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Original Article

Complete Blood Cell Count-Derived Inflammatory Biomarkers in Early-Stage Non-Small-Cell Lung Cancer

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Background: Complete blood cell count (CBC)-derived inflammatory biomarkers are widely used as prognostic parameters for various malignancies, but the best predictive biomarker for early-stage non-small-cell lung cancer (NSCLC) is unclear. We retrospectively analyzed early-stage NSCLC patients to investigate predictive effects of preoperative CBC-derived inflammatory biomarkers.

Patients and Methods: We selected 311 consecutive patients with pathological stage IA NSCLC surgically resected from April 2006 to December 2012. Univariate and multivariate Cox proportional analyses of recurrence-free survival (RFS) were used to test the preoperative systemic immune inflammation index (SII), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and monocyte–lymphocyte ratio (MLR).

Results: Preoperative high MLR levels were significantly associated with patient sex, smoking status, and postoperative recurrence ($p < 0.0001$, $p = 0.0307$, and $p = 0.0146$, respectively), and preoperative high SII levels were significantly correlated with postoperative recurrence ($p = 0.0458$). Neither NLR nor PLR were associated with any related factors. Only preoperative MLR levels ($p = 0.0269$) were identified as an independent predictor of shorter RFS. The relative risk (RR) for preoperative high MLR level versus low level patients was 2.259 (95% confidence interval [CI]: 1.094–5.000). Five-year RFS rates in patients with preoperatively high MLR levels were significantly lower than in those with low MLR levels (82.21% vs. 92.05%, $p = 0.0062$). In subgroup analysis by tumor size and MLR level, the high MLR level subgroup with tumors >2 cm had significantly shorter RFS than other subgroups ($p = 0.0289$).

Conclusions: The preoperative MLR level is the optimal predictor of recurrence in patients with pathological stage IA NSCLC.

Keywords: complete blood cell count-derived inflammatory biomarkers, pathological stage IA non-small-cell lung cancer, prognostic factor

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Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] The most beneficial therapy for early-stage non-small-cell lung cancer (NSCLC) is surgery, but over 10% of pathological stage IA NSCLC patients have postoperative recurrence after undergoing curative resections.[2] This suggests the existence of heterogeneity even within early-stage NSCLC patients not only in terms of tumor factors such as malignant grade but also host factors such as immune nutritional conditions.

We previously reported about both tumor factors and host factors in pathological stage IA NSCLC.[3-7] Moreover, inflammation has recently been highlighted as one of the markers that reflect the host immune condition. Inflammation plays an important role in the development and progression of various cancers by promoting cancer cell proliferation and survival, angiogenesis, and tumor metastases.[8] Indeed, inflammatory cells in the tumor microenvironment influence tumor development, and the systemic inflammatory condition may indicate tumor status.

A complete blood cell count (CBC) examination is routinely used in the preoperative systemic evaluation. Recently, CBC-derived inflammatory biomarkers such as the systemic immune inflammation index (SII), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and monocyte–lymphocyte ratio (MLR) were used as prognostic factors in various malignancies.[9–12] These biomarkers are based on two or three parameters related to neutrophils, lymphocytes, platelets, and monocytes. SII has been investigated as a prognostic factor in several malignancies,[9] while NLR, PLR, and MLR have been used as markers in systemic inflammation and are associated with poor outcomes in solid malignancies.[10] In the case of NSCLC,[11,12] these parameters have also been reported as poor indicators, but few are specifically associated with pathological stage IA disease; therefore, the optimal biomarker for pathological IA NSCLC is unclear.

The present study aimed to retrospectively analyze clinicopathological features of patients with stage IA NSCLC to identify the best predictor of postoperative recurrence among preoperative CBC-derived inflammatory biomarkers.

Materials and Methods

Patients

This study was approved by the Ethics Committee of Kyushu Medical Center. From April 2006 to December 2012, 529 consecutive patients with primary lung cancer underwent complete surgical resection at the Department of Thoracic Surgery, Kyushu Medical Center. Of these patients, we excluded those who had clinical evidence of infection, other inflammation, hematological diseases, or who used drugs that might influence their hematological data. Both Tis and T1mi patients were also excluded in this study. This left 311 patients with pathological stage IA NSCLC who were enrolled in this study. Patient clinical profiles are summarized in **Table 1**.

Table 1 Clinical profiles

	No. (%) or median (range)
Total assessable patients	311 (100)
Follow-up month	63, 0–144
Age, years	68, 30–91
Sex	
Female	154 (49.5)
Male	157 (50.5)
Smoking status	
Never	178 (57.2)
Former	133 (42.8)
Histological type	
Adenocarcinoma	265 (85.2)
Squamous cell carcinoma	33 (10.6)
Others	13 (4.2)
Surgical procedure	
Lobectomy	186 (59.8)
Limited resections (segmentectomy or wedge resection)	125 (40.2)
Recurrence	
No	269 (86.5)
Yes	42 (13.5)

Follow-up examinations were conducted over a median period of 63 months (range, 0–144 months) after surgical resection. These consisted of chest computed tomography (CT), abdominal CT, bone scintigraphy, and brain magnetic resonance imaging (MRI) at 6-month intervals during the first year and yearly thereafter. Chest roentgenography and blood tests that included tumor markers were performed at 3- or 4-month intervals during the first year and at 6-month intervals thereafter.

The study group included 154 women and 157 men, with a mean age at surgery of 68 years (range, 30–91 years). In all, 178 patients (57.2%) had never smoked and the remaining 133 patients were former or current smokers. Histological types were adenocarcinoma: 265 patients (85.2%); squamous cell carcinoma: 33 (10.6%); and other types: 13 (4.2%). In all, 186 patients (59.8%) underwent lobectomies with systemic lymphadenectomies and 125 patients underwent limited resections including segmentectomies or wedge resections in patients with peripheral lesions or poor pulmonary function. No patients received any adjuvant chemotherapy or radiotherapy. Postoperative recurrence occurred in 42 patients (13.5%), and was defined as in a previous report.[13] The first appearance of any new lesion suspected to be recurrence of the original lung cancer was defined as postoperative recurrence, and was clinically diagnosed by combinations of CT, MRI, bone scintigraphy, and fluorodeoxyglucose positron emission tomography (FDG–PET), or was pathologically diagnosed if necessary.

Table 2 Pathologic profiles

	No. (%)
Tumor size	
T1a (≤1 cm)	31 (10.0)
T1b (≤2 cm)	172 (55.3)
T1c (2 ≤ 3 cm)	108 (34.7)
Intratumoral blood vessel invasion	
Without	294 (94.5)
With	17 (5.5)
Intratumoral lymphatic vessel invasion	
Without	282 (90.7)
With	29 (9.3)

Calculation of each CBC-derived biomarkers

Data on preoperative blood cell counts were retrospectively extracted from the medical records. White blood cell count data were analyzed in the general routine laboratory of our hospital within 1 week before surgery. We calculated the SII, NLR, PLR, and MLR as follows: SII = platelet counts × neutrophil counts/lymphocyte counts, NLR = neutrophil counts/lymphocyte counts, PLR = platelet counts/lymphocyte counts, MLR = monocyte counts/lymphocyte counts.

Histopathological evaluation

We retrospectively collected formalin-fixed and paraffin-embedded NSCLC surgical specimens and reviewed them as hematoxylin–eosin-stained sections. Elastic and connective tissues were stained to determine pleural invasion, intratumoral blood vessel invasion (BVI), and lymphatic vessel invasion (LVI). BVI and LVI were distinguished by Elastica van Gieson staining. A specimen was considered positive for intratumoral vessel invasion when cancer cells were observed in the intratumoral vessel lumen. Patients' pathological stages were based on the tumor node metastasis (TNM) classification of the International Union Against Cancer.[14] For TNM staging, all patients underwent CT scans of the thorax and the upper abdomen, bone scintigraphy, and brain CTs, MRIs, or FDG–PETs. Of the 311 patients, 31 (10.0%) had primary tumors ≤1 cm (T1a), 172 (55.3%) had primary tumors ≤2 cm (T1b), and 80 patients had primary tumors ≤3 cm (T1c); 17 patients (5.5%) were found to have BVI and 29 (9.3%) had LVI (**Table 2**).

Statistical analysis

Categorical variables were analyzed using Fisher's exact test; continuous variables were analyzed using two-sided tests. Recurrence-free survival (RFS) was defined as the interval between resection and the first recurrence event including relapse or death from lung cancer. We analyzed patient survival using the Kaplan–Meier method and compared groups using the log-rank test. Uni- and multivariate analyses were performed using a logistic proportional model and Cox proportional hazards model to identify independent predictive and prognostic factors. $p < 0.05$ was considered significant. All statistical analyses were performed using the JMP software program, version 14.0.

Results

Optimal cut-off values of preoperative CBC-derived inflammatory biomarkers

Receiver operating characteristic (ROC) curves of SII, NLR, PLR, and MLR were analyzed, and recurrence was predicted by comparing the area under the curve (AUC). Optimal cut-off values for SII, NLR, PLR, and MLR were 358 (sensitivity: 85.7%; specificity: 30.86%), 1.5 (sensitivity: 76.6%; specificity: 28.6%), 184 (sensitivity: 69.5%; specificity: 35.7%), and 0.19 (sensitivity: 71.4%; specificity: 48.8%), respectively. In all, 227 patients (73.0%) had high SII, and the remaining 84 (27.0%) had lower SII; 113 (36.3%) had high NLR, and the remaining 198 (53.7%) had lower NLR; 97 (31.2%) had high PLR, and the remaining 214 (68.8%) had lower PLR; 161 (51.8%) had high MLR, and the remaining 137 (48.2%) had lower MLR.

Association between patients' characteristics and preoperative CBC-derived inflammatory biomarkers

High SII was significantly associated only with postoperative recurrence ($p = 0.0458$). High MLR was significantly associated with patient sex ($p < 0.0001$), smoking status ($p = 0.0307$), and postoperative recurrence ($p = 0.0146$). Neither NLR nor PLR were associated with any patient characteristics (**Table 3**).

Prognostic factors in patients with stage IA NSCLC

We compared RFS for patients younger versus older than 65 years; male versus female; past or current smokers versus never-smokers; those with primary tumors >2 cm (T1b and T1c) versus ≤2 cm (T1a); those with non-adenocarcinomas versus adenocarcinomas; patients who underwent limited resections versus lobectomies; with versus without BVI; with versus without LVI; high SII versus low SII; high NLR versus low NLR; high PLR versus low PLR; and high MLR versus low MLR status (**Table 4**).

Table 3 Patient characteristics based on preoperative complete blood cell count-derived inflammatory biomarkers

Variables	SII			NLR			PLR			MLR		
	Low (n = 84)	High (n = 227)	p	Low (n = 74)	High (n = 237)	p	Low (n = 214)	High (n = 97)	p	Low (n = 137)	High (n = 161)	p
Age			*0.6863*			*0.2579*			*0.1820*			*0.0569*
>65	55	143		43	155		131	67		79	110	
≤65	29	84		31	82		83	30		58	51	
Sex			*0.5075*			*0.9243*			*0.9937*			*<0.0001*
Male	45	112		37	120		108	49		53	99	
Female	39	115		37	117		106	48		84	62	
Smoking status			*0.7810*			*0.8618*			*0.5334*			*0.0307*
Cur/for	37	96		31	102		89	44		51	80	
Never	47	131		43	135		125	53		86	81	
Histology			*0.8786*			*0.7206*			*0.4183*			*0.1147*
Others	12	34		10	36		34	12		15	28	
Ad	72	193		64	201		180	85		122	133	
Procedures			*0.6456*			*0.4545*			*0.2108*			*0.2123*
Limited	32	93		27	98		81	44		49	69	
Lobectomy	52	134		47	139		133	53		88	92	
p-T factor			*0.7799*			*0.8665*			*0.1735*			*0.5694*
T1bc	74	206		67	213		196	84		119	148	
T1a	10	21		7	24		18	13		15	13	
BVI			*0.7396*			*0.1979*			*0.4832*			*0.5527*
Yes	4	13		2	15		13	4		9	8	
No	80	214		72	222		201	93		128	153	
LVI			*0.3412*			*0.3495*			*0.6877*			*0.5204*
Yes	10	19		9	20		19	10		14	13	
No	74	208		65	217		195	87		123	148	
Recurrence			*0.0458*			*0.6976*			*0.4961*			*0.0146*
Yes	6	36		11	31		27	15		12	30	
No	78	191		63	206		187	82		125	131	

Ad: adenocarcinoma; BVI: intratumoral blood vessel invasion; Cur/for: current/former smoker; limited: limited resection; LVI: lymphatic vessel invasion; MLR: monocyte–lymphocyte ratio; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; p-T factor: pathological T factor; SII: systemic immune inflammation index

Table 4 Univariate and multivariate analyses of disease-free survival in patients with stage IA NSCLC

Variable	Univariate analysis	Multivariate analysis
	RR (95% CI), p value	RR (95% CI), p value
Age (> 65 vs. ≤ 65)	1.150 (0.620–2.217), 0.6622	–
Sex (male vs. female)	2.677 (1.421–5.329), 0.0021	1.297 (0.572–3.045), 0.5386
Smoking status (cur/for vs. never)	2.726 (1.470–5.252), 0.0014	1.664 (0.768–3.757), 0.2011
Tumor size (T1bc vs. T1a)	4.608 (1.004–81.682), 0.0493	4.311 (0.877–78.243), 0.0780
Histology (non-Ad vs. Ad)	2.001 (0.900–4.007), 0.0855	–
Procedure (limited vs. lobectomy)	1.436 (0.763–2.857), 0.2680	–
BVI (yes vs. no)	3.503 (1.327–7.720), 0.0143	2.955 (1.049–7.002), 0.0412
LVI (yes vs. no)	3.262 (1.466–6.536), 0.0053	3.177 (1.353–6.776), 0.0097
Preoperative SII (high vs. low)	2.264 (1.028–5.976), 0.0420	1.924 (0.826–5.275), 0.1355
Preoperative NLR (high vs. low)	1.710 (0.921–3.139), 0.0883	–
Preoperative PLR (high vs. low)	1.328 (0.689–2.464), 0.3854	
Preoperative MLR (high vs. low)	2.474 (1.298–5.029), 0.0054	2.259 (1.094–5.000), 0.0269

95% CI: 95% confidence interval; Ad: adenocarcinoma; BVI: intratumoral blood vessel invasion; Cur/for: current/former smoker; limited: limited resection; LVI: lymphatic vessel invasion; MLR: monocyte–lymphocyte ratio; NSCLC: non–small-cell lung cancer; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; RR: relative risk; SII: systemic immune inflammation index

Univariate analyses showed that patient sex ($p = 0.0021$), smoking status ($p = 0.0014$), tumor size ($p = 0.0493$), BVI ($p = 0.0143$), LVI ($p = 0.0053$), SII status ($p = 0.0420$), and MLR status ($p = 0.0054$) significantly affected RFS. The relative risk (RR) for male patients was 2.677 versus female patients (95% confidence interval [CI]: 1.421–5.329); patients with smoking history was 2.726 versus without smoking history (95% CI: 1.470–5.252); patients with T1bc was 4.608 versus those with T1a (95% CI: 1.004–81.682); patients with BVI was 3.503 versus those without BVI (95% CI: 1.327–7.720); patients with LVI was 3.262 versus those without LVI (95% CI: 1.466–6.536); patients with high SII was 2.264 versus those with low SII (95% CI: 1.028–5.976); and was 2.474 for high MLR patients versus low MLR patients (95% CI: 1.298–5.0029). In multivariate analysis, BVI (RR: 2.955; 95% CI: 1.049–7.002; $p = 0.0412$), LVI (RR: 3.177; 95% CI: 1.353–6.776; $p = 0.0097$), and MLR (RR: 2.259; 95% CI: 1.094–5.000; $p = 0.0269$) were shown to be independent prognostic factors (**Table 4**).

Preoperative CBC-derived inflammatory biomarkers and RFS in patients with stage IA NSCLC

Figure 1 shows the RFS curves for CBC-derived inflammatory biomarkers in patients with stage IA NSCLC. In Kaplan–Meier analysis of RFS by preoperative SII for patients with stage IA NSCLC, the preoperative high SII group had significantly shorter RFS than the preoperative low SII group (p = 0.0438, log-rank test). There were no significant differences among NLR or PLR levels. In Kaplan–Meier analysis of RFS by preoperative MLR for patients with stage IA NSCLC, the preoperative high MLR group had significantly shorter RFS than the preoperative low MLR group ($p = 0.0062$, log-rank test). There were no significant differences among NLR or PLR levels.

Subgroups analysis according to tumor size and preoperative MLR level

We also analyzed subgroups by tumor size (T1a or T1b or T1c) and MLR level (high or low). Patients in the subgroup with high MLR levels and tumors >2 cm (T1c) had significantly shorter RFS than other subgroups ($p = 0.0289$, log-rank test, **Fig. 2**).

Discussion

Previously, we reported that immune nutritional parameters were predictive and prognostic factors in early-stage NSCLC patients.[5-7] These parameters reflect the host nutritional and immune conditions. The nutritional condition is determined by serum albumin or total cholesterol levels, while the immune condition is established only by the lymphocyte count which is influenced by both the neutrophil count and monocyte count. Therefore, it is important to clarify which combination of white blood cell count categories adequately reflects the host immune condition.

Thus, in the present study, we aimed to identify the best CBC-derived inflammatory biomarker to predict

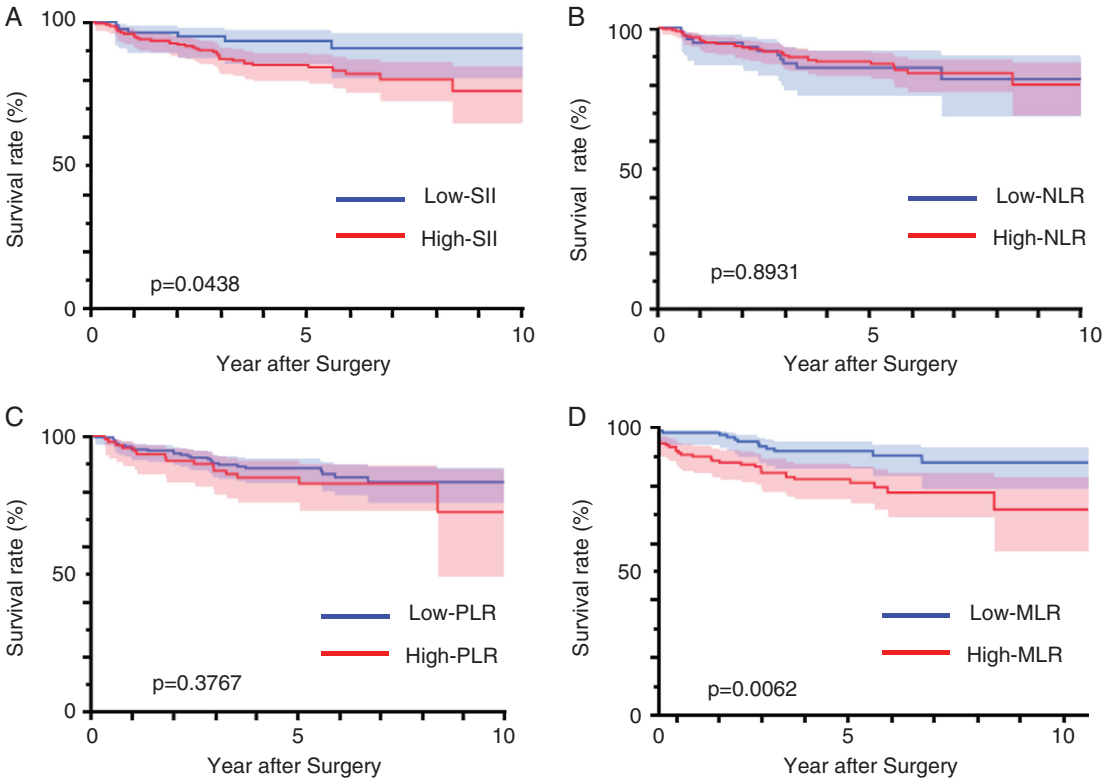
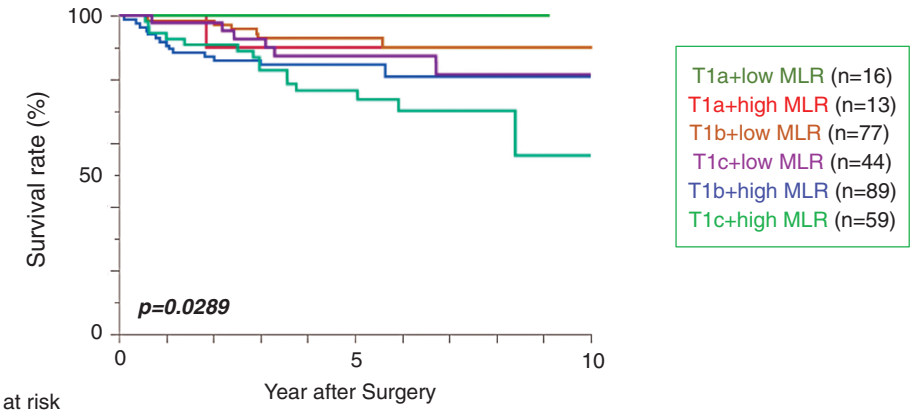


Fig. 1 Kaplan–Meier curve analysis of RFS for 311 patients with stage IA NSCLC by preoperative CBC-derived biomarker levels. (A) SII. (B) NLR. (C) PLR. (D) MLR. Blue line: low level group; red line: high level group. SII and MLR showed significant differences ($p = 0.0438$ and $p = 0.0062$, respectively; log-rank test). CBC: complete blood cell count; MLR: monocyte–lymphocyte ratio; NSCLC: non-small-cell lung cancer; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; RFS: recurrence-free survival; SI: systemic inflammation index



Patient at risk											
T1a+low MLR	16	15	15	14	14	13	8	5	4	2	1
T1a+high MLR	13	11	10	8	8	6	5	5	4	3	2
T1b+low MLR	77	75	72	67	61	57	29	16	10	7	4
T1c+low MLR	44	44	41	37	33	31	21	15	10	7	3
T1b+high MLR	89	80	75	68	66	49	16	11	7	6	6
T1c+high MLR	59	52	48	43	37	35	18	11	7	4	3

Fig. 2 Kaplan–Meier curve analysis of RFS for patients with T1a, T1b, or T1c NSCLC, by the preoperative MLR level. RFS in the T1c group with high MLR was significantly shorter than in other subgroups ($p = 0.0289$, log-rank test). NSCLC: non-small-cell lung cancer; RFS: recurrence-free survival

postoperative recurrence in pathological stage IA NSCLC. Only the MLR status was shown to be an independent predictive factor of postoperative recurrence in pathological stage IA NSCLC. MLR was calculated from the monocyte and lymphocyte counts, so an elevated MLR may be indicative of two phenomena. The first is a simple reduction of lymphocytes. These provide anti-tumor immunity and function in cell-mediated immunity in various cancers. They also have critical roles in the defense of cancer cells by initiating cytotoxic immune responses and inhibiting cancer cell proliferation, invasion, and migration.[15,16] Thus, lymphopenia might reflect the diminishment of immune response to cancers by reducing the influence of their fundamental role.

The second phenomenon refers to monocytes, which contribute to the inflammatory process through their patterns of differentiation into macrophages or dendritic cells in the tissue microenvironment.[17] Monocytes can also stimulate cancer cell migration and inhibit anti-tumor immunity.[15,16] Hamilton et al.[18] reported that macrophages derived from monocytes interact with circulating tumor cells (CTC) to release cytokines, chemokines, and growth factors which result in aggressive CTC invasion behavior in small-cell lung cancer. It is also known that tumor-associated macrophages stimulate tumor cell proliferation, promote angiogenesis, and favor invasion and metastasis by producing growth and angiogenic factors. Thus, a high monocyte count may lead to tumor progression.[19]

As such, the MLR reflected by both the lymphocyte and monocyte conditions may be a strong parameter that reflects the host immune response condition. MLR has previously been proven to have an independent association with various malignancies.[20-25] For example, Yuan et al.[11] reported that MLR was an independent prognostic factor in surgically resected stage I–III NSCLC. However, this cohort study did not focus on early-stage NSCLC patients and also did not analyze disease-free survival (DFS) in early-stage NSCLC patients. Our study specifically highlighted early-stage NSCLC patients and concluded that MLR was an independent predictive factor of postoperative recurrence in these patients. Moreover, we also analyzed subgroups according to tumor size and MLR (**Fig. 2**), which revealed that DFS in high preoperative MLR level patients with tumors exceeding 2 cm (T1c) was significantly worse than in other subgroups. This suggested that it might be necessary for patients in this subgroup to undergo careful follow-up and/or to receive further treatment including postoperative adjuvant chemotherapy. However, current National Comprehensive Cancer Network guidelines recommend "observation" after curative resection in all pathological stage IA NSCLC patients.

Some limitations are existed in the present study. First, this study is limited by selection biases due to its single-center and retrospective nature. Second, the sensitivity and specificity of MLR were not very high, although our results showed that MLR was an independent predictor of pathological stage IA NSCLC patients. Thus, perspective studies to verify the impact of MLR level in pathological stage IA NSCLC patients by multi-centric collaborative prospective study are needed to confirm these preliminary results.

In conclusion, a high preoperative MLR level is a novel predictor of postoperative recurrence in patients with pathological stage IA NSCLC. The preoperative measurement of MLR is a simple but valuable assessment to identify high-risk pathological stage IA NSCLC patients. However, because this was a retrospective study from a single institution, a multi-centric prospective study might be warranted to evaluate both the criteria of MLR in this study and the survival benefit of multimodality therapies, such as adjuvant chemotherapy, against pathological stage IA NSCLC for patients with high preoperative MLR levels.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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