

The association between plasma fibrinogen levels and lung cancer: a meta-analysis

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Background: Published studies have presented an inconsistent association between plasma fibrinogen level and poor prognosis or clinicopathological characteristics in lung cancer.

Methods: In the absence of significant quality difference, combined hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated according to overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS). Risk ratio (RR), odds ratio (OR) and standardized mean difference (SMD) with CIs were pooled to appraise the effect of plasma fibrinogen on clinicopathological characteristics. Furthermore, we directly combined the P values to estimate the association of plasma fibrinogen and tumor size. We adjusted the publication bias using trim-and fill method. **Results:** Twenty studies with 6,494 patients were contained in meta-analysis. The pooled data indicated that elevated fibrinogen level associated with poor prognosis in lung cancer. Typically, the pooled HRs were 1.44 (95% CI, 1.34–1.55), 1.49 (95% CI, 1.24–1.80) and 1.69 (95% CI, 1.31–2.17) for OS, PFS and DFS of lung cancer, respectively. In addition, the combined ORs were 1.50 (95% CI, 1.23–1.84) and 2.01 (95% CI, 1.66–2.44) for lymph node metastasis and III–IV stage; and the combined RR was 2.15 (95% CI, 1.11–4.15) for disease control rate (DCR). Moreover, patients with distant metastasis or III–IV stage had significantly higher plasma fibrinogen level (SMD: 0.20, 95% CI, 0.04–0.36; SMD: 0.31, 95% CI, 0.18–0.44, respectively).

Conclusions: The summary results indicated that plasma fibrinogen was a marker of prognosis and clinicopathological characteristics in lung cancer.

Keywords: Plasma fibrinogen; lung cancer; prognosis; clinicopathological characteristics; meta-analysis

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Introduction

Lung cancer was considered to be the leading cause of cancerrelated mortality (1). There were 1.8 million new lung cancer cases and 1.6 million cancer-related deaths worldwide (2). In spite of great advances in diagnosis and therapy, 5-year survival rates are only 18% for lung cancer (3). Independent prognostic factors, including disease stage, performance status, age, sex, weight loss and KRAS mutation, have been identified (4-8). However, there is a lack of blood biochemical indicators for the prognosis and clinicopathological

Journal of Thoracic Disease, Vol 11, No 11 November 2019

characteristics in patients suffering from lung cancer.

Fibringen, a easily measured biochemical indicator, is a kind of the principal acute phase proteins generated by the liver (9). The activation of coagulation and fibrinolysis is encountered among malignancy and about 90% of cancer patients with metastatic disease and 50% of cancer patients have abnormal coagulation parameters (10). Moreover, high plasma fibrinogen level is frequently observed in cancer patients and influence metastatic potential (11,12). Several meta-analysis indicated that elevated plasma fibrinogen associated with poor prognosis (overall survival, OS; progression-free survival, PFS; disease-free survival, DFS) in epithelial ovarian, digestive cancer (13,14). Moreover, elevated plasma fibrinogen level in lung cancer implied short survival (15). Then, anticoagulant therapy would be valuable for patients with lung cancer. However, conflicting data were reported (16,17).

Therefore, we conducted a meta-analysis to assess the prognostic significance of fibrinogen in patients with lung cancer.

Methods

Search strategy

A systemic search in PubMed, Web of science, EMBASE and the Cochrane Central Register of Controlled Trials databases were employed to identify all articles published up to September 2018, using the items "fibrinogen", "hyperfibrinogen", "fibrinogenemia", "predictive", "recurrence", "relapse", "prognosis", "survival", "lung cancer" and "lung neoplasms". In addition, we manually searched abstracts of the World Lung Cancer Conference, the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) to identify unpublished studies.

Selection criteria

Eligible studies included in the meta-analysis had to meet the following criteria: (I) assessment of the association of plasma fibrinogen and lung cancer prognosis or clinicopathological characteristics; (II) the value of plasma fibrinogen detection before chemotherapy; (III) only including the most recent and informative studies if duplicate articles were from the same participants; (IV) full text articles in English or Chinese language were retained.

Data extraction

Data from the included studies were extracted independently by two investigators (K Zhang and Y Xu). The information, including first author, year of publication, patient source, number of patients, histology, disease stage, cut-off value and outcomes, was extracted. Two reviewers (K Zhang and Y Xu) determined study eligibility independently and any disagreements were solved after discussion.

Quality assessment

The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist was used to assess the quality of these studies for cohort studies (18). The overall score assessed the following dimensions of methodology, grouped into eight main categories: (I) hypothesis and/or objective(s) stated; (II) tumor stage clearly described; (III) clear description of eligibility criteria; (IV) patients with inflammatory disease or coagulation disorders excluded; (V) predictors and outcome(s) clearly predefined; (VI) confounders considered in multivariate analysis; (VII) long enough for outcomes to occur; (VIII) bias and limitations considered. Each category had 1 point, and then an overall maximum theoretical score was 8 points. Finally, the scores were expressed as numbers from 0 to 8, and better methodological quality was provided with higher values (Table S1).

Definition of outcomes

The primary outcomes were the OS, PFS, DFS or clinicopathological characteristics, including disease control rate (DCR), objective response rate (ORR), tumor stage, lymph node metastasis, distant metastasis, stage, differentiation, Eastern Cooperative Oncology Group (ECOG), histology and tumor size. Then, we conducted stratified analysis by histology type, stage, region of study and cut-off value for plasma fibrinogen. The effective value of OS, PFS and DFS was determined by the combination of HR and 95% confidence interval (CI). Estimated value was conducted indirectly from Kaplan-Meier plot using the methods reported by Tierney et al. (19) if a direct report of HR and corresponding 95% CI was not available. To assess the reliability, we calculated pooled HRs in studies with multivariate analysis. We employed relative risk (RR), odds ratio (OR) and standardized mean difference (SMD) to evaluate clinicopathological characteristics, including



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

DCR, ORR, tumor stage, lymph node metastasis, distant metastasis, stage, differentiation, ECOG and histology.

Statistical analysis

Significant heterogeneity was identified if I^2 more than 50% and P<0.05 with the Cochran's Q-test and I^2 , then the random-effects model was used. Otherwise, it was calculated by the fixed-effects model without significant heterogeneity. The combination of the estimated risk was calculated by the Z test, and P<0.05 was considered statistically. Publication bias, assessed by rank correlation and linear regression method, was adjusted by the trim and fill method if publication bias existed (P<0.05). The R Statistical Software (version 3.5.1) was performed for statistical analyses. The "meta" package was applied to generate the pooled estimates and publication bias assessment. The "forestplot" package was used to produce forest plot. All P values were two sided.

Results

Trial flow

The result of the study searching process depicts in *Figure 1*. A total of 327 potentially relevant articles were identified, and 83 of them were excluded for the following reasons: 11 cell lines or animals, 8 mechanism researches, 32 method or other treatment researches, 27 comments, reviews, letters

or case reports and 5 published in non-English and non-Chinese language. After reviewing full-text carefully, 20 articles were included in the analysis.

Study characteristics

From 1997 to 2018, a total of 6,494 patients suffering from lung cancer were enrolled into the meta-analysis, the median sample size was 235 (ranged from 58 to 856). In this analysis, cut-off value of plasma fibrinogen was 4.0 g/L in eight studies. Besides, 16 (15-17,20-32), four (22,26,29,31) and 3 studies (25,29,33) were estimated by HR and corresponding 95% CI for OS, PFS and DFS, respectively. Two studies were evaluated by OR for histology (29,33), differentiation (29,33), chemotherapy response (DCR and ORR) (26,31) and performance status (26,33) and four (24,29,33,34) and three articles (24,29,33) for stage and lymph node metastasis, respectively. Furthermore, SMD was applied to appraise the effect of fibrinogen on clinicopathological characteristics, in which four studies (16,31,35,36) for histology and three for distant metastasis (16,24,35), tumor stage (24,35,36) and two for stage (24,35) (Table 1). Fourteen studies (15,20-32) investigated elevated plasma fibrinogen as an indicator of poor OS, and the other two studies (16,17) showed no significant impact on OS. Moreover, three studies (22,26,29) indicated that elevated plasma fibrinogen as a marker for poor PFS, and only one study (31) showed no effect on PFS.

Journal of Thoracic Disease, Vol 11, No 11 November 2019

First author (reference)*	Year	S. of pts.	NP (M/F)	Histology	Stage	Cut-off value	Outcomes
Fan (15)	2018	CN	120 (86/34)	SCLC	LD-ED	400 mg/dL	OS
Li (23)	2018	CN	412 (317/95)	NSCLC, SCLC	I–IV	3.3 mg/dL	OS
Jiang (22)	2017	CN	153 (109/44)	NSCLC	I–IV	4.0 g/L	OS, PFS, tumor size
Pan (17)	2017	CN	355	SCLC	LD-ED	4.0 g/L	OS
Qi (28)	2017	CN	539 (350/189)	NSCLC	I–IV	3.98 g/L	OS
Wang (25)	2017	CN	134 (81/53)	ADC	I–IIIA	4.0 g/L	OS, DFS
Zeng (24)	2017	CN	856 (612/244)	NSCLC	I–IV	3.7 g/L	OS, stage, lymph node metastasis
Zhu (26)	2016	CN	74 (57/17)	SCLC	LD-ED	4.0 g/L	OS, PFS, chemotherapy response, ECOG
Jiang (33)	2014	CN	184 (122/62)	NSCLC	I–IIIA	4.0 g/L	DFS, histology, differentiation, ECOG, stage, lymph node metastasis
Kim (27)	2014	KR	854 (558/296)	NSCLC	IIIA–IV	4.5 g/L	OS
Li (30)	2014	CN	604 (409/195)	NSCLC	I–IV	4.21 g/L	OS
George (34)	2013	UK	564 (305/259)	NSCLC	I–III	4.0 g/L	stage, tumor size
Sheng (29)	2013	CN	567 (428/139)	NSCLC	I–IIIB	4.0 g/L	OS, PFS, DFS, histology, stage, lymph node metastasis
Zhao (31)	2012	CN	160 (102/58)	NSCLC	III–IV	4.4 g/L	OS, PFS, chemotherapy response, differentiation, histology
Jiang (35)	2009	CN	60 (46/14)	NSCLC, SCLC	I–IV	NA	histology
Altiay (20)	2007	TK	78 (73/5)	NSCLC, SCLC	III–IV	380 mg/dL	OS
Jones (36)	2006	UK	93 (62/31)	NSCLC	I–IV	5.0 g/L	histology, tumor size
Unsal (16)	2004	TK	58 (55/3)	NSCLC, SCLC	IB–IV	3.5 g/L	OS, histology
Ferrigno (21)	2001	IT	343 (304/39)	NSCLC, SCLC	NA	447 mg/dL	OS
Buccheri (32)	1997	IT	286 (255/31)	NSCLC, SCLC	I–IV	429 mg/dL	OS

Table 1 Characteristics of studies included from the meta-analysis

*, references as described in manuscript; S. of pts., source of patients; NP, number of patients; TK, Turkey; CN, China; IT, Italy; KR, Korea; UK, United Kingdom; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; NA, not available.

Meta-analysis of OS, PFS and DFS

Figures 2 and *S1-S3* shows results of each meta-analysis. The overall studies were systematic analyzed, with the combined HR 1.44 (95% CI =1.34–1.55), 1.49 (95% CI =1.24–1.80) and 1.69 (95% CI =1.31–2.17) for OS (*Figure 2A*), PFS (*Figure 2B*) and DFS (*Figure 2C*), respectively. In addition, the association was also validated in studies with multivariable analyses (HR=1.48, 95% CI =1.36–1.61 for OS, *Figure S1A*; HR=1.53, 95% CI =1.11–2.12 for PFS, *Figure S1B*). The results were consistent with analysis in overall studies. The pooled HR was 1.46 (95% CI =1.34–1.60) in studies excluded

inflammatory disease (*Figure S2*). As shown in *Figure 3*, the results implied that elevated plasma fibrinogen level effected on poor OS in subgroup analyses about histology type, stage, region of study and cut-off value for plasma fibrinogen. The combined HR was 1.54 (95% CI =1.40–1.69) for NSCLC, 1.25 (95% CI =1.05–1.48) for SCLC, 1.99 (95% CI =1.50–2.65) for stage I–III, 1.52 (95% CI =1.36–1.71) for stage III–IV, 1.45 (95% CI =1.34–1.57), 1.42 (95% CI =1.21–1.67), 1.48 (95% CI =1.35–1.63), 1.39 (95% CI =1.25–1.56) for Asian, non-Asian, China, non-China, respectively. The pooled HRs were 1.40 (95% CI =1.22–1.59), 1.47 (95% CI =1.35–1.59)

Zhang et al. Plasma fibrinogen levels and lung cancer

A	Study	TE	seTE	os	HR	95%–Cl	Weight (fixed)	Weight (random)
	Fan (2018)	0.41	0.1995	- ie	1.50	[1.02: 2.23]	3.4%	4.2%
	Li (2018)	0.36	0.1819	<u></u>	1.43	[1.00; 2.04]	4.1%	4.9%
	Jiang (2017)	0.50	0.2460	<u>t</u>	1.65	[1.02; 2.67]	2.2%	2.9%
	Pan (2017)	0.12	0.1007		1.13	[0.93; 1.38]	13.2%	11.8%
	Qi (2017)	0.57	0.1575	}≡	1.77	[1.30; 2.41]	5.4%	6.2%
	Wang (2017)	0.72	0.2191	1 m	2.04	[1.33; 3.14]	2.8%	3.5%
	Zeng (2017)	0.34	0.1124		1.40	[1.12; 1.74]	10.6%	10.2%
	Zhu (2016)	1.30	0.6214	<u>i</u> +	— 3.66	[1.08; 12.37]	0.3%	0.5%
	Kim (2014)	0.29	0.0855	-	1.34	[1.13; 1.58]	18.4%	14.3%
	Li (2014)	0.51	0.1153	 	1.67	[1.33; 2.09]	10.1%	9.9%
	Sheng (2013)	0.49	0.2219		1.64	[1.06; 2.53]	2.7%	3.5%
	Zhao (2012)	0.51	0.1995		1.67	[1.13; 2.47]	3.4%	4.2%
	Altiay (2007)	0.62	0.2779		1.86	[1.08; 3.21]	1.7%	2.3%
	Unsal (2004)	0.24	0.2849		1.28	[0.73; 2.23]	1.7%	2.2%
	Ferrigno (2001)	0.25	0.1108	1. T	1.28	[1.03; 1.59]	10.9%	10.4%
	Buccheri (1997)	0.48	0.1221		1.61	[1.27; 2.05]	9.0%	9.1%
	Fixed effect model			Å	1.44	[1.34: 1.55]	100.0%	
	Random effects model			\$	1.47	[1.35; 1.60]		100.0%
	Heterogeneity: $I^2 = 21\%$, τ	$^{2} = 0.0$	060, $p = 0.21$		٦			
			0.1	0.5 1 2 1	10			
D							Weight	Weight
В	Study	TE	seTE	PFS	HR	95%-CI	Weight (fixed)	Weight (random)
В	Study Jiang (2017)	TE	seTE 0.1709	PFS	HR 1.44	95%–Cl [1.03: 2.01]	Weight (fixed) 31.0%	Weight (random) 31.2%
В	Study Jiang (2017) Zhu (2016)	TE 0.36 1.29	seTE 0.1709 0.6331	PFS	HR 1.44 — 3.62	95%–Cl [1.03; 2.01] [1.05; 12.52]	Weight (fixed) 31.0% 2.3%	Weight (random) 31.2% 3.0%
B	Study Jiang (2017) Zhu (2016) Sheng (2013)	TE 0.36 1.29 0.53	seTE 0.1709 0.6331 0.1589	PFS	HR 1.44 — 3.62 1.70	95%–Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32]	Weight (fixed) 31.0% 2.3% 35.8%	Weight (random) 31.2% 3.0% 34.7%
В	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012)	TE 0.36 1.29 0.53 0.22	seTE 0.1709 0.6331 0.1589 0.1710	PFS	HR 1.44 - 3.62 1.70 1.25	95%–Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75]	Weight (fixed) 31.0% 2.3% 35.8% 30.9%	Weight (random) 31.2% 3.0% 34.7% 31.1%
В	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012)	TE 0.36 1.29 0.53 0.22	seTE 0.1709 0.6331 0.1589 0.1710	PFS	HR 1.44 - 3.62 1.70 1.25	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75]	Weight (fixed) 31.0% 2.3% 35.8% 30.9%	Weight (random) 31.2% 3.0% 34.7% 31.1%
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Pandom effects model	TE 0.36 1.29 0.53 0.22	seTE 0.1709 0.6331 0.1589 0.1710	PFS	HR - 1.44 - 3.62 1.70 1.25 1.49 1.50	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0%	Weight (random) 31.2% 3.0% 34.7% 31.1%
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model	TE 0.36 1.29 0.53 0.22	seTE 0.1709 0.6331 0.1589 0.1710	PFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0%	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0%
В	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $l^2 = 20\%$, or	TE 0.36 1.29 0.53 0.22 $^{2} = 0.0$	seTE 0.1709 0.6331 0.1589 0.1710 100, <i>p</i> = 0.29	PFS	HR 1.44 - 3.62 1.70 1.25 1.49 1.50	95%-Cl [1.03; 2.01] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% 	Weight (random) 31.2% 30% 34.7% 31.1% 100.0%
В	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, τ	TE 0.36 1.29 0.53 0.22 ² = 0.0	seTE 0.1709 0.6331 0.1589 0.1710 100, p = 0.29 0.1	PFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% 	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0%
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: I ² = 20%, to	TE 0.36 1.29 0.53 0.22 ² = 0.0	seTE 0.1709 0.6331 0.1589 0.1710 100, p = 0.29 0.1	PFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 10	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed)	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0% Weight (random)
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, τ Study	TE 0.36 1.29 0.53 0.22 ² = 0.0 TE	seTE 0.1709 0.6331 0.1589 0.1710 100, <i>p</i> = 0/29 0.1 seTE	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 0 HR	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed)	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0% Weight (random)
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, τ Study Wang (2017)	TE 0.36 1.29 0.53 0.22 $^{2} = 0.0$ TE 0.62	seTE 0.1709 0.6331 0.1589 0.1710 100, $p = 0.29$ 0.1 seTE 0.2268	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 1.0 HR 1.86	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7%	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0% Weight (random) 35.9%
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, or Study Wang (2017) Jiang (2014)	TE 0.36 1.29 0.53 0.22 ² = 0.0 TE 0.62 1.21	seTE 0.1709 0.6331 0.1589 0.1710 100, <i>p</i> = 0 ¹ 29 0.1 seTE 0.2268 0.5234	PFS 0.5 1 2 1 DFS	HR - 1.44 1.70 1.25 1.49 1.50 HR 1.86 - 3.36	95%-Cl [1.03; 2.01] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91] [1.20; 9.37]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7% 6.1%	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0% Weight (random) 35.9% 8.4%
C	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, or Study Wang (2017) Jiang (2014) Sheng (2013)	TE 0.36 1.29 0.53 0.22 $^{2} = 0.0$ TE 0.62 1.21 0.40	seTE 0.1709 0.6331 0.1589 0.1710 100, $p = 0.29$ 0.1 seTE 0.2268 0.5234 0.1659	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 0 HR 1.86 3.36 1.49	95%-Cl [1.03; 2.01] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91] [1.20; 9.37] [1.08; 2.06]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7% 6.1% 61.2%	Weight (random) 31.2% 34.7% 31.1% 100.0% Weight (random) 35.9% 8.4% 55.7%
C	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $l^2 = 20\%$, or Study Wang (2017) Jiang (2014) Sheng (2013) Fixed effect model	TE 0.36 1.29 0.53 0.22 $^{2} = 0.0$ TE 0.62 1.21 0.40	seTE 0.1709 0.6331 0.1589 0.1710 100, $p = 0/29$ 0.1 seTE 0.2268 0.5234 0.1659	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 HR - 1.86 3.36 1.49 1.69	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91] [1.20; 2.91] [1.20; 2.91] [1.08; 2.06] [1.31; 2.17]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7% 6.1% 61.2% 100.0%	Weight (random) 31.2% 3.0% 34.7% 31.1% 100.0% Weight (random) 35.9% 8.4% 55.7%
C	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%, \tau$ Study Wang (2017) Jiang (2014) Sheng (2013) Fixed effect model Random effects model	TE 0.36 1.29 0.53 0.22 ² = 0.0 TE 0.62 1.21 0.40	seTE 0.1709 0.6331 0.1589 0.1710 100, <i>p</i> = 0.29 0.1 seTE 0.2268 0.5234 0.1659	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 1.50 HR 1.86 1.49 1.86 1.49 1.86 1.49 1.86 1.49 1.70 1.70 1.25	95%-Cl [1.03; 2.01] [1.05; 12.52] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91] [1.20; 9.37] [1.08; 2.06] [1.31; 2.17] [1.27; 2.35]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7% 6.1% 61.2%	Weight (random) 31.2% 3.0% 34.7% 1100.0% Weight (random) 35.9% 8.4% 55.7%
B	Study Jiang (2017) Zhu (2016) Sheng (2013) Zhao (2012) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, τ Study Wang (2017) Jiang (2014) Sheng (2013) Fixed effect model Random effects model Heterogeneity: $I^2 = 20\%$, τ	TE 0.36 1.29 0.53 0.22 $^2 = 0.0$ TE 0.62 1.21 0.40	seTE 0.1709 0.6331 0.1589 0.1710 100, $p = 0.29$ 0.1 seTE 0.2268 0.5234 0.1659 1160, $p = 0.29$	PFS 0.5 1 2 1 DFS	HR - 1.44 3.62 1.70 1.25 1.49 1.50 HR - 1.86 1.86 1.49 1.86 1.49 1.69 1.73	95%-Cl [1.03; 2.01] [1.25; 2.32] [0.89; 1.75] [1.24; 1.80] [1.21; 1.86] 95%-Cl [1.20; 2.91] [1.20; 9.37] [1.08; 2.06] [1.31; 2.17] [1.27; 2.35]	Weight (fixed) 31.0% 2.3% 35.8% 30.9% 100.0% Weight (fixed) 32.7% 6.1% 61.2% 100.0%	Weight (random) 31.2% 34.7% 31.1% 100.0% Weight (random) 35.9% 8.4% 55.7% 100.0%

Figure 2 Meta-analysis for assessing the association between plasma fibrinogen and OS (A), PFS (B), DFS (C) of lung cancer. OS, overall survival; PFS, progression-free survival; DFS, disease-free survival.

Subgroups	NS	NP		HR (95% CI)	tau^2	I-squared	Ρ
All patients	16	5593	-	1.44 (1.34–1.55) 0.01	0.21	0.21
Histology							
NSCLC	9	4203	H	1.54 (1.40–1.69)	0.00	0.00	0.47
SCLC	4	607		1.25 (1.05–1.48)	0.05	0.46	0.14
Stage							
1–111	3	948		1.99 (1.50-2.65)	0.02	0.24	0.27
III–IV	6	2060		1.52 (1.36–1.71)	0.01	0.31	0.20
Region							
Asian	14	4964	HH	1.45 (1.34–1.57)	0.01	0.24	0.20
Non-Asian	2	629	⊢ =→	1.42 (1.21–1.67)	0.01	0.48	0.16
China	11	3974	HH	1.48 (1.35–1.63)	0.01	0.33	0.13
Non–China	5	1619	H===	1.39 (1.25–1.56)	0.00	0.00	0.50
Cut-off value	9						
4.0g/L	7	1678		1.40 (1.22–1.59)	0.03	0.46	0.08
non-4.0g/L	10	4190	HI-I	1.47 (1.35–1.59)	0.00	0.00	0.58
			1 1.5 2 HR	2.5			

Overall survival

Figure 3 Meta-analysis in subgroups about histology type, stage, region of study and cutoff value.

Journal of Thoracic Disease, Vol 11, No 11 November 2019

A	Study	Experin Events	nental Total	C Events	ontrol Total	Lym	nph node	metastas	sis	OR	95%-CI	Weight (fixed)	Weight (random)
	Zeng (2017) Jiang (2014) Sheng (2013)	225 56 118	373 74 224	242 64 156	2 483 4 110 5 343		-	-	1 2 1	.51 2.24 .33	[1.15; 1.99] [1.16; 4.29] [0.95; 1.87]	54.2% 8.1% 37.7%	54.6% 9.6% 35.8%
	Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, τ	$p^2 = 0, p = 0$	671 0.39		936		0.5		1	.50 .50	[1.23; 1.84] [1.23; 1.84]	100.0%	 100.0%
							0.5	1 2					
В	Study	Experin Events	nental Total	C Events	ontrol Total		Stage (I	-II/III-IV) ∣		OR	95%-CI	Weight (fixed)	Weight (random)
	Zeng (2017)	230	373	205	5 483				2	2.18	[1.66; 2.87]	46.9%	39.6%
	Jiang (2014)	26	74	14	110			1 1 ×	- 3	3.71	[1.78; 7.76]	5.0%	10.4%
	George (2013)	48	269	31	265			<u></u>	1	.64	[1.01; 2.67]	17.6%	20.1%
	Sheng (2013)	84	224	90	343			- <u>B</u>	1	.69	[1.17; 2.42]	30.5%	29.8%
	Fixed effect model		940		1201				,	01	[1 66 2 44]	100.0%	
	Bandom effects mode	4	040		1201			-	-	2.02	[1.56: 2.61]		100.0%
	Heterogeneity: $l^2 = 35\%$.	$\tau^2 = 0.023$	6. $p = 0$.21		Г	1	Ť	Ъ		[]		10010/0
			.,,			0.2	0.5	12	5				
\sim		Exper	imental		Cor	ntrol	_					Weight	Weight
C	Study T	otal Mean	SD	Total I	lean	SD	Tum	or stage		SMD	95%-C	I (fixed)	(random)
	Zeng (2017)	223 4.33	1,4600	633	3.57 1.2	2400				0.58	f 0.43: 0.74	1 88.4%	34.7%
	Jiang (2009)	27 4.14	1.1600	17	4.69 1.5	5600	-	+11		-0.4	[-1.02; 0.21	5.7%	32.6%
	Jones (2006)	25 4.72	0.3400	68	4.10 0.1	800				2.64	[2.04; 3.24] 5.9%	32.7%
	Fixed effect model Bandom effects model	275		718				\$	_	0.65	[0.50; 0.79] 100.0%	100.0%
	Heterogeneity: $I^2 = 96\%$, $\tau^2 =$	1.3702, p <	0.01					1 1 1		0.00	. [,	1001070
		_				-	3 -2 -1	0 1 2	2 3				
D	Study T	Exper otal Mean	imental SD	Total I	Co: Mean	ntrol SD	Distant	t metasta	sis	SMI	95%-0	Weight (fixed)	Weight (random)
	Zeng (2017)	144 4.06	1.4000	712	3.71 1.3	3300		- 1 4000 - 1 4000		0.2	6 [0.08; 0.44	81.4%	66.5%
	Jiang (2009)	19 4.21	1.1200	41	4.44 1.3	3900 -				-0.1	7 [-0.72; 0.3]	3 8.8%	16.0%
	Unsal (2004)	26 5.87	1.8800	32	5.80 2.1	1500			_	0.0	3 [-0.48; 0.55	6] 9.8%	17.5%
	Fixed effect model	189		785				\sim		0.2	0 [0.04; 0.36] 100.0%	
	Random effects model Heterogeneity: $l^2 = 24\%$, $\tau^2 =$	0.0135.0	0.27					+		0.1	5 [-0.08; 0.39	·]	100.0%
		0.0100, p	0.27				-0.6-0.4-0.	2 0 0.2 0.4	4 0.6				
Е	Study T	Exper otal Mean	imental SD	Total I	Co Mean	ntrol SD	Stage	e (I-II/III-I\	/)	SMD	95%-C	Weight (fixed)	Weight (random)
	Zeng (2017) Jiang (2009)	435 3.98 48 4.38	1.3500	421 12	3.55 1.3 4.32 1.4	3300 4900		+	-	0.3	2 [0.19; 0.46 [-0.59; 0.68	95.7% 4.3%	95.7% 4.3%
	Fixed effect model	483		433				-	-	0.3	[0.18; 0.44	100.0%	
	Random effects model								-	0.3	[0.18; 0.44	1	100.0%
	Heterogénéity: $\Gamma = 0\%$, $\tau^{e} = 0$	0, p = 0.40					-0.6-0.4-0	2 0 0 2 0	4 0 6				

Figure 4 Meta-analysis about TNM stage in lymph node metastasis (A) and stage (B) estimated by odds ratio; tumor stage (C), distant metastasis *vs.* no distant metastasis (D), stage III–IV *vs.* stage I–II (E) estimated by standardized mean difference.

for studies with cut-off value equal to 4 g/L and was not 4 g/L.

Meta-analysis of clinicopathological characteristics

Similarly, the meta-analysis indicated that fibrinogen associated with clinicopathological characteristics. The pooled RRs and corresponding 95% CI were 2.15 (95% CI, 1.11–4.15) and 1.34 (95% CI, 0.68–2.62) for DCR (*Figure S3A*) and ORR (*Figure S3B*), respectively. In meta-analysis about TNM stage, the combined ORs were 1.50 (95% CI, 1.23–1.84) and 2.01 (95% CI, 1.66–2.44) lymph node metastasis (*Figure 4A*) and stage III–IV vs. stage I–II (*Figure 4B*), respectively. Moreover, the SMDs were 0.93 (95% CI, -0.42 to 2.29), 0.20 (95% CI, 0.04–0.36) and 0.31 (95% CI, 0.18–0.44) for tumor stage (*Figure 4C*), distant metastasis vs. no distant

metastasis (*Figure 4D*) and stage III–IV vs. stage I–II (*Figure 4E*). No significance was found in poor differentiation (*Figure S4A*), and performance status (*Figure S4B*). In addition, the results showed no differences in histology (NSCLC and SCLC, adenocarcinoma and squamous cell carcinoma) (*Figure S5A,B,C*). The P value directly combined implied that plasma fibrinogen might affect tumor size ($P=2.82\times10^{-5}$).

Test of beterogeneity

We analyzed the heterogeneity in all included studies between fibrinogen and the prognosis of lung cancer. The heterogeneity, sixteen studies for OS, four studies for PFS, three studies for DFS, were evaluated in a fixed-effects model. Moreover, the heterogeneity of included studies was 21%, 20% and 20% with the I^2 value, respectively. Heterogeneity was no significance in the OS subgroup analysis (*Figure 2A,B,C*).

Publication bias

As shown in *Figures S6*,*S7*, the rank correlation and linear regression method were used to evaluate publication bias of the meta-analysis. We found a significant funnel plot asymmetry, with P=0.011 in the linear regression test and P=0.072 in the rank correlation test, demonstrating the existence of publication bias in OS. However, in PFS and DFS, no significant funnel plot asymmetry was observed, with P=0.323 and P=0.125 in the linear regression test. Furthermore, we used a trim-and-fill method to adjust the bias, which was developed by Duval and Tweedie (37). The adjusted result was similar with our results (HR =1.39, 95% CI, 1.30–1.49) in OS (*Figure S7*).

Discussion

Elevated pretreatment plasma fibrinogen predicted poor prognosis by meta-analysis in epithelial ovarian, digestive cancer (13,14). However, it was inconsistent whether fibrinogen was a prognosis factor in lung cancer. To our knowledge, this is the first systemic analysis about the association between fibrinogen and lung cancer prognosis. We performed a comprehensive analysis including 6,494 patients. It was showed that elevated pretreatment plasma fibrinogen levels could predict poor survival of lung cancer. Subgroup analysis also validated the result, according to region of study, histology type, cut-off value for plasma fibrinogen and HR estimated method for survival. Therefore, fibrinogen could play as a predictive factor of OS, PFS and DFS.

In addition, we also analyzed the association between fibrinogen and clinicopathological characteristics. We observed that elevated plasma fibrinogen affected TNM stage excluding tumor stage due to significant heterogeneity in lung cancer patients. However, plasma fibrinogen did not associate with differentiation and performance status and histology neither ADC vs. SCC nor NSCLC vs. SCLC. Due to limited sample size, the results of DCR and ORR were inconsistent. Considering the smoking was as a risk factor in lung cancer (38), we further found that smoking may affect plasma fibrinogen level and the pooled OR was 2.06 (95% CI, 1.64–2.59) analyzed in two studies (24,29).

In terms of fibrinogen in the prognosis of lung cancer, the evidence supported our conclusion as follow. Stromaderived Fibrinogen-like Protein 2 promote tumor growth by activating cancer-associated fibroblasts in the tumor microenvironment in lung cancer (39). Meanwhile, the study revealed that fibrinogen levels are significantly high among different pathologic types of lung cancer patients (40). In addition, elevated fibrinogen was associated with performance status after lung cancer resection surgery (41). Moreover, high plasma fibrinogen was associated with poorer lymph node status, recurrence and advanced pathologic stage (33). Due to the close relationships between fibrinogen and worse clinical pathological features of lung cancer, the relation between fibrinogen and poor survival of lung cancer was understandable. Plasma fibrinogen level of lung cancer patients reduced obviously after surgery indicated the higher tumor burden the elevated plasma fibrinogen (33). Therefore, the plasma fibrinogen in pretreatment lung cancer may affect prognosis and metastasis by tumor microenvironment.

Though our study provided a relatively convincing conclusion that fibrinogen could play as a prognosis biomarker of lung cancer, certain inevitable limitations should be stated: (I) we did not exclude the study that reported the relation between serum fibrinogen and lung cancer prognosis. Fibrinogen do not exist in serum and we recognized that author was clerical error; (II) studies was excluded due to unavailable data for meta-analysis which may lead to publication bias (35,42,43). Moreover, this metaanalysis indicated existence of publication bias, however, we searched conference abstracts and the heterogeneity test and the trim and fill method demonstrated the conclusion was stable; (III) the therapeutic regimen was different may lead to bias. So, conducting high-quality research is necessary.

Overall, our meta-analysis indicated that pretreatment may as a poor prognosis factor in lung cancer. Moreover, plasma fibrinogen associated with TNM stage rather than ORR. Nonetheless, a well-designed prospective study with a large sample to confirm our results and cover the above limitations is essential.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 The score of included studies for meta-analysis

Study (reference)*	Year	А	В	С	D	Е	F	G	Н	Quality score (0-8)
Fan (15)	2018	Y	Y	Y	Y	Y	Y	Ν	Y	7
Li (23)	2018	Y	Y	Y	Υ	Υ	Υ	Y	Ν	7
Jiang (22)	2017	Y	Y	Y	Υ	Υ	Ν	Y	Ν	6
Pan (17)	2017	Y	Y	Y	Ν	Υ	Υ	Ν	Ν	5
Qi (28)	2017	Y	Ν	Y	Υ	Ν	Υ	Y	Ν	5
Wang (25)	2017	Y	Ν	Y	Υ	Ν	Ν	Y	Ν	4
Zeng (24)	2017	Y	Y	Y	Υ	Υ	Υ	Ν	Ν	6
Zhu (26)	2016	Y	Y	Y	Υ	Υ	Υ	Ν	Ν	6
Jiang (33)	2014	Y	Ν	Y	Υ	Υ	Υ	Ν	Ν	5
Kim (27)	2014	Y	Y	Y	Υ	Υ	Υ	Y	Ν	7
Li (30)	2014	Y	Y	Y	Ν	Υ	Υ	Y	Y	7
George (34)	2013	Y	Y	Ν	Ν	Υ	Ν	Ν	Ν	3
Sheng (29)	2013	Y	Y	Y	Υ	Υ	Υ	Y	Ν	7
Zhao (31)	2012	Y	Y	Y	Υ	Υ	Υ	Y	Ν	7
Jiang (35)	2009	Y	Y	Y	Υ	Υ	Ν	Ν	Ν	5
Altiay (20)	2007	Y	Ν	Y	Υ	Υ	Υ	Y	Ν	6
Jones (36)	2006	Y	Y	Ν	Ν	Υ	Υ	Ν	Ν	4
Unsal (16)	2004	Y	Y	Y	Υ	Υ	Ν	Y	Ν	6
Ferrigno (21)	2001	Y	Ν	Ν	Y	Υ	Ν	Y	Ν	4
Buccheri (32)	1997	Y	Ν	Y	Ν	Y	Y	Ν	Ν	4

*, references as described in manuscript; A, hypothesis and/or objective(s) stated; B, tumor stage clearly described; C, clear description of eligibility criteria; D, patients with inflammatory disease or coagulation disorders excluded; E, predictors and outcome(s) clearly predefined; F, confounders considered in multivariate analysis; G, long enough for outcomes to occur; H, bias and limitations considered; Y, yes; N, no.

A Study	TE	seTE	OS (m	ultivar)		HR	95	%–CI	Weight (fixed)	Weight (random)
Fan (2018)	0.41	0.1995				1.50	[1.02;	2.23]	4.6%	4.6%
Li (2018)	0.36	0.1819				1.43	[1.00;	2.04]	5.5%	5.5%
Jiang (2017)	0.50	0.2460				1.65	[1.02;	2.67]	3.0%	3.0%
Pan (2017)	0.10	0.1653	-	a		1.10	[0.80;	1.52]	6.7%	6.7%
Wang (2017)	0.72	0.2191		<u> </u>		2.04	[1.33;	3.14]	3.8%	3.8%
Zeng (2017)	0.34	0.1124		- <u>+</u> -		1.40	[1.12;	1.74]	14.5%	14.5%
Zhu (2016)	1.30	0.6214				3.66	[1.08; *	12.37]	0.5%	0.5%
Kim (2014)	0.29	0.0855		•		1.34	[1.13;	1.58]	25.0%	25.0%
Li (2014)	0.51	0.1153		-		1.67	[1.33;	2.09]	13.7%	13.7%
Sheng (2013)	0.49	0.2219				1.64	[1.06;	2.53]	3.7%	3.7%
Zhao (2012)	0.51	0.1995		- <u>i</u> æ		1.67	[1.13;	2.47]	4.6%	4.6%
Unsal (2004)	0.24	0.2849	_			1.28	[0.73;	2.23]	2.2%	2.2%
Buccheri (1997)	0.48	0.1221				1.61	[1.27;	2.05]	12.2%	12.2%
Fixed effect model						1.48	[1.36;	1.61]	100.0%	
Random effects model				\$		1.48	[1.36;	1.61]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p	= 0.46								
		0.1	0.5	12	10					
B Study	TE	seTE	PFS (m	ultivar)		HR	95	%–CI	Weight (fixed)	Weight (random)
,									(,	(*******)
Jiang (2017)	0.36	0.1709				1.44	[1.03;	2.01]	93.2%	71.9%
Zhu (2016)	1.29	0.6331				3.62	[1.05;	12.52]	6.8%	28.1%
Fixed effect model				\diamond		1.53	[1.11;	2.12]	100.0%	
Random effects model			-			1.87	[0.83;	4.21		100.0%
Heterogeneity: $I^2 = 49\%$. τ^2	$^{2} = 0.2$	2099, p = 0.16		i ı			,			
2		0.1	0.5	12	10					

Figure S1 Meta-analysis for assessing the association between plasma fibrinogen and OS (A) and PFS (B) in studies with multivariable analyses in lung cancer. OS, overall survival; PFS, progression-free survival; multivar, analysis in studies with multivariable analyses.

Study	TE	seTE	OS (ex-	inflam)	ł	IR	95	%–CI	Weight (fixed)	Weight (random)
Fan (2018)	0.41	0.1995			1.	50	[1.02;	2.23]	5.0%	5.0%
Li (2018)	0.36	0.1819			1.	43	[1.00;	2.04]	6.0%	6.0%
Jiang (2017)	0.50	0.2460			1.	65	[1.02;	2.67]	3.3%	3.3%
Qi (2017)	0.57	0.1575		- <u>-</u>	1.	77	[1.30;	2.41]	8.0%	8.0%
Wang (2017)	0.72	0.2191		<u> </u>	2.	04	[1.33;	3.14]	4.1%	4.1%
Zeng (2017)	0.34	0.1124		+	1.	40	[1.12;	1.74]	15.7%	15.7%
Zhu (2016)	1.30	0.6214			<u> </u>	66	[1.08; 1	2.37]	0.5%	0.5%
Kim (2014)	0.29	0.0855		· ·	1.	34	[1.13;	1.58]	27.1%	27.1%
Sheng (2013)	0.49	0.2219		<u> </u>	1.	64	[1.06;	2.53]	4.0%	4.0%
Zhao (2012)	0.51	0.1995			1.	67	[1.13;	2.47]	5.0%	5.0%
Altiay (2007)	0.62	0.2779			1.	86	[1.08;	3.21]	2.6%	2.6%
Unsal (2004)	0.24	0.2849	_	-	1.	28	[0.73;	2.23]	2.4%	2.4%
Ferrigno (2001)	0.25	0.1108		-	1.	28	[1.03;	1.59]	16.2%	16.2%
Fixed effect model				\$	1.	46	[1.34;	1.60]	100.0%	
Random effects mode	el			ò	1.	46	[1.34;	1.60]		100.0%
Heterogeneity: $I^2 = 0\%$, a	$c^2 = 0, p$	= 0.56								
		(0.1 0.5 1	2	10					

Figure S2 Meta-analysis for assessing the association between plasma fibrinogen and OS in excluded inflammatory disease or coagulation disorders group. OS, overall survival; ex-inflam, analysis in studies excluded inflammatory disease or coagulation disorders.

A Study	Experim Events	iental Total	Co Events	ontrol Total	D	CR	RR	95%-CI	Weight (fixed)	Weight (random)
Zhu (2016) Zhao (2012)	10 22	42 98	3 7	32 62	-		—— 2.54 — 1.99	[0.76; 8.48] [0.90; 4.38]	28.4% 71.6%	30.0% 70.0%
Fixed effect model Random effects mode Heterogeneity: $f^2 = 0\%$, τ^2	$p^{2} = 0, p = 0$	140 .74		94	0.2 0.5	1 2	- 2.15 - 2.14	[1.11; 4.15] [1.11; 4.14]	100.0%	 100.0%
B Study	Experim Events	iental Total	Co Events	ontrol Total	0	RR	RR	95%-CI	Weight (fixed)	Weight (random)
Zhu (2016) Zhao (2012)	23 77	42 98	9 47	32 62	-		1.95 1.04	[1.05; 3.61] [0.87; 1.23]	15.1% 84.9%	40.6% 59.4%
Fixed effect model		140		94			1.17	[0.98; 1.41]	100.0%	
Random effects mode Heterogeneity: $I^2 = 78\%$, γ	$l_{\tau^2} = 0.1893$	3, <i>p</i> = 0	0.03		0.5		- 1.34	[0.68; 2.62]		100.0%

Figure S3 Meta-analysis about DCR (A), ORR (B) estimated by odds ratio. DCR, disease control rate; ORR, objective response rate.

A Study	Experiment Events Tot	al Co al Events	ontrol Total	Differentiation	OR	95%-CI	Weight (fixed)	Weight (random)
Jiang (2014) Sheng (2013)	20 94 22	74 22 24 146	110 343		- 1.48 0.98	[0.74; 2.97] [0.69; 1.37]	16.2% 83.8%	22.8% 77.2%
Fixed effect model Random effects mode Heterogeneity: $I^2 = 11\%$,	29 $\tau^2 = 0.0094, p$	98 = 0.29	453		1.06 1.07	[0.78; 1.44] [0.76; 1.51]	100.0% 	 100.0%
				•·• · _				
B Study	Experiment Events Tot	al Co al Events	ontrol Total	ECOG	OR	95%-CI	Weight (fixed)	Weight (random)
B Study Zhu (2016) Jiang (2014)	Experiment Events Tot 34 19	al Co al Events 42 22 74 27	Total 32 110	ECOG	OR 1.93 1.06	95%–Cl [0.66; 5.65] [0.54; 2.09]	Weight (fixed) 22.8% 77.2%	Weight (random) 28.6% 71.4%

Figure S4 Meta-analysis about differentiation (A) and performance status (B). ECOG, Eastern Cooperative Oncology Group.



Figure S5 Meta-analysis about histology in ADC vs. SCC (A) estimated by odds ratio, NSCLC vs. SCLC (B), ADC vs. SCC (C) estimated by standardized mean difference. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma.



Figure S6 Publication bias of meta-analysis assessing the association between plasma fibrinogen and overall survival and progression-free survival of lung cancer in rank correlation method (A,B) and linear regression method (C,D).



Figure S7 Adjusting the bias using a trim-and-fill method in the association between plasma fibrinogen and overall survival with rank correlation method (A), linear regression method (B) and funnel plot (C).