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Prognostic Value of Pretreatment D-Dimer Level in Small-Cell Lung Cancer: A Meta-Analysis

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Abstract

Purpose: Pretreatment plasma D-dimer has been reported to be a potential prognostic indicator of lung cancer. To determine the prognostic significance of pretreatment D-dimer level in predicting clinical outcomes, such as the overall survival (OS) and progression-free survival (PFS), of patients with small cell lung cancer (SCLC). **Methods:** A systematic search in PubMed, Web of Science, EMBASE, Cochrane Library, CNKI, SinoMed, Wanfang and VIP databases was performed to identify available studies. The pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were applied to assess the association of pretreatment D-dimer level with prognosis of SCLC patients. All statistical analyses were conducted via the STATA 12.0 version software. **Results:** A total of 7 studies involving 964 patients were included in this meta-analysis and all patients were from China. The results showed that elevated pretreatment D-dimer level was significantly correlated with worse OS (HR = 1.90, 95% CI: 1.55-2.34, $P < 0.001$) and PFS (HR = 1.52, 95% CI: 1.24-1.85, $P<0.001$). Subgroup analyses based on the treatment, D-dimer cut-off, detection method and source of HR were also performed to further verify the prognostic value of pretreatment D-dimer level in SCLC. **Conclusions:** Pretreatment blood concentration of D-dimer may deserve as a reliable factor to predict prognosis of Chinese patients with SCLC. More well-designed prospective studies with large samples are still needed to verify our findings.

Keywords

D-dimer, small cell lung cancer, prognosis, meta-analysis

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Introduction

Lung cancer is the leading cause of cancer-related deaths globally.[1] In 2014, it was estimated that 781,000 new cases of lung cancer and 682,000 deaths due to lung cancer occurred in China.[2] Small cell lung cancer (SCLC) accounts for appropriately 15% of all lung cancer cases.[2] Although several achievements have been witnessed in the diagnosis and treatment of SCLC, the prognosis of this cancer remains poor. It is important to identify effective risk assessment factors and treatment strategies to improve the prognosis of SCLC.

Several studies have reported hemostatic abnormalities in malignancies and hypercoagulability is associated with many factors.[3-5] The release of inflammatory cytokines, inhibition of natural anticoagulants, and expression of hemostatic proteins in tumor cells leads to the activation of the coagulation system and hyperfibrinolysis.[6,7] D-dimer is a degradation product of fibrin monomers that is crosslinked by activated factor XIII and hydrolyzed by fibrinolytic enzyme.[8] It is also a marker of fibrinolysis and its concentration in blood can reflect the degree of activation of the coagulation system and fibrinolytic system.[8]

Previous studies have demonstrated a strong relationship between high pretreatment D-dimer level and poor prognosis of lung cancer, especially in Asian patients.[9-11] It has been proven that enhanced coagulation and hyperfibrinolysis promote tumor progression and metastasis in non-small lung cancer.[12,13]As a major histology type of lung cancer, SCLC is characterized by rapid progression, high invasive ability and high incidence of endocrine abnormalities or carcinoid

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syndrome.[2] The prognosis of SCLC patients is fairly poor.[1,2] Therefore, it is imperative to identify factors that can predict the survival of patients accurately and develop optimal treatment strategies for SCLC patients.

Several studies have explored the association between pretreatment D-dimer level and the prognosis of patients with SCLC,[14-20] but findings from such studies have been inconsistent. Thus, we conducted this meta-analysis to determine prognostic value of pretreatment D-dimer level in SCLC.

Methods

Search Strategy

A comprehensive search for relevant studies was conducted in the PubMed, Web of Science, EMBASE, Cochrane library, CNKI, SinoMed, VIP, and Wanfang databases from January 1, 1966 to May 28, 2019. The following search strategy was applied: (D-dimer) AND (cancer OR tumor OR carcinomas OR neoplasm) AND (pulmonary OR lung). The references of included articles were also reviewed manually to identify additional studies.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) articles investigating the correlation of pretreatment plasma D-dimer level with prognosis of patients with SCLC; (2) levels of D-dimer were collected before any treatment including surgery, chemotherapy, radiotherapy and targeted therapy; (3) the hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) or progression-free survival (PFS) were reported in articles directly or they could be calculated from the provided data indirectly.

Exclusion criteria were: (1) letters, editorials, expert opinions, case reports, and reviews; (2) articles with insufficient data; (3) duplicate or overlapping studies; (4) patients with thrombosis or homeostasis disorders; (5) patients with other malignant diseases other than SCLC; (6) patients with severe heart, liver, kidney or infectious diseases; (7) patients receiving anticoagulant or anti-aggregate therapies; (8) patients with venous or arterial thromboembolism.

Literature retrieval and selection were performed by 2 independent investigators.

Data Collection

Data were collected from studies by 2 authors independently. Any disagreement was settled through team discussion. The following data were collected from the selected studies: the name of first author for each study, publication time, study design, study period, sample size, sex ratio, tumor-node-metastasis (TNM) stage, treatment, cut-off value, detection method, endpoint events with corresponding HRs and 95% CIs and source of HR.

Statistical Analyses

In the meta-analysis, the association of pretreatment D-dimer level with long-term survival of patients with SCLC was measured based on the pooled HR with 95% CI; and they were estimated from the Kaplan-Meier curves as described before.[21] if they were not presented directly in the articles. Statistical heterogeneity among studies was calculated using the Cochran's Q test and Higgins I^2 statistic; significant heterogeneity was defined as $P < 0.05$ and/or $I^2 > 50\%$.[22] The random-effects model was adopted to calculate the pooled effect estimates if significant heterogeneity was observed, otherwise the fixed-effects model was applied. All statistical analyses were conducted by using STATA (version 12.0; Stata Corporation).

Quality Assessment

The quality of eligible studies was measured based on the Newcastle-Ottawa quality assessment scale (NOS) by 2 researchers independently.[23] The NOS contains 3 parameters: selection, comparability, and outcomes. Studies with 6 or higher points were considered as high-quality studies.

Results

Basic Characteristics of Selected Studies

Results shown in Figure 1 indicate that 3258 records were identified from the searched databases. After eliminating duplicates, 2512 articles were found to be eligible. After reading the titles and abstracts of the studies, 2490 articles were excluded. Next, we read the full texts of 22 studied which were found to be eligible. In the end, 7 articles involving 964 patients were included in this meta-analysis.

All included studies were retrospective and from China, with sample sizes ranging from 57 to 393. The cut-off value of DD was 0.5 mg/L or 0.55 mg/L. Other details are summarized in Table 1.

Association of Pretreatment D-Dimer Level With OS

A total of 6 studies involving 804 patients investigated the association of pretreatment D-dimer level with OS in SCLC patients. The fixed-effects model was adopted because no significant heterogeneity was found ($I^2 = 0.0\%$, $P = 0.551$). A pooled HR of 1.90 (95% CI: 1.55-2.34; $P < 0.001$) indicated that elevated pretreatment D-dimer level was significantly associated with worse OS (Figure 2; Table 2).

The results of subgroup analyses stratified by the type of treatment, cut-off value of D-dimer, detection method and source of HR were similar to those of pooled results and none of these factors affected the prognostic value of pretreatment D-dimer in SCLC patients (Table 2).

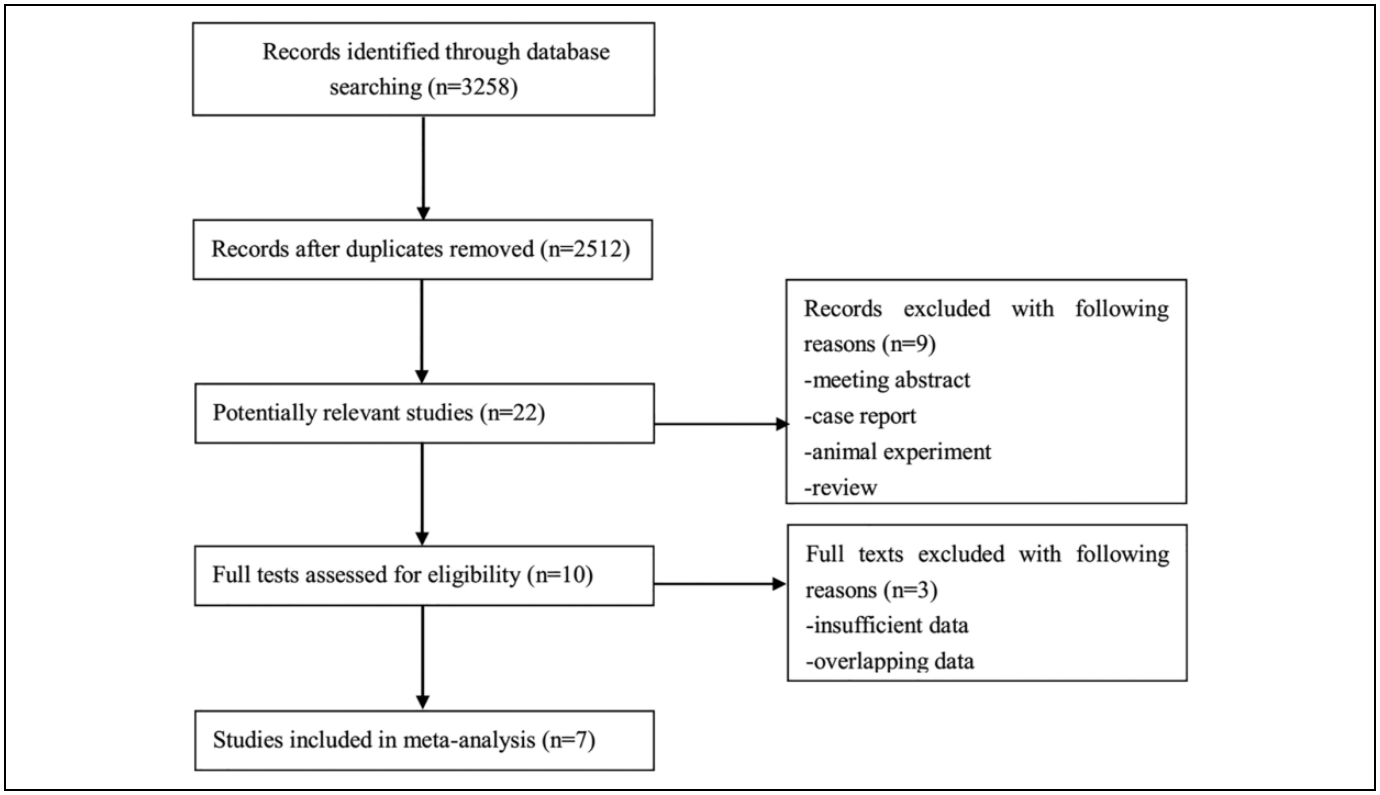

Figure 1. Flow diagram of the literature review.

Table 1. Basic Characteristics of Included Studies.

Author	Year	Study period	Sample size	F/M	TNM stage	Treatment	DD cut-off	Detection method	Endpoint	Source of HR	NOS score
Zhu L [14]	2015	2009-2014	74	17/57	I-IV	CRT	0.55	Immunoturbidimetric assay	OS/PFS	R	8
Chen Y [15]	2016	2004-2014	393	71/322	I-IV	CRT	0.5	Immunoturbidimetric assay	OS/PFS	R	8
Jiang X [16]	2017	2010-2013	107	23/84	I-IV	CRT	0.55	NR	OS	R	7
Zhang C [17]	2018	2011-2016	160	31/129	I-IV	CRT	0.5	Nephelometry immunoassay	PFS	E	7
Chen R [18]	2018	2010-2016	91	22/69	I-IV	Mixed	0.55	NR	OS	E	7
Chen C [19]	2019	2005-2017	57	15/42	I-III	Surg	0.5	Latex assay	OS	R	8
Fan S [20]	2019	2012-2015	82	15/67	I-IV	CRT	0.55	Immunoturbidimetric assay	OS/PFS	R	8

F: female; M: male; TNM: tumor node metastasis; CRT: chemoradiotherapy; Surg: surgery; DD: D-dimer; NR: not reported; R: reported; E: estimated; OS: overall survival; PFS: progression free survival; HR: hazard ratio; NOS: Newcastle-Ottawa scale.

Association of Pretreatment D-dimer Level With PFS

Only 4 studies involving 709 patients explored the impact of pretreatment D-dimer level on PFS in SCLC patients. Patients in the low D-dimer level group had a significantly longer PFS compared with those in the high D-dimer level group (HR = 1.52, 95% CI: 1.24-1.85, $P<0.001$) with no heterogeneity ($I^2 = 0.0\%$, $P = 0.578$). (Figure 3) (Table 2).

Subgroup analysis was conducted based on the cut-off value of D-dimer, detection method and source of HR to further determine the correlation between pretreatment D-dimer level and PFS in SCLC patients and none of these 3 factors were found to affect the prognostic value of pretreatment D-dimer in SCLC (Table 2).

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed to assess the stability of pooled results by excluding each study from the meta-

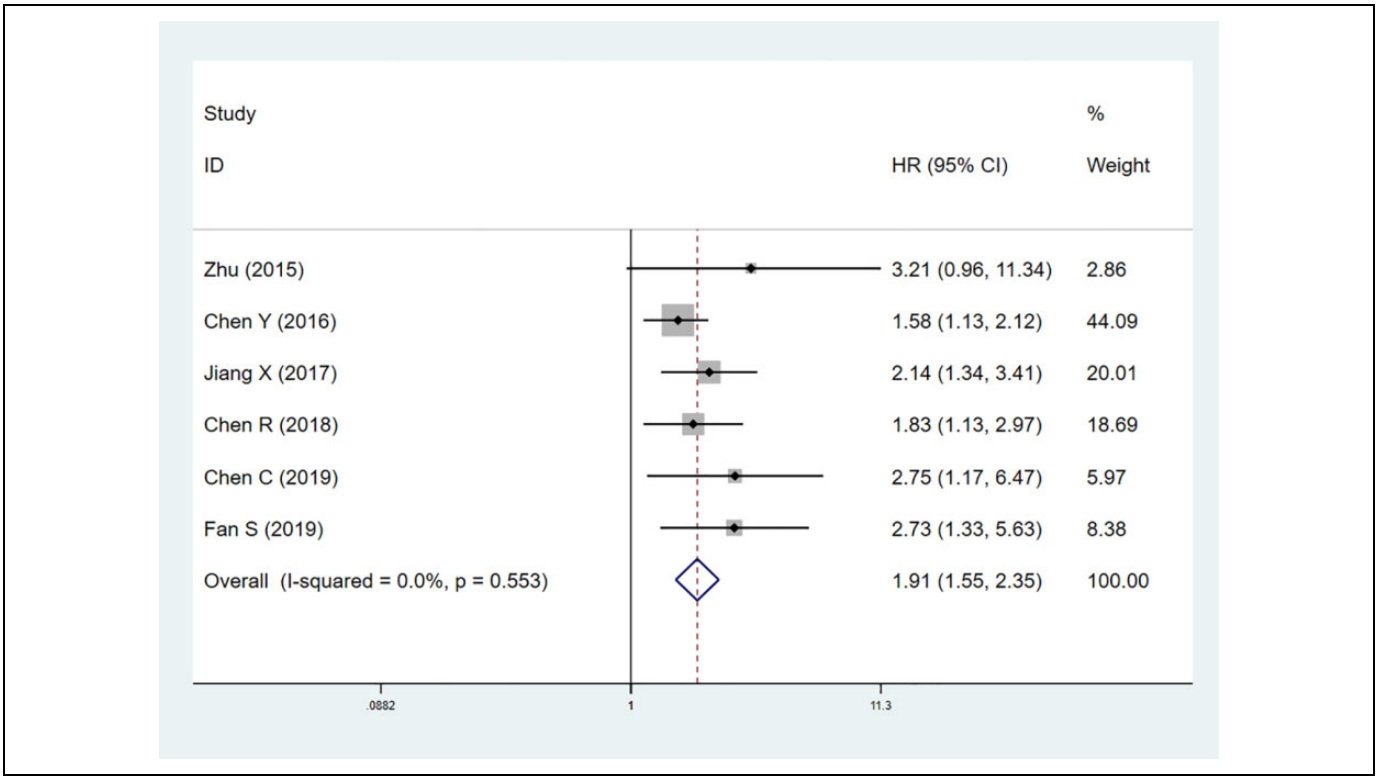

Figure 2. Forest plot of the association between pretreatment D-dimer level and overall survival. HR: hazard ratio; CI: confidence interval.

Table 2. Meta and Subgroup Analyses.

	No. of studies	HR	95% CI	P value	Heterogeneity (P, I^2 (%))
Overall survival	6	1.90	1.55-2.34	<0.001	0.551, 0.0
Treatment					
Chemoradiotherapy	3	1.87	1.47-2.37	<0.001	0.357, 7.2
Surgery	1	2.75	1.17-6.47	0.021	-
Mixed	1	1.83	1.13-2.97	0.011	-
Cut-off					
0.55	4	2.15	1.60-2.89	<0.001	0.740, 0.0
0.5	2	1.69	1.26-2.26	<0.001	0.235, 29.2
Detection method					
Immunoturbidimetric assay	3	1.78	1.34-2.35	<0.001	0.248, 28.3
Latex assay	1	2.75	1.17-6.47	0.021	-
Source of HR					
Reported	5	1.92	1.52-2.42	<0.001	0.412, 0.0
Estimated	1	1.83	1.13-2.97	0.011	-
Progression-free survival	4	1.52	1.24-1.85	<0.001	0.578, 0.0
Cut-off					
0.55	2	2.15	1.15-4.04	0.017	0.454, 0.0
0.5	2	1.46	1.18-1.80	<0.001	0.770, 0.0
Detection method					
Immunoturbidimetric assay	3	1.52	1.19-1.93	0.001	0.373, 0.0
Nephelometry immunoassay	1	1.52	1.07-2.15	0.013	-
Source of HR					
Reported	3	1.52	1.19-1.93	0.001	0.373, 0.0
Estimated	1	1.52	1.07-2.15	0.013	-

HR: hazard ratio; CI: confidence interval.

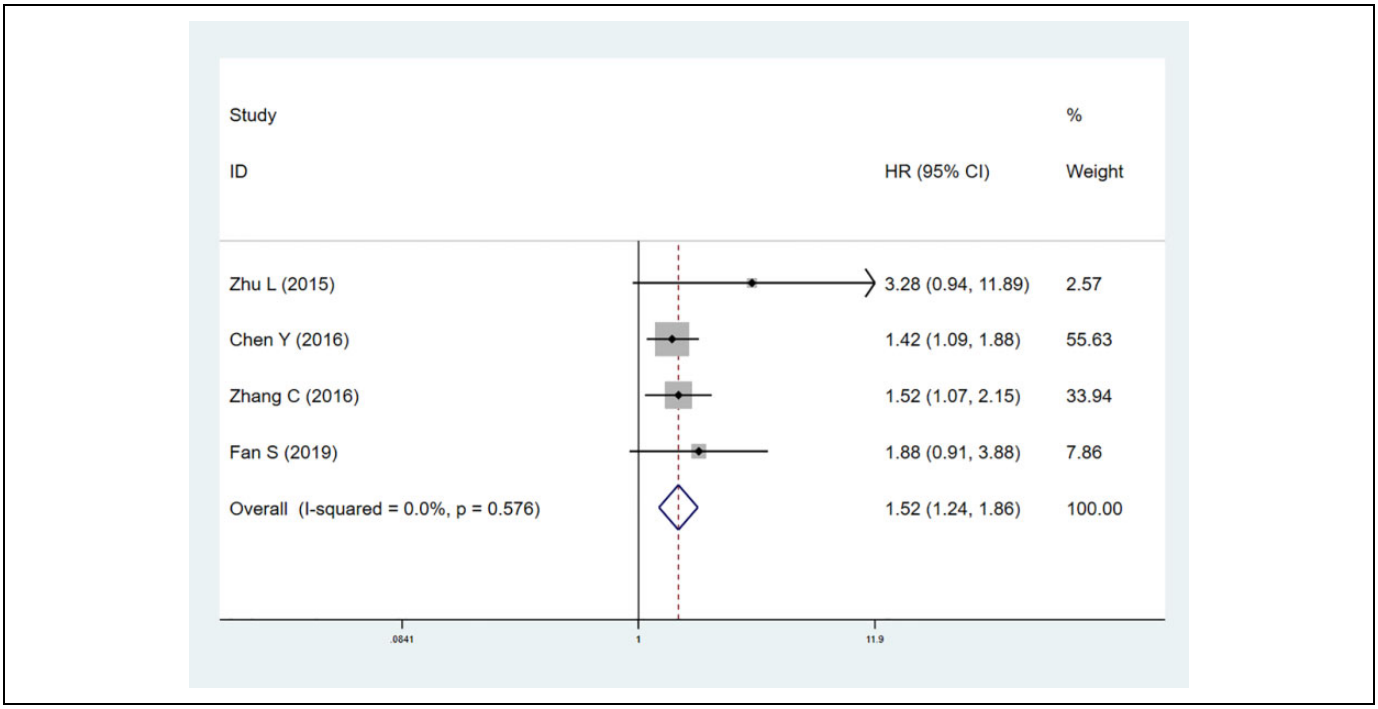

Figure 3. Forest plot of the association between pretreatment D-dimer and progression-free survival. HR: hazard ratio; CI: confidence interval.

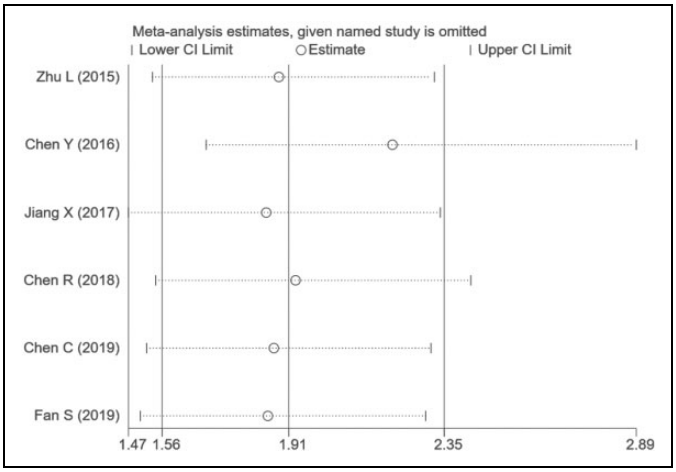

Figure 4. Sensitivity analysis of the association between pretreatment D-dimer and overall survival.

analysis at time. Results indicated that the pooled results were stable (Figure 4).

Discussion

This meta-analysis summarized the data of 7 retrospective studies involving a total of 964 patients with SCLC. Results showed that patients with low pretreatment D-dimer level had better OS and PFS than patients those with high pretreatment D-dimer level. Our results are consistent with those reported by Ma et al.[11] in lung cancer. This meta-analysis therefore suggests that pretreatment plasma D-dimer level may be a promising biomarker for predicting the survival of patients with SCLC.

Several studies investigated the association of D-dimer level with cancer.[11,24,25] Han et al. found a significant association between elevated D-dimer level and the risk of occult cancer in patients with unprovoked venous thromboembolism (VTE).[26] Elsewhere, Fei et al. proved that both levels of D-dimer and tissue factor pathway inhibitor-1 (TFPI-1) can predict deep vein thrombosis (DVT) in cancer patients.[27] This implies that the poor prognosis of patients with elevated D-dimer level may be due to the high incidence of venous thrombosis in cancer patients.[28] Furthermore, Heit et al. reported that tumor cells may not only activate coagulation system, but also damage vascular endothelial cells and increase platelet activity.[29] Another study reported that activation of coagulation system correlated with invasive biological behavior of tumors.[30] Mechanistically, this may be due to the knowledge that tumor cells can destroy the function of normal cells by releasing some cytokines and proteins which disrupt the balance between anticoagulation and fibrinolysis, causing the release of cytokines and agglutinants such as cancer procoagulants and tissue factors.[31] Second, tumor cells can cause abnormal activation of coagulation-fibrinolysis system by secreting tissue factors and some inflammatory factors, such as the IL-1β and TNF-α.[32] Third, it has been reported that there is a significant correlation of plasma D-dimer levels with the vascular endothelial growth factor (VEGF) which is the most important angiogenic factor regulating angiogenesis in lung cancer.[31,33]

As for the clinical significance of D-dimer in SCLC, it is currently unclear whether anticoagulant treatment before cancer-specific treatment will improve the long-term prognosis

of cancer patients. In addition, the relationship between pretreatment D-dimer and the clinicopathological characteristics of SCLC such as clinical stage of disease and histologic tumor type remains poorly defined. Moreover, the prognostic value of dynamic changes in D-dimer levels during treatment is not clear, especially in patients receiving chemoradiotherapy.

Further studies are needed to determine the clinical significance of D-dimer in SCLC. Subgroup analysis based on the TNM stage is important because D-dimer level is associated with tumor progression.[17] It may be better to determine the optimal cut-off value of D-dimer based on the receiver operating characteristics (ROC) curve or other statistical methods rather than literature reports.

There are several limitations in the current meta-analysis. First, only 7 retrospective studies with 964 patients from China were identified, which may present some level of bias. Second, subgroup analysis based on baseline information of patients, such as the TNM stage, gender and age, could not been conducted due to the lack of original data.

In conclusion, elevated pretreatment D-dimer level is associated with poor prognosis of Chinese SCLC patients. However, more multicenter prospective studies are required to further verify the prognostic role of D-dimer in SCLC.

Author Contribution

Jialong Li and Yan Wang contributed equally to this work. Guowei Che conceived and designed the analyses. Jialong Li and Yan Wang performed the literature search and selection, collected data and wrote the paper. Jue Li performed statistical analyses. All authors contributed substantially to its revision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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Informed Consent

Informed consent was obtained from all individual participants included in this study.

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