



Overexpression of COX-2 and clinicopathological features of gastric cancer: a meta-analysis

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Background: To evaluate the correlation between COX-2 overexpression and clinicopathological features of gastric cancer, thus providing theoretical basis for anti-COX-2 targeted therapy.

Methods: The literature about COX-2 expression and gastric cancer was searched in PubMed, Wangfang, VIP, CNKI from the inception to September 2019, with “gastric cancer”, “COX-2”, “cyclooxygenase” as keywords. Stata 15.0 was used to analyze. Age, gender, differentiation, infiltration depth, lymph node metastasis, tumor size, TNM staging were analyzed by OR (95% CI).

Results: Nine studies involving 1,289 patients with gastric cancer were identified, among which 878 cases existed COX-2 overexpression. COX-2 overexpression was related to the infiltration depth (OR=1.76; 95% CI: 1.01–1.306; P<0.01) and lymph node metastasis (OR=3.08; 95% CI: 1.64–5.79; P<0.01). While, it was not related to age, gender, differentiation and tumor size.

Conclusions: COX-2 overexpression is valuable in predicting infiltration depth and lymph node metastasis, and could be a predictor of poor prognosis in gastric cancer. COX-2-targeted therapy can be considered as one of the comprehensive treatments for gastric cancer.

Keywords: COX-2; gastric cancer; lymph node metastasis; meta-analysis

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Introduction

According to the latest global cancer statistics, gastric cancer is the fifth most common malignant tumor in the world, ranking behind breast cancer, prostate cancer, lung cancer and colorectal cancer (1). Also, the World Health Organization (WHO) indicates that the annual incidence of gastric cancer is 13.86/100,000 and there are about 1.39 million cases and 1.09 million deaths every year in the world (1). More than 70% of patients are from developing countries (456 thousand male, 221 thousand female), and more than 50% are from East Asia, especially China (2).

The number of gastric cancer cases and deaths in China accounted for 42.6% and 45.0% of the global gastric cancer morbidity and deaths, respectively, ranking fifth in morbidity and sixth in mortality among 183 countries in the world.

China has a high incidence of gastric cancer, accounting for about 50% of the world's morbidity and deaths (1,3,4). The occurrence of gastric cancer is a multi-step and multi-stage process based on the activation of multiple proto-oncogene and inactivation of anti-oncogene, the former acts on the cell growth, differentiation and metabolism through its expression products, leading to canceration (5,6).

Also, malignant tumors are characterized by metastasis and invasion, both pathways are complex and acts upon the gene regulatory network between oncogene and tumor suppressor gene. Therefore, the invasion and metastasis of gastric cancer are the main factors affecting the life quality and prognosis of the patients. Many researches are concern about the relationship between cyclooxygenase (COX)-2 and invasion and metastasis. COX-2 is a rate-limiting enzyme in the synthesis of inducible prostaglandin (PG). It metabolizes arachidonic acid into a variety of PG products and participates in the maintenance of various physiological and pathological functions of the body (7). COX-2, an inducible enzyme, begins to synthesize and express stimulated by cytokines (EGF, TGF, INR, TNF), growth factors, nitric oxide synthetase, oncogenes, mitogen, bacterial toxins. PGs can enter the cell directly to regulate the transcription of target genes, and then participate in a variety of pathophysiological processes, including inflammatory reaction, tumorigenesis and its development (8). In recent years, it has been found that there are amplification of COX-2 gene and high expression of its protein in many kind of tumor cells and tissues, such as gastric cancer, breast cancer, thyroid cancer and colon cancer (9). Moreover, multiple studies have shown that protein expression of COX-2 gene is closely related to the occurrence of gastric cancer, but the relationship between it and the clinicopathological behavior of gastric cancer is unclear. Therefore, the aim of this study is to investigate the relationship between COX-2 and clinicopathological characteristics of gastric cancer, and the mechanism of invasion and metastasis of gastric cancer is explored, thus providing theoretical basis for further elucidating the pathogenesis of gastric cancer. To this end, Meta-analysis was used to analyze previous literature related to COX-2 and gastric cancer.

Methods

Literature retrieval

The literature about the expression of COX-2 and gastric cancer was searched in Pubmed, Wangfang, VIP, CNKI from the inception to September 2019, with “gastric cancer”, “COX-2”, “cyclooxygenase” as keywords. And then the literature was manually screened by reading the abstract

and the full text.

Inclusion and exclusion criteria

Inclusion criteria: (I) the case-control studies published at home and abroad with original data and immunohistochemistry (IHC) detection; (II) studies about the clinicopathological features or prognosis of gastric cancer and COX-2 overexpression, excluding the studies of adenoma of stomach or esophagogastric junction cancer; (III) In the case group, the patients, with definite pathological diagnostic criteria and their complete clinicopathological data, were not treated with radiotherapy and chemotherapy before operation; in the control group, the patients with adjacent tissues or benign diseases tissues; (IV) Chinese literature was published in the Peking University core journals or in the key magazine of China technology; (V) appropriate statistical method, reliable data, clear expression of results, and at least one of the pathological features, such as differentiation, lymph node metastasis and TNM stage, could calculate OR (95% CI).

Exclusion criteria: (I) review, abstract, letter; (II) the same group of people reported repeatedly without good quality, insufficient reporting information and OR (95% CI).

Literature quality evaluation

After reading the full text and according to the Newcastle-Ottawa scale (10), the literature quality was evaluated. Literature awarded less than 6 stars as low quality literature, and 6 stars or more as high quality one. The latter one was included in this study. According to the uniform quality standard, two assessors evaluated the literatures independently to extract data, and then the collecting data was cross-checked. Discrepancies were resolved by discussion or assistance of the third researcher.

Data extraction

The unified data extraction table was adopted, in which the relevant information included as following: (I) general data: title, first author, year of publication; (II) characteristics: gender, age, COX-2 expression, differentiation, infiltration depth, lymph node metastasis, tumor size and TNM stage;

(III) methodological information: detection method of COX-2.

Statistical method

Meta-analysis was performed by Stata 15.0. OR (95% CI) was calculated as effect size. Q test was used to test the heterogeneity of the research results. $I^2 \geq 50\%$ or $P \leq 0.05$ suggested heterogeneity, so the fixed effect model (FEM) was used. $I^2 < 50\%$ and $P > 0.05$ suggested no heterogeneity, so the random effect model (REM) was used. Z test was

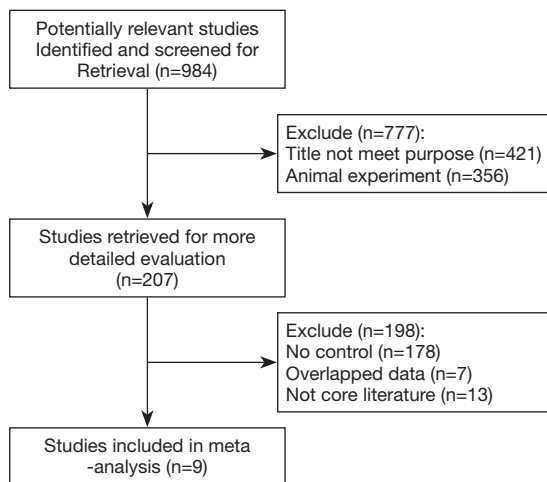


Figure 1 A flow diagram of the study selection process.

used to test the significance of the pooled OR. This Meta-analysis used the symmetry of funnel plot to evaluate publication bias. Standard error of log (OR) and OR were used to draw funnel plot. The asymmetric plot indicated publication bias. Egger's Test was used to test the publication bias.

Results

Literature retrieval result

According to the inclusion and exclusion criteria and quality evaluation, a total of 9 literature was included after researching and cross-checking. The specific screening process was shown in *Figure 1*. The basic characteristics of the literature were shown in *Table 1*. There were 1,289 gastric cancer patients, and the positive expression rate was 68.1% (n=878).

Relationship between COX-2 overexpression and clinicopathological features of gastric cancer

COX-2 overexpression and infiltration depth

A total of 6 literature was included, including 431 extraserous patients and 284 intraserous patients. The two groups had statistical heterogeneity ($P=0.012$), so the REM was used (*Table 2*). The result showed that there was significant difference between the two groups. Compared

Table 1 basic characteristics of the literature on the relationship between Cox-2 and gastric cancer

First author	Year	Cox-2 expression, n (%)	Cox-2 Detection method	Clinical characteristics	NOS score
Okano	2004	54.8%	IHC	Infiltration depth, lymph node metastasis	8
Ji-Ren Yu	2005	57.9%	IHC	Infiltration depth, lymph node metastasis	7
Joo	2006	60.5%	IHC	Gender, Infiltration depth, lymph node metastasis, TNM stage, tumor size	8
Park	2009	81.0%	IHC	Gender, age, differentiation degree, lymph node metastasis, TNM stage	8
Jun-Shan Zhai	2016	62.7%	IHC	Gender, infiltration depth, lymph node metastasis, TNM stage	7
Xiao-Lan Lv	2018	60.0%	IHC	Gender, age, differentiation degree, infiltration depth, lymph node metastasis, TNM stage, tumor size	7
Ye Liu	2018	72.9%	IHC	Gender, age, differentiation degree, tumor size	6
Jian-Jun Zhang	2018	63.8%	IHC	Gender, age, lymph node metastasis, tumor size	7
Ying-Hui Zhang	2018	66.1%	IHC	Gender, infiltration depth, lymph node metastasis, TNM stage, tumor size	7

Table 2 Meta analysis of Cox-2 overexpression and pathological characteristics of gastric cancer

Pathological features	n	case	OR	95% CI	P	I ² (%)	P for heterogeneity	Model	P for publication bias
Gender	7	Man: 620 Woman: 318	1.08	0.79–1.46	0.642	0.00	0.892	FEM	0.305
Age	4	≥60: 235 <60: 439	1.27	0.85–1.89	0.246	0.00	0.410	FEM	0.492
Differentiation degree	3	Medium and high: 210 Low: 309	0.77	0.14–4.23	0.761	88.70	0.000	REM	0.559
Infiltration depth	6	Outside serous: 431 Inside serous: 284	1.76	1.01–3.06	0.045	65.70	0.012	REM	0.308
Lymph node metastasis	8	Yes: 969 No: 282	3.08	1.64–5.79	0.000	70.60	0.001	REM	0.097
Tumor size	5	>5 cm: 178 ≤5 cm: 220	1.04	0.68–1.57	0.860	0.00	0.502	FEM	0.106
TNM stage	5	I-II: 511 III-IV: 310	2.39	0.91–6.26	0.075	83.60	0.000	REM	0.025

with the control group (invasion intraserous group), OR=1.76 (95% CI: 1.01–3.06, P=0.045) and the forest plot (*Figure 2A*) showed that with the increase of COX-2 expression, the infiltration depth was deeper.

COX-2 overexpression and lymph node metastasis

A total of 9 literature (11-19) was included, including 969 patients with lymph node metastasis and 282 without lymph node metastasis. The two groups had statistical heterogeneity (P=0.001), so the REM was used (*Table 2*). Compared with the control group (without lymph node metastasis), OR=3.08 (95% CI: 1.64–5.79, P<0.001) and the forest plot (*Figure 2B*) showed that with the increase of COX-2 expression, the risk of lymph node metastasis increased.

COX-2 overexpression and tumor size

A total of 5 literature was included, including 178 patients with tumor size >5 cm and 220 with tumor size ≤5 cm. The two groups had no statistical heterogeneity (P=0.502), so the FEM was used (*Table 2*). Compared with the control group (tumor size ≤5 cm), OR=1.04 (95% CI: 0.68–1.57, P>0.05) and the forest plot (*Figure 2C*) showed that COX-2 overexpression was not related to tumor size of gastric

cancer.

COX-2 overexpression and TNM stage

A total of 5 literature was included, including 511 patients in T1+T2 and 310 in T3+T4. The two groups had statistical heterogeneity (P=0.000), so the REM was used (*Table 2*). Compared with the control group (patients in T1+T2), OR=2.39 (95% CI: 0.91–6.26, P=0.075) and the forest plot (*Figure 2D*) showed that COX-2 overexpression was not related to TNM stage of gastric cancer.

COX-2 overexpression and gender, age and differentiation

Based on whether having heterogeneity, the corresponding statistical model was selected. The differentiation had heterogeneity (P<0.05), so the REM was used (*Table 2*). *Table 2* showed that there was no correlation between COX-2 overexpression and gender, age and differentiation (P>0.05).

Publication bias

The included literature was analyzed by funnel plot, and then the symmetry of the funnel plot was analyzed by

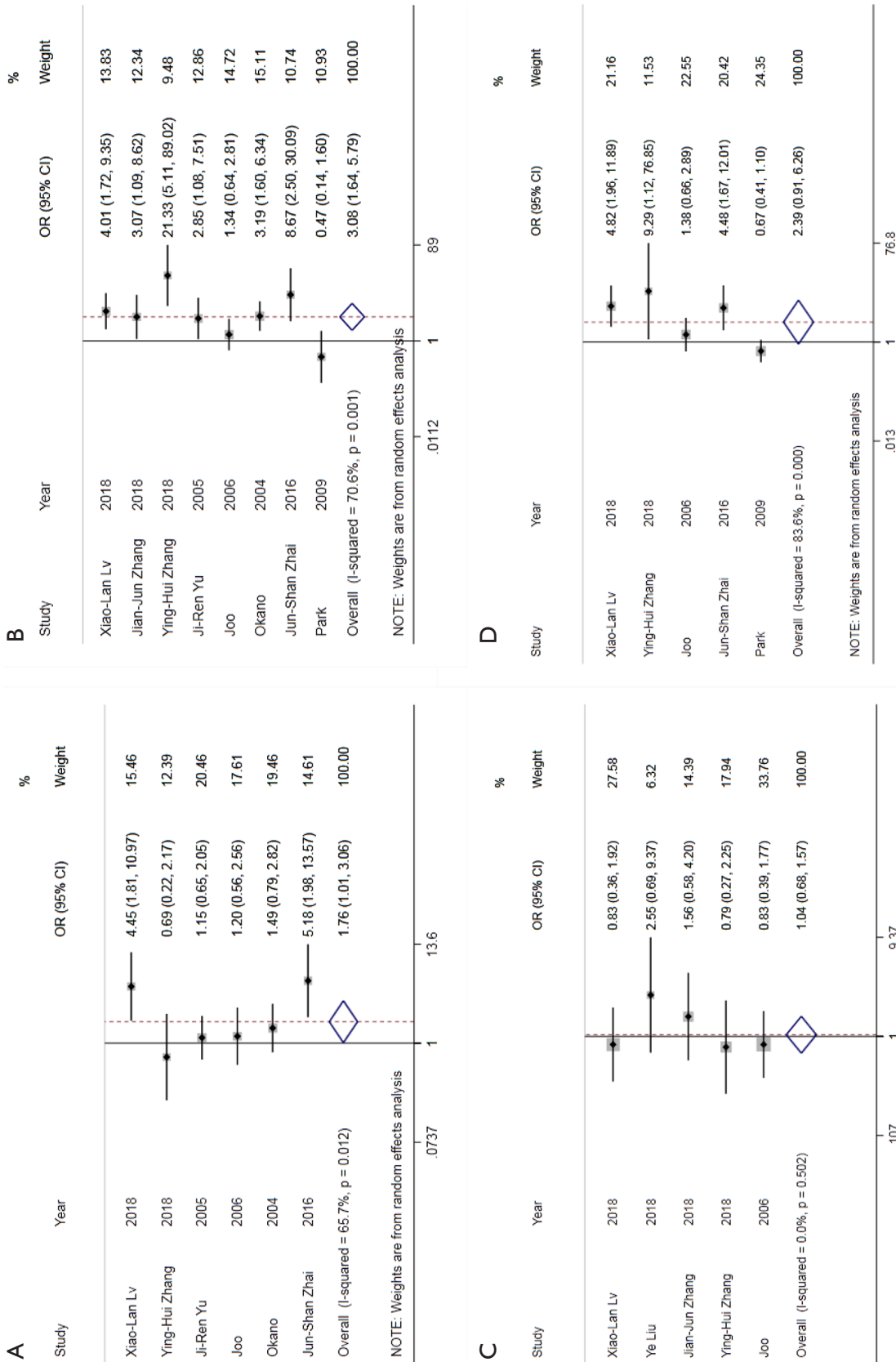


Figure 2 correlation between Cox-2 overexpression and pathological characteristics of gastric carcinoma meta analysis of forest plot. (A) Cox-2 and depth of invasion; (B) Cox-2 and lymph node metastasis; (C) Cox-2 and tumor size; (D) Cox-2 and TNM staging.

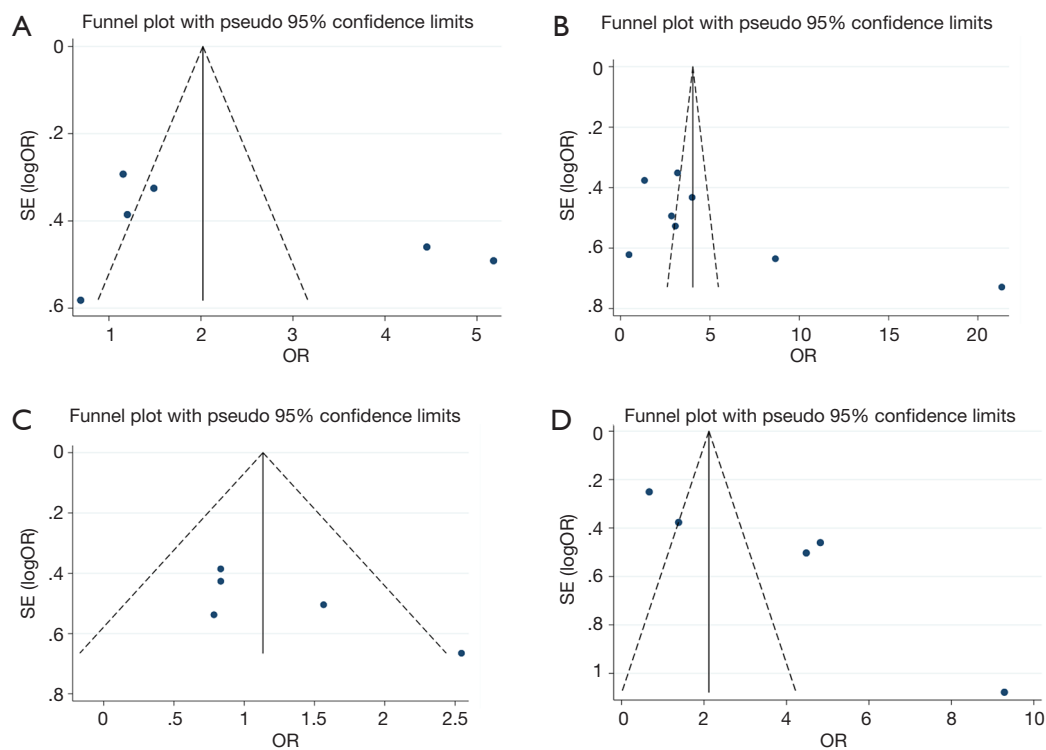


Figure 3 Meta analysis of funnel plot. (A) Cox-2 and depth of invasion; (B) Cox-2 and lymph node metastasis; (C) Cox-2 and tumor size; (D) Cox-2 and TNM staging.

Egger's Test. The specific results were shown in *Table 2*, and part of the funnel plot was shown in *Figure 3*. The results showed that there was no publication bias in gender, age, differentiation, infiltration depth, lymph node metastasis and tumor size, but there was partial publication bias in TNM stage.

Sensitivity analysis

The result of sensitivity analysis was shown in *Figure 4*. After excluding a single study in order, the Meta-analysis was repeated. The result showed that, after excluding 5 of the literature, the difference of infiltration depth became not statistical significant while only one literature had no effect on the result (18). Lymph node metastasis, tumor size and TNM stage had good stability because the conclusion remained unchanged after excluding one of the literature. On the whole, the Meta-analysis result was stable.

Discussion

Gastric cancer is one of the most common malignant

tumors of the digestive system. According to the findings released by the International Cancer Research Center (IARC) in 2012, the number of new case has dropped from 989,600 in 2008 to 951,600 in 2012, and the mortality from 738,000 to 723,100 over the same period. Although the morbidity and mortality have shown a downward trend in most countries and regions of the world (20), over the same period, an increase of 1,422,600 new cases of malignant tumors and 7,571,500 new deaths have occurred (20). COX-2 gene is located long arm of human chromosome 1, about 8 kb and with 9 introns and 10 exons. The mRNA, about 4 kb, encodes an open reading frame of 604 amino acids, consisting of signal peptide of 17 amino acid residues (21). COX-2 is one of the three isomerases of cyclooxygenase, which is the key enzyme to catalyze the conversation of arachidonic acid to PG. COX-2 expression and stability are regulated by many elements of intron and 5'-untranslated region (5'-UTR) and 3'- untranslated region (3'-UTR) in transcription template. The polymorphism of COX-2 gene in the promoter region plays a key role in the regulation of transcription with tissue specificity (22). The gene polymorphism may eliminate or increase binding sites, or

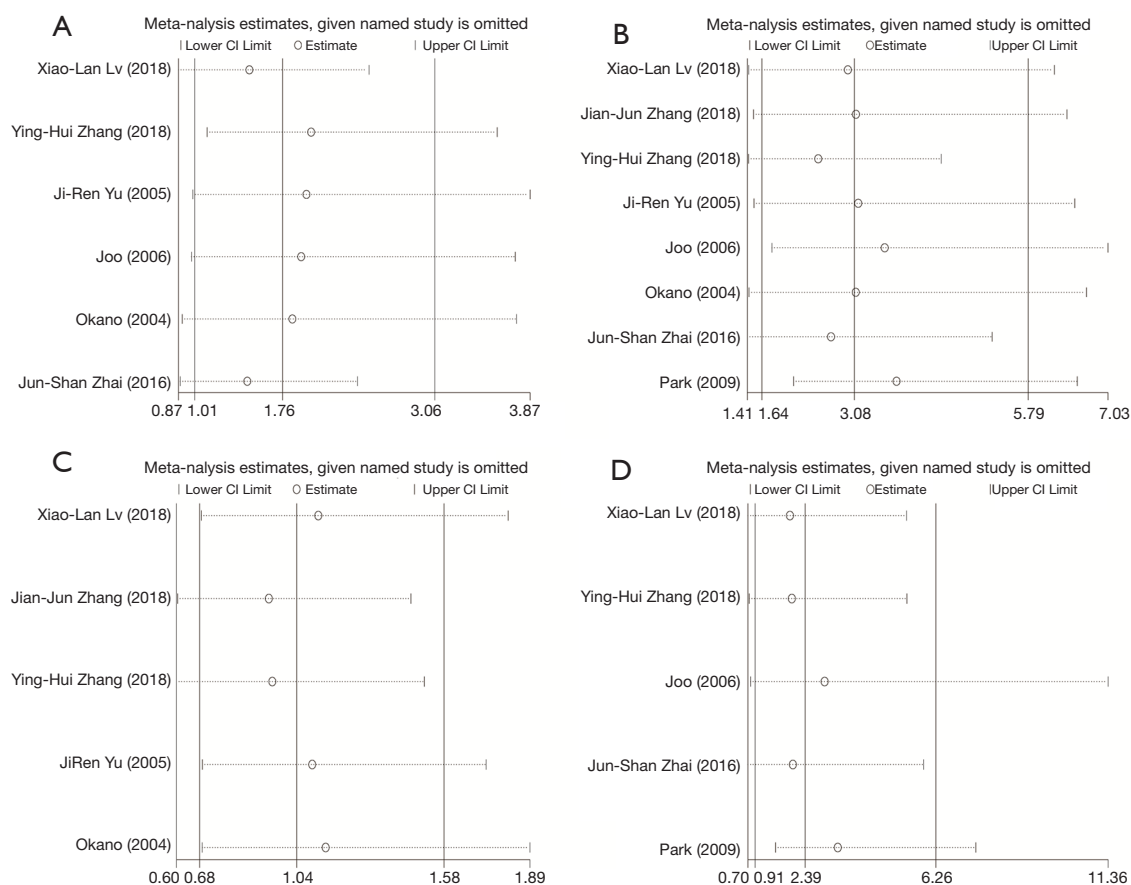


Figure 4 Sensitivity analysis results. (A) Cox-2 and depth of invasion; (B) Cox-2 and lymph node metastasis; (C) Cox-2 and Tumor size; (D) Cox-2 and TNM staging.

change the affinity between binding sites and regulatory factors, thus changing COX-2 expression and affecting the biosynthesis of PGs (23). The occurrence and development of gastric cancer is complex, which provides a opportunity for the effective intervention and prevention. COX-2 has the potential to be an effective target for intervention and prevention of gastric cancer (24). Some clinical studies have shown that nonsteroidal antiinflammatory drugs(NSAIDs) can significantly reduce the incidence of gastric cancer (25), and COX is the main target of NSAIDs. COX has three structural types, among which the role of COX-1 and COX-2 is relatively clear. COX-1 continuously expresses in many tissues while COX-2 is mainly responsible for the inflammatory reaction and tumor development, usually without expression or with expression at a very low level (26,27). Some studies have found that COX-2 is associated with inhibiting apoptosis, promoting tumor neovascularization and increasing metastatic potential

(28,29). Also, some researches have shown that COX-2 expression is significantly increased in gastric cancer and precancerous lesion while it is less in non-gastric cancer lesions, and almost no expression in normal gastric mucosa (30). Moreover, the relationship between COX-2 overexpression and clinicopathological features of gastric cancer is not clear. Zhang *et al.* (18) have believed that COX-2 is not related to infiltration depth of gastric cancer. However, Zhai *et al.* (11) have suggested that Cox-2 overexpression increases the risk of invasion depth of gastric cancer. Therefore, in order to explore the relationship between COX-2 overexpression and clinicopathological features of gastric cancer, such as lymph node metastasis, infiltration depth, TNM stage, a number of previous studies on the COX-2 expression in gastric cancer detected by IHC were analyzed, thus providing clinical guidance for evidence-based medicine.

Nine literature (11-19) was included in this meta analysis,

including 1289 patients with gastric cancer. The overall positive rate of COX-2 was 68.1%. The results showed that COX-2 overexpression was correlated with infiltration depth and lymph node metastasis, which meant that the both had predictive value. Also, COX-2 overexpression was not correlated with TNM stage, differentiation, tumor size, age and gender. From statistical heterogeneity, age, gender and tumor size was homogeneity, so the FEM was selected for statistical analysis, while differentiation, infiltration depth, lymph node metastasis and TNM stage all had great heterogeneity, so the REM was selected. From publication bias, there was no publication bias in infiltration depth, lymph node metastasis, age, gender and differentiation, except TNM stage ($P < 0.05$). The sensitivity analysis showed that the study on infiltration depth had poor stability, so the conclusion of it should be careful. Moreover, the result between COX-2 overexpression and other clinicopathological features of gastric cancer was stable, so basically, the result of Meta-analysis was stable, indicating that the conclusion of this study was reliable. The meta analysis by Zhuo *et al.* (31) has showed that COX-2 was correlated with infiltration depth and lymph node metastasis, but not with differentiation. The Meta-analysis by Zeng *et al.* (32) on COX-2 expression and lymph node metastasis of gastric cancer has showed that COX-2 overexpression was associated with lymph node metastasis, which promotes lymph node metastasis of gastric cancer. These conclusions are consistent with that in this study. As this study was more cautious in the inclusion of literature, excluding the literature of non-core journals, and including several latest studies, the conclusion of this study is persuasive.

However, this study also has some limitations: (I) there are differences in the scoring criteria of IHC for COX-2 expression; (II) there is high heterogeneity in several factors related to COX-2 overexpression; (III) although all the researches were use IHC, the manufacturer, dilution concentration and judgment criteria of the antibody were not completely consistent, which may also affect the result of Meta-analysis.

In conclusion, this study indicates that COX-2 high expression in gastric cancer could increase infiltration depth and risk of lymph node metastasis. The result of Song *et al.* (33) show that COX-2 high expression is correlated with poor prognosis of gastric cancer. Therefore, COX-2-targeted therapy combined with radiotherapy and chemotherapy may achieve certain efficacy in the comprehensive treatment of gastric cancer. Certainly,

because of the limitations, more clinical data should be collected and the prognosis need to be observed. Further study on the effect of COX-2 overexpression on gastric cancer is required to provide a more sufficient theoretical basis for the application of anti-COX-2 therapy in gastric cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.52>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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