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The relationship of plasma fibrinogen with clinicopathological stages and tumor markers in patients with non-small cell lung cancer

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Abstract

Numerous studies have shown that the blood of cancer patients are generally in hypercoagulable statement. The aim of the present research is to study the relationships of plasma fibrinogen (Fbg) levels with clinicopathological stages (CS) and tumor markers of non-small cell lung cancer (NSCLC).

Baseline information, plasma Fbg levels, CS, and expression level of tumor markers were collected from medical records retrospectively. Unitary linear regression was used to analyze the relationships between continuous variables and Fbg, and multiple linear regression was used to analyze the relationships between categorical variables and Fbg. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (Version 4) for NSCLC were adopted to evaluate CS.

A total of 652 NSCLC patients were included. Compared with the females, male patients had higher mean plasma Fbg levels ($P < .001$). The later the N stages ($P = .002$), M stages ($P = .002$), and CS ($P = .001$) were, the higher the average plasma Fbg levels were. The levels of squamous cell carcinoma antigen ($P = .001$), carbohydrate antigen 125 ($P = .041$), and neuron-specific enolase ($P < .001$) were positively correlated with plasma Fbg concentration. The plasma level of Fbg in lung adenocarcinoma patients ($P < .001$) was the lowest, while that of lung squamous cell carcinoma patients ($P < .001$) was the highest in NSCLC patients.

The plasma Fbg concentration is related to gender, CS, and tumor markers in patients with NSCLC.

Abbreviations: CA125 = carbohydrate antigen 125, CEA = carcinoembryonic antigen, CS = clinicopathological stages, CYFRA21-1 = cytokeratin (CK19) fragment, Fbg = fibrinogen, NSCLC = non-small cell lung cancer, NSE = neuron-specific enolase, SCC = squamous cell carcinoma, SCCA = squamous cell carcinoma antigen, SCLC = small cell lung cancer, ULR = unitary linear regression.

Keywords: clinicopathological stages, fibrinogen, non-small cell lung cancer, tumor makers

1. Introduction

The morbidity and mortality of patients with lung cancer are increasing year by year in both developed and developing countries.[1] Non-small cell lung cancer (NSCLC) accounts for the vast majority of lung cancers, mainly including lung adenocarcinoma and squamous cell carcinoma (SCC).[2–4] When diagnosed, most patients have been already in locally advanced or metastatic stages of cancer.[4,5] The blood of cancer patients often stays in hypercoagulable state, especially in the patients with advanced clinicopathological stages (CS).[6–8] Activation of the coagulation system and procoagulant changes have been relevant to angiogenesis, tumor invasion, cancer progression, and distant metastasis.[7,9] Fibrinogen (Fbg) is an important protein in the process of coagulation and can accumulate in tumor sites. In addition, Fbg plays a critical role in the development of malignant tumors, which is associated with prognosis.[7,10,11]

Although a large number of studies have shown that the patients with high plasma Fbg have much poorer prognosis for both NSCLC and small cell lung cancer (SCLC) patients, it is still unclear which clinical parameters are associated with elevated plasma Fbg.[2,6–10,12–15] Moreover, few studies have researched the relationship between tumor markers and plasma Fbg.[16] Therefore, the aim of this study is to analyze the relationships of plasma Fbg with tumor markers and several clinical parameters in patients with NSCLC.

2. Materials and methods

2.1. Study design and patients

This study retrospectively analyzed 652 NSCLC patients diagnosed by lung biopsy by means of thoracic surgery or thoracoscopic surgery in the Department of Thoracic Surgery, Beijing Chao-yang Hospital from January 2011 to December 2016. The inclusion criteria were:

(1) pathological diagnosis of NSCLC;
(2) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (Version 4) for NSCLC were used to evaluate CS of cancer[17];

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(3) preoperative plasma Fbg levels were measured within 10 days before surgery;
(4) (iv) no history of preoperative adjuvant therapy;
(5) have complete presurgery laboratory data.

Patients who received regular anticoagulation therapy were excluded.

In addition to plasma Fbg levels, we reviewed the following clinicopathological information from the medical records of patients: age, sex, serum concentration of squamous cell carcinoma antigen (SCCA), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), cytokeratin (CK19) fragment (CYFRA21–1), D-dimer, histological types, CS, T/N/M stages.

This study was approved by the Ethics Committee of Beijing Chao-yang Hospital.

2.2. Fbg levels

Blood samples were taken at admission and before any treatment (radiation therapy, chemotherapy, surgery, targeted therapy, etc). 4 mL vacutainer tubes containing 3.2% sodium citrate were used for collection of blood samples. Tubes were centrifuged at 3000 rpm at 4°C for 10 minutes. Fbg levels were measured by immunoturbidimetry (Sysmex CA-7000/CS-50100, Sysmex Corp., Kobe, Japan) using clotting method. The normal range for the test was 170 to 400 mg/dL,[7,18] stemming from 95% confidence interval of a normal distribution of people. Plasma Fbg level above 400 mg/dL was defined as hyperfibrinogenemia in this study.

2.3. Statistical analysis

Statistical analysis was conducted using SPSS version 22.0 software (IBM Corporation, Armonk, NY). Continuous data were expressed as mean and range if normally distributed. Categorical data were expressed as percentages. Unitary linear regression (ULR) was used to analyze the relationship between continuous variables and Fbg, and multiple linear regression was used to analyze the relationship between categorical variables and Fbg. $P < .05$ was considered statistically significant.

3. Result

3.1. Patient characteristics

In total, 652 NSCLC patients were enrolled in the present retrospective study. Patients were divided into 2 groups

Table 1

Characteristics and fibrinogen median of 652 patients with non-small cell lung cancer.

Characteristic	Group A, Fbg ≤400 mg/dL	Group B, Fbg >400 mg/dL	Total	Median, mg/dL
	n = 475 n (72.9%)	n = 177 n (27.1%)	n = 652 n (100%)	311.9
Age				
<60	221 (33.9%)	84 (12.9%)	305 (46.8%)	316.5
≥60	254 (39.0%)	93 (14.2%)	347 (53.2%)	310.7
Gender				
Male	256 (39.3%)	145 (22.2%)	401 (61.5%)	334.2
Female	219 (33.6%)	32 (4.9%)	251 (38.5%)	287.9
Histological type				
Adenocarcinoma	330 (50.6%)	61 (9.3%)	391 (59.9%)	288.1
SCC	106 (16.3%)	95 (14.6%)	201 (30.9%)	389.9
Large cell lung cancer	11 (1.7%)	3 (.4%)	14 (2.1%)	280.5
Others	28 (4.3)	18 (2.8%)	46 (7.1%)	338.4
CS				
Carcinoma in situ	2 (0.3%)	4 (.6%)	6 (.9%)	256.1
IA	198 (30.4%)	23 (3.5%)	221 (33.9%)	292.6
IB	87 (13.3%)	38 (5.8%)	125 (19.1%)	316.6
IIA	78 (12.0%)	29 (4.4%)	107 (16.4%)	314.6
IIB	21 (3.2%)	24 (3.7%)	45 (6.9%)	318.9
IIIA	73 (11.2%)	41 (6.3%)	114 (17.5%)	327.4
IIIB	7 (1.1%)	3 (.5%)	10 (1.6%)	428.2
IV	9 (1.4%)	15 (2.3%)	24 (3.7%)	304.4
T stage				
Tis	2 (.3%)	4 (.6%)	6 (.9%)	256.1
1a	168 (25.8%)	16 (2.5%)	184 (28.3%)	299.9
1b	92 (14.1%)	22 (3.4%)	114 (17.5%)	315.3
2a	153 (23.5%)	63 (9.7%)	216 (33.2%)	321.7
2b	27 (4.1%)	22 (3.4%)	49 (7.5%)	299.4
3	25 (3.8%)	42 (6.4%)	67 (10.2%)	329.9
4	8 (1.2%)	8 (1.2%)	16 (2.4%)	326.4
N stage				
0	321 (49.2%)	91 (14.0%)	412 (63.2%)	295.1
1	73 (11.2%)	47 (7.2%)	120 (18.4%)	366.1
2	77 (11.8%)	35 (5.4%)	112 (17.2%)	319.4
3	4 (.6%)	4 (.6%)	8 (1.2%)	379.3
M stage				
0	466 (71.5%)	162 (24.8%)	628 (96.3%)	310.4
1	9 (1.4%)	15 (2.3%)	24 (3.7%)	418.2

CS = clinicopathological stage, SCC = squamous carcinoma cancer.

Table 2

The number of observations of 652 non-small cell lung cancer patients, and the frequency, the median and the *P*-value for all the clinical and laboratory variables.

Characteristic	Observations	Median (range) or Frequency	Beta	*t*-value	*P*-value
Age	652	60 (26–86)	0.046	1.182	1.238
CS	652	6/221/125/107/45/114/10/24	0.125	3.199	.001
T stage	652	9/184/114/215/48/66/16	0.048	1.237	.217
N stage	652	413/119/112/8	0.121	3.113	.002
M stage	652	628/24	0.119	3.054	.002
SCCA	393	0.80 (0.10–56.30)	0.160	3.210	.001
CYFRA21–1	354	2.38 (0.54–52.40)	0.090	1.692	.092
CA125	629	12.30 (0.12–2108.02)	0.082	2.049	.041
NSE	631	13.28 (5.87–97.97)	0.177	4.520	<.001
CEA	639	2.61 (0.00–469.80)	0.022	0.567	.571
D-Dimer	154	0.71 (0.00–70.00)	−0.008	−0.103	.918

CA125 = carbohydrate antigen 125, CEA = carcinoembryonic antigen, CS = clinicopathological stage, CYFRA21–1 = cytokeratin (CK19) fragment, NSE = neuron-specific enolase, SCCA = squamous carcinoma cancer antigen.

according to Fbg level: Group A, ≤400 mg/dL (n = 475, 72.9%); Group B, >400 mg/dL (n = 177, 27.1%). Patient characteristics and the median of Fbg are shown in Table 1. Participants comprised 401 (61.5%) men and 251 (38.5%) women (the means are 316.5 mg/dL and 310.7 mg/dL, respectively). The median age was 60 years' old with the range from 26 to 86 years. The frequency, median and *P* value of the clinical and laboratory variables are shown in Table 2. The Fbg levels were correlated with gender ($P < .001$) and male NSCLC patients had higher Fbg levels than that of female (Table 3).

3.2. Correlation between Fbg and pathological types as well as CS

On the basis of World Health Organization/International Association for the Study of Lung Cancer stratification criteria for lung cancers, 391 (59.9%) patients were histologically diagnosed as adenocarcinoma, 201 (30.9%) patients were diagnosed as SCC, 14 (2.1%) patients as large cell lung cancer, and 46 (7.1%) patients as others. Patients with lung adenocarcinoma had the lowest Fbg level (set the dummy variable to 1 for adenocarcinoma and 0 for SCC, large cell lung cancer and others, $P < .001$) which are shown in Table 4 and those with lung SCC had the highest Fbg level (set the dummy variable to 1 for SCC and 0 for adenocarcinoma, large cell lung cancer and others, $P < .001$) shown in Table 5.

In the present study, 6 (.9%) patients were diagnosed with carcinoma in situ, 221 (33.9%) on stage IA, 125 (19.1%) on stage IB, 107 (16.4%) on stage IIA, 45 (6.9%) on stage IIB, 114 (17.5%) on stage IIIA,10 (1.6%) on stage IIIB and 24 (3.7%) on stage IV, and the medians of Fbg were 256.1 mg/dL, 292.6 mg/dL, 316.6 mg/dL, 314.6 mg/dL, 318.9 mg/dL, 327.4 mg/dL, 428.3 mg/dL, and 304.4 mg/dL, respectively. CS and Fbg were corresponded to a linear unary correlation ($P = .001$) and the later the CS stages were, the higher the Fbg levels were (Fig. 1). Similarly, as shown in Figures 2 and 3 , the later the N stages ($P = .002$) and M stages ($P = .002$) were, the higher the Fbg levels were. Nevertheless, we did not observe a linear correlation between T stages ($P = .217$) and Fbg levels.

Table 3

The relationship between gender and fibrinogen.

	Unstandardized coefficient		Standardized coefficient			Correlation	
Model	*B*	Standard error	Beta	*T*	*P*	Zero-order	Part
Constant	309.216	7.545		40.986	<.001		
Gender	49.588	9.620	0.198	5.155	<.001	0.198	0.198

a. coefficient[a] a. dependent variable\: Fbg.

Table 4

The relationship between fibrinogen and adenocarcinoma, large cell lung cancer and others.

Model	Unstandardized coefficient		Standardized coefficient			Correlation
	B	Standard error	Beta	*T*	*P*	Zero-order
Constant	395.075	8.128		48.607	<.001	
Large cell lung cancer	−79.660	31.852	−0.095	−2.501	.013	−0.029
Others	−23.777	19.004	−0.050	−1.251	.211	0.071
Adenocarcinoma	−86.911	10.001	−0.350	−8.690	<.001	−0.316

b. coefficient[b] b. dependent variable\: Fbg.

Table 5

The relationship between fibrinogen and SCC, large cell lung cancer and others.

	Unstandardized coefficient		Standardized coefficient			Correlation
Model	***B***	**Standard error**	**Beta**	***T***	***P***	**Zero-order**
Constant	308.164	5.828		52.880	<.001	
SCC	86.911	10.001	0.330	8.690	<.001	0.305
Large cell lung cancer	7.251	31.344	0.009	0.231	.817	−0.029
Others	63.134	18.140	0.132	3.480	.001	0.071

c. coefficient[c] c. dependent variable\: Fbg.

SCC = squamous carcinoma cancer.

3.3. Relationship between Fbg and tumor markers

The study researched pretreatment tumor markers related with NSCLC, including SCCA ($P = .001$), CYFRA21–1 ($P = .092$), CA125 ($P = .041$), NSE ($P < .001$), and CEA ($P = .571$). In conclusion, Fbg levels were correlated to SCC, CA125, NSE, and they were linearly related and positively correlated (Figs. 4–6). However, Fbg levels were not correlated to CYFRA21–1 and CEA. And there is not a linear correlation between Fbg and D-dimer ($P = .918$).

4. Discussion

Hyperfibrinogenemia can exist in many patients with malignant tumors including NSCLC and SCLC, which suggests a poor prognosis.[4,5,7,10,19] Fbg, synthesized by liver, is the highest content of coagulation proteins in plasma and can be converted to fiber polymer (insoluble fibrin) by activated thrombin. It plays a vital role in blood coagulation, fibrinolysis, inflammatory response, wound healing, and tumorigenesis. Moreover, the crosslink of Fbg and various blood cells can form blood clots and protect circulating cancer cells from the killing effect of immune cells, thereby increasing the potential of cancer metastasis. Fbg may promote stable adhesion among tumor cells, platelets, and endothelial cells,[3,7,20,21] thereby further protecting the tumor cells from the impact of the immune system, enhancing the ability of cell establishment, deep infiltration, and metastasis.[4,22] Therefore, in our research and early studies, we found the later the N, M, and CS were, the higher the average levels of plasma Fbg were.[19]

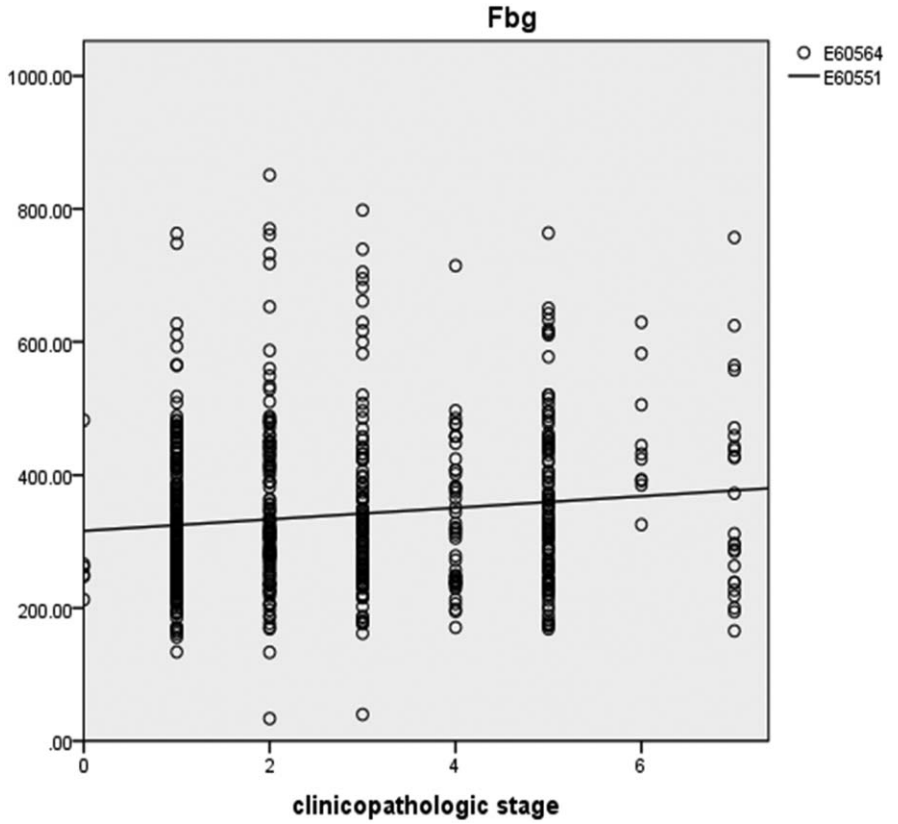

Figure 1. The relationship between Fbg and CS stages in patients with non-small cell lung cancer (A) CS stages and Fbg were corresponded to a linear unary correlation ($P = .001$), and (B) the later the CS stages were, the higher the Fbg levels were. CS = clinicopathological stages, Fbg = fibrinogen.

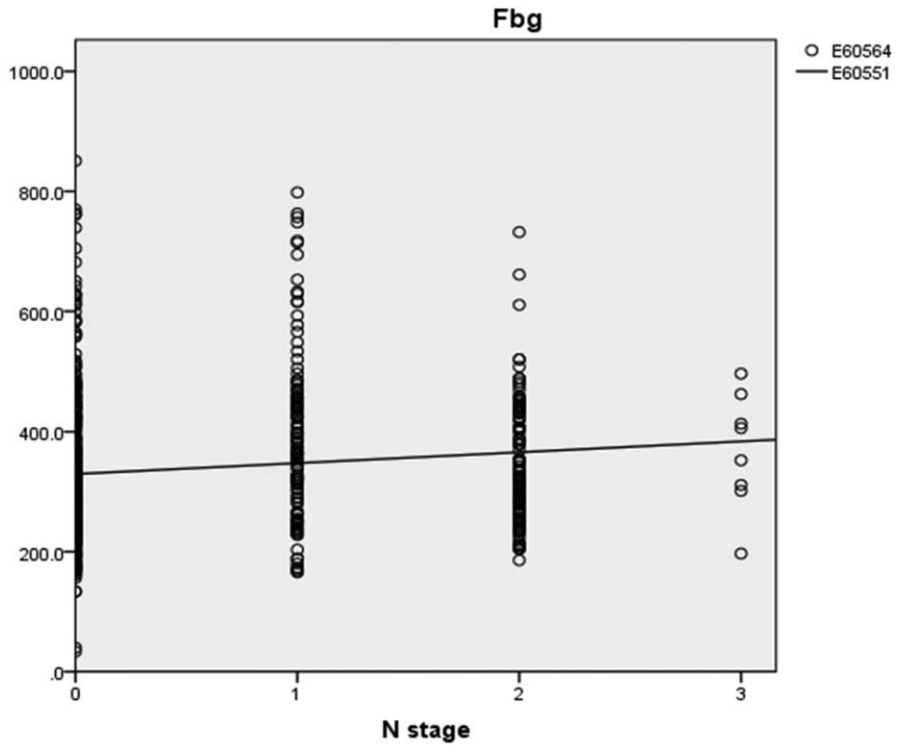

Figure 2. The relationship between fibrinogen and N stages in non-small cell lung cancer patients (A) N stages and Fbg were corresponded to a linear unary correlation ($P = .002$), and (B) the later the N stages were, the higher the Fbg levels were. Fbg = fibrinogen.

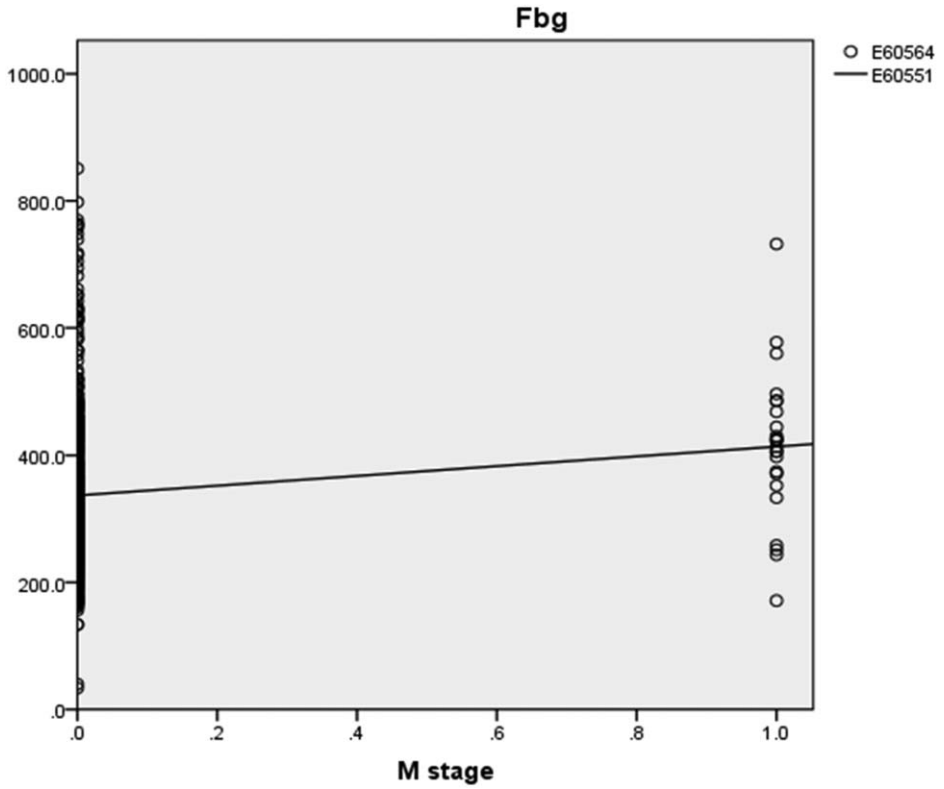

Figure 3. The relationship between fibrinogen and M stages of non-small cell lung cancer patients (A) M stages and Fbg were corresponded to a linear unary correlation ($P = .002$), and (B) the later the M stages were, the higher the Fbg levels were. Fbg = fibrinogen.

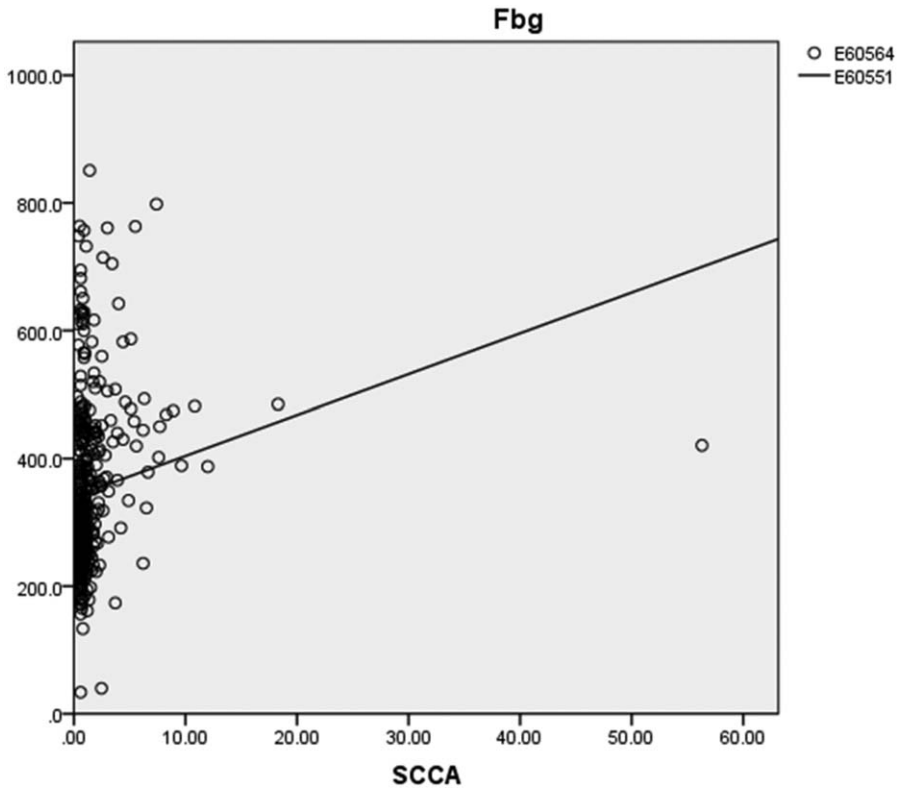

Figure 4. The relationship between fibrinogen and SCCA in patients with non-small cell lung cancer (A) SCCA and Fbg were linearly related and positively correlated ($P = .001$), and (B) the higher the SCCA was, the higher the Fbg levels were. Fbg = fibrinogen, SCCA = squamous cell carcinoma antigen.

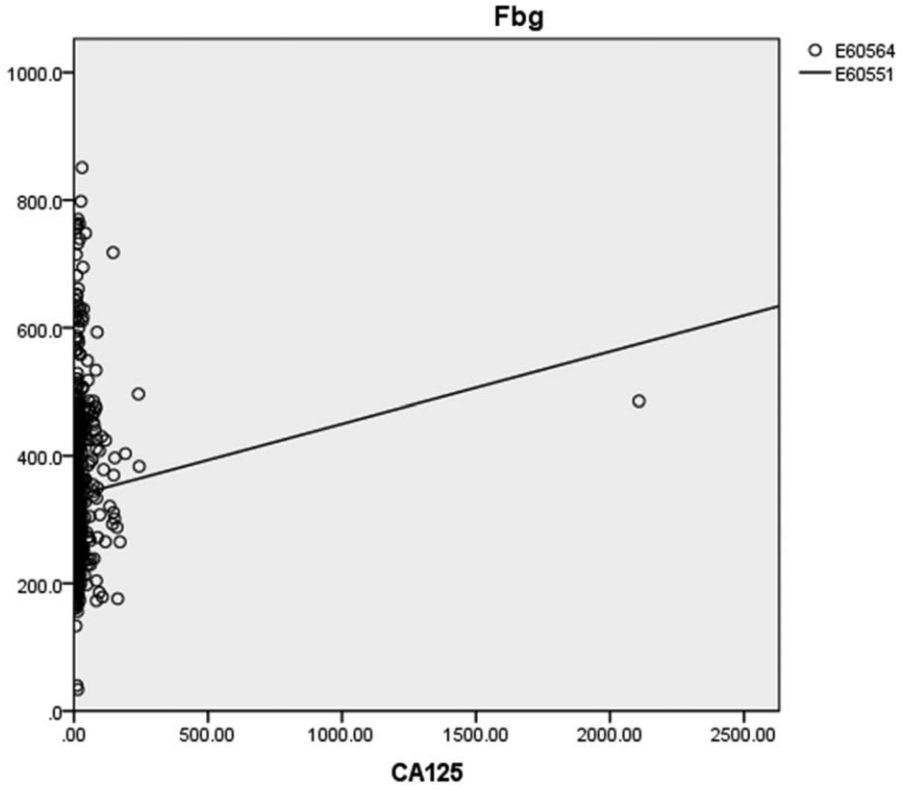

Figure 5. The relationship between fibrinogen and CA125 in patients with non-small cell lung cancer (A) Fbg levels were correlated to CA125 ($P = .041$), and (B) they were linearly related and positively correlated, that is the higher the concentration of CA125 were, the higher the level of Fbg were. CA125 = carbohydrate antigen 125, Fbg = fibrinogen.

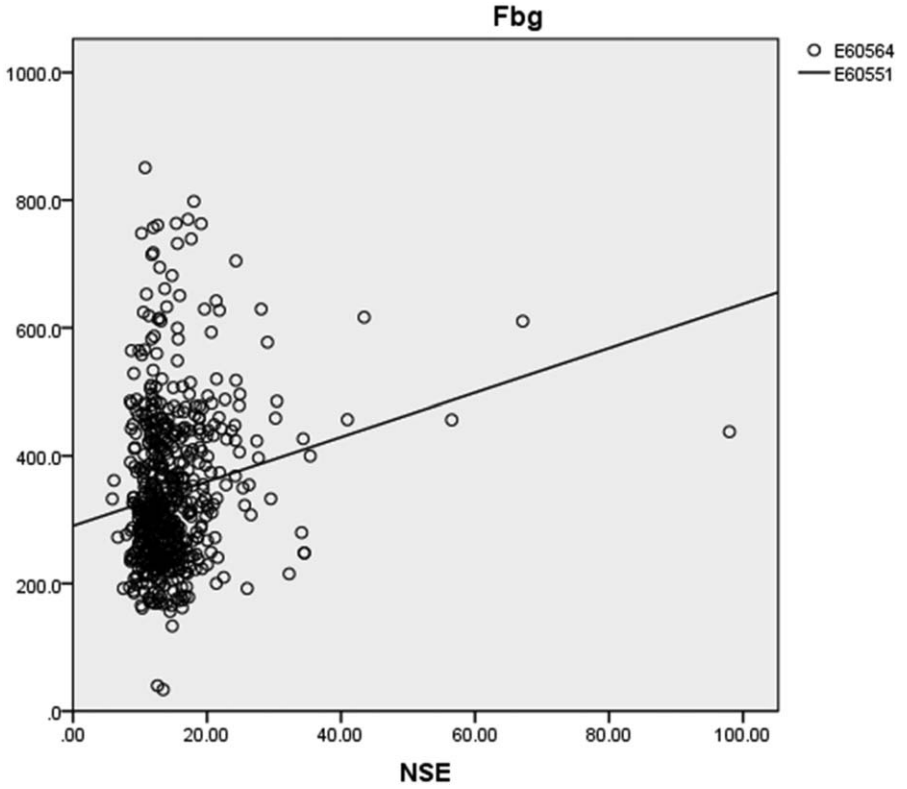

Figure 6. The relationship between fibrinogen and NSE in non-small cell lung cancer patients (A) NSE and Fbg were linearly related and positively correlated ($P <$ .001), and (B) the higher the NSE levels were, the higher the Fbg concentrations were. Fbg = fibrinogen, NSE = neuron-specific enolase.

Studies by Tas et al have also shown that male patients have higher Fbg levels than the females, probably because the coagulation cascades of males are easier to be activated than that of females.[23] This is consistent with our findings.

The expression of coagulation factors may vary with the pathological type of lung cancer, and the level of anti-thrombin in patients with SCC is significantly lower than that in adenocarcinoma patients.[24] Tas et al have found that D-dimer levels in patients with SCC are higher than those in other pathological types.[23] Li and other studies have also shown that SCC has significantly higher Fbg levels than adenocarcinoma, and Fbg and platelet count levels are higher in stage III and IV than in stage I-II.[3,25] In our study, we observed that patients with SCC have higher levels of Fbg than patients with adenocarcinoma, but the mechanism is still unclear.

SCCA is a member of the serine protease inhibitor family of endogenous serine protease inhibitors.[26] Multiple studies have shown that high levels of SCCA are usually associated with poorly differentiated and advanced metastatic SCC.[26,27] Fbg levels are also associated with advanced tumor metastasis.[18,22,28–30] The relationship between SCCA and Fbg was accorded with ULR in our study, and the higher the SCCA concentration was, the higher the Fbg levels were.

NSE is a type of tumor markers of SCLC,[31] and related studies have shown that plasma Fbg often increases obviously in SCLC patients.[7,32] The mechanisms activating coagulation and fibrinolysis in SCLC patients and NSCLC patients are different. In SCLC, tumor cells can release tissue factor to activate coagulation system directly, whereas in NSCLC, host macrophages release factors that activate the fibrinolytic system.[33] NSE levels are reported to be elevated in SCLC patients and are significantly higher in patients with advanced stages.[34,35] This is consistent with the positive correlation between Fbg and NSE in our study.

CA125 is a kind of tumor markers of adenocarcinoma. Wang et al revealed that breast cancer patients with distant metastases have higher plasma CA125 than those do not.[36] Also, Jiang et al's study suggested that renal cancer patients with elevated plasma CA125 are often in a hypercoagulable state.[37] Xie et al's study showed that elevated levels of CA125 lead to hypercoagulation.[38] In our study, we found that Fbg level also increased with elevating CA125.

Up to now, there was a great deal of studies on Fbg and NSCLC, but the results were not consistent and the mechanism was still unclear. We observed positive correlation among Fbg concentration and sex, N stages, M stages, CS, SCCA, NSE, and CA125 in our research, supported by the results of Tas, Li, Xie et al.

Many studies have found that cancer patients with higher Fbg have lower resectability and poorer prognosis. Fbg is an independent prognostic factor for cancer patients, which suggests active anticoagulation therapy can improve the prognosis of them.[15,18] Patients with significantly increased tumor markers also have poor prognosis. In our study, the change of several tumor markers (SCCA, CA125, and NSE) was consistent with that of plasma Fbg. Now we suspect that the elevated tumor markers may be associated with poor prognosis in patients with high Fbg levels.

Cancer constitutes an enormous burden on families and the society in more and less economically developed countries alike.[1,39] As an independent prognostic factor, Fbg can help doctors reasonably choose palliative treatment in combination with other indicators in order to reduce unnecessary pain and improve the quality of life. Further studies are needed to focus on the mechanism and the relationship between Fbg and survival, including overall survival and progression-free survival.

Author contributions

Data curation: Nannan Bian, Xin Hu, Yang Ge.
Methodology: Nannan Bian, Xinyu Shi, Guangyu An, Guosheng Feng.
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Writing – review and editing: Guosheng Feng.

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