.622)		39.140 (25.619-52.661)	
	Grade 3	54.823 (34.957-74.688)		16.953 (9.774-24.131)	
	Grade 4	27.256 (12.357-42.155)		4.860 (1.245-8.475)	0.163
Progression status under ICI	No	164.466 (146.784-182.147)	<0.001		
	Yes	40.120 (32.515-47.725)			
SII category	<1156.3705	110.868 (88.205-133.531)	<0.001	28.553 (22.017-35.088)	
	>1156.3705	36.069 (28.473-43.665)		13.100 (7.805-18.395)	0.015

HALP score and OS-PFS correlations were evaluated using Kaplan-Meier curves with log-rank statistics. OS: Overall survival, PFS: Progression free survival, Min: Minimum, Max: Maximum, SII: Systemic immune-inflammation index, CI: Confidence Interval, ICI: Immune checkpoint inhibitor, RCC: Renal cell carcinoma TKI: Tyrosine kinase inhibitör, CT: Chemotherapy, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease, and irAEs: Immune-related adverse events.

Table III: Cox regression analysis results of the OS.

	Univariate		Multivariate	
	HR (95% CI) (Min-Max)	**p-value**	**HR (95% CI) (Min-Max)**	**p-value**
Age	1.452 (0.877-2.404)	0.147		
Gender	0.929 (0.529-1.631)	0.797		
Presentation of metastasis (De novo)	2.494 (1.434-4.337)	<0.001	1.686 (0.847-3.358)	0.137
Adjuvant therapy status	0.807 (0.291-2.237)	0.681		
BRAF status in malignant melanoma				
Negative		0.709		
Unknown	1.160 (0.145-9.290)	0.889		
Positive	1.641 (0.509-5.287)	0.407		
Disease subtypes				
Other		0.042	0.342 (0.050-2.315)	0.089
RCC	0.407 (0.213-0.777)	0.006	2.083 (0.745-5.820)	0.271
Malignant melanoma	0.827 (0.433-1.580)	0.566	2.536 (0.855-7.521)	0.162
Lung	1.167 (0.440-3.097)	0.757		0.093
Metastasis Status				
Lung	0.903 (0.540-1.509)	0.697		
Liver	1.381 (0.796-2.395)	0.251		
Brain	1.624 (0.876-3.008)	0.123		
Bone	1.286 (0.747-2.216)	0.364		
LN	0.959 (0.551-1.667)	0.881		
Other	0.960 (0.580-1.588)	0.874		
Number of metastasis sites	1.078 (0.652-1.783)	0.769		
Type of ICI used				
Nivolumab		0.014	3.526 (1.232-10.089)	0.044
Atezolizumab	2.847 (1.447-5.600)	0.002	5.949 (1.581-22.379)	0.019
Pembrolizumab	1.446 (0.567-3.688)	0.440	1.131 (0.352-3.630)	0.008
Ipilimumab	2.197 (0.920-5.246)	0.076		0.837
Type of treatment given prior to ICI				
No therapy		0.004		0.961
TKI	0.264 (0.128-0.546)	<0.001	0.668 (0.121-3.697)	0.644
CT	0.490 (0.257-0.936)	0.031	0.845 (0.373-1.914)	0.687
TKI and CT	0.785 (0.259-2.378)	0.668	0.919 (0.247-3.415)	0.900
Reason for discontinuation of ICI				
Other		0.024		<0.001
Progression	3.293 (1.020-10.636)	0.046	5.067 (1.410-18.207)	0.013
Hyperprogression	7.029 (1.792-27.567)	0.005	7.112 (1.513-33.433)	0.013
irAEs	4.671 (1.041-20.952)	0.044	38.22 (6.35-229.99)	<0.001
Follow-up after complete response	0.626 (0.065-6.025)	0.685	1.284 (0.102-16.191)	0.847
Best response to ICI				
PR		<0.001		0.002
CR		0.070	0.173 (0.031-0.977)	0.047
SD	0.262 (0.062-1.114)	0.085	1.291 (0.540-3.089)	0.566
PD	1.994 (0.909-4.374)	<0.001	3.360 (1.531-7.374)	0.003
	5.173 (2.855-9.375)			
Number of lines received for treatment	0.887 (0.695-1.132)	0.336		
1 Line		0.219		
2 Line	2.329 (0.949-5.720)	0.065		
3 Line	1.129 (0.538-2.366)	0.749		
≥4 Line	1.505 (0.723-3.132)	0.274		
irAEs				
Grade 1		0.090		
Grade 2		0.378		
Grade 3	0.528 (0.127-2.189)	0.839		
Grade 4	1.170 (0.259-5.293)	0.092		
	3.323 (0.821-13.455)			
SII category (>1156.3705)	3.376 (1.986-5.739)	<0.001	2.792 (1.495-5.215)	<.0.001

Risk factors affecting overall survival were analysed by Cox regression analysis as univariate and multivariate models. OS: Overall survival, SII: Systemic immune-inflammation index, ICI: Immune checkpoint inhibitor, RCC: Renal cell carcinoma TKI: Tyrosine kinase inhibitör, CT: Chemotherapy, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease. irAEs: Immune-related adverse events.

The results of the Cox regression analysis for survival were examined both univariate and multivariate values were found to be significant in the type of ICI used, the type of treatment given before ICI, the reason for discontinuation of ICI, and the best response to ICI and SII categories (Table III). The risk of death was found to be 3.376 times higher according to the univariate analysis and 2.792 times higher according to the multivariate analysis in patients with SII value >1156.3705 compared to those with low SII. This reinforces the SII score as a strong and independent variable in predicting survival.

DISCUSSION

It is accepted that inflammation is a mechanism that supports tumour formation or plays a fundamental role in tumour maintenance and spread as a component of the tumour microenvironment after its formation.[14,15] It has also been observed that systemic inflammation impairs the immune response and allows tumour cells to evade immune surveillance. As one of the inflammatory markers measured in peripheral blood and neutrophils are central players in this mechanism as they mediate the production of cancer-related chemokines and cytokines. Moreover, it is involved in the proliferation, invasion, and metastatic spread of tumour cells and also induces drug resistance.[16] Platelets confer invasion and metastatic potential to tumour cells by increasing endothelial permeability *via* vascular endothelial growth factor (VEGF). For these reasons, the increase in neutrophils and platelets is associated with the progression of tumour cells. Decreased lymphocyte count has also been associated with poor prognosis, such as increased neutrophils and thrombocytes, as it may be responsible for a weak and inadequate immune response against tumours.[15,16] The method of creating the SII score is also based on this logic.

Although the SII score was previously used for prognosis and response to treatment in many cancers, it was first evaluated in patients receiving ICI (nivolumab) as reported by Jin Suh *et al* in 2018, with the SII score calculated with laboratory values measured at the 6th week of the treatment in NSCLC patients. In this study, PFS (HR=2.00, 95% CI, 1.04–3.86, p=0.038) and OS (HR=2.70, 95% CI, 1.33–5.46, p=0.006) were found to be significantly lower in patients with high SII scores compared to those with low scores.[15-17] Thus, it has been shown that the SII score may be an independent prognostic marker of PFS and OS in those treated with ICI. In the same patient group, the SII score was evaluated by Liu *et al.* on 44 patients in 2019. In this study, patients with lower SII scores were associated with longer PFS (HR=0.34, 95% CI, 0.15-0.76, p=0.006) and OS (HR=0.16, 95%CI 0.05-0.51, p=0.005).[8] The prognostic significance of the SII score was investigated in the same year by De Giorgi *et al.* in a very large population of 313 patients with RCC treated with nivolumab. Those with higher SII scores had worse survival in both univariate analysis (HR=3.35, 95% CI, 2.38–4.73, p<0.0001) and multivariate (HR=2.99, 95% CI, 2.07–4.31, p<0.0001) analysis, and this was considered statistically significant.[11]

Prognostic analysis of the SII score continues to be carried out in more recent studies. In 2021, 62 patients with stage III/IV melanoma, who received ICI treatment, were examined. SII was not significantly associated with clinical parameters including best response to ICI treatment (p=0.64), PFS (p=0.91), and melanoma-specific survival (p=0.17). Also, the SII score was not significant for the time from onset to progression/death (p=0.52). This study is encouraging for further studies that are needed to determine the prognostic significance of the SII score. Patients in the same diagnostic group receiving both nivolumab and ipilimumab were evaluated in another study of 44 patients by Guven *et al*. This study reveals that the SII score did not reach statistical significance in terms of PFS (HR=1.571, 95% CI, 0.824-2.993, p=0.170). Undoubtedly, the low number of patients should be considered as a factor here. However, it was found to be statistically significant in terms of OS (HR=2.209, 95% CI, 1.105-4.417, p=0.025).[18]

The prognostic significance of the SII score in NSCLC patients receiving nivolumab or pembrolizumab was investigated in a recent study by Kauffmann-Guerrero *et al*. which had a different design from the other studies. This study showed that patients who progressed under ICI treatment had a higher SII score (p=0.011). Compared with the patients with lower scores, those with higher SII scores had significantly reduced PFS; median PFS 7.51 weeks (95% CI, 3.26-11.88) and 40.0 weeks (95% CI, 11 .48-68.52, p=0.001). Patients with a long response to ICI treatment were also examined, and inflammatory scores such as interleukin 6 (p=0.002), CRP (p<0.001), NLR (p=0.002), PLR (p=0.003), and SII (p<0.001) which were checked before treatment, were found to be statistically and significantly lower.[19] The small number of patients seems to be the main limitation of this study.

In this study, consistent with the literature, those with high SII scores were associated with worse prognosis in both univariate (HR=3,376, 95% CI, 1,986-5.739, and p<0.000) and multivariate (HR=2.792, 95% CI, 1.495-5.215, and p=0.011) analysis compared to those with low scores. However, the most important aspect of this study is the demonstration of this relationship in pooled data regardless of the ICI treatment agent used and disease type.

Although different markers have been studied like PNI and GPS,[20] SII score has not been studied as a predictor of irAEs before. Unlike the literature, it has also been shown that those with low SII scores have more irAEs than those with high SII scores (p=0.010).

The major limitation of this study is the use of a retrospective analysis method with the potential for bias in patient selection. Another point is that the SII index does not have an ideal cut-off value that prevents routine use.

CONCLUSION

Patients with a high SII score have worse prognosis and develop fewer irAEs. This paves the way for the routine use of a predictive index with a simple, accessible, and inexpensive method for those undergoing ICI treatment.

ETHICAL APPROVAL:
The Health Sciences Ethics Committee approved this study of Manisa Celal Bayar University, Faculty of Medicine with the decision dated 23/12/2020 and No: E-20478486-050.04.04-2275.

PATIENTS' CONSENT:
Written consents were obtained from all the participants.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
FE, APE: Concept design, supervision, materials, analysis, interpretation, literature review, and manuscript writing.
OYB, BD, AO, PG: Data collection, processing, analysis, and interpretation.
APE: Supervision, literature search, and critical review.
All the authors have approved the final version of the manuscript to be published.

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