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Immunonutritional Indices in Non-small-cell Lung Cancer Patients Receiving Adjuvant Platinum-based Chemotherapy

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Abstract. *Background/Aim: Adjuvant platinum-based chemotherapy (APC) has been the standard of care for patients with non-small-cell lung cancer (NSCLC) who have undergone complete pulmonary resection. This study analyzed the clinical and prognostic significance of immunonutritional indices in NSCLC patients receiving APC. Patients and Methods: We retrospectively reviewed 110 patients from 2008 to 2016. Three immunonutritional indices were calculated: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI). Results: The median age was 64 years, and 66 patients were males. Each index showed a significant correlation with primary tumor length. NLR and PLR were significantly correlated with vascular invasion. Prognostic analyses revealed that each index was significantly correlated with postoperative recurrence-free survival (RFS) and overall survival (OS). On multivariate analyses, PNI was an independent predictor of RFS and OS. Conclusion: Host immunonutritional status may have a significant effect on the postoperative prognosis of NSCLC in patients receiving APC.*

Lung cancer is a leading cause of cancer-related death worldwide, and non-small-cell lung cancer (NSCLC) accounts for approximately 80% of the cases of lung cancer (1). The development of multidisciplinary strategies for treating lung cancer, including surgery, radiotherapy, chemotherapy, and immunotherapy, has improved the outcomes of patients with NSCLC. Surgical resection is a radical treatment option for patients with stage I-III cancers. Based on several clinical trials and a meta-analysis, adjuvant platinum-based chemotherapy (APC) after the complete resection of stage II-III NSCLC has proven clinical benefits and is now considered the standard of care (2-5). However, approximately half of these patients experience disease recurrence after APC (6, 7). Thus, it is important to identify a recurrence- or survival-associated indexes in these patients. Recently, several studies have investigated the prognostic factors for malignant tumors, including NSCLC, based on both tumor characteristics and patient factors. In these studies, postoperative survival for resected NSCLC has been associated with host immunonutritional indices (8-11), which are well-known and can be easily calculated from blood tests: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index (PNI). However, the reports which identified these as survival-associated markers enrolled a heterogeneous population with respect to pathological stage, including patients who received adjuvant therapy. Thus, the significance of immunonutritional indices in a group of patients receiving adjuvant therapy remains unclear. Herein, we examined the clinical and prognostic significance of immunonutritional indices in patients with NSCLC who received APC after complete pulmonary resection.

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Key Words: Non-small-cell lung cancer, prognostic factor, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognostic nutritional index.

Patients and Methods

Patients. We retrospectively investigated 1123 consecutive patients who were diagnosed with NSCLC and underwent surgical pulmonary resection at the Department of Thoracic Surgery, Kitakyushu Municipal Medical Center from April 2008 to December 2016. Among these patients, we excluded those who did not undergo complete resection or receive neoadjuvant therapy, and included patients who received APC after surgery. A consort diagram of this study is presented in Figure 1. The following clinicopathological characteristics were collected: age at surgery, sex, smoking history, performance status, histological type, primary lesion (left or right, upper/middle/lower lobe), surgical procedures, TNM classification, tumor diameter, pleural invasion, lymphatic invasion, vascular invasion, and kind of platinum in the APC regimen (cisplatin or carboplatin). Pathological stage was defined according to the International Association for the Study of Lung Cancer 7th edition (12).

This study was approved by the Institutional Review Board of Kitakyushu Municipal Medical Center on October 30th, 2019 (IRB No. 2019100010), and written informed consent was obtained from all patients preoperatively.

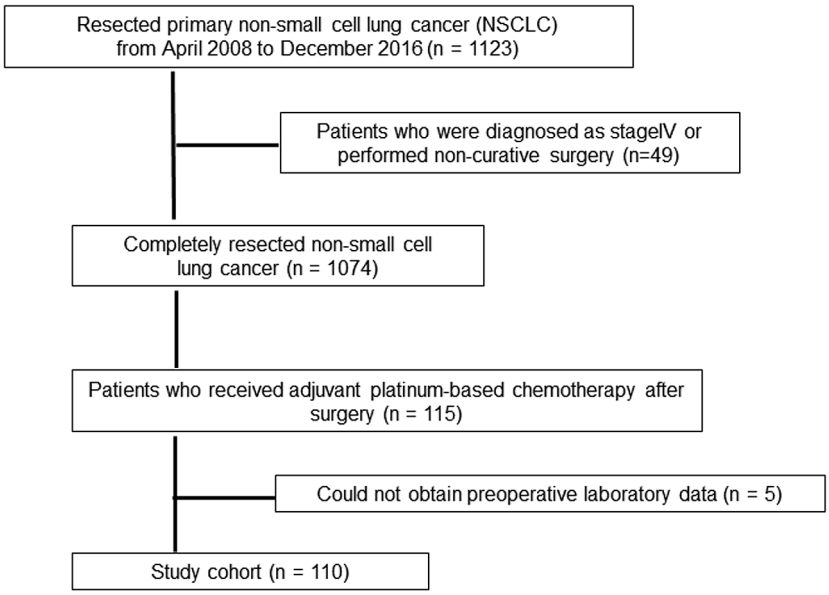

Figure 1. *CONSORT diagram of the study design and inclusion and exclusion criteria.*

Patient follow-up and adjuvant platinum-based chemotherapy. After surgical resection, routine check-up examinations (including a physical examination, blood tests including serum tumor marker tests, and chest x-ray) were performed at 3-month intervals for the first 2-3 years, and thereafter at 6-month intervals. Computed tomography was performed twice each year for the first 2-3 years, and at least annually thereafter. Brain magnetic resonance imaging was performed as clinically required. The last follow-up review was performed on June 30, 2020.

The eligibility criteria for patients receiving APC were as follows: pathological stages II-III, Eastern Cooperative Oncology Group performance status of 0 and 1, and acquisition of informed consent. Although age was important in the consideration of APC administration, it was not a stringent factor. Patients received APC intravenously every 3-4 weeks. The APC regimens were as follows: cisplatin (CDDP)/vinorelbine, carboplatin (CBDCA)/paclitaxel, CDDP/Tegafur, Gimeracil, Oteracil (TS-1), CBDCA/gemcitabine, and others.

Immunonutritional indices. We evaluated the following preoperative immunonutritional indices determined from blood tests: NLR, PLR, and PNI. NLR was calculated as follows: number of whole neutrophils/whole lymphocytes. Similarly, PLR was calculated as follows: number of platelets/whole lymphocytes. The PNI was calculated as follows: 10× serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3).

Statistical analysis. All statistical analyses were performed using JMP software version 14 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as mean±standard deviation, and categorical variables are reported as numbers. The cutoff value of each immunonutritional parameter was determined by a receiver operative characteristic (ROC) curve using 5-year survival as the state variable. Associations between each variable were analyzed *via* two-sided Fisher's exact test. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the date of recurrence or death, which was censored at the last follow-up. Overall survival (OS) was defined as the interval between the date of surgery and the date of the last follow-up or death. Kaplan–Meier survival curve was used to estimate survival rates. Univariate and multivariate analyses were used to estimate the hazard ratios (HRs) for independent prognostic values by Cox regression hazard models using the backward stepwise elimination method. *p*-values of <0.05 were considered statistically significant.

Results

Patients and clinical characteristics. We enrolled 110 eligible patients in the present study, of whom 60% were male and approximately 72% were never smokers. The median age was 64 years (range=41-80 years). There were 74 (67.3%) patients with adenocarcinoma and 36 (32.7%) with cancers of other histological types, including squamous cell carcinoma. During the follow-up period, disease recurrence was observed in 46 patients (41.8%). Almost all patients underwent lobectomy as a radical surgery, and 59 received cisplatin-based APC and 51 received carboplatin-based APC (Table I).

Immunonutritional indices and their clinical significance. According to the ROC curves, the optimal cutoff values of NLR, PLR, and PNI were 3.0216, 157.7655, and 46.810, respectively (Figure 2). The patients were divided into two groups according to these cutoff values. There were 37, 53, and 73 patients with high NLR, PLR, and PNI, respectively. We further analyzed the relationship between each immunonutritional index and the clinical characteristics. As shown in Table II, all parameters were

Table I. *Clinical characteristics of the enrolled patients (n=110).*

Factors	Number of patients (% or range)
Age (median)	64 (40-81)
Gender	
Male	66 (60.0%)
Female	44 (40.0%)
Smoking status	
Absent	78 (72.2%)
Present	32 (27.8%)
Histological type	
Adenocarcinoma	74 (67.3%)
Others	36 (32.7%)
Adjuvant platinum regimen	
Cisplatin-based	59 (53.6%)
Carboplatin-based	51 (46.4%)
Surgical procedures	
Lobectomy	107 (97.3%)
Sublober resection	3 (2.7%)
Pathological stage	
II	57 (51.8%)
III	53 (48.2%)
Recurrence	
None	46 (41.8%)
Occurred	64 (58.2%)

significantly associated with tumor size. There were no significant relationships between pleural invasion or lymphatic invasion and immunonutritional indices, but NLR and PLR were significantly correlated with the presence or absence of vascular invasion.

Prognostic significance of each immunonutritional index. We analyzed the RFS and OS after surgery according to the NLR, PLR, and PNI status (high or low). As shown in Figure 3, high NLR, high PLR, and low PNI groups had significantly poor survival as indicated by RFS (NLR: HR=1.88, p=0.0272; PLR: HR=1.98, p=0.0222; PNI: HR=1.97, p=0.0174). Regarding OS, all three parameters were significantly correlated with poor prognosis as indicated by RFS (NLR: HR=3.14, p=0.0007; PLR: HR=2.49, p=0.0088; PNI: HR=2.81, p=0.0022) (Figure 4).

Finally, we performed univariate and multivariate analyses to determine the independent prognostic factors. In the multivariate analysis, the following factors assessed in the univariate analysis were included: age (≥70 *vs*. <70 years), sex, smoking status, surgical procedures, tumor diameter (≥30 *vs*. <30 mm), histological type, APC regimen (CDDP *vs*. CBDCA), pathological stage (III *vs*. II), lymphovascular invasion, pleural invasion, NLR, PLR, and PNI. The multivariate analysis of RFS revealed that PNI (HR=2.16, p=0072) and lymphatic invasion (HR=2.51, p=0015) were independent prognostic factors of poor RFS (Table III). Similarly, the multivariate analysis revealed that PNI was an independent prognostic factor of poor OS (HR=2.69; p=0.0034) (Table III).

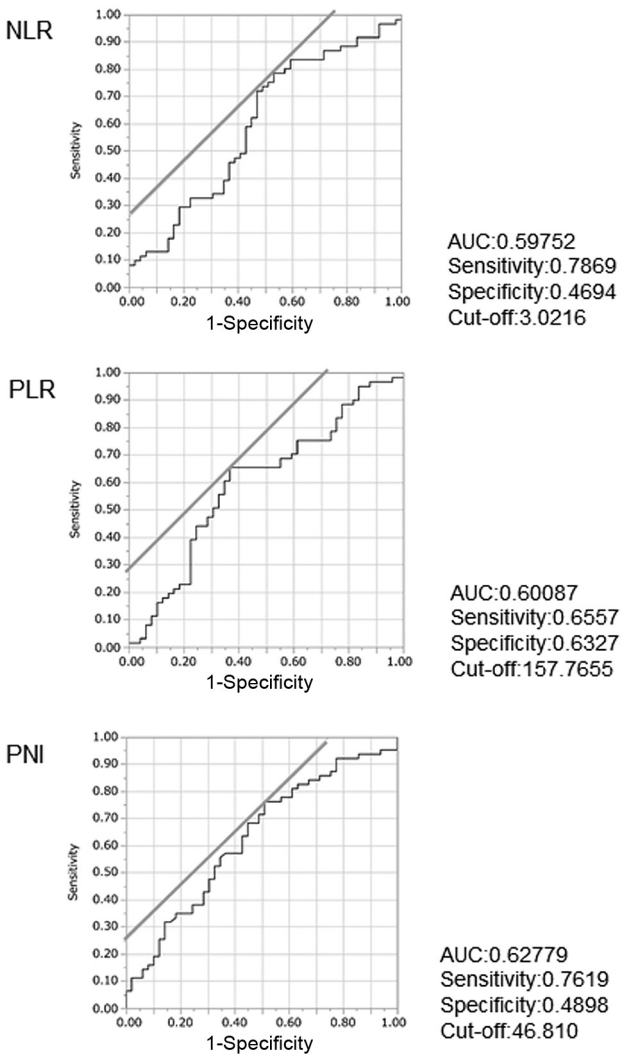

Figure 2. *ROC curve of the NLR, PLR, and PNI dependent on 5-year overall survival. The cutoff values were 3.0216, 157.7655, and 46.81, respectively. NLR: Neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; ROC: receiver operative characteristic.*

Discussion

We investigated the clinical and prognostic significance of immunonutritional indices for patients receiving APC. In the present study, the patients were divided into high and low groups based on the optimal cutoff values of each index, which were determined using an ROC curve. The three immunonutritional indices were significantly associated with postoperative RFS and OS. Low PNI was also found to be an independent prognostic factor of poor RFS and OS.

Host immunonutritional status is known to be a valuable prognostic factor for malignant tumors, including NSCLC

Table II. *Relationships between immunonutritional indices and clinicopathological characteristics.*

	NLR			PLR			PNI		
	High	Low	*p*-Value	High	Low	*p*-Value	High	Low	*p*-Value
Age	62.8	62.9	0.9386	61.8	63.8	0.2703	62.4	63.8	0.4912
Mean (95%CI)	(60.0-65.9)	(60.7-65.1)		(59.3-64.4)	(61.4-66.3)		(60.2-64.6)	(60.7-66.8)	
Gender									
Male	28 (75.7%)	38 (52.1%)	0.0231	34 (64.2%)	35 (56.1%)	0.4393	39 (53.4%)	27 (73.0%)	0.0638
Female	9 (24.3%)	35 (47.9%)		19 (35.8%)	25 (33.9%)		34 (46.6%)	10 (27.0%)	
Tumor diameter (mm)	49.5	37.7	0.0231	48.8	35.0	0.0047	36.9	51.1	0.0061
Mean (95%CI)	(41.2-57.9)	(31.8-43.5)		(42.0-55.7)	(28.5-41.6)		(31.1-42.7)	(42.9-59.4)	
Histological type									
Adenocarcinoma	23 (62.2%)	51 (69.9%)	0.5193	36 (67.9%)	38 (66.7%)	1.0000	52 (71.2%)	22 (59.5%)	0.2823
Others	14 (37.8%)	22 (30.1%)		17 (32.1%)	19 (33.2%)		21 (38.8%)	15 (40.5%)	
Pathological stage									
III	22 (59.5%)	35 (48.0%)	0.3139	28 (52.8%)	29 (50.9%)	0.8510	36 (49.3%)	21 (59.8%)	0.5460
II	15 (40.5%)	38 (52.0%)		25 (47.2%)	28 (49.1%)		37 (50.7%)	16 (40.2%)	
Lymphatic invasion									
Present	10 (27.8%)	23 (31.5%)	0.8253	18 (34.6%)	15 (26.3%)	0.4063	21 (29.2%)	12 (32.4%)	0.8263
Absent	26 (72.2%)	50 (68.5%)		34 (65.4%)	42 (73.7%)		51 (70.8%)	25 (67.6%)	
Vascular invasion									
Present	9 (24.3%)	5 (6.9%)	0.0146	11 (20.8%)	3 (5.3%)	0.0208	8 (11.0%)	6 (16.2%)	0.5463
Absent	28 (75.7%)	68 (93.1%)		42 (79.2%)	54 (94.7%)		65 (89.0%)	31 (83.8%)	
Pleural invasion									
Present	20 (54.1%)	26 (35.6%)	0.0700	25 (47.2%)	21 (36.8%)	0.3345	30 (41.1%)	16 (40.2%)	0.8407
Absent	17 (45.9%)	47 (64.4%)		28 (52.8%)	36 (63.2%)		43 (58.9%)	21 (59.8%)	

CI: Confidence interval; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

Table III. *Multivariate analyses of RFS (A) and OS (B) in patients with NSCLC who received adjuvant platinum-based chemotherapy (n=110).*

(A) RFS		Multivariate analysis		(B) OS		Multivariate analysis	
Factor		HR (95%CI)	*p*-Value	Factor		HR (95%CI)	*p*-Value
Lymphatic invasion	Present	2.51	0.0015	Vascular invasion	Present	2.70	0.0102
	Absent	(1.42-4.42)			Absent	(1.27-5.78)	
PNI	Low	2.16	0.0072	PNI	Low	2.69	0.0034
	High	(1.23-3.80)			High	(1.39-5.22)	

CI: Confidence interval; HR: hazard ratio; NSCLC: non-small cell lung cancer; RFS: recurrence free survival; OS: overall survival: PNI: prognostic nutritional index.

(13). Several studies have reported a significant correlation of NLR, PLR, and PNI with postoperative prognosis (14-16), but these studies analyzed a heterogenous population of patients with stage I-III cancers who had undergone resection, including those who received adjuvant therapy. Thus, it is important to analyze the prognostic power of immunonutritional indices in a group with background characteristics. Toda *et al*. analyzed preoperative PLR and its prognostic value in patients treated surgically with or without adjuvant chemotherapy (17) and found that PLR predicted poor prognosis in surgically treated patients with NSCLC, especially those who received adjuvant chemotherapy. The cutoff of PLR was also determined using the ROC curve. Conversely, Shimizu *et al*. investigated the clinical and prognostic significance of PNI before adjuvant chemotherapy and demonstrated that PNI was significantly correlated with RFS at a cutoff value of 50 for patients with NSCLC who received adjuvant tegafur or APC. According to these previous reports and the present study, it is likely that the host immunonutritional status is indeed associated with poor survival in patients with NSCLC who have undergone surgical resection, including those who received APC.

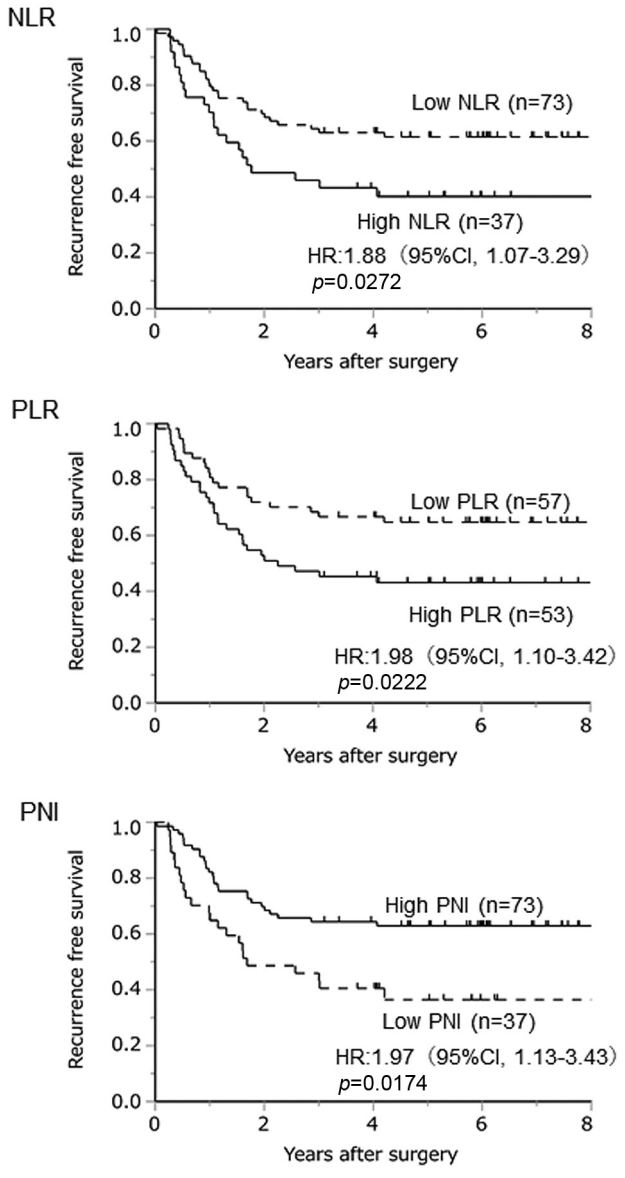

Figure 3. *Recurrence free survival analysis of patients with NSCLC who underwent curative pulmonary resection and subsequent adjuvant platinum-based chemotherapy according to NLR, PLR, and PNI status. NLR: Neutrophil-to-lymphocyte ratio; NSCLC: non-small-cell lung cancer; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.*

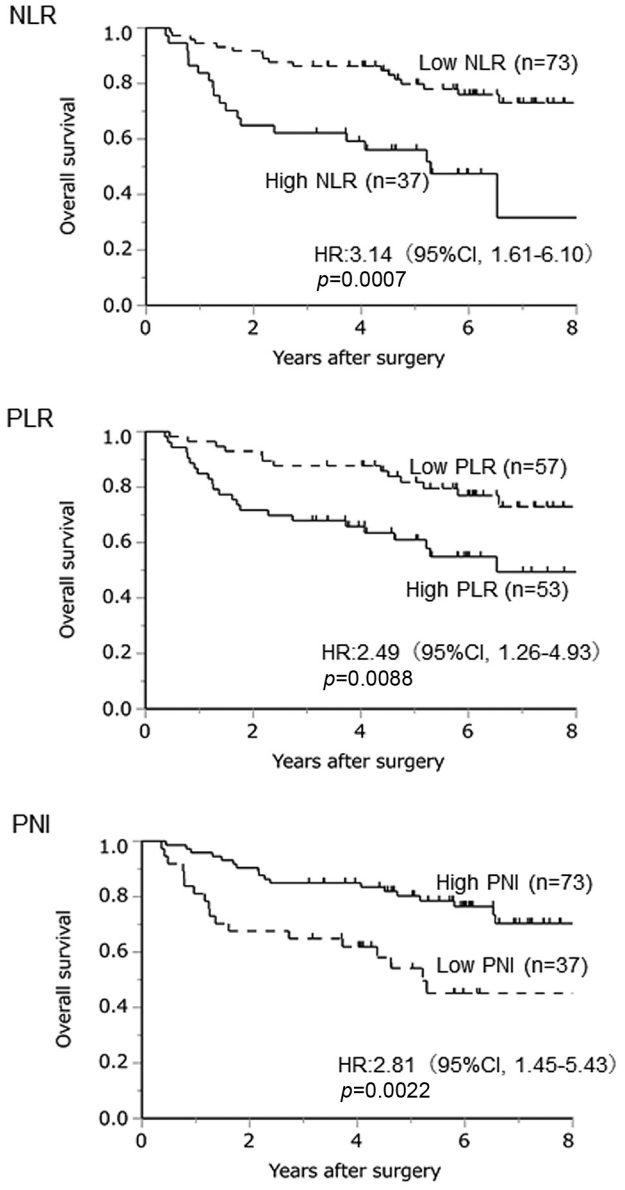

Figure 4. *Overall survival analysis of patients with NSCLC who underwent curative pulmonary resection and subsequent adjuvant platinum-based chemotherapy according to NLR, PLR, and PNI status. NLR: Neutrophil-to-lymphocyte ratio; NSCLC: non-small-cell lung cancer; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.*

The present study demonstrated that low PNI was an independent predictive factor of poor survival, but NLR and PLR were not. Further, all these parameters fluctuated based on total lymphocyte counts, with low lymphocyte counts resulting in high NLR, high PLR, and low PNI. Lymphocytes induce tumor cell apoptosis, and a decrease in lymphocytes is known to be proportional to tumor growth and invasion (18), which could subsequently promote the metastatic potential of the tumor. However, NLR and PLR seem to be affected by inflammatory conditions, which are changed at that moment. A decrease in PNI can result from a decrease in serum albumin and/or total lymphocyte count. In summary, PNI is affected by both host nutritional and inflammation status, which is highlighted in the present study. Albumin synthesis is suppressed by inflammatory cytokines such as interferon-γ or interleukin-6, which act on the liver (19). Thus, albumin levels

may have relatively long-term consequences on inflammatory signals compared with NLR and PLR, and thus may affect prognosis more strongly. It is suggested that nutritional intervention can decrease the disease occurrence or improve prognosis of patients with lung cancer (20). In fact, the body mass index, which may be affected by nutritional intervention, was significantly associated with postoperative prognosis in patients with NSCLC (21). This nutritional intervention trial will be needed in future.

Recently, the treatment strategies for patients with advanced lung cancer have changed due to the emergence of immune-checkpoint inhibitors (ICIs). This change has also affected the field of perioperative treatment. In fact, several clinical trials of perioperative treatment using ICIs have proven their clinical significance in the adjuvant or neoadjuvant setting (22-25). Host immunonutritional indices were identified as potential biomarkers for the response and post-treatment prognosis of ICIs (26, 27). Because ICIs are expected to play an important role in perioperative treatment, including postoperative adjuvant therapy, it is important to study the effects of the immunonutritional status of patients.

The present study has some limitations. First, this is a single-center retrospective study in which the cutoff values were determined from within the study cohort. Second, the APC regimens were diverse in terms of the kind of platinum used, which could affect the postoperative prognosis. However, in this study, there were no significant differences in the investigated parameters among the groups that had undergone different APC regimens.

Conclusion

In conclusion, the host preoperative immunonutritional status may be associated with postoperative prognosis in patients with NSCLC who received APC. Further multicenter studies are warranted to verify the results of this study.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

TM contributed to all aspects of the study's design. TM wrote the article. All listed Authors collected patient information. TM performed all statistical analyses. FH, MY and MH supervised the article and prepared the final version of the article. All listed Authors have contributed to the arguments of the article and have read and approved the final submission.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68(6)*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F, National Cancer Institute of Canada Clinical Trials Group and National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators: Vinorelbine plus cisplatin *vs*. observation in resected non-small-cell lung cancer. N Engl J Med *352(25)*: 2589-2597, 2005. PMID: 15972865. DOI: 10.1056/NEJMoa043623

3 Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T and LACE Collaborative Group: Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol *26(21)*: 3552-3559, 2008. PMID: 18506026. DOI: 10.1200/JCO.2007.13.9030

4 Butts CA, Ding K, Seymour L, Twumasi-Ankrah P, Graham B, Gandara D, Johnson DH, Kesler KA, Green M, Vincent M, Cormier Y, Goss G, Findlay B, Johnston M, Tsao MS and Shepherd FA: Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol *28(1)*: 29-34, 2010. PMID: 19933915. DOI: 10.1200/JCO.2009.24.0333

5 Douillard JY, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, Veillard AS, Seymour L, Le Chevalier T, Spiro S, Stephens R, Pignon JP and LACE Collaborative Group: Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol *5(2)*: 220-228, 2010. PMID: 20027124. DOI: 10.1097/JTO.0b013e3181c814e7

6 Kenmotsu H, Ohde Y, Wakuda K, Nakashima K, Omori S, Ono A, Naito T, Murakami H, Kojima H, Takahashi S, Isaka M, Endo M and Takahashi T: Survival data for postoperative adjuvant chemotherapy comprising cisplatin plus vinorelbine after complete resection of non-small cell lung cancer. Cancer Chemother Pharmacol *80(3)*: 609-614, 2017. PMID: 28761967. DOI: 10.1007/s00280-017-3400-z

7 Sonobe M, Hamaji M, Motoyama H, Menju T, Aoyama A, Chen-Yoshikawa TF, Sato T and Date H: Adjuvant vinorelbine and cisplatin after complete resection of stage II and III non-small cell lung cancer: long-term follow-up of our study of Japanese patients. Surg Today *48(7)*: 687-694, 2018. PMID: 29502152. DOI: 10.1007/s00595-018-1646-7

8 Toyokawa G, Kozuma Y, Matsubara T, Haratake N, Takamori S, Akamine T, Takada K, Katsura M, Shimokawa M, Shoji F, Okamoto T and Maehara Y: Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma. J Thorac Dis *9(9)*: 2942-2951, 2017. PMID: 29221266. DOI: 10.21037/jtd.2017.07.108

9 He H, Guo W, Song P, Liu L, Zhang G, Wang Y, Qiu B, Tan F, Xue Q and Gao S: Preoperative systemic immune-inflammation index and prognostic nutritional index predict prognosis of

patients with pulmonary neuroendocrine tumors after surgical resection. Ann Transl Med *8(10)*: 630, 2020. PMID: 32566567. DOI: 10.21037/atm-19-4476

10 Park S, Ahn HJ, Yang M, Kim JA, Kim JK and Park SJ: The prognostic nutritional index and postoperative complications after curative lung cancer resection: A retrospective cohort study. J Thorac Cardiovasc Surg *160(1)*: 276-285.e1, 2020. PMID: 31859072. DOI: 10.1016/j.jtcvs.2019.10.105

11 Takada K, Takamori S, Matsubara T, Haratake N, Akamine T, Kinoshita F, Ono Y, Wakasu S, Tanaka K, Oku Y, Oba T, Osoegawa A, Tagawa T, Takenoyama M, Shimokawa M, Oda Y and Mori M: Clinical significance of preoperative inflammatory markers in non-small cell lung cancer patients: A multicenter retrospective study. PLoS One *15(11)*: e0241580, 2020. PMID: 33137158. DOI: 10.1371/journal.pone.0241580

12 Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L, International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions: The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol *2(8)*: 706-714, 2007. PMID: 17762336. DOI: 10.1097/JTO.0b013e31812f3c1a

13 Shoji F, Haratake N, Akamine T, Takamori S, Katsura M, Takada K, Toyokawa G, Okamoto T and Maehara Y: The preoperative controlling nutritional status score predicts survival after curative surgery in patients with pathological stage I non-small cell lung cancer. Anticancer Res *37(2)*: 741-747, 2017. PMID: 28179325. DOI: 10.21873/anticanres.11372

14 Zhang H, Xia H, Zhang L, Zhang B, Yue D and Wang C: Clinical significance of preoperative neutrophil-lymphocyte *vs* platelet-lymphocyte ratio in primary operable patients with non-small cell lung cancer. Am J Surg *210(3)*: 526-535, 2015. PMID: 26105800. DOI: 10.1016/j.amjsurg.2015.03.022

15 Wang J, Kalhor N, Hu J, Wang B, Chu H, Zhang B, Guan Y and Wu Y: Pretreatment neutrophil to lymphocyte ratio is associated with poor survival in patients with stage I-III non-small cell lung cancer. PLoS One *11(10)*: e0163397, 2016. PMID: 27695079. DOI: 10.1371/journal.pone.0163397

16 Hayasaka K, Shiono S, Suzuki K, Endoh M and Okada Y: Postoperative prognostic nutritional index as a prognostic factor after non-small cell lung cancer surgery. Gen Thorac Cardiovasc Surg *68(10)*: 1163-1171, 2020. PMID: 32328993. DOI: 10.1007/s11748-020-01366-7

17 Toda M, Tsukioka T, Izumi N, Komatsu H, Okada S, Hara K, Miyamoto H, Ito R, Shibata T and Nishiyama N: Platelet-to-lymphocyte ratio predicts the prognosis of patients with non-small cell lung cancer treated with surgery and postoperative adjuvant chemotherapy. Thorac Cancer *9(1)*: 112-119, 2018. PMID: 29105365. DOI: 10.1111/1759-7714.12547

18 Martínez-Lostao L, Anel A and Pardo J: How do cytotoxic lymphocytes kill cancer cells? Clin Cancer Res *21(22)*: 5047-5056, 2015. PMID: 26567364. DOI: 10.1158/1078-0432.CCR-15-0685

19 Lampinen M, Carlson M, Håkansson LD and Venge P: Cytokine-regulated accumulation of eosinophils in inflammatory disease. Allergy *59(8)*: 793-805, 2004. PMID: 15230810. DOI: 10.1111/j.1398-9995.2004.00469.x

20 Kasprzyk A, Bilmin K, Chmielewska-Ignatowicz T, Pawlikowski J, Religioni U and Merks P: The role of nutritional support in malnourished patients with lung cancer. In Vivo *35(1)*: 53-60, 2021. PMID: 33402449. DOI: 10.21873/invivo.12231

21 Takada K, Shimokawa M, Akamine T, Ono Y, Haro A, Osoegawa A, Tagawa T and Mori M: Association of low body mass index with poor clinical outcomes after resection of non-small cell lung cancer. Anticancer Res *39(4)*: 1987-1996, 2019. PMID: 30952742. DOI: 10.21873/anticanres.13309

22 Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, Zahurak M, Yang SC, Jones DR, Broderick S, Battafarano RJ, Velez MJ, Rekhtman N, Olah Z, Naidoo J, Marrone KA, Verde F, Guo H, Zhang J, Caushi JX, Chan HY, Sidhom JW, Scharpf RB, White J, Gabrielson E, Wang H, Rosner GL, Rusch V, Wolchok JD, Merghoub T, Taube JM, Velculescu VE, Topalian SL, Brahmer JR and Pardoll DM: Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med *378(21)*: 1976-1986, 2018. PMID: 29658848. DOI: 10.1056/NEJMoa1716078

23 Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, Majem M, Rodríguez-Abreu D, Martínez-Martí A, De Castro Carpeño J, Cobo M, López Vivanco G, Del Barco E, Bernabé Caro R, Viñolas N, Barneto Aranda I, Viteri S, Pereira E, Royuela A, Casarrubios M, Salas Antón C, Parra ER, Wistuba I, Calvo V, Laza-Briviesca R, Romero A, Massuti B and Cruz-Bermúdez A: Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol *21(11)*: 1413-1422, 2020. PMID: 32979984. DOI: 10.1016/S1470-2045(20)30453-8

24 Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, Garofano RF, Stoopler MB, Cheng SK, White A, Lanuti M, D'Ovidio F, Bacchetta M, Sonett JR, Saqi A and Rizvi NA: Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol *21(6)*: 786-795, 2020. PMID: 32386568. DOI: 10.1016/S1470-2045(20)30140-6

25 Wakelee H, Altorki N, Zhou C, Csöszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-marti A, Kenmotsu H, Chen Y, Chella A, Sugawara S, Gitlitz B, Bennett E, Wu F, Yi J, Deng Y, Mccleland M and Felip E: IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). Journal of Clinical Oncology *39(15_suppl)*: 8500-8500, 2021. DOI: 10.1200/JCO.2021.39.15_suppl.8500

26 Shoji F, Takeoka H, Kozuma Y, Toyokawa G, Yamazaki K, Ichiki M and Takeo S: Pretreatment prognostic nutritional index as a novel biomarker in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer *136*: 45-51, 2019. PMID: 31437663. DOI: 10.1016/j.lungcan.2019.08.006

27 Takamori S, Takada K, Shimokawa M, Matsubara T, Fujishita T, Ito K, Toyozawa R, Yamaguchi M, Okamoto T, Yoneshima Y, Tanaka K, Okamoto I, Tagawa T and Mori M: Clinical utility of pretreatment Glasgow prognostic score in non-small-cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer *152*: 27-33, 2021. PMID: 33341085. DOI: 10.1016/j.lungcan.2020.11.026

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