ORIGINAL ARTICLE

Prognostic value and clinicopathological significance of epithelial cadherin expression in non-small cell lung cancer

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Keywords
E-cadherin; meta-analysis; metastasis; non-small cell lung cancer (NSCLC); overall survival (OS).

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Abstract

Background: Epithelial cadherin (E-cadherin), a calcium-dependent cell-cell adhesion molecule, as an important adhesion and signaling pathway mediator plays key roles in the maintenance of tissue integrity. However, the available results of E-cadherin expression and its prognostic value on non-small cell lung cancer (NSCLC) remain controversial. Therefore, a meta-analysis of published studies investigating the prognostic value of E-cadherin expression and its association with clinicopathological characteristics with NSCLC was performed.

Methods: A literature search via PubMed, EMBASE, and MEDLINE (Ovid) databases was conducted. Data from eligible studies were extracted. Statistical analysis was performed using STATA 12.0.

Results: A total of 2412 patients from 15 studies were included in the meta-analysis. The results showed that the pooled hazard ratio (HR) for overall survival was 0.55 (95% confidence interval [CI]: 0.44–0.69) by univariate analysis and 0.68 (95% CI: 0.43–1.08) by multivariate analysis. In addition, the results showed a significant association between E-cadherin expression and the presence of lymph node metastasis (odds ratio = 0.37, 95% CI=0.05–0.69, $P = 0.001$).

Conclusion: Our study showed that positive expression of E-cadherin was associated with a favorable prognosis in patients with NSCLC, and might act as an inhibition factor of metastasis. However, adequately designed prospective studies are required to confirm this finding.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC) represents 85% of lung tumors.[1] As patients are usually diagnosed in advanced stage and cancer metastases are resistant to conventional therapy, the overall survival for patients with lung cancer is still less than 15%, despite great advances in the treatment of cancer in recent years.[2–4]

Several biological markers have been recognized as prognosticators, as well as indicators of potential therapeutic targets for different types of human cancers, including NSCLC. Because of complicated molecular biology, multiple factors including cell growth and cell cycle control, angiogenesis, morphogenesis, apoptosis, and metastatic adhesion have been researched with the aim of creating biological risk assessment and biological staging models for NSCLC.[5,6] E-cadherin, as the prime mediator of intercellular adhesion in epithelial cells, is a transmembrane glycoprotein that functions to maintain stable cell-cell contact in epithelial cell types.[7] It has an important role in cell adhesion specificities and morphogenesis, and it may have a signaling effect through interaction with the intracellular cytoskeleton where the tyrosine kinase of the *src* family is localized.[8,9] Additionally, because cell discohesiveness and detachment are important for tumor invasiveness, decreased expression or loss of E-cadherin may facilitate tumor invasion and metastasis.[9,10] Recently, E-cadherin′s downregulation or loss of regulation was a sign of poor prognosis, and showed invasion and metastasis for multiple types of epithelial carcinomas in cases of the breast,[11] prostate,[12] esophagus,[13–15] stomach,[16–18] colon,[19] liver,[20,21] pancreas,[22] and urinary bladder.[23,24] However, the relationship of E-cadherin expression levels to NSCLC patients′ survival and clinicopathological variables remains controversial. Therefore, based on the discordant results obtained by a number of studies, we conducted this meta-analysis to quantify the role of E-cadherin as a prognostic and clinicopathological marker among patients with NSCLC.

Materials and methods

Literature search

A literature search via PubMed, EMBASE and MEDLINE (Ovid) databases was conducted to find articles that evaluated the role of E-cadherin in NSCLC (the last search was updated on 5 December 2013) using the following text and keywords: (i) epithelial cadherin or E-cadherin; (ii) non-small cell lung cancer or NSCLC or lung cancer; (iii) survival analysis or prognostic; (iv) expression; and (v) tissue.

Selection criteria

There was no restriction on the language in which the articles were published and all eligible studies that examined the association between the expression of E-cadherin and clinicopathological characteristics, progression-free survival (PFS) or overall survival (OS) were included. We carefully searched the titles and abstracts of publications to find those studies that examined the relationship between the expression of E-cadherin and clinicopathological variables and PFS or OS in patients with NSCLC. After the abstracts met these conditions, the full texts were analyzed and included into our meta-analysis according to the following criteria: (i) articles were published as a full paper; (ii) expression levels of E-cadherin were compared to patient's PFS or OS; (iii) the expression of proteins were evaluated in tumor tissues by immunohistochemistry (IHC) or reverse transcription polymerase chain reaction (RT-PCR) analysis; (iv) sufficient data on hazard ratios (HR) and 95% confidence interval (CI) for survival were provided or could be calculated; (v) patients had NSCLC without receiving neoadjuvant therapy or radiochemotherapy before complete surgical resection; and (vi) if the same group of patients were used in the analysis more than once, the most complete research was selected.

Data extraction

Two investigators independently checked all potentially relevant articles and extracted data. In the case of disagreement, a third author would assess these articles. The following information was collected from each study: first author's name, year of publication, ethnicity, number of patients, laboratory methodology, follow-up time, cut-off value, information about neoadjuvant therapy, smoking status, histological type, lymph node metastasis, clinical stage, and HR with 95% CI.

Statistical analysis

The intensity of the relationship between the expression levels of E-cadherin and survival were described as HRs, and the strength of the association between E-cadherin and clinicopathological parameters was expressed as an odds ratio (OR). Positive expression of E-cadherin indicated poor prognosis in patients with NSCLC if HR > 1 with 95% CI did not overlap 1. In some of the studies, HR and 95% CI were directly obtained using univariate or multivariate survival analysis. Otherwise, HR and 95% CI were calculated by Kaplan–Meier survival curves using Engauge Digitizer Version 4.1 software (http://digitizer.sourceforge.net/) and a method previously reported by Parmar *et al*.[25] Extracted data were then utilized to reconstruct the HR and its variance (GraphPad Software Inc., La Jolla, CA, USA).

The pooled HR corresponding to 95% CI were used to assess the prognostic value of E-cadherin in patients. Statistical heterogeneity was tested by Cochrane's Q test (Chi-squared test; Chi^2) and inconsistency (I^2).[26,27] If there was no obvious heterogeneity, a Mantel-Haenszel fixed-effects model was used to estimate the pooled HR; otherwise, the DerSimonian and Laid random-effects model was used.[28] Funnel plot and Begg's rank correlation method were utilized for assessing the risk of publication bias. STATA 12.0 (STATA Corp., College, TX, USA) was used to perform statistical analysis. A *P*-value of less than 0.05 was considered statistically significant.

Results

Study selection and characteristics

Forty-three articles were retrieved from PubMed and 78 articles from EMBASE and MEDLINE (Ovid) (Fig 1). After careful examination of the abstracts, 53 studies that focused

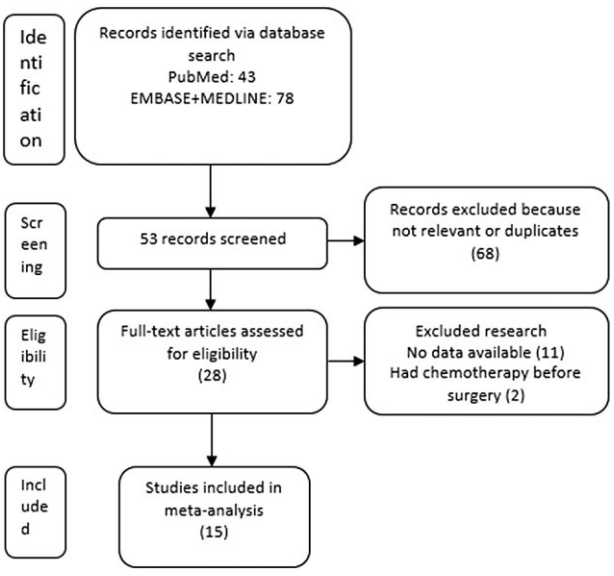

Figure 1 Flow chart summarizing the literature search and study selection.

on the association between the expression of E-cadherin and survival were included in our full-text review process. After reading the full text, 11 papers were excluded because data were not extractable or did not provide enough survival information, and two papers were excluded because the patients underwent neoadjuvant therapy before complete surgical resection. Finally, 15 studies including 2412 cases were included in the meta-analysis. Among the included studies, 10 papers were in English and five papers were in Chinese.

The characteristics of the eligible studies are summarized in Table 1. Eleven studies included patients from Asia, three from America, and one from Europe. Expressions of E-cadherin were detected via IHC or RT-PCR. None of these studies analyzed the relationship between E-cadherin expression and PFS in patients with NSCLC; therefore we could only conduct a meta-analysis on the association between the expression level of E-cadherin and OS. According to univariate analysis, two studies directly provided HR with 95% CI, and 13 studies detailed survival curves from which the HR could be calculated. In multivariate analysis, eight studies directly provided the HR with 95% CI, while the remaining seven papers had no data available. ORs were calculated from articles that provided sufficient data comparing the expression of E-cadherin with clinical characteristics (data is not shown).

Meta-analysis

We first evaluated whether E-cadherin expression levels were associated with OS in patients with NSCLC. Of the 15 trials eligible for systematic review, seven articles could not be included in the meta-analysis by multivariate analysis because there was insufficient data to estimate the HR and 95% CI.

Fifteen studies, including 2412 patients, reported the effect of E-cadherin on OS using analyses unadjusted for other factors.[2,7,10,29–40] As shown in Figure 2a, according to univariate analysis, E-cadherin was significantly correlated with favorable OS (HR = 0.55, 95% CI = 0.44–0.69, $P < 0.05$). The DerSimonian and Laird random effects model was used as significant heterogeneity was observed among the studies ($P = 0.000$, $I^2 = 70.1\%$). Eight studies demonstrated the effect of E-cadherin on OS using analyses adjusted for other factors, including 1119 patients.[2,7,10,37,41–44] As shown in Figure 2b, statistical significance was observed between the expression levels of E-cadherin and OS (HR = 0.68, 95% CI = 0.43–1.08, $P < 0.05$). The DerSimonian and Laird random-effects model was again used because of significant heterogeneity among the studies ($P = 0.000$, $I^2 = 80.3\%$).

We performed subgroup analyses to investigate whether there were differences in results with respect to the year of publication, ethnicity, cut-off values and follow-up time in

Table 1 Main characteristics and results of eligible studies

												Overall Survival						
												Univariate			Multivariate			
First Author	Year	Ethnicity	Cases	P/N	Method	Follow-up Time	Cutoff-value	Neoadjuvant Therapy	Smoking Status (Yes/No)	Histological Type (SCC/ADC/ Others)	Lymph Node Metastasis (Yes/No)	Stage (I/II/III/IV)	HR Estimate	HR	95% CI	HR Estimate	HR	95% CI
Shinichiro Kase	2000	Japanese	331	193/138	IHC,	60M	>70%	NA	NA	104/227	125/206	174/41/104/12	Sur. Curve	0.73	0.51–1.04	NA	NA	NA
Tang Xiao-jun	2002	Chinese	112	59/53	IHC	60M	NA	NA	77/35	44/50/18	79/33	17/24/59/12	Sur. Curve	0.21	0.13–0.34	NA	0.965	NA
Chen Xiao-feng	2002	Chinese	138	57/81	IHC	60M	≥40%	NA	NA	57/55/26	99/39	26/32/80	Sur. Curve	0.43	0.26–0.70	NA	NA	NA
George Deeb	2004	American	130	65/53	IHC	57.2M	>10%	NA	105/12	37/81	39/79	97/21(II-IIIa)	HR 95%CI	0.5	0.3–0.8	HR 95%	0.5	0.3–0.9
Yan Hong	2005	Chinese	129	49/80	IHC	60M	NA	NA	NA	56/52/21	66/63	44/22/48/15	Sur. Curve	0.69	0.46–0.95	NA	NA	NA
Shi Rui	2005	Chinese	76	25/51	IHC,	40M	>60%	NA	NA	44/32	41/35	23/11/37/5	Sur. Curve	0.45	0.21–1.3	NA	0.376	NA
S Al-Saad	2008	Norwegian	335	201/120	IHC	96M	scores>2	NA	320/15	191/95/49	103/232	212/91/32	Sur. Curve	0.72	0.54–0.97	HR 95%	1	0.997–2.158
Yang Liu	2008	Chinese	138	97/41	IHC	120M	NA	NA	NA	75/63	79/59	65/58/15(III-IV)	Sur. Curve	0.65	0.43–0.99	HR 95%	0.465	0.252–0.858
MI Galleges	2009	American	178	32/135	IHC	18Y	NA	24% of patients	130/3/45	77/64/37	NA	90/52/36	Sur. Curve	0.79	0.49–1.3	HR 95%	0.38	0.19–0.77
Qiang Lin	2010	Chinese	185	90/95	IHC	51M	≧50%	NA	93/92	53/132	NA	185(I)	Sur. Curve	1.96	1.07–3.57	HR 95%	1.51	1.03–2.22
Toshihiro Yamashita	2010	Japanese	117	70/47	IHC	NA	≧70%	NA	53/64	31/86	NA	NA	HR 95%CI	1.346	0.737–2.460	HR 95%	1.783	0.948–3.353
WU Shiwu	2012	Chinese	50	24/26	IHC,RT-PCR	41.6 ± 29.5M	scores>1	No	NA	36/14	26/24	8/28/14	Sur. Curve	0.36	0.09–0.94	HR 95%	0.159	0.39–0.649
Jian Feng	2012	Chinese	103	35/68	IHC,RT-PCR	60M	>10%	NA	NA	46/55/2	50/53	50/27/26(III-IV)	Sur. Curve	0.6	0.31–1.14	HR 95%	0.491	0.268–0.900
Nagaraj S	2012	American	310	161/123	IHC	50M	NA	NA	243/67	188/191	NA	NA	Sur. Curve	0.35	0.27–0.46	NA	NA	NA
Miao Xiao-hui	2012	Chinese	80	27/53	IHC	60M	>50%	NA	38/42	38/42	31/49	62(I-II)/18(III-IV)	Sur. Curve	0.54	0.27–1.07	NA	NA	NA

ADC, adenocarcinoma; HR, hazard ratio; IHC, immunohistochemistry; M, month; NA, not available or not applicable; P/N, positive expression/negative expression; SCC, squamous cell carcinoma; Y, year.

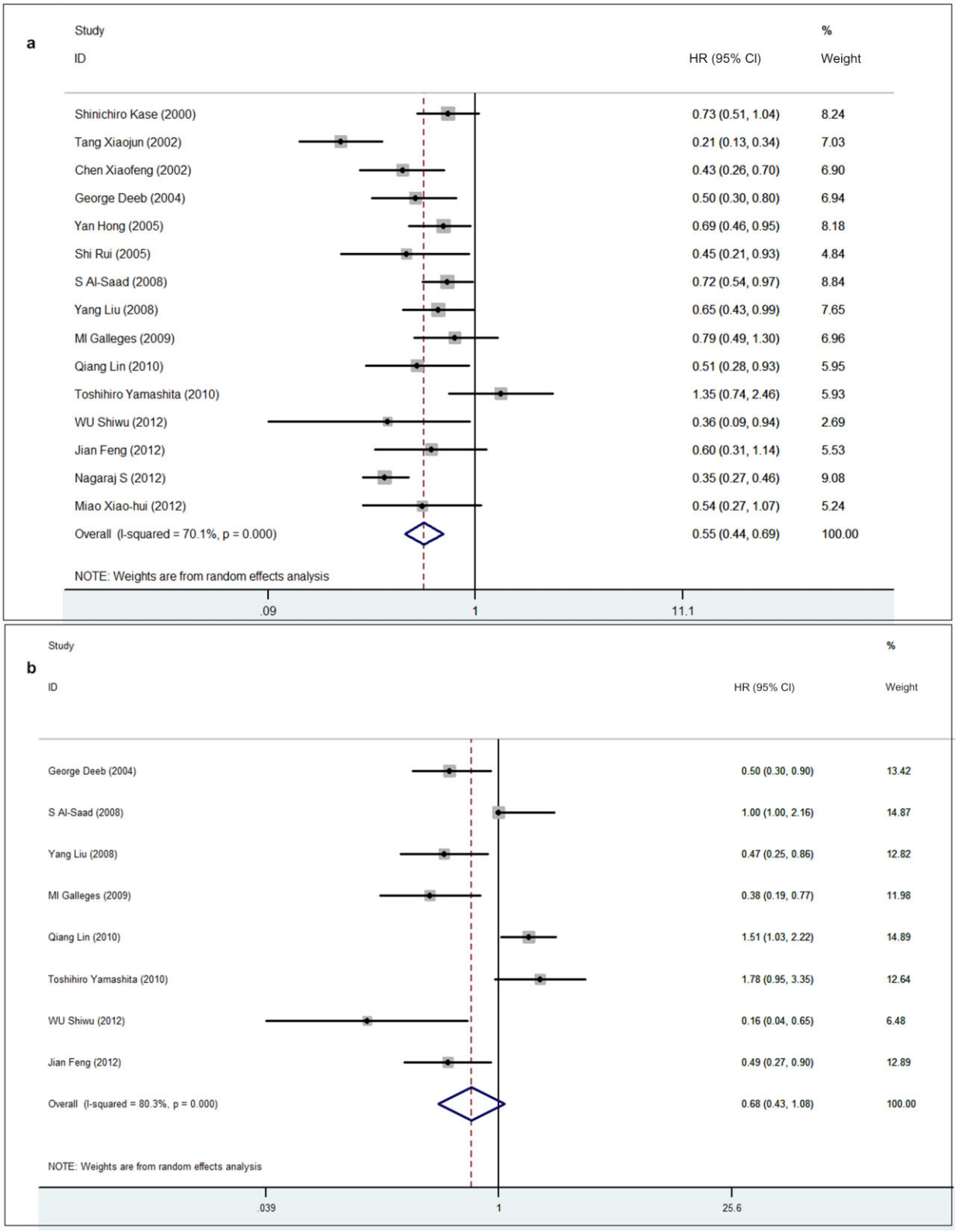

Figure 2 Forest plots showing the combined relation hazard ratio (HR) from the random effects model for overall survival. (**a**) Univariate analysis. (**b**) Multivariate analysis. CI, confidence interval.

Table 2 Meta-analysis assessing the association between E-cadherin expression and clinicopathological variables

Clinicalpathological Variable	No. of Studies	Pooled Data(Random)				Test for Heterogeneity		
		Cases	OR	95% CI	*P*-value	Chi^2	*P*-value	I^2 (%)
Gender(male/female)	5	508	0.89	0.50–1.29	0.000	1.44	0.837	0.000
Age(<60/ ≥ 60)	3	206	0.95	0.30–1.60	0.004	0.04	0.980	0.000
Histological Type(SCC/ADC)	8	1106	0.68	0.36–1.00	0.087	14.63	0.041	52.200
Differentiation(well-moderate/poor)	4	555	1.71	0.91–2.52	0.000	0.79	0.851	0.000
Lymph Node Metastasis	5	744	0.46	0.08–0.79	0.025	20.78	0.001	75.850
TNM Stage (I-II/III-IV)	4	555	1.23	0.59–1.87	0.000	1.57	0.666	0.000

ADC, adenocarcinoma; No., number; SCC, squamous cell carcinoma.

which the study was conducted. Despite the limited number of studies that were eligible for this meta-analysis, in the stratified analysis by ethnicity, decreased risks were found in Chinese (HR = 0.48, 95%CI = 0.36–0.82, P = 0.020) and American patients (HR = 0.50, 95% CI = 0.31–0.82, P = 0.013). Moreover, subgroup analyses regarding the year of publication revealed that articles published in 2012 showed a favorable prognostic value for survival in NSCLC (HR = 0.40, 95% CI = 0.31–0.52, P = 0.363). However, statistically significant results from other factors were unavailable (Supporting Information Figure S1A and B).

Publication bias was determined using the Begg's test (Supporting Information Figure S1C). No publication biases were found in the 15 OS studies using univariate analysis (P = 0.889) or in the eight OS studies using multivariate analysis (P = 0.061). Sensitivity analysis was performed to investigate the effect of each study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

In order to gain further insight into the role of E-cadherin as biological marker, we investigated the relationship between E-cadherin expression and clinicopathological variables (Table 2). Although there were a limited number of studies, a random effects model revealed an association between the expression of E-cadherin and the presence of lymph node metastasis (Fig 3). The number of patients with positive lymph node metastasis was lower in the group of E-cadherin positive expression (OR = 0.46, 95% CI = 0.08–0.79, P = 0.001).

Discussion

Immortalization and invasiveness are important characteristics of cancer tissues, and postoperative recurrence and metastasis are the principal causes for treatment failure and death in patients with NSCLC. Based on these reasons, identifying the specific molecular markers to distinguish resectable NSCLC patients with a high risk of recurrence is crucial to improving therapeutic outcome. Therefore, several biological effectors related to cell growth, differentiation, and adhesions have been studied in individuals who have developed NSCLC. In earlier studies, various kinds of genetic alterations have been identified as prognostic factors, such as human epidermal growth factor receptor 2 in breast carcinoma and the epidermal growth factor receptor gene in NSCLC.[45] However, most other clinically useful molecular markers with a prognostic value and predictive value of therapeutic response failed to demonstrate usefulness in subsequent investigations.

E-cadherin is a cell-cell adhesion transmembrane molecule that connects epithelial cells via homotypic calcium-dependent interactions. It also plays an important role in cellular adhesion activity and as an invasion or metastasis suppressor by signal transduction.[7] In recent years, some studies have shown that E-cadherin expression was highly downregulated in a variety of cancers, including hepatocellular cancer, retinoblastoma, endometrial carcinoma and gastric cancer,[41–44,46] which correlated with malignancy, metastasis, and clinical stage. Moreover, several studies reported that a low expression of E-cadherin in NSCLC was associated with more aggressive behavior of tumor epithelial cells and a poor prognosis.[2,47] Lee *et al.*, however, studied 115 patients with NSCLC for E-cadherin expression using IHC, and found that E-cadherin expression had no prognostic value in multivariate analysis, although it was associated with differentiation, invasiveness, and advanced stage.[48] Kase *et al.* assessed the expression of E-cadherin in 331 cases of NSCLC using IHC, and concluded that there was no independent predictive value of E-cadherin as a disease prognosticator.[34] Thus, because of contrasting results of the prognostic implication of E-cadherin in NSCLC, we undertook a meta-analysis to determine whether E-cadherin could serve as a prognostic marker for patients with NSCLC.

Our meta-analysis focused on the relationship between E-cadherin expression and OS or clinicopathological parameters in resected NSCLC. We also collected information on the relationship between the E-cadherin expression and PFS, but could not conduct a meta-analysis because of insufficient data. Although the results of six studies[7,29,34,35,38,40] which reported the impact of E-cadherin expression on OS had no statistical significance compared with the other nine

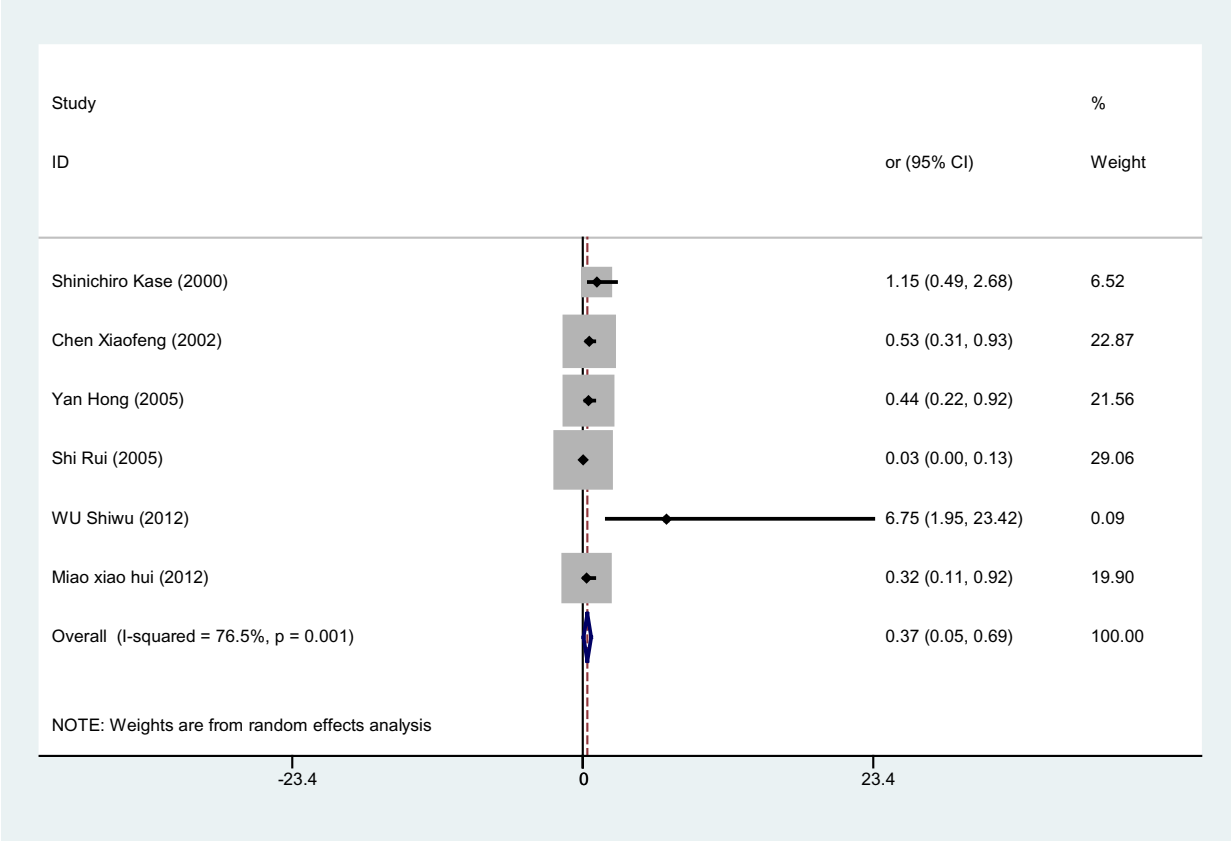

Figure 3 Forest plots reflects the combined odds ratio (OR) with 95% confidence interval (CI) for the association between E-cadherin expression and lymph node metastasis.

studies[2,10,32,33,36,37,39] in the meta-analysis, our meta-analysis with accumulated data suggested that an overexpression of E-cadherin was associated with longer OS and predicted favorable prognosis in patients with NSCLC. The pooled HR for OS was 0.55 (95% CI: 0.44-0.69) by univariate analysis and 0.68 (95% CI: 0.43–1.08) by multivariate analysis. Furthermore, a small number of studies investigated the association between E-cadherin expression and lymph node metastasis or histological type, and interestingly found that the expression of E-cadherin correlated with the existence of lymph node metastasis (OR: 0.37, 95% CI: 0.05–0.69).

Our meta-analysis was based on published data and was performed using univariate analysis followed by further multivariate analysis, which, to our knowledge is the first evaluation of the effect of E-cadherin on OS for NSCLC. However, some limitations exist in our study. We did not include unpublished studies and abstracts in our meta-analysis because the required data was not available. Additionally, the risks calculated in our meta-analysis might be overestimated as a result of publication and reporting bias. Positive results tend to be accepted by journals, whereas negative results are often rejected or not submitted. Another potential source of bias is related to the method used to extrapolate the HR. HR was extracted from the data included in the article directly or calculated from survival curves. The method of extrapolating HR from survival curves did not completely eliminate inaccuracy in the extracted survival rates. Furthermore, we included studies that used IHC. Prognostic markers based on IHC can provide inconsistent or contradictory results, because of the use of different antibodies and processing methods, as well as different scoring and categorization systems.[34] It would be desirable to have IHC findings reported carefully and in detail. Moreover, different therapy strategies used for patients after surgery in these studies had different impacts on OS, and should be taken into consideration. Unfortunately, only one of these studies described the therapy strategy after the patients had been diagnosed with lung cancer. Therefore, more meticulous research should be conducted. We performed stratified analysis because of the limited number of studies; however, the results had no statistical significance. Nevertheless, no publication bias was detected using the Begg′s test ($P > 0.05$), indicating that the statistics obtained approximated the actual results. Sensitivity analysis was also conducted to investigate the influence of a

single study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, suggesting that our results were statistically reliable.

Conclusion

In summary, on univariate analysis the over-expression of E-cadherin was associated with favorable OS in patients with NSCLC and it might act as an inhibition factor of lymph node metastasis. Undoubtedly, these results should be confirmed by more prospective and randomized clinical studies; however, they provide new insights that support E-cadherin as a potential prognostic biomarker and biological target for anticancer therapies in NSCLC.

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Disclosure

No authors report any conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 A. Stratified analysis by ethnicity. B. Stratified analysis by year of publication. C. Funnel blots of meta-analysis.

