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Original Article

Prognostic and clinicopathological differences of DcR3 in gastrointestinal cancer: evidence from meta-analysis

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Abstract: Many studies reported that DcR3 participated in the clinicopathological characteristics of gastrointestinal cancer, however, they all included few patients and had inconsistent results. So we conducted a meta-analysis to explore the correlation between overexpression of DcR3 and the clinicopathological characteristics of gastrointestinal cancer. Identical search strategies were used to search relevant literatures in PubMed, Web of Science and Chinese Biomedical Literature Database. The prognostic significances and clinicopathological differences of DcR3 in gastrointestinal cancer were analyzed. A total of 28 studies comprising 3294 gastrointestinal cancer patients met the inclusion criteria. Overexpression of DcR3 was closely related with these clinicopathological features, including TNM stages (OR = 1.63, 95% CI 1.35-1.98), grade of differentiation (OR = 1.31, 95% CI 1.10-1.56), lymph node metastasis (OR = 2.02, 95% CI 1.66-2.47), infiltration degree (OR = 1.72, 95% CI 1.38-2.12), and metastasis (OR = 1.66, 95% CI 1.27-2.16). DcR3 may play an important role in gastrointestinal cancer, and DcR3 indicated distinct clinicopathologic features.

Keywords: DcR3, gastrointestinal cancer, prognostic, metastasis

Introduction

Decoy receptor 3 (DcR3) is a newly discovered member of tumor necrosis factor receptor (TNFR) family; it is a soluble secretory protein lacking a transmembrane sequence [1].

DcR3 is mostly expressed in tumor cells and competitively inhibits TNF signaling. Overexpression of DcR3 in tumor cells protects them from apoptosis. Studies have shown that DcR3 expression and amplification are closely correlated with the development of various malignant tumors as well as their immune escape [2, 3]. Wu et al. [4] reported that DcR3 could not be detected in non-tumor patients, but could be detected in 98.8% (82/83) of patients with malignant cancers. However, the numbers of patients they included were small, and the conclusions they drew were inconsistent. For example, Meisongzhu Yang et al. [5] reported that there was no correlation between DcR3 expression and tumor cell differentiation; Guo-Hong Li [6] reported that DcR3 was correlated with tumor cell differentiation; Therefore, we made a meta-analysis from eligible studies to investigate the relationship between DcR3 expression and clinicopathological characteristics of gastrointestinal cancer patients.

Experimental procedure

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (I) evaluating DcR3 expression in the gastrointestinal cancer tissues; (II) assessing the relationships between DcR3 expression with gastrointestinal cancer clinicopathologic features; (III) sufficient information provided to estimate odds ratio (OR) about clinicopathologic features; (IV) articles written in English or Chinese. The exclusion criteria were as follow: (I) letters, reviews, case reports, conference abstracts, or editorials; (II) articles had no sufficient data to calculate odds ratio (OR) or haz-

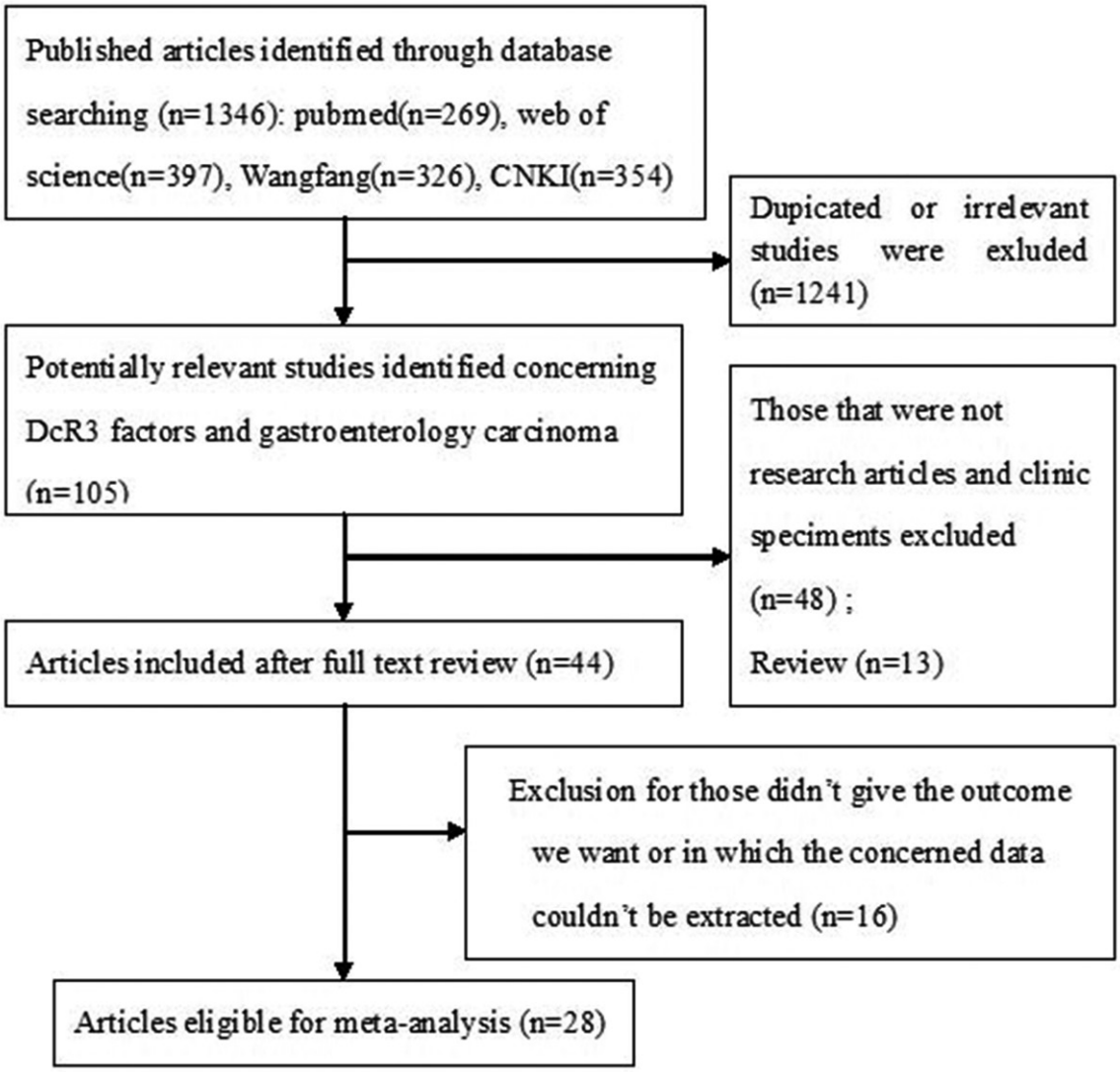

Figure 1. Flow diagram of study selection procedures.

ard ratio (HR); and (III) studies had duplication data.

Search strategy

PubMed, WanFang, CNKI and Web of Science databases were searched using the terms: "DcR3"or "TR6" or "M68". Bibliographies, review articles and other pertinent studies were searched for additional eligible studies. In addition, colleagues in Gastroenterology field were involved for providing details of clinical trials. Two investigators conducted the research independently, and they also evaluated study quality using Cochrane recommendations. Disagreement was solved by discussion with others.

Study screening and data extraction

Two reviewers screened each study independently to determine whether it met the inclusion criteria, and resolved disagreementsby consensus. For each included study, Jing T and Ran Ao independently extracted the following data using a standard form: first author, year of publication, country, kind, number of patients, test method, clinicopathological parameters (TNM stage, differentiation, lymph node metastasis, infiltration degree, Metastasis).

Methodological assessment

Newcastle-Ottawa quality assessment scale (NOS) was used to assess the quality of each

Table 1. Main characteristics of all studies included in Meta-analysis

First author (Ref.)	*Year*	*Country*	*Kind*	*NO of Case (control)*	*Method*	*Clinicopathological factors*	*Quality score*
YANG [5]	2010	China	HCC	67 (28)	SC	①②⑤	7
Qi [8]	2009	China	CRC	100 (100)	IHC/RT-PCR	⑤	7
AO [9]	2013	China	EC	150 (30)	IHC	①②④⑤	7
Li [10]	2005	China	EC	28 (40)	IHC	②	6
Xiong [11]	2010	China	EC	109 (109)	RT-PCR	②③④	7
Yusushi [12]	2002	Japan	GC	84	RT-PCR	③⑤	6
Chen [13]	2008	China	GC	79 (42)	IHC	①②③⑤	8
Yang [14]	2012	China	GC	50 (50)	RT-PCR	①②	7
Liu [15]	2008	China	CC	66	IHC	①②③	5
Zhu [16]	2011	China	CRC	60 (10)	IHC	②③④	6
Li [6]	2008	China	CRC	100 (100)	IHC	②③	8
Yang [17]	2008	China	CRC	101 (21)	IHC	②③④	8
Cai [18]	2010	China	CG	38 (42)	IHC	①②③④	8
Chen [19]	2009	China	HCC	40 (20)	RT-PCR	①③⑤	6
Shen [20]	2003	China	HCC	48 (48)	RT-PCR	⑤	6
Chen [21]	2007	China	HCC	69 (69)	RT-PCR	①②⑤	6
Yu [22]	2005	China	GC	62 (62)	RT-PCR	②③④	8
Zhang [23]	2009	China	CRC	70 (10)	IHC	②	8
Cui [24]	2012	China	HCC	40 (40)	IHC	②	6
Liu [25]	2011	China	EC	84 (84)	IHC	①②③④	5
Zhang [26]	2010	China	GC	60 (30)	IHC	②③④	5
Yue [27]	2010	China	EC	98 (20)	IHC	①②③④	6
Li [28]	2004	China	GC	98 (56)	IHC	①②③④	7
Zhao [29]	2009	China	GC	75 (15)	IHC	①③④	7
Guo [30]	2009	China	GC	86 (86)	RT-PCR	①②③④	7
Zhou et al. [31]	2012	China	PC	50 (50)	RT-PCR	①③	6
Shen et al. [32]	2005	China	HCC	48 (48)	RT-PCT	①⑤	7
Liu et al. [33]	2013	China	CRC	62 (62)	IHC	①②③④	6

HCC, hepatocellular carcinoma; CRC, colorectal cancer; EC, esophageal cancer; GC, gastric carcinoma; PC, pancreatic carcinoma; CG, carcinoma of gallbladder; IHC, immunohistochemistry; SC, serum concentration; ①TNM stage; ②differentiation; ③lymph node metastasis; ④infiltration degree; ⑤metastasis.

Table 2. DcR3 clinicopathological features for gastroenterology carcinoma

				Heterogeneity			
Clinicopathological features	No. of studies	No. of patients	Pooled OR (95% CI)	PHet	I2 (%)	*P* value	Model used
TNM stage	16	1862	1.63 [1.35, 1.98]	0.969	0	0	FEM
differentiation	21	2568	1.31 [1.10, 1.56]	0.771	0	0.003	FEM
Lymph node metastasis	18	2161	2.02 [1.66, 2.47]	0.656	0	0	FEM
Infiltration degree	13	1710	1.72 [1.38, 2.12]	0.993	0	0	FEM
metastasis	9	1070	1.66 [1.27, 2.16]	0.568	0	0	FEM

REM, random-effects model; FEM, fixed-effects model; OR, odds ratio; CI, confidence interval.

study [7]. The scale assigned 0-9 stars to each study based on three categories (selection, comparability and outcome).

Data analysis and statistical methods

Meta-analyses were carried out by using the Stata software version 12.0. There was no statistically significant heterogeneity in this analysis (I^2 < 50%, P-Het > 0.1), so fixed effect model was applied. Statistical heterogeneity between studies was evaluated with the chi-square test and the I^2 statistic. Potential causes of heterogeneity were explored by carrying out sensitivity and subgroup analyses. The odds ratio (OR) was calculated for dichotomous data with 95%

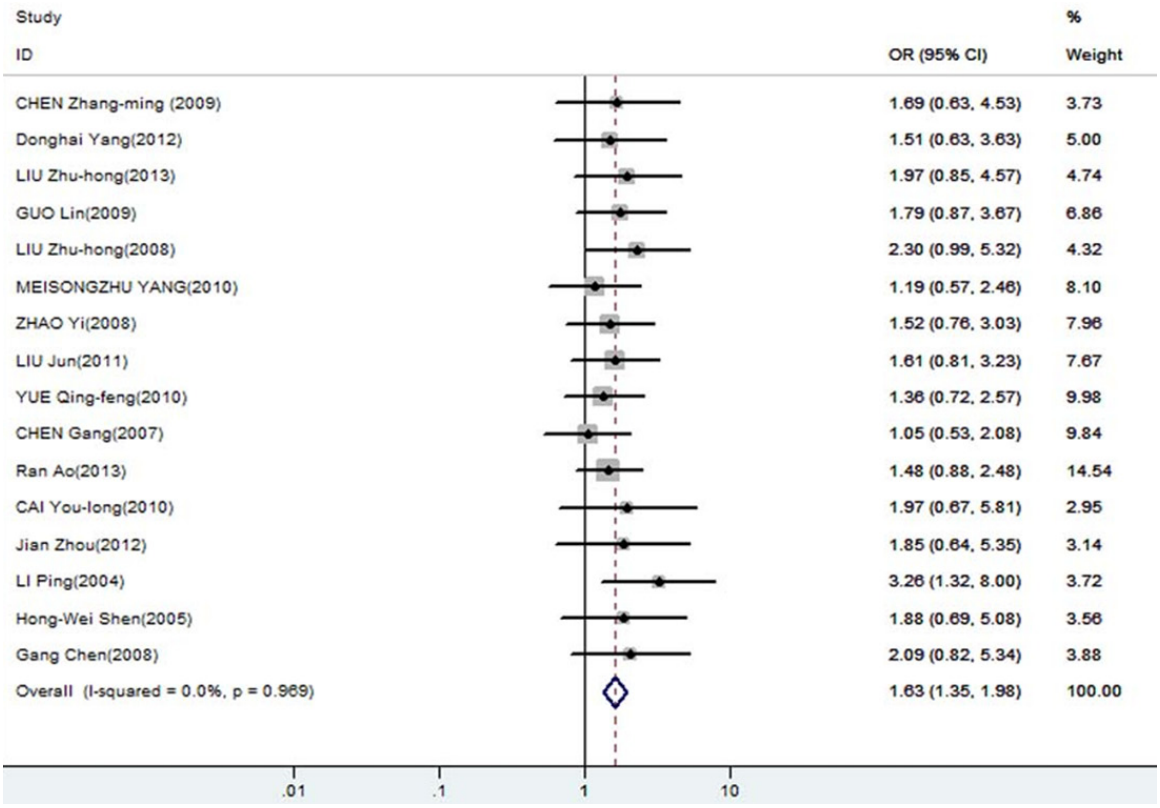

Figure 2. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with TNM stages.

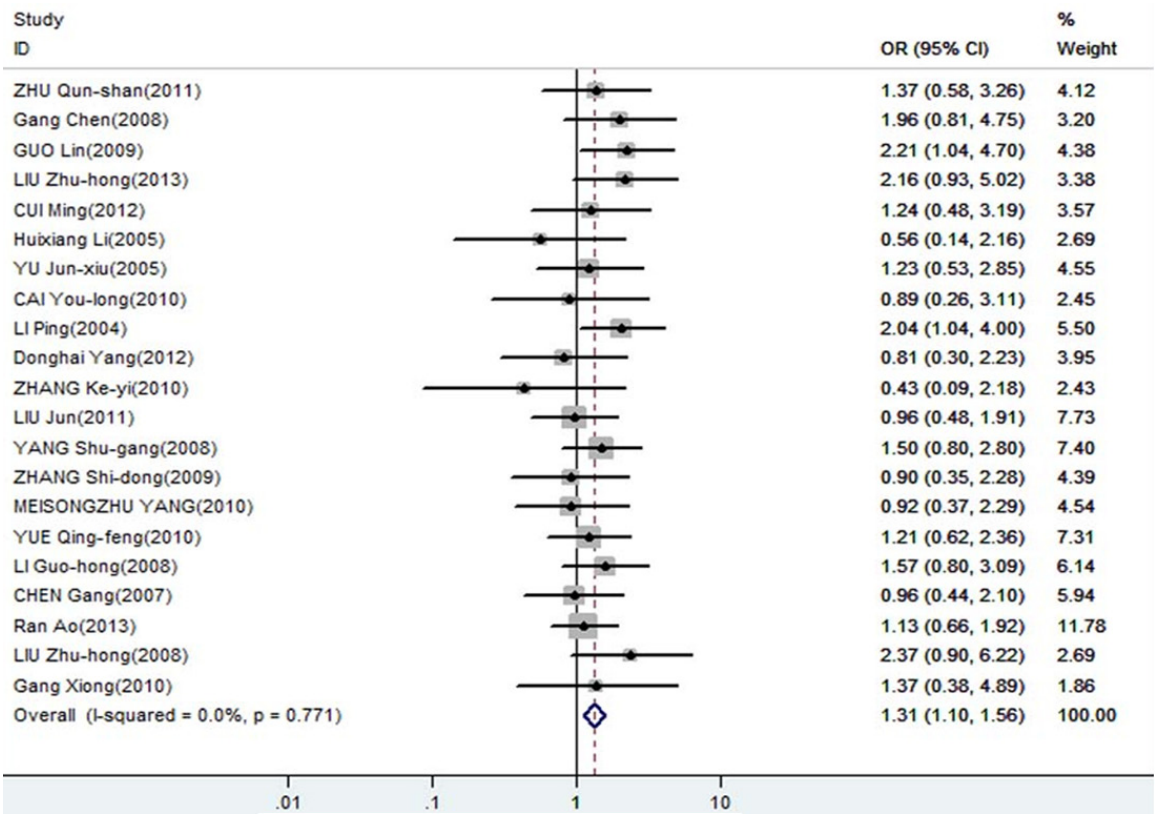

Figure 3. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with differentiation.

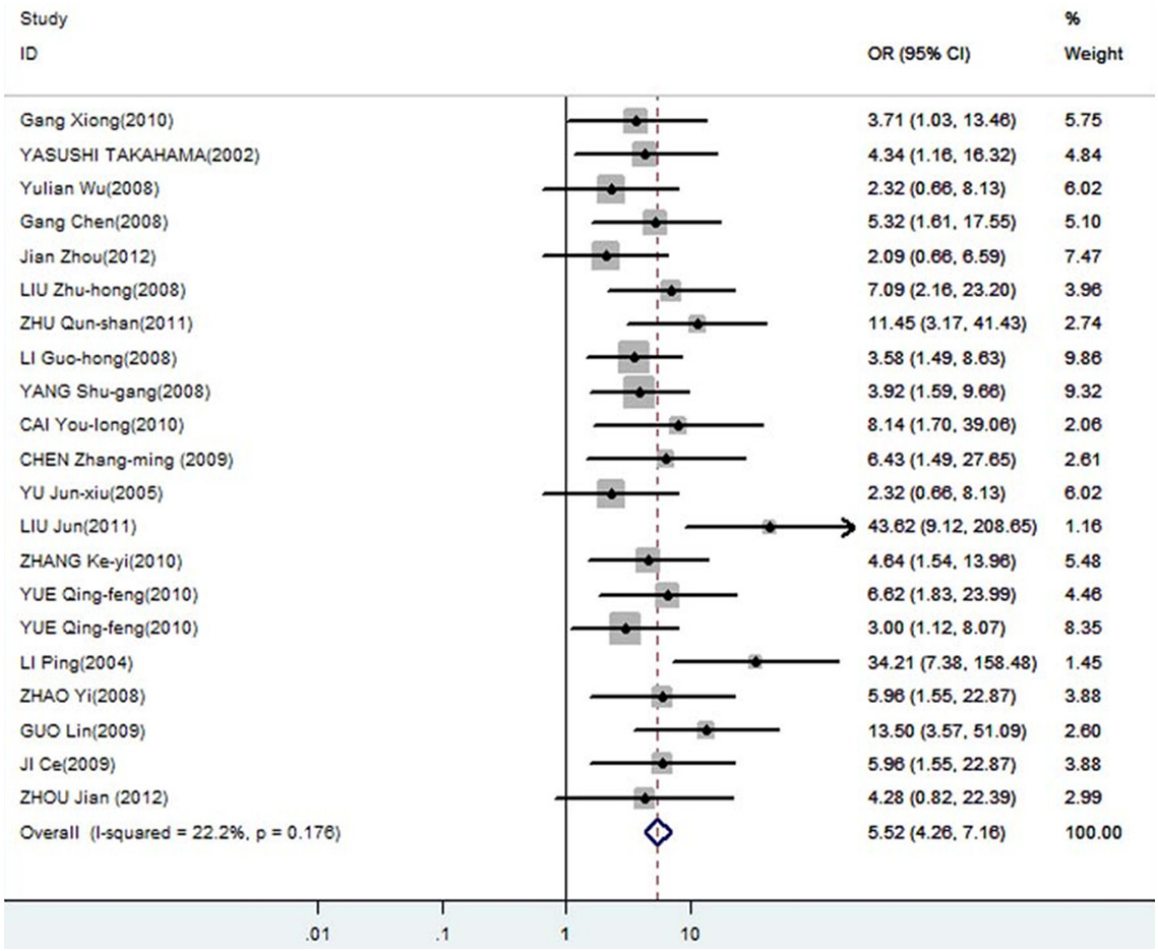

Figure 4. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with lymph node metastasis.

confidence intervals (CIs) for all analyses. *P* values that were < 0.05 were considered statistically significant.

Result

Description of studies

As shown in **Figure 1**, 1346 published records were identified from a search of the above databases using the search strategy as described above. After exclusion of the studies that were out of the scope of our systematic review, a total of 28 eligible studies were included in the final meta-analysis. These 28 studies assessed the relationships between DcR3 expression and gastrointestinal cancer clinicopathologic features. The clinical features of these 28 included studies were summarized in **Table 1**. These studies were published from 2002 to 2013, and total 3294 gastrointestinal cancer patients were enrolled. Sample sizes ranged from 60 to 218 patients (mean 118). 13 of these studies enrolled less than 100 patients and 15 studies included more than 100 patients. 27 of these studies evaluated patients from China, 1 from Japan. 25 of these studies got 6 scores or more in methodological assessment, which meant they had high qualities.

Correlation of DcR3 expression with clinicopathological parameters

The meta-analysis was assessed the correlation between DcR3 expression and clinicopath-

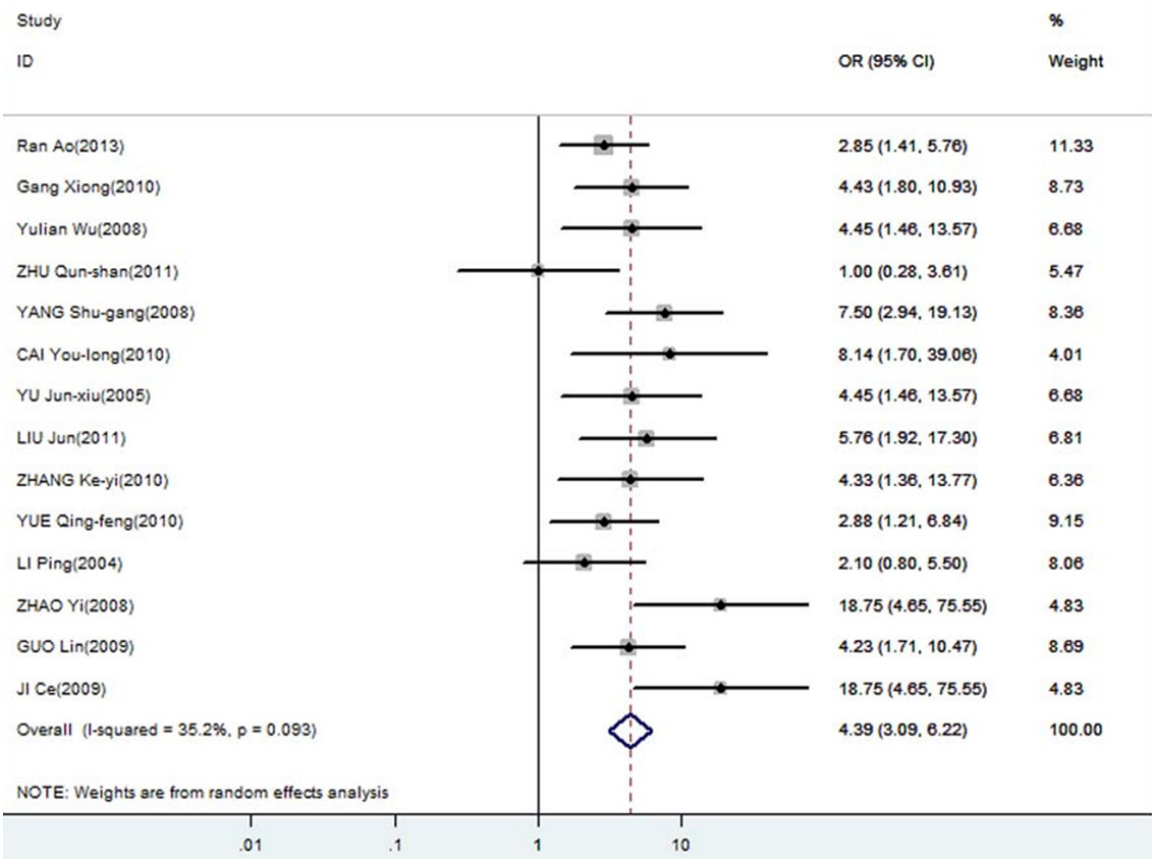

Figure 5. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with infiltration degree.

ological of gastroenterology carcinoma. As shown in **Table 2**, overexpression of DcR3 was significantly associated with TNM stages (OR, 1.63; 95% CI: 1.35, 1.98), differentiation (OR, 1.31; 95% CI: 1.10, 1.56), lymph node metastasis (OR, 2.02; 95% CI: 1.66, 2.47), infiltration degree (OR, 1.72; 95% CI: 1.38, 2.12), metastasis (OR, 1.66; 95% CI: 1.27, 2.16). The funnel plot for the outcome of correlation between DcR3 expression and TNM stage, differentiation, lymph node metastasis, infiltration degree, metastasis on gastroenterology carcinoma (**Figures 2**-**6**). Egger's test indicated that there was no evidence of significant publication bias after assessing the funnel plot (**Figure 7**) for the studies included in our meta-analysis. And the results of the sensitivity analysis are stable.

Discussion

Decoy receptor 3 (DcR3) is a member of the tumor necrosis factor receptor (TNFR) superfamily. It has been shown to be the decoy receptor for Fas ligand (FasL), LIGHT and TL1A [34-36]. As DcR3 lacks a transmembrane structure in its amino acid sequence, it belongs to a kind of secretory protein. DcR3 is not expressed or only slightly expressed in normal tissues and serum, but highly expressed in malignant tumor tissues. Overexpression of DcR3 in tumor cells protects them from apoptosis. DcR3 protects tumor cells from immune surveillance as it contributes to the suppression of the host antitumor immunity. The overexpression of DcR3 can be found in multiple human malignant tumors such as gastric carcinoma [12], colon carcinoma [4], esophageal carcinoma [10], lung carcinoma [34], hepatic carcinoma [37, 38], spongioblastoma [39], oophoroma [40, 41], etc.

From a clinical perspective, therefore, it is of great significance to identify the most useful biomarkers, which can help clinicians to adopt preventive strategies for patients at high risk

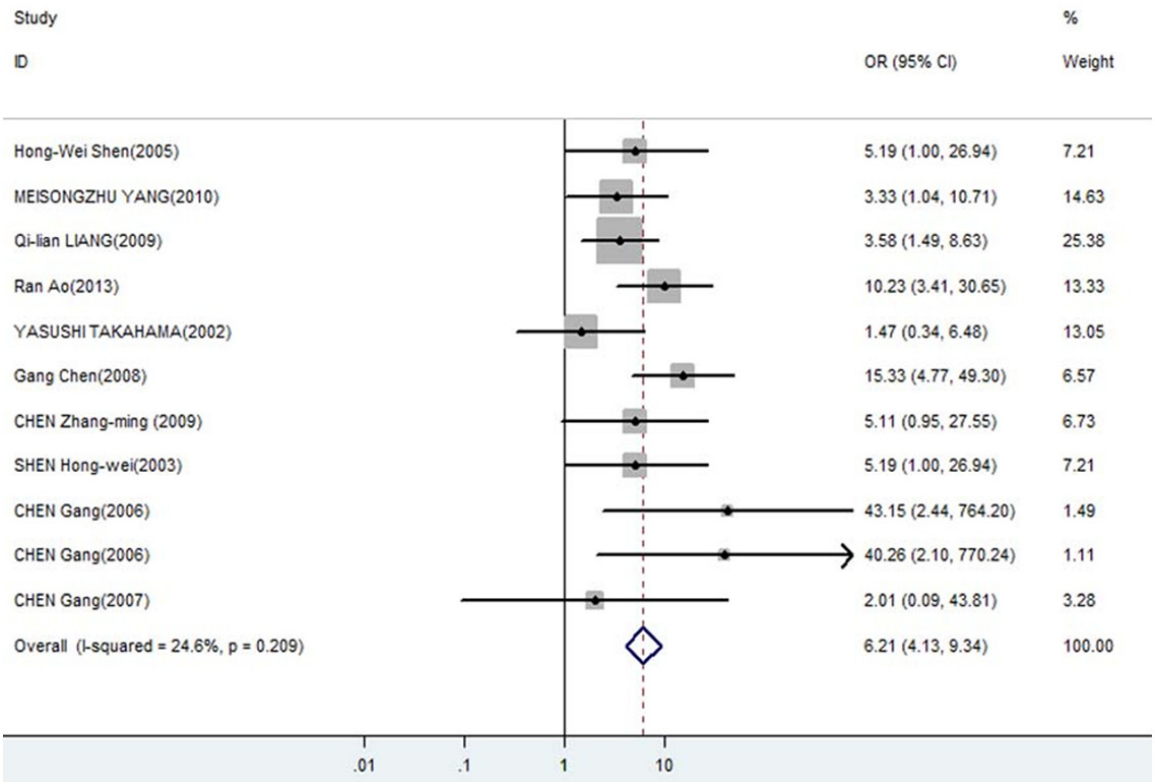

Figure 6. Forest plot of odds ratios (ORs) with corresponding 95% CIs for the association of DcR3 expression with metastasis.

and further improve outcome of patient with gastrointestinal cancer. Although the association of DcR3 with gastrointestinal cancer and clinicopathologic features has been explored for several years, the available data have not yet been fully analyzed Considering that meta-analysis is a valuable tool in biomarker validation [42], here we conducted a meta-analysis to investigate the association between DcR2 expression of gastrointestinal cancer patients and clinicopathologic features.

In this meta-analysis, we first assessed the association between DcR3 expression of gastrointestinal cancer patients and clinicopathologic features. We analyzed the data of 3294 gastrointestinal cancer patients from 28 individual studies, and showed that overexpression of DcR3 was significantly associated with TNM stage, differentiation, lymph node metastasis, infiltration degree, metastasis. Thus, DcR3 indicate distinct clinicopathologic features. Additionally, the results of sensitivity analysis showed that the association was not changed after removing any study.

In summary, we showed that both overexpressed DcR3 were significantly associated with TNM stage, differentiation, lymph node metastasis, infiltration degree, metastasis on gastroenterology carcinoma patients. But our study had some limitations. Firstly, given all the included studies investigated gastrointestinal cancer patients from China and Japan, the results just represent the correlation between DcR3 expression and gastrointestinal cancer patients from Asia. Secondly, only 28 studies (including 3294 gastrointestinal cancer patients) had available data to calculate HRs, in which just 9 studies (including 1070 gastrointestinal cancer patients) investigated the correlation between DcR3 expression and metastasis. The sample size was not big enough so that the association of DcR3 expression and metastasis was not significant. Third, the study included in our meta-analysis was restricted only to articles published in English or Chinese, which probably provided additional bias. So large, well-designed prospective studies are required to investigate the precise clinicopathologic differences of DcR3 expression.

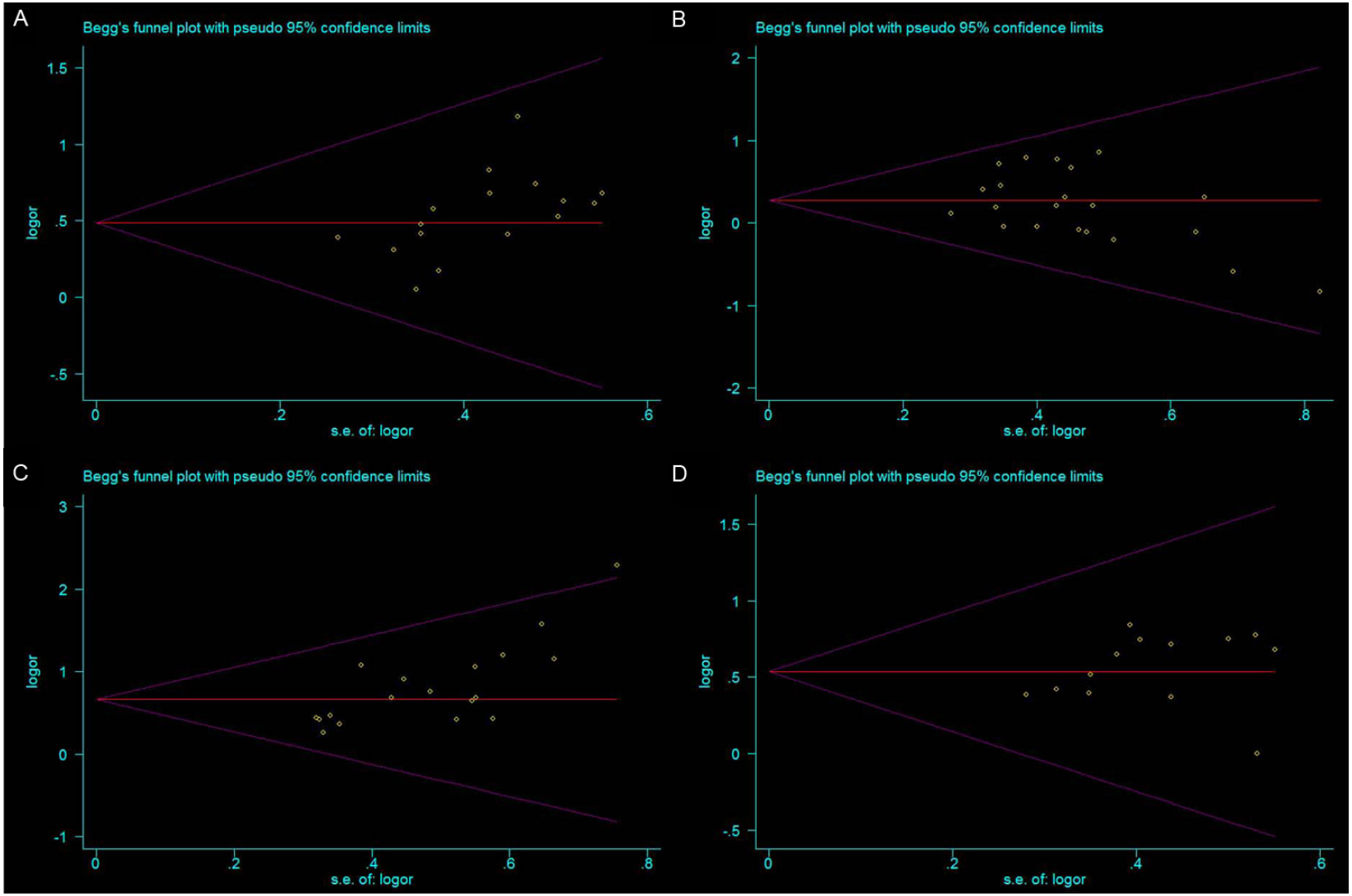

Figure 7. A. Egger's publication bias plot showed no publication bias for studies regarding overexpressed DcR3 and TNM stage in the meta-analysis; B. Egger's publication bias plot showed no publication bias for studies regarding overexpressed DcR3 and differentiation in the meta-analysis; C. Egger's publication bias plot showed no publication bias for studies regarding overexpressed DcR3 and lymph node metastasis in the meta-analysis; D. Egger's publication bias plot showed no publication bias for studies regarding overexpressed DcR3 and infiltration degree in the meta-analysis.

Disclosure of conflict of interest

None.

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