Systematic Review and Meta-Analysis

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High pretreatment D-dimer level is an independent unfavorable prognostic factor of small cell lung cancer

A systematic review and meta-analysis

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Abstract

Background: High pretreatment level of D-dimer in small cell lung cancer (SCLC) is commonly encountered, but the impact of high pretreatment D-dimer level on the prognosis of SCLC patients remains undetermined. Therefore, we conducted this meta-analysis focusing specifically on the prognostic value of high pretreatment D-dimer level in SCLC patients comprehensively.

Methods: We searched systematically in PubMed, Embase, and Web of Science for relevant studies published before January 28, 2019. Outcomes including 1-year overall survival (OS), progression-free survival (PFS) rates, and hazard ratios (HRs) of OS and PFS from multivariate analysis were extracted and analyzed.

Results: A total of 5 cohort studies consisting of 813 SCLC patients (473 patients with high pretreatment level of D-dimer and 340 with normal level of D-dimer) were finally included for meta-analysis. We found that patients with high pretreatment level of D-dimer had significantly shorter 1-year OS (47.6% vs 79.9%; fixed effects: risk ratio [RR] = 2.506; 95% confidence interval [CI] = [1.948, 3.224]; $P < .001$) and PFS (15.8% vs 34.0%; random effects: RR = 1.294; 95% CI = [1.060, 1.579]; $P = .011$) rates than those with normal level of D-dimer. Moreover, high pretreatment D-dimer level was further proved to remain as an unfavorable predictor of OS (fixed effects: HR = 1.865; 95% CI = [1.469, 2.367]; $P < .001$; $I^2 = 7.6\%$) and PFS (fixed effects: HR = 1.513; 95% CI = [1.183, 1.936]; $P = .001$; $I^2 = 0.0\%$) in patients with SCLC.

Conclusion: High pretreatment level of D-dimer was found to be an independent unfavorable prognostic factor in SCLC patients. However, more studies with sufficient adjustment for confounding factors are encouraged to confirm our conclusions.

Abbreviations: CI = confidence interval, HR = hazard ratio, NOS = the Newcastle-Ottawa Scale, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, RCT = randomized controlled trial, SCLC = small cell lung cancer.

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

1. Introduction

Lung cancer, which mainly consists of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), has become the commonest malignant tumor and the most important cause of cancer death worldwide.[1] SCLC was reported to account for about 15% of all lung cancers and due to its high aggressiveness, SCLC still remains a frustrating disease to be treated with significantly poor prognosis.[2] For patients with limited-stage disease, the median survival time was reported to be 15 to 20 months and it decreased to 8 to 13 months for those with extensive-stage disease.[3] Therefore, it seems valuable to figure out potential prognostic factors for patients with SCLC, which could help tailoring therapeutic decision-making as well as optimum surveillance.

D-dimer, as the fibrinolytic degradation product of crosslinked fibrin, remains primarily to be one of the most useful markers in diagnosing pulmonary embolism, which exhibited high sensitivity but low specificity.[4,5] Recently, previous studies have showed that various malignant tumors were associated with high D-dimer level before treatment and high pretreatment D-dimer level was found to remain as an unfavorable predictor for these malignant tumors.[6] In SCLC patients, >50% of them were found to have a high pretreatment level of D-dimer,[7] but the impact of high pretreatment level of D-dimer on survival of SCLC

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patients remains unclear due to the fact that only several relevant studies were recently available with limited sample size.[7–11] Although previous meta-analyses have explored the role of high pretreatment D-dimer level in predicting prognosis of lung cancer, all of them failed to conduct subgroup analysis for SCLC specifically since they could only mix SCLC and NSCLC together for analysis because of lacking of relevant studies specifically focusing on SCLC.[6,12,13] However, it should be noted that SCLC and NSCLC were generally believed to be different diseases clinically treated with different therapeutical strategies because they exhibited distinct biology and genomic abnormalities,[14] and the hemostatic system activation mechanisms were also reported to be different in SCLC and NSCLC.[15] Therefore, it is reasonable that previous meta-analyses all had significant heterogeneities.[6,12,13] As a result, the impact of high pretreatment D-dimer level on the survival of SCLC patients remains unclear. With several relevant studies specifically focusing on the prognostic value of high pretreatment D-dimer level in SCLC patients available recently,[7–11] we aimed to conducted this systematic review and meta-analysis to investigate the role of high pretreatment level of D-dimer in predicting survival of patients with SCLC. To our knowledge, our study is the first meta-analysis specifically focusing on the prognostic value of high pretreatment D-dimer level in SCLC patients.

2. Methods and materials

2.1. Literature search

Three website literature databases were comprehensively searched for retrieving relevant papers: PubMed, Embase, and Web of Science. We conducted a systematic computerized search with following search terms: "d-dimer" and "lung cancer" on January 28, 2019. All the references from these studies selected by electronic search were also checked for further retrieving potential relevant papers.

2.2. Study inclusion and exclusion

Our study inclusion criteria were as follow: Either observational studies or randomized controlled trials (RCTs) compared survival of SCLC patients with high pretreatment D-dimer level with SCLC patients with normal D-dimer level; sufficient outcomes of overall survival (OS) and progression-free survival (PFS) could be obtained for analysis; if studies were conducted based on overlapping patients, the most recent or completed one was chosen. The following criteria were used for study exclusion: studies including patients with other types of lung cancers except for SCLC; studies with no sufficient data obtained for analysis; studies not in English; case reports, conference abstracts, reviews, and experiment studies.

2.3. Data extraction and quality assessment

We developed a standardized data collection form for data extraction, which consisted of the following data: first author, publication year, origin of study, disease stage, patient age, study sample size, therapeutic strategies, follow-up time, and study design. Two authors independently applied the standardized data form to collect the data for analysis and compared those outcome data independently. Another author would handle the discrepancy if there existed one. The main outcomes for analysis in our meta-analysis included 1-year OS and PFS rates, and hazard ratios (HRs) of OS and PFS. We would apply the Jadad scale[16] to evaluate the quality of RCTs and the Newcastle-Ottawa Scale (NOS),[17] which included 3 factors: patient selection, comparability of the study groups, and assessment of outcome, to assess the quality and risk-of-bias of observational studies. For observational study, we would assign a score of 0 to 9 (allocated as stars) to each study using the NOS and here we defined the high-quality study as one with a quality score ≥7. In our current meta-analysis, we used the name of the first author and year of publication for identification.

2.4. Statistical analysis

We used the STATA 12.0 package (StataCorp, College Station, TX) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18] to perform this meta-analysis. We extracted 1-year OS and PFS rates either directly from the text or from the Kaplan–Meier curve from each original study and applied risk ratio (RR) with 95% confidence interval (CI) for comparison. We also retrieved HRs and 95% CI of OS and PFS directly from those original articles based on the multivariate analysis after adjusting for confounding factors and used them to compare OS and PFS between patients with high pretreatment level of D-dimer and those with normal pretreatment level of D-dimer. We assessed the between-study heterogeneity via the Chi-squared-based Q statistics and I^2 test, and we defined a high heterogeneity as $P < .1$ or $I^2 > 50\%$. In the case of high heterogeneity, we would use the random effects models while in other cases, we would applied the fixed effects models. We also conducted a sensitivity analysis by sequentially removing each included study. For publication bias assessment, we used a funnel plot, which was further tested by Begg test and Egger test.[19] A 2-sided $P < .05$ was considered as statistical significance.

3. Results

3.1. Description of the included studies

We showed the progress of study evaluation in our meta-analysis in Fig. 1. After comprehensive search in the above literature databases, 823 papers were totally retrieved. After initial evaluation of the titles and abstracts of those papers, a total of 39 potential papers were found eligible for detailed evaluation of their full texts. Three review papers were excluded,[6,12,13] and 31 papers were also excluded because of the fact that they included NSCLC patients for analysis without subgroup analysis for SCLC patients. Finally, we included a total of 5 cohort studies with a total of 813 patients (473 patients with high pretreatment level of D-dimer and 340 with normal pretreatment level of D-dimer) for current meta-analysis. The main baseline characteristics extracted from these original studies for analysis were listed in Table 1. All these included studies were carried out in Chinese patients and consisted of both patients with limited-stage disease and those with extensive-stage disease. Moreover, all these patients were treated with chemotherapy with or without radiotherapy. The median age of these patients in the original studies ranged from 57 to 63 years old. Considering the poor prognosis of SCLC, the median follow-up time ranging from 9 to 12 months seemed enough for the endpoints of main outcomes. All these studies shared a similar cut-off value for defining high

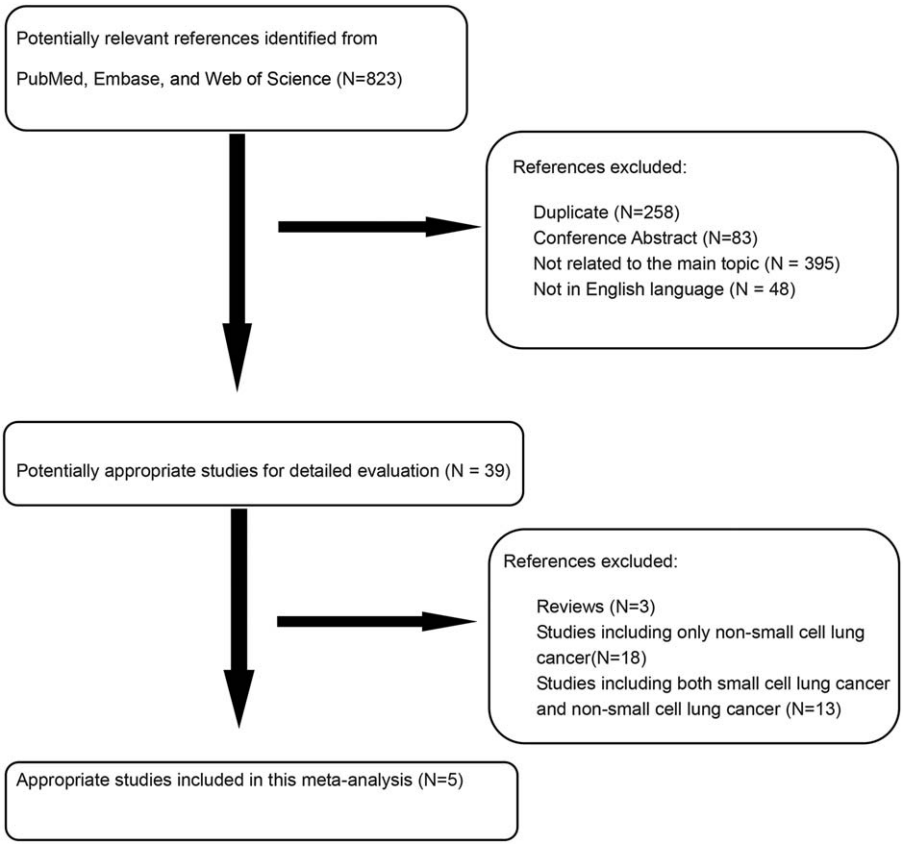

Figure 1. PRISMA flow diagram showing the progress of study evaluation throughout the review.

Table 1

Characteristics of the included studies in this meta-analysis.

Author	Country	Patients	Age, y	Follow-up, mo	Sample size (N)	Cut-off value	High D-dimer level group (N)	Normal D-dimer level group (N)	Study design	Quality assessment
Zhu 2016	China	Patients with limit-stage (N = 29) or extensive-stage (N = 45) SCLC treated with chemotherapy with/without radiotherapy	Median: 57 (range, 41–80)	Median: 11.5 (range, 3.5–61)	74	0.55 μg/mL	50	24	Cohort study	NOS: 8 stars
Chen 2016	China	Patients with limit-stage (N = 157) or extensive-stage (N = 236) SCLC treated with chemotherapy with/without radiotherapy	Median: 57	Median: 12 (range, 3–108)	393	0.5 μg/mL	214	179	Cohort study	NOS: 7 stars
Jiang 2017	China	Patients with limit-stage (N = 42) or extensive-stage (N = 65) SCLC treated with chemotherapy with/without radiotherapy	Median: 63	Median: 9 (range, 6–16)	107	0.55 μg/mL	61	46	Cohort study	NOS: 7 stars
Fan 2018	China	Patients with limit-stage or extensive-stage SCLC treated with chemotherapy with/ without radiotherapy	Median: 60 (range, 28–82)	NA	82	0.55 μg/mL	53	29	Cohort study	NOS: 7 stars
Zhang 2018	China	Patients with limit-stage or extensive-stage SCLC treated with chemotherapy with/ without radiotherapy	Median: 59	NA	157	0.5 μg/mL	95	62	Cohort study	NOS: 7 stars

NA = not available, NOS = Newcastle-Ottawa Scale, SCLC = small cell lung cancer.

Table 2

Main outcomes extracted from the studies included in our meta-analysis.

	1-year OS rate*		1-year PFS rate†		OS		PFS	
Author	High pretreatment D-dimer group	Normal D-dimer group	High pretreatment D-dimer group	Normal D-dimer group	HR	95% CI	HR	95%CI
Zhu 2016	18/32 (36.0%)	20/4 (83.3%)	14/36 (28.0%)	18/6 (75.0%)	3.21	0.96–11.34	3.28	0.94–11.89
Chen 2016	138/76 (64.5%)	151/28 (84.4%)	39/175 (18.2%)	62/117 (34.6%)	1.58	1.14–2.12	1.42	1.09–1.86
Jiang 2017	14/47 (23.0%)	28/18 (60.9%)	NA	NA	2.14	1.34–3.41	NA	NA
Fan 2018	10/43 (18.9%)	23/6 (79.3%)	2/51 (3.8%)	9/20 (31.0%)	2.73	1.33–5.63	1.88	0.91–3.88
Zhang 2018	NA	NA	10/85 (10.5%)	11/51 (17.7%)	NA	NA	NA	NA

CI = confidence interval, HR = hazard ratio, NA = not available, OS = overall survival, PFS = progression-free survival.

* Expressed as no. alive/ no. dead and percentage.

† Expressed as no. alive without disease progression/no. with other status.

pretreatment level of D-dimer (>0.5 μg/mL or 0.55 μg/mL). The main outcomes of 1-year OS and PFS rates and HRs with 95% CI for OS and PFS were shown in Table 2. Three studies reported 1-year OS and PFS rates as well as HRs and 95% CI for OS and PFS while one study only reported 1-year OS rate and HRs and 95% CI for OS and another one only reported 1-year PFS rate. The HRs with 95 CI% for OS and PFS extracted for meta-analysis were all calculated by these original studies via multivariate analysis methodology to adjust for potential confounding factors.

3.2. Quality assessment and risk of bias

We conducted the quality assessment and risk-of-bias analysis of these cohort studies by using the NOS. The result for quality assessment of each study was also presented in Table 1. All these included studies were assigned with a NOS score of no <7 and therefore were deemed as high quality, which indicated a low risk of bias in our meta-analysis.

3.3. Meta-analysis of the impact of pretreatment D-dimer level on survival of SCLC patients

Four studies with a total of 656 SCLC patients (378 patients with high pretreatment D-dimer level and 278 patients with normal level of D-dimer) reported the impact of high pretreatment D-dimer level on 1-year OS rate of these patients. Patients with high pretreatment level of D-dimer yielded a significantly lower 1-year OS rate than those with normal D-dimer level (47.6% vs 79.9%; fixed effects: RR = 2.506; 95% CI = [1.948, 3.224]; $P < .001$; $I^2 = 26.0\%$) (Fig. 2A). Four studies with a total of 706 SCLC patients (412 patients with high pretreatment D-dimer level and 294 patients with normal level of D-dimer) reported the impact of high pretreatment D-dimer level on 1-year PFS rate of these patients. There was also significant difference of 1-year PFS rate between patients with high pretreatment D-dimer level and those with normal level of D-dimer (15.8% vs 34.0%; random effects: RR = 1.294; 95% CI = [1.060, 1.579]; $P = .011$; $I^2 = 73.3\%$) (Fig. 2B). Moreover, high pretreatment D-dimer level was found to be an unfavorable predictor of OS (fixed effects: HR = 1.865; 95% CI = [1.469, 2.367]; $P < .001$; $I^2 = 7.6\%$) and PFS (fixed effects: HR = 1.513; 95% CI = [1.183, 1.936]; $P = .001$; $I^2 = 0.0\%$) in SCLC patients (Fig. 3). Potential heterogeneity was only observed in the analysis of 1-year PFS rate, and as a result, the random effects models were applied during analysis.

3.4. Sensitivity analysis and publication bias

In our meta-analysis, sensitivity analysis was conducted by sequentially removing each study to test the stability of our results based on 1-year OS and PFS rates. Our sensitivity analysis found that sequential removal of each study did not make any significant impact on the primary outcomes (Fig. 4). We then evaluated the publication bias by using a funnel plot based on the analysis of 1-year OS rate. The funnel plot was found to have an

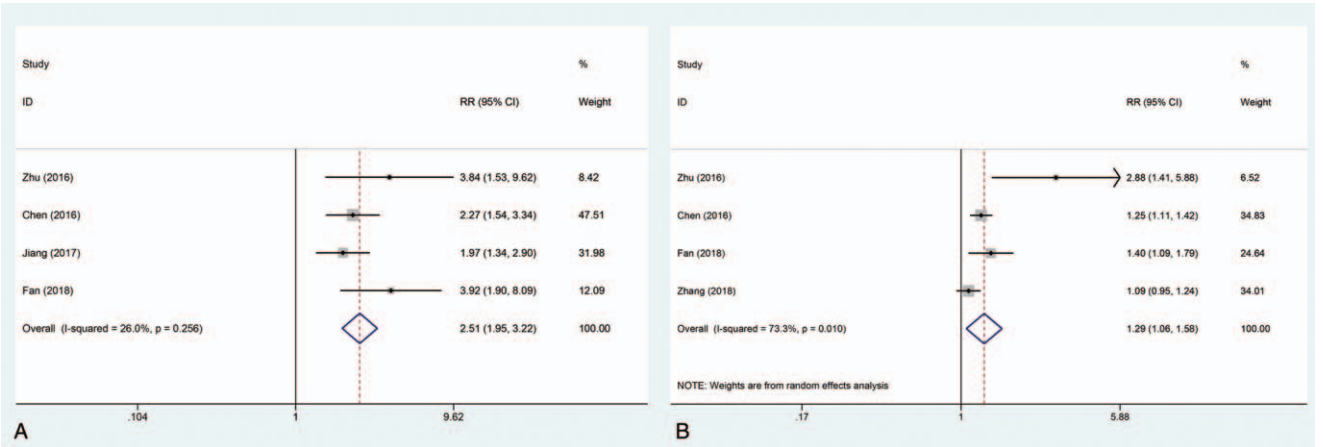

Figure 2. Forest plots of (A): 1-year overall survival rate, and (B): 1-year progression-free survival rate.

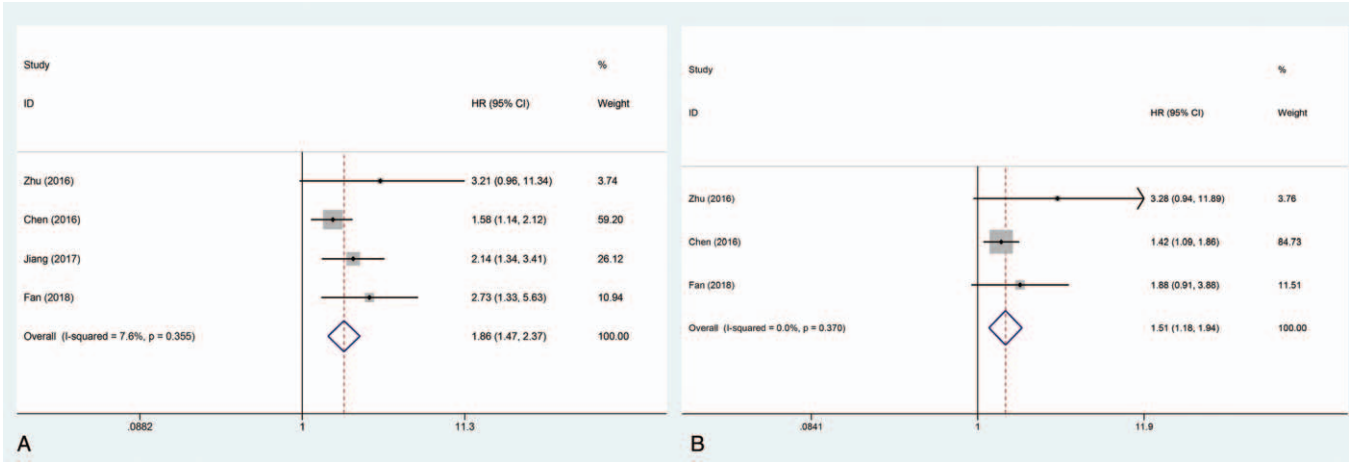

Figure 3. Forest plots of (A): overall survival, and (B): progression-free survival.

asymmetrical appearance (Begg test: $P = .487$; Egger test: $P = .069$), which may indicate potential publication bias (Fig. 5).

4. Discussion

Subclinically activated coagulation and fibrinolysis systems were commonly seen in lung cancer patients, and in SCLC patients it was believed that tumor cells released tissue factors and directly activated the coagulation system, thus leading to a hypercoagulable status.[20] D-dimer, also known as the fibrinolytic degradation product of crosslinked fibrin, served as an indicator of hypercoagulable status especially evident in patients with thrombosis formed by the activation of coagulation and fibrinolysis.[21] It is reported that >50% of SCLC patients was found to have a high pretreatment level of D-dimer.[7] Since there was significant correlation between activation of coagulation and tumor angiogenesis, metastasis, and invasion,[15] the specific prognostic role of D-dimer level in SCLC patients has been recently investigated in several cohort studies.[7–11] However, due to the limited sample size in each study, the impact of high pretreatment D-dimer level on survival of SCLC patients remains undetermined. Therefore, we carried out this meta-analysis to investigate the prognostic value of high pretreatment D-dimer level in SCLC patients for the first time.

In our meta-analysis, a total of 5 cohort studies with 813 patients (340 patients with normal pretreatment level of D-dimer and 473 with high pretreatment level of D-dimer) were included for analysis after comprehensive literature search and evaluation. We found that SCLC patients with high pretreatment level of D-dimer yielded significantly shorter 1-year OS and PFS rates than those with normal level of D-dimer. Moreover, high pretreatment level of D-dimer was found to be an unfavorable prognostic factor of OS and PFS in SCLC patients. Therefore, our study added to the evidence that high pretreatment D-dimer level may act as an independent predictor of poor prognosis in SCLC patients.

The correlation between high level of D-dimer and poor prognosis of SCLC patients remains complex. In cancers, tumor cells can activate the coagulation cascade via the production of procoagulant proteins and lipids as well as inflammatory cytokines, which subsequently causes a hypercoagulable status.[22] As a result of increased procoagulant activity, the level of

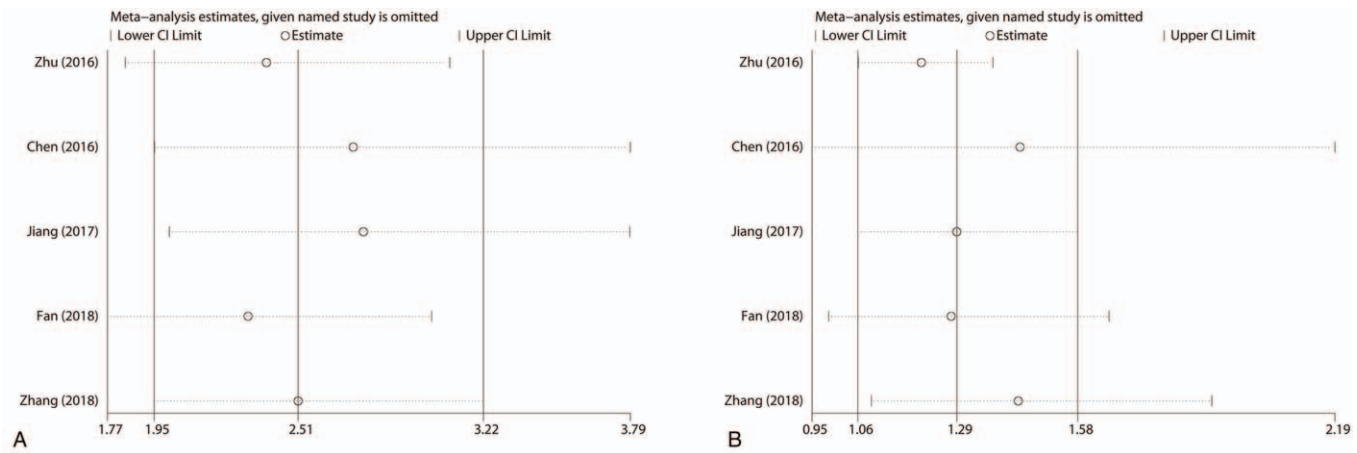

Figure 4. Sensitivity analysis for (A): 1-year overall survival rate, and (B): 1-year progression-free survival rate.

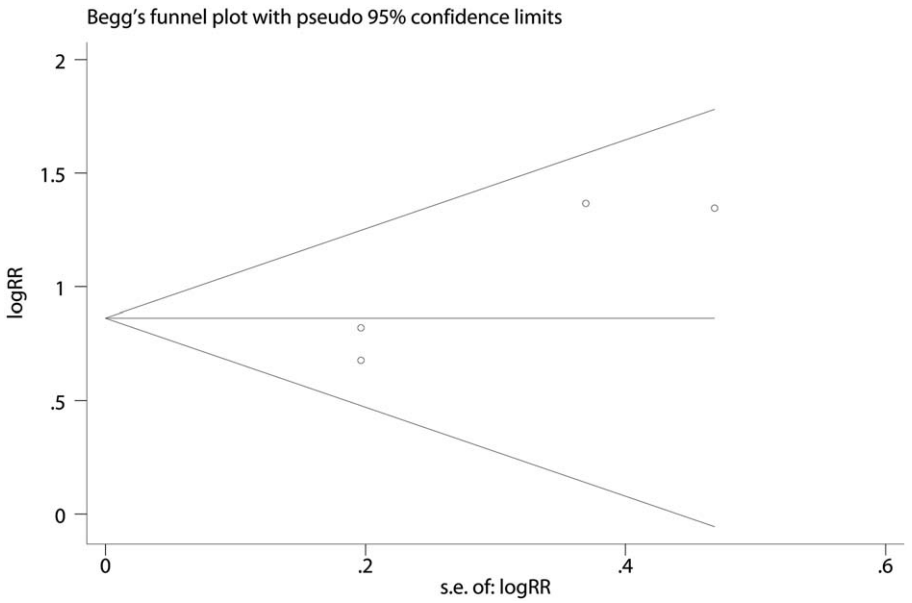

Figure 5. Funnel plot of the included studies for analysis of 1-year overall survival rate. Begg test: $P = .487$; Egger test: $P = .069$. Note: because only 4 studies reported 1-year overall survival rates and as a result, in the publication analysis, there were only 4 points in the funnel plot.

fibrinogen and fibrin degradation products (D-dimer for example) increases significantly in cancer patients,[23] and high level of D-dimer is deemed as an indicator of hypercoagulable status. Because of the fact that the hypercoagulable status greatly contributes to tumor growth, neoagiogenesis, tumor cell invasion, and metastasis,[22,24] it is reasonable that high level of D-dimer may be correlated significantly to tumor aggressiveness. Previous study showed that the level of D-dimer in SCLC patients was significantly higher than patients with benign pulmonary diseases,[11] and high level of D-dimer was significantly correlated to advanced tumor stage, presence of distant metastasis, and poor Karnofsky performance status score.[7–11] Moreover, the level of D-dimer could also act as a predictor of lymph node metastasis in lung cancer.[25,26] Therefore, it seems reasonable that SCLC patients with high pretreatment level of D-dimer had a worse prognosis than those with normal level of D-dimer. Previous studies also found that D-dimer level would increase after disease progression while it would decrease after response to chemoradiotherapy, indicating that D-dimer level could also serve as a predictor for treatment efficacy, and it could also monitor disease progression.[8,27] In conclusion, high pretreatment level of D-dimer was an independent unfavorable prognostic factor for SCLC patients. As a result, correction of D-dimer level by applying anticoagulant drugs (low-molecular weight heparin for example) should be carefully planned for SCLC patients with high level of D-dimer, which may help not only improve cancer survival but also prevent hemostatic complications.[28–30] However, further studies concerning the effects of anticoagulant drugs on survival of SCLC patients especially for these with high level of D-dimer are needed.

Several limitations should be addressed in our meta-analysis. First, our meta-analysis could only include retrospective cohort studies with limited sample size for analysis. As a result, the statistical power of our meta-analysis could be decreased. Second, the main outcomes could not be fully obtained from all these original studies, and potential publication bias was also observed in our meta-analysis, which may decrease the validity of our results. Moreover, all studies included both patients with limited-stage SCLC and extensive-stage SCLC without subgroup analysis based on tumor stage. The actual impact of high D-dimer level on survival of SCLC patients should be further elucidated after adjusting those confounding factors such as disease stage, performance status, and therapeutic strategies. Finally, all those studies were conducted in Chinese patients without external validity, and therefore, the impact of high pretreatment level of D-dimer on the prognosis of Western patients with SCLC requires further investigation.

5. Conclusion

We conducted the first meta-analysis to elucidate the prognostic value of high pretreatment level of D-dimer for SCLC patients. We found that SCLC patients with high pretreatment level of D-dimer yielded significantly shorter 1-year OS and PFS rates than those with normal level of D-dimer. And high pretreatment level of D-dimer was found to be an independent unfavorable prognostic factor in SCLC patients. Further studies, however, are needed to confirm our findings.

Author contributions

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Visualization: Xiao-Ming Qiu.
Writing – original draft: Han-Yu Deng, Xing-Sheng Ma.
Writing – review & editing: Xiao-Ming Qiu.

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