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ORIGINAL ARTICLE

Elevated pretreatment plasma fibrinogen level is associated with metastasis of non-small cell lung cancer (NSCLC)

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Abstract

Objective The aim of this study was to investigate the correlation between pretreatment fibrinogen levels and metastasis in non-small cell lung cancer (NSCLC).

Methods The study included 503 NSCLC patients with a clear pathological diagnosis and 168 patients diagnosed with benign lung diseases by histological examination. Pretreatment plasma fibrinogen values were quantified, and the relationship between plasma fibrinogen level and clinical variables comprising tumor size, metastasis, and clinical stage was examined using Kruskal-Wallis test, Wilcoxon rank sum test, and Chi-square test.

Results The median plasma fibrinogen values were statistically higher in NSCLC patients with metastasis than patients with benign lung diseases and NSCLC patients without metastasis (Kruskal-Wallis test; $P < 0.001$). Plasma fibrinogen values were also significantly higher in advanced clinical stages (Wilcoxon rank sum test; $P < 0.001$). A significant relationship was observed between elevated fibrinogen (> 2.974 g/L) and metastasis, clinical stage, and tumor size (Chi-square test; $P < 0.001$).

Conclusion This correlation suggests that elevated pretreatment plasma fibrinogen levels can predict metastasis and advanced tumor stage in NSCLC patients.

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Key words: fibrinogen; metastasis; NSCLC; tumor stage

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths, with non-small cell lung cancer (NSCLC) representing 80% of all cases [1]. Majority of these cases are advanced or have metastasized by the time of diagnosis. Fibrinogen, which is synthesized mainly by the liver epithelium, plays overlapping roles in blood clotting, fibrinolysis, cellular and matrix interactions, inflammatory response, wound healing, and neoplasia [2–3]. Recently additional evidence has demonstrated that serum fibrinogen is associated with operable malignant cell growth, progression, and metastasis, such as in esophageal cancer [4], gastric cancer [5], renal cell carcinoma [6], colon cancer [7], and hepatocellular cancer [8]. In NSCLC, there is evidence that fibrinogen contributes to tumor progression, metastasis, and poor survival in operable NSCLC patients [9] and is related with the chemotherapy outcomes in advanced NSCLC patients [10]. However, as far as we know, the association of pretreatment plasma fibrinogen levels with metastasis in patients has not been well defined. Therefore, in this study, we investigated the correlation between pretreatment plasma fibrinogen levels, clinicopathological parameters, and metastasis in NSCLC patients.

Patients and methods

Patients

A retrospective study on patients with NSCLC or benign lung disease was conducted at the Harbin Medical University Cancer Hospital from January to December 2018. We retrospectively collected data from medical records and obtained oral informed consent. All data were collected and analyzed anonymously. The inclusion

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criteria were as follows: (1) all patients have a clear pathological diagnosis; (2) in operable patients, surgical specimens (lung tumor tissue or lymph nodes) were used to confirm the pathological diagnosis; (3) in inoperable patients, fine needle aspiration biopsy or bronchoscopic biopsy were used to confirm the pathological diagnosis. Patients who met the following criteria were excluded from the study: (1) received preoperative chemotherapy or radiotherapy; (2) clinical evidence of infection or other bone marrow, hematological, or autoimmune disease; (3) history of another cancer; (4) thrombosis in lower limbs. Based on the inclusion and exclusion criteria, a total of 503 NSCLC and 168 benign lung disease patients were analyzed in this study. All patients were Chinese. The pretreatment evaluation included a detailed clinical history and physical examination along with a series of biochemistry tests, complete blood cell count, and coagulation tests. Further investigations included radiography, flexible bronchoscopy, chest and upper abdominal computed tomography (CT), radionuclide bone scan, and CT or magnetic resonance imaging (MRI) of the brain. NSCLC stages were based on the 8th edition of the TNM Classification.

Fibrinogen measurement

Blood samples were collected before the initial diagnosis and invasive detection techniques. Venous blood sampling was performed one week prior to treatment, and collected in ethylenediaminetetraacetic acid (EDTA) containing tubes. Fibrinogen values were measured by an automatic coagulation analyzer.

Statistical analysis

All statistical analyses were carried out using SPSS 18.0 software (SPSS Inc., Chicago, USA). Differences between the analyzed categories were identified using the Chi-square test, Kruskal-Wallis test, and the Wilcoxon rank sum test. In order to classify the patients into two groups, the cut-off values of clinicolaboratory variables were determined using receiver operating characteristic (ROC) curve analyses. The value of the maximum combined sensitivity and specificity on the ROC plot was defined as the recommended cut-off value. Differences were considered significant when the *P* value was less than 0.05.

Results

Clinical characteristics of patients

Patient characteristics are shown in Table 1. Out of the total 671 enrolled patients, 503 patients (75.0%) were diagnosed with NSCLC with clear pathology, and the remaining (25%) were diagnosed with benign lung disease, including hamartoma, pulmonary sclerosing hemangioma, and atypical hyperplasia of the alveolar epithelium. Among all patients, 274 (40.83%) were women, and 397 (59.17%) were men. The median age was 57.24 years, with an age range from 15 to 81 years. We defined people who smoked currently or had in the past as smokers, and there were 391 smokers in this study. A total of 360 patients were diagnosed with adenocarcinoma, 127 were diagnosed with squamous cell carcinoma, and the rest were diagnosed with other types of NSCLC. The distribution of pathological stages was as follows: stage I, 205; stage II, 18; stage III, 120, and stage

Table 1 Characteristics of the 671 patients

	Benign lung disease (*n*=168)	NSCLC without metastasis (*n*=210)	NSCLC with metastasis (*n*=293)	*P*
Sex				< 0.001
Male	103	98	196	
Female	65	112	97	
Age (years)	53.95 ± 11.937	59.10 ± 8.989	57.80 ± 9.152	< 0.001
Smoking history				0.004
Yes	86	97	178	
No	82	113	115	
Histological types of NSCLC				< 0.001
Adenocarcinoma	–	164	196	
Squamous cell carcinoma	–	35	92	
Others	–	11	5	
Tumor size (cm)				< 0.001
Median	–	2	3.5	
Range	–	0.6–8.0	0.6–9.5	
Fibrinogen (g/L)				< 0.001
Median	2.695	2.509	3.620	
Range	1.203–5.506	1.530–5.223	1.577–6.539	

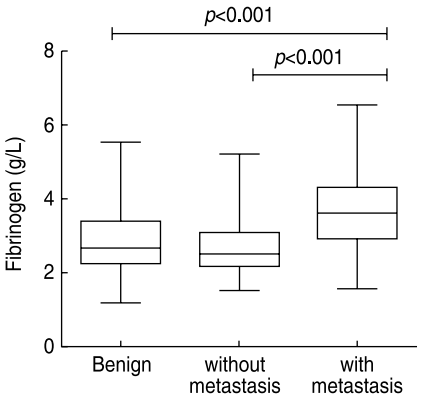

Fig. 1 Median fibrinogen values were higher in NSCLC patients with metastasis compared with the other groups

IV, 160. Among the NSCLC patients, 293 (43.67%) were diagnosed with metastasis, with 133 patients (19.82%) diagnosed as NSCLC with only lymph nodes metastasis (TxN1-3M0) and the remaining 160 patients diagnosed with at least one distant metastatic lesion (TxNxM1). NSCLC patients had a mean tumor size of 3.12 cm (range, 0.6 to 9.5 cm). Patients diagnosed with metastasis showed higher fibrinogen level than patients without metastasis and patients with benign lung disease.

All patients were divided into three groups: patients with benign lung diseases (n = 168), NSCLC patients without metastasis (n = 210), and NSCLC patients with metastasis (n = 293). As shown in Fig.1, the median fibrinogen value of patients with benign lung disease, NSCLC patients without metastasis, and NSCLC patients with metastasis was 2.695, 2.509, and 3.620 g/L, respectively. Statistically higher median fibrinogen values were exhibited by the metastasis group (Kruskal-Wallis test, P< 0.001). This result indicated that the median fibrinogen values of NSCLC patients with metastasis were higher than patients without metastasis.

Kruskal-Wallis test was used to compare the fibrinogen values among the benign, NSCLC without metastasis, and NSCLC with metastasis groups. The Wilcoxon rank sum test was used to compare the fibrinogen values between the NSCLC patients with and without metastasis. P< 0.05 was considered as statistically significant. The results demonstrated that the fibrinogen values in NSCLC patients with metastasis were higher than in the other groups, and the difference showed statistical significance.

To exclude the interference of age, sex, smoking history, and histological types of NSCLC, the difference in the fibrinogen values between cancer patients 60 years and older versus those younger than 60 years, smokers versus non-smokers, men versus women, and adenocarcinoma versus squamous cell carcinoma were compared in Fig. 2. We found that the median fibrinogen values were higher in the metastasis group regardless of age, sex, smoking history, and histological types of NSCLC.

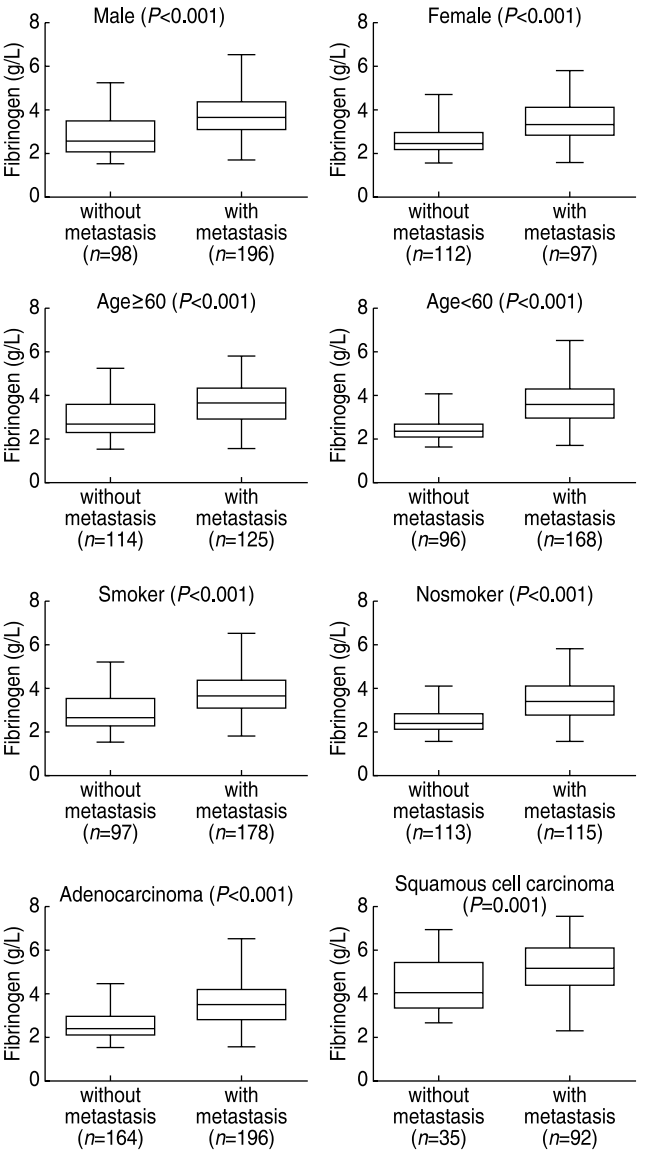

Fig. 2 Fibrinogen values were higher in NSCLC patients with metastasis than those without metastasis regardless of age, sex, smoking history, and histological types of NSCLC. The Wilcoxon rank sum test was used to compare the fibrinogen values between the two group. P < 0.05 were considered as statistically significant. A Male NSCLC patients, B Female NSCLC patients, C NSCLC patients aged 60 years and older, D NSCLC patients aged less than 60 years, E Smoker NSCLC patients, F Non-smoker NSCLC patients, G Adenocarcinoma patients, H Squamous cell carcinoma patients

Fibrinogen values in different stages of lung cancer

Since metastasis affects the TNM stage, we concluded that fibrinogen values may also have a statistically significant impact on the different TNM stages. Spearman rank correlation test was used to analyze the correlation

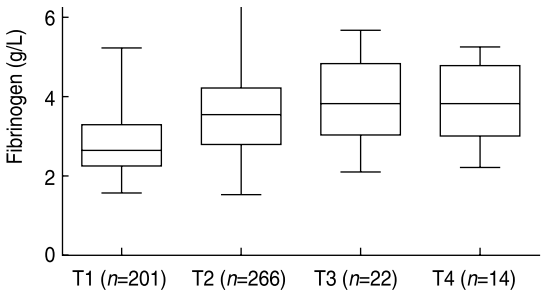

Fig. 3 Fibrinogen values in different T stages. Median fibrinogen values were 2.607, 3.522, 3.814, and 3.805g/L

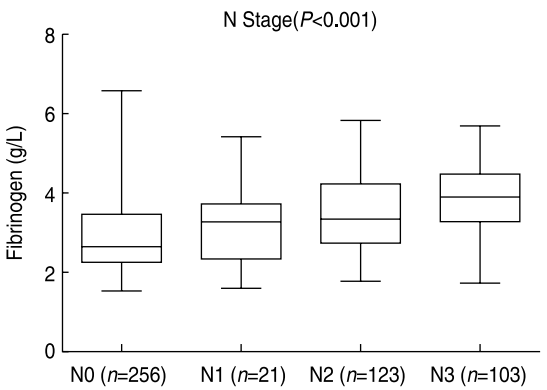

Fig. 4 Fibrinogen values in different N stages. Median fibrinogen values were 2.643, 3.267, 3.321, 3.878g/L. A statistically significant difference in the fibrinogen values was observed between the different N stages (Kruskal-Wallis test, $P < 0.001$) and the highest fibrinogen value was obtained in N3 patients

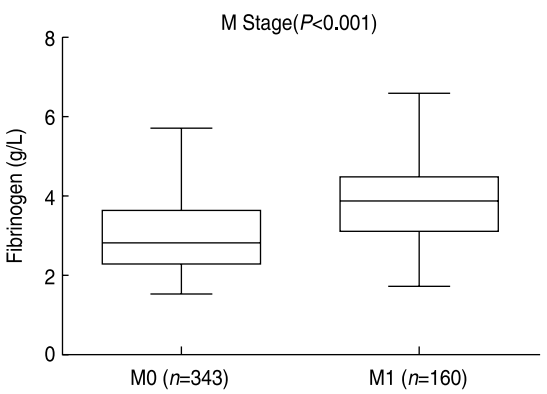

Fig. 5 Fibrinogen values in different M stages. Median fibrinogen values were 2.816 and 3.866 g/L in M0 and M3, respectively. M1 patients showed higher fibrinogen values (Wilcoxon rank sum test, $P < 0.001$)

between fibrinogen values and the TNM stage. The results of Spearman rank correlation test indicated that fibrinogen values correlated significantly with T, N, and M stages (Spearman's rho was 0.401, 0.418, and 0.378,

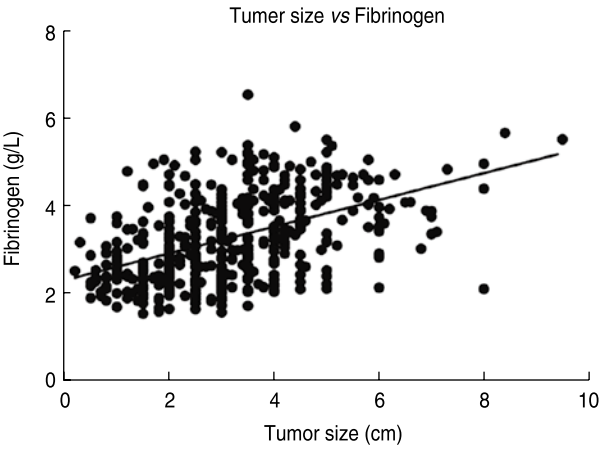

Fig. 6 Correlation between fibrinogen values and tumor size
Pearson correlation test indicated that the fibrinogen values correlated positively and significantly with tumor size (Pearson correlation coefficient = 0.480, $P < 0.001$)

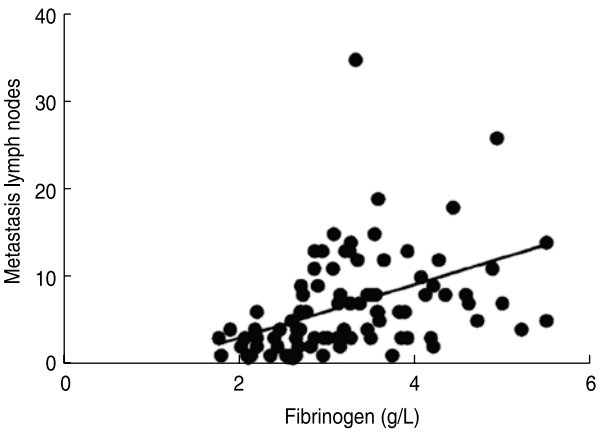

Fig. 7 Correlation between fibrinogen values and number of metastases
A total of 97 operable patients were confirmed to have lymph nodes metastasis, and Pearson correlation test was used to evaluate the relationship between fibrinogen values and lymph metastasis (Pearson correlation coefficient = 0.445, $P < 0.001$)

respectively; Fig. 3–5). Moreover, the results of the Pearson correlation coefficient analysis indicated that fibrinogen values correlated positively and significantly with the tumor size (Pearson correlation coefficient = 0.480, $P < 0.001$; Fig. 6). A total of 97 operable patients were confirmed to have lymph nodes metastasis, and Pearson correlation was used to detect the relationship between fibrinogen values and lymph metastasis. The results are shown in Fig. 7. The Pearson correlation coefficient of lymph node metastasis and fibrinogen values was 0.445 ($P < 0.001$) Although a statistically significant difference was demonstrated between the M0 and M1 patients (Wilcoxon rank sum test, $P < 0.001$; Fig. 5), neither distant metastatic lesions (Kruskal-Wallis test,

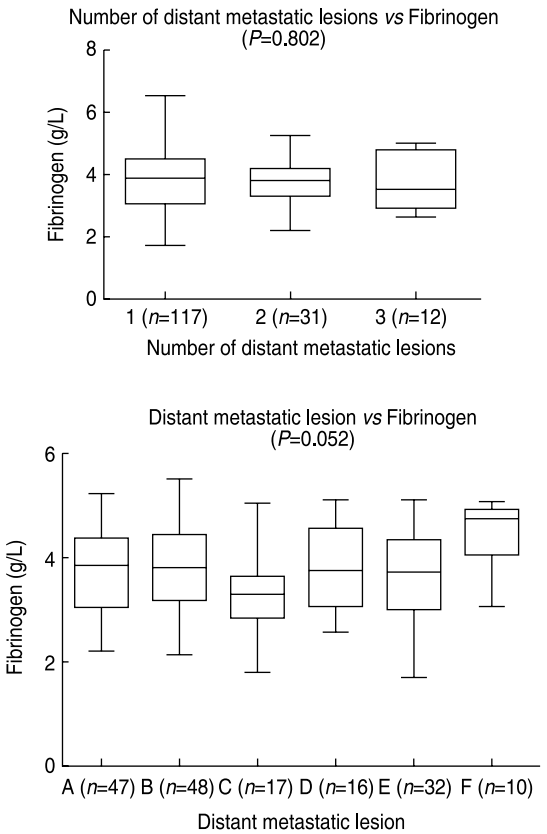

Fig. 8 Fibrinogen values in different distant metastatic lesions and the number of distant metastatic lesions. Fibrinogen values in different distant metastatic lesions (Kruskal-Wallis test, $P = 0.052$) and the number of distant metastatic lesions (Kruskal-Wallis test, $P = 0.802$) showed no statistically significant difference (A: pleural metastasis; B: lung metastasis; C: brain metastasis; D:liver metastasis; E: bone metastasis; F:adrenal gland metastasis)

$P = 0.052$), nor the number of distant metastatic lesions (Kruskal-Wallis test, $P = 0.802$) showed a statistically significant difference (Fig. 8). Overall, with regard to the TNM stage, the fibrinogen values in advanced lung cancer patients (stage III–IV) were significantly higher than those in early lung cancer patients (stage I–II) (Wilcoxon rank sum test, $P<0.001$, Fig. 9).

Fibrinogen values as a predictor of metastasis

Statistically significant difference in the fibrinogen values was observed between patients with metastasis and patients without metastasis, as shown in Fig. 1. Furthermore, fibrinogen values showed the highest correlation with the TNM stage. Therefore, we hypothesized that fibrinogen values may be used to predict metastasis and (ROC) curve analysis was used to prove this hypothesis.

The area under the curve (AUC) was 0.788 ($P < 0.001$). The value of the maximum combined sensitivity and specificity on the ROC plot was defined as the

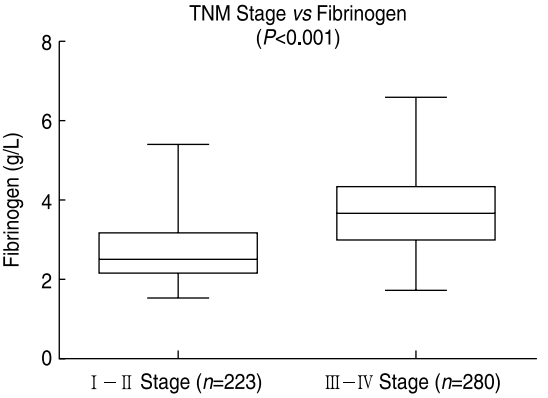

Fig. 9 Fibrinogen values and TNM stage. With regard to the TNM stage, the fibrinogen values in advanced lung cancer patients (stage III–IV) were significantly higher than in early lung cancer patients (stage I–II) (Wilcoxon rank sum test, $P < 0.001$)

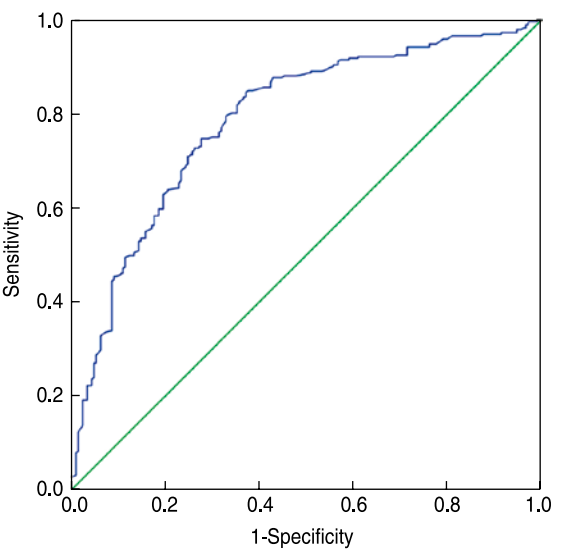

Fig. 10 Receiver operating characteristic (ROC) curve of fibrinogen values for predicting metastasis. Area under the receiver operating characteristic curve (AUC) values were used for predicting metastasis (AUC= 0.788; 95 % confidence interval [CI], 0.748–0.829; $P<0.001$)

recommended cut-off value. Therefore, we defined the cut-off value as 2.974 g/L, with a sensitivity of 0.747 and specificity of 0.724 (Fig. 10).

As a dichotomous variable (≤ 2.974 or > 2.974 g/L), a significant correlation was observed between fibrinogen values and NSCLC metastasis, tumor stage, tumor size, and histological types of NSCLC (Table 2).

Discussion

In other studies, fibrinogen values were shown to correlate with chemotherapy efficacy and prognosis in lung cancer [9, 11–16]. However, these studies were mainly

Table 2 Relationship between Fibrinogen values and NSCLC metastasis, tumor stage, tumor size

Variables	≤2.974 g/L (*n* = 226)	>2.974 g/L (*n* = 277)	*P*
Sex			< 0.001
Male	106	188	
Female	120	89	
Age	57.62 ± 9.13	58.93 ± 9.05	0.110
Tumor size (cm)			< 0.001
Median	2	3.5	
Range	0.6–8	0.6–9.5	
Histological types of NSCLC			< 0.001
Adenocarcinoma	187	173	
Squamous cell carcinoma	27	100	
others	12	4	
Metastasis			< 0.001
None	152	58	
Lymph node only	43	90	
Distant metastasis	31	129	
T stage			< 0.001
T1	137	64	
T2	81	185	
T3	5	17	
T4	3	11	
N stage			<0.001
N0	162	94	
N1	7	14	
N2	43	80	
N3	14	89	
M stage			< 0.001
M0	195	148	
M1	31	129	
TNM stage			< 0.001
Stage I–II	159	64	
Stage III–IV	67	213	
Number of metastasis lymph nodes			< 0.001
Median	3	8	
Range	1–35	1–13	

focused on the relationship between the fibrinogen value and survival rate or chemotherapy efficacy in patients with lung cancer. Additionally, these studies only investigated the operable or advanced patients, and none of the studies included patients of all stages.

In this study, the clinicopathology of 671 lung disease patients, including 503 NSCLC patients, were retrospectively analyzed and the association with pretreatment fibrinogen values in NSCLC patients was examined. The fibrinogen values in NSCLC patients were found to be significantly associated with metastasis and tumor stage. The median fibrinogen value in NSCLC patients with metastasis was significantly higher than in patients with benign lung diseases and NSCLC patients without metastasis. However, there was no statistical difference in fibrinogen values between patients with benign diseases and NSCLC patients without metastasis. When we reviewed the literature [17–18], there were no reports exploring the difference in the fibrinogen values between NSCLC patients without metastasis and patients with benign lung diseases. A study by Chen found that the plasma D-dimer level showed no statistical difference between NSCLC patients without metastasis and benign lung disease patients [19]. We concluded that after the development of NSCLC metastasis, the cancer cells can cause systemic reactions, thus impacting the fibrinogen level. However, in NSCLC patients without metastasis, the influence of the tumor is confined to the primary site, and it cannot cause increase in the fibrinogen level. Therefore, this result also indicates that metastasis is the critical event responsible for an increase in the fibrinogen level. Moreover, these results were not influenced by age, sex, smoking history, and histological types of NSCLC.

In case of tumor stage, significant statistical differences were observed in the fibrinogen levels between different T, N, and M stages. For N stage, median fibrinogen values increased from N0 to N3, and the number of metastatic lymph nodes was higher in patients with high fibrinogen values. The relationship between lymph node metastasis and fibrinogen values is still controversial, but it has confirmed that lymph metastasis are always accompanied by high fibrinogen values in gastric and esophageal cancers [4, 20]. With regard to M stage, fibrinogen values in distant metastasis patients (M1) were clearly higher than patients without distant metastasis (M0). However, in distant metastasis patients, the location of distant metastasis and the number of distant metastatic lesions did not have an influence on the fibrinogen values. Based on these results, we concluded that once the metastasis occurs, the cancer becomes a systemic disease, and therefore, the number and location of distant metastatic lesions does not affect the fibrinogen level. Surprisingly, patients with metastasis to the liver did not show different fibrinogen values when compared with patients with metastasis to others organs that cannot produce fibrinogen, and this may be related to the sample size of this study. In advanced NSCLC patients (Stage III–IV), higher fibrinogen values were observed when compared to early stage NSCLC patients (Stage I–II). Tumor size also exhibited a positive correlation with the fibrinogen values.

In addition, our study showed that a plasma fibrinogen cutoff value of 2.974 g/L was associated with a specificity of 0.724 and sensitivity of 0.747 for predicting metastasis. When the fibrinogen values were higher than 2.974 g/L, there were statistically significant differences in tumor size, tumor stage, metastasis, and histological types of NSCLC. Our results were in agreement with previous studies that demonstrated that high plasma fibrinogen values correlated with metastasis and advanced stage in

patients with NSCLC [9, 12–15]. Moreover, some previous research studies about NSCLC have reported similar results, showing that most of the lung squamous cell carcinoma patients had high fibrinogen values, and the results showed statistical significance [21]. Previous research has also revealed that squamous cells can biosynthesize fibrinogen and increase the fibrinogen produced by hepatocytes [22].

Fibrinogen is a modest acute-phase response protein that increases in concentration in response to most physiological and pathological conditions, such as acute infection, tissue injury, shock, hypercoagulable state, acute myocardial infarction, and malignant tumor [2]. Nevertheless, the exact mechanism underlying the association between elevated fibrinogen values and metastasis of NSCLC remains unknown. At present, two leading theories may explain this. One of them is that an inflammatory reaction to tumor growth, hypercoagulable state, and hypoxia associated with cancer may induce the elevated plasma fibrinogen values. Amrani advocated for the first time the ability of purified human recombinant interleukin-6 (originally BSF-2) to stimulate fibrinogen production in primary chicken hepatocytes [23]. Lawrence further suggested that extrahepatic fibrinogen biosynthesis evoked only during inflammation plays a role in localized injury and repair to restore tissue homeostasis [24]. The other leading theory is that fibrinogen is produced by the tumor itself. When immunohistochemistry was used to detect fibrinogen in resected pancreatic cancer in Bloomston's study, fibrinogen gamma was found to be overexpressed and discriminated cancer sera from normal sera [25]. Sahni's research also indicated that endogenously synthesized fibrinogen promotes the growth of lung and prostate cancer cells through interaction with FGF-2 [26]. Furthermore, Simpson-Haidaris's study indicated that fibrinogen functioned as an extracellular matrix protein in breast carcinoma, and affected tumor cell growth and metastasis. Close relationship between fibrinogen and metastasis has been shown in studies. In two studies by Palumbo, it was suggested that fibrinogen plays an important role in spontaneous metastasis, facilitating the stable adhesion and/or survival of metastatic emboli after tumor cell intravasation. However, in tumor models, fibrinogen deficiency strongly diminished but did not prevent the development of lung metastasis [27, 28]. In Shu's study, an *in vitro* experiment showed that fibrinogen induced Epithelial-Mesenchymal Transition (EMT) in gallbladder cancer by increasing the expression of vimentin and reducing expression of E-cadherin [29]. With regard to clinical treatment, Kuderer's in vitro study and animal findings have demonstrated that anticoagulants, in particular low molecular weight heparins (LMWHs), exert an antineoplastic effect through multiple mechanisms including interference with tumor cell adhesion, invasion, metastasis formation, angiogenesis, and immune system [30]. A recent study of Park revealed that anticoagulant use (LMWH in particular) is an independent predictor of improved survival in men with metastatic castration-resistant prostate cancer receiving docetaxel [31]. In contrast, in a randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer, the results showed that LMWH did not improve overall survival in patients with lung cancer [32]. Additionally, in a meta-analysis by Che and Sanford, the use of LMWH did not show a survival benefit in cancer patients [33–34]. Currently, the relationship between fibrinogen level and cancer, along with the effectiveness of anticoagulants, is still open to dispute. However, we can confirm that fibrinogen is closely correlated with metastasis on the basis of our results.

Some studies have indicated that coagulation could be activated by tissue factor (TF) expressed by NSCLC cells [35]. A limitation of the present study is its retrospective nature; therefore, all data were collected from clinical examination, and the TF (tissue factor) and plasmin concentration were not included. However, in the inclusion and exclusion criteria, we excluded patients with clinical evidence of infection or other bone marrow, hematological, or autoimmune diseases. Furthermore, lower limb vascular ultrasound was used to exclude the influence of phlebothrombosis on the fibrinogen values.

There were some limitations of this study: single medical center, small number of participants, and retrospective research might potentially lead to an inappropriate conclusion, and the association between plasma fibrinogen level and prognosis in patients with NSCLC was not evaluated. Therefore, a large-scale multi-center prospective validation study is needed to further investigate the results. On the other hand, further basic medical research and clinical trials are also needed to identify the mechanism by which elevated plasma fibrinogen level might function to enhance metastasis, and to evaluate the usefulness of anticoagulants as a new therapy in cancer.

In conclusion, this study supports the role of elevated pretreatment plasma fibrinogen levels in predicting metastasis and advanced tumor stage in NSCLC patients.

References

1. Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. CA Cancer J Clin, 2015, 65: 87–108.
2. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost, 2005, 3: 1894–1904.
3. Kim I, Kim HG, Kim H, *et al*. Hepatic expression, synthesis and secretion of a novel fibrinogen/angiopoietin-related protein that prevents endothelial-cell apoptosis. Biochem J, 2000, 346: 603–610.
4. Zhang SS, Lei YY, Cai XL, *et al*. Preoperative serum fibrinogen is

an independent prognostic factor in operable esophageal cancer. Oncotarget, 2016, 7: 25461–25469.
5. Yu X, Hu FL, Yao Q, *et al*. Serum fibrinogen levels are positively correlated with advanced tumor stage and poor survival in patients with gastric cancer undergoing gastrectomy: a large cohort retrospective study. BMC Cancer, 2016, 16: 480.
6. Lee H, Lee SE, Byun SS, *et al*. Preoperative plasma fibrinogen level as a significant prognostic factor in patients with localized renal cell carcinoma after surgical treatment. Medicine (Baltimore), 2016, 95: e2626.
7. Tang L, Liu K, Wang JF, *et al*. High preoperative plasma fibrinogen levels are associated with distant metastases and impaired prognosis after curative resection in patients with colorectal cancer. J Surg Oncol, 2010, 102: 428–432.
8. Kinoshita A, Onoda H, Imai N, *et al*. Elevated plasma fibrinogen levels are associated with a poor prognosis in patients with hepatocellular carcinoma. Oncology, 2013, 85: 269–277.
9. Sheng LM, Luo M, Sun XJ, *et al*. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. Int J Cancer, 2013, 133: 2720–2725.
10. Ge LP, Li J, Bao QL, *et al*. Prognostic and predictive value of plasma D-dimer in advanced non-small cell lung cancer patients undergoing first-line chemotherapy. Clin Transl Oncol, 2015, 17: 57–64.
11. Tas F, Kilic L, Serilmez M, *et al*. Clinical and prognostic significance of coagulation assays in lung cancer. Respir Med, 2013, 107: 451–457.
12. Zhu LR, Li J, Chen P, *et al*. Clinical significance of plasma fibrinogen and D-dimer in predicting the chemotherapy efficacy and prognosis for small cell lung cancer patients. Clin Transl Oncol, 2016, 18: 178–188.
13. Jiang, HG, Li J, Shi SB, *et al*. Value of fibrinogen and D-dimer in predicting recurrence and metastasis after radical surgery for non-small cell lung cancer. Med Oncol, 2014, 31: 22.
14. Kim KH, Park TY, Lee JY, *et al*. Prognostic significance of initial platelet counts and fibrinogen level in advanced non-small cell lung cancer. J Korean Med Sci, 2014, 29: 507–511.
15. Zhu JF, Cai L, Zhang XW, *et al*. High plasma fibrinogen concentration and platelet count unfavorably impact survival in non-small cell lung cancer patients with brain metastases. Chin J Cancer, 2014, 33: 96–104.
16. Zhao J, Zhao MF, Jin B, *et al*. Tumor response and survival in patients with advanced non-small-cell lung cancer: the predictive value of chemotherapy-induced changes in fibrinogen. BMC Cancer, 2012, 12: 330.
17. Wang Z, Wang C, Huang XB, *et al*. Differential proteome profiling of pleural effusions from lung cancer and benign inflammatory disease patients. Biochim Biophys Acta, 2012, 1824: 692–700.
18. Shilov NI. Hemostasis system in lung cancer, benign tumors and chronic nonspecific pneumonias. Vopr Onkol, 1979, 25: 21–25.
19. Chen F, Wang MJ, Li J, *et al*. Plasma D-dimer value as a predictor of malignant lymph node involvement in operable non-small cell lung cancer. Tumour Biol, 2015, 36: 9201–9207.
20. Yu W, Wang Y, Shen B. An elevated preoperative plasma fibrinogen level is associated with poor overall survival in Chinese gastric cancer patients. Cancer Epidemiol, 2016, 42: 39–45.
21. Sheng L, Luo M, Sun X, *et al*. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. Int J Cancer, 2013, 133: 2720–2725.
22. Lee SY, Lee KP, Lim JW. Identification and biosynthesis of fibrinogen in human uterine cervix carcinoma cells. Thromb Haemost, 1996, 75: 466–470.
23. Amrani DL. Regulation of fibrinogen biosynthesis: glucocorticoid and interleukin-6 control. Blood Coagul Fibrinolysis, 1990, 1: 443–446.
24. Lawrence SO, Simpson-Haidaris PJ. Regulated de novo biosynthesis of fibrinogen in extrahepatic epithelial cells in response to inflammation. Thromb Haemost, 2004, 92: 234–243.
25. Bloomston M, Zhou JX, Rosemurgy AS, *et al*. Fibrinogen gamma overexpression in pancreatic cancer identified by large-scale proteomic analysis of serum samples. Cancer Res, 2006, 66: 2592–2599.
26. Sahni A, Simpson-Haidaris PJ, Sahni SK, *et al*. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemost, 2008, 6: 176–183.
27. Simpson-Haidaris PJ, Rybarczyk B. Tumors and fibrinogen. The role of fibrinogen as an extracellular matrix protein. Ann N Y Acad Sci, 2001, 936: 406–425.
28. Palumbo JS, Potter JM, Kaplan LS, *et al*. Spontaneous hematogenous and lymphatic metastasis, but not primary tumor growth or angiogenesis, is diminished in fibrinogen-deficient mice. Cancer Res, 2002, 62: 6966–6972.
29. Shu YJ, Weng H, Bao RF, *et al*. Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer patients following surgical resection: a retrospective and *in vitro* study. BMC Cancer, 2014, 14: 566.
30. Kuderer NM, Ortel TL, Francis CW. Impact of venous thromboembolism and anticoagulation on cancer and cancer survival. J Clin Oncol, 2009, 27: 4902–4911.
31. Park JC, Pratz FC, Tesfaye A, *et al*. The effect of therapeutic anticoagulation on overall survival in men receiving first-line docetaxel chemotherapy for metastatic castration-resistant prostate cancer. Clin Genitourin Cancer, 2015, 13: 32–38.
32. Macbeth F, Noble S, Evans J, *et al*. Randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMATIC Trial. J Clin Oncol, 2016, 34: 488–494.
33. Che, DH, Cao JY, Shang LH, *et al*. The efficacy and safety of low-molecular-weight heparin use for cancer treatment: a meta-analysis. Eur J Intern Med, 2013, 24: 433–439.
34. Sanford D, Lazo-Langner A, The effect of low molecular weight heparin on survival in cancer patients: an updated systematic review and meta-analysis of randomized trials. J Thromb Haemost, 2014, 12: 1076–1085.
35. Fei X, Wang H, Yuan WF, *et al*. Tissue factor pathway inhibitor-1 is a valuable marker for the prediction of deep venous thrombosis and tumor metastasis in patients with lung cancer. Biomed Res Int, 2017, 2017: 8983763.

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