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Prognostic value of combination fibrinogen, platelet, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in advanced lung adenocarcinoma

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Abstract: **A combination of fibrinogen (FBG), platelet (PLT), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) (abbreviated as CO-NPF) has been recently evaluated as a marker for prognostication in lung cancer. While previous study on CO-NPF has evaluated in lung adenosquamous patients, the combination of these four markers has not been evaluated in advanced lung adenocarcinoma yet. In this study, we investigated the significance of CO-NPF in predicting the survival of patients with advanced lung adenocarcinoma. 225 patients with pathologically diagnosed lung adenocarcinoma were enrolled. The cutoff values for FBG, PLT, NLR and PLR were defined by receiver operating characteristic (ROC). The CO-NPF was calculated as the combination of FBG, PLT, NLR and PLR based on these cutoff values. Kaplan-Meier analysis and Cox proportional hazard models were used to assess the prognostic value of CO-NPF. Kaplan-Meier analysis reveals that CO-NFP was associated with poorer progressive free survival (PFS) [hazard ratio (HR), 0.657; 95% confidence interval (CI), 0.501-0.862; P=0.002] and overall survival (OS) (HR, 0.701; 95% CI, 0.523-0.938; P=0.016). Cox proportional hazard models further reveals CO-NFP as an independent prognostic factor for PFS (HR, 0.665; 95% CI, 0.504-0.876; P=0.004) and OS (HR, 0.672; 95% CI, 0.495-0.914; P=0.011). CO-NPF can serve as a useful biomarker to predict recurrence and death for patients with advanced lung adenocarcinoma.**

Keywords: Biomarker; Lung adenocarcinoma; Prognosis; CO-NPF

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1. Introduction

Lung cancer is currently one of the most serious cancer-related death worldwide and non-small cell lung cancer (NSCLC) accounts for about 75-85% of all cancer cases[1,2]. Lung adenocarcinoma is a histological subtype of NSCLC with no obvious clinical symptoms in early stage, leading to the losses of the best time for treatment[3]. Despite rapid advances in surgical techniques and adjuvant therapy, the prognosis of lung adenocarcinoma is still poor. Therefore, identifying biomarkers which are sensitive and easy obtained for the prediction of lung adenocarcinoma prognosis is of clinical significance.

Gathering evidence have indicated that inflammation could promote tumor progression and metastasis by inhibiting apoptosis and promoting angiogenesis[4]. Neutrophil-to-lymphocyte ratio (NLR) is one of the systemic inflammation markers, and it was reported that NLR was associated with poor prognosis in various malignancies, including breast cancer, lung cancer, gastric cancer etc[5-9]. Platelet-to-lymphocyte (PLR) is another index of systemic inflammation. Previous studies have reported the prognosis role of PLR in many types of cancers, such as NSCLC, nasopharyngeal cancer and breast cancer[10-12]. Additionally, growing number of evidence suggested the existence of a correlation between hemostatic abnormalities and tumor angiogenesis, invasion, progression and metastatic spread[13-17]. And the elevated plasma fibrinogen (FBG) and platelet (PLT) levels are associated with worse outcome in lung cancer[18-20]. While previous study on (a combination of FBG, PLT, NLR and PLR) has evaluated its prognostic value in lung adenosquamous patients, the CO-NPF has not been assessed as marker of tumor progression and prognosis in advanced lung adenocarcinoma[21]. The aims of this study were to document the clinical features of lung adenocarcinoma and determine whether CO-NPF is independent prognostic indicator in these patients.

2. Patients and methods

2.1. Patients

This study group consisted of 225 patients with advanced (IIIB-IV stage) lung adenocarcinoma who admitted consecutively to The Affiliated Hospital of Qingdao University between January 2009 and December 2015. Inclusion criteria for the present study were as follows: 1) histologically confirmed lung adenocarcinoma; 2) Eastern Cooper-active Oncology Group-performance status (ECOG-PS) ≤ 2; 3) underwent active anticancer treatment; 4) no signs of infection; 5) no concomitant hematological or autoimmune disease; 6) no other malignancy. Clinical, laboratory, pathological and follow-up information of

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these patients were obtained from the electronic medical records, including age, sex, smoking history, tumor location, tumor-node-metastasis (TNM) stage and ECOG-PS.

Patients who lacked complete information were excluded from this study. Laboratory blood tests from lung adenocarcinoma patients were obtained within 7 days before treatment. All patients were restaged using the 7th International Classification System for Lung Cancer. The response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. This study was approved by the Ethics Committee consent of The Affiliated Hospital of Qingdao University and written informed consent was obtained from all patients or their families.

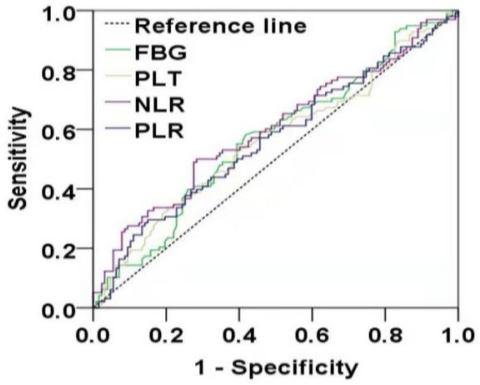


Figure 1. Receiver operating characteristic (ROC) curves of pretreatment FBG, PLT, NLR and PLR for predicting survival in patients with advanced adenocarcinoma.

Table 1. Clinicopathological features of the entire cohort (n=225)

characteristics		n	%
Gender			
	Female	102	45.3
	Male	123	54.7
Age, median (range)		58.83±9.65	
	<60	109	48.4
	≥60	116	51.6
Tumor location			
	Right	131	58.2
	Left	94	41.8
Tumor stage			
	III	40	17.8
	IV	185	82.2
Smoking history			
	None	125	55.6
	Yes	100	44.4
Performance status			
	0	20	8.9
	1	180	80.0
	2	25	11.1
FBG, mean ± SD		3.62 ± 1.01	
PLT, mean ± SD		258.39 ± 73.23	
NLR, mean ± SD		2.75 ± 1.43	
PLR, mean ± SD		152.37 ± 71.52	

2.2. CO-NPF definition

NLR was defined as a ratio of peripheral neutrophil count to peripheral lymphocyte count, while PLR was calculated as a ratio of peripheral platelet count to peripheral lymphocyte count. Optimal cutoff value for FBG, PLT, NLR and PLR were calculated based on receiver operating characteristics (ROC) curve analysis (Figure 1). According to the ROC curve analysis, the most appropriate cutoff point for FBG was 3.48. Therefore, we recommended 3.48 as the cutoff value for FBG. Similarly, the optimal point based on the ROC curve for predicting prognosis in lung adenocarcinoma patients was 297 for PLT, 2.85 for NLR and 181.79 for PLR. Based on these cutoff values, we calculated the CO-NPF score. Patients with a high FBG was given a score of 1, otherwise, it was given a score of 0. Other three indicators were scored in the same way. Add up the scores of four indicators, and the result is CO-NPF. There are five possible scores for CO-NPF: 0, 1, 2, 3 and 4. For example, patients with a high FBG (≥3.48), PLT (≥297), NLR (≥2.85) and PLR (≥181.79) were given a score of 4. Patients without either abnormality were scored 0. For CO-NPF, patients were divided into two groups based on their values: CO-NPF<2 and CO-NPF≥2. Progression free survival (PFS) was defined as the time from diagnosis

until the time of disease progression during 1st line treatment or the time of the last follow-up. Overall survival (OS) was defined as the time from diagnosis until the time of death or the time of the last follow-up. The last follow-up visit occurred in November 2018.

Table 2. Relationships between clinicopathological characteristics and CO-NPF

Variables		CO-NPF < 2 N=133	%	CO-NPF ≥ 2 N=92	%	P-value
Gender						
	Female	64	48.1	38	41.3	0.313
	Male	69	51.9	54	58.7	
Age						
	<60	60	45.1	49	53.3	0.229
	≥60	73	54.9	43	46.7	
Tumor location						
	Right	76	57.1	55	59.8	0.693
	Left	57	42.9	37	40.2	
Tumor stage						
	III	25	18.8	15	16.3	0.631
	IV	108	81.2	77	83.7	
Smoking history						
	None	75	56.4	50	54.3	0.762
	Yes	58	43.6	42	45.7	
Performance stage						
	0	12	9.0	8	8.7	0.487
	1	109	82.0	71	77.2	
	2	12	9.0	13	14.1	
FBG						
	<3.48	95	71.4	20	21.7	0.324
	≥3.48	38	28.6	72	78.3	
PLT						
	<297	122	91.7	44	47.8	0.000
	≥297	11	8.3	48	52.2	
NLR						
	<2.85	117	88.0	23	25.0	0.000
	≥2.85	16	12.0	69	75.0	
PLR						
	<181.79	132	99.2	45	48.9	0.000
	≥181.79	1	0.8	47	51.1	

FBG, fibrinogen; PLT, platelet; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

2.3. Statistical analysis

The analysis was performed through Statistical Package for Social Science software program version 20.0 (SPSS Inc., Chicago, IL, USA) statistical package. Data were presented as absolute number of patients or mean ± standard deviation (SD). Comparison between two groups was analyzed using $\chi 2$ texts or Fisher's exact tests. Survival curves were determined via the Kaplan-Meier methods, and the log-rank test was used to assess the difference between groups. Variables that were found to be statistically significant at the univariate analysis were then enter into Cox proportional hazards regression model for multivariate analysis. P-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The patients' characteristics are shown in Table 1. A total of 225 advanced lung adenocarcinoma patients were included. Among these patients, 102 (45.3%) were female, and 123 (54.7%) were male. The median age of the patients was 58.83 years, and 51.6% were ≥ 60-years-old. 131 (58.2%) patients' tumor were located in the right and 94 (41.8%) were located in the left. In total, 40 (17.8%) patients had TNM stage III disease and 185 (82.2%) had TNM stage IV disease. Of the 225 patients, 125 (55.6%) had never smoked as compared with 100 (44.4%) who were former or currently smokers. 20 had ECOG-PS 0, 180 had

ECOG-PS 1, and 25 had ECOG-PS 2. The median NLR and PLR in the 225 patients were 2.75 and 152.37, respectively, the median FBG level was 3.62 g/L, and the median PLT count was 152.37 × 10^3 cells/mm^3.

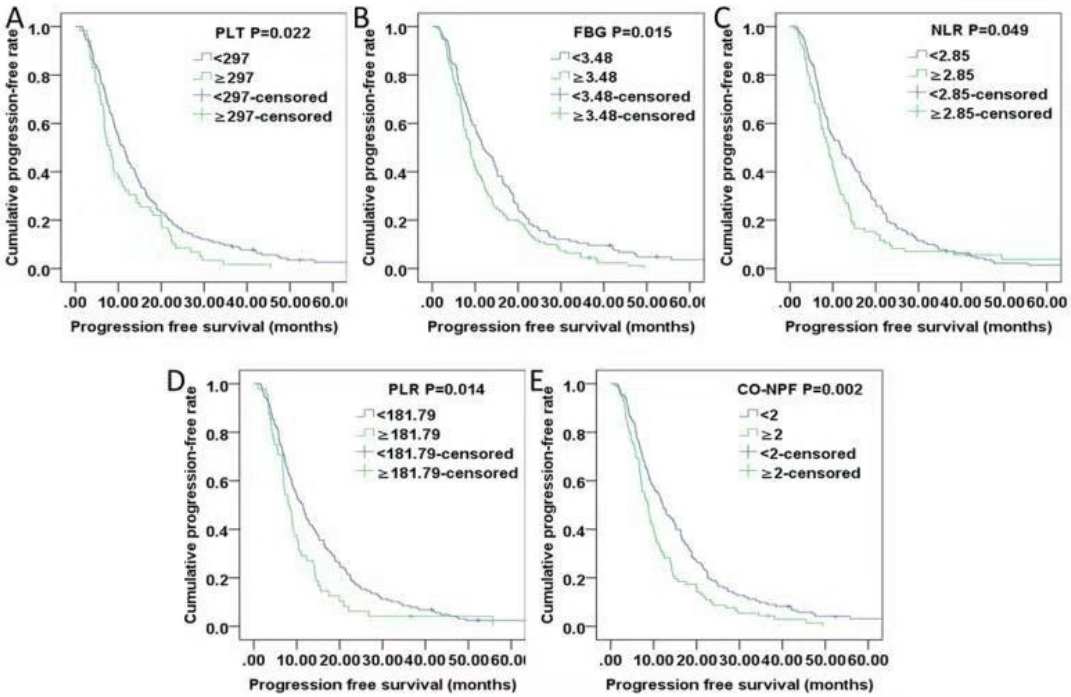


Figure 2. Kaplan-Meier survival curves for progressive free survival (PFS) in lung adenocarcinoma patients after diagnosis. (A) PFS of patients with PLT<297 was longer than those with PLT≥297 (P=0.022, log-rank). (B) PFS of patients with FBG<3.48 was longer than those with FBG≥3.48 (P=0.015, log-rank). (C) PFS of patients with NLR<2.85 was longer than those with NLR≥2.85 (P=0.049, log-rank). (D) PFS of patients with PLR<181.79 was longer than those with PLR≥181.79 (P=0.014, log-rank). (E) PFS of patients with CO-NPF<2 was longer than those with CO-NPF≥2 (P=0.002, log-rank).

3.2. Association of CO-NPF with clinical factors

As for CO-NFP analysis, patients were stratified into two groups: CO-NPF < 2 and CO-NPF ≥ 2. The clinical and laboratory data were presented in Table 2. Our study revealed that CO-NFP was prominently associated with PLT (P=0.000), NLR (P=0.000) and PLR (P=0.000). For CO-NPF groups < 2 and ≥ 2, median PFS were 12.13 and 8.75 months, respectively, while median OS were 30.80 and 22.02 months, respectively. In CO-NPF < 2 group, the 1-, 2-, and 3-year PFS rates were 51.1, 18.8 and 9.8%, while in the CO-NPF ≥ 2 group, the PFS rates were 30.4, 8.7, and 4.3% (Figure 2E). Correspondingly, the 1-, 2-, and 3-year OS rates were 90.2, 65.4 and 41.4% in the CO-NPF < 2 group and 79.3, 43.5 and 29.3% in the CO-NPF ≥ 2 group (Figure 3E). On the whole, PFS and OS of patients in the CO-NPF < 2 group were obviously improved compared with the patients in the CO-NPF ≥ 2 group.

3.3. Association of CO-NPF with overall survival and progression free survival

For all patients included in the present study, we calculated the association between PFS and OS with clinical parameters by Kaplan-Meier method. Prognosis in the low CO-NPF group was better than that in the high CO-NPF group (Figure 2E and Figure 3E). Compared patients in the low PLT, FBG, NLR and PLR groups, the patients in the high PLT, FBG, NLR and PLR groups showed poorer PFS (P=0.022; P=0.015; P=0.049; P=0.014, respectively) (Figure 2A-D). Similarly, compared patients in the low PLT, FBG, NLR and PLR groups, the patients in the high PLT, FBG, NLR and PLR groups showed poorer OS (P=0.005; P=0.026; P=0.013; P=0.050, respectively) (Figure 3A-D). Supplementary Table 3 and 4 shows the results of univariate and multivariate analysis of the gender, age, tumor location, tumor stage, smoking history, performance status and inflammatory parameters associated with PFS and OS. According to this analysis, high PLT, FBG, NLR, PLR and CO-NPF were significantly associated with shorter PFS and OS. Therefore, these factors with significance in the univariate analysis were then entered into the subsequent multivariate analysis. PLT (hazard ratio [HR]: 0.691; 95% CI: 0.507-0.942; P=0.019), FBG (HR: 0.723; 95% CI: 0.551-0.949; P=0.019), PLR (HR:

0.638; 95% CI: 0.452-0.900; P=0.011) and CO-NPF (HR: 0.665; 95% CI: 0.504-0.876; P=0.004) were prognostic factor for PFS (Table 3). PLT (HR: 0.668; 95% CI: 0.474-0.940; P=0.021), FBG (HR: 0.646; 95% CI: 0.479-0.872; P=0.004), NLR (HR: 0.685; 95% CI: 0.502-0.933; P=0.017), PLR (HR: 0.682; 95% CI: 0.476-0.976; P=0.037) and CO-NPF (HR: 0.672; 95% CI: 0.495-0.914; P=0.011) were defined as independent factors for OS (Table 4).

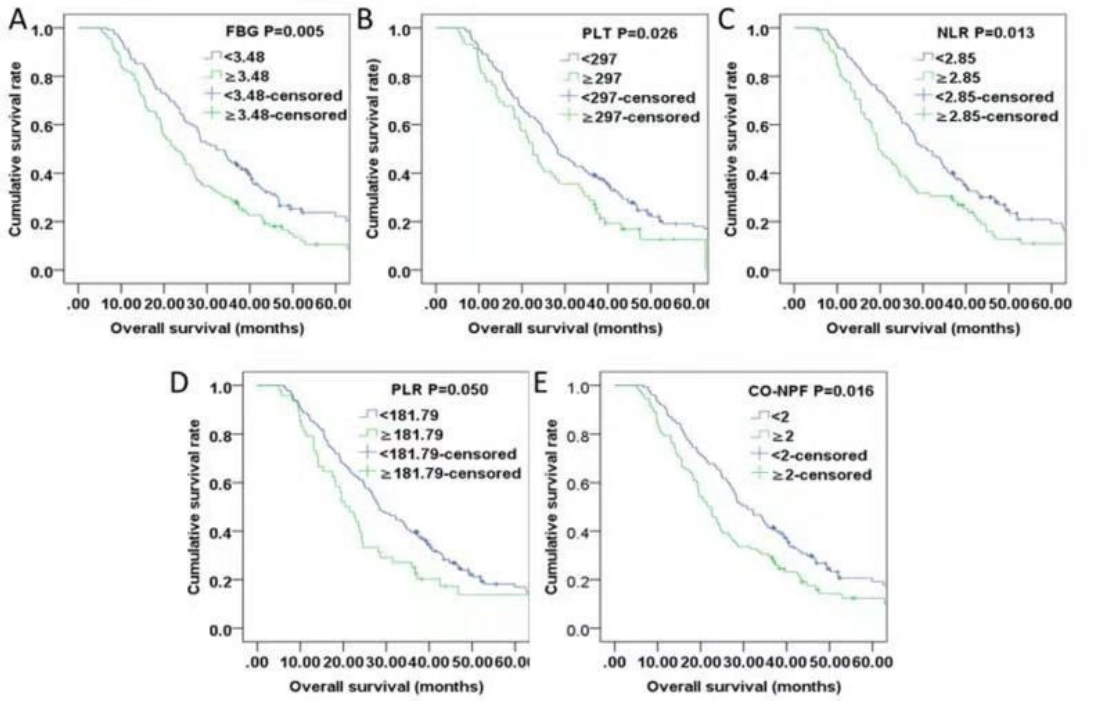


Figure 3. Kaplan-Meier survival curves for overall survival (OS) in patients with lung adenocarcinoma after diagnosis. (A) OS of patients with FBG<3.48 was longer than those with FBG≥3.48 (P=0.005, log-rank). (B) OS of patients with PLT<297 was longer than those with PLT≥297 (P=0.026, log-rank). (C) OS of patients with NLR<2.85 was longer than those with NLR≥2.85 (P=0.013, log-rank). (D) OS of patients with PLR<181.79 was not obvious different from those with PLR≥181.79 (P=0.050, log-rank). (E) OS of patients with CO-NPF<2 was longer than those with CO-NPF≥2 (P=0.016, log-rank).

Table 3. Univariate and multivariate analysis of clinical characteristics in relation to PFS

		univariate analysis			multivariate analysis		
Prognostic factors		HR	95%CI	P	HR	95%CI	P
Gender	Female/Male	0.837	0.639-1.097	0.197	0.853	0.605-1.204	0.366
Age	<60/≥60	1.196	0.916-1.562	0.189	1.207	0.919-1.586	0.176
Tumor location	Right/Left	0.959	0.733-1.254	0.759	0.980	0.748-1.283	0.883
Tumor stage	III/IV	0.882	0.624-1.248	0.479	0.841	0.591-1.197	0.337
Smoking history	None/Yes	0.859	0.657-1.122	0.264	0.888	0.629-1.255	0.502
Performance stage	0+1/2	0.826	0.540-1.264	0.380	0.822	0.530-1.276	0.383
FBG	<3.48/≥3.48	0.718	0.549-0.939	0.014	0.723	0.551-0.949	0.019
PLT	<297/≥297	0.705	0.522-0.954	0.022	0.691	0.507-0.942	0.019
NLR	<2.85/≥2.85	0.759	0.576-1.000	0.049	0.793	0.597-1.053	0.108
PLR	<181.79/≥181.79	0.667	0.481-0.924	0.014	0.638	0.452-0.900	0.011
CO-NPF	<2/≥2	0.657	0.501-0.862	0.002	0.665	0.504-0.876	0.004

PFS, progressive free survival; HR, hazard ratio; CI, confidence interval; FBG, fibrinogen; PLT, platelet; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

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Table 4. Univariate and multivariate analysis of clinical characteristics in relation to OS

		univariate analysis			multivariate analysis		
Prognostic factors		HR	95%CI	P	HR	95%CI	P
Gender	Female/Male	0.879	0.657-1.176	0.385	0.878	0.583-1.322	0.533
Age	<60/≥60	1.143	0.856-1.525	0.364	1.200	0.892-1.616	0.228
Tumor location	Right/Left	0.968	0.722-1.298	0.829	0.977	0.726-1.315	0.878
Tumor stage	III/IV	0.906	0.612-1.341	0.622	0.893	0.601-1.328	0.577
Smoking history	None/Yes	0.904	0.676-1.208	0.495	0.959	0.636-1.146	0.843
Performance stage	0+1/2	1.180	0.745-1.870	0.481	1.247	0.776-2.004	0.362
FBG	<3.48/≥3.48	0.660	0.494-0.881	0.005	0.646	0.479-0.872	0.004
PLT	<297/≥297	0.690	0.497-0.959	0.026	0.668	0.474-0.940	0.021
NLR	<2.85/≥2.85	0.688	0.512-0.926	0.013	0.685	0.502-0.933	0.017
PLR	<181.79/≥181.79	0.708	0.500-1.002	0.050	0.682	0.476-0.976	0.037
CO-NPF	<2/≥2	0.701	0.523-0.938	0.016	0.672	0.495-0.914	0.011

OS, overall survival; HR, hazard ratio; CI, confidence interval; FBG, fibrinogen; PLT, platelet; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

4. Discussion

Prognostic factors are important in lung cancer patients for suitable risk classification and assignment of appropriate prospective treatment. In the last few decades, increasing evidence has revealed that systematic inflammation responses are crucial prognostic indicators[22]. In the meantime, most studies have demonstrated that thrombocytosis and elevated fibrinogen levels showed poor prognosis in patients with lung cancer[23-25]. Therefore we combined FBG, PLT, NLR and PLR together as CO-NPF to access its association with clinical characteristics and prognosis. Our results showed that CO-NPF was an independent predictor for shorter PFS and OS in advanced lung adenocarcinoma patients.

The association between the progression of malignancies and coagulation has attracted considerable attention in recent years. Serum FBG converted to insoluble fibrin by activated thrombin, play an important role in tumor metastasis, stroma formation, and angiogenesis[26-28]. Hypercoagulability is a sign of a more aggressive disease. Previously, studies shown that pre-operative FBG level was an independent prognostic factor in operable NSCLC patients, and FBG levels had been reported to be increased in patients with more advanced stage and poor prognosis[29-30]. Meanwhile, anticoagulant drugs, such as warfarin and heparin, have been proven to have antitumor effects *in vivo* and *in vitro[31]*. In our current study, analysis demonstrated that the positivities of FBG was predictive of worse PFS and OS, which accord with previous studies addressing the clinical and prognostic significance of FBG in cancer patients in general. However, further studies are required and may identify more effective uses of FBG as predictive and markers for NSCLC patients.

Thrombocytosis is associated with poor prognosis in NSCLC[25,32,33]. Some scholars hold the opinion that PLT is a source of various cytokines such as vascular epidermal growth factor (VEGF), transforming growth factor beta (TGF-β) and platelet-derived growth which have significant effect on cancer metastasis, tumor cell invasion, migration and arrest with blood[34-36]. Another opinion is PLT provides a procoagulation surface to shield circulating tumor cell from immune attack and protect these cells from shearing stresses during circulation, thus facilitating them to growth and metastasis[37-39]. In the 225 cases we studied, elevated PLT was identified as an independent factor for poor prognosis in lung adenocarcinoma patients, which consistent with the results of previous studies.

Lymphocytes perform important function in host immune response and contribute to the inhibition of tumor cell proliferation migration[22,40]. Furthermore, increased lymphocytes are an advantageous prognostic index in various tumors, including NSCLC[41,42]. In a word, the high PLR means an increased PLT count and a decreased lymphocyte count. The results in our present study showed that high level of PLR was associated with poor prognosis of advanced lung adenocarcinoma patients. This was consisted with previous studies.

Peripheral blood neutrophil is a marker of acute and chronic inflammation, and upregulation of peripheral neutrophils can promote tumor development, progression and metastasis via secreting vascular endothelial growth factor and matrix

metalloproteinase-9[43-45]. With the combination of neutrophil and lymphocyte counts, NLR can be used as a representative index to reflex the balance between pro-tumor inflammatory status and anti-tumor immune status in patients with various cancers.[5] Our study show patients with elevated NLR had significantly worse OS than those with low NLR, but was not associated PFS in lung adenocarcinoma patients.

In the present study, we noted that CO-NPF presents a good prognostic indicator for advanced lung adenocarcinoma patients. Further validation tests are required to verify whether CO-NPF could predict the prognosis in patients with advanced lung adenocarcinoma. There are several limitations in our study. First, it was a retrospective study of patients from a single institution, and multi-center studies are needed to confirm the results we identified here. Second, although we restricted the influence of other factors, selection bias and unidentified factors might have influence the outcomes. Third, the cutoff values in our present study differ from the previous studies. Therefore, a reasonable cutoff values which could predict the prognosis of advanced lung adenocarcinoma should be identified.

5. Conclusion

Pretreatment CO-NPF can be used to predict short PFS and OS in lung adenocarcinoma patients. Further research is needed to elucidate the underlying pathophysiological background for predictability of combined thrombocytosis and inflammatory biomarkers.

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Disclosure

No authors report any conflict of interest.

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