RESEARCH ARTICLE

High plasma D-dimer level is associated with decreased survival in patients with lung cancer: a meta-analysis

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Abstract An elevated plasma D-dimer level indicates the activation of coagulation and fibrinolysis. Several studies suggested that high level of plasma D-dimer was associated with the prognosis of lung cancer. In the present study, we performed a meta-analysis to evaluate the relationship between plasma D-dimer level and the prognosis of lung cancer based on larger sample size. We retrieved the literature, assessed and selected the data, and performed the statistical analysis according to the RevMan 5.0 guidelines. Literature-based searching was guided to gather data, and fixed-effects model was used to pool the hazard ratio according to the test of heterogeneity. A total of seven eligible studies including 1,377 lung cancer patients were analyzed. Survival time was significantly better in patients in the low D-dimer group than those in the high D-dimer group (hazard ratio for high D-dimer group = 1.12; 95 % confidence interval 1.02 to 1.23). Patients with high levels of D-dimer have a poorer overall survival compared with those patients with low levels of D-dimer.

Keywords D-dimer · Prognosis · Lung cancer

Introduction

Lung cancer has become the first cause of cancer death in the world. The activation of coagulation and fibrinolysis is reported

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to be associated with malignancy, although the mechanism involved is not completely understood. About 90 % of cancer patients with metastatic disease and one half of patients with cancer have abnormal coagulation parameters [1]. The extent of such activation has been reported to correlate with tumor stage and prognosis in lung cancer.

Kalweit et al. [2] performed a prospective study to compare the plasma levels of thrombin–antithrombin complexes, prothrombin fragment 1+2, and D-dimers in blood samples that simultaneously were drawn from the superior vena cava and the pulmonary vein of a tumor-bearing pulmonary lobe. The authors found that D-dimers plasma levels were significantly higher in the pulmonary venous blood than in the blood simultaneously drawn from the superior vena cava, and the results indicate that malignant lung tumors directly contribute to the activation of hemostasis and fibrinolysis in these clinical settings. Lung cancer is one of the most common tumors of concurrent thrombosis accompanied by hypercoagulable state in patients with deep venous thrombosis and pulmonary thromboembolism. Activation of the coagulation process, hypercoagulable state of blood, and fibrinolysis are all involved in tumor development [3, 4]. Recently, there were many studies [5–11] reporting the relationship between plasma levels of D-dimer and the prognosis of lung cancer. It has been reported that tumors which activate the coagulation system to a higher degree behave in a more aggressive manner biologically [12–14]. There are data suggesting that D-dimer levels individually predict the prognosis and therefore may be a criterion for treatment [12]. D-dimer levels have been found to be significantly higher in lung cancer metastatic disease [14]. Although many literatures suggested that high level of D-dimer is associated with the prognosis of lung cancer, the meta-analysis related to these issues has not been performed up to date.

In the present study, we performed a meta-analysis of published studies to evaluate further the prognostic value of D-dimer level before treatment in patients with lung cancer.

Table 1 The characteristics of enrolled studies

Studies	Published year	Sample size	HR	95 % CI	Outcomes
Komurcuoglu	2011	100	5.1	1.015–11.9	Overall survival
Altiay	2007	78	3.14	1.82–5.93	Overall survival
Buccheri	2003	826	1.3	1.0–1.6	Overall survival
Taguchi	1997	70	4.7	1.8–11.7	Overall survival
Ay	2011	182	1.3	1.2–1.4	Overall survival
Wang	2011	56	4.89	1.2–20.1	Overall survival
Ursavas	2010	65	2.4	1.71–4.92	Overall survival

Materials and methods

Inclusion and exclusion criteria

The inclusion criteria are the following: (1) the clinical research of direct comparison of D-dimer levels in lung cancer before and after treatment, without any restriction on language or publication year; (2) the research objects are lung cancer patients without any restriction on age or racial; and (3) outcome indicators include overall survival.

Exclusion criteria are the following: (1) no clear follow-up and survival analysis and (2) cannot provide valid data required for prognostic evaluation of patients with lung cancer.

Literature collection and screening

We conducted a computerized literature search of PubMed, Embase, Chinese Biomedical Literature Database, Wanfang database, and Chinese CNKI using the terms "D-dimer" and "lung cancer" and "prognosis."

Literature quality assessment and data extraction

Literature filtering and quality assessment was performed independently by two reviewers. Firstly, we excluded literatures that obviously do not meet the inclusion criteria. Inconsistencies were resolved through discussion. We used the Cochrane Handbook 5.0 Quality evaluation criteria to evaluate methodological quality of included studies. The detection method, D-dimer cutoff value, sample size, and treatment programs were all included.

Data analysis

We performed the meta-analysis by using RevMan 5.0 software provided by the Cochrane Collaboration. Q test and I^2 test were used directly to examine the heterogeneity between each study. By heterogeneity test, if $P > 0.05$, we select the fixed-effect model, and if $P < 0.05$, we select the random effect model to merge hazard ratio (HR). We used HR value to evaluate the relationship between the D-dimer level and overall survival in lung cancer. To test the publication bias, we used the RevMan 5.0 statistical software to make the funnel plot. $P < 0.05$ was considered as significant difference.

Results

Literature screening

Three hundred thirteen literatures were preliminarily detected, 306 literatures were excluded due to duplicate publication and non-clinical-based research literature. A total of seven literatures were included, all of them were clinical study and were written in English. These seven studies included 1,377 patients in this research (Table 1).

Fig. 1 Forest plot of prognosis of lung cancer and D-dimer levels, the *horizontal lines* correspond to the study-specific OR and 95 % CI, respectively. The *area of the squares* reflects the study-specific weight. The *diamond* represents the pooled results of OR and 95 %CI. In this analysis, fixed-effects model was used
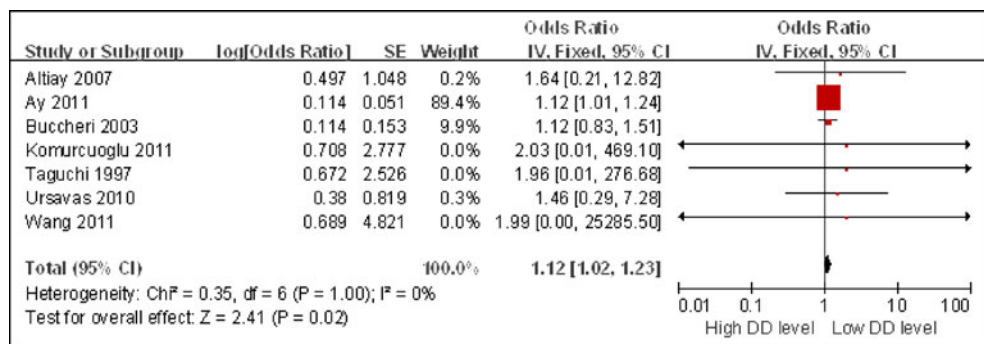
Fig. 2 Begg's funnel plot for publication bias test. Each *circle* denotes an independent study for the indicated association. Log [OR], natural logarithm of OR. *Horizontal line* stands for mean effect size
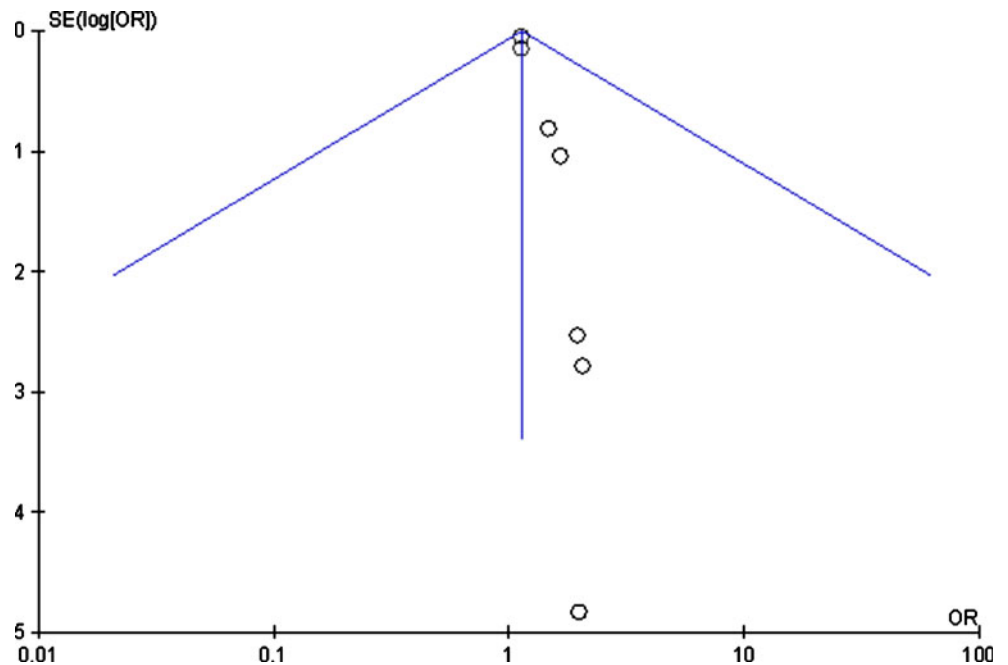
Methodology assessment of D-dimer level detection

D-dimer detection methods included immunoturbidimetric assay and enzyme-linked immunoassay (ELISA). There are five studies using the ELISA method, two studies using the immunoturbidimetric assay. In these seven studies, by the institute with a cutoff value, an average of more than about 77.3 % of the patients have higher levels of D-dimer.

D-dimer level and prognosis

All of these seven studies, the HR values and their 95 % CI can be extracted directly to be used for the evaluation of the value of D-dimer levels and the prognosis of lung cancer. There was better homogeneity between each study ($P=1.00$). The hazard ratio for overall survival of the patients with high levels of D-dimer concentration before treatment was 1.12 times as the patients with low level of D-dimer (Fig. 1).

Publication bias analysis

We analyzed publication bias by use of RevMan 5.0 software; the funnel plot (Fig. 2) shows the points evenly distributed, symmetrical, and most of the points within the 95 % confidence interval. It indicates there is no publication bias, and the result of the study is credible.

Discussion

The biological significance of the hemostatic abnormalities in cancer is not clear. There is some evidence to suggest that the capacity of neoplastic cells to activate the coagulation system and to express increased fibrinolytic activity facilitates their growth and contributes to their invasive and metastatic behavior [15]. D-dimer is a sensitive marker of the fibrinolytic process. Several studies suggested that tumors which activate the coagulation system to a higher degree behave biologically more aggressive and that the increased D-dimer levels may be associated with advanced tumor stage and poor prognosis [5–11].

The present study included seven research studies which all are clear diagnostic criteria, inclusion criteria, and exclusion criteria. And the patients were grouped according to D-dimer levels, and the overall survival was the main outcome. HR value was a statistical indicator to assess the impact of different levels of D-dimer for overall survival of patients with lung cancer.

The present studies included only English literature which can provide the full texts, and the summary of the unpublished studies were excluded. However, this method may cause selection bias. Because the baseline data and the detailed therapy were not available, the results may be impacted by the selection. In addition, the different detection technology also was a main confounder of the present study. In these seven studies, the ELISA method for D-dimer level detected was used in the majority of studies, and the reagents used in each study was from different companies, although with the same kind of detection technology, it is difficult to ensure that the detection result was homogeneous. This fact may be another confounder.

In summary, this meta-analysis of seven studies showed that the D-dimer level is an important factor in the prognosis of lung cancer patients. The patients with a high level of D-dimer concentrations have poor prognosis than that with a low level of D-dimer concentrations.

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