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

Fumihiro Shoji, MD, PhD, Yuka Kozuma, MD, PhD, Gouji Toyokawa, MD, PhD, Koji Yamazaki, MD, PhD, and Sadanori Takeo, MD, PhD

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

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,\(^9\)\(^-\)\(^12\) 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.
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. 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 nonadenocarcinomas 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               | p     |
|--------------------|-------------------|-------------------|-------------------|-------------------|-------|
|                    | Low (n = 84)      | High (n = 227)    | Low (n = 74)      | High (n = 237)    | 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             |       |
| Others             | 0.8786            | 0.7206            | 0.4183            | 0.1147            |       |
| Ad                 | 12 34             | 10 36             | 34 12             | 15 28             |       |
| 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           | 0.5527|
| 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.
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 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: 1.298–5.029). 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).

### 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 (0.826–5.725), 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...
**CBC-Derived Biomarkers in Stage IA NSCLC**

**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.

**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.
As such, the MLR reflected by both the lymphocyte and monocyte counts 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. Monocytes can also stimulate cancer cell migration and inhibit anti-tumor immunity. It is 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.

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.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number JP17K10793. We thank Sarah Williams, PhD, from Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1) Siegel RL, Miller KD, Jemal A. Cancer statistics. 2019 CA Cancer J Clin 2019; 69: 7-34.
2) Okami J, Shintani Y, Okumura M, et al. Demographics, safety and quality, and prognostic information in both the seventh and eighth editions of the TNM classification in 18,973 surgical cases of the Japanese Joint Committee of Lung Cancer Registry Database in 2010. J Thorac Oncol 2019; 14: 212-22.
3) Shoji F, Haro A, Yoshiida T, et al. Prognostic significance of intratumoral blood vessel invasion in pathological stage IA non-small cell lung cancer. Ann Thorac Surg 2010; 89: 864-9.
Shoji F, Yamazaki K, Kouso H, et al. Predictive impact for postoperative recurrence of preoperative serum Krebs von den Lungen-6 concentration in pathologic stage IA non-small cell lung cancer. Ann Thorac Surg 2016; 101: 1903-8.

Shoji F, Morodomi Y, Akamine T, et al. Predictive impact for postoperative recurrence using the preoperative prognostic nutritional index in pathological stage I non-small cell lung cancer. Lung Cancer 2016; 98: 15-21.

Shoji F, Haratake N, Akamine T, et al. The preoperative controlling nutritional status score predicts survival after curative surgery in patients with pathologically stage I non-small cell lung cancer. Anticancer Res 2017; 37: 741-7.

Shoji F, Matsubara T, Kozuma Y, et al. Preoperative geriatric nutritional risk index: a predictive and prognostic factor in patients with pathological stage I non-small cell lung cancer. Surg Oncol 2017; 26: 483-8.

Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008; 454: 436-44.

Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 2017; 8: 75381-8.

Dolan RD, Lim J, McSorley ST, et al. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: systematic review and meta-analysis. Sci Rep 2017; 7: 16717.

Yuan C, Li N, Mao X, et al. Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: results from a large cohort. Thorac Cancer 2017; 8: 350-8.

Zhang Y, Chen B, Wang L, et al. Systemic immune-inflammation index is a promising noninvasive marker to predict survival of lung cancer: a meta-analysis. Medicine (Baltimore) 2019; 98: e13788.

Varlotto JM, Recht A, Flickinger JC, et al. Factors associated with local and distant recurrence and survival in patients with resected non-small cell lung cancer. Cancer 2009; 115: 1059-69.

Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11: 39-51.

Cousseens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-7.

Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008; 454: 436-44.

Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2011; 11: 762-74.

Hamilton G, Rath B, Klameth L, et al. Small cell lung cancer: recruitment of macrophages by circulating tumor cells. Oncoimmunology 2016; 5: e1093277.

Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 2017; 14: 399-416.

Stotz M, Pichler M, Absenger G, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer 2014; 110: 435-40.

Ni XJ, Zhang XL, Ou-Yang QW, et al. An elevated peripheral blood lymphocyte-to-monocyte ratio predicts favorable response and prognosis in locally advanced breast cancer following neoadjuvant chemotherapy. PLoS ONE 2014; 9: e111886.

Cananzi FCM, Minerva EM, Samà L, et al. Preoperative monocyte-to-lymphocyte ratio predicts recurrence in gastrointestinal stromal tumors. J Surg Oncol 2019; 119: 12-20.

Chen L, Zeng H, Yang J, et al. Survival and prognostic analysis of preoperative inflammatory markers in patients undergoing surgical resection for laryngeal squamous cell carcinoma. BMC Cancer 2018; 18: 816.

Jan HC, Yang WH, Ou CH. Combination of the preoperative systemic immune-inflammation index and monocyte-lymphocyte ratio as a novel prognostic factor in patients with upper-tract urothelial carcinoma. Ann Surg Oncol 2019; 26: 669-84.

Shi L, Qin X, Wang H, et al. Elevated neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio and decreased platelet-to-lymphocyte ratio are associated with poor prognosis in multiple myeloma. Oncotarget 2017; 8: 18792-801.