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ORIGINAL RESEARCH

The Prognostic Value of Combined Systemic Immune-Inflammatory Index (SII) and Prognostic Nutritional Index (PNI) in Solid Tumor

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Background: Inflammation and nutrition status were the essential factors for cancer initiation and progression. Previous studies have confirmed systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI) could predict the prognosis of cancer patients. The aim of this study was to evaluate the pre-treatment SII and PNI in predicting outcomes in different cancers.

Methods: The retrospective study included 508 cancer cases diagnosed between June 2013 and June 2022. The pre-treatment SII and PNI were calculated from peripheral blood samples, and the cutoff value was determined by receiver operating characteristic (ROC). The association of SII, PNI with clinicopathological characters and prognosis were assessed by Cox regression and Kaplan–Meier methods.

Results: The ideal preoperative SII and PNI cutoff values were 792.0 and 49.825, respectively. High SII group as well as low PNI group had worse prognosis. Patients satisfied both high SII and low PNI had the lowest overall survival (OS) rate ($p < 0.001$). Multivariable Cox regression analysis identified that the tumor stage ($p < 0.001$), BMI ($p = 0.042$), SII ($p = 0.001$) and AGR ($p = 0.047$) were independently prognostic markers for OS.

Conclusion: High level of pretreatment SII may be an independent prognostic factor for cancer patients. Patients with both high SII and low PNI had the worst prognosis.

Keywords: systemic immune-inflammatory index, prognostic nutritional index, prognosis, solid tumor

Introduction

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world, according to Global Cancer Statistics 2022.[1] With the diagnostic and curative level of cancer improved in recent years, the 5-year survival rate among cancer patients in China has increased to 40.5% from 30% 10 years ago.[2] Despite the improved survival rate, a few of cancer patients in China still live less after treatment as real-world experience confirmed. This therefore reminds us of the importance to suggest personalized therapy strategies for different patients with different clinical characteristics. The established prognostic factors were tumor, node, tumor-node-metastasis (TNM) stage, pathological type, and so on.[3,4] However, even the same cancer type patients with same stage may have distinct survival outcomes. It is critical to identify reliable biomarkers to predict patients' prognosis and guide their individualized treatment.

There is growing evidence that systematic immune inflammation plays a part in the mechanism of tumor initiation, progression, and metastasis.[5,6] Though the concept of inflammation-based scores, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) has been revealed as negative prognostic factors in various types of solid tumors,[7–9] no specific factors were recognized as reliable biomarkers. New available and non-invasive prognostic indicators were looked for. The systemic immune-inflammatory index (SII) is calculated based on peripheral blood neutrophils, platelets and lymphocytes. It is a novel indicator that can predict the clinical outcomes of cancer patients confirmed by a few of studies.[10,11]

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It is generally accepted that cancer patients with malnutrition have a lower tolerance to treatment, as well as worse prognosis and short life span. At the same time, nutritional status is also an essential part of the immune status of cancer patients.[12,13] The prognostic nutritional index (PNI), which is calculated based on the serum albumin and circulating peripheral blood lymphocyte count, has been used to assess the immunonutritional status of cancer patients.[14,15] It is now also used to predict the prognosis of various malignancies, including lung cancer,[16] breast cancer[17] and liver cancer.[18] Our previous study has confirmed that PNI was an independent prognostic factor for gastric cancer.[19]

Most of the studies focused on the value of either SII or PNI, but a single marker may not precisely predict the prognosis of cancer patients. We conducted this study to evaluate the combined effects between PNI, SII and clinical outcomes in cancer patients.

Materials and Methods

Patients

Five hundred and eight cancer patients were enrolled from June 2013 to June 2022 in the Affiliated Kunshan Hospital of Jiangsu University. The following inclusion criteria were applied: histologically or cytologically confirmed stage I–IV cancer patients; more than 18 years old; the Eastern Cooperative Oncology Group (ECOG) activity status score of <2; the expected survival should more than 12 months. Patients with the second primary tumor or active concurrent infection as well as incomplete follow-up data were excluded. The study was conducted in accordance with the Declaration of Helsinki, and all the patients provided written informed consent. This observational study was reviewed and approved by the Institutional Review Board of Affiliated Kunshan Hospital of Jiangsu University (2013-03-020-H04).

Data Collection and Follow-up

The detailed clinical characteristics including age, sex, pathologic type, smoking history, body mass index (BMI), TNM stage (AJCC 8th ed., 2018), ECOG PS, peripheral blood count and liver function were got from the electronic medical record system, which was authentic and reliable. One of the researchers collected the survival time by phone contact, with a follow-up deadline of June 30, 2023. The PNI was calculated as albumin level (g/L) + 5×total lymphocyte count (10^9 /L). The SII was defined as platelet × neutrophil/ lymphocyte counts. The AGR was calculated using the following equations: AGR = ALB/(total protein-ALB). The overall survival (OS) was defined as time from the date of diagnosis to the date of death or last contact. The data were double-checked.

Statistical Analysis

SPSS 16.0 software (SPSS, Chicago, IL, USA) was utilized to perform statistical analyses. The receiver operating characteristic (ROC) curves were carried out to get the optimal cutoff values for AGR, SII and PNI. Comparisons between groups were performed using chi-squared test. Survival analysis was performed using the Kaplan–Meier method and comparisons between survival curves were performed by the Log rank test. Univariate and multivariable analyses were investigated by the Cox proportional hazards regression model. The Cox proportional hazards model was also used to check proportional hazard assumption. The hazard ratio (HR) and 95% confidence interval (CI) were used to assess relative risks. Statistically significance was defined as p values (two sides) <0.05.

Results

Clinicopathologic Characteristics of the Patients

The baseline characteristics of the 508 patients enrolled in the study are summarized in Table 1. There were 239 males (47.05%) and 269 females (52.95%). The median age of the patient was 61 years old, ranging from 25 to 89, of which 191 (37.6%) were ≥65 years old. The most common cancer type was lung cancer (44.69%). 167 (32.88%) patients with stage I–II and 341 (67.12%) patients were diagnosed at stage III–IV. One hundred and seventy-three cases (34.06%) had a history of smoking. There were 68 patients with BMI < 18.5kg/m^2 (13.39%), 379 patients with 18.5 to 24.9 kg/m^2 (74.61%), and 61 patients with BMI > 24.9 kg/m^2 (12.0%). Two hundred and eighty-three (55.71%) patients had PS score of 0 and 225 (44.29%) had PS score of 1.

Table 1 Association of the Patients' Characteristics with the SII and PNI

Characteristics	All n=508 (%)	SII		*P* value	PNI		*P* value
		<792.837 n=359 (%)	≥792.837 n=149 (%)		<49.828 n=238 (%)	≥49.828 n=270 (%)	
Age (years)				0.423			**<0.001**
<65	317 (62.40)	228 (63.51)	89 (59.73)		112 (47.06)	205 (75.93)	
≥65	191 (37.60)	131 (36.49)	60 (40.27)		126 (52.94)	65 (24.07)	
Sex				0.339			**<0.001**
Male	239 (47.05)	164 (45.68)	75 (50.34)		140 (58.82)	99 (36.67)	
Female	269 (52.95)	195 (54.32)	74 (49.66)		98 (41.18)	171 (63.33)	
Cancer type				0.549			**<0.001**
Breast	170 (33.46)	126 (35.10)	44 (29.53)		42 (17.65)	128 (47.41)	
Lung	227 (44.69)	156 (43.45)	71 (47.65)		131 (55.04)	96 (35.56)	
Esophageal	39 (7.68)	27 (7.52)	12 (8.05)		27 (11.35)	12 (4.44)	
Colon & rectal	26 (5.12)	21 (5.85)	5 (3.36)		12 (5.04)	14 (5.18)	
Gastric	11 (2.17)	7 (1.95)	4 (2.68)		8 (3.36)	3 (1.11)	
Others	35 (6.88)	22 (6.13)	13 (8.73)		18 (7.56)	17 (6.30)	
Stage				0.101			**<0.001**
I	65 (12.80)	51 (14.21)	14 (9.39)		19 (7.98)	46 (17.04)	
II	102 (20.08)	68 (18.94)	34 (22.83)		40 (16.81)	62 (22.96)	
III	141 (27.75)	107 (29.80)	34 (22.83)		66 (27.73)	75 (27.78)	
IV	200 (39.37)	133 (37.05)	67 (44.97)		113 (47.48)	87 (32.22)	
Smoking				**0.002**			**<0.001**
No	335 (65.94)	248 (69.08)	87 (58.39)		137 (57.56)	198 (73.33)	
Yes	173 (34.06)	111 (30.92)	62 (41.61)		101 (42.44)	72 (26.67)	
BMI				0.698			**<0.001**
L<18.5	68 (13.39)	43 (11.98)	25 (16.78)		59 (24.79)	9 (3.33)	
18.8–24.9	379 (74.61)	274 (76.32)	105 (70.47)		164 (68.91)	215 (79.63)	
>24.9	61 (12.0)	42 (11.70)	19 (12.75)		15 (6.30)	46 (17.04)	
ECOG PS				**0.004**			**<0.001**
0	283 (55.71)	215 (59.89)	68 (45.64)		82 (34.45)	201 (74.44)	
1	225 (44.29)	144 (40.11)	81 (54.36)		156 (65.55)	69 (25.56)	
AGR				**<0.001**			**<0.001**
Low	197 (38.78)	120 (33.43)	77 (51.68)		138 (57.98)	59 (21.85)	
High	311 (61.22)	239 (66.57)	72 (48.32)		100 (42.02)	211 (78.15)	

Notes: The bold values highlighted that *p*-value less than 0.05 was statistical significance. The cutoff value of AGR is 1.39, according to the ROC analyses.

Abbreviations: AGR, albumin/globulin ratio; PNI, prognostic nutrition index; SII, systemic immune-inflammatory index.

Relationships Between SII, PNI and Clinicopathological Features

The optimal SII and PNI cutoff values were analyzed by ROC curves for the OS of patients. According to the ROC curve and the Youden index, the ideal preoperative PNI and SII cutoff values were 792.0 (Youden index is 0.214) and 49.825 (Youden index is 0.356), respectively. The SII level before treatment was elevated in 149 (29.33%) patients and a total of 238 (46.85%) patients had lower PNI levels. As shown in Table 1, increased SII level was significantly associated with smoking history ($p = 0.02$),

ECGO PS ($p = 0.004$) and AGR level ($p < 0.001$). The high PNI and low PNI groups showed significant differences in gender, age, smoking history, BMI group, cancer type, TNM stage, ECGO PS and AGR. Consider both of SII and PNI, smoking history, ECGO PS and AGR level may be the major related factors.

Univariate and Multivariable Analyses

We performed Cox regression analyses for OS. Table 2 demonstrated the univariate and multivariable analyses for OS. After multivariable analyses, the tumor stage of III/IV ($p < 0.001$), BMI<18.5kg/m2 ($p = 0.042$), high SII ($p = 0.001$, Figure 1) and low AGR ($p = 0.047$, Figure 2) were independently negative prognostic markers for OS.

Table 2 Univariate and Multivariate Analyses of Factors for the Prediction of Overall Survival

Characteristics	Univariate Analysis	*P* value	Multivariate Analysis	*P* value
	HR (95% CI)		HR (95% CI)	
Age (years)				
<65	1.000		1.000	
≥65	1.767 (1.248–2.502)	**0.001**	0.833 (0.565–1.227)	0.354
Sex				
Female	1.000		1.000	
Male	2.851 (1.969–4.127)	**<0.001**	1.254 (0.838–1.878)	0.271
BMI				
L<18.5	2.751 (1.520–4.084)	**<0.001**	2.312 (1.101–2.759)	**0.042**
18.8–24.9	1.000		1.000	
>24.9	0.918 (0.613–1.377)	0.105	0.777 (0.363–1.663)	0.516
Smoking				
No	1.000		1.000	
Yes	3.817 (2.733–5.332)	**<0.001**	1.297 (0.494–3.407)	0.597
ECOG PS				
0	1.000		1.000	
1	1.695 (1.430–2.832)	**<0.001**	0.728 (0.408–1.297)	0.281
Stage				
I/II	1.000		1.000	
III/IV	4.757 (3.638–9.456)	**<0.001**	2.970 (1.567–5.015)	**<0.001**
SII				
Low SII	1.000		1.000	
High SII	2.464 (1.739–3.490)	**<0.001**	1.910 (1.293–2.823)	**0.001**
AGR				
Low AGR	1.000		1.000	
High AGR	0.335 (0.234–0.480)	**<0.001**	0.654 (0.430–0.994)	**0.047**
PNI				
Low PNI	1.000		1.000	
High PNI	0.366 (0.248–0.540)	**<0.001**	0.723 (0.458–1.139)	0.162

Note: The bold values highlighted that *p*-value less than 0.05 was statistical significance.

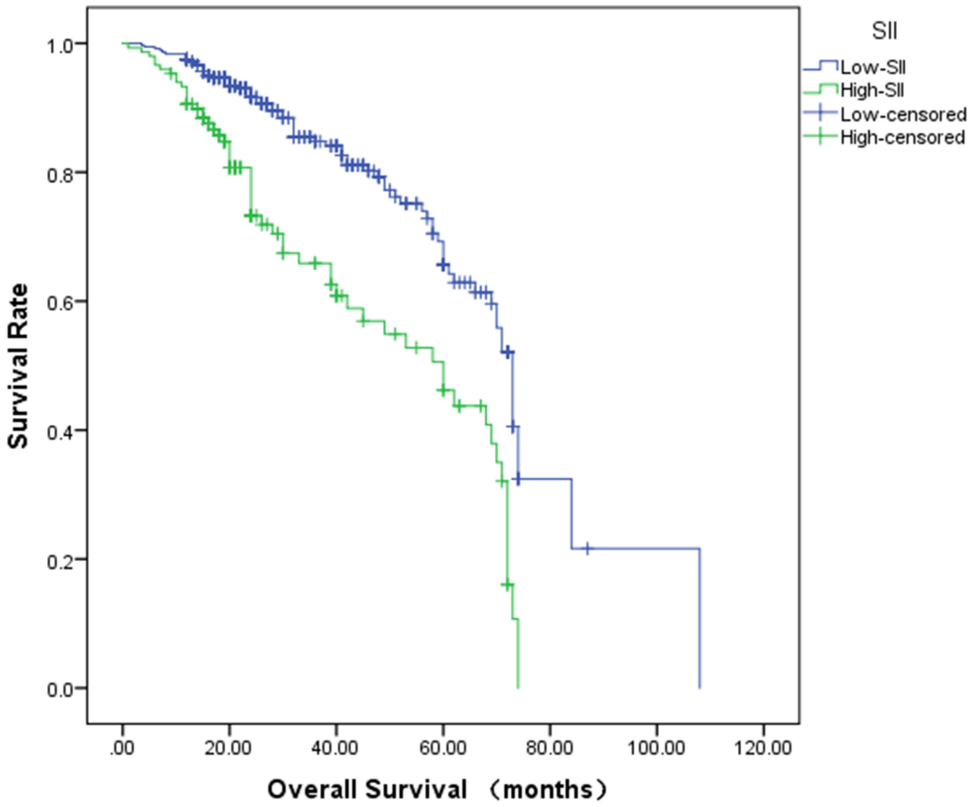


Figure 1 Kaplan-Meier survival curves of overall survival according to SII (p=0.001).

The patients were also divided into four groups based on both the SII and PNI levels: high SII and low PNI (n = 101); high SII and high PNI (n = 48); low SII and high PNI (n = 222); low SII and low PNI (n = 137). At the last follow-up in this study, 377 patients (74.21%) were still alive. The median OS for all patients were 24 months. We performed joint analysis and showed in Figure 3. The results presented that both high SII and low PNI group had the worst prognosis (p < 0.001). The median OS of high SII and low PNI group was 21 months.

Discussion

Despite significant advancements in cancer treatment in recent years, not all patients benefit equally, primarily due to variations in their baseline health status, such as nutrition status and inflammatory conditions. Many blood-derived markers were applied for their cost-effectiveness and prognostic reliability. A great number of research studies have found that the PNI and SII play an important role in the cancer development and prognosis.[10,20–22] Our results have added evidence that SII is an independent influencing factor of overall survival. Moreover, the joint analysis showed both high SII and low PNI had the lowest OS rate. This adds to the growing body of evidence supporting the utility of SII and PNI as prognostic markers in cancer patients, underscoring the importance of considering both inflammatory and nutritional status in prognostic prediction models.

SII derives from peripheral lymphocyte, neutrophil and platelet counts, which could provide a comprehensive reflection of the local immune status and systemic inflammation in the whole body at the same time.[23] SII alone has been proven to predict prognosis of various malignant tumors.[24–26] PNI, a simple and feasible nutritional factor, has been used to assess the immunonutritional status of cancer patients.[27,28] However, single factor may not reflect the complicated mechanism of tumor micro-microenvironment. More and more studies have focused on the joint predictive value of SII and PNI. Fan et al evaluated the value of SII combined with PNI to predict outcomes in non-small cell lung cancer (NSCLC) patients treated with platinum-doublet chemotherapy, and they found that patients with a higher SII-PNI score had a worse prognosis.[29] Another prospective study showed lower SII-PNI scores were associated with better efficacy of

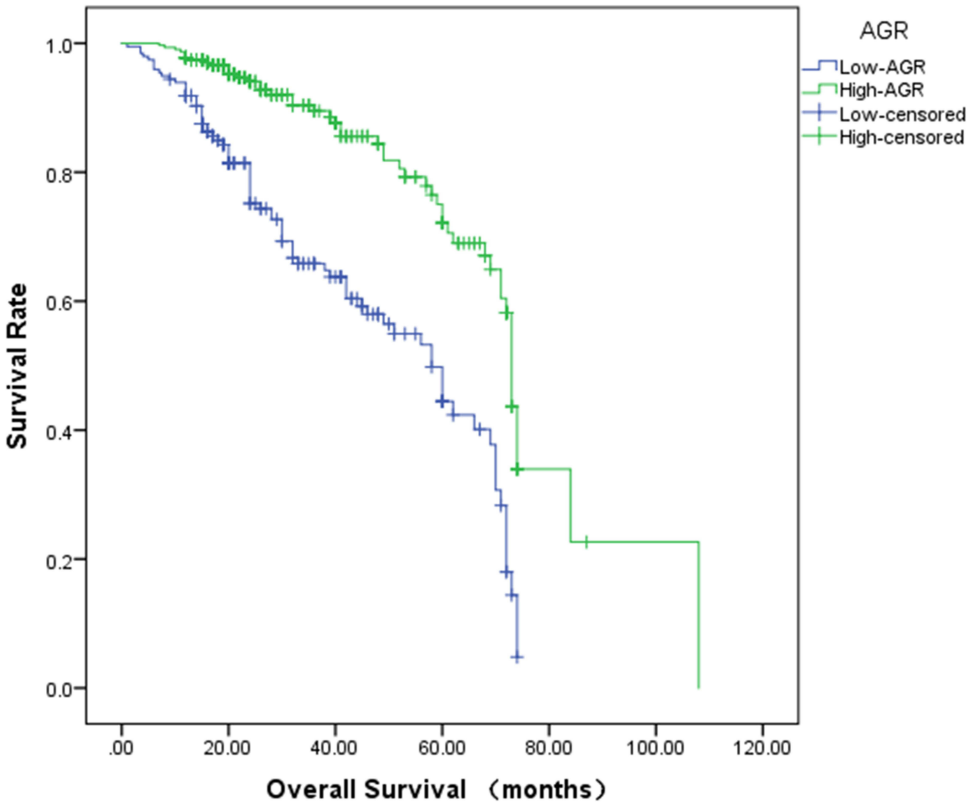


Figure 2 Kaplan-Meier survival curves of overall survival according to AGR (p=0.047).

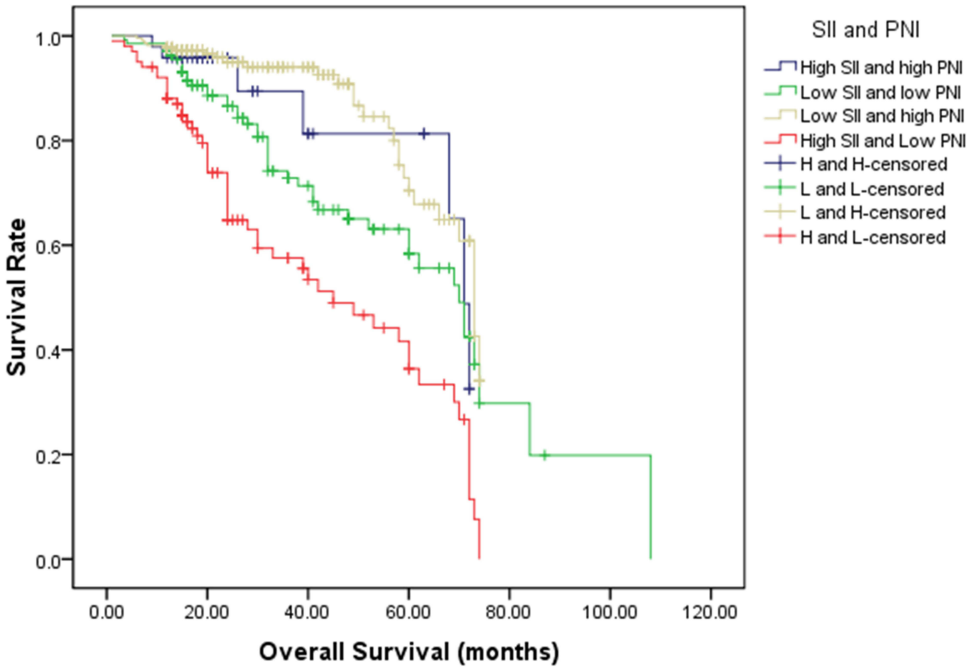


Figure 3 Kaplan-Meier survival curves of overall survival according to both SII and PNI (p<0.001).

chemotherapy combined with immunotherapy in patients with locally advanced gastric cancer.[10] Yang et al developed a nomogram that incorporated the PIIN score, which includes SII and PNI, for predicting overall survival in post-operative pancreatic cancer patients.[30] These studies collectively demonstrate the significance of PNI and SII in cancer

development and prognosis, highlighting their potential as valuable biomarkers in clinical practice. The results could be explained that chronic inflammation associated with malnutrition could paradoxically suppress activation of the adaptive immune system, which is a vicious cycle.[31] We could also tell that the patients with severe inflammatory reaction and poor nutritional condition had poor response to treatment and the overall survival was short. As an accessible, simple, and cost-effective marker derived from blood tests, preliminary evidence supports the potential clinical utility of PNI and SII.

Going forward, it will be important to comprehend the interaction of nutritional status, inflammatory reaction and cancer survival. Malnutrition usually occurs in patients with malignant tumors and gradually leads to cachexia.[32] The incidence of cachexia is particularly high in patients with tumors and lung cancer. Patients with digestive tract tumors are naturally more prone to malnutrition and even cachexia due to the decline or loss of their own digestion and absorption function, coupled with the serious depletion of the body's nutrient reserves by cancer.[33] Cytokines secreted by tumors are one of the causes of cachexia.[34] These cytokines including IL-6, TGF-β and heat shock proteins (HSPs) which directly causes the catabolism and metabolism of the target tissue. Some studies have confirmed that nutritional intervention can improve the quality of life of patients with cachexia, and even prolong the survival of patients.[35,36] Our findings revealed that patients with cancers and low BMI (<18.5) have short overall survival. In clinical practice, individualized nutrition intervention can effectively improve the nutritional status, life quality and the survival prognosis of locally advanced carcinoma patients.

A few limitations of current study also should be explained. First of all, this retrospective analysis was conducted in a single center. It means the sample size is relative small and selection bias is inevitable Another aspect should be pointed out was that we assessed only the pretreatment level of these factors but did not focus on the dynamic change of them. However, the serum levels of these factors were easily affected by nutritional status and side effects of chemotherapy and radiotherapy. Moreover, other factors related to nutrition, inflammation, and immunity, such as weight, waist-to-hip ratio, C-reactive protein (CRP), procalcitonin, even treatments were not included in the final analysis. Though we have tried our best to minimize the risk of bias and unmeasured confounders by applying strict inclusion criteria (complete medical records) and dual-data verification, further research should aim to address these limitations and explore the full potential of SII and PNI as valuable biomarkers in clinical practice.

Conclusion

In conclusion, cancer patients with both high SII and low PNI had poor survival outcome. Pretreatment level of SII may be an independent prognostic factor for cancer patients.

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Disclosure

The authors report no competing interests for this work.

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