

Systemic Immune-inflammation Index Predicts Survival of Patients After Curative Resection for Non-small Cell Lung Cancer

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Abstract. *Background:* The systemic immune-inflammation index (SII) is reported to be associated with clinical outcomes and has been proven to be a promising prognostic indicator in several solid tumor types. To the best of our knowledge, however, no studies regarding SII in patients with resectable non-small cell lung cancer (NSCLC) are available. *Materials and Methods:* Three hundred forty-one patients with NSCLC who underwent surgery at our Institution between 2008 and 2012 were included. The SII was calculated using the formula: platelet count \times neutrophil/lymphocyte count. The optimal cut-off value was calculated using the Cutoff Finder (<http://molpath.charite.de/cutoff>). Univariate and multivariate analyses were calculated by the Cox proportional hazards regression model. *Results:* The optimal cut-off value was $471.2 \times 10^9/l$ for SII. A low SII was associated with female gender, never smoking status, adenocarcinoma histology, higher pathological TNM stage and low level of serum C-reactive protein, but not age, serum carcinoembryonic antigen or cytokeratin 19 fragment level. Patients of the low SII group had a significantly better 5-year overall survival than those with high SII (83.61% vs. 60.39%, $p < 0.001$). Multivariate analysis revealed that the SII was a significant independent predictive indicator for cancer-specific survival ($p = 0.007$). *Conclusion:* This is the first study to demonstrate that the SII could represent an independent prognostic factor for patients with resectable NSCLC.

Cancer-related inflammation is an essential component of the tumor microenvironment, and inflammatory cells may play a critical role in tumor development and progression (1). It has been shown that markers of inflammation and scoring systems based on the systemic inflammatory response are of prognostic value in patients with non-small cell lung cancer (NSCLC) (2). In particular, various combinations of hematological parameters [including C-reactive protein (CRP) concentration, the neutrophil-to-lymphocyte ratio (NLR), and the Glasgow prognostic score (GPS)] have been evaluated as predictors of recurrence or survival in NSCLC (3-6).

Recently, a novel index named the systemic immune-inflammation index (SII), based on the peripheral lymphocyte, neutrophil and platelet counts, was investigated as a prognostic marker in several tumor types (7). Geng *et al.* suggested that SII was superior to other such indices, such as NLR, and served as a more objective marker that reflects the balance between host inflammatory and immune response status in patients with esophageal squamous cell carcinoma (8).

With regard to lung cancer, the prognostic significance of SII was reported for small cell lung cancer (9) and stage III NSCLC (10). However, to our knowledge, there are no previous studies that evaluated the significance of SII for resectable NSCLC. Therefore, in the present study, we examined the prognostic significance of SII in patients with resectable NSCLC.

Patients and Methods

This retrospective study was approved by our Institutional Review Board (O-0255) and the need to obtain patient consent was waived. We retrospectively reviewed data from 341 patients (with 173 men and 168 women, median age of 69 years) who underwent complete resection for NSCLC at our hospital from January 2008 to December 2012. The inclusion criteria were as follows: histologically confirmed NSCLC and complete clinical, laboratory, imaging and follow-up data. The exclusion criteria included: preoperative chemotherapy/radiotherapy or death during the

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Table I. Clinical characteristics of patients based on the systemic immune-inflammation index (SII).

Characteristic	SII (%)		p-Value
	Low	High	
Age			
<65 Years	62 (58.49)	44 (41.51)	0.276
≥65 Years	152 (64.68)	83 (35.32)	
Gender			
Male	93 (53.76)	80 (46.24)	0.001
Female	121 (72.02)	47 (27.98)	
Smoking status			
Never	114 (53.27)	44 (34.65)	0.001
Current/former	100 (46.73)	83 (65.35)	
Histology			
Adenocarcinoma	182 (67.91)	86 (32.09)	<0.001
Other	32 (43.84)	41 (56.16)	
pStage			
I	178 (67.17)	87 (32.83)	0.002
II-III	36 (47.37)	40 (52.63)	
pT status			
pT1	157 (66.81)	78 (33.19)	0.022
pT2-3	57 (53.77)	49 (46.23)	
pN status			
pN0	192 (65.75)	100 (34.25)	0.006
pN1-2	22 (44.9)	27 (55.1)	
Serum CEA			
Normal	159 (62.6)	95 (37.4)	0.918
High	55 (63.22)	32 (36.76)	
CYFRA21-1			
Normal	181 (63.96)	102 (36.04)	0.314
High	33 (56.9)	25 (43.1)	
CRP			
Low	167 (69.01)	75 (30.99)	<0.001
High	47 (47.47)	52 (52.53)	

CEA: Carcinoembryonic antigen, CYFRA21-1: cytokeratin 19 fragments, CRP: C-reactive protein.

perioperative period, clinical evidence of infection or other bone marrow, hematological or autoimmune disease. The last follow-up was in December 2017. Disease in all patients in this study was staged according to the eighth edition cancer staging manual (11). The blood samples for this analysis were collected before surgery. Data on preoperative peripheral neutrophil, lymphocyte and platelet counts, serum levels of CRP, carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (CYFRA21-1) were extracted from the medical records. The SII was defined as follows: SII= platelet count × neutrophil/lymphocyte count. The optimal cut-off value of SII for overall survival was determined using the Cutoff Finder (<http://molpath.charite.de/cutoff>) (12).

Association between categorical variables was assessed using Fisher's exact test. The Kaplan–Meier method was used to estimate cancer-specific survival after surgery. The log-rank test and Cox proportional hazards regression were used to test for differences between groups. After univariate analysis, a multivariate analysis was carried out using Cox regression model. Estimated hazard

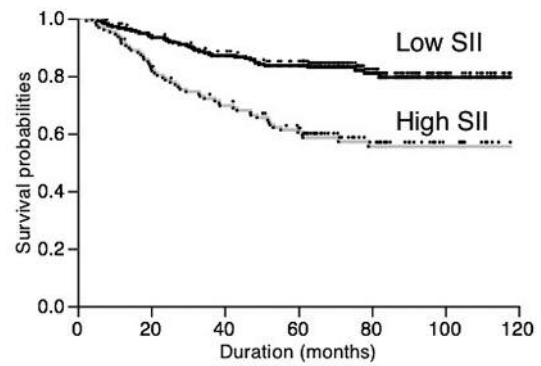


Figure 1. Overall postoperative cancer-specific survival of patients based on the systemic immune-inflammation index (SII). Patients were divided into two groups using the optimal cut-off value for SII of $471.2 \times 10^9/l$.

ratios, their 95% confidence intervals (95% CI), and *p*-values were calculated from the Cox proportional hazards regression models. Statistical analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant when $p < 0.05$.

Results

The optimal cut-off value for SII was $471.2 \times 10^9/l$ according to the Cutoff Finder. Patients then were divided into two groups using this cut-off. There were 214 (62.76%) patients with low SII ($\leq 471.2 \times 10^9/l$) and 127 (37.24%) patients with high SII ($> 471.2 \times 10^9/l$). The relationships between SII and clinical characteristics are shown in Table I. In the present series, a low SII was significantly associated with female gender ($p=0.001$), never smoking status ($p=0.001$), adenocarcinoma histology ($p < 0.001$), lower pathological TNM stage ($p=0.002$) and low serum CRP level ($p < 0.001$), but not age ($p=0.276$), nor serum CEA ($p=0.918$) or CYFRA21-1 ($p=0.314$) levels.

The 5-year cancer-specific survival of patients with low SII was 83.61%, while that of the high SII group was 60.39% ($p < 0.001$). As shown in Figure 1, high SII was also associated with reduced overall cancer-specific survival.

On univariate Cox regression analysis, gender, smoking status, histology, pT status, pN status, serum CEA, CYFRA21-1 and CRP levels, and SII were significantly correlated with cancer-specific survival (all $p < 0.001$, Table II). All nine clinicopathological characteristics were further investigated in multivariate analysis. As shown in Table III, gender ($p=0.002$), histology ($p=0.001$), pN status ($p=0.003$), serum CEA level ($p=0.001$), CRP ($p=0.028$) and SII ($p=0.007$) were independent factors in predicting overall postoperative cancer-specific survival, while smoking status, pT status and serum CYFRA21-1 level were not.

Table II. Univariate analysis of patients based on the systemic immune-inflammation index (SII).

Variable	Favorable	Unfavorable	Hazard ratio	95% Confidence interval		<i>p</i> -Value
				Lower	Upper	
Age	<65 Years	≥65 Years	0.755	0.461	1.193	0.235
Gender	Female	Male	0.329	0.204	0.514	<0.001
Smoking status	Never	Current/former	0.349	0.215	0.549	<0.001
Histology	Adenocarcinoma	Other	0.250	0.165	0.382	<0.001
pT status	pT1	pT2-3	0.450	0.298	0.683	<0.001
pN status	pN0	pN1-2	0.330	0.211	0.534	<0.001
CEA	Normal	High	0.382	0.252	0.586	<0.001
CYFRA21-1	Normal	High	0.353	0.229	0.556	<0.001
CRP	Low	High	0.393	0.260	0.594	<0.001
SII	Low	High	0.368	0.241	0.556	<0.001

CEA: Carcinoembryonic antigen, CYFRA21-1: cytokeratin 19 fragments, CRP: C-reactive protein.

Table III. Multivariate analysis of patients based on the systemic immune-inflammation index (SII).

Variable	Favorable	Unfavorable	Hazard ratio	95% Confidence interval		<i>p</i> -Value
				Lower	Upper	
Gender	Female	Male	0.358	0.178	0.700	0.002
Smoking status	Never	Current/former	0.687	0.337	1.430	0.313
Histology	Adenocarcinoma	Other	0.443	0.275	0.720	0.001
pT status	pT1	pT2-3	0.940	0.572	1.526	0.804
pN status	pN0	pN1-2	0.431	0.255	0.743	0.003
CEA	Normal	High	0.438	0.280	0.694	0.001
CYFRA21-1	Normal	High	0.767	0.465	1.295	0.315
CRP	Low	High	0.604	0.386	0.947	0.028
SII	Low	High	0.540	0.343	0.844	0.007

CEA: Carcinoembryonic antigen, CYFRA21-1: cytokeratin 19 fragments, CRP: C-reactive protein.

Discussion

The link between inflammation and cancer has been widely investigated. Tumor cells influence expression of proinflammatory mediators, and systemic inflammation promotes tumor cell proliferation, migration and invasion by inhibiting apoptosis and promoting angiogenesis (1,13,14). To the best of our knowledge, this is the first report to demonstrate the prognostic role of SII in patients with resectable NSCLC. In this study, we revealed that SII was an independent significant predictive factor ($p=0.007$).

Several studies may give explanations for the prognostic value of SII in patients with tumors. Various studies have suggested that systemic immune and inflammatory cells, such as neutrophils, monocytes, platelets and lymphocytes, are associated with prognostic value in many malignancies (15-18).

Previous studies reported a prognostic significance of the NLR in NSCLC (4,5). Lymphocytes play a fundamental role in cell-mediated immunological destruction of cancer cells (19). Furthermore, neutrophils have a crucial role in the pathogenesis of a broad range of diseases, including cancer (20). Therefore, the prognostic mechanism of the NLR is easy to understand.

Thrombocytosis is a paraneoplastic syndrome, and previous studies have found a significant role of platelets during tumor development and progression (21). Indeed, there is increasing evidence that a high platelet count is associated with worse survival in patients with NSCLC (22). Patients with a high SII often have thrombocytosis, neutrophilia, or lymphopenia. Thus, due to high numbers of neutrophils and platelets while having a low level of lymphocytes, a high SII usually indicates a stronger inflammatory and a weaker immune response in patients. It

may be associated with invasion and metastasis of tumor cells and hence lead to poor survival. Thus, a high SII reflects alterations in the cancer microenvironment that favor cancer initiation, progression, and metastasis.

In the present series, a low SII was significantly associated with female gender, never smoking status, adenocarcinoma histology, lower pathological TNM stage and low CRP. This indicates that the SII is correlated with a more aggressive disease phenotype. However, the results of multivariable analysis showed that the prognostic significance of the SII was independent of standard characteristics of aggressive disease.

SII was based on the counts of three types of circulating immune cells, while NLR, GPS, platelet-to-lymphocyte ratio and monocyte-to-lymphocyte ratio, are based on two types. The SII should be a more objective marker that reflects the balance between host inflammatory and immune responses than all the other systemic inflammation scores. Geng *et al.* showed SII to be superior to the above indices as a prognostic predictive factor in patients with esophageal squamous cell carcinoma (8). A previous study showed that non-steroidal anti-inflammatory drugs have a role in the prevention and treatment of cancer (23) Therefore, there is a possibility that pw NSCLC who have a high SII may especially benefit from targeted anti-inflammatory with aspirin and non-steroidal anti-inflammatory drugs. In addition, the SII is simple and inexpensive to derive, and does not require extra equipment to that needed for day-to-day analyses. Thus, the SII should be routinely considered preoperatively for patients with NSCLC.

The present study had certain limitations. It was a retrospective, single-center study. Therefore, a large-scale prospective study is required to validate the results of the present study.

In conclusion, to our knowledge, this is the first study to demonstrate that the SII could represent an independent prognostic factor for patients with resectable NSCLC.

Conflicts of Interest

The Authors have declared that no conflict of interest exists in regard to this study.

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