Original Article

Preoperative D-dimer level is an independent prognostic factor for non-small cell lung cancer after surgical resection: a systematic review and meta-analysis

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Background: Whether high preoperative D-dimer level has any impact on long-term survival of patients with surgically treated non-small cell lung cancer (NSCLC) remains unclear. Therefore, we conducted the first meta-analysis focusing specifically on prognostic value of high preoperative D-dimer level in NSCLC patients after surgical resection comprehensively.

Methods: We conducted a systematic search for relevant studies in PubMed, Embase, and Web of Science on January 28, 2019. Data for analysis consisted of hazard ratio (HR) with 95% confidence interval (CI) of overall survival (OS) and disease-free survival (DFS) from multivariate analysis and were analyzed by using the STATA 12.0 package.

Results: Finally, we included a total of 6 cohort studies consisting of 1,817 patients with surgically treated NSCLC for analysis. Our meta-analysis found that NSCLC patients with high preoperative D-dimer level had a significantly worse OS (random effects: HR =2.04; 95% CI: 1.30–3.20; P=0.002; I^2=67.4%) and DFS (fixed effects: HR =1.98; 95% CI: 1.41–2.78; P<0.001; I^2=0.0%) than these with normal preoperative D-dimer level after surgery. However, potential heterogeneity and publication bias was observed during analysis.

Conclusions: High pretreatment level of D-dimer remains to be an independent predictor of poor prognosis in NSCLC patients after surgery. Further well-conducted studies with appropriate adjustments are needed to confirm and update our conclusions.

Keywords: D-dimer; non-small cell lung cancer (NSCLC); surgery; prognosis; meta-analysis

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Introduction

Lung cancer is the most common malignant tumor and also the leading cause of cancer death worldwide (1). There are two major histological types of lung cancer, namely non-small cell lung cancer (NSCLC), which is reported to account for 85% of all lung cancers, and small cell lung cancer (SCLC), which accounts for only 15% of lung cancers (2). Currently, for resectable NSCLC, surgery still remains to be the preferred therapeutic option. Despite of advancement of surgical techniques, the 5-year survival rate for surgically treated NSCLC varied from 25% to 73% based on different disease stages (3). Moreover, even after curative surgical resection of NSCLC, the recurrence rate was reported to be as high as about 30% to 70% (4). Therefore, in order to better direct

therapeutic and follow-up strategies for individualized therapy for each patient, it is of great value to explore potential prognostic factors for surgically treated NSCLC patients.

Despite of disease stage at diagnosis and performance status being the most important prognostic factors (5), D-dimer level has also recently been investigated as a potential prognostic factor of lung cancer patients (6-8). D-dimer is the fibrinolytic degradation products of crosslinked fibrin and is applied as a useful marker for the diagnosis of pulmonary embolism (9,10). It is reported that high pretreatment D-dimer level was observed in various malignant tumors and it was found to be an unfavorable prognostic factor for these malignant tumors including lung cancer (8). Even though several meta-analyses found the prognostic role of high D-dimer level in lung cancer, none of them conducted subgroup analysis for NSCLC, let alone for these surgically treated NSCLC, because no relevant studies focusing on surgically treated NSCLC specifically were available when these meta-analyses were conducted, and as a result, they all mixed NSCLC and SCLC together for analysis (6-8). However, NSCLC and SCLC were different pathologic types of lung cancers with different therapeutical strategies because of their distinct biology and genomic abnormalities (11) and even for NSCLC patients, surgical resection and non-surgical therapy yielded significantly different outcomes (12). As a result, it is reasonable that significant heterogeneities were observed in previous meta-analyses (6-8). Moreover, none of these previous meta-analyses focused on the outcome of disease-free survival (DFS) in lung cancer patients, which was an important parameter for evaluation of disease recurrence. Therefore, the value of preoperative D-dimer in predicting overall survival (OS) and DFS in patients with surgically treated NSCLC remains undetermined. In this study, we aimed to conducted a systematic review and meta-analysis to investigate the impact of high preoperative level of D-dimer on long-term survival of patients with surgically treated NSCLC. To our knowledge, this is the first meta-analysis specifically focusing on patients with surgically treated NSCLC.

Methods

Literature search

In order to retrieve relevant studies comprehensively, we systematically searched the following three website literature databases on January 28, 2019: PubMed, Embase, and Web of Science. We used the following search terms for search: “d-dimer” and “lung cancer”. We also comprehensively scanned all the references from the selected studies to further retrieve potential relevant studies.

Study inclusion and exclusion

Our study inclusion criteria were as follows: (I) either randomized controlled trials (RCTs) or observational studies compared survival of NSCLC patients with high preoperative D-dimer level with that of patients with normal preoperative D-dimer level; (II) all patient should be diagnosed with NSCLC and be surgically treated; (III) sufficient data of OS and DFS from multivariate analysis could be obtained for analysis; (IV) If studies were based on overlapping patients, the most completed one was chosen. We used the following criteria for study exclusion: (I) studies including patients with other types of lung cancers apart from NSCLC; (II) studies including NSCLC patients treated without surgical resection; (III) studies not published in English; (IV) conference abstracts, reviews, case reports, and experiment studies.

Data extraction and quality assessment

A standardized data collection form, which included first author, year of publication, study origin, disease stage, age, sample size, follow-up time, and study design, was applied for data extraction. Two authors (X Zheng and R Jiang) independently extracted and analyzed the outcome data by using the standardized data form. If there was a discrepancy between the two authors, the third author (HY Deng) would resolve it. The main outcomes for analysis consisted of hazard ratio (HR) of OS and DFS from multivariate analysis. The Jadad scale (13) would be applied to evaluate the quality of RCTs and the Newcastle-Ottawa Scale (NOS) as described previously (14), which consisted of three factors: patient selection, comparability of the study groups, and assessment of outcome, would be used to assess the quality and risk-of-bias of the observational studies. During the application of NOS, we would give out a score of 0–9 (allocated as stars) to each observational study. Here, the high-quality study was defined as one with a quality score of more than 6. The name of the first author and publishing year was used for identification in our meta-analysis.

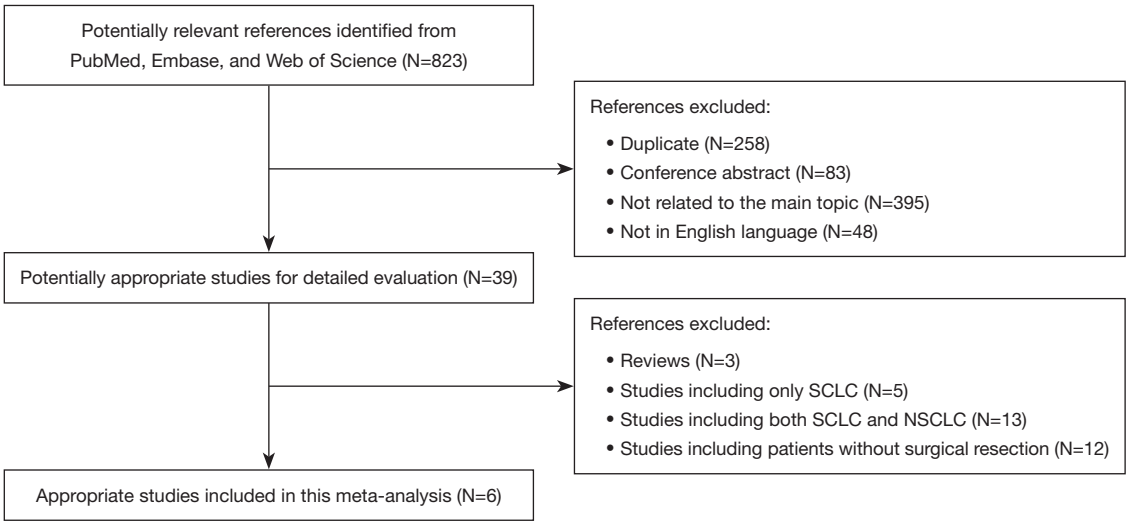

Figure 1 A flow chart showing the progress of study evaluation throughout the meta-analysis. SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Statistical analysis

We applied the STATA 12.0 package (StataCorp., College Station, TX, USA) to perform this meta-analysis based on the PRISMA guidelines (15) (Supplement file). We extracted HRs with 95% confidence interval (CI) directly from each original article and used them for comparing OS and DFS between patients with high preoperative level of D-dimer and these with normal preoperative level of D-dimer. The between-study heterogeneity was evaluated by the χ^2-based Q statistics and I^2 test, and a significant heterogeneity was defined as $P<0.1$ or $I^2>50\%$. When significant heterogeneity was observed, we would apply the random effects models for analysis. Otherwise, we would apply the fixed effects models. A sensitivity analysis was also conducted by sequential removal of each study. Here we applied a funnel plot as well as Begg's test and Egger's test (16) to assess publication bias. A two-sided P value of <0.05 was deemed as statistical significance.

Results

Description of the included studies

A flow chart for the process of study evaluation in our meta-analysis was shown in *Figure 1*. After systematic search, we retrieved a total of 823 papers. After initial assessment with titles and abstracts, we found 39 potential relevant papers for detailed evaluation with full text. Three review papers were excluded (6-8) and 30 papers were further excluded due to the fact that they included SCLC patients or NSCLC patients without surgical resection. Finally, only a total of 6 cohort studies with a total of 1,817 patients with surgically treated NSCLC were included for final analysis (17-22). One study (19) reported the results subgrouped by different cut-off values, and as a result, we extracted the data individually from its subgroup analysis for analysis. The main characteristics of these included studies were listed in *Table 1*. All these included patients had a stage I–III disease and were treated with surgical resection. The median age for all patients ranged from 60 to 69 years old. All studies except two had a relative long follow-up time. However, the cut-off value among these studies differed from each other. The main outcomes of OS and DFS were extracted from the multivariate analysis in each study, which could significantly avoid bias caused by confounding factors. We listed these main outcomes in *Table 2*, and four of these studies reported HRs for OS, while only three studies reported HRs for DFS.

Quality assessment and risk of bias

With only cohort studies included for analysis, we conducted the quality assessment and risk-of-bias analysis of these studies based on the NOS. Here we listed the quality assessment result of each study in *Table 1*. All these studies were evaluated as high quality, suggesting a very low risk of bias.

Table 1 Characteristics of the included studies in this meta-analysis

Author	country	Patients	Age (years)	Follow-up (months)	Sample size (N)	Cut-off value (μg/mL)	High D-dimer level group (N)	Normal D-dimer level group (N)	Study design	Quality assessment
Zhang 2013	China	Patients with stage I–IIIa NSCLC treated with lobectomy, wedge resection, or pneumonectomy	Median: 61 (range, 30–86)	Median: 47.0 (range, 0–64)	232	0.3	34	198	Cohort study	NOS: 8 stars
Jiang 2014	China	Patients with I–IIIa NSCLC treated with surgical resection	Median: 60 (range, 40–78)	Median: 18.5 (range, 9.5–32)	184	0.55	96	88	Cohort study	NOS: 7 stars
Fukumoto 2015-1[a]	Japan	Patients with stage I–III NSCLC treated with lobectomy, sublobar resection, or pneumonectomy	Median: 69 (range, 31–85)	Mean: 51.6 (range,1–76)	155	0.51–0.86 *vs.* ≤0.50	79	76	Cohort study	NOS: 8 stars
Fukumoto 2015-2[a]	Japan	Patients with stage I–III NSCLC treated with lobectomy, sublobar resection, or pneumonectomy	Median: 69 (range, 31–85)	Mean: 51.6 (range,1 –76)	158	>0.86 *vs.* ≤0.50	82	76	Cohort study	NOS: 8 stars
Kaseda 2017	Japan	Patients with stage I–III NSCLC treated with segmentectomy, lobectomy or more	Median: 69 (range, 31–85)	Mean: 60.0 (range, 2–110)	237	1.0	67	170	Cohort study	NOS: 8 stars
Hou 2019	China	Patients with stage I–III NSCLC treated with lobectomy, sublobar resection, or pneumonectomy	Median: 64	Median: 13.2 (range, 3–18.5)	395	0.20	NA	NA	Cohort study	NOS: 7 stars
Liang 2019	China	Patients with stage I–IIIa NSCLC treated with lobectomy or pneumonectomy	Median: 61 (range, 35–81)	Median: 42 (range, 3–108)	456	0.50	131	325	Cohort study	NOS: 8 stars

[a], those studies with the same author and year of publication were extracted from the same article analyzing subgroup based on different cut–off values; therefore, they shared the same identification code. NSCLC, non-small cell lung cancer; NOS, Newcastle-Ottawa Scale; NA, not available.

Table 2 Main outcomes extracted from the studies included in our meta-analysis

Author	Comparisons	OS		DFS	
		HR	95% CI	HR	95% CI
Zhang 2013	High D-dimer *vs.* normal D-dimer	1.54	1.11–2.78	NA	NA
Jiang 2014	High D-dimer *vs.* normal D-dimer	NA	NA	3.28	1.22–9.65
Fukumoto 2015-1[a]	High D-dimer *vs.* normal D-dimer	4.25	1.65–10.91	NA	NA
Fukumoto 2015-2[a]	High D-dimer *vs.* normal D-dimer	4.11	1.64–10.28	NA	NA
Kaseda 2017	High D-dimer *vs.* normal D-dimer	2.24	1.05–4.69	1.92	1.33–2.91
Hou 2019	High D-dimer *vs.* normal D-dimer	NA	NA	1.61	0.66–3.93
Liang 2019	High D-dimer *vs.* normal D-dimer	1.27	0.998–1.61	NA	NA

[a], those studies with the same author and year of publication were extracted from the same article analyzing subgroup based on different cut–off values; therefore, they shared the same identification code. OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; NA, not available.

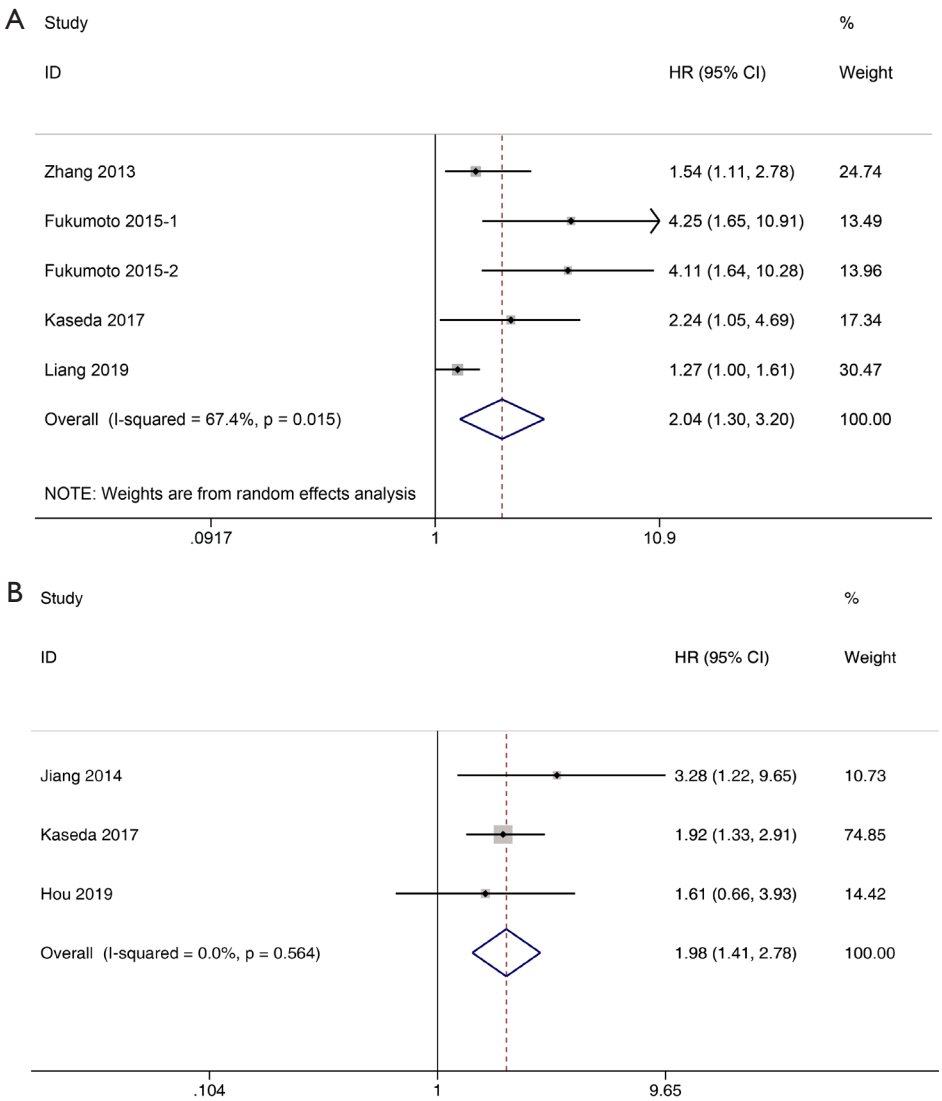

Figure 2 Forest plots of (A) overall survival, and (B) disease-free survival rate. HR, hazard ratio; CI, confidence interval.

Meta-analysis of the impact of high preoperative D-dimer level on long-term survival of patients with surgically treated NSCLC

Four studies with a total of 1,338 patients compared OS between NSCLC patients with high preoperative D-dimer level and these with normal preoperative D-dimer level after surgery. Our meta-analysis found that NSCLC patients with high preoperative D-dimer level had a significantly worse OS than these with normal preoperative D-dimer level (random effects: HR =2.04; 95% CI: 1.30–3.20; P=0.002; I^2=67.4%) (*Figure 2A*) after surgery. Three studies with a total of 816 patients compared DFS between patients with high preoperative D-dimer level and those with normal preoperative D-dimer level after surgical resection. And our meta-analysis found that NSCLC patients with high preoperative D-dimer level also had a significantly worse DFS than those with normal preoperative D-dimer level (fixed effects: HR =1.98; 95% CI: 1.41–2.78; P<0.001; I^2=0.0%) (*Figure 2B*) after surgery. Significant heterogeneity was only observed during the analysis of OS.

Sensitivity analysis and publication bias

A sensitivity analysis was conducted by sequential removal of each study to evaluate the stability of our primary results

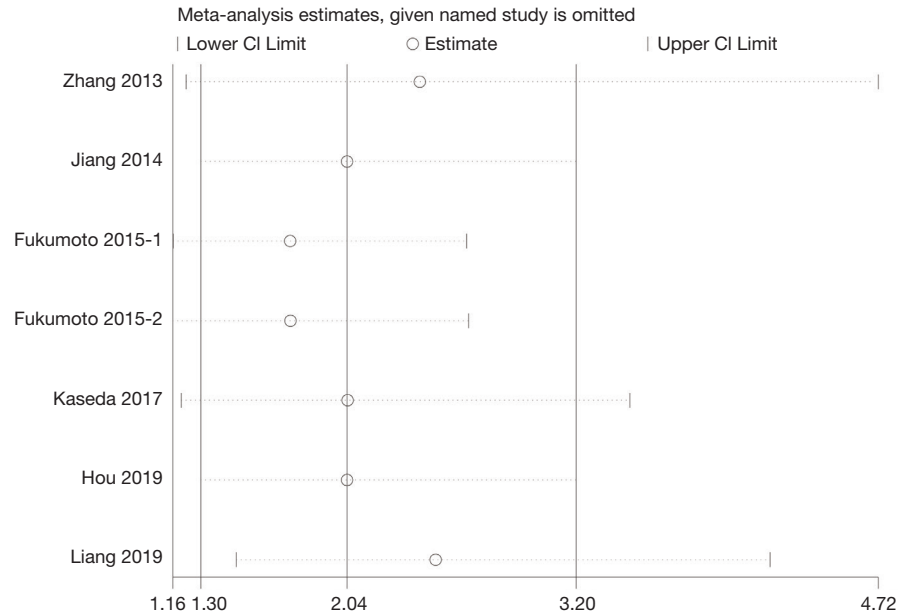

Figure 3 Sensitivity analysis for overall survival. CI, confidence interval.

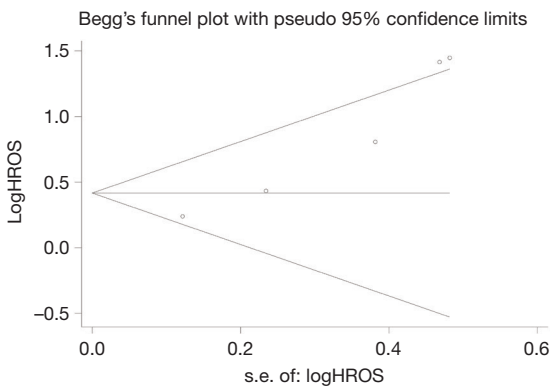

Figure 4 Funnel plot of the included studies for analysis of overall survival. Begg's test: P=0.014; Egger's test: P=0.007.

based on OS. Sensitivity analysis found that sequential removal of each study did not change the result of above analysis (*Figure 3*). Publication bias was evaluated with a funnel plot for the analysis of OS. However, the funnel plot exhibited an asymmetrical appearance (Begg's test: P=0.014; Egger's test: P=0.007), indicating potential publication bias (*Figure 4*).

Discussion

D-dimer, which is the fibrinolytic degradation products of crosslinked fibrin, is generally utilized as a useful marker for the diagnosis of pulmonary embolism with high sensitivity but low specificity (9,10). Recent study found that D-dimer level in NSCLC patients was significantly higher than that of healthy controls (23) and the prevalence of high pretreatment D-dimer level in NSCLC patients was reported to be as high as about 67.9% (19). However, the impact of high preoperative D-dimer level on long-term prognosis of patients with surgically treated NSCLC remains to be determined. Hence, we conducted the first meta-analysis to figure out the prognostic value of high preoperative D-dimer level in patients with surgically treated NSCLC. In this meta-analysis, we finally included 6 cohort studies with a total of 1,817 patients with surgically treated NSCLC. Our meta-analysis found that high preoperative D-dimer level was significantly correlated with worse OS (HR =2.04; 95% CI: 1.30–3.20; P=0.002) and DFS (HR =1.98; 95% CI: 1.41–2.78; P<0.001) for NSCLC patients after surgical resection. Therefore, our meta-analysis adds to the evidence that high preoperative D-dimer level could serve as an independent unfavorable prognostic factor of patients with surgically treated NSCLC.

In malignancies, tumor cells could activate the coagulation system by producing procoagulant factors, such as proteins, lipids, and inflammatory cytokines, which could lead to a hypercoagulable state (24). Because of the enhanced procoagulant activity, the levels of fibrinogen and subsequent fibrin degradation products (such as D-dimer) were significantly increased in cancer patients (25), and

therefore, high level of D-dimer could serve as an indicator of hypercoagulable status. Previous evidence showed that hypercoagulable status could greatly facilitate tumor growth, angiogenesis, tumor cell invasion, and metastasis (24,26). Therefore, it is reasonable that high level of D-dimer could significantly contribute to tumor aggressiveness and invasiveness. As a result, high level of D-dimer was found to be significantly correlated with advanced tumor stage, and more number of metastatic sites (18,27). Moreover, D-dimer level could also serve as a clinically important predictor for the positive lymph node involvement in operable NSCLC patients (28) and it was also found to gradually increase as terminal stage cancer patients approaching to death (29). In addition, the level of D-dimer was also correlated significantly with tumor biomarker level (such as carcinoembryonic antigen) (20) and performance status (30). It is reported that D-dimer level decreased after response to chemoradiotherapy but increased after disease progression, which suggested that D-dimer level change could also serve as a predictor for treatment efficacy and monitoring disease progression (31,32). Taken together, we believe that high preoperative level of D-dimer could serve as an independent unfavorable prognostic factor for NSCLC patients after surgical resection. However, more efforts should be made to elucidate the detailed interactive mechanisms between D-dimer level and lung cancer. As for clinical implications, we think that preoperative monitoring of D-dimer level for NSCLC patients intended for surgery is of great importance. And for NSCLC patients with high preoperative level of D-dimer intended for surgical resection, lowering D-dimer level with anticoagulant drugs such as low-molecular weight heparin may be considered, which may help not only prevent thromboembolism complications but also improve long-term survival (33). Moreover, postoperative monitoring of D-dimer level in NSCLC patients after surgery may be also incorporated into postoperative follow-up strategies, which may help with directing postoperative treatment strategies and predicting early recurrence. And for NSCLC patients with high postoperative D-dimer level, decreasing D-dimer level should also be recommended for both thromboembolism prevention and decreasing cancer recurrence.

There were several limitations in our meta-analysis. First, with only six retrospective cohort studies included in our analysis, the validity of our meta-analysis may be influenced due to small sample size and patient selection bias. Second, the cut-off value for defining high level of D-dimer varied among those studies, which may cause heterogeneities. Finally, potential heterogeneity and publication bias was observed during analysis, which could influence our results.

Conclusions

We conducted the first meta-analysis to investigate the prognostic value of high preoperative level of D-dimer in NSCLC patients after surgical resection. We found that high preoperative level of D-dimer was an independent predictor of poor OS and DFS in surgically treated NSCLC patients. Therefore, routinely monitoring D-dimer level in NSCLC patients intended for surgery may be recommended for daily practice. Further studies with appropriate adjustments, however, are needed to confirm and update our conclusions.

Acknowledgment

None.

Footnote

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

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Supplementary

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2, *Figure 1*
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2, *Figure 1*
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2, *Figure 1*
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2-3, *Table 1, Table 2*
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3, *Figure 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3, *Table 1*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3, *Table 1*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3,5, *Table 1, Table 2, Figure 2*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5, *Figure 2*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

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