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RESEARCH ARTICLE

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Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab

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Abstract

Background: Explore markers to predict the clinical outcomes of checkpoint inhibitors have high unmet needs. The following study investigates whether hematologic parameter such as systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) is associated with nivolumab efficacy in advanced non-small-cell lung cancer (NSCLC).

Methods: Advanced/metastatic NSCLC patients treated with nivolumab monotherapy for second-line or further-line treatment at Jilin Cancer Hospital between March 2016 and July 2018 were enrolled in this retrospective study. The optimal cutoff values of SII, NLR, and PLR for predicting efficacy and prognosis were determined according to receiver operating characteristic (ROC) curve and the areas under the ROC curve. Progression-free survival (PFS) and overall survival (OS) were calculated and compared using Kaplan-Meier method and log-rank test. Prognostic values of each variable were evaluated with univariate and multivariate Cox proportional hazard regression (PHR) analyses.

Results: A total of 44 patients with advanced NSCLC were included; the median age was 60 (range: 43-74). The optimal cutoff value of SII/NLR/PLR predicted PFS and OS was 603.5, 3.07, and 144. Low SII, NLR, and PLR were associated with longer PFS (HR for SII = 0.34, 95%CI 0.15-0.76, $P = 0.006$; HR for NLR = 0.46, 95%CI 0.22-0.99, $P = 0.048$; HR for PLR = 0.39, 95%CI 0.17-0.94, $P = 0.025$) and OS (HR for SII = 0.16, 95%CI 0.05-0.51, $P = 0.005$; HR for NLR = 0.20, 95%CI 0.06-0.62, $P = 0.002$; HR for PLR = 0.20, 95%CI 0.06-0.73, $P = 0.008$). NLR ≤ 3.07, PLR ≤ 144, SII ≤ 603.5 were independently associated with longer PFS and OS.

Conclusion: The SII, NLR, and PLR are promising prognostic predictor for patients with metastatic NSCLC patients.

Jingjing Liu and Shuang Li equally contributed to this study.

KEYWORDS
neutrophil-to-lymphocyte ratio, nivolumab, non-small-cell lung cancer, platelet-to-lymphocyte ratio, systemic immune-inflammation index

1 | INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers, with an estimated 2 093 876 new lung cancer cases that will occur worldwide in 2018.[1] According to National Cancer Center, the incidence and mortality rates of lung cancer in China are very high, and they are increasing year by year.[2]

Over the recent years, the treatment strategies for advanced and metastatic NSCLC have been dramatically changed. Immune checkpoint inhibitors (ICIs), including programmed death 1 (PD-1) inhibitors (nivolumab, pembrolizumab) and programmed cell death ligand-1 (PD-L1) inhibitors (atezolizumab) monotherapy or combined chemotherapy have become one of the standard treatments for NSCLC patients without treatable driver mutations.[3-7] Nivolumab (a fully human IgG4 PD-1 antibody) is the first ICIs to be approved for previously treated advanced NSCLC.[3,4] Despite the improved survival benefit with ICIs compared with conventional chemotherapy, but a considerable proportion of NSCLC patients still failed to respond.[8-12] Up to date, PD-L1 and tumor mutational burden (TMB) were used to screen patients who would potentially benefit from ICIs, but they are not the ideal biomarker due to different test platform, panel, cutoff value and many patients could not provide sufficient tumor tissue for testing. Explore markers to predict the clinical outcomes of checkpoint inhibitors have high unmet needs.[13]

Inflammation is an important feature of tumor microenvironment and associated with poor prognosis of various types of tumor.[14] Hematological inflammatory parameters such as neutrophil, lymphocyte, monocytes, and platelets can reflect the immune status and have important predictive value for the prognosis of tumors.[15,16] Some studies have evaluated the value of some blood cell count indexes, particularly the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and demonstrated these biomarkers have the prognostic role in different tumors include NSCLC.[17-24] Recently, several studies suggested that NLR and PLR also strongly associated with poor clinical outcomes in patients treated with ICIs.[25-28] Systemic immune-inflammation index (SII) is a novel inflammatory marker which combines NLR and platelet is an independent risk factor for the development of solid cancer.[29] Higher SII was independently associated with worse outcomes for metastatic renal cell carcinoma (RCC) patients treated with nivolumab.[30] However, rare studies reported whether SII is associated with the prognosis of NSCLC patients treated with ICIs. Consequently, the aim of this retrospective study was to examine the correlation between SII and efficacy in patients with NSCLC treated with ICIs.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients with advanced or metastatic NSCLC treated with nivolumab monotherapy for second-line or further-line treatment at the Jilin Cancer Hospital between March 2016 and July 2018 were enrolled in this study. Data were analyzed by professional statisticians; treatment records were evaluated by clinical experienced doctors; all information were extracted in accordance with uniform requirements. The electronic medical records of patients were reviewed, and all patients had complete blood parameters collected on the date of initial clinic visit or within 7 days prior to starting nivolumab. The last follow-up was on November 9, 2018.

This study was approved by Jilin Cancer Hospital ethic committee. In addition, all patients have signed the informed consent before receiving the nivolumab treatment.

2.2 | Determination of efficacy, immune-related adverse reactions and SII, NLR, PLR

Low-dose computed tomography (LDCT)/magnetic resonance imaging (MRI) scan examinations were performed every 6 weeks. Responses to treatment were evaluated based on Response Evaluation Criteria of Solid Tumor (RECIST) ver.1.1,[31] and they were categorized as progressive disease (PD), stable disease (SD), partial remission (PR), and complete remission (CR) according to the therapeutic effect evaluated in the medical record. Toxicity assessment was performed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Immune-related adverse events (irAEs) were defined as adverse events with a potential immunologic basis that required frequent monitoring and potential intervention with immune suppression or endocrine therapy.[32,33] IrAEs were determined and graded independently by two experienced physicians and re-evaluated according to the course record. The onset time and end time of irAE were recorded according to management of immunotherapy-related toxicities NCCN 2018 Version 1. A third higher level physician examined the information above. All disagreements were resolved by discussion between three doctors until the consensus was reached.

SII = platelet count × neutrophil count/lymphocyte count. The NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes, the PLR as the absolute number of platelets by the absolute number of lymphocytes.

2.3 | Statistical analyses

Overall survival (OS) was defined as the interval from treatment initiation until death. Patients who were still alive were censored at the

TABLE 1 Baseline characteristics of patients

Characteristics	Overall (n = 44)
Age at diagnosis, median (range)	60 (43-74)
Sex	
Male	33
Female	11
ECOG PS	
1	44
Smoking history	
Never	15
Current	8
Former	21
Histology	
Squamous	13
Adenocarcinoma	31
Radiotherapy history	
Yes	12
No	32
Stage	
IIIB	9
IV	35
CNS metastasis	
Yes	2
No	42
Pulmonary metastasis	
Yes	20
No	24
Liver metastasis	
Yes	7
No	37
Bone metastases	
Yes	11
No	33
Adrenal metastases	
Yes	2
No	42
EGFR mutation status	
Positive	5
Negative	28
Not examined	11
ALK fusion status	
Positive	3
Negative	21
Not examined	20

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.

final follow-up. Progression-free survival (PFS) was defined as the interval from treatment initiation until disease progression or death. Patients still manifested disease control were censored at the final follow-up. ORR was defined as the percentage of the best overall remission confirmed by the investigator, that is, PR + CR accounted for the proportion of enrolled patients. DCR was defined as the proportion of patients whose RECIST, CR or PR or SD lasted longer than 24 weeks.

Descriptive analysis was used for all variables. Counting variables were presented as percentages. The optimal cutoff values of SII, NLR, and PLR for predicting efficacy and prognosis were determined according to receiver operating characteristic (ROC) curve and the areas under the ROC curve (AUC). Patients were divided into high SII/NLR/PLR groups and low SII/NLR/PLR groups based on cutoff values. PFS and OS were calculated and compared using the Kaplan-Meier method and the log-rank test. The prognostic values of each variable were evaluated with univariate and multivariate Cox proportional hazard regression (PHR) analyses. Reverse Kaplan-Meier method was used to compute the median follow-up time. $P < 0.05$ was considered statistically significant. All analyses were statistically analyzed using R 3.4.3 and SPSS24.0 (Chicago, Illinois, USA).

3 | RESULTS

3.1 | Patients

A total of 44 patients with advanced NSCLC treated with nivolumab (3 mg/kg, every 2 weeks) were enrolled in this study. The median age at diagnosis was 60 (range: 43-74) years with 33 (75%) men. PD-1/PD-L1 status of all patients was unknown. Baseline characteristics of patients are presented listed in Table 1.

3.2 | Treatment response and survival

The median follow-up time was 6.9 m (range: 0.6-28.5). The median PFS was 4.8 m (95%CI: 3.7-NA), median OS was 13.4 m (95%CI: 10.5-NA). ORR was 31.8%, DCR was 65.9%. No patients achieved complete response, 31.8% achieved partial response, 34.1% had SD, and 29.5% had PD. 27 (61.4%) patients experienced disease progression and 20 (45.5%) patients died at the time of follow-up date.

3.3 | The association between hematological inflammatory parameters and PFS/OS

According to the ROC curve, the optimal cutoff value of SII predicted PFS and OS was 603.5, the sensitivity of this point was 0.89, the specificity was 0.67, and the AUC was 0.83. Patients were divided into two groups according to the optimum cutoff value of SII, 22 patients in low SII group (SII ≤ 603.5) and 22

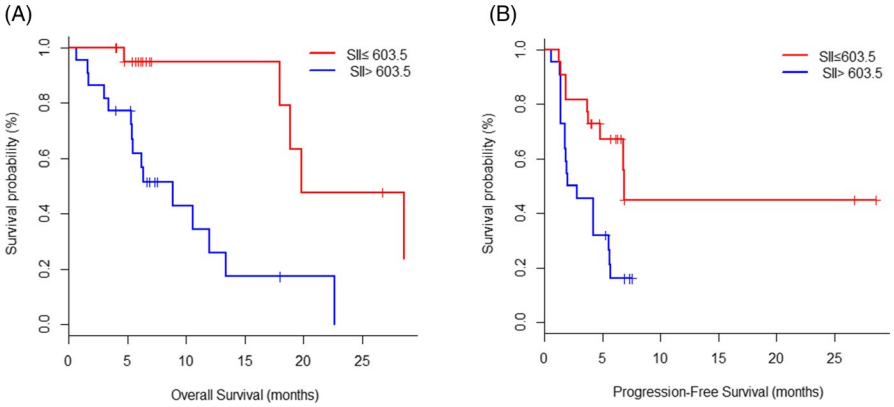

FIGURE 1 Kaplan-Meier plots of overall survival (A) and progression-free survival (B) according to systemic immune-inflammation index (SII) at baseline

patients in high SII group (SII > 603.5). Patients in low SII group before treatment had longer OS and PFS compared with high SII group (median OS: 8.9 m [5.3-12.0] vs 19.8 m [17.9-NA], *P* = 0.005; HR and 95%CI: 0.16 [0.05-0.51]; Median PFS: 2.4 m [1.4-5.6] vs 6.9 m [3.7-NA], *P* = 0.006, HR and 95%CI: 0.34 [0.15-0.76]; Figure 1A,B).

The optimal cutoff value of NLR predicted PFS and OS was 3.07, the sensitivity of this point was 0.81, the specificity was 0.73, and the AUC was 0.84. Patients were divided into two groups according to the optimum cutoff value of NLR, 24 patients in low NLR group (NLR ≤ 3.07) and 20 patients in high NLR group (NLR > 3.07). Patients in low NLR group before treatment had longer OS and PFS compared with high NLR group (median OS: 8.9 m [3.4-13.4] vs 19.8 m [17.9-NA], *P* = 0.002; HR and 95%CI: 0.20 [0.06-0.62]; Median PFS: 3.9 m [1.4-5.6] vs 6.7 m [2.7-NA], *P* = 0.048; HR and 95%CI: 0.46 [0.22-0.99]; Figure 2A,B).

The optimal cutoff value of PLR predicted PFS and OS was 144, the sensitivity of this point was 0.67, the specificity was 0.65, and the AUC was 0.67. Patients were divided into two groups according to the optimum cutoff value of PLR, 18 patients in low PLR group (PLR ≤ 144) and 26 patients in high PLR group (PLR>144). Patients in low PLR group before treatment had longer OS and PFS compared with high PLR group (median OS: 10.5 m [6.2-17.9] vs 28.5 m [19.8-NA], *P* = 0.008; HR and 95%CI: 0.20 [0.06-0.73]; Median PFS: 3.9 m [1.7-5.6] vs 6.9 m [3.7-NA], *P* = 0.025; HR and 95%CI: 0.39 [0.17-0.94]; Figure 3A,B).

3.4 | The association between hematological inflammatory parameters and irAEs

A total of 15 (34.1%) patients developed irAEs. Grade and duration of irAEs for different treatment regimens are shown in Table 2.

The most common irAEs were hypothyroidism (n = 6, 13.6%) followed by hyperthyroidism (n = 5, 11.4%). Grade 3 or higher irAE was observed in 1 case (2.3%), which was pneumonia. irAE leading to discontinuation were reported in 2 cases, with 1 case of grade 2 pneumonia, and 1 case of grade 2 AST elevation. No irAE-related deaths occurred.

The relationship between SII/NLR/PLR and irAE was also analyzed, but we found there were no statistically significant. (For SII and irAE: *P* = 0.738; For NLR and irAE: *P* = 0.665; For PLR and irAE: *P* = 0.814).

3.5 | Univariate and multivariate analyses

Univariate and multivariate analyses of PFS and OS were performed using COX regression model, and factors considered included age, gender, smoking status, pathological typing, disease stage, pretreatment NLR level, pretreatment PLR level, and pretreatment SII level. In univariate analysis, we found that NLR ≤ 3.07 before treatment, PLR ≤ 144 before treatment, and SII ≤ 603.5 before treatment were associated with longer PFS and OS (Tables 3 and 4).

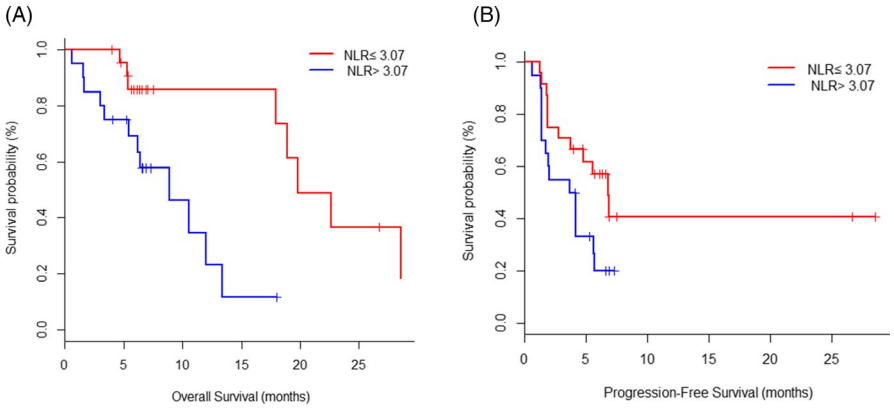

FIGURE 2 Kaplan-Meier plots of overall survival (A) and progression-free survival (B) according to neutrophil-to-lymphocyte ratio (NLR) at baseline

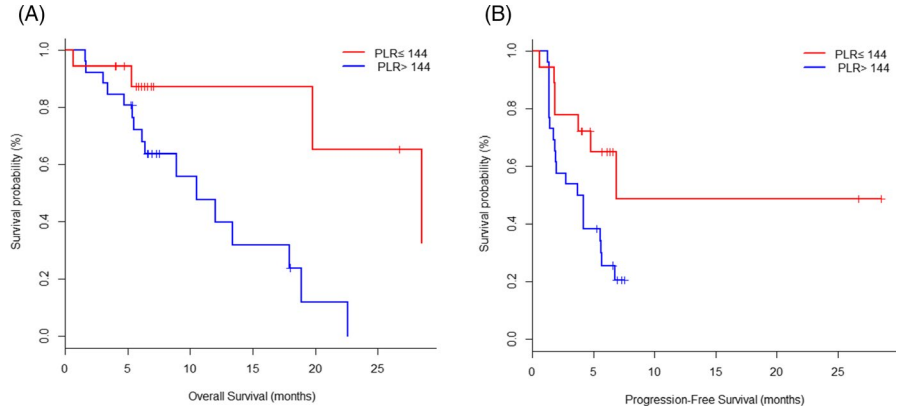

FIGURE 3 Kaplan-Meier plots of overall survival (A) and progression-free survival (B) according to platelet-to-lymphocyte ratio (PLR) at baseline

In multivariate analysis, in order to avoid the multicollinearity among NLR, PLR, and SII, we established three independent COX regression models, respectively, and only one of the three indicators was included in each test. The results revealed that NLR ≤ 3.07, PLR ≤ 144, SII ≤ 603.5 were independently associated with longer PFS and OS (Tables 3 and 4).

4 | DISCUSSION

ICIs have become one of the important treatment strategies for NSCLC. Inflammatory cells have important effects on tumor development and systemic inflammation markers can be of use in determining prognosis.[34] In this study, we found that SIIs, NLR, PLR were significantly associated with the prognosis of metastatic NSCLC patients treated with nivolumab for second-line or further-line treatment.

Inflammation is regarded as an important factor in tumor progression and is one of the hallmarks of cancer.[35] In addition, inflammation can supply the tumor microenvironment with bioactive molecules and the products of inflammatory processes can be considered as potential biomarkers.[36-38] Numerous studies have elucidated in hematological markers, the NLR and PLR can reflect inflammation and host immune reaction, high pretreatment NLR and/or PLR level are potential prognostic predictor for poor PFS and OS in RCC,[26] melanoma,[39] gastric cancer[40] and NSCLC patients received ICIs,[27,41,42] some meta-analysis[43,44] results also demonstrated this conclusion. The results of our analysis further confirm that pretreatment NLR and PLR are the prognostic factors for NSCLC, low NLR and PLR is associated with better outcomes for ICIs. Previous studies reported the cutoff value of NSCLC patients treated with immunotherapy was 2.8-5 and 169-262, respectively. The cutoff values selected in our study were NLR = 3.07, PLR = 144, which is close to the value in previous studies.

Although NLR and PLR can help evaluate the prognosis of ICI treatment, however, these two indexes only integrate two cell types. SII is a new composite measure of the neutrophil, lymphocyte, and platelet counts in the peripheral blood and significantly associated with prognosis in metastatic NSCLC. SII also has been confirmed to be more promising than NLR or PLR.[45-48] De Giorgi et al[30] found that SII is one of the critical prognostic factors for OS in patients with RCC treated with nivolumab. Lower ORR and DCR were associated with higher values of SII at baseline and SII ≥ 1375 can independently predicted OS. Our results also confirm that in patients with metastatic NSCLC, low SII have longer PFS and OS after nivolumab treatment. But Putzu et al[27] showed that SII at 6 weeks was significantly correlated only with PFS, but SII at baseline was not. This conclusion is in contrast with our finding. Further analysis of the reasons may be due to racial differences or different analysis methods. In our study, we performed ROC analysis to determine

TABLE 2 Summary of irAE (N = 44)

	Nivolumab		
irAE	Grade1-2 N (%)	Grade ≥ 3 N (%)	Total N (%)
Skin			
Rash	2 (4.5)	0	2 (4.5)
Dermatitis	1 (2.3)	0	1 (2.3)
Pneumonia	1 (2.3)	1 (2.3)	2 (4.5)
Endocrine			
Hyperthyroidism	5 (11.4)	0	5 (11.4)
Hypothyroidism	6 (13.6)	0	6 (13.6)
Pancreatic toxicity			
Lipase increase	2 (4.5)	0	2 (4.5)
Amylase increase	2 (4.5)	0	2 (4.5)
Liver toxicity			
ALT increase	2 (4.5)	0	2 (4.5)
AST increase	2 (4.5)	0	2 (4.5)
GGT increase	2 (4.5)	0	2 (4.5)
Others			
Thirsty	1 (2.3)	0	1 (2.3)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; irAEs, immune-related adverse events.

TABLE 3 Univariate and multivariate analysis of PFS

Characteristics	HR for PFS (95% CI)			
	Univariate	*P*	Multivariate	*P*
Age at diagnosis (>65 vs ≤65)	0.59 (0.18-1.97)	0.361	0.50 (0.13-1.84)	0.293
Gender (female vs male)	1.06 (0.45-2.52)	0.892	0.98 (0.37-2.56)	0.974
Smoking history (ever vs never)	0.82 (0.37-1.79)	0.620	0.63 (0.27-1.50)	0.298
Histology (squamous vs adenocarcinoma)	1.56 (0.71-3.40)	0.278	1.23 (0.51-2.98)	0.640
Stage (IIIB vs IV)	0.94 (0.38-2.32)	0.888	1.29 (0.48-3.49)	0.615
NLR ≤ 3.07 vs >3.07	0.46 (0.22-0.99)	0.048	0.38 (0.17-0.90)	0.027
PLR ≤ 144 vs >144	0.39 (0.17-0.94)	0.025	0.33 (0.13-0.85)	0.021
SII ≤ 603.5 vs >603.5	0.34 (0.15-0.76)	0.006	0.23 (0.09-0.60)	0.003

TABLE 4 Univariate and multivariate analysis of OS

Characteristics	HR for OS (95% CI)			
	Univariate	*P*	Multivariate	*P*
Age at diagnosis (>65 vs ≤65)	0.80 (0.23-2.79)	0.716	0.53 (0.12-2.30)	0.395
Gender (female vs male)	0.56 (0.19-1.70)	0.284	0.49 (0.15-1.64)	0.249
Smoking history (ever vs never)	1.22 (0.47-3.21)	0.677	0.91 (0.32-2.54)	0.851
Histology (squamous vs adenocarcinoma)	1.37 (0.55-3.44)	0.506	1.04 (0.36-3.01)	0.949
Stage (IIIB vs IV)	0.83 (0.31-2.21)	0.711	0.85 (0.28-2.59)	0.775
NLR ≤ 3.07 vs >3.07	0.20 (0.06-0.62)	0.002	0.18 (0.05-0.60)	0.005
PLR ≤ 144 vs >144	0.20 (0.06-0.73)	0.008	0.13 (0.03-0.60)	0.009
SII ≤ 603.5 vs >603.5	0.16 (0.05-0.51)	0.005	0.13 (0.03-0.47)	0.002

cutoffs value of SII, but Putzu et al used the median. Therefore, we suggest that cutoff values of SII at baseline may be more prognostic than median. We calculated the best cutoff value of SII to be 603.5, further verification is needed in future studies. Compared with PD-L1 and TMB, these three hematological parameters are the most cost-effective and easily obtained in clinical practice.

To our knowledge, there are no data on the correlation between baseline SII and the efficacy of nivolumab in NSCLC patients. We have confirmed this association in NSCLC for the first time. Although some investigators proposed that immune-modified RECIST (imRECIST) criteria may better identify patients with survival benefit than RECIST criteria.[49] But we have used RECIST v1.1 to reflected efficacy and survival benefit due to the key clinical studies of nivolumab such as Checkmate017 and Checkmate 057 are both used this evaluation method. In addition, challenges remain for advancing the broad utility of imRECIST because this conclusion was derived from post hoc and need to be further validated. Furthermore, our study had several limitations mainly due small cohort size and retrospective design, which may need further verified by prospective study with adequate sample sizes.

5 | CONCLUSIONS

Our study demonstrated that at baseline, SII, NLR, and PLR are an independent prognostic predictor in advanced NSCLC patients with the efficacy of nivolumab. These results also offer potential predictive biomarkers and cutoff values to be explored further. In the future, these hematologic parameters could also be used to help stratify patients in randomized studies of ICIs.

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ETHICAL APPROVAL

For this type of study, formal consent is not required.

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