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*Review Article*

# Prognostic value of CD44 expression in non-small cell lung cancer: a systematic review

Zhuang Luo[1*], Rong-Rong Wu[2,3*], Liang Lv[2*], Peng Li[2], Li-Yan Zhang[1], Qing-Lin Hao[1], Wei Li[1]

*[1]Department of Respiratory Medicine, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, China; [2]Department of Radiology, The First People's Hospital of Yunnan Province Affiliated to Kunming University of Science and Technology, Kunming, Yunnan, China; [3]Kunming Medical University, Kunming, Yunnan, China. [*]Equal contributors.*

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**Abstract:** Background: CD44 is a potentially interesting prognostic marker and therapeutic target in non-small cell lung cancer (NSCLC). Although the expression of CD44 has been reported to correlate with poor prognosis of NSCLC in most literatures, some controversies still exist. Since the limited patient numbers within independent studies, here we performed a meta-analysis to clarify the correlations between CD44 expression and prognosis and clinicopathological features in NSCLC. Methods: Relevant literatures were identified using PubMed, EMBASE and CNKI (China National Knowledge Infrastructure) databases (up to February 2014). Data from eligible studies were extracted and included into meta-analysis using a random effects model. Studies were pooled. Summary hazard ratios (HR) and clinical parameters were calculated. Results: We performed a final analysis of 1772 patients from 23 evaluable studies for Prognostic Value and 2167 patients from 28 evaluable studies for clinicopathological features. Our study shows that the pooled hazard ratio (HR) of overexpression CD44-V6 for overall survival in NSCLC was 1.63 [95% confidence interval (CI): 1.20-2.21] by univariate analysis and 1.29 (95% CI: 0.71-2.37) by multivariate analysis.The pooled HR of overexprssion panCD44 for overall survival in NSCLC was 1.53 (95% CI: 0.58-4.04) by univariate analysis and 3.00 (95% CI: 1.53-5.87) by multivariate analysis. Overexpression of CD44-V6 is associated with tumor differentiation (poor differentiation, OR = 1.66, 95% CI: 1.12-2.45), tumor histological type [squamous cell carcinomas (SCC), OR = 2.6, 95% CI: 1.63-5.02], clinical TMN stage (TMN stage III, OR = 2.22, 95% CI: 1.44-3.43) and lymph node metastasis (N1-3, 3.52, 95% CI: 2.08-5.93) in patients with NSCLC. However, there was no significant association between CD44-V6 and tumor size [T category, OR = 1.42, 95% CI: 0.73-2.78]. Conclusion: Our meta-analysis showed that CD44-V6 is an efficient prognostic factor for NSCLC. Overexpression of CD44-V6 was significantly associated with tumor differentiation, tumor histological type, clinical TMN stage and lymph node metastasis. However, there was no significant association between CD44-V6 and tumor size. Large prospective studies are now needed to confirm the clinical utility of CD44 as an independent prognostic marker.

**Keywords:** Non-small cell lung cancer (NSCLC), CD44, panCD44, CD44-V6, clinicopathological features, overall survival, meta-analysis

## Introduction

Lung cancer is one of the most common human cancers and the leading cause of cancer-related deaths with non-small cell lung cancer (NSCLC) accounting for 80% of all primary lung cancers. Despite early detection screening protocols, improved surgical techniques, and advanced radio and chemotherapeutic regimens, little progress has been made in altering the natural progression of the disease, the 5-year survival rate of patient with NSCLC is only 15% [1]. Thus, the lack of major improvements in the 5-year survival rate of NSCLC has driven the search for new strategies aimed at improving lung cancer management. Current knowledge regarding NSCLC is not a single disease but a collection of diseases with distinct pathogeneses by molecular mechanisms. Genetic and epigenetic alternations play an integral role in the transformation, promotion and progression of cancer [2].

A number of cell surface markers, including CD133, CD24 and CD44, are responsible for tumor initiation, progression, metastasis and

drug resistance [3]. It was reported that overexpression of these markers indicated bad clinical features and poor prognosis [4-6]. CD44 includes standard form of CD44 (CD44s) and its variant isoforms. CD44 has been accepted as a promising prognostic indicator in solid tumors, and it was revealed to be a target of the Wnt pathway [7], which is accepted as a key pathway for the stemness maintenance of cancer stem cell (CSC) markers. The CSC hypothesis also has been connected to a number of solid tumors including lung cancer and other types of cancers, particularly NSCLC, harbor CSC populations [8-10]. The CD44 is a polymorphic family of cell surface glycoproteins with a cytoplasmic domain and seven extracellular domains, a transmembrane domain [11]. CD44 is with a variety of functions including participation in cell adhesion and migration as well as modulation of cell-matrix interactions. Expression of CD44 has been shown in both normal and neoplastic tissue and holds promise as a prognostic indicator. The prognostic value of CD44 for patients with cancer has been reported in various solid tumors, including breast cancer, colon cancer, and lung cancer [12-14].

The effect of abnormalities expression of CD44 has been investigated for NSCLC by using univariate or multivariate analysis, however, the relationships between CD44 and prognosis value were still controversial mainly because of the limited patient numbers of independent reports. Based on the discordant results obtained by numbers of studies, we conducted this meta-analysis to quantify the prognostic impact of CD44 expression on overall survival and clinicopathological features among patients with NSCLC.

## Materials and methods

### *Literature search*

A literature search via PubMed, EMBASE and CNKI (China National Knowledge Infrastructure) databases was conducted to find articles that evaluated the role of CD44 in NSCLC. The keywords and text words were used as follows: (1) CD44, and (2) non-small cell lung cancer or NSCLC or lung cancer or lung carcinoma or carcinoma of lung and (3) outcome or survival or prognosis.

### *Study selection*

All languages were included, and all eligible articles that examined the association between the expression of CD44 and overall survival or CD44 and clinicopathological features were gathered. However, the papers which only have abstracts were excluded because of insufficient data for meta-analysis. Therefore, we first read the titles of the publications and the abstracts to find exactly those articles that examined the relationship between CD44 and overall survival (OS) or CD44 and clinicopathological features 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: (1) an original paper (2) expression levels of CD44 were compared to patient's overall survival; (3) expression of the proteins were evaluated in tumor tissues by immunohistochemistry (IHC) or reverse transcription and polymerase chain reaction (RT-PCR) analysis; (4) studies that reported a hazard ratio (HR)and confidence interval (CI) or could be calculated from the sufficient data; (5) expression levels of CD44 were compared to patient's clinicopathological features; (6) including three or more clinical characteristics of lymph node metastasis, TMN stage, tumor size, tumor differentiation and histological type (5) if the same group of patients were used to analyze more than once, the most complete research was selected for our study.

The major exclusion criteria were (1) reviews, non-original articles, abstracts and letters; (2) non-CD44 or NSCLC; (3) duplication of a previous publication; and (4) examination of specimens collected after chemotherapy or radiotherapy.

### *Data extraction*

Two reviewers (Zhuang Luo and Rong-rong Wu) independently checked all articles and extracted data in separate databases. The following information were collected from each study: first author's name, type of CD44, year of publication, ethnicity, sample size, laboratory methodology, cut-off value, lymph node metastasis, tumor size, tumor differentiation, histological type, clinical TMN stage and HR with 95% CI. Disagreements were resolved through discussion among the authors.

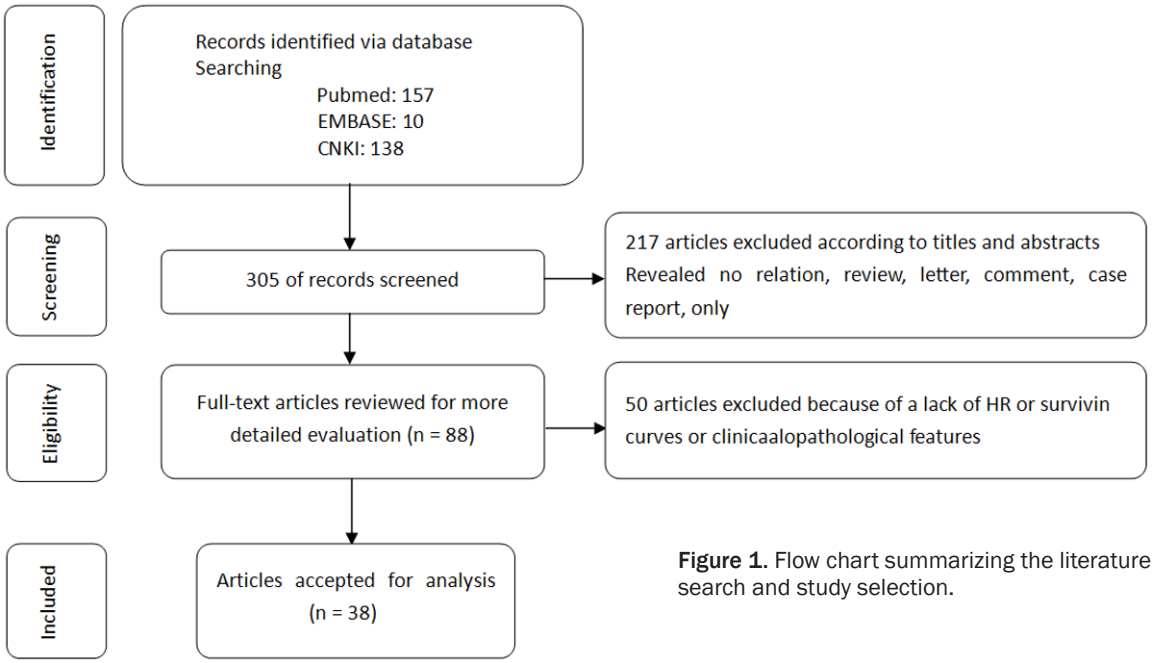


**Figure 1.** Flow chart summarizing the literature search and study selection.

*Statistical analysis*

The intensity of relationship between the expression levels of CD44 and overall survival were described as HRs. Overexpression of CD44 indicated poor prognosis in patients with NSCLC if HR > 1 with the 95% CI did not overlap 1. From some published researches, HR and 95% CI could be directly obtained by using univariate or multivariate survival analysis. Otherwise, HR and 95% CI were calculated by Kaplan-Meier survival curves using the software Engauge Digitizer Version 4.1 (http://digitizer.sourceforge.net/) and the method presented by Parmar et al. before [15, 16]. Then, extracted data were utilized to reconstruct the HR and its variance (GraphPad Software, Inc, La Jolla, CA, USA).

The pooled HR corresponding to the 95% CI was used to assess the prognostic value of CD44 in patients. Statistical heterogeneity was tested by Cochrane's Q test (Chi-squared test; $Chi^2$) and inconsistency ($I^2$) [17, 18]. If there was no obvious heterogeneity, the fixed-effects model (Mantel-Haenszel method) was used to estimate the pooled HR; otherwise, the random-effects model (DerSimonian and Laid method) was used [15]. We assessed the possibility of publication bias using a funnel plot and tested it with Egger's test [19]. A *P* value less than 0.05 was considered statistically significant. STATA 12.0 (STATA Corp., College, TX) was used to perform statistical analysis.

## Results

*Characteristics of eligible studies*

One hundred fifty, 10, 138 articles were retrieved from PubMed, EMBASE and CNKI electronic database according to our defined keywords and text words, respectively (**Figure 1**). Then, via careful reading the abstracts, 81 researches that focused on the association between the expression of CD44 and survival were included in our full-text review process. After reading the full-text researches, 43 papers had to be excluded because data were not extractable or could not provide enough information about overall survival or complete clinicopathological features. As a result, 38 eligible studies were included in this meta-analysis [20-57]. Twenty Three studies including 1772 cases were available for our meta-analysis for the expression of CD44 and prognosis. Among all the included studies, twenty four studies including 1871 cases were available for our meta-analysis for the expression of CD44 and clinicopathological features. The individual characteristics and results of eligible prognostic studies evaluating surviving are summarized in **Table 1**. Main clinicopathological features and results of eligible studies are summarized in **Table 2**.

*Impact of CD44 expression on OS in NSCLC*

We evaluated whether CD44v6 and panCD44 expression levels were associated with the overall survival in patients with NSCLC. Of the 23 trials evaluable for systematic review, 15 and 5 could be included in meta-analysis by univariate and multivariate analysis effect of CD44v6 on overall survival due to sufficient data to estimate the HR and 95% CI. Only 5 and 3 could be included in meta-analysis by univariate and multivariate analysis effect of panCD44 on overall survival.

The relationship between CD44 expression and NSCLC prognosis is illustrated in **Figure 2**. Seventeen studies(including a total of 1378 patients) that demonstrated the association of CD44-V6 expression and OS rate were obtained from the published information. According to univariate analysis of CD44-V6 expression and OS rate in fifteen studies(including a total of 1067 patients), with a combined HR of 1.63 (95% CI: 1.20-2.21, $P = 0.000$, $I^2 = 81.6\%$, random-effect). According to multivariate analysis of CD44-V6 expression and OS rate in six studies(including a total of 656 patients), with a combined HR of 1.29 (95% CI: 0.71-2.37, $P = 0.00$, $I^2 = 75.1\%$). Six studies (including a total of 394 patients) that demonstrated the association of panCD44 expression and OS rate were obtained from the published information. Furthermore, according to univariate analysis of panCD44 expression and OS rate in five studies(including a total of 362 patients), there was no significant disparities for the effective value of OS was determined (HR of 1.53, 95% CI: 0.58-4.04, $P = 0.0000$, $I^2 = 89.5\%$). According to multivariate analysis of panCD44 expression and OS rate in three studies (including a total of 291 patients), with a combined HR of 3.00 (95% CI: 1.53-5.87, $P = 0.623$, $I^2 = 0.0\%$).

Univariate HR of subgroup analyses for CD44-v6 on NSCLC survival are ummarized in the **Table 3**. When grouped according to the ethnicity, combined HRs of Asian and Non-Asian written were 1.78 (CI: 1.34-2.35) and 0.53 (CI: 0.29-2.92), respectively. In the subgroup analysis according to Written Language the combined HR was 0.88 (CI: 0.47-1.63) for English written and 2.05 (CI: 1.59-2.64) for non English written. When the survival data calculated indirectly from Kaplan-Meier based survival curve were pooled, the combined HR was 1.83 (95% CI: 1.26-2.65), also suggesting CD44-v6 status was of prognostic value. Although we also observed statistically significant effects of CD44-v6 expression on survival from studies reported I-III with an HR of 1.61 (95% CI: 1.01-2.58) from 7 studies reported, when we aggregated the studies that reported results for I-II early-stage NSCLC, the combined HR were 1.78 (95% CI: 0.78-4.09). Moreover, when the survival data calculated by follow-up time, combined HRs of 36 months and 60 months showed an inverse effects on survival (HR 1.79 CI: 0.9-3.58 and 1.82 CI: 1.29-2.56, respectively). Finally, grouped according to the positive threshold for CD44-v6 expression, as defined by the studies' authors, the combined HR of 0% and 10% cut off value were 1.31 (95% CI: 0.73-2.35) and 2.03 (95% CI: 0.79-5.22), respectively.

Publication bias statistics were determined using the method of Begg's test (**Figure 3**) between CD44 (including CD44-v6 and pan-CD44) expression and NSCLC prognosis. In all included studies, no funnel plot asymmetry was found Sensitively analysis was performed to investigate the effect of every study on the overall meta-analysis by omitting one study each time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

*Correlation of CD44-v6 expression with clinicopathological parameters*

The forest plot of OR was assessed for association between CD44-v6 and clinicopathological features such as tumor category (A), tumor size (B), tumor differentiation (C), tumor histological type (D), clinical TMN stage (E), lymph node metastasis in **Figure 4**. In pooled analysis, CD44-v6 expression was significantly associated with tumor differentiation [poor differentiation, OR (odds ratio) = 1.66, 95% CI: 1.12-2.45 and, $P = 0.00001$ and $I^2 = 76.8$, random-effect], tumor histological type (SCC, OR = 2.6, 95% CI: 1.63-5.02 and $P = 0.014$ and $I^2 = 51.3$, random-effect), clinical TMN stage (TMN stage III, OR = 2.22, 95% CI: 1.44-3.43, $P = 0.0001$ and $I^2 = 64.5$, random-effect) and lymph node metastasis (N1-3, 3.52, 95% CI: 2.08-5.93, $P = 0.0001$ and $I^2 = 78.5$, random-effect) in patients with NSCLC. However, there was no significant association between CD44-V6 and tumor size (T category, OR = 1.42, 95% CI: 0.73-

**Table 1.** Individual characteristics and results of eligible prognostic studies evaluating survival

| First Author | CD44 type | Year | Ethnicity | case | Method | Cutt off value | Univariate HR | Univariate 95% CI | Muti-variate HR | Muti-variate 95% CI | SCC/ADC/ Others | Stage (I/II/III/IV) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clarke MR | pan-CD44 | 1995 | America | 31 | IHC | > 0% | 0.45 | 0.28-0.73 | NA | NA | NA | 31/0/0/0 |
| Hirata T | CD44-V6 | 1998 | Japan | 69 | IHC | ≥ 20% | 2.42 | 0.91-6.43 | 2.55 | 1.31-4.98 | 25/43/1 | 69/0/0/0 |
| Fukuse T | CD44-V6 | 1999 | Japan | 34 | IHC | ≥ 20% | 0.95 | 0.50-1.81 | 0.29 | 0.05-1.63 | 12/21/1 | NA |
| Pirinen R | CD44-V6 | 2000 | Finlang | 231 | IHC | > 66% | NA | NA | 2 | 1.20-3.0 | 146/58/27 | 149/78/0/0 |
| Ramasami S | CD44-V6 | 2000 | UK | 120 | IHC | ≥ 10% | 0.59 | 0.40-0.87 | NA | NA | 0/120/0 | 69/35/16/0 |
| Zhang HZ | CD44-V6 | 2001 | China | 42 | IHC | > 0% | 1.59 | 0.92-2.75 | NA | NA | 15/27/0 | 25/12/4/1 |
| Zhang GR | CD44-V6 | 2003 | China | 62 | IHC | ≥ 10% | 2.81 | 1.75-4.51 | NA | NA | 33/29/0 | 9/26/27/0 |
| Zhang YC | CD44-V6 | 2003 | China | 79 | IHC | > 0% | 0.82 | 0.48-1.42 | NA | NA | 42/37/0 | 32/32/15/0 |
| Cheng C | pan-CD44 | 2004 | China | 32 | IHC | > 0% | NA | NA | 1.217 | 0.054-2.87 | 19/12/1 | 0/0/32/0 |
| Zhang L | CD44-V6 | 2004 | China | 43 | IHC | ≥ 10% | 3.2 | 1.59-6.45 | NA | NA | 24/19/0 | 17/12/14/0 |
| Liu B | CD44-V6 | 2005 | China | 108 | IHC | > 4 score | 1.5 | 1.13-1.98 | NA | NA | 56/44/8 | NA |
| Wu QP | CD44-V6 | 2005 | China | 52 | IHC | > 0% | 1.53 | 0.92-2.53 | 1.88 | 1.15-2.76 | 31/21/0 | 19/20/12/1 |
| Le QT | CD44-V6 | 2006 | Ireland | 20 | IHC | > 0% | 1.98 | 0.56-6.95 | NA | NA | 2/10/8 | 12/8/0/0 |
| Li GH | pan-CD44 | 2007 | China | 36 | RT-PCR | NA | 2.15 | 0.95-4.85 | NA | NA | 19/13/4 | 25/0/11/0 |
| Weng MX | CD44-V6 | 2008 | China | 86 | IHC | > 5 score | 1.68 | 1.32-2.14 | NA | NA | 50/36/0 | 47/18/21/0 |
| Xie ZM | CD44-V6 | 2008 | China | 80 | IHC | > 0% | NA | NA | 1.87 | 0.298-4.72 | 28/52/0 | 80/0/0/0 |
| Wu Y | pan-CD44 | 2009 | China | 36 | RT-PCR | > 0.5 | 1.11 | 0.24-5.13 | NA | NA | 7/19/2 | 12/0/9/0 |
| Zhang XH | CD44-V6 | 2009 | China | 46 | IHC | > 0% | 2.43 | 1.11-5.32 | NA | NA | 15/27/4 | NA |
| Meng L | CD44-V6 | 2010 | China | 56 | IHC | ≥10% | 3.41 | 2.08-5.57 | NA | NA | 32/24/0 | 22/34/0/0 |
| Situ DR | CD44-V6 | 2010 | China | 190 | IHC | > 0% | 0.318 | 0.14-0.15 | 0.325 | 0.14-0.77 | 71/60/59 | 190/0/0/0 |
| Ko YH | pan-CD44 | 2011 | South Korea | 82 | IHC | > 3 score | 3.32 | 2.12-5.2 | 3.152 | 1.26-7.91 | 0/82/0 | 43/18/21/0 |
| Wei MC | CD44-V6 | 2011 | China | 60 | IHC | ≥ 4 score | 3.03 | 1.70-5.41 | NA | NA | 33/27/0 | 60/0/0/0 |
| Okudela K | pan-CD44 | 2012 | Japan | 177 | IHC | ≥ 10% | 2.29 | 0.89-5.90 | 3.73 | 1.2-11.58 | NA | 177/0/0/0 |

Abbreviation: P/N, positive expression/negative expression; IHC, immunohistochemistry; SCC, Squamous cell carcinoma; ADC, Adenocarcinoma; HR, hazard ratio; NA, no available or no applicable.

**Table 2.** Main clinicopathological features and results of eligible studies

| First Author | CD44 type | Year | Ethnicity | case | lymph node metastasis | | TMN stage | | Tumor size | | Tumor differentiation | | Histological type | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CD44+ | CD44- | CD44+ | CD44- | CD44+ | CD44- | CD44+ | CD44- | CD44+ | CD44- |
| | | | | | N/P | N/P | I II/III IV | I II/III IV | < 3 cm/> 3 cm | < 3 cm/> 3 cm | I II/III | I II/III | SCC/ADC | SCC/ADC |
| Miyoshi T | CD44-V6 | 1997 | Japan | 61 | 13/23 | 19/6 | 15/21 | 13/12 | 7/29 | 13/12 | NA | NA | NA | NA |
| Dai BJ | CD44-v6 | 1998 | China | 62 | 19/24 | 4/4 | 20/23 | 14/5 | 17/26 | 10/9 | NA | NA | 19/17 | 6/10 |
| Hirata T | CD44-v6 | 1998 | Japan | 69 | 14/6 | 37/12 | NA | NA | NA | NA | NA | NA | 13/1 | 12/35 |
| Zhao HY | CD44-V6 | 1998 | China | 96 | 26/31 | 25/3 | 25/14 | 35/16 | NA | NA | 31/26 | 17/11 | NA | NA |
| Zhao ZS | CD44-v6 | 1999 | China | 62 | 24/18 | 21/1 | 20/22 | 17/3 | 9/33 | 14/6 | 24/18 | 15/5 | 11/20 | 8/7 |
| Pirinen R | CD44-V6 | 2000 | Finlang | 231 | 67/17 | 88/54 | NA | NA | 19/65 | 44/98 | 46/30 | 65/56 | 72/6 | 74/52 |
| Zhang HZ | CD44-V6 | 2001 | China | 42 | 8/21 | 10/3 | 41754 | 12/1 | NA | NA | NA | NA | NA | NA |
| Wang ZT | CD44-v6 | 2002 | China | 147 | 54/40 | 31/22 | 63/31 | 32/21 | NA | NA | 83/11 | 38/15 | 49/35 | 14/31 |
| Sun L | CD44-v6 | 2002 | China | 90 | 23/36 | 21/10 | 10/36 | 21/23 | NA | NA | 28/15 | 25/19 | NA | NA |
| Zuo WL | CD44-v6 | 2003 | China | 79 | 15/33 | 23/8 | NA | NA | NA | NA | NA | NA | 20/28 | 11/10 |
| Gao K | CD44-v6 | 2003 | China | 74 | 14/19 | 30/11 | 9/24 | 21/20 | NA | NA | 21/12 | 25/16 | NA | NA |
| Zhang GR | CD44-V6 | 2003 | China | 62 | 5/38 | 7/12 | 18/25 | 17/2 | 21/22 | 8/11 | NA | NA | 21/22 | 11/7 |
| Zhang YC | CD44-V6 | 2003 | China | 79 | 21/20 | 22/14 | 35/6 | 29/9 | 11/30 | 10/28 | NA | NA | 28/6 | 4/20 |
| Zhang Q | CD44-v6 | 2004 | China | 116 | 36/23 | 43/3 | 45/14 | 44/2 | 19/40 | 27/19 | 38/20 | 40/6 | 46/13 | 23/23 |
| Zhang L | CD44-V6 | 2004 | China | 43 | 6/21 | 12/4 | 6/21 | 11/5 | NA | NA | NA | NA | 14/13 | 10/6 |
| Lin H | CD44-v6 | 2005 | China | 101 | 15/65 | 16/5 | 45/35 | 11/6 | 19/61 | 5/16 | 42/38 | 11/10 | 45/35 | 14/7 |
| Wu GZ | CD44-v6 | 2005 | China | 50 | NA | NA | 14/13 | 16/7 | NA | NA | 20/6 | 20/4 | 29/6 | 3/6 |
| Wu QP | CD44-V6 | 2005 | China | 52 | 1/18 | 13/20 | 22/8 | 17/4 | NA | NA | 20/16 | 15/1 | 28/8 | 3/13 |
| YU J | CD44-V6 | 2006 | China | 69 | 12/26 | 25/6 | 27/11 | 15/16 | NA | NA | 9/29 | 4/27 | 25/13 | 10/21 |
| Li GH | pan-CD44 | 2007 | China | 36 | 2/19 | 8/7 | 12/9 | 13/2 | 5 | 4/11 | 20/1 | 12/3 | 12/7 | 7/6 |
| Yang Yj | CD44-V6 | 2007 | China | 65 | NA | NA | 18/25 | 20/2 | NA | NA | 16/27 | 12/10 | 30/13 | 5/17 |
| Weng MX | CD44-V6 | 2008 | China | 86 | 22/16 | 38/10 | 23/15 | 42/6 | NA | NA | 23/26 | 27/19 | 27/11 | 23/25 |
| Eren B | CD44-V6 | 2008 | Turkey | 33 | 15/3 | 6/9 | 3/15 | 3/12 | NA | NA | NA | NA | 16/1 | 7/8 |
| Wu Y | pan-CD44 | 2009 | China | 36 | 2/19 | 8/7 | 12/9 | 13/2 | 5/16 | 4/11 | NA | NA | 12/7 | 7/6 |
| Zhang XH | CD44-V6 | 2009 | China | 46 | 14/12 | 18/2 | NA | NA | 11/16 | 10/9 | NA | NA | NA | NA |
| Yuan H | pan-CD44 | 2010 | China | 75 | 14/35 | 15/11 | 17/32 | 20/6 | NA | NA | 22/19 | 21/15 | NA | NA |
| Meng L | CD44-V6 | 2010 | China | 56 | 7/26 | 15/8 | 8/26 | 15/8 | NA | NA | NA | NA | 18/15 | 14/9 |
| Ko YH | pan-CD44 | 2011 | South Korea | 149 | 59/43 | 24/17 | 78/29 | 32/10 | 33/92 | 13/28 | 18/89 | 7/35 | 66/41 | 6/36 |

Abbreviation: N/P, negative expression/positive expression; SCC, Squamous cell carcinoma; ADC, Adenocarcinoma; I II/III IV, TMN stageland TMN stage II/TMN stage III and TMN stage IV; Tumor differentiation I II/III, well and moderate differentiation/poor differentiation; NA, no available or no applicable.

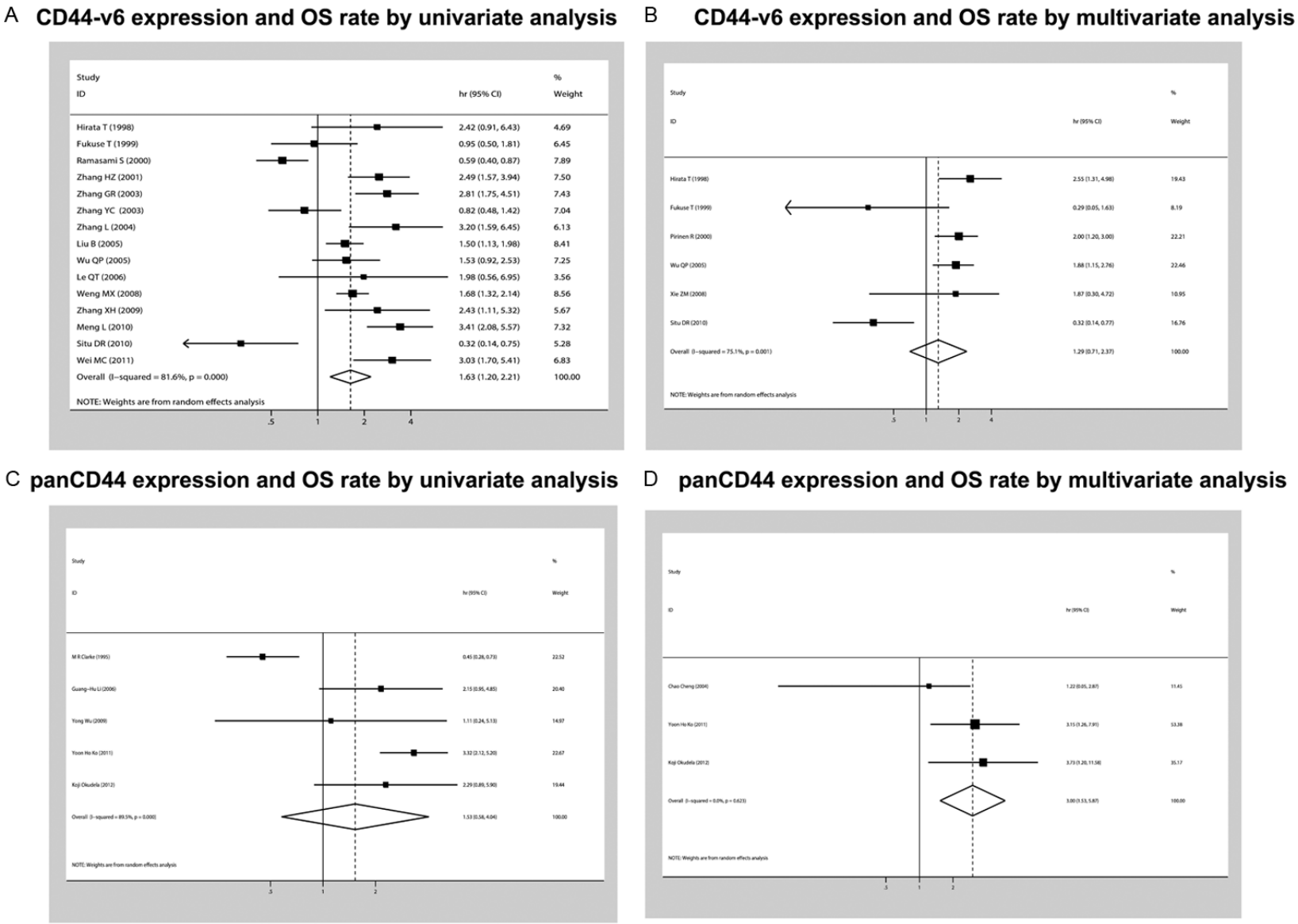


**Figure 2.** Forest plot showing the combined relative HR from the random-effects model for overall survival by univariate and multivariate analysis such as (A), CD44-v6 expression and OS rate by univariate analysis (B), CD44-v6 expression and OS rate by multivariate analysis (C), panCD44 expression and OS rate by univariate analysis (D), panCD44 expression and OS rate by multivariate analysis.

**Table 3.** Summarized Univariate HR of overall and subgroup analyses for CD44v6 on NSCLC survival

| N. of studies | Number of patients | Random effects HR (95% CIs) | Heterogeneity test | | |
|---|---|---|---|---|---|
| | | | chi-squared | $I^2$ | *P*-value |
| Written Language | | | | | |
| English written | 5 | 0.88 (0.47-1.63) | 13.6 | 70.60% | 0.678 |
| Non English written | 10 | 2.05 (1.59-2.64) | 28.1 | 67.90% | 0.0001 |
| HR Estimate | | | | | |
| HR | 2 | 0.73 (0.16-2.3) | 9.58 | 89.6 | 0.683 |
| Sur. Curve | 13 | 1.83 (1.26-2.65) | 62.14 | 82.3 | 0.001 |
| Ethnicity | | | | | |
| Asian | 13 | 1.78 (1.34-2.35) | 48.26 | 75.10% | 0.0001 |
| Non-Asian | 2 | 0.53 (0.29-2.92) | 3.24 | 69.20% | 0.892 |
| Cutoff value | | | | | |
| 0% | 6 | 1.31 (0.73-2.35) | 23.54 | 78.80% | 0.369 |
| 10% | 4 | 2.03 (0.79-5.22) | 43.56 | 93.10% | 0.141 |
| Tumor stage | | | | | |
| I-II | 5 | 1.78 (0.78-4.09) | 23.85 | 83.20% | 0.7114 |
| I-III | 7 | 1.61 (1.01-2.58) | 43.52 | 86.20% | 0.0400 |
| Follow up time | | | | | |
| 36 months | 4 | 1.79 (0.9-3.58) | 12.05 | 75.10% | 0.0035 |
| 60 months | 9 | 1.82 (1.29-2.56) | 35.88 | 77.70% | 0.1915 |

2.78, $P$ = 0.0001 and $I^2$ = 77.5, random-effect).

Next, we performed analyses to investigate clinicopathological parameters if there were differences in results with respect to panCD44 expression. However, because of the limited number of studies that we could not get the statistically significant results mostly. Thus, more studies about panCD44 and NSCLC should be conducted in the future.

Publication bias statistics were determined using the method of Begg's test (**Figure 5**) between CD44 (including CD44-v6 and pan-CD44) expression and clinicopathological features. In all included studies, no funnel plot asymmetry was found Sensitively analysis was performed to investigate the effect of every study on the overall meta-analysis by omitting one study each time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

## Discussion

The correlation between CD44 expression and NSCLC has been widely studied, and most of them showed that over-expression of CD44 was associated with some clinicopathologic features and a poor prognosis, but a great deal of controversy results of the prognostic implications of CD44 in NSCLC remains. To get a better understanding of the relationship between CD44 expression and NSCLC, this meta-analysis was carried out including 1772 patients from 23 evaluable studies for Prognostic Value and 2167 patients from 28 evaluable studies for clinicopathological. The pooled data revealed the CD44 expression in whole tissue sections, revealed a poor prognostic outcome in patients expressing high levels of CD44v6. The results indicate that CD44v6 expression is significantly associated with tumor differentiation, tumor histological type, clinical TMN stage, lymph node metastasis and OS. We also have collected the information about the relationship between the pan-CD44 expression and OS and clinicopathological features at the same time. Although we also observed statistically significant effects of panCD44 expression and OS rate in three studies (including a total of 291 patients) from multivariate analysis, with a combined HR of 3.00 (95% CI: 1.53-5.87, $P$ = 0.623, $I^2$ = 0.0%). Furthermore, because of the limited number of studies that we could not get the statistically significant results about pan-CD44 expression and clinicopathological parameters. Thus, more studies about panCD44 and NSCLC should be conducted in the future.

Extensive evidence showed that CD44 played important roles in tumor progression, especially with cancer stem cell related characteristics. What makes CD44 account for the poor prognosis in NSCLC? On the one hand, recently sev-

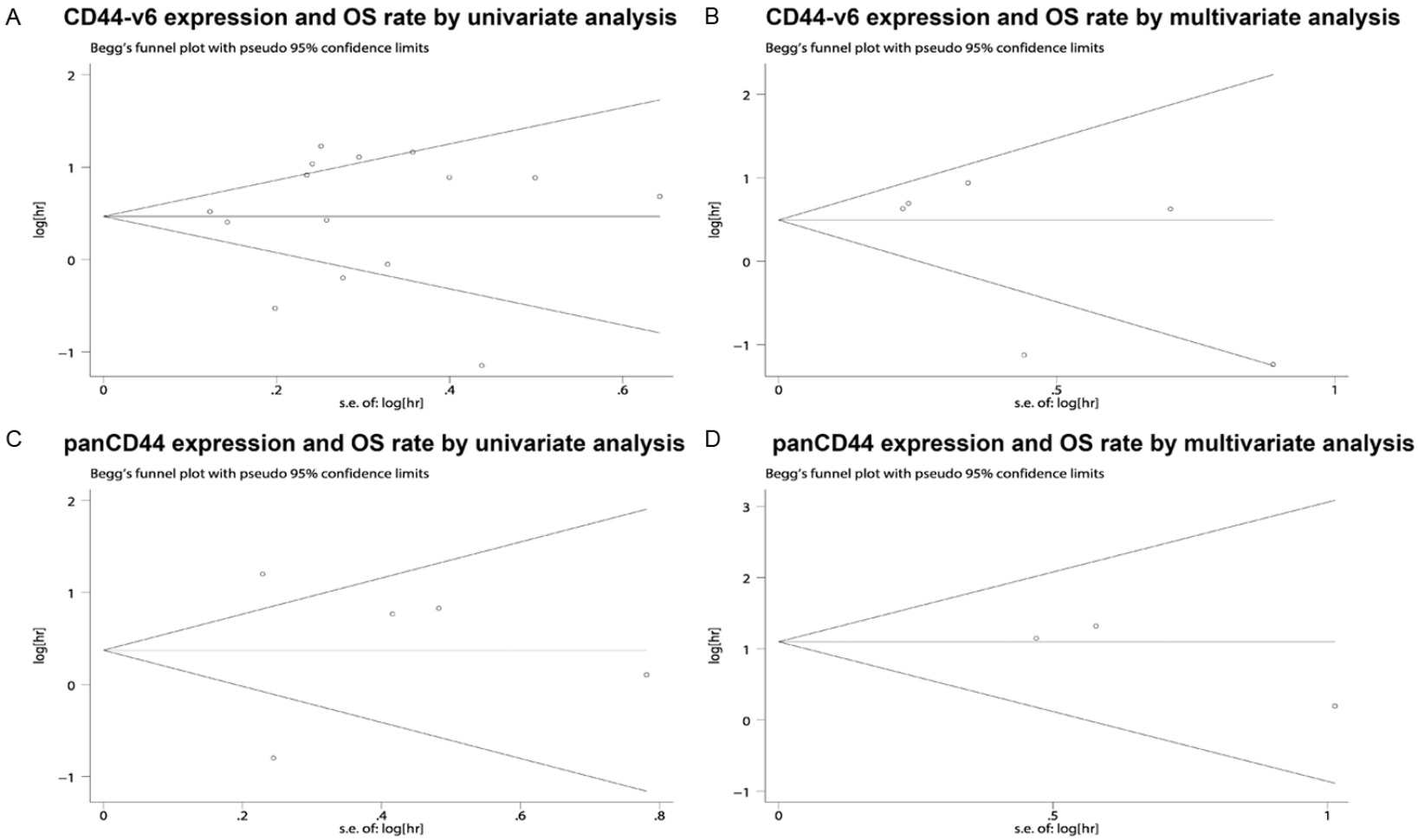


**Figure 3.** Begg's test results of overall survival rate such as (A), CD44-v6 expression and OS rate by univariate analysis (B), CD44-v6 expression and OS rate by multivariate analysis (C), panCD44 expression and OS rate by univariate analysis (D), panCD44 expression and OS rate by multivariate analysis.

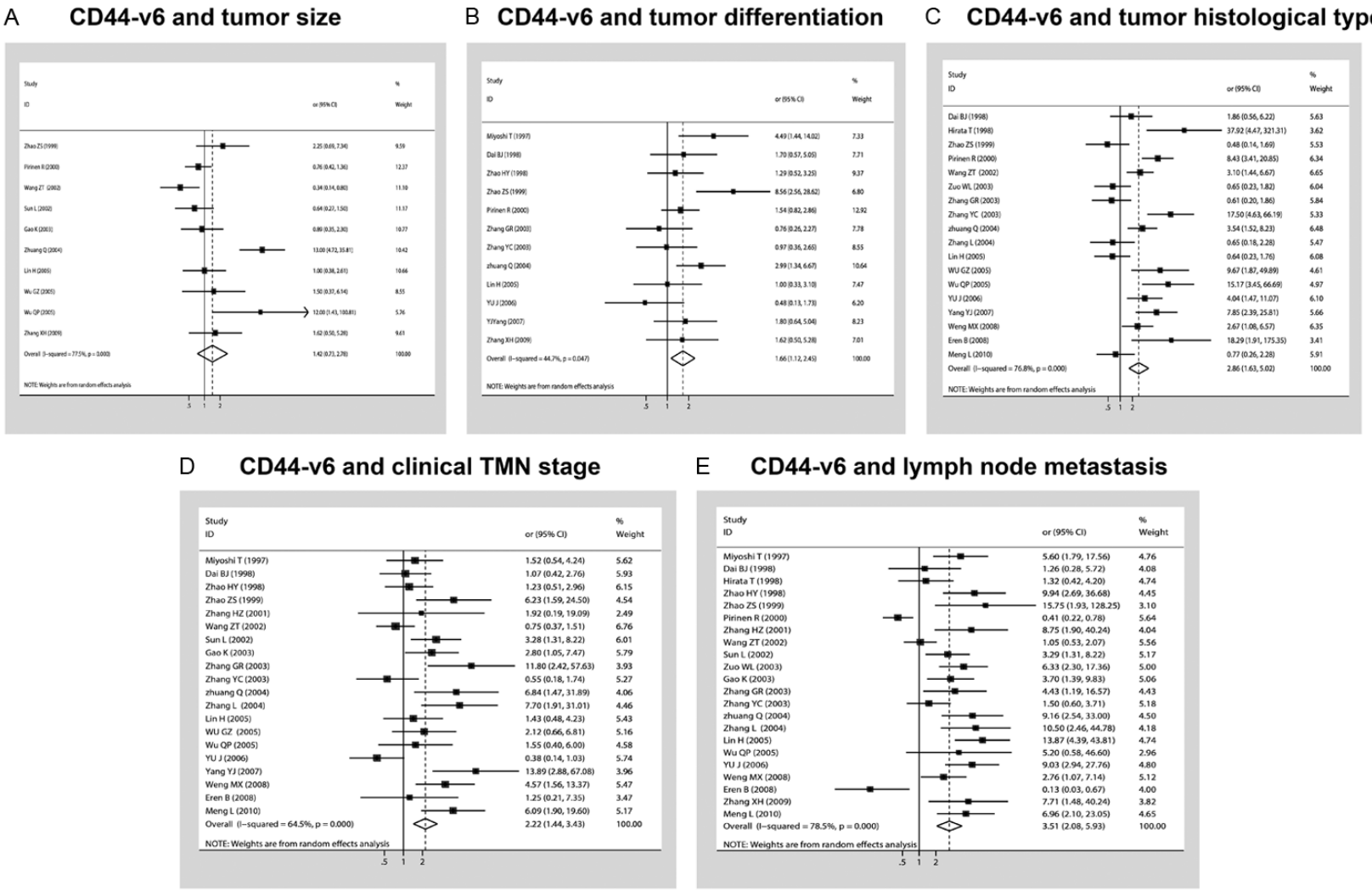


**Figure 4.** Forest plot of OR was assessed for association between CD44-v6 and clinicopathological features such as (A), tumor size (B), tumor differentiation (C), tumor histological type (D), clinical TMN stage (E), lymph node metastasis.

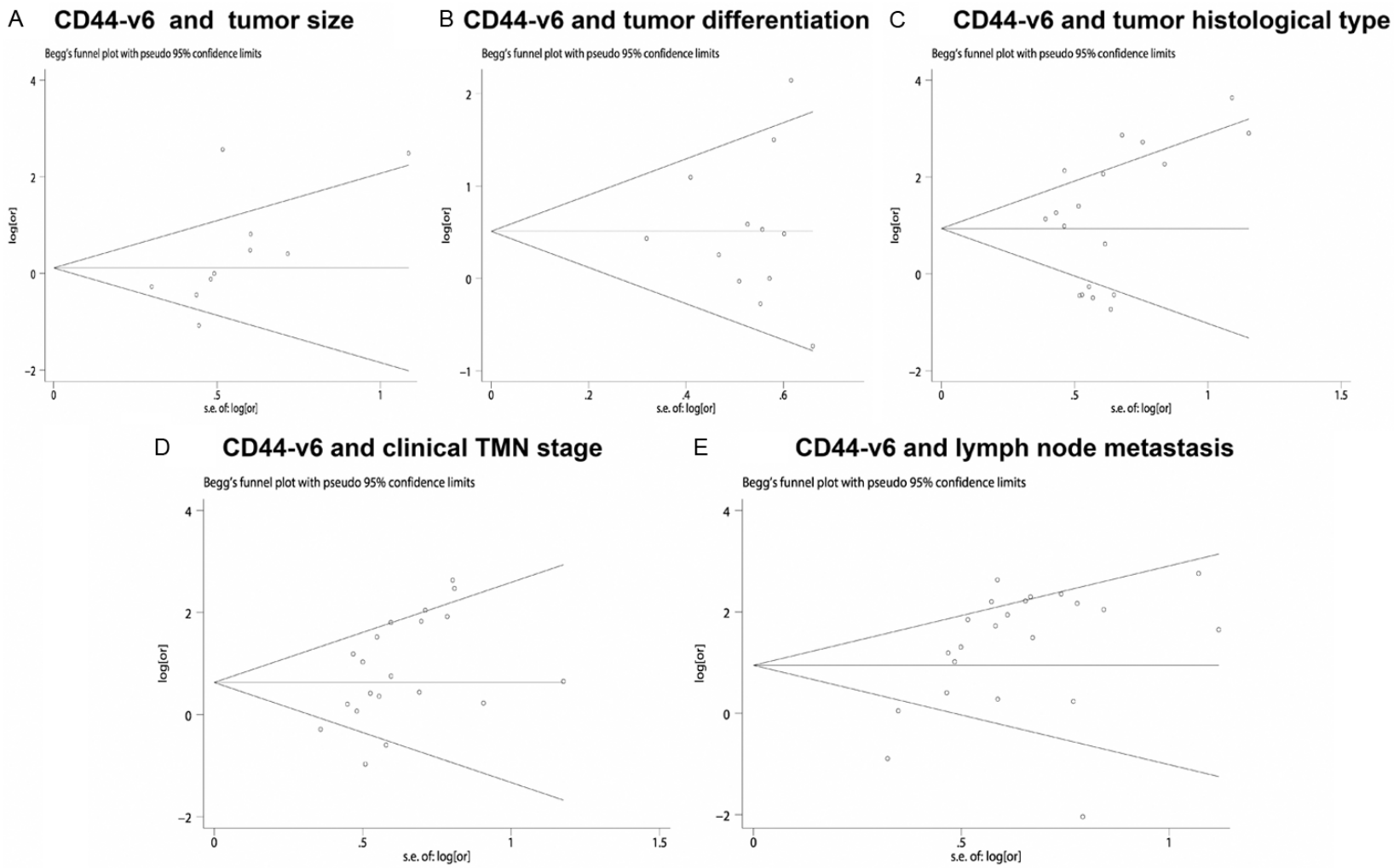


**Figure 5.** Begg's test results of CD44-v6 and clinicopathological features such as tumor category (A), tumor size (B), tumor differentiation (C), tumor histological type (D), clinical TMN stage (E), lymph node metastasis.

eral studies have reported the specific role of CD44v6 and CD44s. CD44 could participate in a important biological event in the invasion process, epithelial mesenchymal transition (EMT) [58, 59]. In some epithelial cells the EMT process was accompanied by a transition in CD44 isoforms from CD44v6 to CD44s, and CD44s has been proved to promote the EMT process [60]. In tumor progression CD44 was related to cancer cell invasion and metastasis. when CD44 interacted with hyaluronan, by virtue of their ability to binded to the actin cytoskeleton, CD44 could move to the leading edge of the migrating cells. Thereafter migrating cells moving to the endothelial cells as the initial step of the extravasation relying on CD44 could bind to CD62 on endothelial cells [61, 62]. Effects of HA and CD44 interaction could activate the ROK pathway, which induced the phosphorylation of the Na+/H+ exchange [63] an decreased of tumor extracellular matrix and invasion. Many articles have proved that CD44 was closely related with lymph node metastasis, which were well supported by our meta-analysis. The results of our meta-analysis supported that the function of the lymph node metastasis might be dependent on CD44v6.

The heterogeneity could be explained by the fact that the technique of detecting CD44 is not comparable among the studies. These differing results in NSCLC may be partially attributed to differences in antibodies used for staining, different criteria for defining stain positivity, and different patient demographics such as tumor stage,histological subtype, adjuvant treatment, and insufficient SCC immunoreactivity. However, obviously, CD44 is a membrane-bound glycoprotein and mediates a complex range of functions. Invasive and metastatic growth can be mediated through the interaction of cell surface CD44 with ECM components such as hyaluronan or cell-cell interactions [64]. CD44-hyaluronan aggregates are essential for activation of metalloproteinase, which induces tissue invasion and tumor growth factor-β [65].

This contradiction could be explained by the relative small burden of some NSCLC cancers that could not change the systemic CD44 level. However, when stratified analysis was conducted about different stages of NSCLC, the association was also found in stage I-III, but not stage I-II, indicating that CD44-v6 could probably predict worse prognosis in advanced-stage NSCLC. Overexpression of CD44-v6 was a negative prognostic marker with significance in patients of with squamous cell carcinomas (SCC). This tendency was reported in previous reports [66, 67]. SCC derives from dysplastic or metaplastic stratified epithelia. In a recent study by Leung et al, evaluating non-cancerous lung tissue, membrane expression of CD44 was confined to the surface of bronchial basal cells, alveolar macrophages, and regenerating cuboidal pneumocytes of injured lung, whereas no CD44 expression was observed in terminally differentiated epithelial cells such as ciliated or nonciliated columnar cells of bronchial epithelium or type I flat pneumocytes lining alveolar spaces [13]. However, squamous metaplasia showed strong CD44 immunoreactivity in the proliferating basal layers, while in premalignant dysplasia, the entire thickness displayed aberrant CD44 expression, indicating that squamous malignant transformation is closely associated with CD44 expression.

Although we performed a comprehensive analysis of the association between CD44 expression and overall survival and patient clinicopathological parameters, there were some limitations to this meta-analysis. The risks calculated in our meta-analysis may be an overestimate due to publication and reporting bias. We did not include unpublished papers and abstracts into meta-analysis because the required data was available only in full publications. Positive results tend to be more acceptable by journals, whereas negative results often are rejected or are not even submitted for review. Furthermore, 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 the survival curves. Actually, the method of extrapolating HR from survival curves seems to be less reliable because this strategy did not completely eliminate inaccuracy in the extracted survival rates. Moreover, we also think different objects included in these studies have different impact on overall survival, so this factor should be taken into consideration. Therefore, more meticulous research should be conducted. Nevertheless, no publication bias was detected using Begg's test ($P > 0.05$), indicating that the statistics obtained approximate the actual results. Sensitivity analysis was also conducted to investigate the influence of a single study on the overall meta-analysis by omit-

ting one study at a time, and the omission of any study made no significant difference, suggesting that our results were statistically reliable.

In summary, overexpression of CD44v6 was associated with poor overall survival in patients with NSCLC on univariate analysis but not multivariate analysis. However, more prospective clinical studies are needed to explore the prognostic value of panCD44 in NSCLC. Overexpression of CD44-V6 is associated with tumor differentiation, tumor histological type, clinical TMN stage and lymph node metastasis in patients with NSCLC. However, there was no significant association between expression of CD44-V6 and tumor size. Large prospective studies are now needed to confirm the clinical utility of CD44 as an independent prognostic marker.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Wei Li, Department of Respiratory Medicine, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, China. Tel: +86 (0871) 85324888-2512; E-mail: fyy6512@gmail.com

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