

REVIEW

Upregulated N-cadherin expression is associated with poor prognosis in epithelial-derived solid tumours: A meta-analysis

Yong Luo¹ | Ting Yu² | Qiongwen Zhang^{1,2} | Qingyu Fu² | Yuzhu Hu² |
Mengmeng Xiang² | Haoning Peng² | Tianying Zheng² | Li Lu³ | Huashan Shi^{1,2} 

¹State Key Laboratory of Biotherapy and Department of Head and Neck Oncology, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

²West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

³College of Computer Science, Sichuan University, Chengdu, Sichuan, China

Correspondence

Huashan Shi, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

Email: hx_natlife@163.com

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Abstract

Background: N-cadherin is an important molecular in epithelial-mesenchymal transition (EMT) and has been reported to be associated with aggressive behaviours of tumours. However, prognostic value of N-cadherin in solid malignancies remains controversially.

Materials and Methods: The Pubmed/MELINE and EMBASE databases were used for a comprehensive literature searching. Pooled risk ratio (RR) and hazard ratio (HR) with their corresponding 95% confidence intervals (CIs) were employed to quantify the prognostic role.

Results: Involving 36 studies with 5705 patients were performed to investigate relationships between N-cadherin upregulation and clinicopathological features, survival. Results suggested upregulated N-cadherin was associated with lymph node metastasis (RR = 1.16, 95% CI [1.00, 1.35]), higher histological grade (RR = 1.36, 95% CI [1.14, 1.62]), angiolymphatic invasion (RR = 1.19, 95% CI [1.06, 1.34]) and advanced clinical stage (RR = 1.32, 95% CI [1.06, 1.64]), while upregulated N-cadherin was apt to be associated with distant metastasis (RR = 1.43, 95% CI [0.99, 2.05]). Moreover, N-cadherin was correlated with poor prognosis of 3-year survival (HR = 1.78, 95% CI [1.51, 2.10]), 5-year survival (HR = 1.57, 95% CI [1.17, 2.10]) and overall survival (OS) (HR = 1.32, 95% CI [1.20, 1.44]). Subgroup analyses according to cancer types were also conducted for applying these conclusions to some tumours more properly. No publication bias was found except subgroup analysis of distant metastasis ($P = .652$ for Begg's test and 0.023 for Egger's test).

Conclusions: Taken together, upregulation of N-cadherin is associated with more aggressive behaviours of epithelial-derived solid malignancies and can be regarded as a predictor of poor survival.

KEYWORDS

clinicopathological features, epithelial-derived solid tumours, N-cadherin, prognosis

Yong Luo and Ting Yu contributed equally to this work.

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1 | INTRODUCTION

As a life-threatening disease, cancer has increasingly been a heavy burden of healthcare system.^{1,2} The failure of cancer therapy and poor outcomes are mostly owing to the development of local invasion and distant metastasis. Activating of invasion and metastasis has been demonstrated as one of the most important hallmark capabilities of cancer.¹ To date, researchers have paid tremendous attention to the biological behaviour of cancer cells, aiming at finding potential therapeutic targets.

Invasion and metastasis are considered as complex processes involving detachment of cancer cell from primary tumour site and formation of new tumour foci in distant organs.³⁻⁵ Epithelial-mesenchymal transition (EMT), a developmental regulatory programme, identified as transformed epithelial cells loss epithelial constraints and then acquire the abilities to invade, resist apoptosis and metastasis, which is believed to play a vital role in broadly regulating invasion and metastasis.^{2,6-9} Cadherins are a family of calcium-dependent glycoproteins, which responsible for Ca²⁺-dependent cell-cell adhesions. Of the members of this family, N-cadherin (neuronal cadherin or cadherin-2), a transmembrane glycoprotein, which is normally expressed in neuroectodermal and mesenchymal-derived tissues, plays crucial role in lots of processes, such as cell-cell adhesion, embryogenesis, gastrulation, neurulation, migration and invasion.^{4,10-13} Today, N-cadherin is regarded as a vital marker of EMT.¹⁴ Neoexpression or upregulated expression of N-cadherin has been reported to accelerate migration and invasion of cancer cells, which showed a contrary function to those of E-cadherin.¹⁵⁻¹⁸ This process of reciprocally downregulating E-cadherin and upregulating N-cadherin is known as cadherin switching that characterizes EMT.¹⁹ Cadherin switching is a necessary procedure during the course of development, while it will lead to an aggressive tumour cell phenotype and enable tumour cells obtain ability of migration from primary site and metastasis to distant tissues.²⁰ Study reveals that N-cadherin-positive cancer cells are capable of building cell-cell adhesion with stromal cells that express N-cadherin, thus facilitating invasion process.²¹ Some studies indicate that N-cadherin boosts the combination of fibroblast growth factor (FGF) with the receptor to initiate FGFR signal transduction, thereby inducing signalling cascades that promote migration and invasion of cancer cells.²² Furthermore, studies have shown that N-cadherin promotes cells survival and protects cancer cells from apoptosis by activating the phosphatidylinositol 3-kinase (PI3K)-AKT (also known as protein kinase B) pathway.^{17,23,24} Therefore, N-cadherin presents distinct functions from its adhesion activity.

Nevertheless, the prognostic role of N-cadherin in tumours still remains controversially. Some studies

suggested that expression of N-cadherin was generally upregulated in prostate, breast cancer and urothelial tumours, and was associated with poorer clinical outcomes.^{10,11,25} In addition, the upregulation of N-cadherin was significantly related with postoperative recurrence in hepatocellular carcinoma (HCC) patients.²⁶ However, it was also reported that the expression of N-cadherin was decreased in glioblastoma, ovarian carcinoma, osteosarcoma and HCC, which may provide a hypothesis that N-cadherin serves as a tumour suppressor and its downregulation links to poor surgical outcomes.^{15,27-29} Therefore, this meta-analysis was conducted to assess the relationship of N-cadherin expression with clinicopathological features and prognosis of different carcinomas, especially in epithelial-derived solid tumours.

2 | MATERIALS AND METHODS

2.1 | Primary search strategy

The Pubmed/MELINE and EMBASE databases were used for related publications search by variably combining the terms “cancer [Title/Abstract],” “tumour [Title/Abstract],” “carcinoma [Title/Abstract],” “neoplasm [Title/Abstract]” and “N-cadherin [Title/Abstract],” without any limitation of publication date. The most recent search update was conducted on 23 February 2017. To avoid missing additional studies, the references of all eligible studies were further explored in these databases. PRISMA and the broader EQUATOR guidelines were referred to in the reporting of our study to comply with the standard of meta-analysis.³⁰

2.2 | Inclusion and exclusion criteria

The included studies were required to meet the following criteria: (i) the patients with solid tumours included in these studies were diagnosed histopathologically; (ii) the correlation of N-cadherin expression and solid tumours was evaluated; (iii) clinicopathological features, 3/5-year survival, OS or Kaplan-Meier survival curves were investigated; and (iv) full text was written in English. Studies were excluded if (i) the study was published in conference abstract, letters, editorials, reviews, expert opinion or case reports; (ii) studies of animals or cell lines; (iii) the relevant clinicopathological features or outcomes of patients were not able to be acquired for necessary analysis; (iv) overlapped or duplicated studies.

2.3 | Data extraction

Data were carefully retrieved independently by 2 reviewers from all the eligible studies, using a standardized form with the following characteristics: author, year, country, study design, number of patients, mean age, method used for

evaluating expression of N-cadherin, antibody source, definition of N-cadherin positive, expression rate of N-cadherin, median follow-up time, clinicopathological features and survival data. Discrepancies between 2 reviewers were solved by discussing until agreement was reached with the third reviewer. Quality assessment of included studies was conducted on the basis of the Newcastle-Ottawa quality assessment scale (NOS scale). Six points or higher were regarded as high quality.

2.4 | Statistical analysis

Included studies were divided into 7 groups for analysing the prognostic value of N-cadherin expression in solid tumour patients regarding histological grade, lymph node status, angiolymphatic invasion, distant metastasis, clinical stage, 3-year survival, 5-year survival and OS. Clinicopathological features were synthesized using the risk ratio (RR) as the calculating measure, while the survival outcome data using the hazard ratio (HR) as calculating measure. RR/HR with 95% confidence interval (CI) value was performed to quantitatively evaluate how increased N-cadherin expression impacts the prognosis of solid tumour patients. Reported RR/HR and their 95% CI were directly extracted from included studies. If RR/HR and 95% CIs were not available in the original articles, the methods demonstrated by Parmer et al³⁰ and Tierney et al³¹ were applied to calculate RR/HR and 95% CIs. Moreover, when the exploitable data were presented in the figure form, Engauge Digitizer version 4.1 (free software downloading from <http://sourceforge.net>) was applied to extract data from Kaplan-Meier curves thereby obtaining HR and 95% CIs. Heterogeneities of included studies were assessed using I^2 metric and Q statistic. If heterogeneity was significantly obvious ($I^2 > 50\%$ or $P < .1$), a random effect model was used. Otherwise, a fixed effect model would be chosen ($I^2 < 50\%$ or $P > .1$). The pooled RRs/HRs and 95% CIs were presented in forest plots. If the 95% CIs of RR/HR did not cover the value 1 with $P < .05$, the difference between groups would be regarded as statistically significant. In addition, funnel plots (Begg's test) and Egger's linear regression method (Egger's test) were performed to evaluate the publication bias through assessing the asymmetry of funnel plots (if $P < .05$, considering to be statistically significant).³² All statistical analyses in this meta-analysis were performed using STATA version 12.0 (STATA corporation, College Station, TS, USA).

3 | RESULTS

3.1 | Study selection and characteristics

According to the initial search algorithm, total 4476 studies were screened out, and 389 candidate studies were read in

full. Eventually, a total of 36 publications were included in this meta-analysis, and the other 353 studies were out of scope, as shown in Figure 1. A total of 5705 patients were included in this study, ranging from 38 to 1035 patients per study, the main characteristics and NOS scale of eligible studies were presented in Table 1. Most of studies were prospective cohort studies ($n = 25$), and 11 studies were retrospective cohort studies. The median follow-up time varied from 10.1 months to 125 months.

Among the eligible studies, 36 studies compared the correlation of clinicopathological features and N-cadherin expression, including lymph node metastasis ($n = 21$), histological grade ($n = 21$), angiolymphatic invasion ($n = 8$), distant metastasis ($n = 7$) and clinical stage ($n = 14$). In addition, 10 studies assessed the association of 3-year survival and N-cadherin positivity, 8 studies for 5-year survival and 22 studies for OS. In terms of NOS scale, 3 articles scored 6 points, 16 articles scored 7 points, 13 articles scored 8 points and 4 articles scored 9 points, hence, all of these inclusive studies were regarded as qualified enough for meta-analysis.

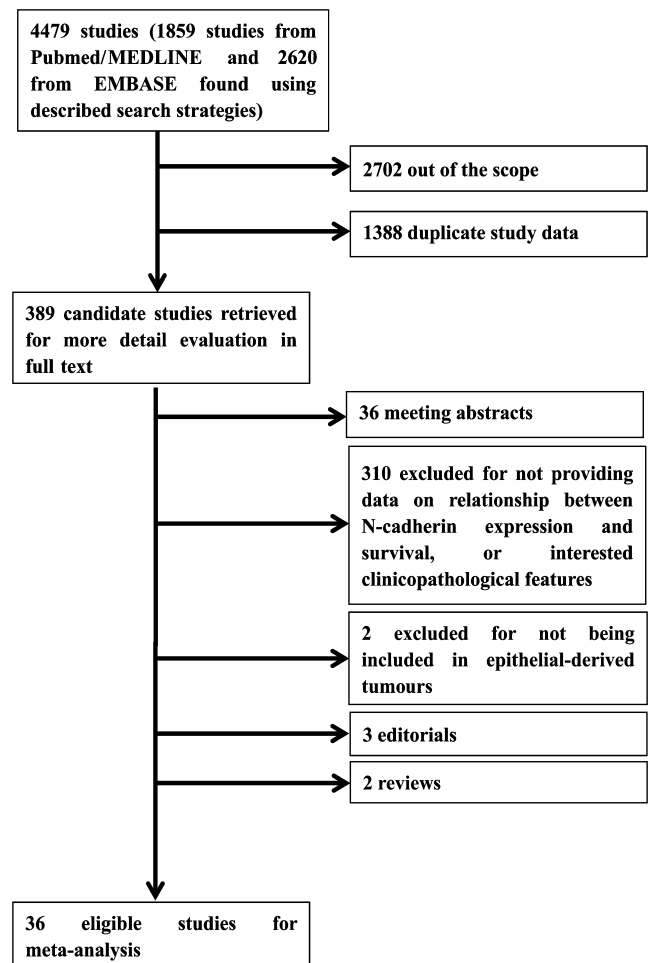


FIGURE 1 Flow chart of the literature search and selection of included studies

TABLE 1 Characteristics of the eligible studies

First author (ref)	Year	Country	Study design	Number (M/F)	Mean age	Method	Antibody source	Definition of N-cadherin positive	Expression rate (%)	Median follow-up (m)	Quality stars (NOS)
HNC (n = 6)											
Nguyen, P.T. ³⁹	2011	Japan	Retro.	80 (NR)	NR	IHC	BD Biosciences	≥20%	NR	NR	7
Gasparotto, D. ⁴¹	2011	Italy	Pro.	69 (65/4)	NR	IHC	Novocastra	≥Median expression level	NR	45	8
Ding, L. ⁴³	2014	China	Pro.	50 (25/25)	53.5	IHC	Zymed	≥20%	NR	60.34	9
Mohan, A. ⁵⁶	2006	India	Retro.	62 (38/24)	2.67	IHC	Upstate Cell Signaling Solutions	≥5%	93.5	NR	8
Luo, W.R. ⁵⁸	2011	China	Pro.	122 (92/30)	47.6	IHC	Zymed	IRS ≥ 6 ^a	NR	51.9	9
Greco, A. ⁶⁷	2015	Italy	Pro.	82 (70/12)	61	IHC	Santa Cruz Biotechnology	NR	NR	NR	7
Breast cancer (n = 7)											
Aleskandarany, M.A. ³²	2014	England	Pro.	1035 (NR)	54	IHC	Sigma	NR	NR	125	8
Choi, Y. ³³	2013	Korea	Retro.	389 (NR)	50.6	IHC	Invitrogen	≥10%	NR	NR	7
Markiewicz, A. ³⁴	2014	Poland	Pro.	108 (NR)	60	IHC	Dako	≥10%	NR	28.8	8
EIMoneim, H.M.A. ³⁵	2011	Egypt	Retro.	132 (NR)	52.67	IHC	Dako	≥10%	NR	NR	7
Kovács, A. ³⁷	2003	England	Pro.	100 (NR)	NR	IHC	Zymed	≥20%	NR	NR	7
Cao, Y.W. ³⁸	2014	China	Retro.	200 (NR)	NR	IHC	Abcam	IRS > 3	NR	NR	6
Carvalho, S.T. ⁶⁴	2011	Brazil	Pro.	82 (NR)	NR	IHC	BD Biosciences	≥10%	NR	120	8
Lung cancer (n = 7)											
Li, X.X. ³⁶	2015	China	Pro.	65 (44/21)	59	IHC	Abcam	IRS ≥ 3	35.4	30.17	8
Nakashima, T. ⁴⁰	2003	Japan	Pro.	150 (NR)	NR	IHC	BD Bioscience	≥20%	30.6	41.4	7
Hui, L. ⁴²	2013	China	Pro.	120 (81/39)	60	IHC	Santa Cruz Biotechnology	IRS ≥ 2	30.7	30.8	8
Zhou, Y. ⁵⁷	2016	China	Pro.	153 (141/12)	NR	IHC	Abcam	IRS > 4	79.08	57	7
Grinberg-Rashi, H. ⁵⁹	2009	Israel	Pro.	107 (76/31)	61.06	IHC	Dako	Mesothelioma as positive control	NR	34	8
Liu, S. ⁶³	2013	China	Pro.	113 (61/52)	60.3	IHC	Santa Cruz Biotechnology	≥10%	40.7	NR	8
Miao, Y. ⁶⁶	2012	China	Pro.	105 (63/42)	60.4	IHC	Abcam	≥10%	44.8	NR	8
Cancer of digestive system (n = 7)											
Kamihara, T. ⁴⁴	2012	Japan	Pro.	146 (99/47)	63	IHC	Dako	≥5%	21.2	43.2	9

(Continues)

TABLE 1 (Continued)

First author (ref)	Year	Country	Study design	Number (M/F)	Mean age	Method	Antibody source	Definition of N-cadherin positive	Expression rate (%)	Median follow-up (m)	Quality stars (NOS)
Araki, K. ⁴⁵	2011	Japan	Pro.	38 (NR)	NR	IHC	Invitrogen Corp.	NR	23.7	NR	7
Nakajima, S. ⁴⁹	2004	Japan	Pro.	40 (NR)	66.3	IHC	Zymed	≥10%	32.5	10.1	7
Guo, S. ⁵⁰	2013	China	Retro.	76 (47/29)	65	IHC	Santa Cruz Biotechnology	IRS ≥ 5	32.9	NR	7
Cho, S.B. ⁵³	2008	Korea	Pro.	68 (55/13)	60	IHC	Dako	≥30%	NR	30	6
Jie, D. ⁵⁴	2013	China	Pro.	108 (65/43)	54	IHC	R&D Systems	IRS ≥ 1	41.7	NR	7
Fu, H. ⁶⁵	2016	China	Retro.	74 (63/11)	NR	IHC	NR	IRS ≥ 2	36.48	NR	7
Urothelial carcinoma (n = 3)											
Abufaraj, M. ⁵¹	2016	Italy	Pro.	678 (380/298)	NR	IHC	Dako	Higher than normal bladder and prostate tissues	43.1	37.5	9
Fondreville, M.E. ⁶⁰											
	2009	France	Pro.	70 (52/18)	69	IHC	Zymed	Higher than normal myocardium tissue	17.14	30	8
Baumgart, E. ⁶¹											
	2007	America	Pro.	572 (NR)	NR	IHC	Zymed	NR	8.2	61.2	8
Prostate cancer (n = 2)											
Liu, GL. ⁴⁶	2014	China	Retro.	59 (NR)	68	IHC	Bioss Biotechnology	≥5%	NR	NR	7
Drivalos, A. ⁴⁷	2015	Greece	Retro.	157 (NR)	66	IHC	Dako	IRS > 3	NR	NR	7
Gynecologic Cancer (n = 4)											
Li, B. ⁴⁸	2016	China	Retro.	127 (NR)	NR	IHC	Santa Cruz Biotechnology	IRS ≥ 3	3.1	72	8
Ma, Y. ⁵²	2015	China	Retro.	81 (NR)	48.1	IHC	Beijing Zhong Shan Biotechnology	≥10%	28.4	NR	7
Marques, F.R. ⁵⁶	2004	Brazil	Pro.	47 (NR)	51	IHC	Zymed	≥10%	NR	48	7
Do, TV. ⁶²	2008	America	Pro.	40 (NR)	62.4	IHC	Invitrogen	IRS ≥ 1.5	NR	NR	6

Abbreviations: F, female; IRS, immuno-reactive score; IHC, immunohistochemistry; m, month; M, male; NOS, Newcastle-Ottawa quality assessment scale; NR, not reported; Pro., prospective study; Retro., retrospective study; ref, reference.

*IRS = percentage score of stained tumour cells is considered as follows: no staining (score = 0), <10% stained (score = 1), 10%-50% stained (score = 2), 51%-80% stained (score = 3) and 81%-100% stained (score = 4). Intensity score is estimated as no staining (score = 0), weak staining (score = 1), moderate staining (score = 2) and strong staining (score = 3).

3.2 | Lymph node metastasis

Lymph node metastasis was evaluated in 21 studies with 3900 patients (positive lymph node metastasis versus negative lymph node metastasis).³³⁻⁵³ Pooled RR indicated that increased N-cadherin apt to cause lymph node metastasis (RR = 1.16, 95%CI [1.00, 1.35], $I^2 = 57.6\%$, $P = .806$; Figure 2A). Thus, a random effect mode was employed due to obvious heterogeneity. According to the subgroup analyses of different tumour types, N-cadherin overexpression in prostate cancer contributed to a significantly positive lymph node metastasis (RR = 2.94, 95%CI [1.29, 6.70]) in 2 studies with 216 patients.^{47,48}

3.3 | Histological grade

A total of 21 studies with 2995 patients assessed the impact of N-cadherin expression and histological grade (poor differentiation vs well/moderate differentiation).^{34-36,38-44,48-58}

Pooled RR showed that increased N-cadherin expression was significantly associated with worse differentiation (RR = 1.36, 95% CI [1.14, 1.62]) (Figure 2B). Because of obvious heterogeneity, random effect model was performed ($I^2 = 65.1\%$, $P = .000$). Subgroup analyses of different tumour types showed N-cadherin upregulation was significantly associated with worse differentiation of breast cancer (RR = 1.47, 95% CI [1.24, 1.74]), while no statistically significant relationships were found between upregulation of N-cadherin and oestrogen receptor (ER), progesterone receptor (PR) or HER2 expression in breast cancer in 5 studies with 821 patients (RR = 0.79, 95% CI [0.61, 1.02]; RR = 0.88, 95% CI [0.73, 1.06]; RR = 1.04, 95% CI [0.80, 1.34]; respectively) (Figure S1A).^{33,34,36,38,39}

3.4 | Angiolympathic invasion

Pooled RR of 8 inclusive studies with 2239 patients showed the upregulation of N-cadherin was significantly

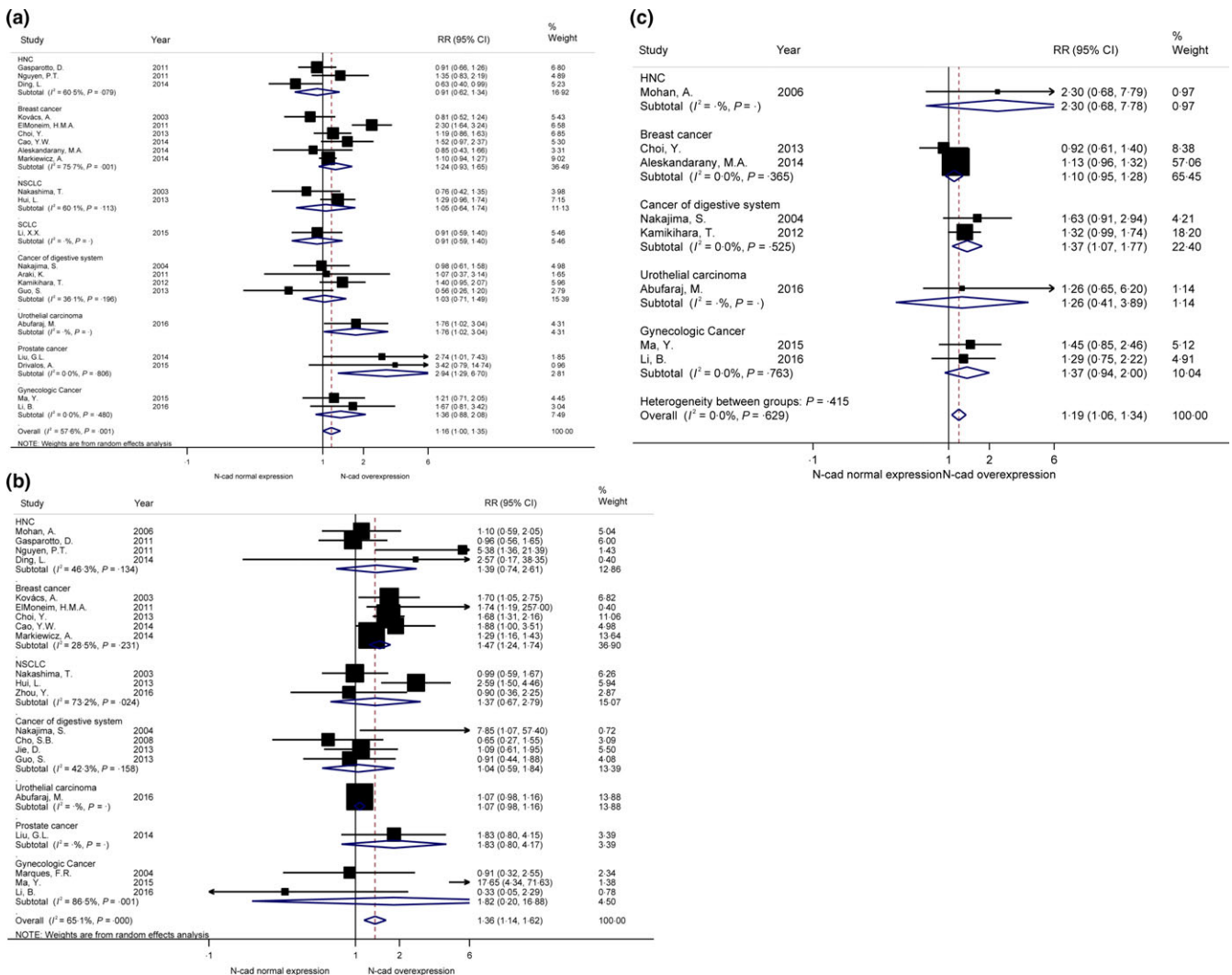


FIGURE 2 Forrest plots of risk ratios (RRs) for correlation between N-cadherin upregulation and clinicopathological features. A, Lymph node metastasis; B, histological grade; C, angiolympathic invasion

correlated with angiolymphatic invasion (RR = 1.19, 95% CI [1.06, 1.34]) (Figure 2C).^{34,36,45,49,50,52,53,57} A subgroup analysis suggested that upregulation of N-cadherin was significantly associated with angiolymphatic invasion in cancers of digestive system in 2 studies with 186 patients (RR = 1.37, 95%CI [1.07, 1.77]).^{45,50} No obvious heterogeneity was observed, hence a fixed effect model was employed ($I^2 = 0.0%$, $P = .629$; Table 2).

3.5 | Distant metastasis

Distant metastasis was investigated in 7 studies with 434 patients.^{37,45,47,50,51,55,59} Pooled RR showed a no statistically significant relationship between N-cadherin upregulation and distant metastasis (RR = 1.43, 95%CI [0.99, 2.05]) (Figure 3A). A fixed effect model was used for observing no obvious heterogeneity ($I^2 = 5.9%$, $P = .382$). Subgroup analysis in cancers of digestive system demonstrated significant association between N-cadherin upregulation and distant metastasis, in 4 studies with 370 patients (RR = 1.90, 95%CI [1.01, 3.59]).^{45,50,51,55}

3.6 | Clinical Stage

A total of 14 studies with 1479 patients discussed the relationship between N-cadherin upregulation and clinical stage (III/IV vs I/II).^{36,37,39,40,43-46,48,50,54,55,58,59} Pooled RR showed higher N-cadherin expression was related to advanced clinical stage (RR = 1.32, 95% CI [1.06, 1.64]) (Figure 3B). A random effect model was performed for obvious heterogeneity ($I^2 = 68.9%$, $P = .000$). Subgroup analysis of head and neck cancers (HNC) indicated an association between N-cadherin upregulation and advanced clinical stages, in 3 studies with 252 patients (RR = 1.59, 95% CI [1.33, 1.91]).^{40,44,59}

3.7 | 3-year and 5-year survival

Quantitative analysis of pooled RR confirmed that upregulation of N-cadherin was shown to be an unfavourable prognostic marker of 3-year survival (HR = 1.78, 95%CI [1.51, 2.10]) with no obvious heterogeneity in 10 studies with 2370 patients (Figure 4A).^{33,43-45,55,59-63} Subgroup analysis showed N-cadherin overexpression was related to worse 3-year survival in HNC (HR = 2.24, 95%CI [1.31, 3.81]), nonsmall cell lung cancer (NSCLC) (HR = 2.02, 95%CI [1.52, 2.70]) and cancer of digestive system (HR = 2.19, 95%CI [1.35, 3.56]). Similar result was also found in 5-year survival (HR = 1.57, 95%CI [1.17, 2.10]) in 8 studies with 2180 patients (Figure 4B).^{33,44,45,55,59,60,62,63} Subgroup analysis indicated the upregulation of N-cadherin was associated with worse 5-year survival in HNC (HR = 1.87, 95%CI [1.05, 3.33]) and cancer of digestive system (HR = 1.66, 95%CI [1.13, 2.44]). Considering the heterogeneity, a fixed effect model and a random effect model were performed in 3-year ($I^2 = 29.4%$, $P = .174$) and 5-year survival analysis ($I^2 = 58.2%$, $P = .019$), respectively.

3.8 | Overall survival

N-cadherin upregulation was proved to have a significant association with worse OS, with pooled HR = 1.32 (95% CI [1.20, 1.44]), in 22 studies with 4081 patients (Figure 4C).^{33,41-46,49,50,52,55,58-68} According to subgroup analyses of different cancer types, N-cadherin upregulation in breast cancer (HR = 1.40, 95% CI [1.22, 1.61]), NSCLC (HR = 1.56, 95% CI [1.26, 1.93]) (n = 6, with 748 patients) and cancers of digestive system (HR = 1.42, 95% CI [1.10, 1.85]) (n = 5, with 406 patients) acted as an unfavourable indicator of OS. Due to no obvious heterogeneity was observed, a fixed effect model was performed ($I^2 = 48.0%$).

TABLE 2 Summary of the outcomes presented in this meta-analysis

Group	No. of studies	No. of total patients	RR/HR (95% CI) (N-cad overexpression vs N-cad normal expression)	P for heterogeneity	I^2	References
Lymph node metastasis	21	3900	1.16 (1.00, 1.35)	.001	57.6%	32-52
Histological grade	21	2995	1.36 (1.14, 1.62)	.000	65.1%	33-35,37-43 47-57
Angiolymphatic invasion	8	2239	1.19 (1.06, 1.34)	.629	0.0%	33,35,44,48,49,51,52,56
Distant metastasis	7	434	1.43 (0.99, 2.05)	.382	5.9%	36,44,46,49,50,54,58
Clinical stage	14	1479	1.32 (1.06, 1.64)	.000	68.9%	35,36,38,39,42-45,47,49,53,54,57,58
3-year survival	10	2370	1.78 (1.51, 2.10)	.174	29.4%	32,42-44,54,58-62
5-year survival	8	2180	1.57 (1.17, 2.10)	.019	58.2%	32,43,44,54,58,59,61,62
OS	22	4081	1.32 (1.20, 1.44)	.007	48.0%	32,40-45,48,49,51,54,57-67

HR, hazard ratio; RR, risk ratio; OS, overall survival.

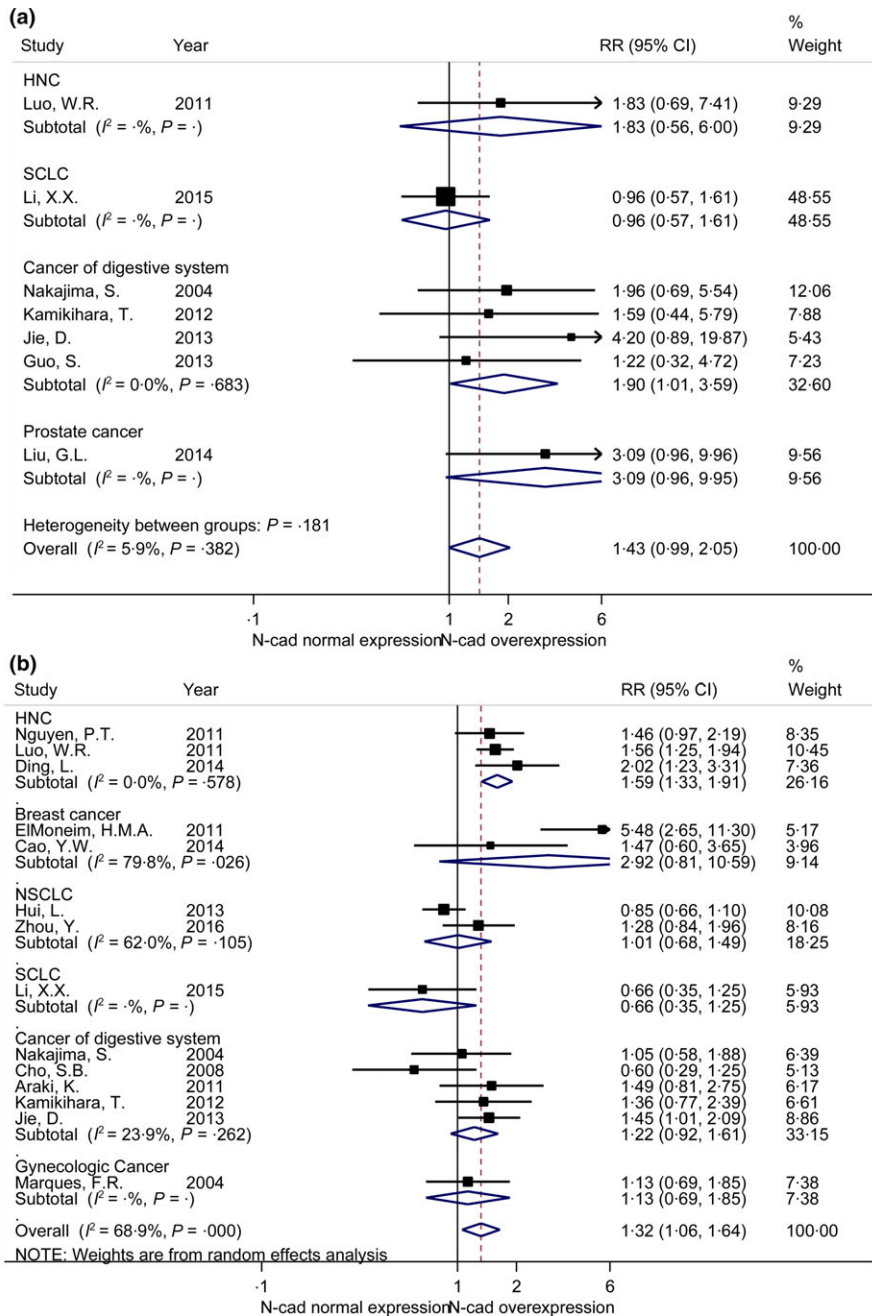


FIGURE 3 Forrest plots of risk ratio (RRs) for correlation between N-cadherin upregulation and clinicopathological features. A, Distant metastasis; B, clinical stage

3.9 | Publication bias

Both Begg's funnel plot and Egger's test were employed to evaluate the publication bias in all studies, including lymph node metastasis, histological grade, angiolymphatic invasion, distant metastasis, clinical stage, 3-year and 5-year survival and OS, respectively (Figure 5). In addition, Begg's funnel plot of molecular markers of breast cancer (ER, PR and HER2) was shown in Figure S1B. Begg's funnel plot showed no statistically significant asymmetry in this meta-analysis, involving lymph node metastasis ($P = .629$), histological grade ($P = .763$), angiolymphatic invasion ($P = .322$), distant metastasis ($P = .652$), clinical stage ($P = .477$), 3-year and 5-year survival and OS ($P = .655$,

$P = .216$, $P = .933$, respectively). Furthermore, no evidence of publication bias was observed in Egger's test of lymph node metastasis ($P = .735$), histological grade ($P = .115$), angiolymphatic invasion ($P = .159$), clinical stage ($P = .772$), 3-year and 5-year survival and OS ($P = .920$, $P = .492$, $P = .634$, respectively), and molecular markers of breast cancer ($P = .741$). Egger's test showed potential publication bias in analysis of distant metastasis ($P = .023$).

4 | DISCUSSION

Many laboratorial evidences have revealed that N-cadherin could drive tumour cells to move into surrounding stroma,

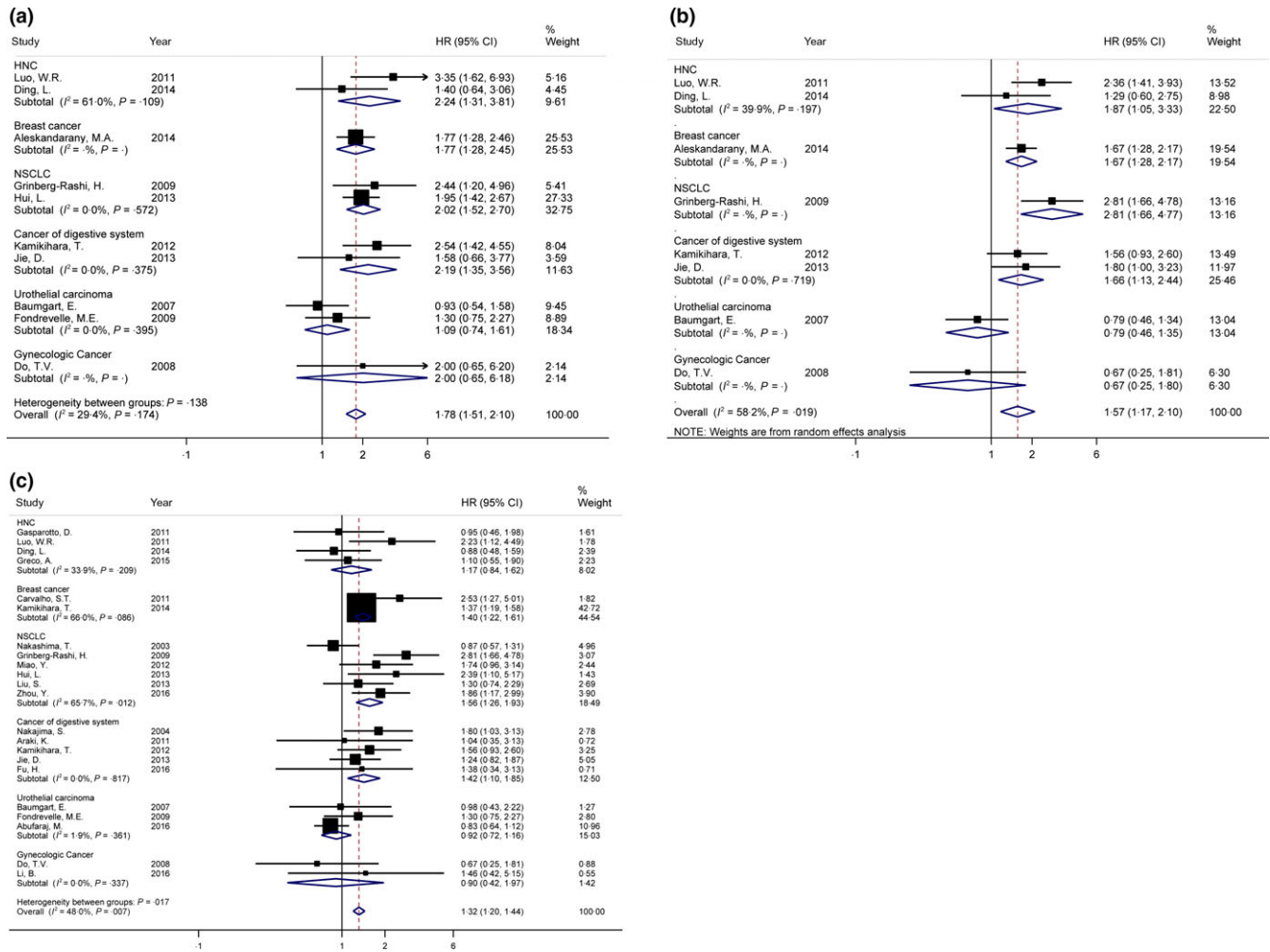


FIGURE 4 Forrest plots of hazard ratios (HRs) for correlation between N-cadherin upregulation and survival outcomes. A, 3-year survival; B, 5-year survival; C, overall survival (OS)

thereby promoting tumour cells migration, invasion and metastasis.^{15,18,20,69} In addition, the upregulation of N-cadherin was also noticed in different cancer types and was also hinted to link to higher histological grade and metastatic tendency.⁶⁹⁻⁷¹ Hence, N-cadherin has been implicated as potential target for anticancer therapy.⁷² Monoclonal antibody targeting of N-cadherin has been reported to be effective in inhibiting proliferation, metastasis and castration resistance of prostate cancer.¹⁰ Moreover, a kind of N-cadherin antagonist has been developed by researchers, a synthetic cyclic pentapeptide (known as ADH-1). In an animal model of pancreatic cancer, ADH-1 showed the inhibitory effect against tumour growth and metastasis.⁷³ Importantly, a phase I/II clinical trial has shown combination of ADH-1 and melphalan could suppress tumour growth in patients with locally advanced melanoma.⁷⁴ Furthermore, ADH-1 was evaluated to be well tolerable both in animal models and humans.^{75,76} However, according to current clinical evidences, the clinical significance of N-cadherin still was unclear. The majority of studies

demonstrated N-cadherin as an unfavourable prognostic marker in a variety of tumours, while some studies showed the tumour suppressor role of N-cadherin. Therefore, an integrated study is urgently needed to answer this question.

As far as we know, this study is the first comprehensive and most full-scale meta-analysis to investigate the prognostic value of N-cadherin upregulation in epithelial-derived solid tumours. At the beginning, 38 studies were involved in this meta-analysis, while 2 studies were about nonepithelial solid tumours, including melanoma and sarcoma.^{77,78} Thus, we excluded these 2 studies for making our conclusions more applicable to epithelia-derived solid tumours. In summary, upregulation of N-cadherin was shown to be significantly associated with lymph node metastasis, higher histological grade, angiolymphatic invasion and advanced clinical stage. According to different cancer types, subgroup analyses further explored relationships between some special cancer types and clinicopathological features. Results suggested upregulation of N-cadherin was associated with lymph node metastasis in

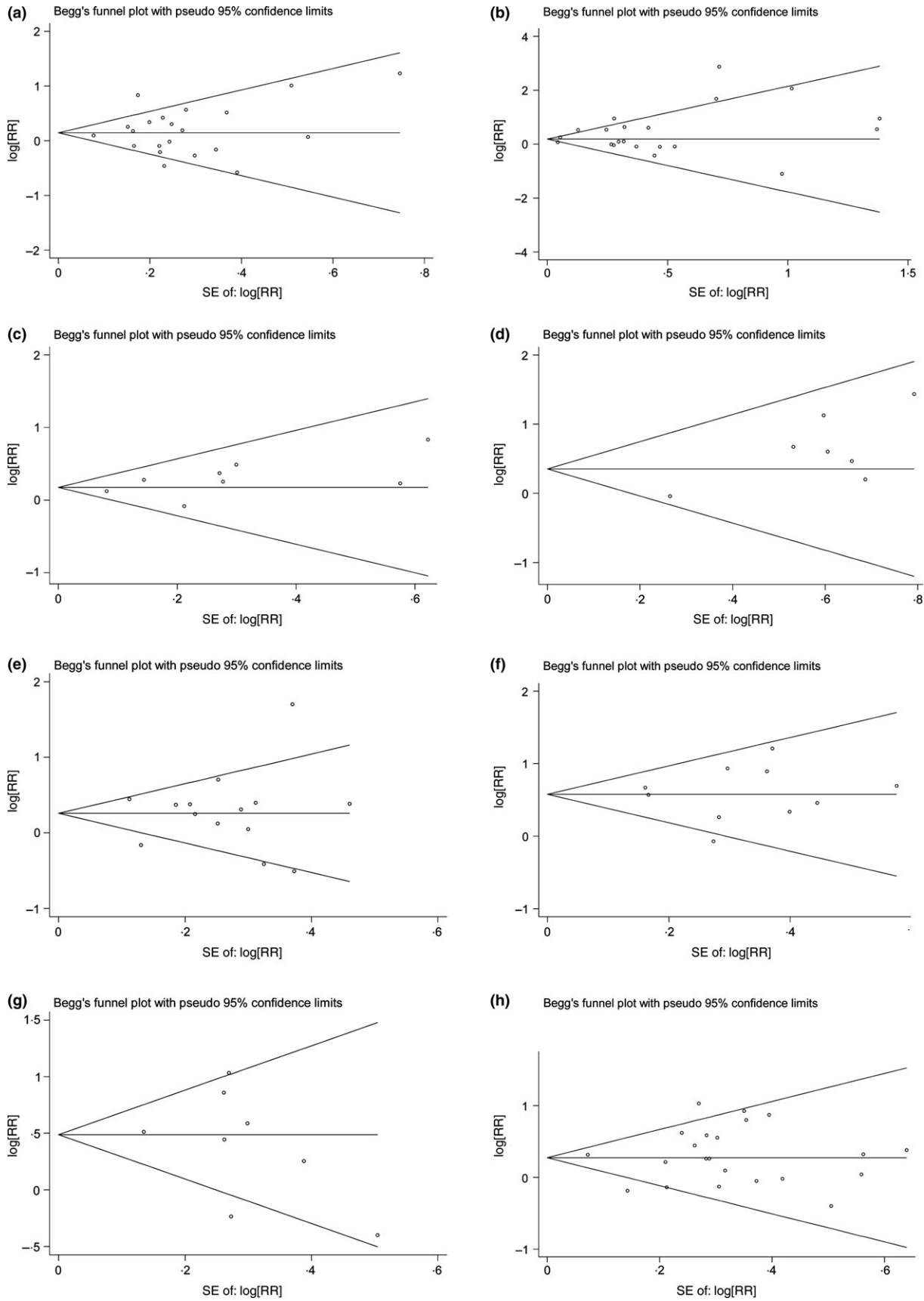


FIGURE 5 Funnel graph for assessing the potential publication bias of this meta-analysis. A, Lymph node metastasis; B, histological grade; C, angiolymphatic invasion; D, distant metastasis; E, clinical stage; F, 3-year and 5-year survivals; G, overall survival (OS)

prostate cancer, higher histological grade in breast cancer, advanced clinical stage in HNC, positive angiolymphatic invasion and distant metastasis in cancers of digestive system. Importantly, pooled HRs showed upregulation of N-cadherin was an obvious unfavourably prognostic factor in analyses of 3-year survival, 5-year survival and OS, especially for NSCLC and cancers of digestive system according to results from subgroup analyses of OS. Therefore, patients with higher N-cadherin expression may need more aggressive treatment, especially for NSCLC and cancers of digestive system.

In spite of the inspiring outcomes, some limitations could not be ignored. First, although all of the included studies used IHC method to measure expression level of N-cadherin, different antibody sources or various cut-off values could lead to potential bias. However, limited by insufficient number of studies, the subgroup analyses of antibody sources or cut-off values were unable to be carried out. Second, obvious heterogeneity was existed in analyses of lymph node metastasis, histological grade, clinical stage, 5-year survival and OS, which may be derived from different cancer types, cancer stages, follow-up time, etc. Random effect model was employed to reduce the effect of heterogeneity on outcomes. In addition, corresponding subgroup analyses were also conducted to make outcomes more reliable and decrease potential bias. Finally, it would be better if we could conduct a comprehensive analysis about prognostic value of cadherin switching in tumours. Loss of E-cadherin always accompanied with upregulation of N-cadherin in tumours. Besides, loss of E-cadherin has been proved to be associated with unfavourable outcomes in various tumours.⁷⁹⁻⁸² The analysis in combination of E-cadherin and N-cadherin might be more valuable in prognostic evaluation of some special tumours, while only a few studies assessed the impact of cadherin switching.⁸³

In conclusion, our study suggests that positivity of N-cadherin is associated with more aggressive behaviour of epithelial-derived solid malignancies, linked to lymph node metastasis, higher histological grade, angiolymphatic invasion and advanced clinical stage. Moreover, N-cadherin could be regarded as a useful predictor for unfavourable prognosis of 3-year survival, 5-year survival and OS in epithelial-derived solid malignancies. The expression status of N-cadherin can provide a reference for treatment strategy and prognostic prediction of epithelial-derived solid malignancies.

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DISCLOSURE OF POTENTIAL CONFLICT OF INTERESTS

No potential conflict of interests were disclosed.

AUTHOR CONTRIBUTIONS

Y Luo, T Yu and HS Shi contributed to the design of the study and manuscript writing. T Yu, QW Zhang, QY Fu, MM xiang, HN peng and Li LU contributed to the data extraction and analysis process of this study. YZ Hu and TY Zheng contributed to the revision of the manuscript. QW Zhang and HS Shi contributed to the financial support of this study.

ORCID

Huashan Shi  <http://orcid.org/0000-0003-1841-639X>

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SUPPORTING INFORMATION

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