

Prognostic value of pretreatment D-dimer level in small-cell lung cancer: a meta-analysis

Yan Wang

Sichuan University West China Hospital

Jialong Li

Sichuan University West China Hospital

Yanming Wu

Sichuan University West China Hospital

Jue Li

Sichuan University West China Hospital

Guwei Che (✉ hxxiongwei@126.com)

Sichuan University West China Hospital <https://orcid.org/0000-0003-2187-6346>

Research article

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Abstract

Purpose 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 big samples are still needed to verify our findings.

Background

Lung cancer is the leading cause of cancer-related death globally [1]. In 2014, it was estimated that 781 thousand new lung cancer cases and 682 thousand lung cancer deaths occurred in 2014 China [2]. Small cell lung cancer (SCLC) accounts for appropriately 15% of all lung cancer cases [2]. Despite the significant progress on the diagnosis and treatment of SCLC, the prognosis remains poor. More effective and reliable factors which contribute to risk assessment and therapy strategy formulation are urgently needed in clinic.

Hemostatic abnormalities in malignancies has been reported by a mass of studies 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 all lead to the activation of the coagulation system and hyperfibrinolysis [6,7]. D-dimer is a specific degradation product of fibrin monomers crosslinked by activated factor XIII and hydrolyzed by fibrinolytic enzyme [8]. Meanwhile, it is also a marker of fibrinolysis and its concentration in blood signifies the activating degree of coagulation system and [fibrinolytic system](#) [8].

Previous studies have demonstrated the significant 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 are associated with the risk of tumor progression and metastasis in non-small lung cancer (NSCLC) [12,13].

As the other major histology type of lung cancer, SCLC is widely known for its rapid progression, high invasive ability and high incidence of endocrine abnormalities or carcinoid syndrome [2]. The prognosis of SCLC patients remains fairly poor [1,2]. Therefore, how to predict the survival accurately and develop the optimal treatment strategy for each SCLC patient is still an urgent problem we need to solve.

Although accumulating evidence has explored the association between pretreatment D-dimer level and the prognosis of patients with SCLC [14-20], their results are inconsistent. Thus, we conducted the current meta-analysis to further determine prognostic value of pretreatment D-dimer level in SCLC.

Methods

Search strategy

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

Inclusion and exclusion criteria

Inclusion criteria were as follow: (1) articles investigating the correlation of the pretreatment plasma D-dimer level and 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 with provided data indirectly.

Exclusion criteria were as follow: (1) letters, editorials, expert opinions, case reports, and reviews; (2) articles with insufficient data; (3) duplicative or overlapped 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.

The literature retrieval and selection work were finished by two independent investigators (Yan Wang and Jialong Li)

Data collection

All the data needed were extracted by two authors (Yan Wang and Jialong Li) independently. Any disagreement was settled by team discussion. The following data were collected from all retrieved 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 this meta-analysis, the association of pretreatment D-dimer level and long-term survival of patients with SCLC was measured by the pooled HR with 95% CI; and they were estimated from the Kaplan-Meier curves according to the methods reported by Tierney et al. [21] if they were not presented directly in the articles. The statistical heterogeneity among studies was calculated via the Cochran's Q test and Higgins I^2 statistic; and 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 the significant heterogeneity analysis was observed, otherwise the fixed-effects model was available. All statistical analyses were conducted by using STATA (version 12.0; Stata Corporation).

Quality assessment

The quality of eligible studies was measured by the NOS (Newcastle-Ottawa quality assessment scale) [23]. The NOS contains three parameters: selection, comparability, and outcomes. Studies with 6 or higher points were considered as high-quality studies and quality assessment was performed by two researchers independently (Yan Wang and Jialong Li).

Results

Literature retrieval process and basic characteristics of included studies

As shown in Figure 1, initially 3258 records were identified through database searching. After eliminating the duplicates, 2512 articles were detected for eligibility. Then, the full texts of 22 studied were read after excluding 2490 records by reading titles and abstracts. In the end, 7 articles involving 964 patients were included in this meta-analysis.

All included studies were retrospective and from China, with the sample size ranged from 57 to 393. The cut-off value of D-dimer was 0.5 mg/L or 0.55 mg/L. Other information was summarized in Table 1.

Association between pretreatment D-dimer level and OS

A total of 6 studies involving 804 patients manifested the relation of pretreatment D-dimer level with OS of SCLC patients. The fixed-effects model was adopted because no significant heterogeneity was detected ($I^2=0.0%$, $P=0.551$). The 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 treatment, cut-off value of D-dimer, detection method and source of HR were similar to the pooled result and none of these factors had an influence on the prognostic value of pretreatment D-dimer in SCLC patients (Table 2).

Association between pretreatment D-dimer level and PFS

Only 4 studies involving 709 patients explored the impact of pretreatment D-dimer level on PFS of SCLC patients. Patients in the low D-dimer level group had a significantly prolonged PFS compared with patients 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).

We also conducted subgroup analysis based on the cut-off value of D-dimer, detection method and source of HR to further determine the significant correlation between pretreatment D-dimer level and PFS of SCLC patients and none of these three factors caused an impact on 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 every single study from the meta-analysis each time. It indicated that the results of the current meta-analysis were stable (Figure 4).

Discussion

This meta-analysis summarized the data of 7 retrospective studies involving a total of 964 patients with SCLC and demonstrated that patients with low pretreatment D-dimer level had improved OS and PFS than patients with high pretreatment D-dimer level. Our results were consistent with the ones of Ma et al. [24] who conducted a meta-analysis to testify prognostic significance of pretreatment D-dimer in lung cancer. The current meta-analysis suggested that pretreatment plasma D-dimer level was a promising biomarker which can be used to predict survival and played an important role in clinical practice for SCLC patients in China.

There were plenty of articles working on the relation between D-dimer and cancer [11,25]. Han et al. demonstrated the significant association between elevated D-dimer concentrations and the possibility of occult cancer in patients with unprovoked venous thromboembolism (VTE) [26]. Furthermore, Fei et al. proved that the combination of D-dimer and tissue factor pathway inhibitor-1 (TFPI-1) measurement played an important role in predicting deep vein thrombosis (DVT) in cancer patients [27]. These researches implied that the poor prognosis of patients with elevated D-dimer level may be correlated with high incidence of venous thrombosis in cancer patients [28]. Furthermore, John et al. reported that tumor cells could not only activate coagulation system, but also damage vascular endothelial cells and increase platelet activity [29]. Meanwhile, Beer et al. manifested that the activation of coagulation system was correlated with more invasive biological behavior of tumors for the following mechanisms [30]. First, tumor cells can destroy the function of normal cells by releasing some cytokines and proteins and then damage 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-1 β 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 and play an essential role in angiogenesis of lung cancer [33,34].

As for the clinical significance of D-dimer in SCLC, there are still many fields which deserve further investigations. It was unclear whether the anticoagulant treatment before cancer-specific treatment could 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 was still unknown. Furthermore, the prognostic value of dynamic change of D-dimer level during the treatment was not clear yet, especially in patients who receive chemoradiotherapies.

For future studies focusing on the clinical significance of D-dimer in SCLC, we would like to provide some suggestions. Subgroup analysis based on the TNM stage is important because the 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 this meta-analysis. First, only 7 retrospective studies involving a total of 964 patients from China were identified, which increased the risk of bias. Second, the further subgroup analysis based on baseline information of patients, such as the TNM stage, gender and age, could not be conducted because of the unobtained original data.

Conclusions

Elevated pretreatment D-dimer level was 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.

Abbreviations

SCLC: Small cell lung cancer; NSCLC: Non-small cell lung cancer; HR: Hazard ratio; CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival; TNM: Tumor-node-metastasis; NOS: Newcastle-Ottawa quality assessment scale; VTE: Venous thromboembolism; TFPI-1: Tissue factor pathway inhibitor-1; DVT: Deep vein thrombosis; ROC: Receiver operating characteristics.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that there are no competing interests associated with this manuscript.

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Authors' contributions

GWC conceived and designed the analyses. YW and JLL performed the literature search and selection, collected data and wrote the paper. YMW and JL performed statistical analyses. All authors have read and approved the manuscript.

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Author details

Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, 610041, P.R. China

* Yan Wang and Jialong Li contributed equally to this work

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Tables

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	0-0	CRT	0.55	Immunoturbidimetric assay	OS/PFS	R	8
Chen Y [15]	2016	2004-2014	393	71/322	0-0	CRT	0.5	Immunoturbidimetric assay	OS/PFS	R	8
Jiang X [16]	2017	2010-2013	107	23/84	0-0	CRT	0.55	NR	OS	R	7
Zhang C [17]	2018	2011-2016	160	31/129	0-0	CRT	0.5	Nephelometry immunoassay	PFS	E	7
Chen R [18]	2018	2010-2016	91	22/69	0-0	Mixed	0.55	NR	OS	E	7
Chen C [19]	2019	2005-2017	57	15/42	0-0	Surg	0.5	Latex assay	OS	R	8
Fan S [20]	2019	2012-2015	82	15/67	0-0	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.

Table 2. Meta and subgroup analyses

	No. of studies	HR	95% CI	P value	Heterogeneity (P, I2 (%))
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.

Figures

Figure 1. The flow diagram of this meta-analysis.

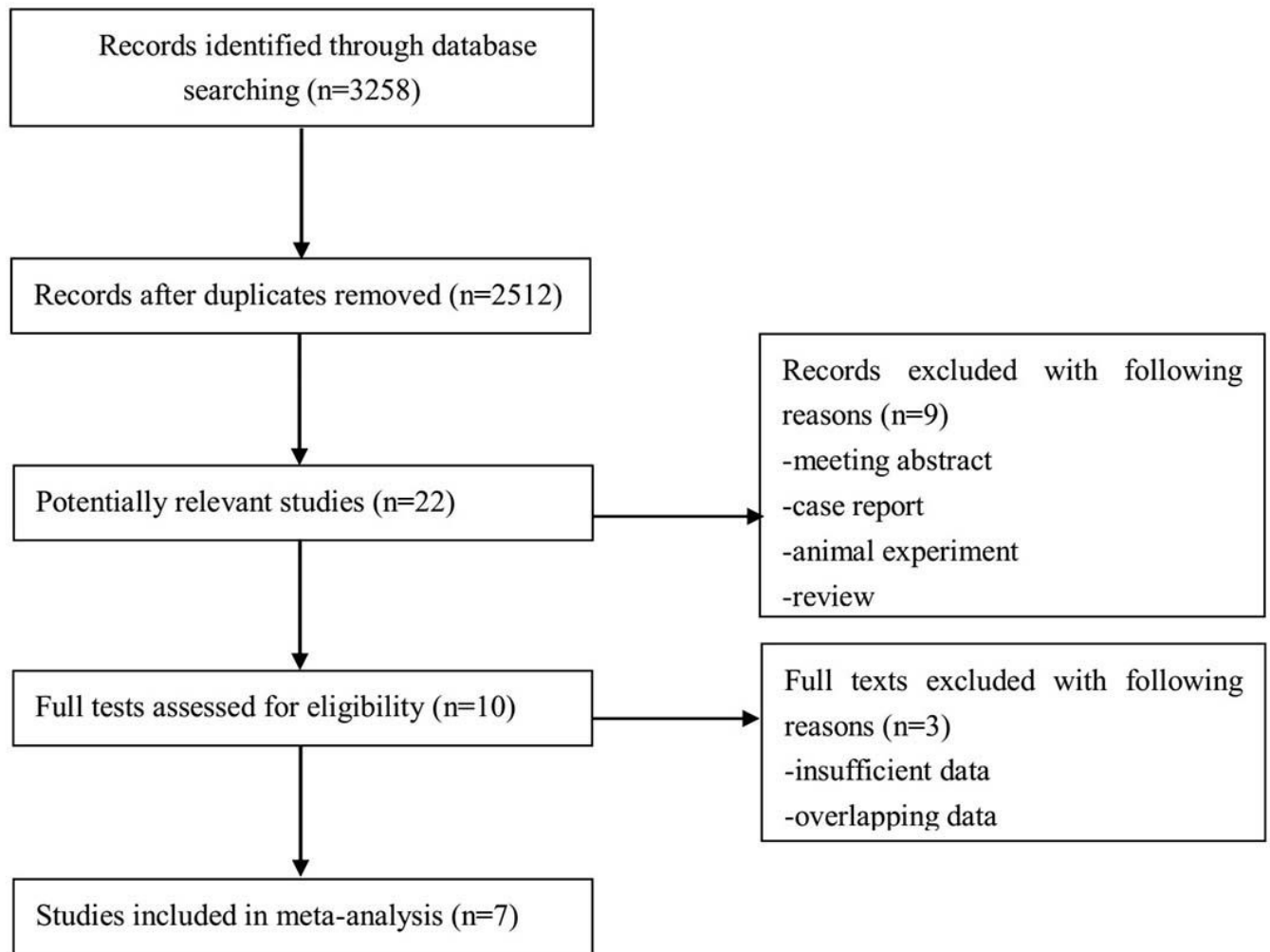


Figure 1

Flow diagram of the literature review.

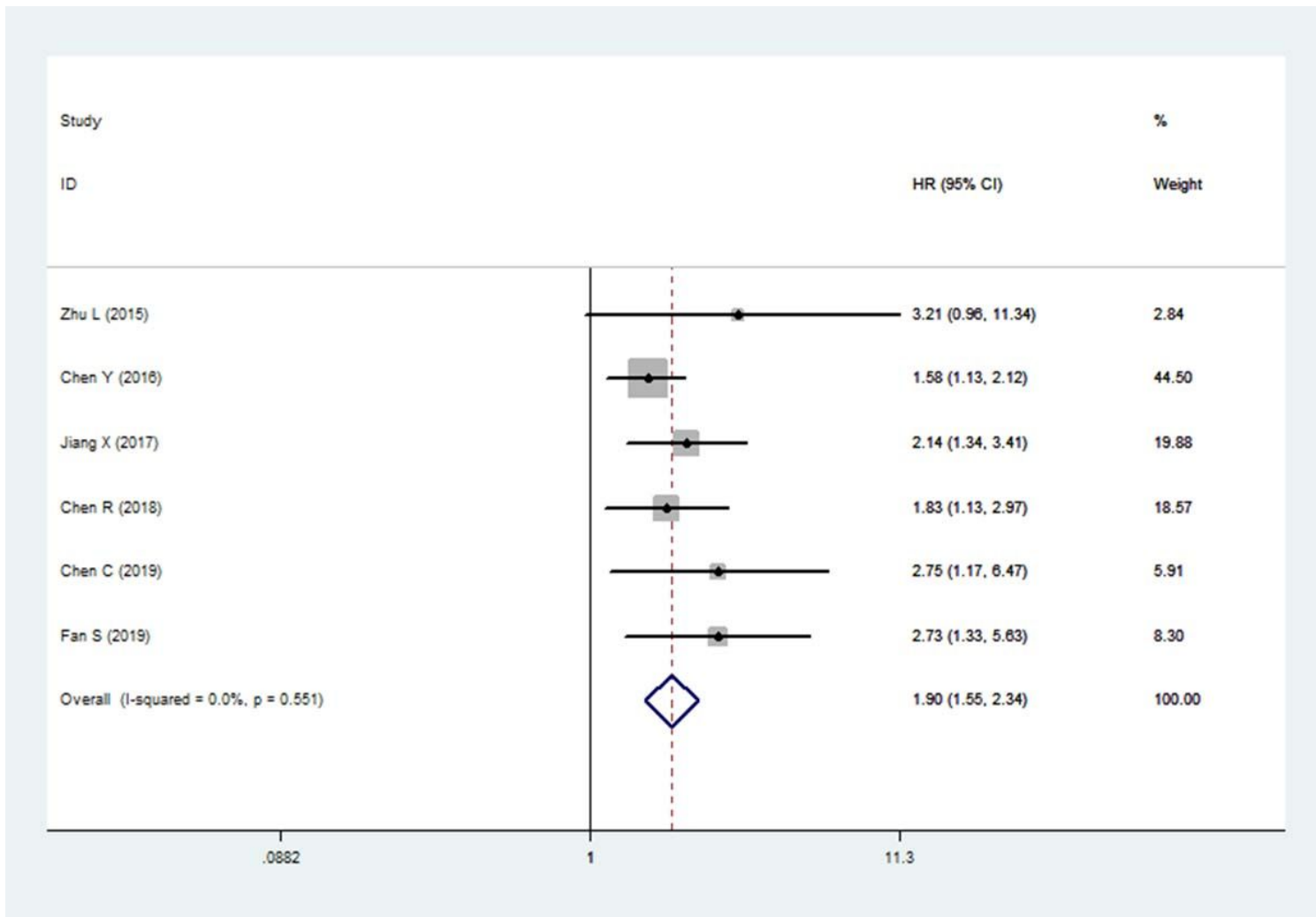


Figure 2

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

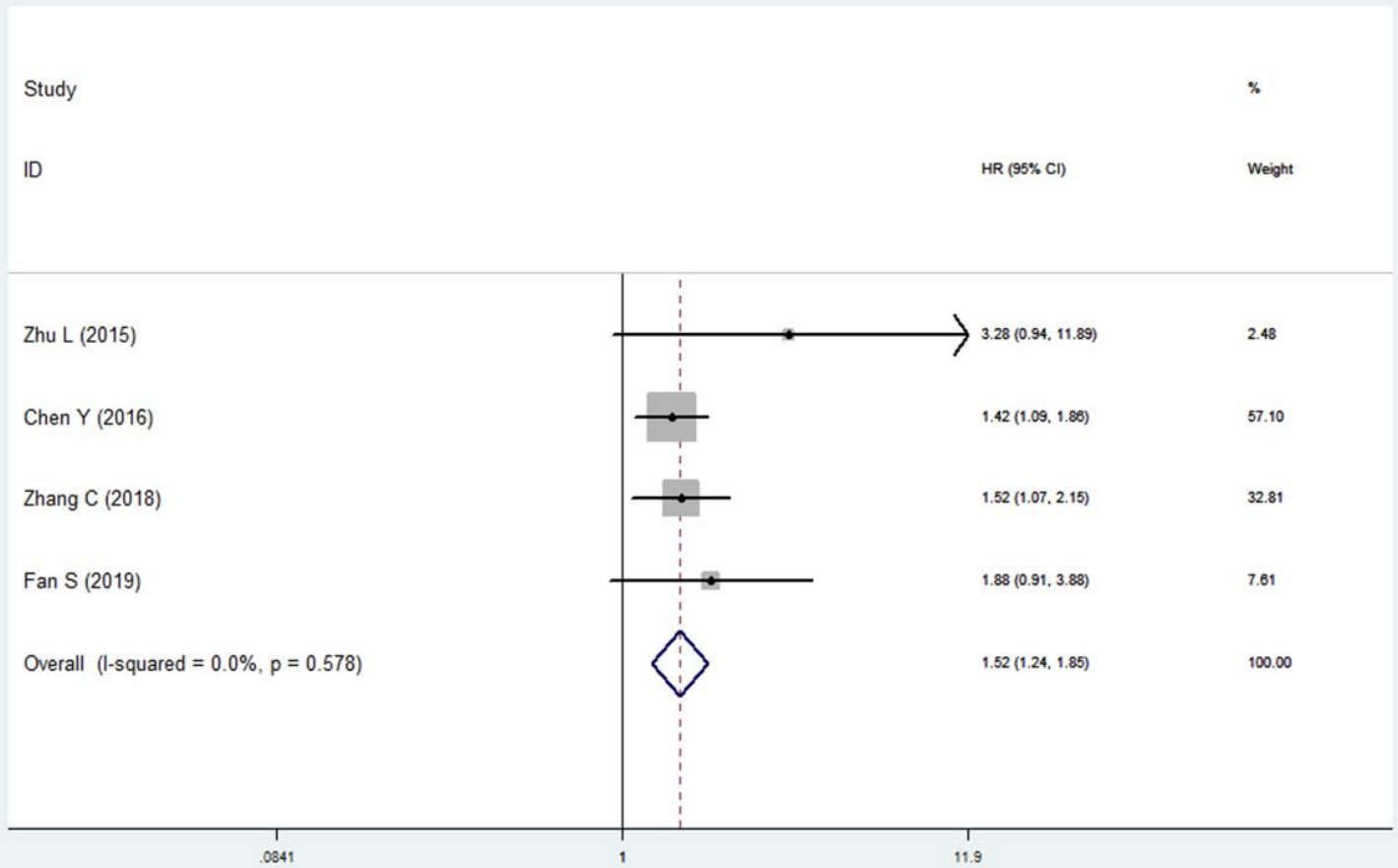


Figure 3

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

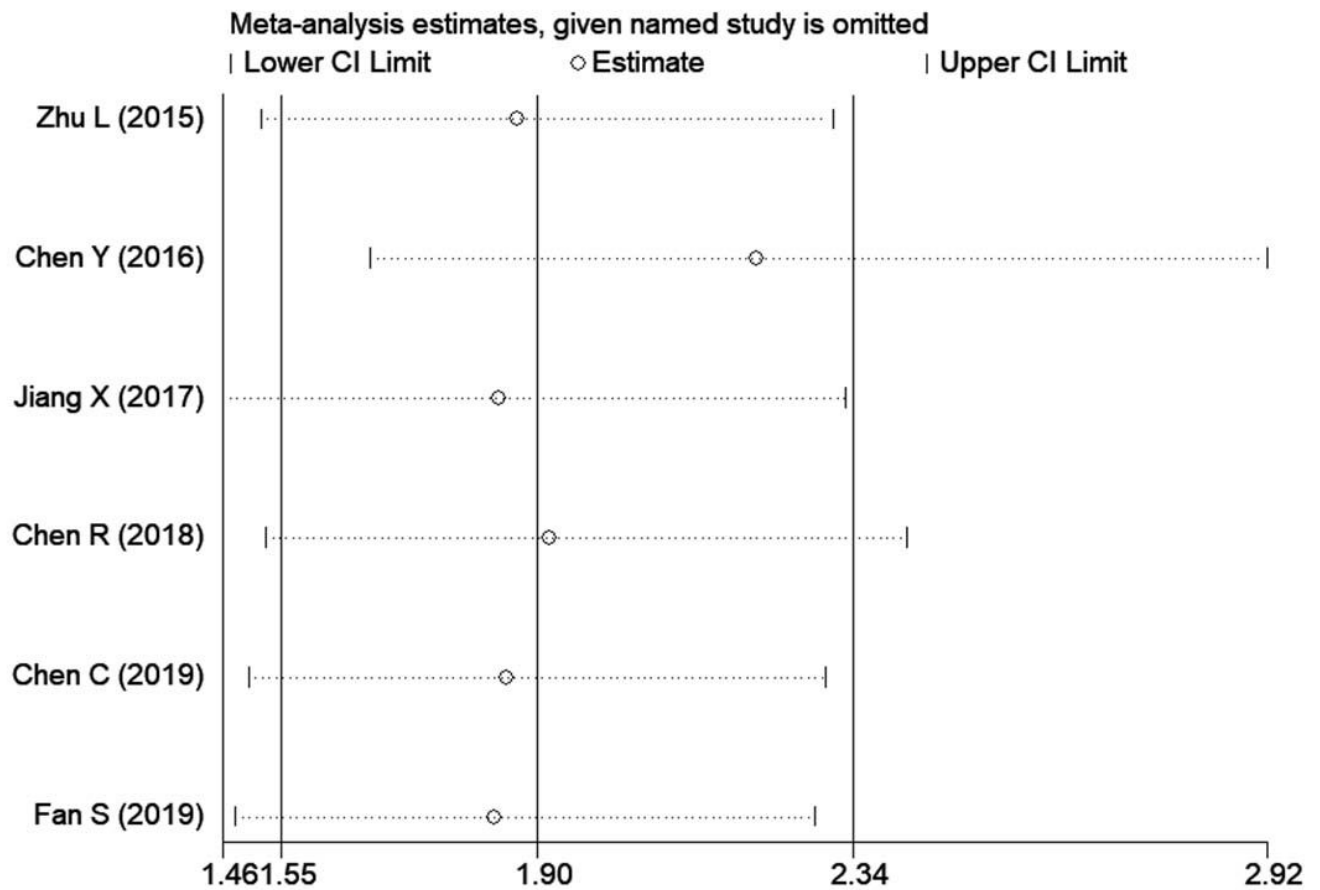


Figure 4

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

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