High plasma fibrinogen concentration and platelet count unfavorably impact survival in non–small cell lung cancer patients with brain metastases

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Abstract

High expression of fibrinogen and platelets are often observed in non–small cell lung cancer (NSCLC) patients with local regional or distant metastasis. However, the role of these factors remains unclear. The aims of this study were to evaluate the prognostic significance of plasma fibrinogen concentration and platelet count, as well as to determine the overall survival of NSCLC patients with brain metastases. A total of 275 NSCLC patients with brain metastasis were enrolled into this study. Univariate analysis showed that high plasma fibrinogen concentration was associated with age $\geq$ 65 years ($P = 0.011$), smoking status ($P = 0.009$), intracranial symptoms ($P = 0.022$), clinical T category ($P = 0.010$), clinical N category ($P = 0.003$), increased partial thromboplastin time ($P < 0.001$), and platelet count ($P < 0.001$). Patients with low plasma fibrinogen concentration demonstrated longer overall survival compared with those with high plasma fibrinogen concentration (median, 17.3 months versus 11.1 months; $P \leq 0.001$). A similar result was observed for platelet counts (median, 16.3 months versus 11.4 months; $P = 0.004$). Multivariate analysis showed that both plasma fibrinogen concentration and platelet count were independent prognostic factors for NSCLC patients with brain metastases ($R^2 = 1.698, P < 0.001$ and $R^2 = 1.699, P < 0.001$, respectively). Our results suggest that high plasma fibrinogen concentration and platelet count indicate poor prognosis for NSCLC patients with brain metastases. Thus, these two biomarkers might be independent prognostic predictors for this subgroup of NSCLC patients.

Key words Plasma fibrinogen concentration, platelet counts, non–small cell lung cancer, brain metastasis, survival
NSCLC patients with brain metastases. The relationships between PFC, PC, clinicopathologic features, and prognosis were assessed to determine whether PFC and PC are prognostic factors for NSCLC patients with brain metastases.

**Patients and Methods**

**Patient selection**

A total of 275 patients with primary NSCLC and brain metastases who underwent treatment at Sun Yat-sen University Cancer Center between January 2000 and May 2011 were eligible for inclusion in the study. These cases fulfilled the following criteria: (1) newly diagnosed with NSCLC and brain metastases without previous treatment; (2) histologically or cytologically confirmed primary NSCLC and no other types of tumor in history; (3) brain metastases detected by cranial computed tomography (CT), cranial magnetic resonance imaging (MRI), or both; (4) coagulation indices and routine blood tests before treatment; (5) no history of coagulation disorders; and (6) complete profiles of clinical characteristics, and minimum 6 months of follow-up.

Clinical data were obtained from hospital records after treatment. Final confirming for vital status was conducted in November 2011.

**Blood coagulation factors and platelet count tests**

Coagulation function was assessed using plasma from a 4-mL blood sample to which 3.2% sodium citrate was added. Pretreatment PFC was determined using the Clauss method, with thrombin as the reagent (normal range, 2.0 to 4.0 g/L). In addition, PC and serum concentrations of CEA, CYFRA 21-1, NSE, cancer antigen 125 (CA125), cancer antigen 19-9 (CA19-9), and cancer antigen 153 (CA153) were also tested before treatment.

**Statistical analysis**

Statistical analysis was performed using SPSS software (standard version 16.0, SPSS, Chicago, IL). The relationships between coagulation indices and clinicopathologic features were analyzed by two independent sample t tests and chi-square test. Pearson’s correlation coefficient analysis was used to analyze the correlation of PFC with PC and activated partial thromboplastin time (APTT). OS, defined as the time from diagnosis of brain metastases to death, was assessed using the Kaplan-Meier method and compared with the log-rank test. Multivariate survival analysis was performed using the Cox regression model for all of the variables that were significant in the univariate analysis. A two-sided probability less than 0.05 was considered statistically significant.

**Results**

**Patient characteristics**

The clinicalpathologic characteristics for all patients are presented in Table 1. There were 92 females and 183 males, with a median age of 56 years (range, 23–80 years)

**Relationship between PFC, PC, and clinicopathologic features in NSCLC patients with brain metastases**

We assessed several coagulation indices in our patient cohort. PFC was increased (higher than 4 g/L) in 41.1% (113/275) of patients. Median PFC was 3.92 g/L (range, 0.68–9.8 g/L) in pretreated patients. PFC was not associated with gender, number of brain metastases, size of brain metastases, extracranial lesions, or histologic subtype. However, a significant association between PFC and age was observed. Elder patients (≥65 years) had significantly higher level of PFC than younger patients (4.3 g/L vs. 3.8 g/L, P = 0.011; Table 1). The association between PFC and the smoking status was evident (P = 0.009). Patients with intracranial symptoms showed a slightly lower level of PFC compared to those without intracranial symptoms (P = 0.022). Moreover, T category (P = 0.010) and N category (P = 0.003) were associated with PFC (Figure 1). Patients with positive lymph nodes (N1+N2+N3) had a significantly higher PFC than those with negative lymph node (N0) (4.083 ± 1.503 vs. 3.511 ± 1.327, P = 0.003; Figure 1). PC was increased (>300 × 10^9/L) in 27.3% (75/275) of patients. Size of brain metastasis was the only clinicopathologic feature associated with PC (P = 0.036, Table 1).

**Relationship between PFC, PC, and APTT**

We observed a linear correlation between PFC and PC in NSCLC patients with brain metastases (R^2 = 0.146, P < 0.001). We found a similar correlation between PFC and APTT (R^2 = 0.117, P < 0.001), as shown in Figure 2. The correlation between PFC and other coagulation indices was not significant.

**Coagulation factors and overall survival**

All 275 patients were rigorously followed up, with a median follow-up time of 20.7 months. Patients with normal PFC demonstrated longer OS compared with those with increased PFC (median, 17.3 months vs. 11.1 months, P < 0.001; Figure 3, Table 2). Patients with normal PC also demonstrated longer OS compared with those with lifted PC (median, 16.3 months vs. 11.4 months, P = 0.004; Figure 3, Table 2). Other coagulation indices—APTT, prothrombin time (PT), D-dimerization (D-D), and fibrinogen degradation product (FDP)—were also significantly associated with OS, whereas thromboplastin time (TT) was not (Table 2).

**Tumor biomarkers and overall survival**

Patients with normal CA 19-9 level had longer OS compared with those with increased levels (median, 16.5 months vs. 9.7 months, P = 0.004; Table 3). Furthermore, patients with normal CEA level had non-significantly but potential longer OS compared with those with increased levels (median, 16.3 months vs. 14.8 months; Table 3). However, non-significant differences were observed...
**Table 1. The relationship between blood coagulation and clinicopathologic features of non-small cell lung cancer (NSCLC) patients with brain metastases**

| Variable          | No. of patients | PFC (g/L) | P   | PC (×10^9/L) | P   |
|-------------------|-----------------|-----------|-----|--------------|-----|
| Sex               |                 |           |     |              |     |
| Male              | 183             | 4.0 ± 1.6 | 0.167 | 271.8 ± 107.1 | 0.804 |
| Female            | 92              | 3.7 ± 1.3 |       | 274.9 ± 82.9  |     |
| Age (years)       |                 |           | 0.011 |               | 0.470 |
| ≤ 65              | 215             | 3.8 ± 1.4 |       | 270.5 ± 91.8  |     |
| > 65              | 60              | 4.3 ± 1.6 |       | 281.1 ± 124.0 |     |
| Smoking status    |                 |           | 0.009 |               | 0.503 |
| Never             | 136             | 3.7 ± 1.3 |       | 268.8 ± 86.3  |     |
| Ever              | 139             | 4.1 ± 1.6 |       | 276.8 ± 111.1 |     |
| Histology         |                 |           | 0.118 |               | 0.189 |
| AC                | 246             | 3.9 ± 1.4 |       | 275.6 ± 101.7 |     |
| NAC               | 29              | 4.3 ± 1.7 |       | 249.8 ± 76.6  |     |
| Number of BM      |                 |           | 0.592 |               | 0.628 |
| < 3               | 166             | 3.9 ± 1.5 |       | 270.5 ± 102.9 |     |
| ≥ 3               | 109             | 4.0 ± 1.5 |       | 276.4 ± 94.6  |     |
| Size of BM in diameter |           |           | 0.380 |               | 0.036 |
| < 3 cm            | 230             | 4.0 ± 1.5 |       | 267.3 ± 91.9  |     |
| ≥ 3 cm            | 45              | 3.7 ± 1.5 |       | 301.3 ± 129.4 |     |
| Extracranial lesions |             |           | 0.374 |               | 0.559 |
| No                | 161             | 3.9 ± 1.4 |       | 275.8 ± 100.2 |     |
| Yes               | 114             | 4.0 ± 1.6 |       | 268.7 ± 98.9  |     |
| Intracranial symptoms |         |           | 0.022 |               | 0.980 |
| Yes               | 95              | 3.6 ± 1.2 |       | 272.7 ± 97.0  |     |
| No                | 180             | 4.1 ± 1.6 |       | 273.0 ± 104.7 |     |
| T category        |                 |           | 0.010 |               | 0.528 |
| T0                | 8               | 2.9 ± 1.1 |       | 247.0 ± 87.6  |     |
| T1                | 48              | 3.4 ± 1.1 |       | 271.7 ± 126.2 |     |
| T2                | 106             | 4.0 ± 1.5 |       | 265.2 ± 92.2  |     |
| T3                | 25              | 4.4 ± 1.4 |       | 299.8 ± 107.4 |     |
| T4                | 88              | 4.0 ± 1.6 |       | 277.4 ± 90.6  |     |
| N category        |                 |           | 0.003 |               | 0.297 |
| N0                | 80              | 3.5 ± 1.3 |       | 263.0 ± 100.2 |     |
| N1–3              | 195             | 4.1 ± 1.5 |       | 276.9 ± 99.2  |     |

PFC, plasma fibrinogen concentration; PC, platelet count; AC, adenocarcinoma; NAC, non-adenocarcinoma; BM, brain metastases.

between other lung cancer-related tumor markers and OS (**Table 3**).

**Clinicopathologic features and overall survival**

Univariate analysis showed that the following variables significantly associated with OS: age, smoking status, number of brain metastases, size of brain metastasis, clinical T category, clinical N category, and treatment modality (**Table 4**).

**Multivariate analyses**

After multivariate analyses, the remaining independent prognostic factors for OS were smoking status, size of brain metastasis, clinical N category, PFC, PC, and treatment modality (**Table 5**).

**Discussion**

Our study has supported our hypothesis regarding the formation of platelet-fibrin-tumor cell aggregates in developing brain metastases of NSCLC. In our results, PFC and PC were increased in 41.1% (113 of 275) and 27.3% (75 of 275) of patients, respectively. These findings demonstrated that high coagulation state is a common phenomenon in advanced NSCLC[9]. Similar results have been
observed in other human cancers, such as oral\cite{10}, ovarian\cite{11}, liver\cite{12}, and gastric cancers\cite{13}, such that high PFC is closely associated with increased tumor invasion, distant metastases, and poor prognosis for solid tumors. These results suggest that up-regulation of plasma fibrinogen may provide a selective advantage in tumor invasion and regional lymph node metastases in NSCLC.

Fibrinogen is a large glycoprotein synthesized and secreted by hepatic cells\cite{14}. Platelet alpha granules are also rich in fibrinogen, which gets released into the blood upon activation by tumor cells\cite{15}. Fibrinogen is recognized by multiple integrin and non-integrin receptors found on tumor cells, stromal cells, and inflammatory cells. The cellular interactions of fibrinogen mediated by specific receptors may control cell proliferation, cell migration, apoptosis, and expression of inflammatory mediators\cite{16}. Fibrinogen may also play an important role in tumor metastasis, though the mechanism remains unclear. Current research suggests two hypotheses. One proposes that platelet adherence to tumor cells in peripheral blood may prolong the survival of malignant cells by protecting them from immune surveillance, turbulence, and sheer stress, and by enabling them to more easily adhere to the vessel wall\cite{17}. The other proposes that fibrinogen is involved in tumor cell migration\cite{18,19}. Palumbo et al.\cite{20} confirmed that the lack of plasma fibrinogen from rat models...
Table 2. Kaplan-Meier survival analysis (log-rank test) according to the level of coagulation factors in NSCLC patients with brain metastases

| Variable       | No. of patients | Median overall survival (months) | 95% CI (months) | P     |
|----------------|-----------------|----------------------------------|-----------------|-------|
| In total       | 275             | 14.9                             | 13.1–16.7       |       |
| PFC ≤ 4.0 g/L  | 162             | 17.3                             | 14.9–24.7       | < 0.001|
| PFC > 4.0 g/L  | 113             | 11.1                             | 10.5–15.1       |       |
| APTT ≤ 34 s    | 192             | 16.9                             | 13.9–20.0       | 0.001 |
| APTT > 34 s    | 83              | 10.9                             | 8.4–13.4        |       |
| PT ≤ 13.5 s    | 243             | 15.4                             | 13.4–17.3       | 0.046 |
| PT > 13.5 s    | 32              | 10.4                             | 4.3–16.6        |       |
| TT ≤ 21 s      | 247             | 15.0                             | 13.0–16.9       | 0.280 |
| TT > 21 s      | 18              | 11.1                             | 0.0–26.5        |       |
| PC ≤ 300×10^9/L| 200             | 16.3                             | 14.1–18.5       | 0.004 |
| PC > 300×10^9/L| 75              | 11.4                             | 7.2–15.5        |       |
| D-D ≤ 1.5 μg/mL| 54              | 24.4                             | 12.4–36.4       | 0.006 |
| D-D > 1.5 μg/mL| 25              | 11.1                             | 8.2–14.0        |       |
| FDP ≤ 5.0 μg/mL| 57              | 24.4                             | 12.5–36.3       | 0.001 |
| FDP > 5.0 μg/mL| 21              | 11.1                             | 8.4–13.8        |       |

PFC, plasma fibrinogen concentration; PC, platelet count; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thromboplastin time; D-D, D-dimerization; FDP, fibrinogen degradation product.
can reduce lymph node and blood metastases in rat. In our study, we found a linear correlation between PFC and PC in NSCLC patients with brain metastases, which supports the above hypotheses. In addition, tumor cells in the metastatic process require a large amount of coagulation factors, such as APTT and TT, which is also observed in our study.

Coagulation indices have prognostic significance in NSCLC. Pavey et al.\textsuperscript{[7]} and Maeda et al.\textsuperscript{[21]} found that plasma fibrinogen was associated with decreased survival and strongly with stage in 166 patients who underwent surgical resection of NSCLC. To the best of our knowledge, no study has focused on association between coagulation indices and NSCLC with brain metastases.

Distant metastases result poor outcome for NSCLC. Brain metastases are commonly observed in 20%–40% of NSCLC patients during the disease progression\textsuperscript{[22,23]}. Clinical prognostic biomarkers are largely unknown for this disease. Lee et al.\textsuperscript{[24]} demonstrated that the pretreatment serum CEA level was significantly associated with brain metastases in advanced NSCLC. However, in our study, patients with normal CEA level had potential longer survival than those with lifted CEA. Only the level of CA 19-9 was significantly associated with OS. Furthermore, lifted PFC and PC were unfavorable prognostic factors on OS either in univariate or multivariate analyses for NSCLC patients with brain metastases. These results suggest that PFC and PC may be more effective prognostic predictors than tumor biomarkers in NSCLC patients with brain metastases.

For NSCLC, smoking cigarettes is not only the most established risk factor but also a prognostic factor\textsuperscript{[25]}. Tuut et al.\textsuperscript{[26]} suggested a primary role for increased synthesis of fibrinogen in producing the hyperfibrinogenemia associated with smoking status. In this study, there was a strong association between smoking status and PFC. NSCLC patients with brain metastases who have never smoked have longer OS than those who have smoked.

Brain metastases are often presented with cerebral edema, which can endanger a patient’s life. Applying adrenal cortical hormone was initial treatment to control intracranial hypertension of patients with cerebral edema and increased the median survival time to 2–3 months\textsuperscript{[27]}. In our study, NSCLC patients with brain metastases and increased PFC were rarely observed with intracranial symptoms compared to patients with normal PFC. However, the mechanism for this is unclear.

In summary, our results show that PFC and PC may serve as novel markers for predicting the prognosis of NSCLC with brain metastases. Moreover, anticoagulation therapy may improve the survival of patients with this disease. Further studies are required to validate our results.

| Variable | No. of patients | Median overall survival (months) | 95% CI (months) | P |
|----------|----------------|---------------------------------|-----------------|---|
| Total    | 275            | 14.9                            | 13.1–16.7       |   |
| CEA      |                |                                 |                 |   |
| ≤ 5 g/L  | 83             | 16.3                            | 11.2–21.3       | 0.246 |
| > 5 g/L  | 192            | 14.8                            | 13.2–16.5       |   |
| CYFR 21-1|                |                                 |                 |   |
| ≤ 3.5 g/L| 25             | 24.2                            | 9.5–39.0        | 0.083 |
| > 3.5 g/L| 53             | 16.2                            | 13.6–18.9       |   |
| NSE      |                |                                 |                 | 0.050 |
| ≤ 15.2 g/L| 76            | 17.2                            | 13.9–20.7       |   |
| > 15.2 g/L| 49            | 11.1                            | 4.4–17.9        |   |
| CA125    |                |                                 |                 |   |
| ≤ 35 g/L | 35             | 18.7                            | 13.7–23.7       | 0.141 |
| > 35 g/L | 65             | 14.9                            | 11.5–18.3       |   |
| CA153    |                |                                 |                 |   |
| ≤ 25 g/L | 41             | 16.6                            | 11.9–21.4       | 0.257 |
| > 25 g/L | 51             | 14.9                            | 9.1–20.7        |   |
| CA19-9   |                |                                 |                 | 0.004 |
| ≤ 35 g/L | 84             | 16.5                            | 13.0–20.0       |   |
| > 35 g/L | 32             | 9.7                             | 7.5–11.8        |   |

CEA, carcino-embryonic antigen; CYFR21-1, cytokeratin 19 fragments; NSE, neuron-specific enolase; CA125, cancer antigen 125; CA153, cancer antigen 153; CA19-9, cancer antigen 19-9.
Table 4. Univariate survival analyses (log-rank test) according to clinicopathologic features in NSCLC patients with brain metastases

| Variable                      | No. of patients | Median overall survival (months) | 95% CI (months) | P     |
|-------------------------------|-----------------|----------------------------------|-----------------|-------|
| Total                         | 275             | 14.9                             | 13.1 ± 16.7     | 0.200 |
| Sex                           |                 |                                  |                 |       |
| Male                          | 183             | 14.9                             | 12.7 ± 17.1     |       |
| Female                        | 92              | 14.9                             | 10.7 ± 19.1     |       |
| Age (years)                   |                 |                                  |                 | 0.026 |
| ≤ 65                          | 215             | 16.2                             | 14.3 ± 18.1     |       |
| > 65                          | 60              | 10.2                             | 7.2 ± 13.1      |       |
| Smoking status                |                 |                                  |                 | 0.001 |
| Never                         | 136             | 16.9                             | 13.1 ± 20.8     |       |
| Ever                          | 139             | 13.4                             | 10.0 ± 16.8     |       |
| Histology                     |                 |                                  |                 | 0.327 |
| AC                            | 246             | 14.9                             | 12.9 ± 16.9     |       |
| NAC                           | 29              | 17.3                             | 9.0 ± 25.7      |       |
| Number of BM                  |                 |                                  |                 | 0.031 |
| < 3                           | 166             | 17.3                             | 14.1 ± 20.4     |       |
| ≥ 3                           | 109             | 13.4                             | 11.0 ± 15.7     |       |
| Size of BM in diameter        |                 |                                  |                 | 0.022 |
| < 3 cm                        | 230             | 15.7                             | 14.1 ± 17.4     |       |
| ≥ 3 cm                        | 45              | 10.0                             | 6.7 ± 13.4      |       |
| Extracranial lesions          |                 |                                  |                 | 0.221 |
| No                            | 161             | 15.4                             | 13.0 ± 17.7     |       |
| Yes                           | 114             | 13.9                             | 11.9 ± 15.8     |       |
| Intracranial symptoms         |                 |                                  |                 | 0.118 |
| Yes                           | 95              | 13.7                             | 9.2 ± 18.2      |       |
| No                            | 180             | 15.3                             | 13.3 ± 17.5     |       |
| T category                    |                 |                                  |                 | 0.024 |
| T0                            | 8               | 33.6                             | NA              |       |
| T1                            | 48              | 16.5                             | 12.1 ± 21.0     |       |
| T2                            | 106             | 15.2                             | 12.3 ± 18.2     |       |
| T3                            | 25              | 11.4                             | 9.4 ± 13.4      |       |
| T4                            | 88              | 13.7                             | 10.9 ± 16.6     |       |
| N category                    |                 |                                  |                 | <0.001|
| N0                            | 80              | 24.1                             | 14.7 ± 33.4     |       |
| N1–3                          | 195             | 13.3                             | 11.2 ± 15.4     |       |
| Treatment modality            |                 |                                  |                 | <0.001|
| Symptomatic treatment<sup>a</sup> | 57           | 9.0                              | 5.4 ± 12.7      |       |
| Systemic treatment<sup>b</sup> | 218           | 16.5                             | 14.3 ± 18.8     |       |

<sup>a</sup>Symptomatic treatment, given to reduce intracranial pressure: mannitol 125 mg twice per day via intravenous drip; <sup>b</sup>Systemic treatment, systemic chemotherapy plus local treatment. AC, adenocarcinoma; NAC, non-adenocarcinoma; BM, brain metastases; NA, not available.
Table 5. Multivariate survival analyses for overall survival according to the Cox regression model

| Variable          | RR  | 95% CI    | P     |
|-------------------|-----|-----------|-------|
| PFC               | 1.5 | 1.1–2.1   | 0.008 |
| PC                | 1.4 | 1.0–2.0   | 0.042 |
| Smoking status    | 1.5 | 1.1–2.0   | 0.007 |
| Size of BM        | 1.6 | 1.1–2.3   | 0.027 |
| N category        | 1.8 | 1.3–2.5   | 0.001 |
| Treatment modality| 0.5 | 0.3–0.7   | <0.001|

PFC, plasma fibrinogen concentration; PC, platelet count; RR, relative risk; CI, confidence interval; BM, brain metastasis.

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