Prognostic evaluation of patients with resectable lung cancer using systemic inflammatory response parameters

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Abstract. Lung cancer is one of the leading causes of cancer-associated mortality. C-reactive protein (CRP), albumin (ALB), globulin (GLB), lactate dehydrogenase (LDH), neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been identified as general parameters for systemic inflammatory response (SIR). Furthermore, these parameters are also associated with tumor development and metastasis. The present study aimed to investigate the predictive values of these SIR parameters in patients with resectable lung cancer. In total, 101 patients with resectable lung cancer were recruited in the present study. The patients were divided into two groups according to the median value of pre-treatment CRP, ALB, GLB, LDH, NLR or PLR values. The post-/pre-treatment ratios were defined as the ratio of pre-treatment blood parameter values and the corresponding values obtained following therapy. A ratio of ≤1.1 indicated that the values were not increased, while a ratio of >1.1 suggested that the values were increased following treatment. Patients with lower pre-treatment ALB levels had poorer overall survival (OS) rates, whereas GLB, LDH, CRP, NLR or PLR levels were not associated with outcomes. Whole course treatment (surgery combined with adjuvant chemotherapy) significantly increased the value of ALB, but decreased the value of NLR, whereas it had no effect on the values of LDH, CRP or PLR. Post-/pre-treatment LDH and PLR were associated with outcomes. Post-/pre-treatment ALB, GLB, CRP and NLR were not associated with outcomes. Multivariate analysis revealed that a low pre-treatment ALB level and increased post-/pre-treatment PLR were independent risk factors affecting OS. The receiver operating characteristic curve analysis demonstrated that an ALB value of 47.850 g/l was considered to be the optimal cut-off value for prognosis; the sensitivity was 28.8% and specificity was 95.9%. It was suggested that the pre-treatment ALB and post-/pre-treatment PLR may be potential prognostic factors in resectable lung cancer.

Introduction

An estimated 4,292,000 newly diagnosed cases of cancer and 2,814,000 cancer-associated mortalities occurred in China in 2015, and lung cancer accounted for nearly 20% of those cases (1). With a low 5-year survival rate of 17.8% in China (2), lung cancer has become the most common type of cancer and the leading cause of cancer-associated mortality over the past few decades (3). It has been demonstrated that a number of factors are associated with the progression of lung cancer, including tobacco smoke, occupational exposure to asbestos and radon, environmental pollution, chronic pulmonary inflammation and a family history of lung cancer (2,4). In Chinese women, where the prevalence of smoking is low, unpredicted high incidences of lung cancer have been observed due to exposure to indoor air pollution (5). A major precaution in preventing lung cancer is smoking cessation, while early diagnosis and treatment of lung cancer are of vital importance in enhancing the prognosis of lung cancer (4).

Systemic inflammatory response (SIR) is associated with survival in a variety of cancer types, including gastric, esophageal and lung cancer (6-8). Previous studies have examined the role of various SIR indicators in predicting the outcomes of cancer patients (9-12). Albumin (ALB) and globulin (GLB) are

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two major serum proteins. It is well known that low ALB and high GLB levels are associated with malnutrition and chronic inflammation (13). C-reactive protein (CRP) is an acute phase protein, which is produced and secreted by hepatocytes via several inflammatory stimuli, including interleukin (IL)-1 and IL-6 (14). Increased CRP levels have been observed in numerous conditions, including inflammation, infection, tissue infarction and malignancy (15). Lactate dehydrogenase (LDH), a ubiquitous cellular enzyme, which catalyzes anaerobic glycolysis, is increased in patients with malignant tumors (16). The neutrophil-lymphocyte ratio (NLR) refers to the proportion of absolute neutrophils in the lymphocyte count in the blood circulation. The platelet-to-lymphocyte ratio (PLR), the proportion of absolute platelets to the lymphocyte count in peripheral blood, has been proposed as a reliable prognostic indicator for lung cancer (17,18). NLR and PLR have been demonstrated to be associated with the prognosis of a wide variety of tumors (19,20).

The present study evaluated whether these SIR-associated indicators may provide beneficial prognostic information for patients with resectable lung cancer.

Materials and methods

Subjects and inclusion criteria. The present study was conducted as a retrospective investigation of patients with lung cancer that had been referred to the First Affiliated Hospital of Soochow University (Jiangsu, China) between January 2007 and May 2016. Approval for the study was granted by the Medical Ethics Committees of the First Affiliated Hospital of Soochow University. Clinical and pathological records of all the patients participating in the study were reviewed periodically.

A total of 101 patients with resectable lung cancer were recruited in the present study. All cases were confirmed by surgery and pathology. Among the 101 patients, 9 had small cell lung cancer (SCLC). Of the 92 non-small cell lung cancer (NSCLC) samples, 33 were cases of squamous and 59 were cases of adenocarcinoma. The adenocarcinoma included 23 cases with an acinar pattern, 19 cases with a papillary pattern, 11 cases with a micropapillary pattern and 6 cases with a solid growth pattern. All patients underwent pulmonary lobectomy and systematic lymph node dissection. Patients with squamous carcinoma were treated with cisplatin 75 mg/m^2 day 1 and gemcitabine 1250 mg/m^2 day 1,8. Patients with adeno-carcinomas were treated with cisplatin 75 mg/m^2 day 1 and pemetrexed 500 mg/m^2 day 1. Patients with resectable SCLC were treated with cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 day 1,2,3. Patient characteristics are detailed in Table I. The median age of the 101 patients was 60 years (range, 27-80 years), and 63 patients were male (age range, 27-78 years) and 38 were female (age range, 27-80 years). The performance status of the patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status. It was ensured that patients displayed a good performance status (ECOG score ≤1). All the samples with coexisting diseases were excluded to eliminate the differences in general performance status. The staging of cancer was determined according to Tumor-Node-Metastasis classification and was classified using the American Joint Committee

on Cancer (AJCC) recommendations (21). The prognostic analyses were performed regarding overall survival (OS).

Blood samples. Pre-surgery blood samples were collected within one week prior to surgery. Post-surgery blood samples were regarded as pre-chemotherapy samples and were collected three weeks after surgery. Post-chemotherapy samples were collected following three cycles of standard chemotherapy. Peripheral venous blood (5-7 ml) samples were fasted and obtained between 6:30 and 7:30 am in order to standardize the known impact of circulating hormones (circadian rhythm) on the number and subtype distribution of the various white blood cell indices. Blood samples were analyzed using a hematology analyzer (Sysmex XE-2100; Sysmex Corporation, Kobe, Japan) or biochemical analyzer (Olympus AU5421+ISE; Olympus Corporation, Tokyo, Japan). ALB, GLB, LDH, NLR and PLR levels are presented in Table I. The patients were divided into two groups according to the median values. The post/pre-treatment ratios were defined as the ratio of pre-treatment SIR-related indicator values and the corresponding ones obtained following therapy.

Evaluation. Computed tomography (CT) scans were performed for the assessment of response every 2 months and evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 (22).

Follow-up. All the patients were followed-up post-operatively for between 16 and 90 months, with a median follow-up period of 36 months. Survival time was measured from the date of diagnosis until mortality or last clinical evaluation. The prognostic analyses were performed regarding overall survival (OS). OS was defined as the time between the diagnosis date and mortality from any cause.

Statistical analysis. All statistical analyses were performed using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). The associations between blood parameter status and clinicopathological features were determined using χ^2 tests. For analysis of survival data, Kaplan-Meier curves were constructed, and statistical analyses was performed using the log-rank test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive values of SIR-related indicators for resectable lung cancer and to determine the best cut-off value of SIR-related indicators. The associations between changes in the status of SIR-related indicators and surgery or chemotherapy were assessed by Student's t-tests. The multivariate logistic regression model was employed to identify the independent risk factors associated with resectable lung cancer. Numerical data are presented as the mean ± standard error. P<0.05 was considered to indicate a statistically significant difference.

Results

Pre-treatment ALB level is associated with outcomes in patients with resectable lung cancer. The median OS time for all the patients with resectable lung cancer was 36 (33.329-39.542) months (Fig. 1A). Kaplan-Meier plots were used to determine the effect of pre-treatment CRP, ALB, GLB,

Table I. Clinicopathologic features.

Feature	n	CRP Low, n	High, n	χ²	P-value	ALB Low, n	High, n	χ²	P-value	GLB Low, n	High, n	χ²	P-value	LDH Low, n	High, n	χ²	P-value	NLR Low, n	High, n	χ²	P-value	PLR Low, n	High, n	χ²	P-value
Sex																									
Male	63	27	36	3.908	0.048[a]	25	38	1.455	0.228	32	31	0.006	0.938	35	28	1.715	0.190	31	32	0.717	0.397	31	32	0.111	0.739
Female	38	24	14			26	12			19	19			16	22			22	16			20	18		
Age, years																									
≤60	56	32	24	2.222	0.136	26	30	0.831	0.362	26	30	0.831	0.362	26	30	0.831	0.362	32	24	1.098	0.295	27	29	0.262	0.609
>60	45	19	26			25	20			25	20			25	20			21	24			24	21		
Pathological type																									
NSCLC	92	42	50	0.048	0.827	42	50	0.048	0.827	43	49	0.024	0.876	44	48	0.024	0.876	38	54	0.012	0.913	57	35	3.818	0.051
SCLC	9	5	4			5	4			5	4			4	5			3	6			2	7		
Tumor size, cm																									
≤5	73	45	28	13.093	0.000[b]	41	32	3.386	0.066	39	34	0.904	0.342	35	38	4.929	0.026[a]	37	36	0.338	0.561	39	34	0.904	0.342
>5	28	6	22			10	18			12	16			16	12			16	12			12	16		
T stage																									
T1, T2	77	43	34	0.046	0.830	46	31	11.080	0.001[b]	43	34	3.709	0.054	38	39	0.170	0.680	39	38	0.433	0.510	41	36	0.982	0.322
T3, T4	24	14	10			5	19			8	16			13	11			14	10			10	14		
N stage																									
N0, N1	68	35	33	0.079	0.778	37	31	0.313	0.576	39	29	3.916	0.048[a]	40	28	5.775	0.016[a]	35	33	0.079	0.778	37	31	1.277	0.258
N2	33	16	17			16	17			14	19			21	12			16	17			12	21		
AJCC stage																									
I, II	64	37	27	3.742	0.053	35	29	1.228	0.268	36	28	2.315	0.128	30	34	0.916	0.339	35	29	0.343	0.558	35	29	1.228	0.268
III	37	14	23			16	21			15	22			21	16			18	19			16	21		

[a]P<0.05; [b]P<0.01. CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; T, tumor; N, node; AJCC, American Joint Committee on Cancer.
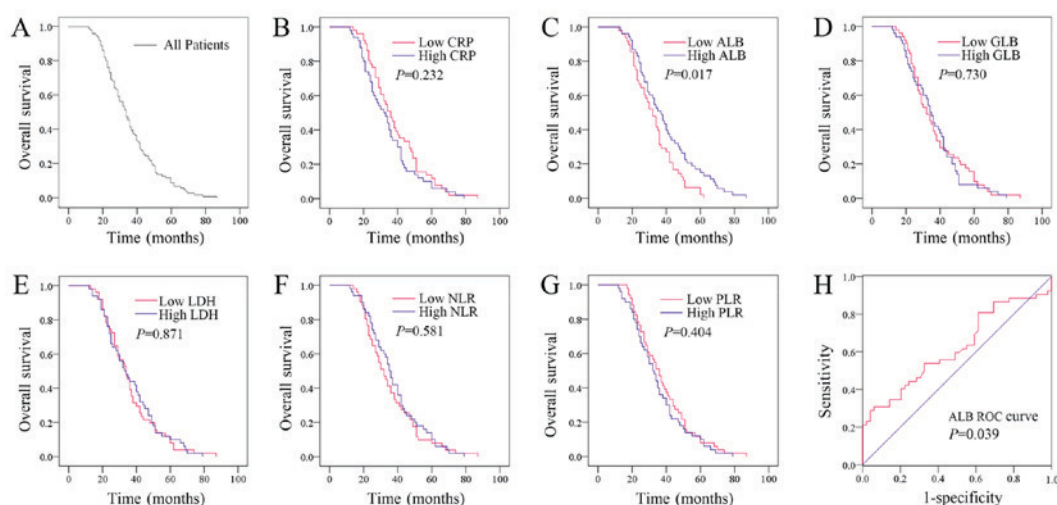
Figure 1. Association between status of pre-treatment systemic inflammatory response-related indicators and outcomes. (A) The OS of all patients with resectable lung cancer. (B) OS according to CRP. (C) OS according to ALB. (D) OS according to GLB. (E) OS according to LDH. (F) OS according to NLR. (G) OS according to PLR. (H) Schematic of the receiver operating characteristic curve for prediction by the pre-treatment ALB value. OS, overall survival; CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
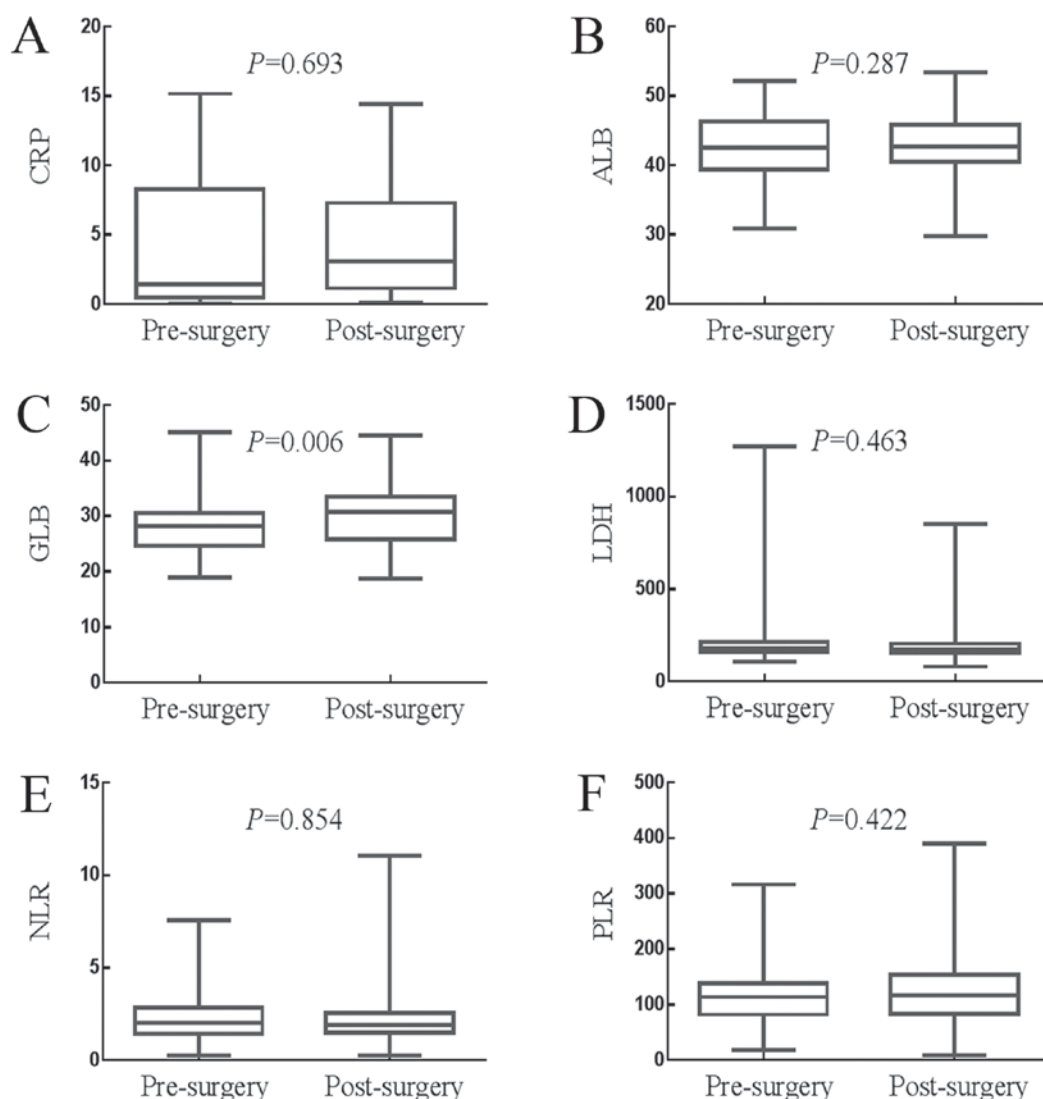

Figure 2. Effects of surgery on the status of systemic inflammatory response-related indicators. (A) Surgery had no influence on the value of CRP. (B) Surgery had no influence on the value of ALB. (C) Surgery increased the value of GLB. (D) Surgery had no influence on the value of LDH. (E) Surgery had no influence on the value of NLR. (F) Surgery had no influence on the value of PLR. CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
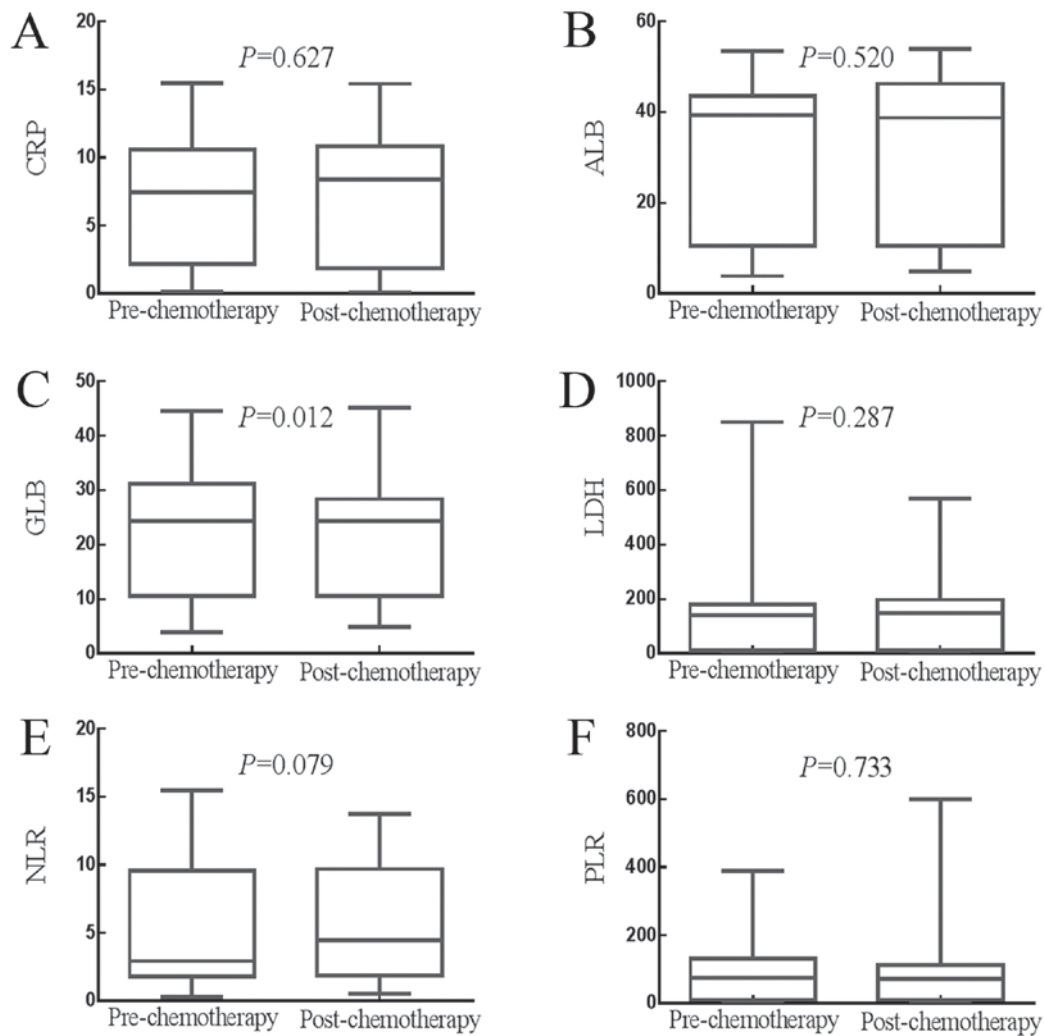
Figure 3. Effects of adjuvant chemotherapy on the status of systemic inflammatory response-related indicators. (A) Adjuvant chemotherapy had no influence on the value of CRP. (B) Adjuvant chemotherapy had no influence on the value of ALB. (C) Adjuvant chemotherapy decreased the value of GLB. (D) Adjuvant chemotherapy had no influence on the value of LDH. (E) Adjuvant chemotherapy had no influence on the value of NLR. (F) Adjuvant chemotherapy had no influence on the value of PLR. CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

LDH, NLR and PLR status on OS (Fig. 1B-G). The patients were divided into two groups according to the median values of CRP (low CRP, ≤1.426 mg/l or high CRP, >1.426 mg/l), ALB (low ALB, ≤42.600 g/l or high ALB, >42.600 g/l), GLB (low GLB, ≤28.227 g/l or high GLB, >28.227 g/l), LDH (low LDH, ≤178.965 U/l or high LDH, >178.965 U/l), NLR (low NLR, ≤2.049 or high NLR, >2.049), or PLR (low PLR, ≤113.534 or high PLR, >113.534). The median OS time of the high CRP group was 32 (25.070-38.930) months, while that of the low CRP group was 36 (30.760-41.240) months (P=0.232). The median OS time of the high ALB group was 37 (30.758-43.242) months, while that of the low ALB group was 32 (27.154-36.846) months (P=0.017). The median OS time of the high GLB group was 34 (30.040-37.960) months, while that of the low GLB group was 32 (26.558-37.442) months (P=0.730). The median OS time of the high LDH group was 33 (26.070-39.930) months, while that of the low LDH group was 34 (29.342-38.658) months (P=0.871). The median OS time of the high NLR group was 35 (31.535-38.465) months, while that of the low NLR group was 32 (27.342-36.658) months (P=0.581). The median OS time of the high PLR group

was 32 (27.050-36.950) months, while that of the low PLR group was 36 (31.010-40.990) months (P=0.404). Therefore, the patients whose pre-treatment ALB levels were lower exhibited a poorer prognosis. However, pre-treatment levels of CRP, GLB, LDH, NLR or PLR had no effect on OS.

ROC curve analysis was subsequently performed to evaluate the predictive value of pre-treatment ALB for resectable lung cancer and determine the optimum cut-off value. As demonstrated in Fig. 1H, the area under the curve of pre-treatment ALB was 0.619 (95% CI 0.509-0.727; P=0.039), and the optimum cut-off point of pre-treatment ALB was 47.850 g/l with a sensitivity of 28.8% and a specificity of 95.9%.

Effects of surgery on the values of SIR-related indicators. The effects of surgery on the levels of SIR-related indicators are presented in Fig. 2A-F. The median value of CRP was 1.430 mg/l (0.980-2.900 mg/l) prior to surgery and 3.070 mg/l (2.140-4.360 mg/l) following surgery (P=0.693). The median value of ALB was 42.600 g/l (41.700-43.880 g/l) prior to surgery and 42.640 g/l (41.900-43.800 g/l) following surgery (P=0.287). The median value of GLB was 28.230 g/l (27.400-29.100 g/l)
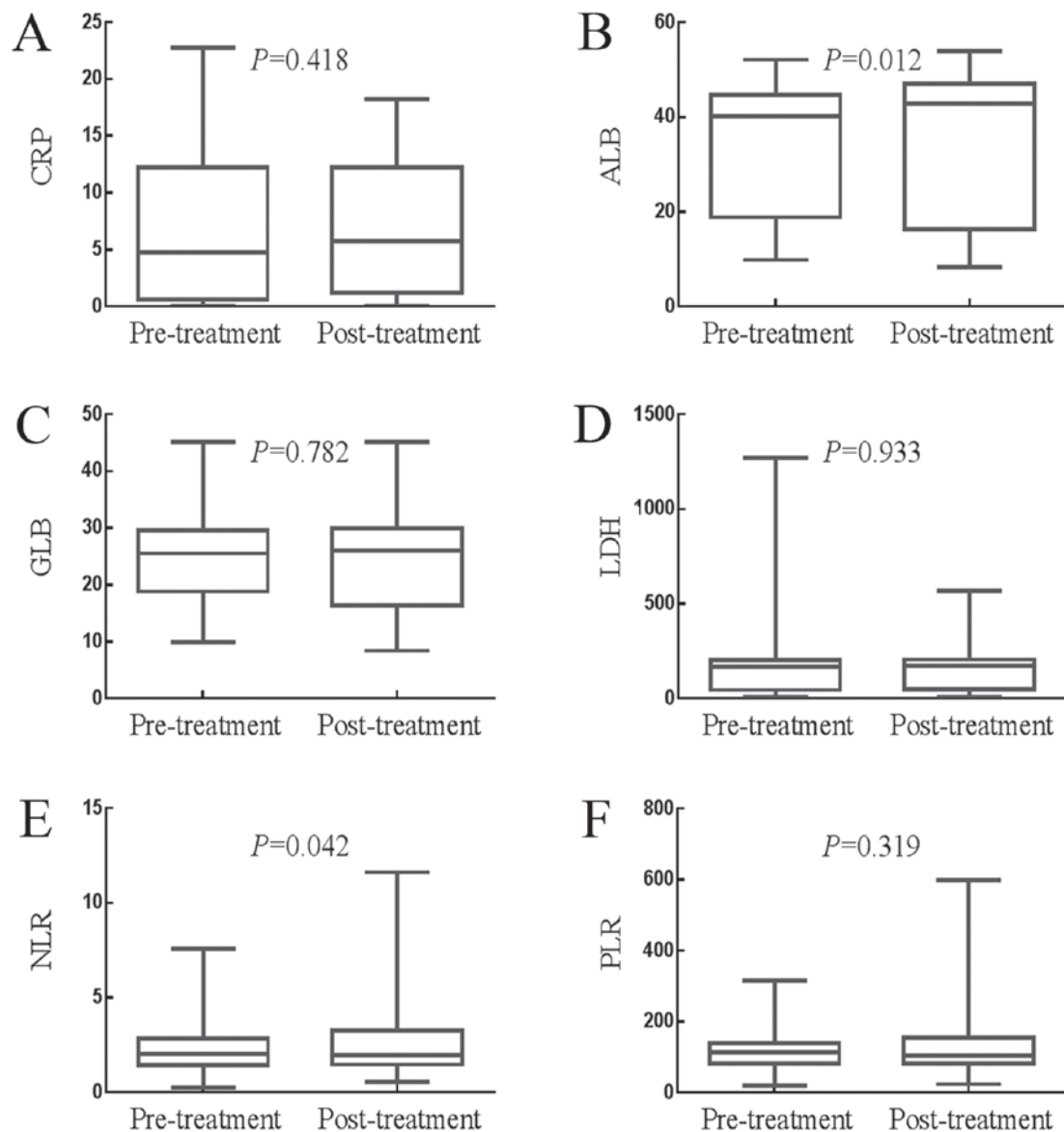
Figure 4. Effects of whole course of treatment on the status of systemic inflammatory response-related indicators. (A) Whole course of treatment had no influence on the value of CRP. (B) Whole course of treatment had no influence on the value of ALB. (C) Whole course of treatment had no influence on the value of GLB. (D) Whole course of treatment had no influence on the value of LDH. (E) Whole course of treatment increased the value of NLR. (F) Whole course of treatment had no influence on the value of PLR. CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

prior to surgery and 30.800 g/l (29.250-31.430 g/l) following surgery (P=0.006). The median value of LDH was 178.970 U/l (170.040-192.610 U/l) prior to surgery and 173.000 U/l (165.000-181.390 U/l) following surgery (P=0.463). The median value of NLR was 2.050 (1.790-2.289) prior to surgery and 1.920 (1.740-2.080) following surgery (P=0.854). The median value of PLR was 113.530 (100.960-125.930) prior to surgery and 116.790 (100.751-135.360) following surgery (P=0.423). Therefore, surgery significantly increased the value of GLB, but had no significant impact on the values of CRP, ALB, LDH, NLR or PLR.

Effects of adjuvant chemotherapy on the values of SIR-related indicators. The effects of adjuvant chemotherapy on the status of SIR-related indicators are shown in Fig. 3A-F. The median value of CRP was 3.070 mg/l (2.140-4.360 mg/l) prior

to chemotherapy and 2.100 mg/l (1.780-3.870 mg/l) following chemotherapy (P=0.627). The median value of ALB was 42.640 g/l (41.900-43.800 g/l) prior to chemotherapy and 45.590 g/l (43.880-46.600 g/l) following chemotherapy (P=0.520). The median value of GLB was 30.800 g/l (29.250-31.430 g/l) prior to chemotherapy and 27.500 g/l (26.700-28.600 g/l) following chemotherapy (P=0.012). The median value of LDH was 173.000 U/l (165.000-181.390 U/l) prior to chemotherapy and 189.150 U/l (178.000-198.850 U/l) following chemotherapy (P=0.287). The median value of NLR was 1.920 (1.740-2.080) prior to chemotherapy and 1.980 (1.830-2.260) following chemotherapy (P=0.079). The median value of PLR was 116.790 (100.751-135.360) prior to chemotherapy and 105.170 (95.442-114.040) following chemotherapy (P=0.733). Therefore, adjuvant chemotherapy significantly decreased the value of GLB, but had no
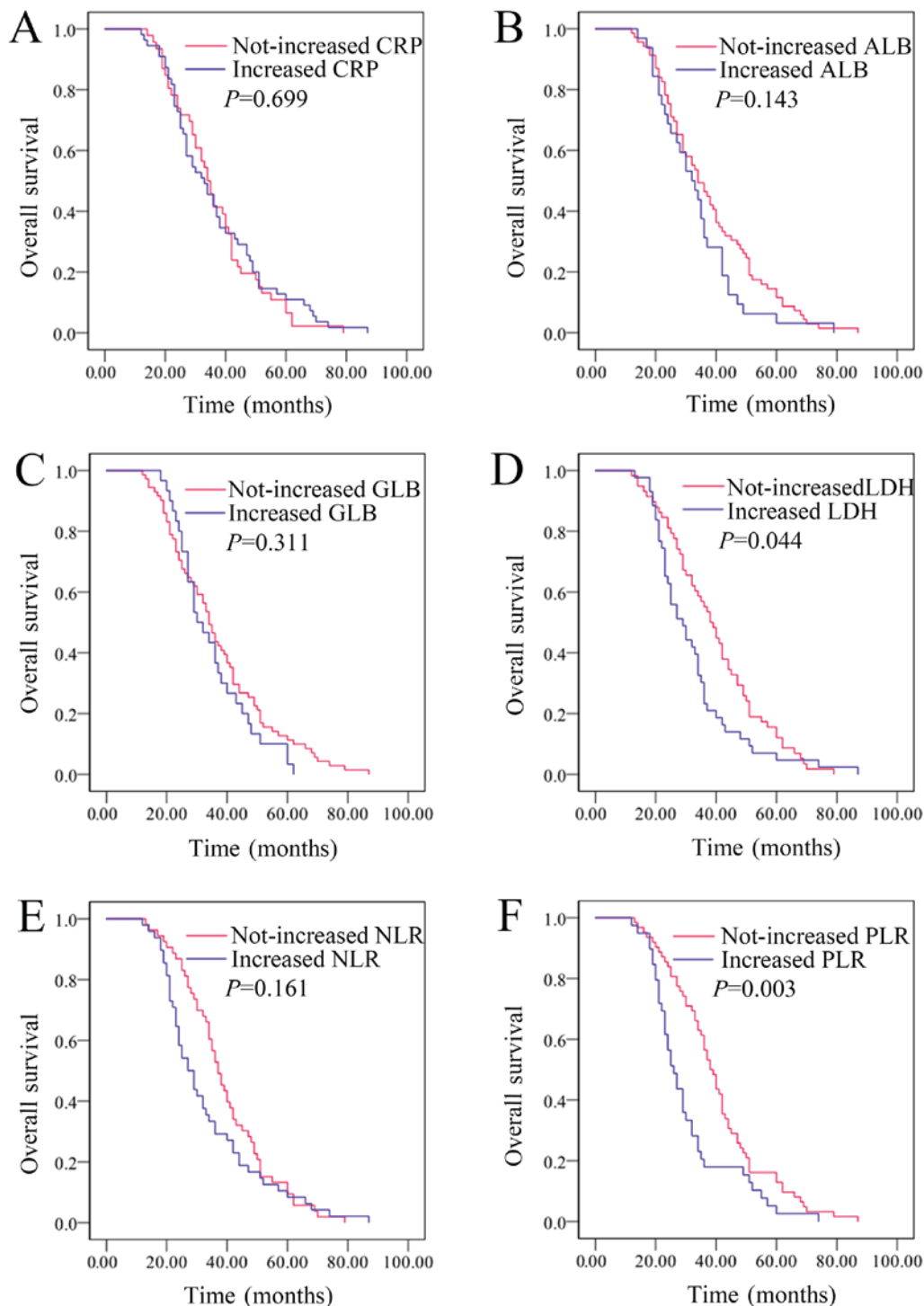
Figure 5. Association between status of changes in systemic inflammatory response-related indicators following whole course of treatment and outcomes. (A) OS according to changes in CRP. (B) OS according to changes in ALB. (C) OS according to changes in GLB. (D) OS according to changes in LDH. (E) OS according to changes in NLR. (F) OS according to changes in PLR. OS, overall survival; CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

significant impact on the values of CRP, ALB, LDH, NLR or PLR.

Effects of whole course of treatment on the values of SIR-related indicators. The impact of whole course of treatment (surgery and adjuvant chemotherapy) on the values of the SIR-related indicators is presented in Fig. 4A-F. The median value of CRP was 1.430 mg/l (0.980-2.900 mg/l) prior to treatment and 2.100 mg/l (1.780-3.870 mg/l) following treatment (P=0.418). The median value of ALB was 42.600 g/l (41.700-43.880 g/l) prior to treatment and 45.590 g/l (43.880-46.600 g/l) following treatment (P=0.012). The median value of GLB was 28.230 g/l (27.400-29.100 g/l) prior to treatment and 27.500 g/l (26.700-28.600 g/l) following treatment (P=0.782). The median value of LDH was 178.970 U/l (170.040-192.610 U/l) prior to treatment and 189.150 U/l

Table II. Univariate and multivariate logistic regression analysis of resectable lung cancer risk factors.

A, Univariate analysis.

	Overall survival (OS)	
Risk factors	OR (95% CI)	P-value
Sex		
(Female or Male)	0.782 (0.517-1.183)	0.245
Age		
(>60 years or ≤60 years)	1.059 (0.713-1.572)	0.776
Pathologic type		
(NSCLC or SCLC)	0.890 (0.446-1.774)	0.740
Tumor size (cm)		
(>5 or ≤5)	0.851 (0546-1.326)	0.476
Depth of invasion		
(T3-4 or T1-2)	1.126 (0.708-1.789)	0.617
Lymphonodus metastasis		
(N2 or N0-1)	1.474 (0.959-2.264)	0.077
AJCC stage		
(III or I-II)	1.538 (1.010-2.340)	0.045[a]
Pre-treatment CRP		
(>1.430 mg/l or ≤1.430 mg/l)	1.265 (0.853-1.875)	0.243
Pre-treatment ALB		
(≤42.600 g/l or >42.600 g/l)	1.625 (1.077-2.452)	0.021[a]
Pre-treatment GLB		
(>28.227 g/l or ≤28.227 g/l)	1.071 (0.721-1.589)	0.735
Pre-treatment LDH		
(>178.965 U/l or ≤178.965 U/l)	0.969 (0.654-1.436)	0.874
Pre-treatment NLR		
(>2.049 or ≤2.049)	0.897 (0.606-1.330)	0.590
Pre-treatment PLR		
(>113.534 or ≤113.534)	1.178 (0.795-1.746)	0.414
Post-/pre-treatment CRP ratio		
(>1.1 or ≤1.1)	0.926 (0.623-1.377)	0.705
Post-/pre-treatment ALB ratio		
(>1.1 or ≤1.1)	1.366 (0.891-2.094)	0.152
Post-/pre-treatment GLB ratio		
(>1.1 or ≤1.1)	1.246 (0.806-1.928)	0.323
Post-/pre-treatment LDH ratio		
(>1.1 or ≤1.1)	1.498 (1.000-2.244)	0.050
Post-/pre-treatment NLR ratio		
(>1.1 or ≤1.1)	1.318 (0.888-1.957)	0.171
Post-/pre-treatment PLR ratio		
(>1.1 or ≤1.1)	1.810 (1.201-2.729)	0.005[b]

B, Multivariate analysis.

	Overall survival (OS)	
Risk factors	OR (95% CI)	P-value
Lymphonodus metastasis		
(N2 or N0-1)	1.423 (0.714-2.838)	0.317
AJCC stage		
(III or I-II)	1.163 (0.596-2.267)	0.658
Pre-treatment ALB		
(≤42.600 g/l or >42.600 g/l)	1.738 (1.143-2.643)	0.010[a]
Post-/pre-treatment LDH ratio		
(>1.1 or ≤1.1)	1.515 (0.997-2.304)	0.052
Post-/pre-treatment PLR ratio		
(>1.1 or ≤1.1)	1.890 (1.238-2.887)	0.003[b]

[a]P<0.05; [b]P<0.01. OR, Odds ratio; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; T, tumor; N, node; AJCC, American Joint Committee on Cancer; CRP, C-reactive protein; ALB, albumin; GLB, globulin; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

(178.000-198.850 U/l) following treatment (P=0.933). The median value of NLR was 2.050 (1.790-2.289) prior to treatment and 1.980 (1.830-2.260) following treatment (P=0.042). The median value of PLR was 113.530 (100.960-125.930) prior to

treatment and 105.170 (95.442-114.040) following treatment (P=0.319). Therefore, whole course of treatment significantly increased the value of ALB, but significantly decreased the value of NLR, but had no significant effect on the values of CRP, GLB, LDH or PLR.

Changes in LDH and PLR levels following whole course of treatment were associated with the outcomes in patients with resectable lung cancer, while CRP, ALB, GLB, and NLR levels were not associated with outcomes. Kaplan-Meier plots were used to determine the effect of individual changes in CRP, ALB, GLB, LDH, NLR and PLR status on OS (Fig. 5A-F). The median OS time of patients whose CRP levels increased following whole course of treatment was 33 (25.733-40.267) months, while that of the not-increased CRP group was 34 (30.202-37.798) months (P=0.699). The median OS time of patients whose ALB levels increased following whole course of treatment was 32 (25.348-38.652) months, while that of the not-increased ALB group was 34 (28.186-39.814) months (P=0.143). The median OS time of patients whose GLB levels increased following whole course of treatment was 30 (23.738-36.262) months, while that of the not-increased GLB group was 34 (30.330-37.670) months (P=0.311). The median OS time of patients whose LDH levels increased following whole course of treatment was 29 (22.575-35.425) months, while that of the not-increased LDH group was 38 (33.024-42.976) months (P=0.044). The median OS time of patients whose NLR levels increased following whole course of treatment was 27 (22.150-31.850) months, while that of the not-increased NLR group was 37 (32.924-41.076) months (P=0.161). The median OS time of patients whose PLR levels increased following whole course of treatment was 26 (22.329-29.671) months, while that of the not-increased PLR group was 38 (34.142-41.858) months (P=0.003). Therefore, changes in LDH and PLR levels following whole course of treatment were associated with outcomes in patients with resectable lung cancer, while CRP, ALB, GLB and NLR levels were not associated with the outcomes

Prognostic factors for resectable lung cancer. Sex, age, pathological type, tumor size, T stage, N stage, AJCC stage, as well as baseline CRP, ALB, GLB, LDH, NLR and PLR, post-/pre-treatment ratios of CRP, ALB, GLB, LDH, NLR and PLR were evaluated by univariate analyses. Risk factors (P<0.1) were evaluated by multivariate analysis. Univariate analyses demonstrated that AJCC stage III [hazard ratio (HR), 1.538; 95% confidence interval (CI), 1.010-2.340; P=0.045], low pre-treatment ALB (HR, 1.625; 95% CI, 1.077-2.452; P=0.021), post-/pre-treatment PLR ratio (HR, 1.810; 95% CI,1.201-2.729; P=0.005) were significant risk factors for a poor prognosis (Table II). In multivariate analysis, low pre-treatment ALB (HR,1.738; 95% CI,1.143-2.643; P=0.010) and increased post-/pre-treatment PLR (HR, 1.890; 95% CI,1.238-2.887; P=0.003) were revealed to be independently associated with poor survival.

Discussion

Cancer-related SIR is associated with the genetic instability of cancer cells, serving a crucial role in tumor development, including proliferation of malignant cells, angiogenesis, metastasis, immune escape and resistance to chemotherapeutic agents (23-25). Chronic obstructive pulmonary disease (COPD) and lung cancer share a common etiological factor, cigarette smoking (26). Furthermore, chronic pulmonary inflammatory diseases, particularly COPD, are risk factors for developing lung cancer, irrespective of smoking history (27). Therefore, a previous study confirmed an association among smoking, COPD and lung cancer (28). Possible mechanisms involving cigarette smoking and chronic inflammation are listed as follows: Firstly, tobacco smoke compromises the integrity of the respiratory epithelium, impairs mucociliary clearance and attenuates the defense against harmful environmental agents (29). Secondly, long-term cigarette smoking activates alveolar macrophages, leading to increased secretion of pro-inflammatory cytokines and reactive oxygen species (ROS), which leads to chronic inflammatory infiltration and tissue damage (30). Reiterative injury of epithelia has been proven to be involved in tumor initiation (31). Thirdly, cigarette smoking and host systemic inflammation may provoke the excessive production of ROS, which causes direct damage to DNA and leads to further somatic mutations, thereby increasing the predisposition to malignant tumors (32). As systemic inflammation is associated with cancer development, the prognostic significance of indicators that assess the state of SIR requires further investigation. For example, NLR, PLR and the CRP/ALB ratio were associated with the prognosis of several types of cancer, including breast, lung and gastric cancer (33-35). The present study investigated the predictive values of CRP, ALB, GLB,LDH, NLR and PLR in patients with resectable lung cancer.

Previous studies have suggested that a high level of CRP is correlated with a poorer prognosis inpatients with resectable lung cancer (36,37). For instance, Hara *et al* (36) demonstrated that disease-specific survival and OS rates in the high-CRP group (CRP ≥5 mg/l) were significantly lower than in the low CRP group (CRP <5 mg/l) in patients with resectable lung cancer. In a study undertaken by Lee *et al* (37), a high pre-operative serum CRP level was considered an independent prognostic indicator in patients with resectable lung cancer. A higher CRP level was correlated with a larger tumor size, increased lymph node metastasis and vascular invasion in patients with NSCLC (37). Tumor-derived inflammatory cytokines (including IL-6), which can block p53-induced apoptosis and maintain a suitable tumor microenvironment for the survival of malignant cells, have been demonstrated to be a primary inducer of CRP production (38). Therefore, a higher CRP level could be an indicator of a poor prognosis in lung cancer. The present study demonstrated that a high pre-treatment CRP level was associated with a lager tumor size. However, surgery combined with adjuvant chemotherapy had no significant effects on the level of CRP. In addition, the pre-treatment level and post-/pre-treatment ratio of CRP had no significant impact on OS.

ALB, a major type of human plasma protein synthesized by the liver, is commonly used as a marker for assessment of individual nutritional status (13). On account of the fact that malnutrition and SIR are induced by malignant cells, the synthesis of ALB was suppressed and the level of serum ALB decreased sharply in patients with advanced cancer (39). A variety of mechanisms are involved in the association between a low ALB level and a poor prognosis. Firstly, patients with malignant tumors suffer from weight loss, nutrition depletion

and even cachexia, typically with decreased serum ALB levels. Secondly, persistent inflammation in convalescent patients following resection are characterized with insufficient ALB recovery, leading to the proliferation of persistent post-operative tumor cells, which leads to a poorer prognosis and early recurrence (40,41). Furthermore, cancer-induced malnutrition leads to numerous clinical consequences, including decreased treatment response, increased treatment-related toxicity and decreased quality of life (11).

Numerous studies have evaluated the association between the serum level of ALB and the survival of patients with cancer. It was identified that a lower serum ALB level is an independent indicator of a poorer survival in various types of cancer (42). For instance, Tolia *et al* (43) indicated that the serum ALB level was significantly associated with OS in univariate analysis. Additionally, Jin *et al* (44) analyzed 101 samples from patients with stage I NSCLC and concluded that patients with low pre-operative ALB levels (<35 g/l) had a significantly poorer survival rate than patients with normal pre-operative serum ALB levels (≥35 g/l). Furthermore, patients with low post-operative ALB levels had a poorer survival rate when compared with patients with normal post-operative serum ALB levels (44). As demonstrated in Table I, the pre-treatment ALB level was associated with T stage. However, the pre-treatment ALB level was not associated with tumor size, N stage or AJCC stage. The present study concluded that a whole course of treatment significantly increased the value of ALB, which was accompanied by improvements in individual nutritional status and reductions in tumor burden. Patients with low pre-treatment ALB levels had poorer outcomes. Multivariate analyses demonstrated that a low pre-treatment ALB level was an independent risk factor for prognosis. The ROC curve analysis demonstrated that a pre-treatment ALB value of 47.850 g/l was considered to be the optimal cut-off value for prognosis, and the sensitivity was 28.8% and specificity was 95.9%. The post-/pre-treatment ratio of ALB had no significant effect on OS. In summary, a high pre-treatment ALB level could be a favorable prognostic indicator in resectable lung cancer.

As an indicator of SIR status, GLB is synthesized by the human monocyte-phagocyte system, serving a crucial role in the antitumor immune response (45). Qu *et al* (46) indicated that a higher percentage of α1-GLB in the serum was significantly associated with a higher pathological stage and poorer tumor status (46). A major possible mechanism to explain the findings of Qu *et al* (46) is that α1-antitrypsin (AAT), a major component of GLB, was increased in several types of tumor, including lung cancer. AAT may regulate host immunodefence mechanisms and may promote tumor progression by inhibiting T cell-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity and activity of natural killer cells (47). In the present study, although surgery upregulated the level of GLB and adjuvant chemotherapy downregulated the level of GLB, a whole course of treatment (a combination of surgery and adjuvant chemotherapy) had no significant effect on the level of GLB. Neither the pre-treatment GLB level nor post-/pre-treatment ratio of GLB had a significant impact on OS.

LDH, which is established as a universal enzyme, catalyzes anaerobic glycolysis, and it is a ubiquitously increased indicator in patients with malignant tumors (16,11,48,49). The

present study included components of the mechanisms that are involved in a poor prognosis, which are associated with LDH. Firstly, hypoxia, high rates of glucose uptake and lactate production are characteristics of malignant tumors, which facilitate anaerobic glycolysis and promote the proliferation of cancer cells (50,51). Therefore, a high level of LDH reflects a highly metabolic and more aggressive tumor status. Secondly, previous studies have focused on the association between LDH levels and tumor angiogenesis, and it was demonstrated that high LDH-5 levels are associated with the overexpression of vascular endothelial growth factor-A (VEGF-A) and vascular endothelial growth factor receptor-1 (VEGFR-1), which facilitate hematogenous metastasis and result in a poorer prognosis (52,53). Thirdly, hypoxia mediated the overexpression of hypoxia-inducible factor-α1 (HIF-α1), which may upregulate LDH-5 activity and, in turn, facilitate the secretion of VEGF and angiogenesis (54-56). However, few studies have focused on the prognostic value of serum LDH in NSCLC. For instance, in a recent study, Koh *et al* (57) revealed that a higher level of LDHB, a subunit of LDH, was significantly associated with the level of serum LDH and improved clinical outcomes in NSCLC. In the present study, the pre-treatment LDH level was not correlated with the outcomes of patients with resectable lung cancer. Neither surgery nor adjuvant chemotherapy had significant effects on the LDH level. Furthermore, patients with increased post-/pre-treatment LDH ratios had better outcomes than those with not-increased LDH ratios.

NLR is accepted as a useful and independent predictor of gastric cancer and hepatocellular carcinoma, in addition to early and advanced stage NSCLC (20,58-61). The mechanisms of poor outcomes that are associated with a high NLR value remain under investigation. Firstly, a high NLR reflects a relative increase outcomes that count and/or lymphopenia. An increased neutrophil response facilitates tumor growth and metastasis by inhibiting the function of the cytotoxic lymphocytes and remodeling the tumor extracellular matrix (62). Secondly, granulocyte colony stimulating factor (GCSF) derived from malignant cells could increase the level of circulating leukocytes, which may further inhibit the activation of cytotoxic lymphocytes, weaken immune-surveillance, remodel the tumor extracellular matrix and promote tumor progression (62-65). Furthermore, lymphocytes are responsible for the adaptive immune response and serve a crucial antitumor role in immunological surveillance and immunoediting (66,67). Therefore, a relative decrease in lymphocytes may also lead to an increased NLR and promote neutrophil-associated inhibition of antitumor cytotoxic lymphocytes. These mechanisms contribute toward increased neutrophils and decreased lymphocytes, which eventually leads to a higher NLR level and poorer survival, suggesting that NLR could be a prognostic indicator. Dirican *et al* (68) concluded that a high level of NLR was associated with poorer outcomes in patients with NSCLC (68). The present study revealed that neither surgery nor adjuvant chemotherapy had significant effects on serum NLR levels, while a whole course of treatment significantly decreased the level of NLR. However, neither the pre-treatment level nor the post-/pre-treatment ratio of NLR had an impact on OS.

As an indicator of systemic inflammation, PLR has been demonstrated to be a prognostic indicator in resectable lung cancer. Platelets facilitate tumor growth by promoting tumor

angiogenesis via the secretion of several types of cytokines and chemokines, including vascular endothelial growth factors. Furthermore, an adhesion molecule from platelets directly binds to malignant cells and facilitates tumor metastasis (69-71). Additionally, platelets are proposed to protect tumor cells from immunological elimination and serve a negative role in the host immune attack against tumor cells, as well as in restraining the cytolytic activity of natural killer cells (72,73). For example, Yuan *et al* (17) concluded that high PLR levels (>204.00) indicated a poorer prognosis in patients with NSCLC (17). Similarly, Toda *et al* (18) indicated that increased post-operative PLR predicted a poorer prognosis in patients with NSCLC, particularly in those who received adjuvant chemotherapy (14). In the present study, the baseline PLR value was not associated with OS, while an increased post-/pre-treatment ratio of PLR was associated with poorer outcomes in patients with resectable lung cancer. Multivariate analysis revealed that an increased post-/pre-treatment PLR ratio was an independent risk factor affecting OS. In addition, treatment had no significant impact on PLR levels.

The present study investigated the predictive values of CRP, ALB, GLB, LDH, NLR and PLR in patients with resectable lung cancer and concluded that patients with low pre-treatment ALB levels and increased post-/pre-treatment PLR ratios following whole course treatment had poorer outcomes, and a low pre-treatment ALB level and increased post-/pre-treatment ratio of PLR were independent risk factors for OS. Since ALB and PLR are inexpensive and easily accessible indicators, they can be easily incorporated into routine use as prognostic factors, combined with tumor markers and imaging examination. However, the present study has a number of limitations. For example, insufficient sample size was attributed to limited manpower and material resources. In order to eliminate the difference in general performance status of patients, those with coexisting diseases, including chronic infection, rheumatic diseases and other chronic inflammatory diseases, were excluded, and only 101 samples were included. Furthermore, the data were obtained from a single center, and the duration of follow-up was relatively short.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WL and MYW made substantial contributions to the conception and design of the work; WJW, RR, MDX and KC revised the manuscript critically for important intellectual content and acquired the data; JZ, LL, WD, FRG, MT, and QZ analyzed and interpreted the data for the present study. All authors have read and approved the final version of the manuscript.

Ethics statement and consent to participate

The present study was approved by the Medical Ethics Committees of The First Affiliated Hospital of Soochow University (Suzhou, China). Written informed consent was obtained from all patients.

Patient consent for publication

All patients provided consent for the publication of their data and associated images.

Competing interests

The authors declare that they have no competing interests.

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