Original Article
Reduced E-Cadherin expression is a prognostic biomarker of non-small cell lung cancer: a meta-analysis based on 2395 subjects

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Abstract: Objective: Previous studies related to the prognostic value of E-Cadherin expression on non-small cell lung cancer (NSCLC) were inconsistent. The present study aimed to evaluate the relation between E-Cadherin expression and the prognosis of NSCLC. Methods: We performed a meta-analysis based on 14 studies including 2395 NSCLC patients. Literature retrieval, data extraction, and meta-analyses were performed according to the Revman 5.0 guidelines. We utilized the fixed-effect model to pool the HR according to the test of heterogeneity in the meta-analysis. Results: A total of 14 eligible studies including 2395 NSCLC patients were analyzed. In total, 51.2% of the patients were considered as having reduced expression of E-Cadherin according to the authors’ cutoff. The pooled hazard ratio (HR) of reduced expression of E-Cadherin for overall survival (OS) was 1.19 (95% CI: 1.01 to 1.40, P=0.04), showing a worse survival when E-Cadherin expression is decreased. Conclusion: Patients with reduced expression of E-cadherin have a poorer OS compared with those with normal or high expression of E-cadherin.

Keywords: E-cadherin, prognosis, non-small cell lung cancer

Introduction

Evidences suggested that lung cancer is the leading cause of cancer-related deaths [1]. In all lung cancer patients, non-small cell lung cancer (NSCLC) accounts for approximately 80% [2]. Although there are several treatments, including surgical resection, chemotherapy, and radiotherapy, the prognosis of NSCLC is poor [3]. Tumor recurrence is the most common cause of disease failure after surgical resection and the main obstacle for long-term survival. The tumor-node-metastasis (TNM) classification indicates the level of disease progression and malignant potential of primary lung cancer [4, 5]. However, even patients with disease at the same stage are split between recurrence and the non-recurrence groups after complete resection. Therefore, the current TNM staging system may have reached the limit of its usefulness [6]. The identification of biomarkers related to prognosis of NSCLC is very important work. Although the prognosis of patients with NSCLC was affected by treatment, recent studies have found that certain parameters change during treatment may be a good prognostic indicator [7]. Recently, many researchers began to focus on E-Cadherin on the prognosis of patients with NSCLC [8-22]. The reduction in E-cadherin expression is a characteristic feature of loss of epithelial cell adhesion which has been frequently extended to the phenotypic changes of increased motility and invasiveness of tumor cells. Several studies have identified that reduced E-cadherin expression is associated with short overall survival in NSCLC [8-15]. However, in some studies, the prognostic value of E-Cadherin has not to be observed [16-22]. These controversial conclusions may result from the relative small sample size of single study. Therefore, we performed a systematic review of the literature with meta-analysis to assess the prognostic value of reduced E-Cadherin expression for survival of NSCLC patients.
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**Materials and methods**

**Inclusion and exclusion criteria**

The inclusion criteria was as follows: 1) the clinical research of direct comparison of E-cadherin expression in NSCLC, without any restriction on language or publication year; 2) the research objects are NSCLC patients without any restriction on age or racial; 3) outcome indicators include overall survival.

The exclusion criteria was as follows: 1) no clear follow-up and survival analysis; 2) can’t provide valid data required for prognostic evaluation of patients with NSCLC.

**Literature collection and screening**

We searched and identified literatures in PubMed, EMBase, Web of Science, Open access database, Chinese Biomedical Literature Database, Chinese CNKI, and Wanfang database using the terms “E-cadherin” and “Lung cancer” or “lung squamous cell carcinoma” or “NSCLC” and “prognosis”.

**Literature quality assessment and data extraction**

The literature filtering and quality assessment was carried out by two independent reviewers (Xing and Guo). We utilized the Cochrane Handbook 5.0 Quality evaluation criteria to evaluate methodological quality of the included studies.

**Data analysis**

We utilized RevMan 5.0 software to perform the meta-analysis and to merge the HR values. We directly used Q-test and I² test to examine the heterogeneity between each study. The hazard ratio (HR) value was utilized to evaluate the relationship between the E-cadherin expression and overall survival in NSCLC. By heterogeneity test, we found there was no heterogeneity between each study, therefore, we select the fixed effect model to merge HR. P<0.05 was considered as significant difference. To test the publication bias, we utilized the RevMan 5.0 statistical software to make the funnel plot.

**Results**

**Literature screening**

437 literatures were preliminarily detected, and 423 literatures were excluded because of duplication, no providing HR and 95% CI, and non-clinical based research literature. A total of 14 literatures were included finally. These 14
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studies including 2395 patients with NSCLC were included in this research.

The immunohistochemistry method was utilized to detect E-cadherin expression in these 14 studies.

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There were 11 studies from which can be extracted the HR and 95% CI directly. And there were three studies from which the HR values and their 95% CI can be calculated according to the data provided by the authors. We did not find significant heterogeneity between each study (P=1.0, I²=0%). Therefore, we utilized the fixed-effect model to merge HR value. The HR for overall survival of the patients with reduced expression of E-cadherin was 1.19 (95% CI: 1.01 to 1.40, P<0.001) (Figure 1).

Publication bias analysis

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

Discussion

The present systematic review shows that the reduced expression of E-cadherin in NSCLC is a poor prognostic factor for survival. E-cadherin conserved gene can play a major role in malignant cell transformation, and especially in tumor development and progression. The suppression of E-cadherin expression is regarded as one of the main molecular events responsible for dysfunction in cell-cell adhesion. Most tumors have abnormal cellular architecture and loss of tissue integrity can lead to local invasion. In other words, loss of function of E-cadherin correlates with increased invasiveness and metastasis of tumors, resulting in it being referred to as a “suppressor of invasion” gene [24, 25].

Previous studies suggested reduced expression was associated with the poor prognosis of NSCLC. The rate of reduced expression of E-cadherin of lung cancer was 44-81% [26-28]. Sulzer et al. [29] stated that when clear staining was present in 50% of the tumor cell population, the result was defined as negative or weakly positive. According to Bohm et al. [30], the E-cadherin expression level was classified as reduced when fluorescence intensity was markedly less than that of adjacent normal epithelium and/or 90-5% of the tumor cells were stained. However, the techniques used to identify the expression of E-cadherin can be a potential source of bias. In these 14 studies, although the immunohistochemistry technique was utilized to detect E-cadherin protein, the experiments were not always performed with the same antibody.

Figure 2. Begg’s funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log HR represents the natural logarithm of HR. The vertical line represents the mean effects size.
In addition, we enrolled literatures which can provide full texts, and that only provide summary and the unpublished studies were excluded. Therefore, this kind of strategy may lead to selection bias. Another potential source of bias is related to the method for extrapolating the HR. If the authors did not report the individual HR together with its variance, we calculated it from the survival comparison statistic and its variance whenever possible. If not, we extrapolated it from the survival curves using several time points during follow-up for reading the corresponding survival rates, assuming that censored observations were uniformly distributed. This methodology is described by Puglisi et al in 1998. Reading the survival rates on the graphical representation of the survival curves was performed independently by two of the authors, but this strategy does not eliminate completely inaccuracy in the extracted survival rates. Consequently, the estimated HR might be less reliable than when obtained from published statistics.

Furthermore, we did not find significant heterogeneity between each study. And we also did not find the publication bias in the present study. Therefore, this meta-analysis of 14 studies showed the E-cadherin expression status is an important factor in the prognosis of NSCLC patients. Patients with reduced expression of E-cadherin have a poorer survival.

Disclosure of conflict of interest

None.

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References


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