

## Expression of epithelial cellular adhesion molecule in gastric cancer: A meta-analysis

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### Abstract

**AIM:** To obtain an accurate evaluation of the association between high expression of epithelial cellular adhesion molecule (EpCAM) and gastric cancer (GC) risk.

**METHODS:** Studies that had examined the association between high expression of EpCAM and GC risk were identified by searching electronic databases PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature database. Risk ratios (RRs) together with their 95% CIs were used to assess the association between high expression of EpCAM and GC risk. We selected eligible studies based on inclusion criteria. RevMan 5.3 software was used to calculate the pooled values.

**RESULTS:** A total of 14 studies were included in this meta-analysis. EpCAM-positive cases were significantly associated with tumor size (RR: 1.68, 95%CI: 1.47-1.91,  $P < 0.00001$  fixed-effect), depth of invasion (RR: 1.37, 95%CI: 1.11-1.68,  $P = 0.003$  random-effect), TNM stage (RR: 2.02, 95%CI: 1.35-3.02,  $P = 0.0007$  random-effect), tumor location (RR: 0.80, 95%CI: 0.71-0.91,  $P = 0.0007$  fixed-effect), histologic differentiation (RR: 1.23, 95%CI: 1.13-1.33,  $P < 0.00001$  fixed-effect) and lymph node metastasis (RR: 1.89, 95%CI: 1.28-2.80,  $P = 0.001$  random-effect). However, we did not observe any significant association between the presence of EpCAM with age, gender, distant metastasis, Borrmann type or Lauren classification. Additionally, EpCAM expression was not associated with the overall survival rate. The pooled HR of the overall effect was 1.39 (95%CI: 0.30-6.48,  $P = 0.67$  random-effect).

**CONCLUSION:** Our meta-analysis indicates that EpCAM contributes to GC risk, which acts as a prognostic factor and a marker of poor outcome.

**Key words:** Epithelial cellular adhesion molecule; Gastric cancer; Prognosis; Progression; Meta-analysis

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**Core tip:** This meta-analysis aimed to obtain an accurate evaluation of the association between high expression of epithelial cellular adhesion molecule (EpCAM) and gastric cancer (GC) risk. EpCAM-positive cases were significantly associated with tumor size, depth of invasion, TNM stage, tumor location, histologic differentiation and lymph node metastasis. EpCAM contributed to GC risk, and acted as a prognostic factor and a marker of poor outcome.

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## INTRODUCTION

Although gastric cancer (GC) rates have decreased substantially in the past few decades, it remains the second most common cause of cancer-related death worldwide<sup>[1]</sup>. Patients with GC have a poor prognosis, especially those with advanced stage disease. The most common cause of this phenomenon is the advanced stage of most cases at the time of initial diagnosis. Additionally, tumor cell spread has occurred in some cases<sup>[1,2]</sup>. Currently, surgery is the primary treatment strategy for localized advanced GC, with an average 5-year survival rate of 20%-30%; however, for unresectable disease such as metastatic or recurrent GC, chemotherapy is regarded as a basic therapeutic approach<sup>[1]</sup>.

The efficacy of current chemotherapeutic agents is still unsatisfactory and these agents with poor specificity have significant side effects. Consequently, multimodality therapy options are needed to improve the prognosis of GC. This necessitates finding new adjuvant therapeutic targets and prognostic markers for GC patients.

The epithelial cellular adhesion molecule (EpCAM) is a 37-42 kDa, 314-amino-acid type I transmembrane glycoprotein with two epidermal growth factor-like repeats in the external domain and two  $\alpha$ -actin binding sites for actin cytoskeleton linkage in the intracellular domain<sup>[2]</sup>. The 9-exon gene TACSTD1, which has been mapped to chromosome 2p21, encodes it. EpCAM functions as a homotypic intracellular adhesion molecule. It is interconnected with E-cadherin during the process of epithelial cell adhesion<sup>[2,3]</sup>.

EpCAM is expressed in most normal epithelial tissues on the basolateral membrane and overexpression of EpCAM has been detected in a variety of epithelial cancers<sup>[4]</sup>. EpCAM was found to be overexpressed in colon cancer tissues, breast cancer squamous cells, ovarian carcinomas and most human adenocarcinomas.

Because its overexpression has effects on differentiation, cell proliferation, signaling and migration, EpCAM can be used as a marker to predict recurrence and metastasis of the tumor and influence survival of cancer patients<sup>[5]</sup>.

Furthermore, EpCAM has been considered as a target antigen for a number of specific immunotherapies because of its frequent and high-level expression<sup>[6,7]</sup>. Catumaxomab, an EpCAM monoclonal antibody, has been used for the intraperitoneal treatment of malignant effusion in patients with EpCAM-positive cells since 2009. Catumaxomab also had a significant overall survival (OS) benefit in GC patients<sup>[8]</sup>. However, the role of EpCAM in GC is still unclear. Although several studies showed high expression of EpCAM in GC<sup>[6-10]</sup>, which was related to cancer progression and survival prognosis, there is no comprehensive study on the correlation of EpCAM expression with survival prognosis or the effects of EpCAM expression on clinicopathologic characteristics in GC patients. Thus, this meta-analysis was conducted to determine the association between high expression of EpCAM and clinicopathologic features and progression as well as prognosis of GC.

## MATERIALS AND METHODS

### Literature search strategy

We conducted a comprehensive literature search in PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature databases. There was no restriction on time period, sample size, population or languages. The search terms included "Stomach Neoplasms" OR "Gastric Neoplasms" OR "Stomach Cancer" OR "GC" OR "Stomach Carcinoma" OR "Gastric Carcinoma" AND "EpCAM" OR "epithelial cellular adhesion molecule". The search was limited to studies in humans. All eligible studies were retrieved and their references were scanned for other relevant studies. Two reviewers (Yi-Bin Xiao and Hong-Qing Xi) independently screened titles and abstracts of all citations. When multiple articles were reported on the same or overlapping data, we selected the study that investigated the most individuals or the most recent study.

### Inclusion and exclusion criteria

Articles were considered if: (1) they provided information on GC verified by pathological examination; (2) they provided information on case control or cohort studies that evaluated the association between EpCAM expression and GC; (3) no preoperative chemotherapy and/or radiotherapy was administered to patients; (4) they had available data for estimating risk ratio (RR) (95%CI); and (5) the control population did not contain patients with malignant tumors.

Studies were excluded if they: (1) had no control population; (2) were duplicates of an earlier publication; (3) reported insufficient data; (4) had cell or animal experiments; and (5) were letters, reviews, case reports and conference abstracts without original data or articles

published in a book.

### Data extraction

Two investigators (Yi-Bin Xiao and Hong-Qing Xi) reviewed all articles. Then the first investigator extracted the following information according to the prespecified selection criteria: (1) Publication details, including first author's name, year of publication and publication journal; (2) Characteristics of the studied population, including country, ethnicity, number of cases and controls; and (3) Number and characteristics of different clinical and pathologic parameters of both the gastric patients and their control group, including age, gender, tumor size, depth of invasion, TNM stage, tumor location, distant metastasis, Borrmann type, Lauren classification, histologic differentiation and lymph node metastasis.

Discrepancies between the two investigators were resolved through consensus discussion.

### Quality assessment

The quality of the studies was assessed according to the Newcastle-Ottawa Scale (NOS) by two investigators (Yi-Bin Xiao and Hong-Qing Xi) independently. The scale includes three major classifications: Selection, comparability and outcome. A maximum score of 1 was graded for each item, except for comparability, where a score of 2 was allowed to be graded. Scores ranged from 0 (lowest) to 9 (highest) and studies that scored equal to or higher than 7 points were assigned as "high-quality" studies, whereas those with scores less than 7 were considered "low-quality" studies. Any disagreement was resolved through consensus discussion.

### Statistical analysis

The association between EpCAM and GC risk was evaluated using hazard ratio (HR, 95%CI) for time-to-event data (OS) and (RR, 95%CI) for dichotomous data (various adverse events). Cochran's  $\chi^2$ -based  $Q$  test and Higgins  $I^2$  statistics were used to check heterogeneity among studies.  $I^2$  lay between 0 and 10%, and a value of 0% meant no observed heterogeneity, with larger values indicating increasing heterogeneity.  $P < 0.05$  or  $I^2 > 50\%$  was considered statistically significant. A value of 0% indicated no observed heterogeneity, and larger values showed increasing heterogeneity, with 25% indicating low, 50% indicating moderate, and 75% indicating high heterogeneity (Higgins, Thompson, Deeks, and Altman, 2003).

We selected the fixed-effect model (the Mantel-Haenszel method) if there was no significant heterogeneity. Otherwise, we selected the random-effect model (the DerSimonian and Laird method) if heterogeneity existed and could not be explained or corrected. Begg's funnel plots were used to examine potential publication bias in this study. For the pooled analysis of the correlation between EpCAM expression and clinicopathological features, RRs and their 95%CI were used to assess the effect. All the statistical tests were performed using

RevMan5.3 (Cochrane collaboration, Oxford, United Kingdom) software. Kaplan-Meier curves were read using an Engauge Digitizer 4.1.  $P < 0.05$  was considered statistically significant. HRs or RRs  $> 1$  meant a worse prognosis for GC patients with EpCAM overexpression and were considered to be statistically significant if the 95%CI did not overlap 1. In addition, sensitivity analysis was conducted by sequential omission of individual studies to evaluate the stability of the results.

## RESULTS

### Literature search and characteristics

A flow diagram of the literature search is shown in Figure 1. The initial search yielded a total of 190 studies according to the search criteria. A total of 28 potential relevant studies were recruited into this meta-analysis. Of these studies, three were excluded because they contained overlapping data. Another 11 studies were excluded because they were unable to offer EpCAM-specific data for calculating HRs or RRs according to the described method. A total of 14 studies that met the inclusion and exclusion criteria were included. Three studies reported an association between EpCAM and the 5-year survival rate<sup>[7,11,12]</sup>, and 13 studies<sup>[1-11,13,14]</sup> were chosen to demonstrate the connection between EpCAM expression and clinical features. As a result, we did not find any additional articles using a manual search of references cited in the published studies. The details of the articles are summarized in Tables 1 and 2.

### Correlation of EpCAM with clinicopathological parameters

Thirteen studies reported correlations between EpCAM expression and some clinical characteristics of GC (including age, gender, tumor size, depth of invasion, TNM stage, tumor location, distant metastasis, Borrmann type, Lauren classification, histologic differentiation and lymph node metastasis). These were pooled to calculate the RRs.

In our study, the expression level of EpCAM was higher in samples of GC than in normal ones (pooled RR = 2.16, 95%CI: 1.54-3.03,  $P < 0.00001$  random-effect) (Figure 2A). In addition, EpCAM expression was significantly associated with tumor size (pooled RR = 1.68, 95%CI: 1.47-1.91,  $P < 0.00001$  fixed-effect) (Figure 2B), depth of invasion (pooled RR = 1.37, 95%CI: 1.11-1.68,  $P = 0.003$  random-effect) (Figure 2C), TNM stage (pooled RR = 2.02, 95%CI: 1.35-3.02,  $P = 0.0007$  random-effect) (Figure 2D), tumor location (pooled RR = 0.80, 95%CI: 0.71-0.91,  $P = 0.0007$  fixed-effect) (Figure 2E), histologic differentiation (pooled RR: 1.23, 95%CI: 1.13-1.33,  $P < 0.00001$  fixed-effect) (Figure 2F), and lymph node metastasis (pooled RR = 1.89, 95%CI: 1.28-2.80,  $P = 0.001$  random-effect) (Figure 2G). However, EpCAM expression in GC was not associated with age (pooled RR = 1.12, 95%CI: 0.93-1.35,  $P = 0.24$  fixed-effect), gender (pooled RR =

**Table 1** Characteristics of included studies

First author	Country	Year	Ethnic	Age (< 50: ≥ 50)	No. of patients (male:female)	No. of patients (EpCAM+: EpCAM-)	Diagnosis of GC (Histo-, Patho-, NR)	Study quality (NOS)
Zhang <i>et al</i>	China	2011	Asian	11:31	24:18	34:8	Patho-	8
Sun <i>et al</i>	China	2010	Asian	31:29	48:12	46:14	Patho-	8
Fang <i>et al</i>	China	2010	Asian	27:31	39:19	46:12	Patho-	8
Lu <i>et al</i>	China	2011	Asian	43:48	70:21	84:7	Patho-	9
Yang <i>et al</i>	China	2014	Asian	33:39	57:15	48:24	Patho-	9
Peng <i>et al</i>	China	2011	Asian	20:11	18:13	21:10	Patho-	9
Yang <i>et al</i>	China	2012	Asian	33:62	66:29	56:39	Patho-	8
Zhang <i>et al</i>	China	2014	Asian	17:25	24:18	37:5	Patho-	7
Li <i>et al</i>	China	2012	Asian	NR	311:125	179:257	Patho-	7
Du <i>et al</i>	China	2009	Asian	26:74	61:39	74:26	Patho-	8
Went <i>et al</i>	Switzerland	2006	Caucasian	NR	311:117	NR	Patho-	7
Kroepil <i>et al</i>	Germany	2013	Caucasian	NR	NR	126:37	Patho-	8
Wang <i>et al</i>	China	2013	Asian	NR	428:173	247:354	NR	8
Songun <i>et al</i>	The Netherlands	2005	Caucasian	NR	NR	NR	Patho-	7

Histo-: Histology; Patho-: Pathology; NR: Not reported; NOS: Newcastle-Ottawa Scale classification; EpCAM: Epithelial cellular adhesion molecule.

**Table 2** Raw data from each included study

First author	Tumor size (≤ 5 cm: > 5 cm)	Depth of invasion (T1-T2: T3-T4)	TNM stage (I-II: III-IV)	Tumor location (upper:middle: lower)	Distant metastasis (yes: no)	Borrma-nn type (I:II: III:IV)	Lauren classificatio-n (intestinal: diffuse: mixed)	Histologic differentiate-on (high: moderate: low)	Lymph node metastasis (NO: N1/2/3)
Zhang <i>et al</i>	NR <sup>2</sup>	NR	NR	NR	23:19			8:12:22	20:22
Sun <i>et al</i>	NR	11:49	NR	NR	NR	NR	NR	20:20:20	NR
Fang <i>et al</i>	NR	17:41	17:41	NR	18:40	NR	NR	11:17:30	15:43
Lu <i>et al</i>	41:50	19:72	34:57	41:25:25	NR	8:12:59:11	NR	3:24:64	31:60
Yang <i>et al</i>	45:27	35:37	35:37	NR	NR	NR	NR	NR	25:47
Peng <i>et al</i>	NR	19:12	19:12	12:13:6	NR	NR	NR	15:13:3	NR
Yang <i>et al</i>	NR	7:88	NR	29:26:40	NR	3:12:61:19	NR	6:19:70	29:66
Zhang <i>et al</i>	14:28	13:29	13:29	NR	NR	NR	NR	16:26:0	11:31
Li <i>et al</i>	256:180	166:270	194:242	55:163:218	61:375	NR	223:213:0	141:295	166:270
Du <i>et al</i>	NR	NR	NR	NR	NR	NR	91:19	25:42:33	50:50
Went <i>et al</i>	NR	42:372	NR	NR	25:445	NR	NR	NR	153:316
Kroepil <i>et al</i>	NR	107:56	NR	NR	9:154	NR	62:61:40	NR	41:122
Wang <i>et al</i>	350:251	221:380	262:339	84:223:294	91:510	NR	299:302	17:175:409	220:381
Songun <i>et al</i> <sup>1</sup>	NR	NR	NR	NR	NR	NR	NR	NR	NR

<sup>1</sup>Article written by Songun *et al.* only provided OS data; <sup>2</sup>NR: Not reported.

0.97, 95%CI: 0.91-1.04,  $P = 0.37$  fixed-effect), distant metastasis (pooled RR = 2.25, 95%CI: 0.77-6.61,  $P = 0.14$ , random-effect), Borrmann type (pooled RR = 1.03, 95%CI: 0.89-1.19,  $P = 0.70$  fixed-effect), or Lauren classification (pooled RR = 1.64, 95%CI: 0.75-3.60,  $P = 0.21$  random-effect).

### Impact of EpCAM expression on OS in GC patients

Meta-analysis of the association between EpCAM expression and OS was determined in three studies. The pooled RR was analyzed using previously described methods. EpCAM expression was not associated with the OS rate. The pooled HR of the overall effect was 1.39 (95%CI: 0.30-6.48,  $P = 0.67$ ) in the random-effect model (Figure 2H).

### Assessment of publication bias

The funnel plot test recommended for meta-analyses

was used to examine publication bias (Figure 3). We inspected its asymmetry visually and found that there was almost no potential for publication bias.

### Sensitivity analysis

One included study was excluded at each time to investigate the influence of the individual data on the overall results. The pooled RR or HR estimates were recalculated for the remaining studies. The statistical significance of the overall results was not changed when any individual study was excluded, which indicates the reliability of our results.

## DISCUSSION

In recent years, many cell adhesion molecules (CAMs) have proven to be responsible for tumorigenesis and metastasis<sup>[2,3]</sup>. The role of EpCAM is not only limited



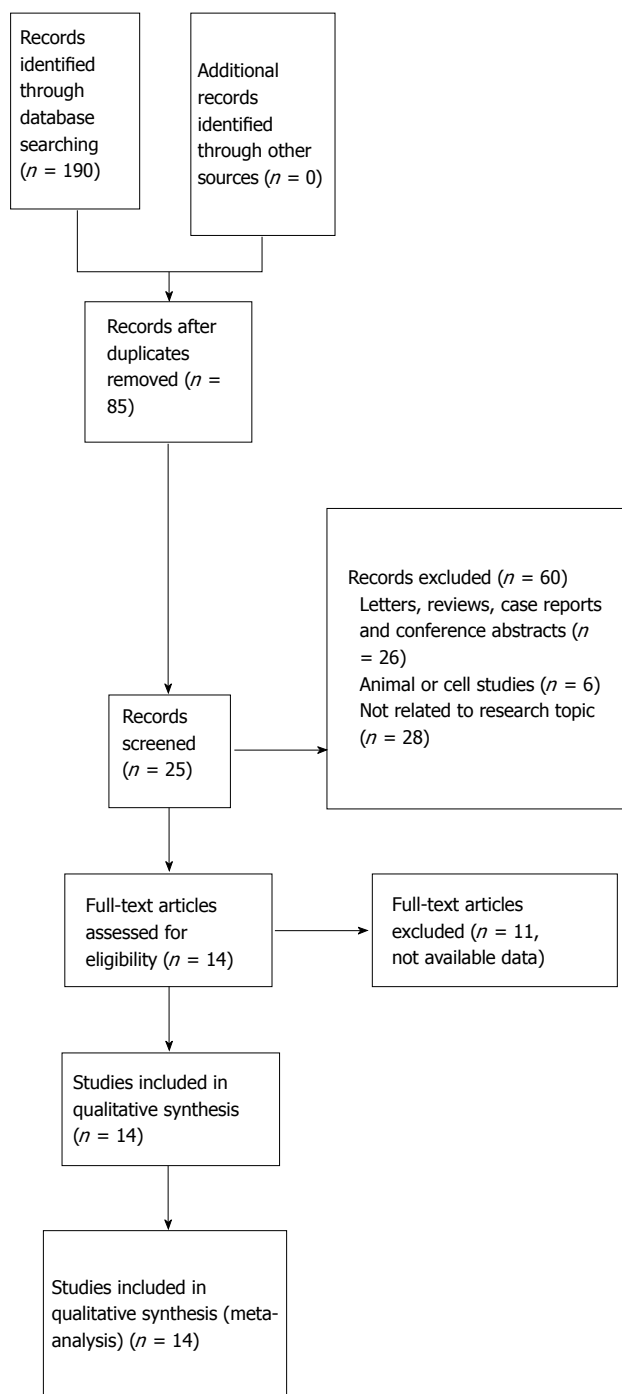


Figure 1 Study selection.

to cell adhesion but is also involved in other cellular processes including signaling, cell migration, proliferation and differentiation<sup>[15]</sup>. EpCAM is a potent signal transducer, which can use components of the Wnt pathway and is involved in the regulation of cell proliferation and cell cycle progression<sup>[5,13,16]</sup>. It is overexpressed in many solid cancers including esophageal, pancreatic, prostate and gastric<sup>[12,17]</sup>, and it has recently been identified as a type of cancer stem cell marker<sup>[14,18,19]</sup>.

Identification of a prognostic factor such as EpCAM is necessary for high-risk patients for whom specific therapy might be necessary<sup>[20,21]</sup>. However, conflicting

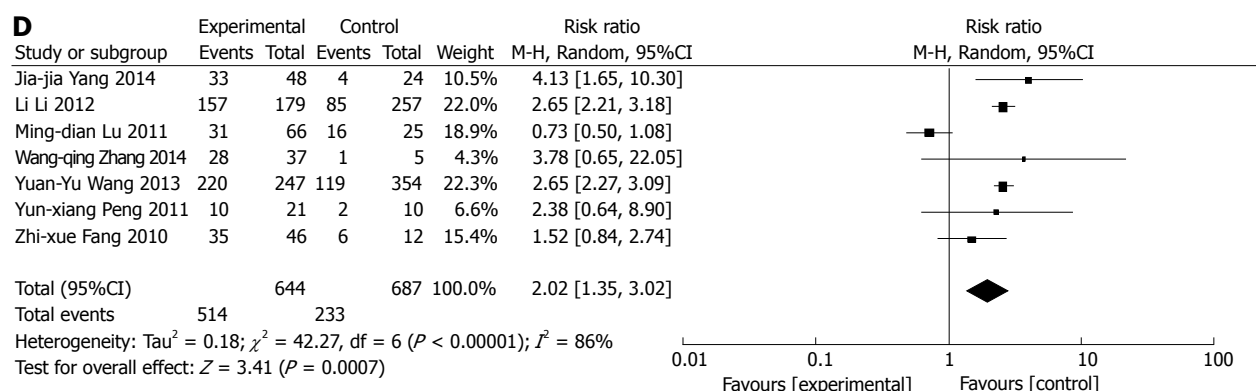
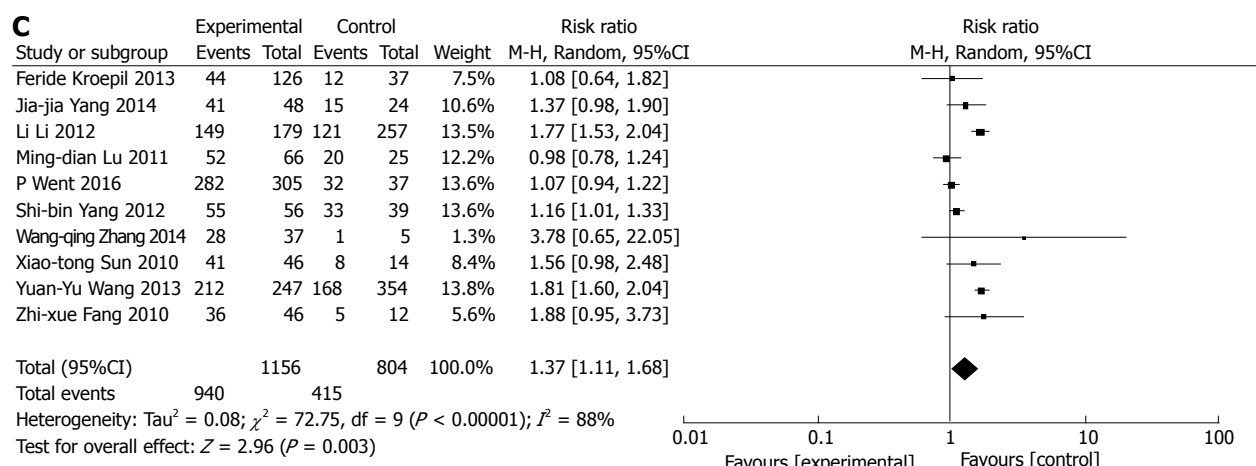
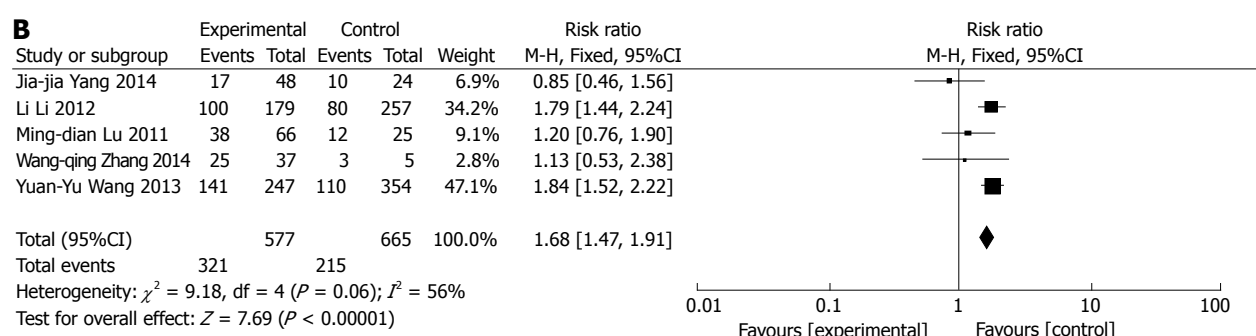
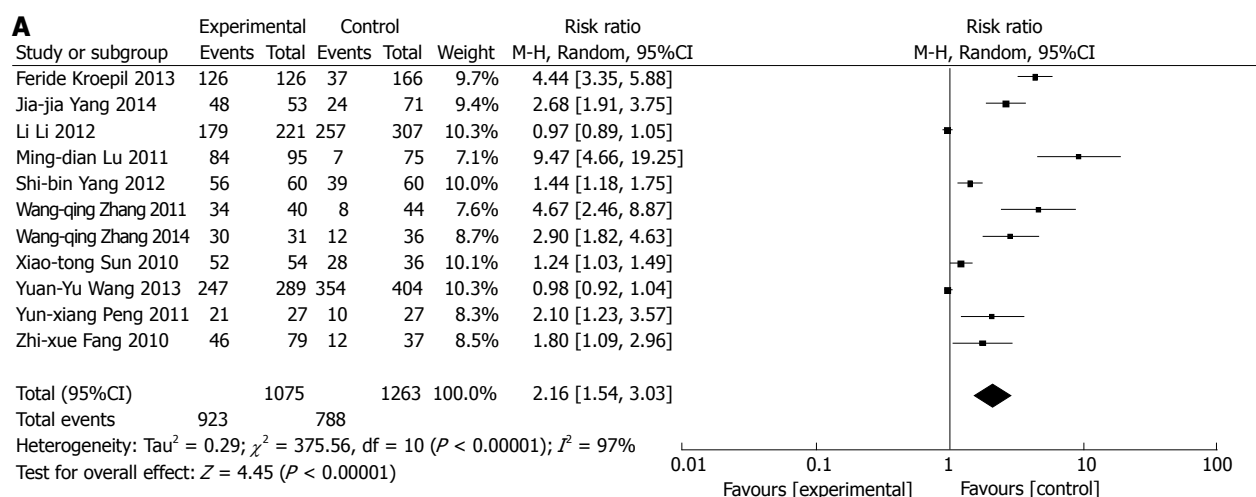
data on the prognostic impact of EpCAM have been reported. Wenqi *et al.*<sup>[22]</sup> reported that EpCAM was overexpressed in gastric cell lines and tumor tissues and downregulation of EpCAM resulted in a decrease in cell proliferation and suppressed tumor formation. In contrast, Songun *et al.*<sup>[23]</sup> reported that 93% of 300 GC patients were EpCAM-positive and the loss of EpCAM expression indicated tumor aggression, especially in patients with stage I and II disease. Thus, the prognostic role of EpCAM in GC is still unclear and the association between clinical characteristics of GC patients and EpCAM expression levels needs to be further elucidated. These conflicting data were likely due to the small sample size and intratumoral heterogeneity of GC, which was observed in the studies.

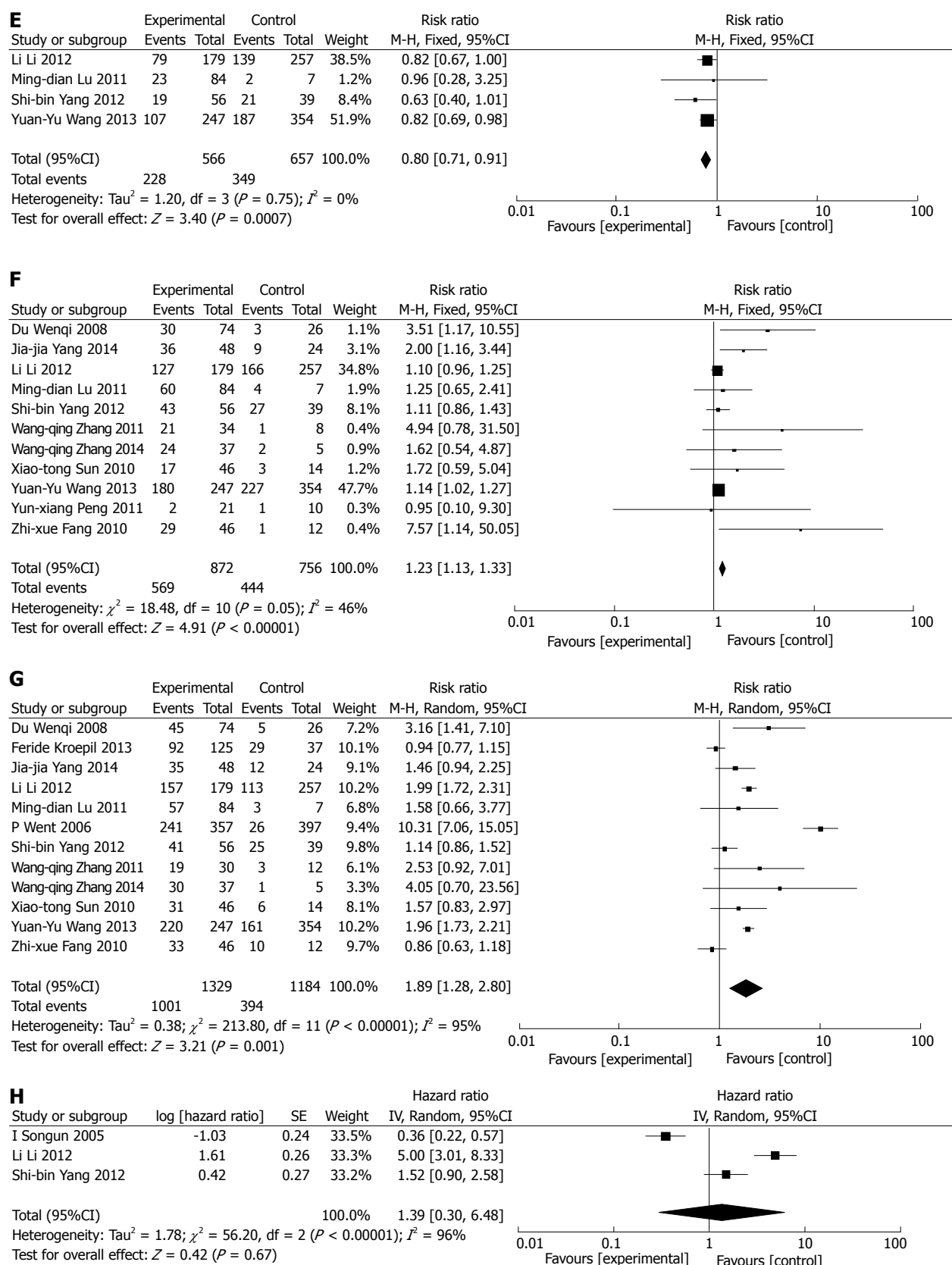
This meta-analysis is the first study to systematically estimate EpCAM expression and its relationship with clinicopathological characteristics and OS rates in GC patients. We calculated pooled RRs to study the correlation of EpCAM with patient clinical characteristics. This showed that EpCAM expression was positively related with poor histological type, lymph node metastasis, high-grade of TNM stage and tumor size (> 5 cm), depth of invasion (T3-T4) and tumor location (lower part of the stomach) in GC patients. This suggests that GC patients with the above-mentioned clinical characteristics were more likely to have a poorer prognosis after the diagnosis was made.

The biological function of EpCAM may be implicated in the relationship between EpCAM expression and cancer outcome mentioned above. Recently, studies have reported that overexpression of EpCAM occurs in a variety of cancers, for example colon, breast and ovarian, and most human adenocarcinomas. Furthermore, it has effects on differentiation, proliferation and migration of cancer cells.

There are certain limitations in the present meta-analysis that need to be pointed out. First, although we tried to avoid biases in performing this meta-analysis, publication bias may have occurred because only published studies were included in the meta-analysis even if the statistical test did not show it. Second, we did not find any significant association between EpCAM expression and OS in GC patients. It is very likely that limited research has been done on EpCAM and its relationship with prognosis. Only three studies were included in the OS meta-analysis, with a relatively small sample size of 831 patients. Finally, there was heterogeneity between studies present in this article, with a *P*-value < 0.05, especially in the evaluation of the relationship between EpCAM expression and some adverse clinical parameters. This was related to insufficient sample size and a lack of certain original data. To adjust for this, we used a trim-and-fill method in the random-effect model to make the outcomes statistically credible.

In conclusion, this meta-analysis suggests that the expression of EpCAM is associated with poor clinicopathological features of GC. However, because of the heterogeneity of included studies and bias of meta-analysis, our conclusions need to be interpreted with caution. More





**Figure 2 Meta-analysis Forest plot.** A: Meta-analysis Forest plot concerning the expression level of epithelial cellular adhesion molecule with gastric cancer between samples of gastric cancer and normal ones; B: Meta-analysis Forest plot concerning tumor size; C: Meta-analysis Forest plot concerning depth of invasion; D: Meta-analysis Forest plot concerning TNM stage; E: Meta-analysis Forest plot concerning tumor location; F: Meta-analysis Forest plot concerning histologic differentiation; G: Meta-analysis Forest plot concerning lymph node metastasis; H: Meta-analysis Forest plot concerning overall survival rate.

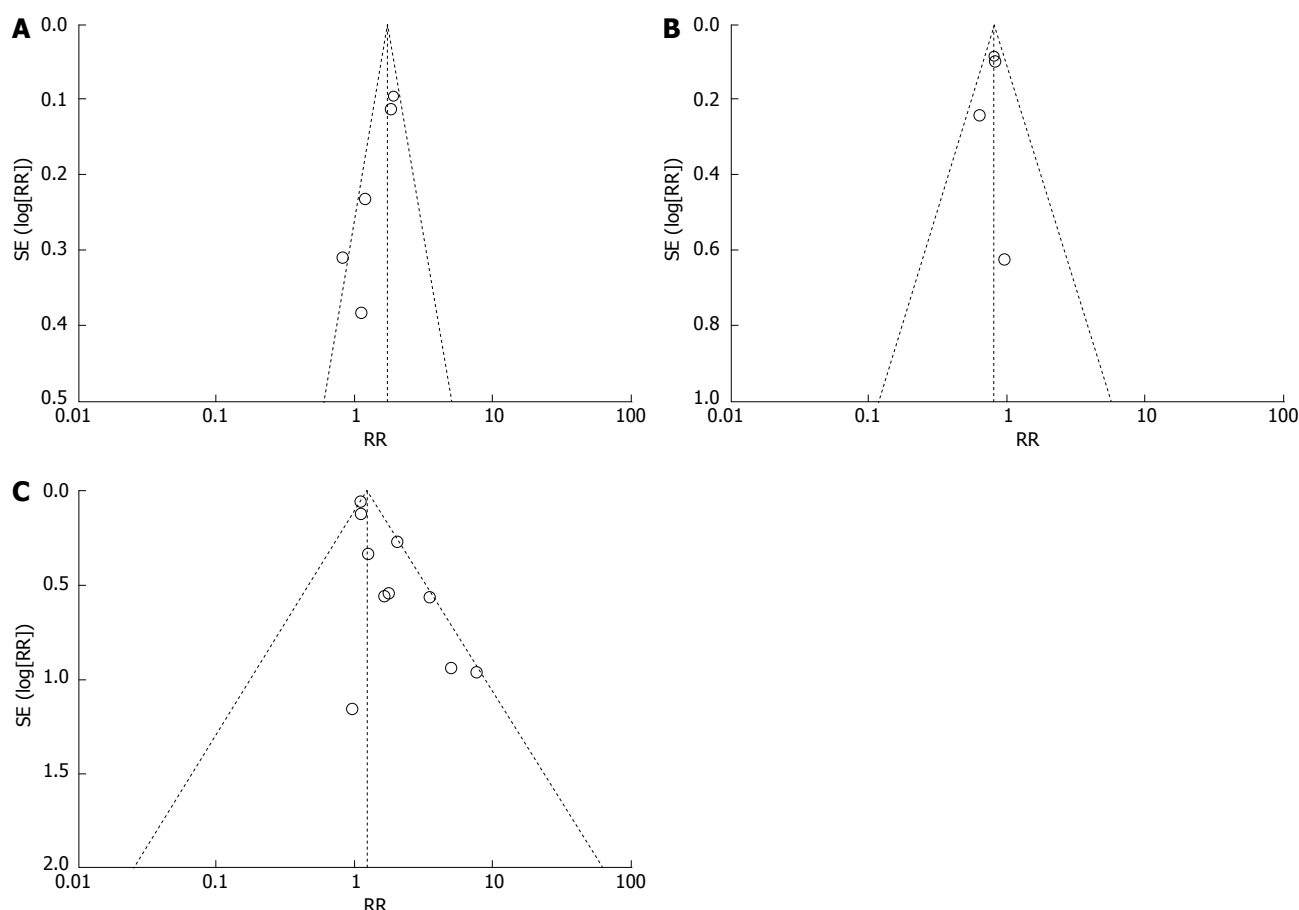


Figure 3 Funnel plot of tumor size (A), tumor location (B) and histologic differentiation (C). RR: Risk ratio.

clinical studies will be required to determine the association between the expression of EpCAM and GC prognosis.

## COMMENTS

### Background

Although gastric cancer (GC) rates have decreased substantially in the past few decades, it remains the second most common cause of cancer-related death worldwide. Although several studies showed high expression of epithelial cellular adhesion molecule (EpCAM) in GC, which was related to cancer progression and survival prognosis, there is no comprehensive study on the correlation of EpCAM expression with survival prognosis or the effects of EpCAM expression on clinicopathologic characteristics in GC patients.

### Research frontiers

This meta-analysis was conducted to determine the association between high expression of EpCAM and clinicopathological features and progression as well as prognosis of GC.

### Innovations and breakthroughs

Studies that had examined the association between high expression of EpCAM and GC risk were identified by searching electronic databases PubMed, EMBASE, Cochrane library and Chinese Biomedical Literature database.

### Applications

This meta-analysis indicates that EpCAM contributes to GC risk, which acts as a prognostic factor and a marker of poor outcome.

### Peer-review

The authors reported the "Expression of epithelial cellular adhesion molecule

in gastric cancer: A meta-analysis". These findings are important to those with closely related research interests. It is well organized and systemically analysed.

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