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Prognostic value of preoperative plasma fibrinogen levels in resected stage I non-small cell lung cancer

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Abstract

Background: The number of surgical procedures has increased among patients with early-stage lung cancer. If the poor prognostic factors for stage I non-small cell lung cancer (NSCLC) can be simply validated preoperatively, appropriate treatment will be provided. The current study aimed to evaluate the prognostic value of preoperative plasma fibrinogen levels in patients with resected stage I NSCLC.

Methods: We retrospectively analyzed the clinicopathological information of patients ($n = 149$) who underwent lobectomy for stage I NSCLC between May 2014 and July 2016. Data about peripheral blood analysis, histopathological finding, and follow-up assessment results were collected from the databases. Patients were divided into the low and high fibrinogen groups. Univariate and multivariate analyses were performed to evaluate the predictors of recurrence and survival.

Results: Compared with the low fibrinogen group (<377 mg/dl), the high fibrinogen group (≥377 mg/dl) had a significantly greater number of male participants ($p = 0.04$), smokers ($p < 0.001$), and those with elevated cytokeratin antigen levels ($p = 0.04$), lymphatic invasion ($p = 0.007$), and squamous cell carcinoma ($p < 0.001$). Plasma fibrinogen level was considered a significant independent factor for recurrence and overall survival on both the univariate and multivariate analyses ($p < 0.001$ and $p = 0.010$) and the multivariate analysis alone ($p = 0.020$ and $p < 0.012$).

Conclusion: Preoperative plasma fibrinogen level might be a useful predictor of recurrence and survival in patients with stage I NSCLC. The treatment strategy for patients with high fibrinogen levels could be cautiously considered preoperatively.

KEYWORDS
fibrinogen, lymphatic invasion, non-small cell lung cancer, prognostic marker

INTRODUCTION

Fibrinogen is an extracellular matrix protein comprising three polypeptide chains and is an important component of the coagulation cascade. Fibrinogen, fibrin, and their degradation products are associated with blood clotting, inflammation, tumor progression, stroma formation, and tumor dissemination.[1–3] Abnormalities in the coagulation system, including fibrinogen, are common in patients with different types of cancers. That is, approximately 55.2% of patients with advanced-stage non-small cell lung cancer (NSCLC) had elevated serum fibrinogen levels.[4] In addition, previous studies showed that plasma fibrinogen had a prognostic impact on resected NSCLC.[5]

Although there are advancements in the treatment of lung cancer, NSCLC remains a major cause of cancer-related death worldwide. If tumor aggressiveness is identified preoperatively, it will be useful for selecting the appropriate preoperative treatments, degree of lymph node dissection, and extent of resection. Different studies have evaluated markers reflecting tumor aggressiveness via peripheral blood analysis, including tumor marker levels, pathological

examination, and immunostaining, and the presence of genetic mutations. However, the significance as prognostic value of these markers remain controversial. In addition, several prognostic factors can be confirmed postoperatively. Therefore, this study aimed to evaluate the usefulness of plasma fibrinogen levels for predicting tumor aggressiveness in early-stage lung cancer via a simple preoperative peripheral blood analysis.

METHODS

We collected the clinicopathological information of patients ($n = 149$) who underwent lobectomy for stage I NSCLC between May 2014 and July 2016 at our institution. This was a single center, retrospective analysis-based study, and the protocol was established in accordance with the principles of the Declaration of Helsinki. Moreover, the research was approved by the Clinical Research Area Ethics Committee of Kobe University Graduate School of Medicine (#B210269).

Patient evaluation included physical examination, medical history taking, computed tomography (CT) scan, and peripheral blood analysis. Assessment of plasma fibrinogen and tumor marker levels was routinely performed within 1 week before surgery. The standard cutoff values were set at 5.0 ng/ml for carcinoembryonic antigen (CEA) and 3.5 ng/ml for cytokeratin antigen (CYFRA), as recommended by the manufacturers of the assay kits. Information about TNM staging based on the 7th edition of the American Joint Committee on Cancer Staging Manual and the Revised International System for staging lung cancer was recorded. Tumor location and size were assessed preoperatively via chest CT scan. All patients were managed with video-assisted thoracic surgery, and underwent systematic dissection of all hilar and mediastinal lymph nodes. Moreover, lymph node metastasis and lymphatic, vascular, and pleural invasion were evaluated. Distant recurrence was defined as metastasis to the remaining lung, lymph nodes outside the dissected area, or other organs. The cutoff values for the clinicopathological factors correlated with plasma fibrinogen levels were calculated via receiver operating characteristic curve analysis.

The demographic characteristics of patients were expressed as mean and standard deviation for continuous variables and as frequency and proportion for categorical variables. Recurrence-free survival (RFS) was defined as the time from the date of surgery until the date of recurrence or death by any cause. Overall survival (OS) was defined as the time from the date of surgery until death by any cause or until the last follow-up visit. RFS and OS were evaluated using the Kaplan–Meier method, and differences in survival curves were assessed using the log-rank test. Receiver operating characteristic (ROC) curve was established to determine the appropriate cutoff of plasma fibrinogen concentrations based on the best tradeoff between sensitivity and specificity. Further, univariate and multivariate Cox regression analyses of the associations between clinicopathological parameters and RFS and OS were performed. All statistical analyses were conducted with EZR version 1.40 (Saitama, Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Stastistical Computing).[6] A p-value of <0.05 was considered statistically significant.

RESULTS

Patients were divided into the low (<377 mg/dl) and high (≥377 mg/dl) fibrinogen groups. ROC curve analysis was performed to determine the best OS rate. The area under the curve was 0.5898 (95% CI: 0.438–0.742), with a cutoff value of 337 mg/dl, sensitivity of 41%, and specificity of 85% (Figure 1). The low and high fibrinogen groups comprised 122 (81.9%) and 27 (18.1%) patients, respectively.

Table 1 depicts the association between high plasma fibrinogen levels and the clinicopathological characteristics of patients. There were 90 male and 59 female participants, with a median age of 70 (range: 50–86) years. The number of patients with a smoking history was 99 (66.4%). No significant difference was observed in terms of age, tumor size, CEA level, and the proportion of patients with adjuvant chemotherapy between the two groups. The numbers of patients receiving anticoagulation and antiplatelet therapy were 8 (5.4%) and 22 (14.8%), respectively. Moreover, there were 38 (25.5%) patients who received adjuvant therapy (oral 5-fluorouracil). In total, eight (5.4%) patients (three with arterial fibrillation, four with postoperative air leak, and one with interstitial pneumonia) presented with postoperative complications.

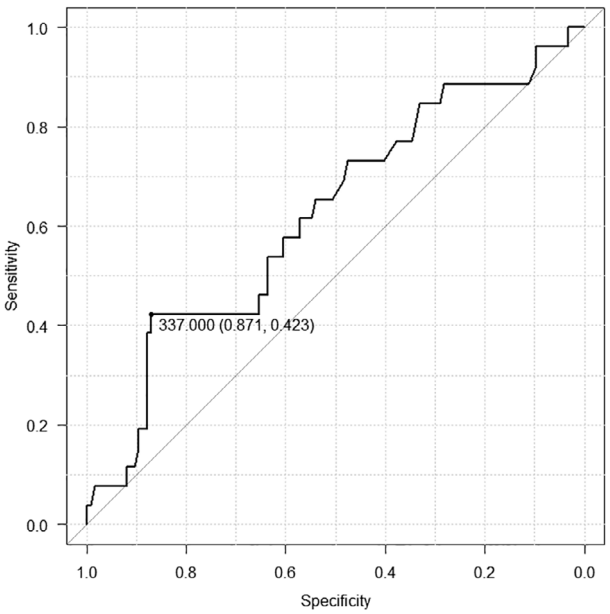

FIGURE 1 A receiver operating characteristic (ROC) curve was established to determine the appropriate cutoff for plasma fibrinogen concentrations based on the best tradeoff between sensitivity and specificity

TABLE 1 The association between high plasma fibrinogen levels and the clinicopathological characteristics of patients

Variables	Total	Patients divided according to fibrinogen levels		*p*-value
		Low fibrinogen group (≤377 mg/dl)($n = 122$)	High fibrinogen group (>377 mg/dl)($n = 27$)	
Age (>70 years)	76	63	13	0.833
Sex (male)	90	67	23	0.004
Smoking history (yes)	99	72	27	<0.001
Tumor size (>20 mm)	84	66	18	0.286
CEA level (>0.05 ng/ml)	43	37	6	0.635
CYFRA level (>3.5 ng/ml)	14	7	7	0.004
Anticoagulation therapy	8	8	0	0.352
Antiplatelet therapy	22	19	3	0.766
Adjuvant chemotherapy	38	32	6	0.809
Histology				<0.001
Squamous	31	16	15	
Others	118	106	12	
Pathological tumor factor				0.083
pStage IA	94	81	13	
pStage IB	55	41	14	
Lymphatic invasion	39	26	13	0.007
Vascular invasion	43	32	11	0.160
Pleural invasion	29	21	8	0.178

Abbreviations: CEA, carcinoembryonic antigen; CYFRA, cytokeratin antigen.

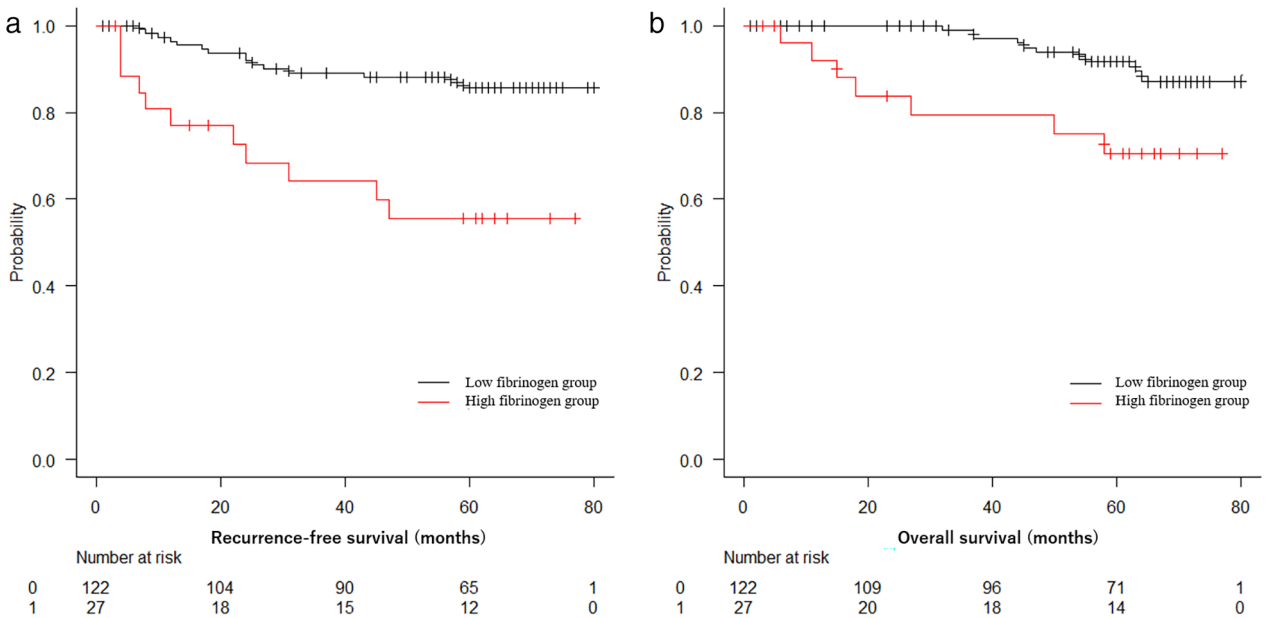

FIGURE 2 (a) Recurrence-free survival curves of the high and low fibrinogen groups. The 5-year recurrence-free survival rates of the high and low fibrinogen groups were 55.6% and 85.7%, respectively. (b) Overall survival curves of the high and low fibrinogen groups. The 5-year overall survival rates were 70.6% in the high fibrinogen group and 91.8% in the low fibrinogen group

Compared with the low fibrinogen group, the high fibrinogen group had a significantly greater number of male participants, smokers, and those with elevated CYFRA levels. In terms of pathological factors, although there was no significant difference in terms of pathological tumor characteristic and vascular and pleural invasion between the two groups, the proportion of patients with lymphatic invasion and squamous cell carcinoma was significantly higher

TABLE 2 Univariate and multivariate analyses of covariables associated with recurrence-free survival

	Recurrence-free survival					
	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*p* value	HR	95% CI	*p* value
Tumor size (>20 mm)	2.773	1.113–6.907	0.029	1.870	0.6631–5.275	0.237
CEA level (>5.0 ng/ml)	2.391	1.09–5.242	0.030	2.377	1.0140–5.574	0.046
CYFRA level (>3.5 ng/ml)	3.697	1.478–9.249	0.005	1.232	0.4086–3.716	0.711
Fibrinogen level (>377 mg/dl)	3.999	1.835–8.715	<0.001	3.076	1.1900–7.950	0.020
Histology (SQ)	2.741	1.244–6.043	0.012	1.164	0.4498–3.013	0.754
Lymphatic invasion	4.551	2.088–9.919	<0.001	1.881	0.7274–4.866	0.192
Vascular invasion	5.411	2.408–12.16	<0.001	2.217	0.7439–6.608	0.153
Pleural invasion	3.33	1.529–7.255	0.002	1.382	0.5639–3.386	0.479

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3 Univariate and multivariate analyses of covariables associated with overall survival

	Overall survival					
	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Tumor size (>20 mm)	1.498	0.5537–4.051	0.426	0.873	0.2281–3.342	0.843
CEA level (>5.0 ng/ml)	7.689	2.479–23.85	<0.001	9.020	2.5910–31.40	<0.001
CYFRA level (>3.5 ng/ml)	4.26	1.384–13.11	0.012	2.197	0.4383–11.01	0.339
Fibrinogen level (>377 mg/dl)	3.542	1.347–9.31	0.010	5.147	1.4400–18.40	0.012
Histology (SQ)	2.342	0.8645–6.343	0.094	1.068	0.2827–4.035	0.923
Lymphatic invasion	3.447	1.329–8.943	0.011	1.096	0.3309–3.631	0.881
Vascular invasion	4.121	1.566–10.84	0.004	2.024	0.4091–10.01	0.388
Pleural invasion	3.84	1.481–9.961	0.006	2.399	0.6909–8.331	0.168

Abbreviations: CI, confidence interval; HR, hazard ratio.

in the high fibrinogen group than in the low fibrinogen group.

Figures 2a,b show the survival curve based on fibrinogen levels. The 5-year RFS rates of the low and high fibrinogen groups were 85.7% and 55.6%, respectively, as shown in Figure 2a ($p < 0.001$). Similarly, as observed in Figure 2b, the 5-year OS rates were 91.8% among patients with low fibrinogen levels and 70.6% among patients with high fibrinogen levels ($p = 0.006$). Tables 2 and 3 present the results of the univariate and multivariate Cox proportional hazard regression analyses. Based on the univariate Cox proportional hazard regression analysis of recurrence, tumor size (>20 mm); CEA, CYFRA, and fibrinogen levels; histology and lymphatic, vascular, and pleural invasion were a significant poor prognostic factor. Fibrinogen levels (hazard ratio: 3.076; 95% confidence interval: 1.190–7.950; $p = 0.020$) and CEA levels (hazard ratio: 2.377; 95% confidence interval: 1.014–5.574; $p = 0.046$) were independent predictive factors subsequent to the multivariate analyses of recurrence. According to the univariate Cox proportional hazard regression analysis of OS, CEA, CYFRA, and fibrinogen levels and lymphatic, vascular, and pleural invasion were significant poor prognostic factors. Fibrinogen level (hazard ratio: 5.147; 95% confidence interval: 1.440–18.40; $p = 0.012$) and CEA level (hazard ratio: 9.020; 95% confidence interval: 2.519–31.40; $p < 0.001$) were independent predictive factors subsequent to the multivariate analyses of OS.

DISCUSSION

This retrospective study assessed the prognostic factors for stage I lung cancer. Results showed that CEA and fibrinogen levels were independent prognostic factors of recurrence and survival. Based on a previous retrospective study of resected stage I NSCLC classified using the seventh edition of the American Joint Committee on Cancer Staging Manual, the 5-year survival rates were 82% in patients with stage IA NSCLC and 66.1% in those with stage IB NSCLC. Moreover, patients with completely resected early-stage lung cancer are at high risk of poor prognosis.[7] Therefore, the predictive factors for prognosis and therapeutic effects in patients with lung cancer should be urgently investigated. The factors that can be confirmed preoperatively include

tumor size, tumor CT ratio, and peripheral blood analysis results including plasma fibrinogen, D-dimer, and tumor marker levels.[8–13] Meanwhile, the factors that can be confirmed postoperatively were histology, lymph node metastasis, and lymphatic, vascular, and pleural invasion.[14]

Fibrinogen is an important coagulation factor produced by the liver and converted into fibrin by thrombin. When a tumor generates and invades adjacent benign tissues, microhemorrhage may occur, and fibrin clots are immediately formed to stop the bleeding. These fibrin clots then follow the same process as normal wound healing, thereby replacing the collagenous stroma.[15] Abnormalities in coagulability, such as concentrations of fibrin and its byproduct and fibrinogen, are observed in different types of cancer. In invasive carcinoma, the formation of fibrin clots is localized at the interface between the tumor and host cells and is often found in the extracellular tumor stroma.[16] The formation of fibrin clots surrounds the tumor internally and presents a so-called "nonhealing wound" condition that persists while the tumor grows asymptomatically.[17] In addition, Palumbo et al. identified hemostatic factors including fibrinogen support metastasis in vivo by impeding tumor cell clearance via natural kill cell-mediated cytotoxicity.[18] Different studies have reported the deposition of fibrin clots in tumors, and some have shown that fibrin deposition is more common in higher-grade tumors.[15] In another study, fibrin was found to promote angiogenesis, a mechanism by which the fibrin-rich extracellular matrix promotes the formation of tumor stroma via a process similar to wound repair.

In the current study, high fibrinogen level was associated with poor prognosis even in early-stage lung cancer, which may reflect local tissue destruction and repair. Previous studies have reported that patients with higher fibrinogen levels are more likely to have poor progression-free survival and OS.[5] Furthermore, a multicenter prospective study on 395 patients with operable NSCLC showed that some elevated preoperative coagulation factors, such as fibrinogen, may have a significant effect on poor progression-free survival and can be used to predict the prognosis of patients with NSCLC after surgery.[19] Even in a meta-analysis of the association between plasma fibrinogen levels and lung cancer, plasma fibrinogen was considered a marker of prognosis and associated with distant metastasis and tumor stage.[20] This study focused on whether fibrinogen is a prognostic factor in patients with resected stage I NSCLC. Further, we recently found that elevated fibrinogen level was a significant prognostic factor even in stage I NSCLC. Lymphovascular invasion is among the causes for differences in prognosis based on the fibrinogen level in patients with early-stage lung cancer. Nathan et al. performed a meta-analysis, and results showed that lymphovascular invasion was a strong prognostic indicator for poor outcome among patients with stage I NSCLC who underwent surgery.[21] In addition, lymphovascular invasion is associated with tumor size and stage and may reflect tumor aggressiveness. The presence of lymphatic invasion is closely correlated with lymph node metastasis. In recent studies of fibrinogen (Aα chain)-deficient transgenic mice, fibrinogen deficiency was found to significantly diminish metastatic potential, and fibrinogen played an important role in spontaneous metastasis including lymphatic metastasis, thereby facilitating stable adhesion and survival emboli after tumor cell intravasation.[22] Our results showed that preoperative fibrinogen is associated with lymphatic invasion, which plays an important role in the progression of diseases, and preoperative fibrinogen examination can be a convenient method for evaluating lymphatic invasion.

In recent years, the number of surgical procedures has increased among patients with lung cancer who present with low lung function due to advanced age, chronic obstructive pulmonary disease, and secondary lung resection for postoperative recurrence or multiple primary lung cancer. The risk of postoperative complications is extremely high in these cases, and sublobar resection is considered in cases of early-stage lung cancer. However, it is challenging to determine whether adequate cure can be achieved; thus, it remains controversial. There is a growing need for standardized criteria to determine the feasibility of curative surgery. The recurrence and survival rates of sublobar resection for specific early-stage lung cancer are similar to those of lobectomy.[23,24] A previous study showed no significant differences between the lobectomy and sublobar resection groups in patients with peripheral cT1N0M0 NSCLC measuring 2 cm or less.[12] In a multicenter study of 610 patients with clinical T1N0M0 stage IA lung adenocarcinoma, those with ground-glass opacity-dominant stage IA adenocarcinoma with a ground-glass opacity component of >50% could be successfully treated with wedge resection of T1a tumors and segmental resection of T1b tumors.[13] In addition to tumor size and CT ratio, preoperative fibrinogen level may be a useful marker in determining the indication for aggressive sublobar resection because it reflects lymphatic invasion.

This study had several limitations. It was retrospective in nature, and the sample size was small. Moreover, it was conducted at a single center. In addition, the current study was based on the seventh edition of the American Joint Committee on Cancer Staging Manual and the Revised International System for staging lung cancer. CT scan size was also considered a covariate and predictor of recurrence in the univariate analysis, but not an independent predictor of recurrence in the multivariate analysis. Nevertheless, further studies based on the eighth edition, which is used to evaluate invasive size, must be conducted.

In conclusion, preoperative plasma fibrinogen level could be a useful predictor of recurrence and survival in patients with stage I NSCLC. In patients with high fibrinogen levels, the treatment strategy, including surgical procedures and preoperative treatment, should be cautiously considered preoperatively.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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