

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.

E-cadherin and NSCLC

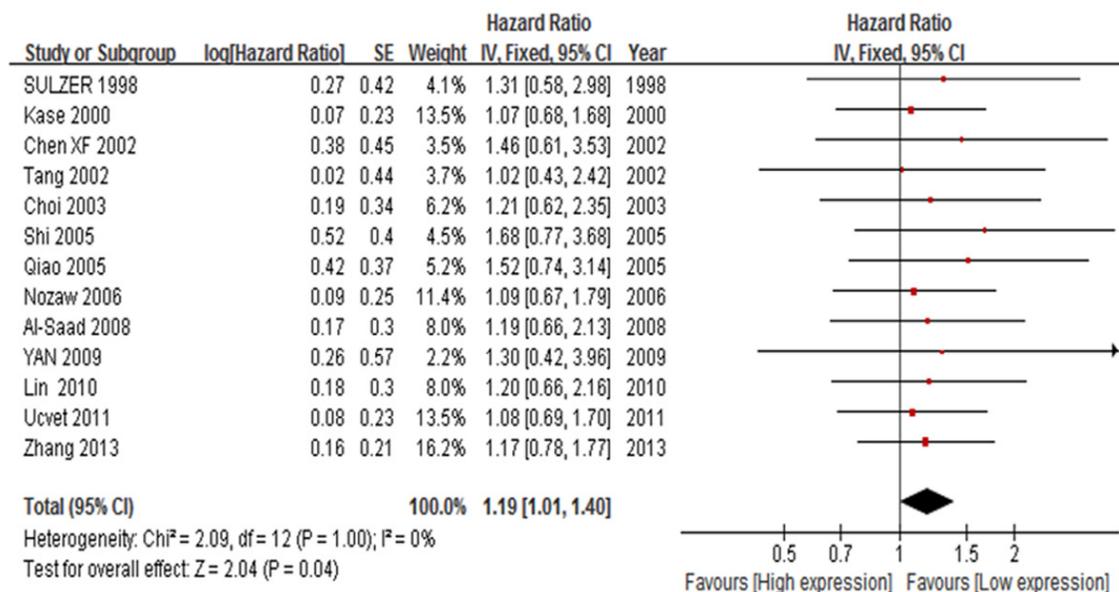


Figure 1. Forest plot of prognosis of NSCLC and E-Cadherin expression. The horizontal lines correspond to the study-specific HR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of HR and 95% CI. In this analysis, the Fixed-effects model was used.

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 I^2 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 mode1 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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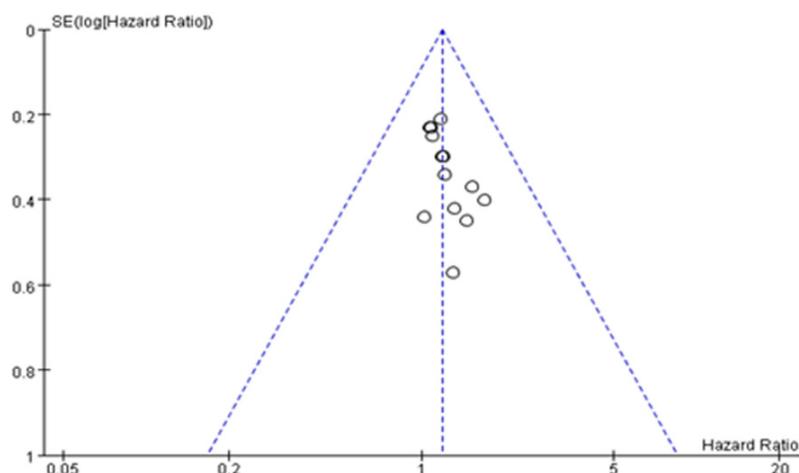


Figure 2. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log HR represents the natural logarithm of HR. The vertical line represents the mean effects size.

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.

E-cadherin expression and prognosis

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 ($P=1.0$, $I^2=0\%$). 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

is one of the most important molecules in cell-cell adhesion. It is localized on the surfaces of cells in regions of cell-cell contact known as adherens junctions. The human epithelial (E)-cadherin gene maps to chromosome 16q22.1. As a member of a large family of genes coding for calcium-dependent cell adhesion molecules (CAMs), the cadherin glycoproteins are expressed by a variety of tissues. It is essential for the formation and maintenance of epithelia [23]. Besides its role in normal cells, this highly

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.

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

- [1] O'Connor SJ. Review of the incidence, prevalence, mortality and causative factors for lung cancer in Europe. *Eur J Cancer* 2011; 47 Suppl 3: S346-7.
- [2] Yen KT, Putzke JD, Staats BA, Burger CD. The prevalence of acute response to bronchodilator in pulmonary lymphangiomyomatosis. *Respirology* 2005; 10: 643-8.
- [3] Quadrelli S, Lyons G, Colt H, Chimondeguy D, Silva C. Lung cancer as a second primary malignancy: increasing prevalence and its influence on survival. *Ann Surg Oncol* 2009; 16: 1033-8.
- [4] Li C, Hong W. Research status and funding trends of lung cancer biomarkers. *J Thorac Dis* 2013; 5: 698-705.
- [5] Watanabe Y. TNM classification for lung cancer. *Ann Thorac Cardiovasc Surg* 2003; 9: 343-50.
- [6] Ganti AK, West WW, Lackner RP, Kessinger A. Current concepts in the diagnosis and management of small-cell lung cancer. *Oncology (Williston Park)* 2010; 24: 1034-9.
- [7] Kyriazi V, Theodoulou E. Assessing the risk and prognosis of thrombotic complications in cancer patients. *Arch Pathol Lab Med* 2013; 137: 1286-95.
- [8] Al-Saad S, Al-Shibli K, Donnem T, Persson M, Bremnes RM, Busund LT. The prognostic impact of NF-kappaB p105, vimentin, E-cadherin and Par6 expression in epithelial and stromal compartment in non-small-cell lung cancer. *Br J Cancer* 2008; 99: 1476-83.
- [9] Chen X, Ding J, Gao W, Yi X, Wang H, Li H. Expression of E-cadherin in non-small cell lung cancer: correlation with lymphatic metastasis and prognosis. *Zhongguo Fei Ai Za Zhi* 2002; 5: 260-2.
- [10] Tang X, Zhou Q, Zhang S, Liu L, Cheng N. A study on the relationship between E-cadherin, β -catenin expression and metastasis and prognosis in non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2002; 5: 263-7.
- [11] Shi R, Zhang D, Fang X, Yu J, Qiu X, Wang E. Expression of integrin-linked kinase and E-cadherin in non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2005; 8: 291-6.
- [12] Choi YS, Shim YM, Kim SH, Son DS, Lee HS, Kim GY, Han J, Kim J. Prognostic significance of E-cadherin and beta-catenin in resected stage I non-small cell lung cancer. *Eur J Cardiothorac Surg* 2003; 24: 441-9.
- [13] Kase S, Sugio K, Yamazaki K, Okamoto T, Yano T, Sugimachi K. Expression of E-cadherin and beta-catenin in human non-small cell lung cancer and the clinical significance. *Clin Cancer Res* 2000; 6: 4789-96.
- [14] Lin Q, Li M, Shen ZY, Xiong LW, Pan XF, Gen JF, Bao GL, Sha HF, Feng JX, Ji CY, Chen M. Prognostic impact of vascular endothelial growth factor-A and E-cadherin expression in completely resected pathologic stage I non-small cell lung cancer. *Jpn J Clin Oncol* 2010; 40: 670-6.
- [15] Liu D, Huang C, Kameyama K, Hayashi E, Yamachi A, Kobayashi S, Yokomise H. E-cadherin expression associated with differentiation and prognosis in patients with non-small cell lung cancer. *Ann Thorac Surg* 2001; 71: 949-54.

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- [16] Nozawa N, Hashimoto S, Nakashima Y, Matsuo Y, Koga T, Sugio K, Niho Y, Harada M, Sueishi K. Immunohistochemical alpha- and beta-catenin and E-cadherin expression and their clinicopathological significance in human lung adenocarcinoma. *Pathol Res Pract* 2006; 202: 639-50.
- [17] Qiao GB, Wu YL, Ou W, Yang XN, Zhong WZ, Lin JY, Zhao J, Xie D, Guan XY. Expressions of E-cadherin in non-small cell lung cancer and its correlation with prognosis. *Zhonghua Wai Ke Za Zhi* 2005; 43: 913-7.
- [18] Sulzer MA, Leers MP, van Noord JA, Bollen EC, Theunissen PH. Reduced E-cadherin expression is associated with increased lymph node metastasis and unfavorable prognosis in non-small cell lung cancer. *Am J Respir Crit Care Med* 1998; 157: 1319-23.
- [19] Ucvet A, Kul C, Gursoy S, Erbaycu AE, Kaya SO, Dinc ZA, Yucel N. Prognostic value of epithelial growth factor receptor, vascular endothelial growth factor, E-cadherin, and p120 catenin in resected non-small cell lung carcinoma. *Arch Bronconeumol* 2011; 47: 397-402.
- [20] Yan H, Jiang Y, Zhang H, Chen X, Ma Y, Wang C. Expression of E-cadherin and β -catenin and their significance in non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2005; 8: 202-6.
- [21] Zhang H, Liu J, Yue D, Gao L, Wang D, Zhang H, Wang C. Clinical significance of E-cadherin, β -catenin, vimentin and S100A4 expression in completely resected squamous cell lung carcinoma. *J Clin Pathol* 2013; 66: 937-45.
- [22] Stoops SL, Pearson AS, Weaver C, Waterson AG, Days E, Farmer C, Brady S, Weaver CD, Beauchamp RD, Lindsley CW. Identification and optimization of small molecules that restore E-cadherin expression and reduce invasion in colorectal carcinoma cells. *ACS Chem Biol* 2011; 6: 452-65.
- [23] Logan PC, Mitchell MD, Lobie PE. DNA methyltransferases and TETs in the regulation of differentiation and invasiveness of extra-villous trophoblasts. *Front Genet* 2013; 4: 265.
- [24] Simões-Correia J, Silva DI, Melo S, Figueiredo J, Caldeira J, Pinto MT, Girão H, Pereira P, Seruca R. DNAJB4 molecular chaperone distinguishes WT from mutant E-cadherin, determining their fate in vitro and in vivo. *Hum Mol Genet* 2014; 23: 2094-105.
- [25] Simões-Correia J, Silva DI, Melo S, Figueiredo J, Caldeira J, Pinto MT, Girão H, Pereira P, Seruca R. DNAJB4 molecular chaperone distinguishes WT from mutant E-cadherin, determining their fate in vitro and in vivo. *Hum Mol Genet* 2014; 23: 2094-105.
- [26] Miao Y, Wang L, Zhang X, Xu X, Jiang G, Fan C, Liu Y, Lin X, Yu J, Zhang Y, Wang E. Promoter Methylation-Mediated Silencing of β -Catenin Enhances Invasiveness of Non-Small Cell Lung Cancer and Predicts Adverse Prognosis. *PLoS One* 2014; 9: e112258.
- [27] Fan C, Miao Y, Zhang X, Liu D, Jiang G, Lin X, Han Q, Luan L, Xu Z, Wang E. Btbd7 contributes to reduced E-cadherin expression and predicts poor prognosis in non-small cell lung cancer. *BMC Cancer* 2014; 14: 704.
- [28] Dong S, Zhao J, Wei J, Bowser RK, Khoo A, Liu Z, Luketich JD, Pennathur A, Ma H, Zhao Y. F-box protein complex FBXL19 regulates TGF β 1-induced E-cadherin down-regulation by mediating Rac3 ubiquitination and degradation. *Mol Cancer* 2014; 13: 76.
- [29] Sulzer MA, Leers MP, van Noord JA, Bollen EC, Theunissen PH. Reduced E-cadherin expression is associated with increased lymph node metastasis and unfavorable prognosis in non-small cell lung cancer. *Am J Respir Crit Care Med* 1998; 157: 1319-23.
- [30] Böhm M, Totzeck B, Birchmeier W, Wieland I. Differences of E-cadherin expression levels and patterns in primary and metastatic human lung cancer. *Clin Exp Metastasis* 1994; 12: 55-62.