Comparison of Inflammation-Based Prognostic Scores in Patients undergoing Curative Resection for Non-small Cell Lung Cancer

Masaki Tomita[a, c], Takanori Ayabe[a], Ryo Maeda[a], Kunihide Nakamura[b]

Abstract

Background: Inflammation-based prognostic scores, including Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII) and advance lung cancer inflammation index (ALI) are reported to be associated with survival in patients with non-small cell lung cancer (NSCLC). However, at present, there are no studies that compared these scoring systems for resectable NSCLC.

Methods: Three hundred forty-one NSCLC patients who underwent surgery at our institution were included. The optimal cut-off values of SII and ALI were calculated by the Cutoff Finder. The area under the receiver operating characteristics curve (AUC) was calculated to compare the predictive ability of each of the scoring systems. Univariate and multivariate analyses were performed to identify the clinicopathological variables associated with overall survival.

Results: The optimal cut-off value of SII and ALI were 471.2×10^9/L and 37.66, respectively. All scores were significantly related to the 5-year cancer-specific survival. The ALI consistently had a higher AUC value in comparison with other inflammation-based prognostic scores. A multivariate analysis showed that GPS and ALI were independently associated with overall cancer-specific survival.

Conclusion: To the best of our knowledge, this is the first study to demonstrate that GPS and ALI appear to be superior to other inflammation-based prognostic scores in patients undergoing potentially curative resection for NSCLC.

Keywords: Inflammation-based prognostic scores; Non-small cell lung cancer; Surgery; Prognosis

[a]Department of Thoracic and Breast Surgery, Faculty of Medicine, University of Miyazaki, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan
[b]Department of Cardiovascular Surgery, Faculty of Medicine, University of Miyazaki, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan
[c]Corresponding Author: Masaki Tomita, Department of Thoracic and Breast Surgery, Faculty of Medicine, University of Miyazaki, Kihara 5200, Kiyotake, Miyazaki 889-1692, Japan. Email: mtomita@med.miyazaki-u.ac.jp

Introduction

Recent studies have begun to unravel the mechanisms linking the host inflammatory response to tumor growth, invasion and metastasis in non-small cell lung cancer (NSCLC) [1].

It has been also recognized that systemic inflammatory responses play an important role in the development of tumor, enhancement of local immunosuppression, thereby worsening the prognosis of the patients [2-7]. Based on this relationship between inflammation and cancer progression, several inflammation-based scores, including Glasgow prognostic score (GPS) [2], neutrophil-to-lymphocyte ratio (NLR) [3], platelet-to-lymphocyte ratio (PLR) [4], prognostic nutritional index (PNI) [5], systemic immune-inflammation index (SII) [6] and advance lung cancer inflammation index (ALI) [7], have been demonstrated to have prognostic value in NSCLC.

In other malignancies, some previous studies compared the prognostic value of selected inflammation-based scores [8-11]. To our knowledge, however, there are no studies elucidating which of these prognostic scores is more suitable in predicting outcomes in patients with NSCLC undergoing surgery. Therefore, the aim of this study was to compare the prognostic value of these inflammation-based scores in patients undergoing potentially curative resection for NSCLC.

Patients and Methods

This retrospective study examined the records of a sequential series of 381 patients with NSCLC who received complete resection and fill the inclusion criteria between January 2008 and December 2012 in our hospital. There were 173 men and 168 women (median age: 69 years old). The inclusion criteria were as following: histologically confirmed NSCLC and complete clinical, laboratory, imaging and follow-up data. The exclusion criteria included: preoperative chemotherapy/radiotherapy or died perioperative period, clinical evidence of infection or other bone marrow, hematological or autoimmune disease. This retrospective study was approved by Medical Ethics Committee of our hospital (O-0296). Complete blood count and routine biochemistry test, including serum C-reactive protein (CRP), serum albumin, serum carcinoembryonic antigen (CEA) and serum cytokeratin 19 fragments (CYFRA21-1), of each patient was applied 1 week before surgery. The GPS, NLR, PLR, PNI,

Table 1. Inflammation-Based Prognostic Scores

	Score
Glasgow Prognostic Score (GPS)	
C-reactive protein ≤ 10 mg/L and albumin ≥ 35 g/L	0
C-reactive protein ≤ 10 mg/L and albumin < 35 g/L	1
C-reactive protein > 10 mg/L and albumin ≥ 35 g/L	1
C-reactive protein > 10 mg/L and albumin < 35 g/L	2
Neutrophil lymphocyte ratio (NLR)	
Neutrophil count/lymphocyte count < 5:1	Low
Neutrophil count/lymphocyte count ≥ 5:1	High
Platelet lymphocyte ratio (PLR)	
Platelet count/lymphocyte count < 150:1	0
Platelet count/lymphocyte count 150 - 300	1
Platelet count/lymphocyte count > 300:1	2
Prognostic nutritional index (PNI)	
Albumin (g/L) + 5 × total lymphocyte count ≥ 45	0
Albumin (g/L) + 5 × total lymphocyte count < 45	1
Systemic immune-inflammation index (SII)	
Platelet count × NLR < cut-off value	Low
Platelet count × NLR ≥ cut-off value	High
Advance lung cancer inflammation index (ALI)	
Body mass index × albumin/NLR ≥ cut-off value	Low
Body mass index × albumin/NLR < cut-off value	High

SII and ALI were constructed as described in Table 1. Cut-off values of NLR, PLR and PNI were determined according to previous reports [3-5]. The optimal cut-off value of SII and ALI for overall cancer-specific survival was determined by Cutoff Finder (http://molpath.charite.de/cutoff) [12].

Association between categorical variables was assessed using the Fisher's exact test. Cancer-specific survival curves were plotted using the Kaplan-Meier method, with comparisons between groups performed using the log-rank test. A receiver operating characteristics (ROC) curve was generated and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each scoring systems. Univariate and multivariate analyses were performed for prognostic factors using the Cox proportional hazards model. Variables that proved to be significant on univariate analysis were subsequently subjected to a multivariate Cox proportional hazards model. Hazard ratios (HRs) estimated using the Cox analysis are reported as relative risks with corresponding 95% confidence intervals (CIs). Statistical analyses were performed using JMP (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant when P < 0.05.

Results

Analysis using the Cutoff Finder showed the recommended cut-off values of SII and ALI for evaluating cancer-specific

survival were $471.2 \times 10^9/L$ and 37.66, respectively.

The relationships between clinical characteristics and each inflammation-based score were shown in Table 2. There is a trend towards an association between these inflammation-based scores and gender, pStage and pN status. However, the results of these scores were not always identical each other.

The relationship between the inflammation-based prognostic scores and cancer-specific overall survival is shown in Figure 1. Based on total number of patients, the 5-year cancer-specific overall survival of patients with GPS 0, low NLR, PLR 0, PNI 1, low SII and high ALI were 83.19%, 76.75%, 80.92%, 79.01%, 83.61% and 84.20%, respectively. On the other hand, those of patients with GPS 1-2, high NLR, PLR 1-2, PNI 0, high SII and low ALI were 64.53%, 40.18%, 62.89%, 67.40%, 860.39% and 57.61%, respectively. All of GPS (P < 0.001), NLR (P < 0.001), PLR (P < 0.001), PNI (P = 0.014), SII (P < 0.001) and ALI (P < 0.001) were associated with a cancer-specific overall survival.

Comparison of the AUCs for cancer-specific overall survival prediction between these inflammation-based prognostic scores was shown in Figure 2. The AUCs of GPS, NLR, PLR, PNI, SII and ALI were 0.642, 0.643, 0.590, 0.608, 0.623 and 0.681, respectively. ALI consistently had a higher AUC value in comparison with other inflammation-based scores.

The univariate analysis showed that gender, smoking status, histology, pT status, pN status, serum CEA level, serum CYFRA21-1 level, serum CRP level, GPS, NLR, PLR, PNI, SII and ALI were significant association with the 5-year cancer-specific survival (Table 3). All 13 clinicopathological characteristics and inflammation-based scores were further investigated in multivariate analysis. As shown in Table 3, gender (P = 0.003), histology (P = 0.001), pN status (P = 0.001), serum CEA level (P = 0.001), GPS (P = 0.009) and ALI (P = 0.026) were independent factors in predicting overall postoperative cancer specific survival, while others were not.

Discussion

The univariate analysis in this study demonstrated that the GPS, NLR, PLR, PNI, SII and ALI were significantly associated with overall cancer-specific survival of NSCLC patients who underwent potentially curative resection. However, the multivariate analysis showed that GPS and ALI were independently associated with overall cancer-specific survival. Moreover, the AUC analysis has shown that ALI was superior to other inflammation-based prognostic scores in terms of predictive accuracy in patients undergoing potentially curative resection for NSCLC. To our knowledge, this was the first report investigating the comparison of inflammation-based scores in operable patients with NSCLC, and showing GPS and ALI to be superior to other inflammation-based prognostic scores for the prediction of prognosis in patients with operable NSCLC.

Inflammation in the tumor microenvironment contributes substantially to tumor proliferation, angiogenesis, invasion, metastasis and survival, suggesting that the systemic inflammatory factors may act as the prognostic markers in NSCLC [1]. CRP is a non-specific inflammatory acute-phase protein,

Table 2. The Relationships Between Clinical Characteristics and Each Inflammation-Based Score

		GPS				NLR			SII		
		GPS 0	GPS 1	GPS 2	P value	Low	High	P value	Low	High	P value
Age (years old)	< 65	68	31	7	0.063	98	8	0.222	62	44	0.276
	≥ 65	123	81	31		225	10		152	83	
Gender	Male	83	65	25	0.007	158	15	0.003	93	80	0.001
	Female	108	47	13		165	3		121	47	
Smoking	Never	109	40	9	<0.001	154	4	0.029	114	44	0.001
	Current/former	82	72	29		169	14		100	83	
Histology	Adeno	163	81	24	0.002	258	10	0.024	182	86	< 0.001
	Others	28	31	14		65	8		32	41	
pStage	I	150	91	24	0.081	256	9	0.008	178	87	< 0.001
	II - III	41	21	14		67	9		36	40	
pT status	pT1	136	82	17	0.004	227	8	0.027	157	78	0.022
	pT2-3	55	30	21		96	10		57	49	
pN status	pN0	163	100	29	0.162	281	11	0.008	192	100	0.006
	pN1-2	28	12	9		42	7		22	27	
CEA	Normal	146	84	24	0.250	241	13	0.822	159	95	0.918
	High	45	28	14		82	5		55	32	
CYFRA	Normal	166	91	26	0.026	272	11	0.023	181	102	0.314
	High	25	21	12		51	7		33	25	

		PLR				PNI			ALI		
		PLR 0	PLR 1	PLR 2	P value	PNI 0	PNI 1	P value	Low	High	P value
Age	< 65	62	40	4	0.084	82	24	0.001	37	69	0.941
	≥ 65	166	61	8		138	97		83	152	
Gender	Male	106	58	9	0.040	109	64	0.554	73	100	0.006
	Female	122	43	3		111	57		47	121	
Smoking	Never	114	41	3	0.086	105	53	0.486	43	115	0.004
	Current/former	114	60	9		115	68		77	106	
Histology	Adeno	185	75	8	0.235	175	93	0.565	82	186	0.001
	Others	43	26	4		45	28		38	35	
pStage	I	186	73	6	0.018	170	95	0.792	83	182	0.006
	II - III	42	28	6		50	26		37	39	
pT status	pT1	162	68	5	0.111	157	78	0.190	76	159	0.103
	pT2-3	66	33	7		63	43		44	62	
pN status	pN0	203	81	8	0.027	191	101	0.403	95	197	0.014
	pN1-2	25	20	4		29	20		25	24	
CEA	Normal	171	74	9	0.946	169	85	0.186	87	167	0.537
	High	57	27	3		51	36		33	54	
CYFRA	Normal	194	80	9	0.334	190	93	0.028	89	194	0.002
	High	34	21	3		30	28		31	27	

GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index; ALI: advance lung cancer inflammation index; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragments.
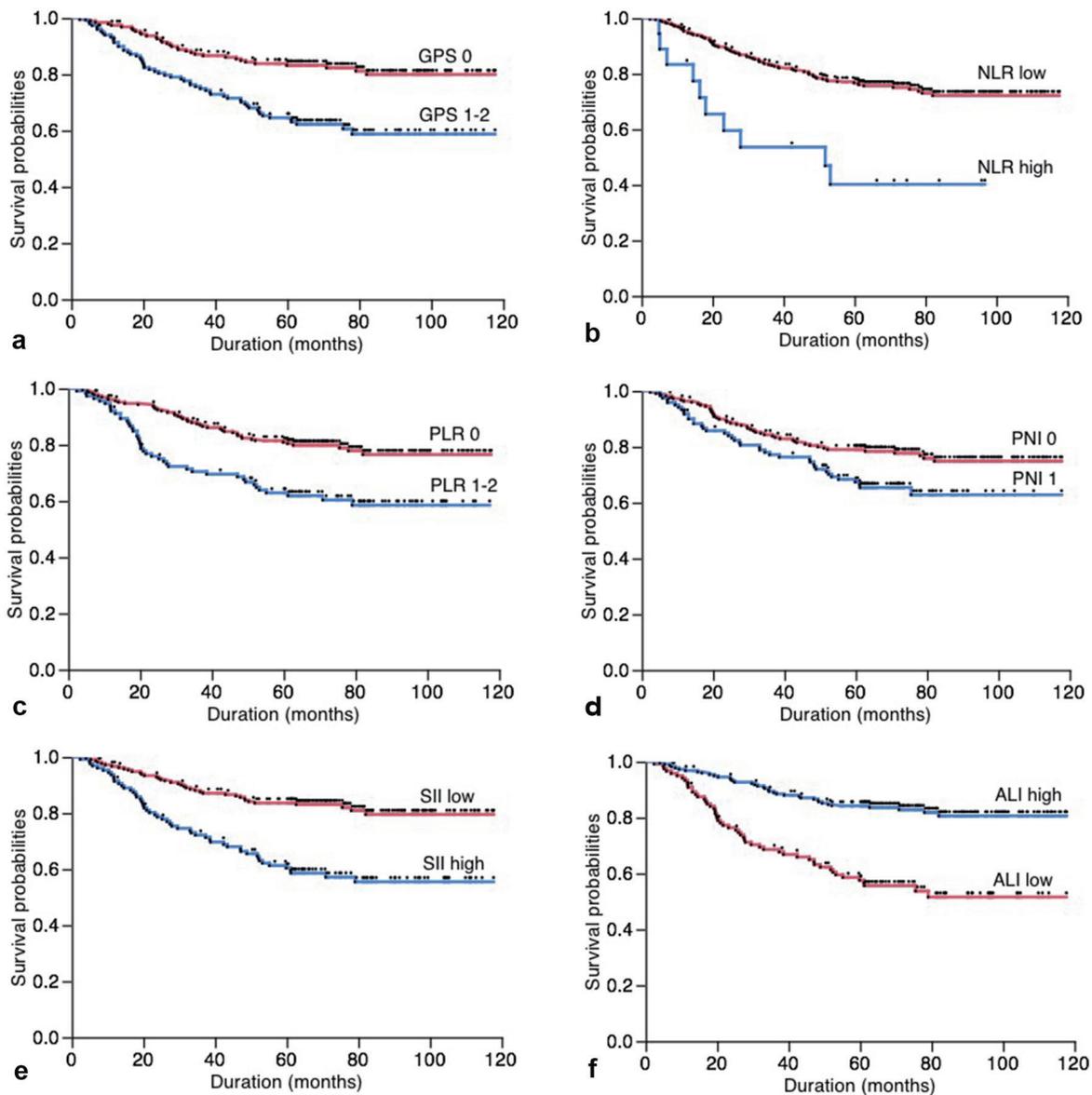
Figure 1. (a) Overall postoperative cancer-specific survival of patients based on Glasgow prognostic score (GPS, P < 0.001); (b) neutrophil-to-lymphocyte ratio (NLR, P < 0.001); (c) platelet-to-lymphocyte ratio (PLR, P < 0.001); (d) prognostic nutritional index (PNI, P = 0.014); (e) systemic immune-inflammation index (SII, P < 0.001); (f) advance lung cancer inflammation index (ALI, P < 0.001).

and an elevated serum CRP level has been reported as an indicator of unfavorable prognosis in patients with NSCLC [13]. Among inflammation-based scores examined in this study, GPS was only based on CRP. Therefore, the superiority of GPS in multivariate analysis might be due to the prognostic power of CRP, at least in part. GPS was defined as the combination of CRP and albumin [2]. Nutritional status of cancer patients, commonly reflected by serum albumin, is also a determinant of survival in NSCLC [14]. Among inflammation-based scores examined in this study, in addition to GPS, PNI and ALI were defined to be based on albumin and other factors. Therefore, the prognostic power of albumin might be offset in multivari-

ate analysis. Another factor to evaluate the nutritional status was body mass index (BMI). A meta-analysis showed that BMI had an inverse association with risk of cancer-specific survival in NSCLC [15]. Among inflammation-based scores examined, only ALI was based on BMI. Therefore, there is a possibility that the superiority of ALI in multivariate analysis and the AUC of ROC curve is also due to the prognostic power of BMI in part.

NLR has been reported to be a useful biomarker to measure the inflammatory status of immune system [3]. The neutrophil is known to be able to aid the proliferation and survival of malignant cells, promote angiogenesis and metastasis [3].
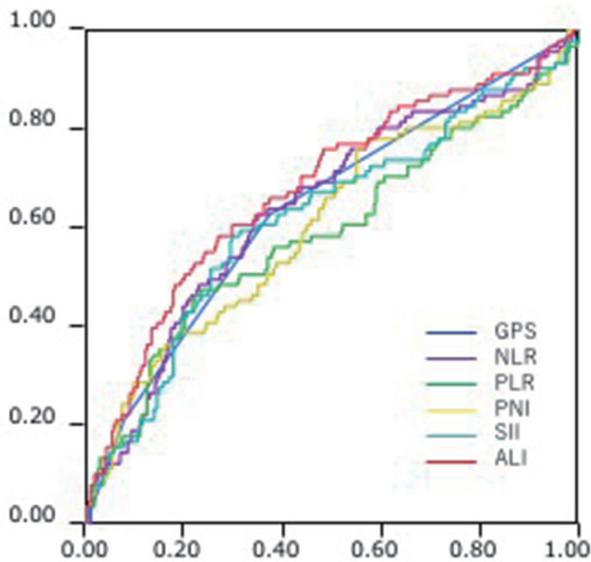
Figure 2. Comparison of the area under the receiver operating characteristics (ROC) for outcome prediction between the inflammation-based prognostic scores.

also based on NLR. Furthermore, PLR and PNI were defined as the combination of lymphocyte count and other factors. Therefore, there is a possibility that the prognostic power of NLR was offset in multivariate analysis.

Several limitations of this study should be acknowledged. First, the study involved a small sample size and single-center design. Second, this study's retrospective design renders it susceptible to selection and analytical biases. Nevertheless, our data indicated that preoperative GPS and ALI might represent independent prognostic factors in patients with resectable NSCLC. GPS and ALI are simple, inexpensive and they do not require extra equipment. Therefore, GPS and ALI should be taken into consideration in the therapeutic program for resectable NSCLC.

In conclusion, to the best of our knowledge, this is the first study to demonstrate that GPS and ALI appear to be superior to other inflammation-based prognostic scores in patients undergoing potentially curative resection for NSCLC.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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Conversely, lymphocytes suppress tumor growth and invasion through their cytolytic activity [3]. Taken together, patients with high NLR have a relative lymphocytopaenia, and, as a result, may exhibit a poorer immune response to malignancy, thereby worsening their prognosis [3]. Among inflammation-based scores examined, in addition to NLR, SII and ALI were

Table 3. Univariate and Multivariate Analyses

	Univariate				Multivariate			
	Hazard ratio	**P value**	**95% CI**		**Hazard ratio**	**P value**	**95% CI**	
			Lower	**Upper**			**Lower**	**Upper**
Age	0.755	0.235	0.461	1.193				
Gender	0.329	< 0.001	0.204	0.514	0.367	0.003	0.183	0.717
Smoking status	0.349	< 0.001	0.215	0.549	0.696	0.323	0.344	1.435
Histology	0.250	< 0.001	0.165	0.382	0.439	0.001	0.271	0.715
pT status	0.450	< 0.001	0.298	0.683	0.958	0.866	0.590	1.580
pN status	0.330	< 0.001	0.211	0.534	0.409	0.002	0.242	0.704
CEA	0.382	< 0.001	0.252	0.586	0.446	0.001	0.287	0.702
CYFRA21-1	0.353	< 0.001	0.229	0.556	0.835	0.502	0.501	1.428
GPS	0.409	< 0.001	0.265	0.622	0.499	0.009	0.296	0.838
NLR	0.309	0.003	0.168	0.635	0.963	0.922	0.472	2.139
PLR	0.462	< 0.001	0.306	0.698	0.834	0.532	0.471	1.473
PNI	0.599	0.017	0.396	0.910	0.772	0.346	0.449	1.323
SII	0.368	< 0.001	0.241	0.556	0.927	0.841	0.444	1.920
ALI	0.312	< 0.001	0.204	0.473	0.444	0.026	0.217	0.907

GPS: Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index; ALI: advance lung cancer inflammation index; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin 19 fragments; CI: confidence interval.

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