Original Article

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Prognostic significance of β-catenin expression in patients with non-small cell lung cancer: A meta-analysis

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Summary **β-Catenin has been reported to play a crucial role in the invasion and metastasis of lung cancer. However, the value of β-catenin as a prognostic factor for non-small cell lung cancer (NSCLC) remains controversial. The present study systematically reviewed the evidence of predicting significance of β-catenin expression in NSCLC patients with meta-analysis. Twelve literatures were included by searching PubMed, Cochrane library, and EMBASE databases. Separate hazard ratio estimates and a 95% confidence interval (CI) for the prognostic value of β-catenin in NSCLC were extracted and merged from the included literatures. The summary hazard ratios were 1.91 (95% CI 1.60-2.28), indicating a worse overall survival for NSCLC patients with reduced β-catenin expression. There was no significant heterogeneity among the studies (X^2 = 12.41, p = 0.413, I^2 = 3.3%). Publication bias was not statistically significant. Sensitivity analysis showed that omission of any single study had little effect on the combined risk estimates. This meta-study revealed that decreased β-catenin expression denoted a poor prognosis in NSCLC patients.**

Keywords: β-Catenin, non-small cell lung cancer, prognosis, overall survival

1. Introduction

Lung cancer is the leading cause of death in malignant neoplasm around the world (*1*), accounting for 1.1 million deaths annually world-wide (*2*). In China, lung cancer is one of the principal malignant neoplasms, with an increasing tendency in both morbidity and mortality in recent years (*3*). The prognosis of lung cancer is also dismal, with a 5-year survival of merely 15% (*4*). Non-small cell lung cancer (NSCLC), mainly including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for nearly 90% of all lung cancer cases (*5*). Though new chemotherapies have remarkably improved the outcome of NSCLC patients, the prognosis remains poor on the whole. Approximately 30% of patients with stage I NSCLC will die within 5 years after surgery (*6*) due to metastasis.

Tumor cells escaping from the primary tumor is the initial step of metastasis, which depends in part on cell adhesion molecules (CAMs) (*7*). Once the CAMs are altered, metastasis would be promoted (*8*) and a poor prognosis will be induced (*9*). β-Catenin, a multifunctional protein encoded in chromosome 3p21 (*10*), is one of the essential components of CAMs and plays a crucial role in cell-cell adhesion and tissue remodeling (*11*). It participates in cell-cell adhesion by binding to the intracellular domain of E-cadherin. The latter is a homotypic cell-cell interaction molecule which is ubiquitously expressed on epithelial cells (*8*) and has proven to be related to a poor outcome in NSCLC (*12*). β-Catenin is also important in Wnt/β-catenin signaling pathway by activating transcription of target genes and leading to cell proliferation, invasion, and metastasis (*13*). It is reported that reduced expression of β-catenin is an important determinant for the metastatic capability of certain cancer cells (*14*). Indeed, decreased β-catenin expression has been widely reported to be related to poor differentiation, lymph node spread, and metastasis in various human

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carcinomas such as breast cancer (*15*), gastric cancer (*16*), and prostate cancer (*17*).

Recently, the relationship between β-catenin expression and survival of patients with NSCLC has been intensively studied. But the prognostic significance of β-catenin expression in NSCLC remains controversial. Actually, several studies claimed that reduced β-catenin expression was associated with poor outcome of NSCLC patients, while others did not support the conclusion. Therefore, we performed this meta-analysis to assess the prognostic value of β-catenin expression for NSCLC patients.

2. Methods

2.1. *Search strategy and study selection*

We searched PubMed, Cochrane library, and EMBASE databases for relevant articles published until November 1st, 2012. Articles were identified using the following search terms: "Beta-catenin, β-catenin, or CTNNB1", "prognostic, prognosis, or survival" and "lung neoplasm, lung cancer, or lung carcinoma". No lower date or language limits were applied initially, but for full-text review and data analysis, only articles in English were included finally. References of identified articles were also searched manually. To make this study meet the high standards, the following criteria were used: (*i*) the patients were diagnosed as NSCLC by pathology; (*ii*) β-catenin expression was measured by immunohistological chemistry (IHC) method in primary lung cancer tissue; (*iii*) information on overall survival comparing patients with and without impaired expression of β-catenin were provided; (*iv*) sufficient data of the value of hazard ratio (HR) and 95% confidence interval (CI) between β-catenin expression and overall survival were given; (*v*) the patients were followed-up for at least 3 years. We excluded articles of studies on animals, reviews and studies with insufficient data. When an individual author published several articles with data obtained from the same patient population, only the newest or most informative article was selected.

In selecting literature, we first screened the title and abstract to see whether they met the including criteria. Then, based on the initial screening, we scrutinized the full manuscript of studies that needed further examination. Two reviewers (Song and Mei) independently verified study eligibility. All disagreements in judging study eligibility were resolved by consensus.

2.2. *Data extraction and quality assessment*

The following information were retrieved independently by 2 reviewers (Mei and Su) from the final set of literatures: publication year, first author, number of patients enrolled, histology and disease stage, method of HR estimation, cut off value, percentage of decreased expression, HR and 95% CI as well as the other related events.

Two reviewers (Mei and Su) read the articles independently and performed quality scoring using the mean global quality score method according to Steele's (*18*). The overall score evaluated various aspects of the methodology, and was grouped into four main categories: scientific design, description of the method used to identify abnormal β-catenin expression, the generality of the results, and the analysis method of data. A maximum of 10 points was given for each category with an inclusive maximum score of 40 points. When an item was not appropriate in a study, its value was abandoned. Final scores were expressed as percentages ranging from 0% to 100%, with higher values indicating better methodology.

2.3. *Statistical analyses*

We chose HR as the effect indicator to compare time-to-event results for its distinctive advantages: accounting for censoring, including all data and describing all of patients' experience. The individual HR estimate was combined into overall HRs with the methods published by Yusuf *et al*. (*19*). Some of the studies that provided HR and a 95% CI value were pooled directly. For studies not provided directly, we obtained the value from the available data or by reading Kaplan-Meier survival cure in the original studies (*20-22*). The way to obtain HR and a 95%CI from the Kaplan-Meier survival cure was reported by Parmar MK (*21*) and has been widely applied in meta-analysis about prognostic factors (*16,18,23,24*). Engauge Digitizer version 2.11 (free software from *http://sourceforge.net*) was used in reading the Kaplan–Meier curves. If a study provided both the results of multivariate analysis and univariate analysis, we chose the former. The available data contained the total number of events, the log-rank statistic and its *p*-value, or the O-*E* statistic (difference between numbers of observed and expected events). Heterogeneity among studies was assessed by the Chi-squared test and *Q*-test. The I^2 value was used to evaluate the heterogeneity (I^2 = 0-40%, no or moderate heterogeneity; I^2 > 40%, significant heterogeneity). Fixed-effect model was used if there was no significant heterogeneity. Otherwise, the random-effect model was used. Funnel plot and Egger's linear regression test were performed to identify the possibility of publication bias. The robustness of the combined results was confirmed by sensitivity analysis in which the data of an individual study were removed each time. The pooled HR > 1 indicated that NSCLC patients with decreased β-catenin expression had a poor survival. The impact of decreased β-catenin expression on overall survival was considered statistically significant if the 95% CI

did not overlap with 1. Nonparametric tests were used to compare the distribution of quality scores according to the value of a discrete variable. All the *p*-values were two sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted with STATA software version 11.0.

3. Results

3.1. *Statistical analyses*

The flow diagram of article selection is shown in Figure 1. Initially, ninety six articles were identified. After reading the title and abstract, twenty-one studies were included for further confirming. Nine studies were excluded by scrutinizing the entire paper. Of those excluded studies, five had insufficient data (*22,25-28*) and one analyzed the relationship between β-catenin mRNA level and the outcome in NSCLC (*29*). One reported pulmonary metastases from colorectal carcinoma (*30*). One evaluated the association between nuclear β-catenin expression and survival in NSCLC (*31*). The influence of decreased β-catenin expression on NSCLC survival was estimated by disease-free survival in another article (*32*). Additionally, one article (*33*) provided information about adenocarcinoma and squamous cell carcinoma, which we processed independently as two studies in the meta-analysis. Eventually, twelve literatures containing thirteen studies that met the inclusion criteria were selected (*17,33-43*).

The major characteristics of the included studies are outlined in Table 1. The total number of patients was 1,964, with sample sizes ranging from 35 to 522 patients. The reduced rate of β-catenin expression varied from 5.26% to 67.5%. HR and 95% CI were obtained from the original studies directly in six of

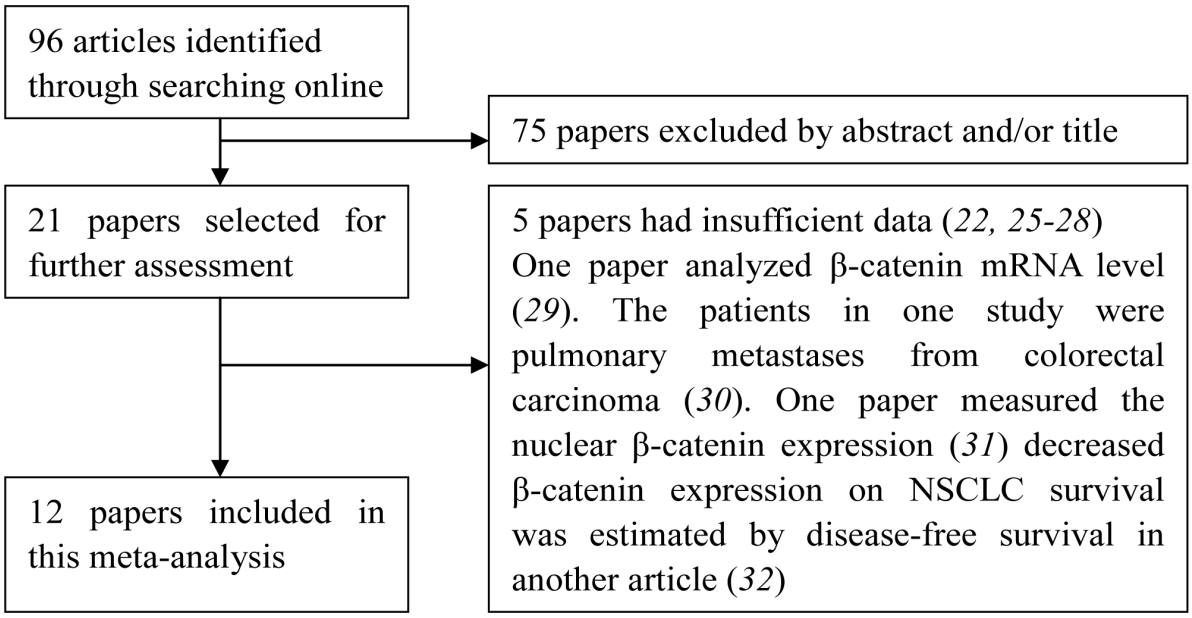

Figure 1. The flow diagram of article selection.

Table 1. Basic characteristics of the included studies in the meta-analysis

First author	Year	Histology	No.	Cut off	Reduced/ negative (%)	HR estimate	HR (95%CI)
Chiu *et al*. (*17*)	2012	NSCLC (AD:219; SQ:242; others:61)	522	5	28.0	HR (M)	3.18 (1.46-6.91)
Zhang *et al*. (*34*)	2012	NSCLC (AD:54; SQ:56)	110	10	50.0	Curve	1.79 (1.17-2.74)
Xu *et al*. (*35*)	2011	NSCLC (AD:165; SQ:97)	262	70	22.9	HR (M)	2.17 (1.09-4.29)
Yamashita *et al*. (*36*)	2010	NSCLC (SQ:31; others:86)	117	70	29.1	HR (M)	1.26 (0.65-2.43)
Yang *et al*. (*37*)	2010	NSCLC (AD:26; SQ:17)	120	50	67.5	HR (M)	2.39 (1.04-5.51)
Zhao *et al*. (*38*)	2010	NSCLC (AD:58; SQ:44)	102	10	62.7	HR (M)	1.13 (0.56-2.26)
Woenckhaus *et al*. (*33*) (*1*)	2008	AD	38	5	5.26	A (U)	2.92 (1.27-6.73)
Woenckhaus *et al*. (*33*) (*2*)	2008	SQ	38	5	13.2	A (U)	1.09 (0.36-3.33)
Nozawa *et al*. (*39*)	2006	AD	35	88	37.1	A (U)	2.41 (1.15-5.05)
Hommura *et al*. (*40*)	2002	NSCLC (AD:108; SQ:92; others:17)	148	25	23.6	A (U)	2.38 (1.03-5.52)
Lee *et al*. (*41*)	2002	NSCLC	75	50	13.3	Curve	3.02 (1.52-5.93)
Kimura *et al*. (*42*)	2000	NSCLC (AD:75; SQ:9; LCC:1; others:1)	86	80	48.8	Curve	1.40 (1.03-2.52)
Kase *et al*. (*43*)	2000	NSCLC (AD:227; SQ:104)	311	70	37.0	HR (M)	2.21 (1.36-3.60)

M: multivariate analysis; U: univariate analysis; AD: adenocarcinoma; SQ: squamous cell carcinoma; A: available data; Curve: Kaplan–Meier curve.

twelve studies (*17,35-38,43*) and calculated from available data in the other three original literatures (*33,39,40*). For the remaining three studies (*34,41,42*), HR and 95% CI were extrapolated from Kaplan-Meier curves. On statistical method, six studies (*17,34-37,43*) provided the results of multivariate analysis and the others (*33,38-42*) provided results with univariate analysis. The cut-off point ranged widely. Three studies (*35,36,43*) selected a proportion of < 70% as reduced staining. Two studies (*17,33*) used 5% as the cut-off value, two studies (*34,38*) selected cut-off points at 10%, and two other studies used 50% (*37,41*). The three remaining studies used < 25% (*40*), < 88% (*39*), and < 80% (*42*), respectively.

3.2. *Quality assessment*

Overall, the mean global quality score of the included studies was 55.3%. There was no statistical difference between the ten positive and three negative studies (55.5% *versus* 55%, $p = 0.25$). All of the results of methodological assessment are shown in Table 2.

3. 3. *Meta-analysis*

Forest plot showed that combined HR was 1.91 and 95% CI 1.60-2.28 by fixed-effect model for all studies and the heterogeneity was not statistically significant ($X^2 = 12.41$, $p = 0.413$, $I^2 = 3.3\%$, Figure 2). Of the thirteen studies, ten studies located in the right side of equivalent line supported the assumption that reduced β-catenin expression was associated with poor survival of NSCLC patients. The bars of 95% CI of the other three studies overlapped with the equivalent line, which did not support the conclusion.

When limiting the histology to adenocarcinoma, two studies were assessable. The combined HR and 95% CI by the fixed-effect model were 2.62 (1.51-4.56) and no heterogeneity was observed. Based on the stage, the results of two studies of stage I patients indicated a significant association between β-catenin expression and overall survival (HR: 1.92, 95% CI: 1.20-3.09).

We also divided the studies on statistical method and analyzed them separately. Of twelve studies, six studies used multivariate analysis while the others used univariate analysis. Both combined results of multivariate and univariate analysis indicated similar statistically significance (HR = 1.91, 95% CI: 1.43-2.50, Figure 3 and HR = 1.91, 95% CI: 1.51-2.41, Figure 4). The results supported the assumption that reduced β-catenin expression was associated with a poor survival in NSCLC patients. Similarly, no significant heterogeneity was observed in any of the subgroups ($I^2 = 18.2\%$, $p = 0.295$ and $I^2 = 4.7\%$, $p = 0.391$, respectively).

Table 2. Results of the methodology assessment

Items	N	Global score (%)	Design (/10)	Laboratory methodology (/10)	Generalizability (/10)	Results analysis (/10)
All studies	13	55.3	5.3	5.1	6.1	5.6
Negative	3	55.0	5.4	5.2	5.9	5.5
Positive	10	55.5	5.3	5.1	6.2	5.6
p-value		0.25	0.36	0.13	0.17	0.09

Score distributions are summarized by the median values; Negative: no significant prognostic factor for survival; Positive: as significant positive prognostic factor for survival.

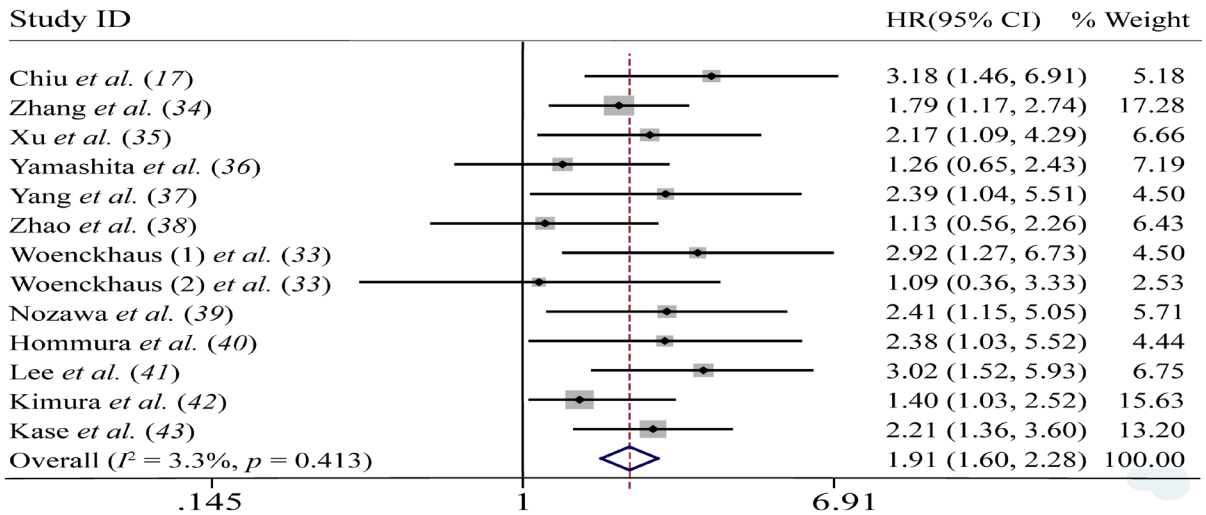

Figure 2. Meta-analysis of roles of β-catenin expression on survival in patients with NSCLC. Hazard ratio (HR) and 95% confidence interval (CI) of reduced β-catenin expression on overall survival for NSCLC patients. Results are expressed as individuals (squares) and overall HRs (diamonds) and their respective 95% CIs (horizontal bars). An HR higher than 1 indicates a poor prognosis for NSCLC patients with reduced β-catenin expression.

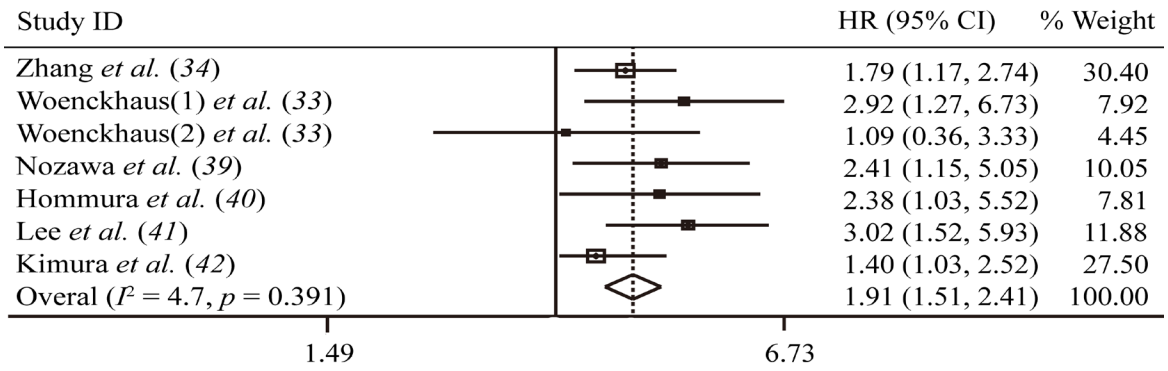

Figure 3. Forest plot of the effect of β-catenin expression on overall survival in NSCLC in studies with multivariate analysis. The bars of 95% CI of four studies do not overlap with the equivalent line compared with the two others. The summary HRs is 1.91 (95% CI: 1.14-2.50) favoring the assumption that decreased β-catenin expression is associated with poor prognosis in NSCLC patients.

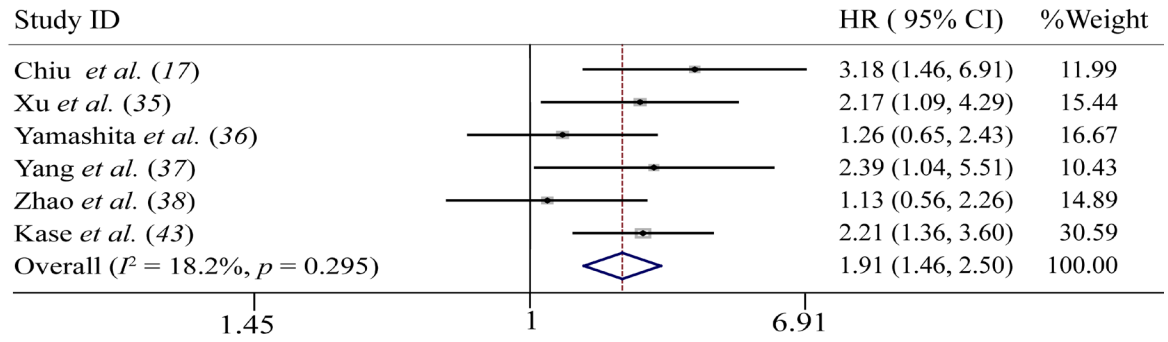

Figure 4. Forest plot of the effect of β-catenin expression on overall survival in NSCLC patients in studies with univariate analysis. The aggregated HR is 1.91 (95% CI: 1.51-2.41) which supports the assumption that reduced β-catenin expression is associated with a poor outcome of NSCLS patients.

3. 4. *Publication bias*

Funnel plot and Egger's test were both performed to evaluate the publication bias. Funnel plot did not reflect obvious asymmetry in this meta-analysis (Figure 5). Also, no indication of publication bias was found from the Egger's test (t = 0.87, p = 0.402 > 0.05).

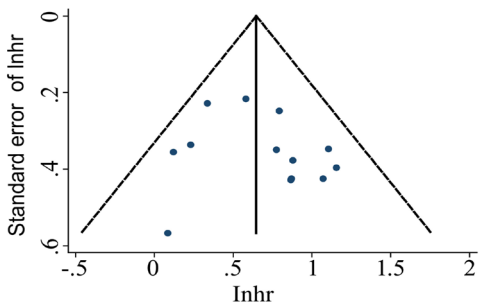

Figure 5. Begg's funnel plot for publication bias test of the studies with pseudo 95% confidence limits. The funnel graph plots hazard ratio against the standard error of the log hazard ratio. Each point represents a separate study for the indicated association. The publication bias is not significant (p = 0.402 > 0.05).

3. 5. *Sensitivity analysis*

To evaluate the robustness of the result of combined HR, sensitivity analysis was performed by removing one study each time. The results were shown in Figure 6. The pooled HRs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the combined risk estimates and confirmed the robustness of the result of this meta-analysis.

4. Discussion

Despite remarkable advances in treatment, the prognosis of NSCLC remains gloomy at present (*4*). Metastasis and recurrence are the main causes of poor prognosis. For better management of NSCLC patients, many efforts have been made to find a predictor of prognosis. Some prognostic markers such as p16 (*44*) and Ki-67 (*45*) were evaluated. Several molecules including mmp9 (*23*), survivin (*24*), p53 (*18*), and cyclinD1 (*16*) have been suggested the prognostic factors for NSCLC. However, none of these markers could predict the outcome of NSCLC patients exactly

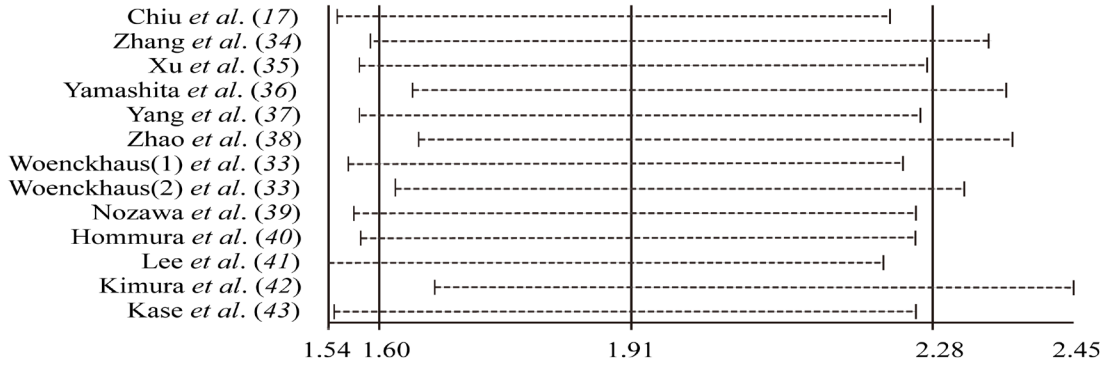

Figure 6. Sensitivity analyses of all the studies. Omission of any study did not affect the whole estimate results significantly.

and reliably and more markers are needed. Recently, one systemic review concluded that reduced E-cadherin expression was associated with a poor survival in NSCLC (*12*) which suggested that CAMs might be underlying predictive factors for NSCLC patients.

In this meta-analysis, the association between reduced β-catenin expression and overall survival in patients with NSCLC was comprehensively reviewed. The aggregation of all included studies produced statistically significant HRs: 1.91 (95% CI: 1.60-2.28), favoring the assumption that reduced β-catenin expression is associated with a poor prognosis in patients with NSCLC. Subgroup analyses on histology, stage and multivariate or univariate analysis also demonstrated similar results.

The initial step of metastasis is tumor cell escaping from the primary tumor, which is regulated by cell adhesion molecules. Decreased cell connection has proven to contribute to invasion and metastasis in tumor development (*46*). It is noted that intact complexes of β-catenin/E-cadherin are important adhesion molecules and inhibitors of cancer invasion and metastasis (*11*). β-Catenin, a component of the β-catenin/E-cadherin complex, has been reported to be involved in tumor metastasis (*7*). When β-catenin expression is decreased, the stability and function of β-catenin/E-cadherin complex will change. The prognostic value of β-catenin expression in NSCLC patients has been extensively investigated recently (*17,33-43*). Many of these articles claimed that reduced β-catenin expression was a predictor for poor outcome of NSCLC patients. The results of our present meta-analysis supports this conclusion in general.

Exploring heterogeneity is one of the important goals of meta-analysis (*47*). One of the advantages of the present meta-analysis is that no significant heterogeneity was found among the included studies ($p = 0.413$, $I^2 = 3.3\%$). Sensitivity analysis also showed that omission of any single study did not have significant impact on the combined risk estimates. Furthermore, funnel plot did not reflect obvious asymmetry, and Egger's test further indicated no considerable publication bias in this meta-analysis. This made the results of this meta-study more reliable to some extent.

Be that as it may, there remained some limitations in this meta-analysis. In the studies included, the antibodies used in detecting β-catenin expression were not the same. The definition of cut off value was also different, and varied from 5% to 88%. Furthermore, in the thirteen studies, six studies used multivariate analysis while the remaining adopted univariate analysis. Besides, other clinical factors such as age, sex and different chemotherapies in each study might lead to bias. Determining whether or not these factors influence the results of this meta-analysis would need further investigation.

We did not include non-English publications in this study. Some HR results were obtained indirectly from available data or by reading the survival curve. These approaches may have produced errors because of possible inaccurate reading. Additionally, among the nine excluded studies, five studies were excluded because of insufficient data. None of the five studies reported significant association between reduced β-catenin expression and survival in NSCLC. All of the above factors could lead to possible bias and should not be neglected.

In conclusion, the results of our meta-analysis suggest, as a whole, that reduced β-catenin expression is associated with a poor overall survival in NSCLC patients. Decreased β-catenin expression could be a prognostic predictor for NSCLC patients. Some limitations mentioned above should not be ignored. More prospective well-designed studies with standardized detecting methods, unified cut-off values and statistical methods are needed to further confirm and establish the utility of prognostic value of β-catenin expression in NSCLC patients.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and

racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61:212-236.
2. Boyle P, Dresler C. Preventing the lung cancer epidemic. Ann Oncol. 2005; 16:1565-1566.
3. Chen W, Zhang S, Zou X. Estimation and projection of lung cancer incidence and mortality in China. Zhongguo Fei Ai Za Zhi. 2010; 13:488-493. (in Chinese)
4. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008; 83:584-594.
5. Brooks DR, Klint A, Dickman PW, Stahle E, Lambe M. Temporal trends in non-small cell lung cancer survival in Sweden. Br J Cancer. 2007; 96:519-522.
6. Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M, Nakanishi Y, Tsuchiya R, Shimokata K, Inoue H, Nukiwa T, Miyaoka E. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol. 2008; 3:46-52.
7. Pignatelli M, Vessey CJ. Adhesion molecules: novel molecular tools in tumor pathology. Hum Pathol. 1994; 25:849-856.
8. Valenta T, Hausmann G, Basler K. The many faces and functions of β-catenin. EMBO J. 2012; 31:2714-2736.
9. Amin N, Vincan E. The Wnt signaling pathways and cell adhesion. Front Biosci. 2012; 17:784-804.
10. Conacci-Sorrell M, Zhurinsky J, Ben-Ze'ev A. The cadherin-catenin adhesion system in signaling and cancer. J Clin Invest. 2002; 109:987-991.
11. Zhu CQ, Shih W, Ling CH, Tsao MS. Immunohistochemical markers of prognosis in non-small cell lung cancer: A review and proposal for a multiphase approach to marker evaluation. J Clin Pathol. 2006; 59:790-800.
12. Wu Y, Liu HB, Ding M, Liu JN, Zhan P, Fu XS, Lu G. The impact of E-cadherin expression on non-small cell lung cancer survival: A meta-analysis. Mol Biol Rep. 2012; 39:9621-9628.
13. Bremnes RM, Veve R, Hirsch FR, Franklin WA. The E-cadherin cell-cell adhesion complex and lung cancer invasion, metastasis, and prognosis. Lung Cancer. 2002; 36:115-124.
14. Chen CH, Chuang SM, Yang MF, Liao JW, Yu SL, Chen JJ. A novel function of YWHAZ/β-catenin axis in promoting epithelial-mesenchymal transition and lung cancer metastasis. Mol Cancer Res. 2012; 10:1319-1331.
15. Cheng CW, Liu YF, Yu JC, Wang HW, Ding SL, Hsiung CN, Hsu HM, Shieh JC, Wu PE, Shen CY. Prognostic significance of cyclin D1, β-catenin, and MTA1 in patients with invasive ductal carcinoma of the breast. Ann Surg Oncol. 2012 .
16. Kim MY, Han SI, Lim SC. Roles of cyclin-dependent kinase 8 and β-catenin in the oncogenesis and progression of gastric adenocarcinoma. Int J Oncol. 2011; 38:1375-1383.
17. Chiu CG, Chan SK, Fang ZA, Masoudi H, Wood-Baker R, Jones SJ, Gilks B, Laskin J, Wiseman SM. β-Catenin expression is prognostic of improved non-small cell lung cancer survival. Am J Surg. 2012; 203:654-659.
18. Steels E, Paesmans M, Berghmans T, Branle F, Lemaitre F, Mascaux C, Meert AP, Vallot F, Lafitte JJ, Sculier JP. Role of p53 as a prognostic factor for survival in lung cancer: A systematic review of the literature with a meta-analysis. Eur Respir J. 2001; 18:705-719.
19. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis. 1985; 27:335-371.
20. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16.
21. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998; 17:2815-2834.
22. Miao Y, Li AL, Wang L, Fan CF, Zhang XP, Xu HT, Han Y, Liu Y, Wang E. Expression of p130cas, E-cadherin and β-catenin and their correlation with clinicopathological parameters in non-small cell lung cancer: p130cas over-expression predicts poor prognosis. Folia Histochem Cytobiol. 2012; 50:392-397.
23. Peng WJ, Zhang JQ, Wang BX, Pan HF, Lu MM, Wang J. Prognostic value of matrix metalloproteinase 9 expression in patients with non-small cell lung cancer. Clin Chim Acta. 2012; 413:1121-1126.
24. Zhang LQ, Wang J, Jiang F, Xu L, Liu FY, Yin R. Prognostic value of survivin in patients with non-small cell lung carcinoma: A systematic review with meta-analysis. PLoS One. 2012; 7:e34100.
25. Lim BJ, Jung SS, Choi SY, Lee CS. Expression of metastasis-associated molecules in non-small cell lung cancer and their prognostic significance. Mol Med Report. 2010; 3:43-49.
26. Ramasami S, Kerr KM, Chapman AD, King G, Cockburn JS, Jeffrey RR. Expression of CD44v6 but not E-cadherin or β-catenin influences prognosis in primary pulmonary adenocarcinoma. J Pathol. 2000; 192:427-432.
27. Pirinen RT, Hirvikoski P, Johansson RT, Hollmen S, Kosma VM. Reduced expression of α-catenin, β-catenin, and γ-catenin is associated with high cell proliferative activity and poor differentiation in non-small cell lung cancer. J Clin Pathol. 2001; 54:391-395.
28. Miao Y, Li AL, Wang L, Fan CF, Zhang XP, Xu HT, Yang LH, Liu Y, Wang EH. Overexpression of NEDD9 is associated with altered expression of E-cadherin, β-catenin and N-cadherin and predictive of poor prognosis in non-small cell lung cancer. Pathol Oncol Res. 2012.
29. Zhu ZH, Sun BY, Ma Y, Shao JY, Long H, Zhang X, Fu JH, Zhang LJ, Su XD, Wu QL, Ling P, Chen M, Xie ZM, Hu Y, Rong TH. Three immunomarker support vector machines-based prognostic classifiers for stage IB non-small-cell lung cancer. J Clin Oncol. 2009; 27:1091-1099.
30. Shiono S, Ishii G, Nagai K, Murata Y, Tsuta K, Nitadori J, Kodama T, Ochiai A. Immunohistochemical prognostic factors in resected colorectal lung metastases using tissue microarray analysis. Eur J Surg Oncol. 2006; 32:308-309.
31. Sterlacci W, Fiegl M, Hilbe W, Jamnig H, Oberaigner W, Schmid T, Augustin F, Auberger J, Obermann EC, Tzankov A. Deregulation of p27 and cyclin D1/D3 control over mitosis is associated with unfavorable prognosis in non-small cell lung cancer, as determined in 405 operated patients. J Thorac Oncol. 2010; 5:1325-1336.
32. Bremnes RM, Veve R, Gabrielson E, Hirsch FR, Baron A, Bemis L, Gemmill RM, Drabkin HA, Franklin WA. High-throughput tissue microarray analysis used to evaluate biology and prognostic significance of the E-cadherin pathway in non-small-cell lung cancer. J Clin Oncol. 2002; 20:2417-2428.
33. Woenckhaus M, Merk J, Stoehr R, Schaeper F, Gaumann

A, Wiebe K, Hartmann A, Hofstaedter F, Dietmaier W. Prognostic value of FHIT, CTNNB1, and MUC1 expression in non-small cell lung cancer. Hum Pathol. 2008; 39:126-136.
34. Zhang Y, Han Y, Zheng R, Yu JH, Miao Y, Wang L, Wang EH. Expression of Frat1 correlates with expression of β-catenin and is associated with a poor clinical outcome in human SCC and AC. Tumour Biol. 2012; 33:1437-1444.
35. Xu X, Sun PL, Li JZ, Jheon S, Lee CT, Chung JH. Aberrant Wnt1/β-catenin expression is an independent poor prognostic marker of non-small cell lung cancer after surgery. J Thorac Oncol. 2011; 6:716-724.
36. Yamashita T, Uramoto H, Onitsuka T, Ono K, Baba T, So T, So T, Takenoyama M, Hanagiri T, Oyama T, Yasumoto K. Association between lymphangiogenesis-/micrometastasis- and adhesion-related molecules in resected stage I NSCLC. Lung Cancer. 2010; 70:320-328.
37. Yang ZQ, Zhao Y, Liu Y, Zhang JY, Zhang S, Jiang GY, Zhang PX, Yang LH, Liu D, Li QC, Wang EH. Downregulation of HDPR1 is associated with poor prognosis and affects expression levels of p120-catenin and β-catenin in nonsmall cell lung cancer. Mol Carcinog. 2010; 49:508-519.
38. Zhao Y, Yang ZQ, Wang Y, Miao Y, Liu Y, Dai SD, Han Y, Wang EH. Dishevelled-1 and dishevelled-3 affect cell invasion mainly through canonical and noncanonical Wnt pathway, respectively, and associate with poor prognosis in nonsmall cell lung cancer. Mol Carcinog. 2010; 49:760-770.
39. Nozawa N, Hashimoto S, Nakashima Y, Matsuo Y, Koga T, Sugio K, Niho Y, Harada M, Sueishi K. Immunohistochemical α- and β-catenin and E-cadherin expression and their clinicopathological significance in human lung adenocarcinoma. Pathol Res Pract. 2006; 202:639-650.
40. Hommura F, Furuuchi K, Yamazaki K, Ogura S, Kinoshita I, Shimizu M, Moriuchi T, Katoh H, Nishimura M, Dosaka-Akita H. Increased expression of β-catenin predicts better prognosis in nonsmall cell lung carcinomas. Cancer. 2002; 94:752-758.
41. Lee YC, Wu CT, Chen CS, Hsu HH, Chang YL. The significance of E-cadherin and α-, β-, and γ-catenin expression in surgically treated non-small cell lung cancers of 3 cm or less in size. J Thorac Cardiovasc Surg. 2002; 123:502-507.
42. Kimura K, Endo Y, Yonemura Y, Heizmann CW, Schafer BW, Watanabe Y, Sasaki T. Clinical significance of S100A4 and E-cadherin-related adhesion molecules in non-small cell lung cancer. Int J Oncol. 2000; 16:1125-1131.
43. Kase S, Sugio K, Yamazaki K, Okamoto T, Yano T, Sugimachi K. Expression of E-cadherin and β-catenin in human non-small cell lung cancer and the clinical significance. Clin Cancer Res. 2000; 6:4789-4796.
44. Tong J, Sun X, Cheng H, Zhao D, Ma J, Zhen Q, Cao Y, Zhu H, Bai J. Expression of p16 in non-small cell lung cancer and its prognostic significance: a meta-analysis of published literatures. Lung Cancer. 2011; 74:155-163.
45. Martin B, Paesmans M, Mascaux C, Berghmans T, Lothaire P, Meert AP, Lafitte JJ, Sculier JP. Ki-67 expression and patients survival in lung cancer: Systematic review of the literature with meta-analysis. Br J Cancer. 2004; 91:2018-2025.
46. Muller T, Bain G, Wang X, Papkoff J. Regulation of epithelial cell migration and tumor formation by β-catenin signaling. Exp Cell Res. 2002; 280:119-133.
47. Petitti DB. Approaches to heterogeneity in meta-analysis. Stat Med. 2001; 20:3625-3633.

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