Research Paper

Prognostic Value of Plasma Fibrinogen in Lung Cancer Patients: A Meta-Analysis

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Abstract

Background: The prognostic role of plasma fibrinogen in lung cancer remains controversial. The aim of this meta-analysis was to assess the prognostic value of plasma fibrinogen in lung cancer.

Methods: We performed a systematic literature search to identify eligible studies in PubMed, Embase and the Cochrane Library database. The hazard ratios (HR) and their 95% confidence intervals (CI) were collected from these eligible studies and were used to assess the relationship between plasma fibrinogen and lung cancer.

Results: A total of 16 studies including 6,881 patients were selected in this meta-analysis. The results showed that elevated plasma fibrinogen in lung cancer patients was correlated with poor overall survival (OS) (HR = 1.38, 95% CI: 1.22-1.55, P < 0.001) and disease-free survival (DFS) / progress-free survival (PFS). (HR = 1.29, 95% CI: 1.01-1.65, P = 0.042). When stratified by cut-off value for OS and DFS/PFS, there was no significant heterogeneity. And the results of "cut-off value ≥ 400mg/dl" group showed that the high level of fibrinogen in serum was associated with worse OS and DFS/PFS of lung cancer. In further subgroup analysis by tumor histology, high plasma fibrinogen was also associated with worse OS in non-small cell lung cancer (NSCLC) (HR = 1.32, 95% CI: 1.14-1.53, P < 0.001). However, there was no significant association between high plasma fibrinogen and poor DFS in NSCLC patients (HR = 1.24, 95% CI: 0.97-1.57, P = 0.08). The Egger's regression test indicated evidence of publication bias for DFS/PFS.

Conclusions: Elevated plasma fibrinogen, particularly defined as a plasma fibrinogen concentration of ≥ 400mg/dl, could be a promising indicator for worse OS in lung cancer patients, including NSCLC.

Key words: Fibrinogen, Lung cancer, Non-small cell lung cancer, Prognosis, Meta-analysis

Introduction

Lung cancer, which threatens seriously human life and health, remains the leading cause of cancer-related death in the world [1]. Despite the development of molecular targeted therapy and improvements of chemoradiotherapy in lung cancer, the prognosis of lung cancer remains poor, with the 5-year survival rate has not improved significantly [2]. Currently several nonspecific tumor markers, such as carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21-1) and neuron-specific-enolase (NSE) have been used to investigate the prognostic value of lung cancer, however, clinical studies have produced conflicting results, and reliable markers are still lacking [3-7].

In recent studies, many researchers have found the relationship between blood coagulation disorders and several malignant tumors [8, 9]. Activation of the coagulation system and procoagulant changes is correlated with tumor invasion, progression, angiogenesis and metastasis [8-12]. Fibrinogen, as a plasma coagulation factor synthesized by the liver, can reflect the degree of activation of coagulation

system by its high levels. Elevated plasma fibrinogen levels are associated with poor outcomes in a variety of malignant tumors [13]. Moreover, the prognostic role of plasma fibrinogen in lung cancer patients has been investigated in several published studies. However, the results remain inconclusive [14-17]. Therefore, we performed this meta-analysis to investigate the correlation between elevated plasma fibrinogen and prognosis in patients with lung cancer.

Materials and Methods

Search strategy and study selection

Relevant literature in the period from inception up to February 2018 was systematically searched using PubMed, Embase and the Cochrane Library database. The key search items used were as follows: (fibrinogen or "plasma fibrinogen") and ("lung carcinoma" or "lung cancer" or "lung tumor" or "lung neoplasm") and (prognosis or prognostic or survival or outcome). In order not to omit the potentially relevant articles, reference lists in the retrieved papers were also screened.

In this meta-analysis, eligible studies were included according to the following criteria: (1) any clinical study comprising the association between plasma fibrinogen and prognosis of lung cancer patients was eligible; (2) data of hazard ratios (HR) and 95% confidence intervals (CI) were provided, or sufficient information that allowed manual calculation of them; (3) the studies were published only in English; (4) for studies with overlapping data, we selected the most complete or the latest study. The studies with the following criteria were excluded: (1) studies that were published as letters, reviews, case reports and conference abstracts; (2) overlapping studies or duplicated data; (3) full text unavailable and non-English article; (4) studies lacking sufficient data to acquire HR and their 95% CI.

Data extraction and quality assessment

In order to reduce the risk of losing a publication, two investigators (Hai Zhong and Yingying Qian) independently surveyed the eligible literatures based on the predefined criteria. In addition, any inconsistent opinions between the two investigators were resolved by consensus involving a third reviewer (Surong Fang). Data were extracted from all eligible studies as follow: name of the first author, year of publication, study country, number of patient enrolled, pathological type, clinical stages, cut-off value, HR and their 95% CI for overall survival (OS) and disease-free survival (DFS) / progress-free survival (PFS).

The two investigators independently evaluated the quality of each included study using the Newcastle-Ottawa scale (NOS) for cohort studies [18]. The three major components of NOS criteria were: selection of cohorts (0-4 points), comparability of cohorts (0-2 points), ascertainment of outcomes (0-3 points). Studies with NOS scores of more than 6 were considered as high quality.

Statistical analysis

HR and 95% CI were used to analyse the prognostic value of elevated plasma fibrinogen in lung cancer patients. Meta-analysis was conducted to merge the results of the included studies. The combined HR >1 and its 95% CI did not overlap 1 indicated that a higher level of plasma fibrinogen could be a poorer prognostic factor in lung cancer patients, whereas the combined HR < 1 indicated better prognosis. Heterogeneity among the included studies was assessed using Cochrane's Q test and I^2 statistic [19]. A P-value < 0.10 and/or I^2 > 50% indicated significant heterogeneity among studies and a random effects was used to calculate the pooled HR and 95% CI. Otherwise, the fixed effects model was adopted [20, 21]. The potential for publication bias was evaluated using the Begg's test and Egger's regression test, and a probability value less than 0.05 was used to indicate a statistically significant difference [22, 23]. Moreover, a sensitivity analysis was conducted to validate the stability of the pooled results by omitting individual study [24]. All data analyses were performed using the STATA 12.0 software.

Results

Study selection and characteristics

The detailed flow diagram for the selection of eligible studies is shown in Figure 1. A total of 459 related records were identified through literature searching according to the abovementioned criteria. After screening the titles and abstracts, 424 independent studies were excluded. The full texts of the remaining 35 studies were further evaluated. Finally, only 16 studies were included in this meta-analysis [14-17, 25-36].

The basic features of the included studies are summarized in Table 1. As presented in Table 1, there were 6,881 lung cancer patients from 4 different countries included in our meta-analysis, with publication year ranging from 1997 to 2017. There were 10 studies included non-small cell lung cancer (NSCLC) patients, only 2 studies included small cell lung cancer (SCLC), and the other 4 studies included all types of lung cancer patients. Among the 16 studies, 15 studies investigated the relationship

between elevated plasma fibrinogen and OS of lung cancer, and the association between elevated plasma fibrinogen and DFS/PFS was evaluated only in 7 studies. A total of 15 studies reported HR and 95% CI. And for the remaining one study [25], we calculated the data of HR and 95% CI using available information based on the methods provided in the literature by Parmar et al [37]. The quality assessment of each included study using the NOS is demonstrated in Table 2.

Relationship between plasma fibrinogen and OS of lung cancer

Among the eligible studies, 15 studies including 6,697 patients had assessed the relationship between plasma fibrinogen and OS of lung cancer. Because of significant heterogeneity (P = 0.004, I^2 = 56.6%), we used a random effect model to calculate the pooled HR. The pooled results indicated a significantly shorter OS in lung cancer patients with high plasma fibrinogen compared to those with low plasma fibrinogen (HR = 1.38, 95% CI: 1.22-1.55, < 0.001; Figure 2A). Then, we performed subgroup analysis according to six potential clinical variables, including analysis of variable, ethnicity, cut-off value, tumor stage, histology, and quality score.

As demonstrated in Table 3, stratified analysis by analysis of variable revealed that high plasma fibrinogen was associated with worse OS of lung cancer patients both in univariate analysis (HR = 1.65, 95% CI: 1.45-1.87, P < 0.001) and multivariate analysis (HR = 1.35, 95% CI: 1.19-1.54, P < 0.001). Subgroup analyses by ethnicity, we found the pooled HR was 1.36 (95% CI: 1.19–1.55) for Asian patients and 1.48 (95% CI: 1.22–1.81) for non-Asian patients. Stratification by cut-off value, the data indicated that

the pooled HR was 1.23 (95% CI: 1.09-1.38) for "cut-off value < 400mg/dl" group and 1.48 (95% CI: 1.34-1.64) for "cut-off value ≥ 400mg/dl" group. Notably, there were no significant heterogeneity both in "cut-off value < 400mg/dl" group (P = 0.226, I^2 = 29.30%) and "cut-off value ≥ 400mg/dl" group (P = 0.616, I^2 = 0.00%). Similarly, subgroup analyses showed that the elevated plasma fibrinogen was a poor prognostic marker of OS regardless of tumor histology and NOS score. In addition, stratified analysis by tumor stage showed high fibrinogen was associated with poor OS in "III-IV stage" group (HR = 1.41, 95% CI: 1.22-1.62, P < 0.001), while there was no statistically significant association in "I-III stage" group (HR = 1.24, 95% CI: 0.99-1.55, P = 0.058).
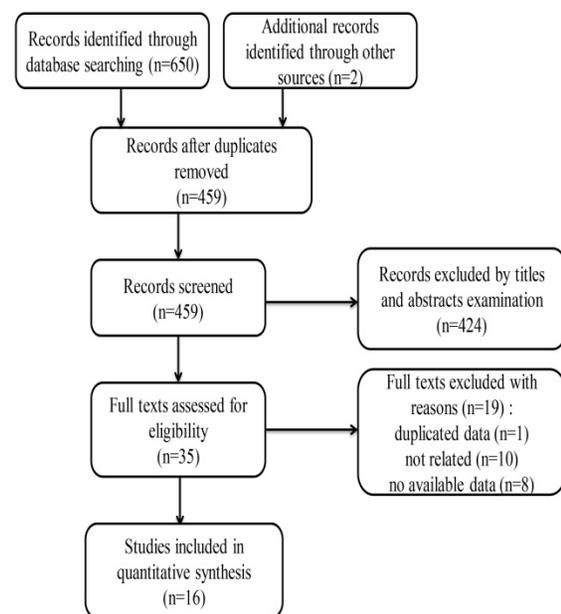

Figure 1. Flow chart of search strategy and study selection.

Table 1. Main characteristics of the included studies in our meta-analysis

Study/Year	Country	Patient number	Histology	Stage	Cut-off value	Outcome	OS: HR(95%CI)		DFS/PFS: HR(95%CI)	
							U	M	U	M
Buccheri G/ 1997	France	247	NSCLC+SLCL	NR	429	OS	1.46(1.16-1.84)	NR	NR	NR
Unsal E/ 2004	Turkey	58	NSCLC+SLCL	I-IV	350	OS	NR	1.28(0.73-2.23)	NR	NR
Altiay G/ 2007	Turkey	78	NSCLC+SLCL	III-IV	380	OS	1.86(1.08-3.21)	NR	NR	NR
Zhao J/ 2012	China	160	NSCLC	III-IV	440	OS	NR	1.673(1.133-2.471)	NR	NR
Sheng L/ 2013	China	567	NSCLC	I-IIIB	400	OS/DFS	2.07(1.37-3.14)	1.64(1.06-2.53)	1.57(1.15-2.13)	1.49(1.07-2.05)
Zhu JF/ 2014	China	275	NSCLC	IV	400	OS	NR	1.5(1.1-2.1)	NR	NR
Kim KH/ 2014	Korea	854	NSCLC	III-IV	450	OS	NR	1.34(1.13-1.58)	NR	NR
Jiang HG/ 2014	China	184	NSCLC	I-IIIA	400	DFS	NR	NR	NR	3.36(1.19-9.26)
Chen YS/ 2014	China	370	NSCLC+SLCL	I-IV	420	OS	NR	1.497(1.115-2.008)	NR	NR
Zhang H/ 2015	China	1238	NSCLC	I-IIIA	NR	OS/DFS	1.370(1.180-1.592)	0.935(0.778-1.119)	1.335(1.149-1.550)	0.871(0.730-1.053)
Zhu LR/ 2016	China	74	SCLC	-	400	OS/PFS	NR	3.66(1.10-12.57)	NR	3.62(1.03-12.32)
Zeng Q/ 2017	China	856	NSCLC	I-IV	370	OS	2.064(1.761-2.420)	1.399(1.122-1.744)	NR	NR
Fan S/ 2017	China	120	SCLC	-	400	OS	1.591(1.085-2.332)	1.505(1.018-2.226)	NR	NR
Liu W/ 2017	China	1120	NSCLC	I-IIIA	360	OS/DFS	1.451(1.242-1.695)	1.079(0.904-1.287)	1.405(1.203-1.641)	1.024(0.859-1.221)
Gao L/ 2017	China	546	NSCLC	I-IIIA	354	OS/DFS	1.580(1.257-1.985)	1.217(0.954-1.554)	1.559(1.241-1.960)	1.164(0.910-1.490)
Wang YQ/ 2017	China	134	NSCLC	I-IIIA	400	OS/DFS	2.131(1.417-3.206)	2.045(1.332-3.141)	1.875(1.202-2.925)	1.865(1.196-2.910)

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; NR: not reported; OS: overall survival; DFS: disease-free survival; PFS: progress-free survival; HR: hazard ratio; CI: confidence interval; U: univariate analysis; M: multivariate analysis

Table 2. Quality assessment of included studies using the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome	Total score
Buccheri G	4	1	3	8
Unsal E	4	0	2	6
Altiay G	4	0	2	6
Zhao J	4	1	2	7
Sheng L	4	1	2	7
Zhu JF	4	1	2	7
Kim KH	4	0	2	6
Jiang HG	4	0	2	6
Chen YS	4	1	2	7
Zhang H	4	0	3	7
Zhu LR	4	1	2	7
Zeng Q	4	1	2	7
Fan S	4	0	3	7
Liu W	4	0	3	7
Gao L	4	0	2	6
Wang YQ	4	0	2	6

Relationship between plasma fibrinogen and DFS/PFS of lung cancer

Only 7 studies with 3,863 cases presented the data of high plasma fibrinogen and DFS/PFS in lung cancer patients. The random effect model was applied owing to significant heterogeneity was tested (P = 0.001, I^2 = 74.90%), and the results of the pooled HR demonstrated that high plasma fibrinogen was correlated with worse DFS/PFS in lung cancer (HR = 1.29, 95% CI: 1.01-1.65, < 0.001; Figure 2B).

As shown in Table 3, subgroup analysis revealed that elevated plasma fibrinogen was associated with unfavorable DFS/PFS of lung cancer both in univariate analysis (HR = 1.43, 95% CI: 1.31-1.57, P < 0.001) and multivariate analysis (HR = 1.29, 95% CI: 1.01-1.65, P = 0.042). Stratified analysis according to ethnicity was not performed due to all the people included in the studies was Asian. In addition, elevated fibrinogen predicted poor DFS/PFS for patients in "cut-off value ≥ 400mg/dl" group. The results of remaining groups including "cut-off value < 400mg/dl" group, "I-III stage" group, "NSCLC" group, low quality studies group (NOS ≤ 6) and high quality studies group (NOS > 6) showed no significant association between high plasma fibrinogen and DFS/PFS.

Table 3. The results of stratified analysis in meta-analysis for OS and DFS/PFS

Outcome	Stratified analysis	No. of studies	HR (95% CI)	P	Heterogeneity		Model used
					I^2 (%)	P_h	
OS	Analysis of variable						
	Univariate	9	1.65(1.45-1.87)	<0.001	59.50%	0.011	Random
	Multivariate	13	1.35(1.19-1.54)	<0.001	59.00%	0.004	Random
	Ethnicity						
	Asian	12	1.36(1.19-1.55)	<0.001	62.40%	0.002	Random
	non-Asian	3	1.48(1.22-1.81)	<0.001	0.00%	0.622	Fixed
	Cut-off value						
	<400mg/dl	5	1.23(1.09-1.38)	<0.001	29.30%	0.226	Fixed
	≥400mg/dl	9	1.48(1.34-1.64)	<0.001	0.00%	0.616	Fixed
	Tumor stage						
	I-III	5	1.24(0.99-1.55)	0.058	73.20%	0.005	Random
	III-IV	3	1.41(1.22-1.62)	<0.001	0.00%	0.54	Fixed
	Histology						
	NSCLC	9	1.32(1.14-1.53)	<0.001	66.70%	0.002	Random
	SCLC	2	1.64(1.13-2.37)	0.01	46.10%	0.173	Fixed
	NSCLC+SCLC	4	1.49(1.26-1.75)	<0.001	0.00%	0.813	Fixed
	Quality score						
	>6	10	1.36(1.17-1.59)	<0.001	64.50%	0.003	Random
	≤6	5	1.37(1.21-1.56)	<0.001	28.40%	0.232	Fixed
DFS/PFS	Analysis of variable						
	Univariate	5	1.43(1.31-1.57)	<0.001	0.00%	0.527	Fixed
	Multivariate	7	1.29(1.01-1.65)	0.042	74.90%	0.001	Random
	Cut-off value						
	<400mg/dl	2	1.07(0.93-1.23)	0.36	0.00%	0.407	Fixed
	≥400mg/dl	4	1.74(1.36-2.23)	<0.001	22.80%	0.247	Fixed
	Tumor stage						
	I-III	6	1.24(0.97-1.57)	0.08	75.30%	0.001	Random
	Histology						
	NSCLC	6	1.24(0.97-1.57)	0.08	75.30%	0.001	Random
	SCLC	1	-	-	-	-	-
	Quality score						
	>6	4	1.13(0.85-1.51)	0.387	75.20%	0.007	Random
	≤6	3	1.65(1.00-2.73)	0.051	69.00%	0.04	Random

OS: overall survival; DFS: disease-free survival; PFS: progress-free survival; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; HR: hazard ratio; CI: confidence interval

Publication bias

The potential for publication bias was detected by Begg's test and Egger's regression test. Visual inspection of the Begg's funnel plot demonstrated evidence of publication bias for OS (Figure 3A), which was confirmed by Begg's test (P = 0.013) and Egger's regression test (P = 0.004). Then we adopted the trim and fill method to adjust the asymmetry of the funnel plot (Figure 3B). The pooled analysis included the hypothetical studies continued to indicate a statistically significant association between high plasma fibrinogen and OS (HR = 1.26, 95% CI: 1.12-1.41, P < 0.001). The result showed that the effect of publication bias was not significant and the conclusion was relatively stable.

We also used the Begg's test and Egger's regression test to evaluated publication bias for DFS/PFS. The Begg's funnel plot funnel plots revealed a low probability of publication bias for DFS/PFS (Figure 3C). Although the Begg's test (P = 0.133) was not statisitically significant, the Egger's regression test (P = 0.007) indicated evidence of publication bias for DFS/PFS. The trim and fill method was used to adjust for publication bias under the random-effects model (Figure 3D), and the corrected pooled HR for DFS/PFS was 1.08 (95% CI: 0.83–1.40, P = 0.592). These indicated that there could be publication bias for DFS/PFS, and the conclusion was not robust.

Sensitivity analysis

We performed a sensitivity analysis by omitting each study by turns to evaluate result reliability. The corresponding pooled HR values for OS (Figure 4A) and DFS/PFS (Figure 4B) were not significantly altered, which suggested the reliability of our conclusions.

Discussion

It is now generally accepted that the coagulation system is often activated in cancer patients [38, 39]. And the extent of coagulation activation, as estimated by the plasma fibrinogen and D-dimer, has been correlated with invasion, progression, angiogenesis and metastasis in several tumors [8, 40-42], including lung cancer [17, 29, 31]. Moreover, several studies have reported conflicting findings on the role of high plasma fibrinogen and prognosis in lung cancer.

Therefore, we performed this meta-analysis to assess the prognostic role of high plasma fibrinogen in lung cancer patients. The results of our meta-analysis demonstrated that elevated plasma fibrinogen could significantly predict poor OS and DFS/PFS of lung cancer. Additionally, significant heterogeneity was observed in the meta-analysis. Thus, we performed subgroup analysis by grouping the eligible studies according
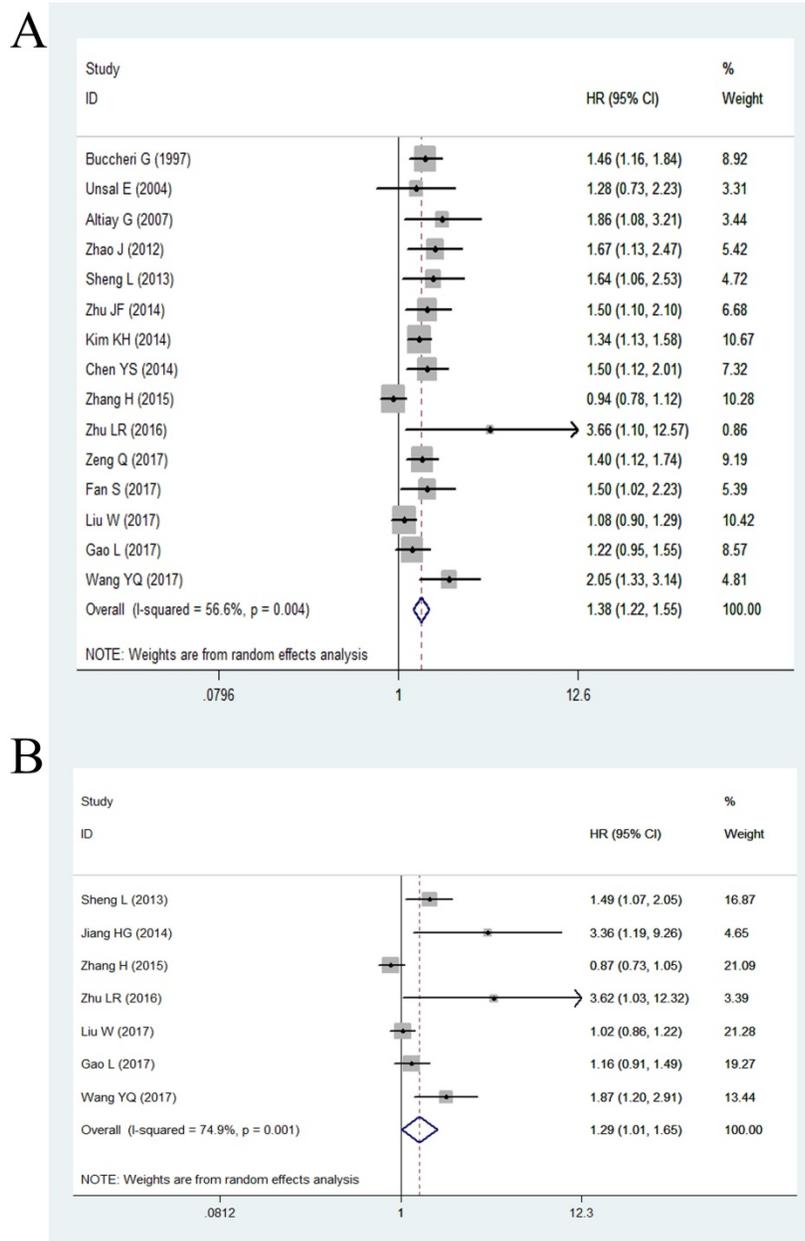

Figure 2. Forest plot showing the pooled HR for the correlation between elevated plasma fibrinogen and OS (A) or DFS/PFS (B) in lung cancer patients.

to analysis of variable, ethnicity, cut-off value, tumor stage, histology, and quality score to explore the source of heterogeneity. Although the heterogeneity could not eliminate, most of the prognostic significance were not unaffected by subgroup analysis stratified by analysis of variable, ethnicity, tumor stage, histology, and quality score. Furthermore, when stratified by cut-off value for OS and DFS/PFS, there were no significant heterogeneity both in "cut-off value < 400mg/dl" group and "cut-off value ≥ 400mg/dl" group. So the definition of cut-off value of hyperfibrinogenemia might be the main source of heterogeneity. And the results of "cut-off value ≥ 400mg/dl" group demonstrated that the high level of fibrinogen in serum was associated with worse OS and DFS/PFS of lung cancer. However, the results of another subgroup indicated that elevated serum fibrinogen was related with poor OS of lung cancer, not related to DFS/PFS. This finding suggested that hyperfibrinogenemia defined as a plasma fibrinogen concentration of ≥ 400mg/dl could help accurately predict the prognosis of lung cancer patients both for OS and DFS/PFS. Because of publication bias for DFS/PFS existed, the elevated plasma fibrinogen could be a promising indicator for worse OS in lung cancer patients, not for DFS/PFS. In addition, hyperfibrinogenemia might be a stratified variable in clinical trials of lung cancer.

The exact reason for the association between elevated plasma fibrinogen and poor survival of patients with lung cancer remained unclear. However, several experimental studies had demonstrated that fibrinogen could play a key role in tumor progression. By promoting the stable adhesion of tumor cells and survival of metastatic emboli after tumor cells intravasation, fibrinogen had been shown to play an important determinant of spontaneous metastatic potential in lung and skin cancer models [43, 44]. In addition, study found that fibrinogen could promote gallbladder cancer cells EMT through increasing the expression of vimentin and decreasing the expression of E-cadherin, thereby enhanced the migration and metastasis of tumor cells [45]. Moreover, with the help of thrombin and platelets, fibrinogen formed dense layers of fibrinogen that adhered to the surrounding of tumor cells and protected them from being killed by natural-killer cells [46]. Furthermore, some reports suggested that tumor cells were capable of endogenous production of fibrinogen, and that fibrinogen binding to FGF-2 and VEGF could potentiate stimulation of endothelial cell proliferation, resulting in augmented angiogenesis [47-49]. As fibrinogen could promote tumor migration, metastasis and angiogenesis, it could become a prognostic factor of lung cancer.
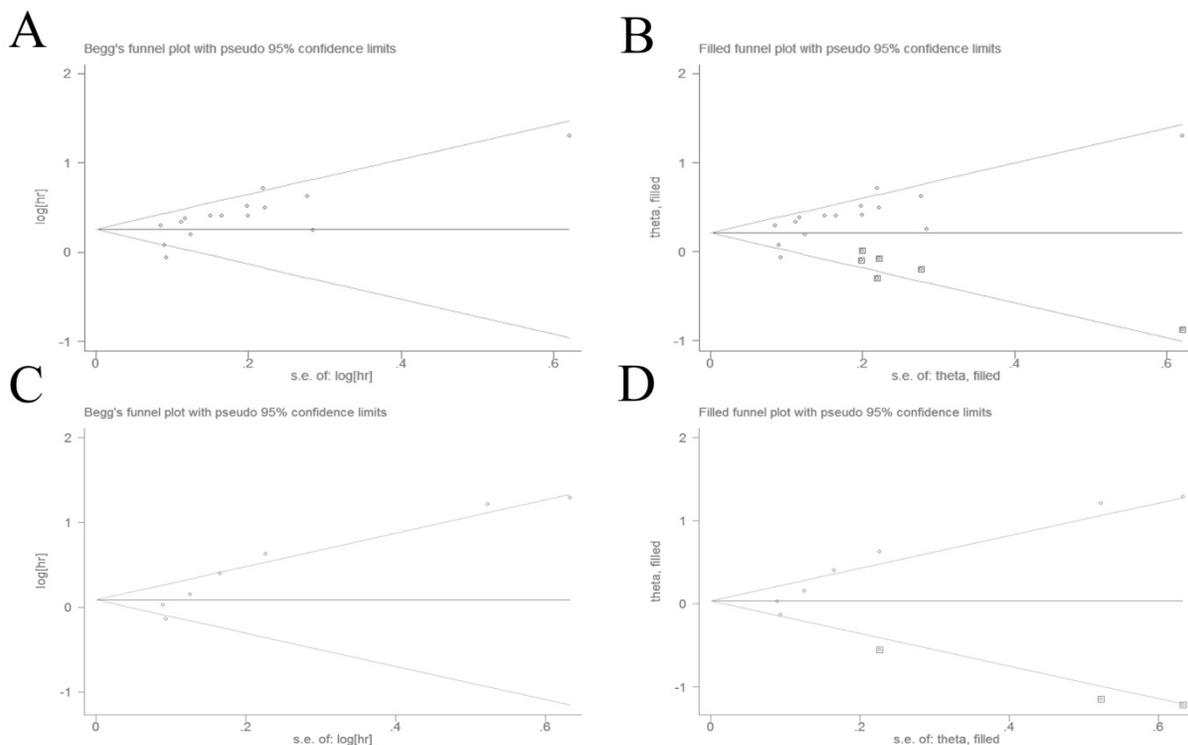

Figure 3. Begg's funnel plots evaluating possible publication bias for (A) OS without trim and fill method; (B) OS with trim and fill method; (C) DFS/PFS without trim and fill method; (D) DFS/PFS with trim and fill method.

Recently, a number of meta-analysis had reported the prognostic role of elevated plasma fibrinogen in a variety of tumors, including, epithelial ovarian cancer [50], Renal Cell Carcinoma [51], esophageal cancer [52]. To the best of our knowledge, this meta-analysis was the first study to systematically assess the prognostic value of plasma fibrinogen in lung cancer. The results of our meta-analysis on the prognostic role of plasma fibrinogen in lung cancer were in accordance with the prognostic value of plasma fibrinogen in other tumors, indicating that high plasma fibrinogen could be widely used as a marker for poor prognosis in solid tumors, which was consistent with the results from Perisanidis's study [13]. Since the important prognostic value of plasma fibrinogen in various malignant tumors, we speculate that plasma fibrinogen can be combined with traditional clinicpathological prognostic parameters, which improve the treatment decision and prognosis evaluation more effectively. And plasma fibrinogen is easily available because it is a conventional, inexpensive and simple repeatable inspection result. Therefore, plasma fibrinogen can be easily integrated into daily clinical use.

In addition to the inherent deficiencies associated with meta-analysis, our study had several other limitations. Firstly, although 16 studies including 6881 lung cancer patients were included in our meta-analysis, most of the patients enrolled came from Asian region, and only 3 studies including 383 patients came from non-Asian regions, which might limit the suitable applicability of our research results to other populations. Secondly, only two studies investigated prognostic role of high plasma fibrinogen in SCLC, so further larger sample studies were needed to confirm the conclusion. Thirdly, our meta-analysis only contained articles published in English, which might lead to an inevitable bias. Fourthly, in spite of no significant publication bias for OS was observed based on the trim and fill method, we could not avoid it completely. Because positive results of studies tended to be accepted by journals easily, while negative results were likely to be rejected or even unpublished. Finally, the studies included in our meta-analysis were retrospective, observational studies, and no prospective cohort study was selected.

Conclusions

In conclusion, our meta-analysis revealed that elevated plasma fibrinogen, particularly defined as a plasma fibrinogen concentration of ≥ 400mg/dl, could be a promising indicator for worse OS in lung cancer patients, including NSCLC. And the prognostic value of plasma fibrinogen for DFS/PFS in lung cancer needed further confirmation. However, since the limitations listed above, better-designed studies on larger sample and other ethnic groups are required to further confirm our conclusion.

Abbreviations

HR: hazard ratio; CI: confidence interval; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; NR: not reported; OS: overall survival; DFS: disease-free survival; PFS: progress-free survival; U: univariate analysis; M: multivariate analysis.
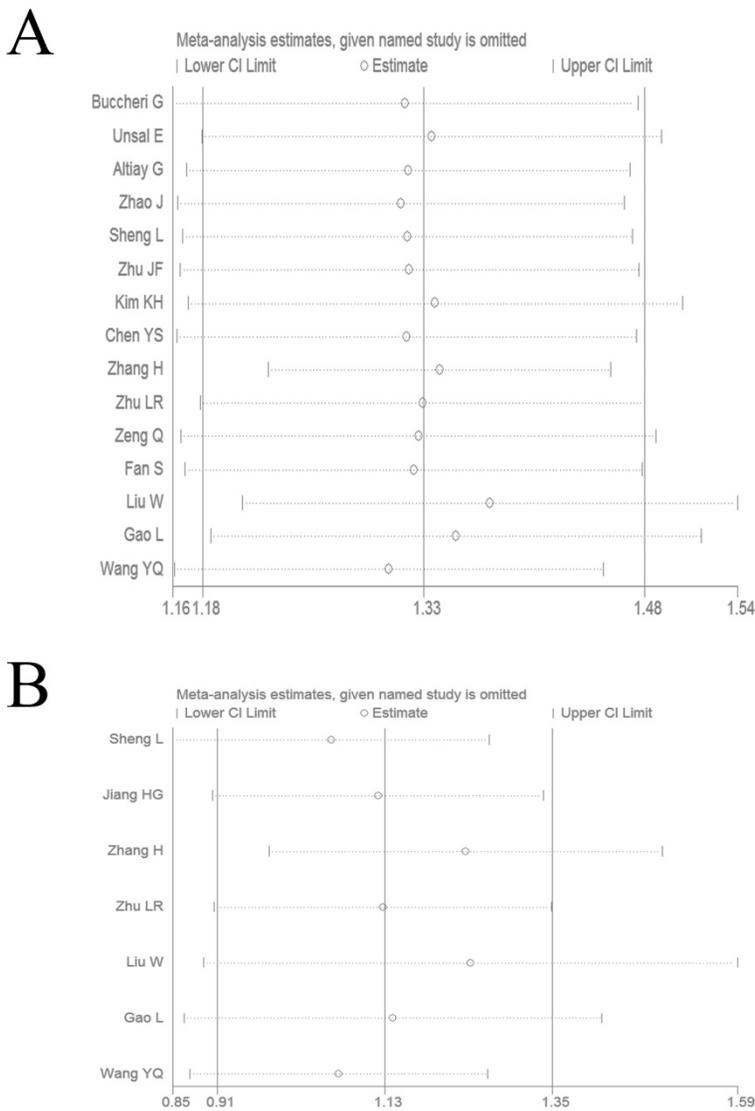

Figure 4. Sensitivity analysis on the relationship between elevated plasma fibrinogen and OS (A) or DFS/PFS (B) in lung cancer patients.

Acknowledgments

Competing Interests

The authors have declared that no competing interest exists.

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