Int J Clin Exp Med 2019;12(1):26-37
www.ijcem.com /ISSN:1940-5901/IJCEM0078592

*Review Article*

# Clinical significance of claudin-1 in gastric cancer: a meta-analysis

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Received April 26, 2018; Accepted September 6, 2018; Epub January 15, 2019; Published January 30, 2019

**Abstract:** Current results have indicated an inconsistent association between claudin-1 expression and the gastric cancer (GC) classification type. The present meta-analysis was conducted to obtain credible conclusions about this relationship. A comprehensive electronic and manual search was performed for records published before December 2017 using the Cochrane Library, Embase, PubMed, and Chinese National Knowledge Infrastructure (CNKI). Conference abstracts were also manually screened. An odds ratio (OR) was presented with 95% confidence interval (CI) for all results. There were nine studies with 920 GC patients included. Claudin-1 expression was significantly associated with the well-to-moderate-differentiated GC cohort (OR: 0.27, 95% CI: 0.17-0.41, P < 0.001). However, no significant differences were detected in terms of gender, TNM staging, lymphoid node metastasis, or vascular invasion. According to subgroup analysis, expression of claudin-1 occurred more frequently in the intestinal type of GC in Western areas (OR: 0.32, 95% CI: 0.19-0.55, P < 0.001) and in Asia (OR: 0.50, 95% CI: 0.28-0.91, P=0.024). In conclusion, this meta-analysis expatiated that claudin-1 is a novel biomarker for differentiation of GC.

**Keywords:** Claudin-1, gastric cancer, clinical significance, biomarker, meta-analysis

## Introduction

Gastric cancer (GC) is a common malignancy of digestive system. The degree of invasion determines the stage and prognosis of GC [1]. The mortality of gastric cancer remains high [2], due to blood or lymphatic metastasis. Recent studies have found that a functional loss of the paracellular barrier is critical for progression of GC [3]. Moreover, tight junctions (TJs) play an important role in the paracellular barrier by mediating cell adhesion between epithelial cells and endothelial cells [4].

Claudins represent a family of proteins which are highly emphasized as components of tight junctions [5]. In various tissues and cells, different Claudin isoforms have specific expression patterns and functions [6]. Recent studies have mentioned that suppression of claudin-1 may contribute to mesenchymal transition (EMT) in GC [7]. It has been associated with the GC classification type. However, these conclusions have not been consistent. For example, Wu et al. [8] found that claudin-1 expression was significantly correlated with well-to-moderately differentiated GC based on 136 GC cases. On the other hand, Wang et al. [9] reported that claudin-1 expression was correlated with poor histological grade. In view of these inconsistent results, the present meta-analysis was conducted to obtain credible conclusions on the inner relationship of claudin-1 expression with GC.

## Materials and methods

### *Search strategy*

A comprehensive electronic and manual search was performed for records published before December 2017 using the Cochrane Library, Embase, PubMed, and Chinese National Knowledge Infrastructure (CNKI). Conference abstracts were also manually screened. Combinations of MeSH and free terms were used as a search strategy, including “gastric cancer”, “claudin-1”, “clinical significance”. All essays were published in English.

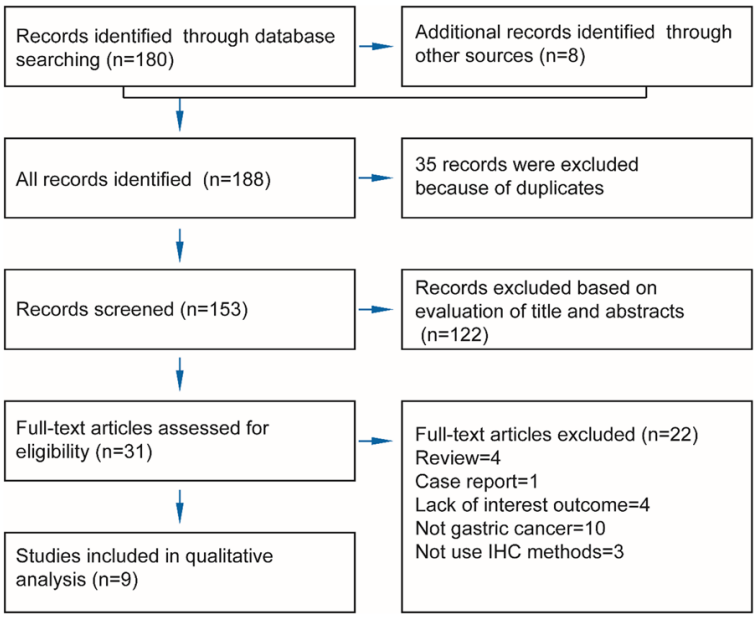



**Figure 1.** Study selection flowchart.

*Inclusion criteria*

All studies were produced by two authors (Lijia Pan and Ziyi Yang), independently. They were recruited only after a consensus was reached by the two reviewers. The kappa value of coherence between the two authors was 0.8. Records were chosen for meta-analysis when satisfying the following three criteria: (1) Patients were diagnosed with GC; (2) Records mentioned correlation between clinical significance and claudin-1 expression of GC patients; and (3) Immunohistochemistry (IHC) was used to diagnose expression of claudin-1 in GC tissues.

*Exclusion criteria*

This meta-analysis excluded studies that were prospective, out of control group, or lacked complete abstracts, reviews, case reports, or outcome of interest.

*Quality assessment of studies*

Quality assessment was performed by two independent reviewers according to the Newcastle-Ottawa Scale (NOS) [10]. This is a tool used for quality assessment of non-randomized researches. Ratings or quality scores of each study were achieved after reaching a consensus. Studies chosen for this meta-analysis were considered as high methodological quality (scores above 6).

*Data extraction*

Data extraction was conducted by two independent reviewers. They extracted the basic information of each research (author name, publication time, country, gender of patients, size of samples), IHC parameters (source of antibody, dilution, diagnostic criteria, and cut-off value), and clinical significance (histological grade, Lauren's cancer type, TNM staging, Lymphoid node metastasis, and vascular invasion). Divisions were resolved by discussion before a consensus was reached.

*Statistical analysis*

Stata 13 software (Stata Corp, College Station, TX) was used to conducted statistical tests. An odds ratio (OR) was presented with 95% confidence intervals (CI) for all results. The cut-off value of statistical significance was $P < 0.05$. Heterogeneity among records was tested by Q test, $I^2$ test, and H test. A fixed-effects model (Mantel-Haenszel method) was used if the Q statistic $P$ value ≥0.05. Otherwise, a random effects model (DerSimonian-Laird method) was used to obtain more conservative conclusions. Reliability of pooled estimates was tested by sensitivity analysis. Using a funnel plot assessed by Egger's test, publication bias exploration was achieved according to recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [11]. When $P < 0.05$, publication bias across studies existed.

## Results

*Search results and involved studies description*

A total of 188 studies were retrieved from the initial electronic and manual search, including

**Table 1.** Characteristics of included studies in the meta-analysis

| Author | Year | Country | Gender (M/F) | Patient number | Antibody source | Dilution | Diagnostic criteria | Cut-off (%) |
|---|---|---|---|---|---|---|---|---|
| Soini et al. | 2006 | Finland | NA | 112 | Zymed | 1:50 | distribution | 50% |
| Wang et al. | 2015 | China | 53/39 | 92 | Abcam | NA | distribution | 10% |
| Tokuhara et al. | 2015 | Japan | 67/27 | 94 | Abcam | 1:100 | distribution | 25% |
| Shinozaki et al. | 2009 | Japan | 30/8 | 43 | Zymed | 1:50 | intensity and distribution | 3 |
| Wu et al. | 2008 | China | 106/30 | 136 | Zymed | 1:100 | intensity and distribution | 2 |
| Resnick et al. | 2005 | America | NA | 146 | Zymed | 1:125 | intensity | 2 |
| Jung et al. | 2011 | Korea | 41/31 | 72 | Lab Vision | 1:200 | distribution | 25% |
| Huang et al. | 2014 | China | 122/51 | 173 | Zymed | 1:100 | intensity and distribution | 6 |
| Chang et al. | 2010 | Singapore | NA | 52 | Zymed | NA | NA | NA |

NA not available.

**Table 2.** Quality assessment of included studies using the Newcastle-Ottawa Scale (NOS)

| Author | Selection | | | | Comparability | Exposure | | | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Soini et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Wang et al. | ★ | ★ | | ★ | ★ | ★ | ★ | ★ | 7 |
| Tokuhara et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Shinozaki et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Wu et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Resnick et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Jung et al. | ★ | ★ | | ★ | ★ | ★ | ★ | ★ | 7 |
| Huang et al. | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Chang et al. | ★ | ★ | | ★ | ★ | ★ | ★ | ★ | 7 |

8 records of conference abstracts. There were nine studies [7-9, 12-17] meeting predefined criteria for this meta-analysis. All included essays were retrospective. **Figure 1** shows a flowchart for the selection process. These nine papers included a total of 920 patients with GC. Three came from China, two from Japan, while the others were from South Korea, Singapore, Finland, and the United States. All of them used IHC methods for membrane staining. Common characteristics included are listed in **Table 1**. Quality assessment is detailed in **Table 2**.

*Histological grade results*

Four studies [8, 9, 12, 17] with 495 patients mentioned the relationship between expression of claudin-1 and histological grade of GC. Results indicated that expression of claudin-1 occurred more frequently in a well-to-moderate-differentiated GC cohort (OR: 0.35, 95% CI: 0.17-0.74, P=0.006) (**Figure 2A**).

However, strong heterogeneity was discovered across these studies (Q=9.47, P=0.024; $I^2$= 68.3%; H=1.8, 95% CI: 1.0-3.0). As shown in **Figure 3A** and **3B**, small sample sizes made a significant impact on irrational results.

Low quality researches (Wang 2015) were excluded and the meta-analysis was conducted again. As a result, heterogeneity was reduced after removal of this individual study (Q=2.07, P=0.356; $I^2$=3.2 %; H=1.0, 95% CI: 1.0-3.2). The new results appeared consistent with previous ones (OR: 0.27, 95% CI: 0.17-0.41, P < 0.001) (**Figure 2B**). The three records left showed consistent results. It was not necessary to re-conduct the meta-analysis and the results were credible. Reliability of pooled estimates was tested by sensitivity analysis (**Figure 3C**). There was no significant publication bias (Begg's test: P=0.296; Egger's test: P=0.141) (**Figure 4A**, **4C**).

*Lauren type results*

Six studies [7, 13-17] with 598 patients provided sufficient information about the correlation between expression of claudin-1 and Lauren type of GC. However, results showed that claudin-1 expression was not significantly associat-

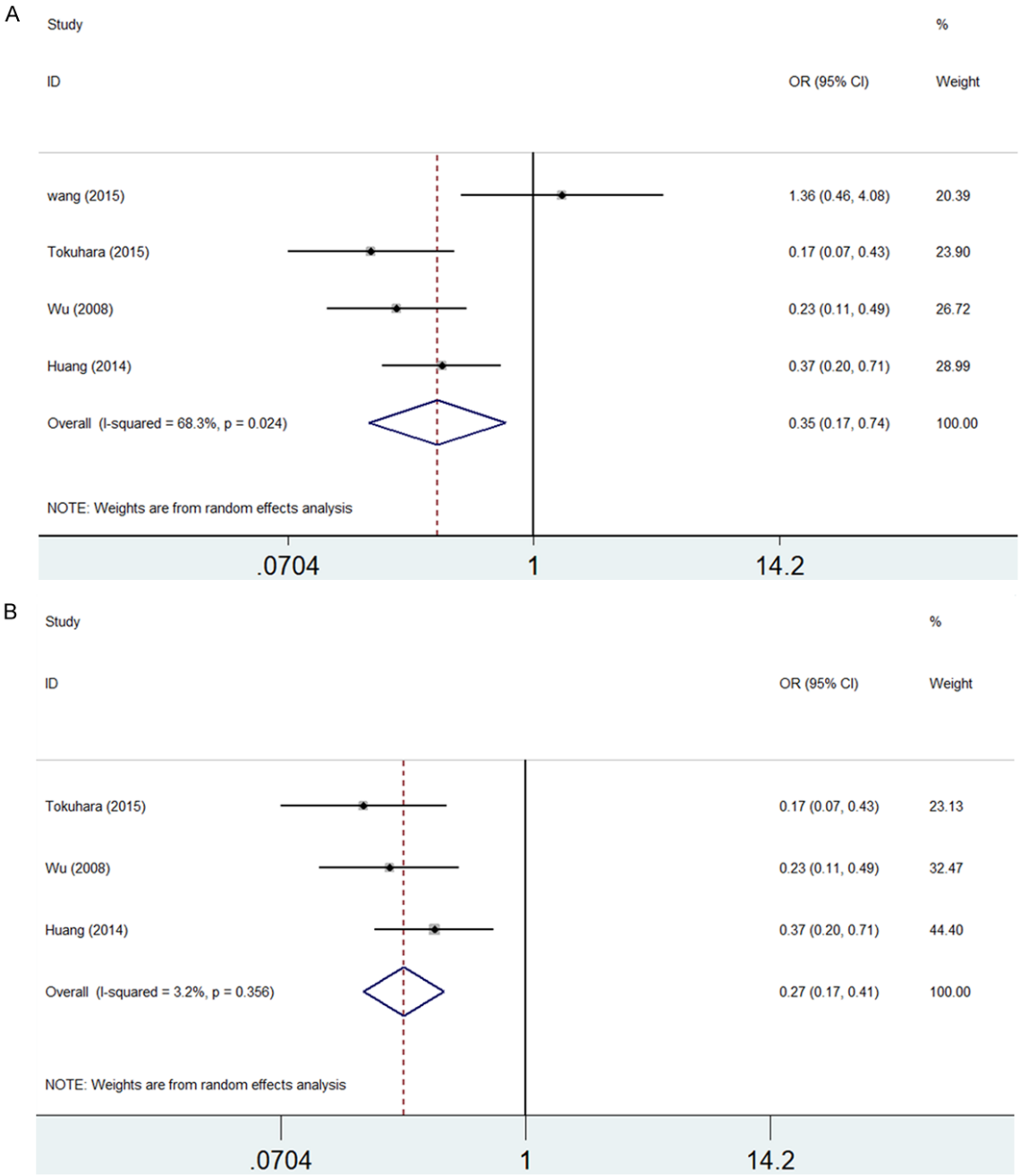



**Figure 2.** Forest plot of claudin-1 expression with histological grade of GC patients. A. Claudin-1 expression was significantly associated with well-to-moderate-differentiated GC patients. However, there was strong heterogeneity. B. Meta-analysis was re-conducted after excluding low quality research (Wang 2015).

ed with intestinal type of GC (OR: 0.57, 95% CI: 0.31-1.1, P=0.074) (**Figure 5A**).

There was strong heterogeneity among these studies (Q=14.42, p=0.013; $I^2$=65.3%; H=1.7, 95% CI: 1.1-2.6). As shown in **Figure 6A** and **6B**, small sample sizes made a significant impact on irrational results.

Meta-analysis was conducted again after excluding the low quality study (Jung 2011). Heterogeneity showed a reducing trend after

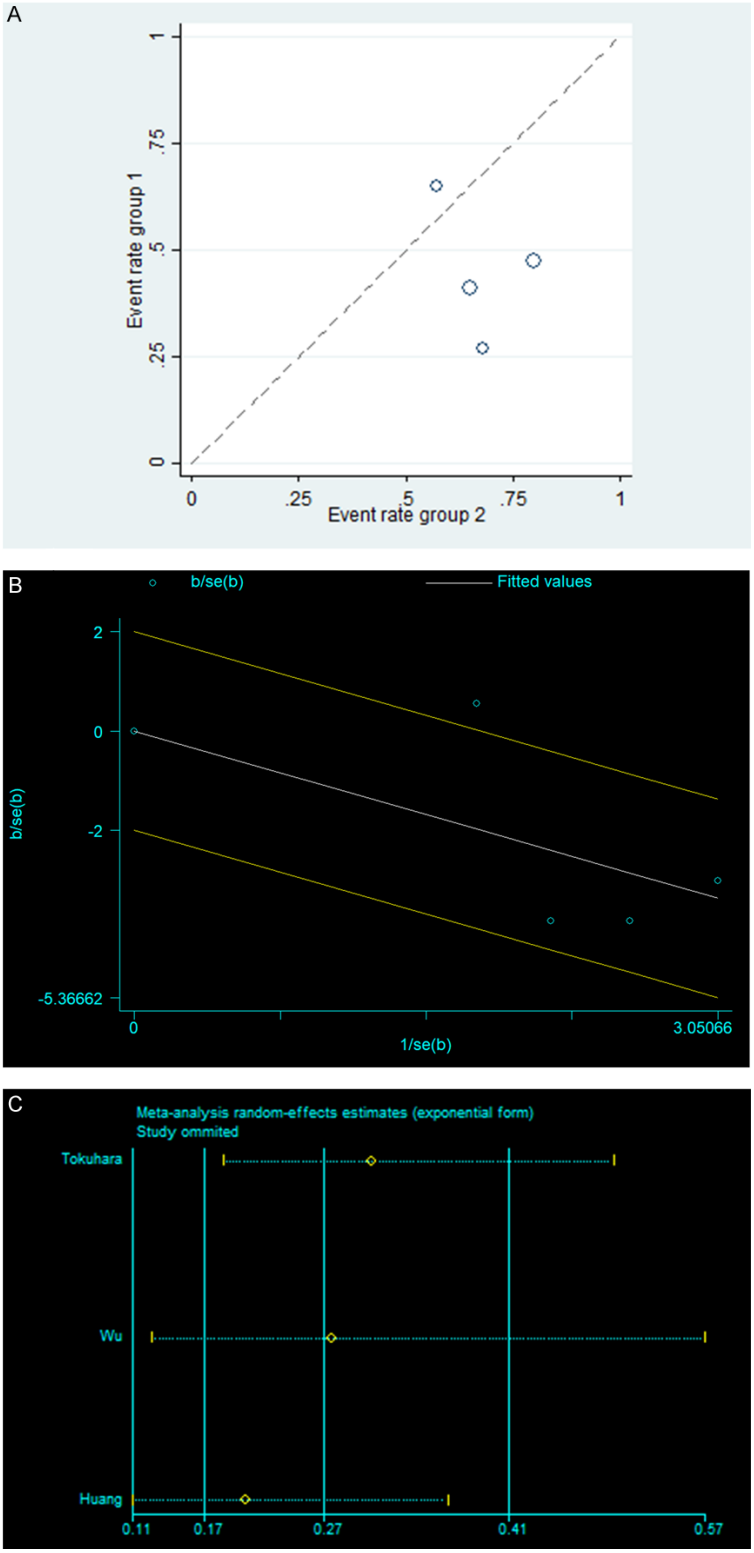



**Figure 3.** Heterogeneity and sensitivity analysis was conducted to check the reliability. A. The L'Abbe plot for claudin-1 expression with histological grade of GC patients. B. The Galbraith plot for claudin-1 expression with histological grade of GC patients. C. The influence of each record for the outcome of the meta-analysis after excluding low quality research (Wang 2015).

removal of this individual study (Q=3.53, P=0.473; $I^2$= 0.0%; H=1.0, 95% CI: 1.0-2.2). Results implied that claudin-1 expression was significantly correlated with intestinal type of GC (OR: 0.39, 95% CI: 0.27-0.57, P < 0.001) (**Figure 5B**). Reliability of pooled estimates was tested by sensitivity analysis (**Figure 6C**). There was no significant publication bias according to Begg's test (P=0.221) However, Egger's test presented poor results (P=0.009) (**Figures 7A**, **4B** and **4C**).

Therefore, subgroup analysis was conducted to obtain a more conservative conclusion. Considering that incidence of GC was linked to geographical variation, country was chosen as grouping criteria. Results were consistent in Western areas (OR: 0.32, 95% CI: 0.19-0.55, P < 0.001) and in Asia (OR: 0.50, 95% CI: 0.28-0.91, P=0.024) (**Figure 5C**).

*Other parameter results*

Six studies [8, 9, 12, 14, 16, 17] with 605 patients provided sufficient information about gender. However, results showed that claudin-1 expression was not significantly associated with gender of GC patients (OR: 1.04, 95% CI: 0.64-1.71, P=0.865).

Four studies [12-14, 17] with 402 patients mentioned TNM staging in their reports. No significant differences were found between expression of claudin-1 and TNM staging of GC patients (OR: 1.11, 95% CI: 0.51-2.41, P=0.788).

Lymphoid node metastasis was also examined in five papers [8, 9, 12, 14, 17] with

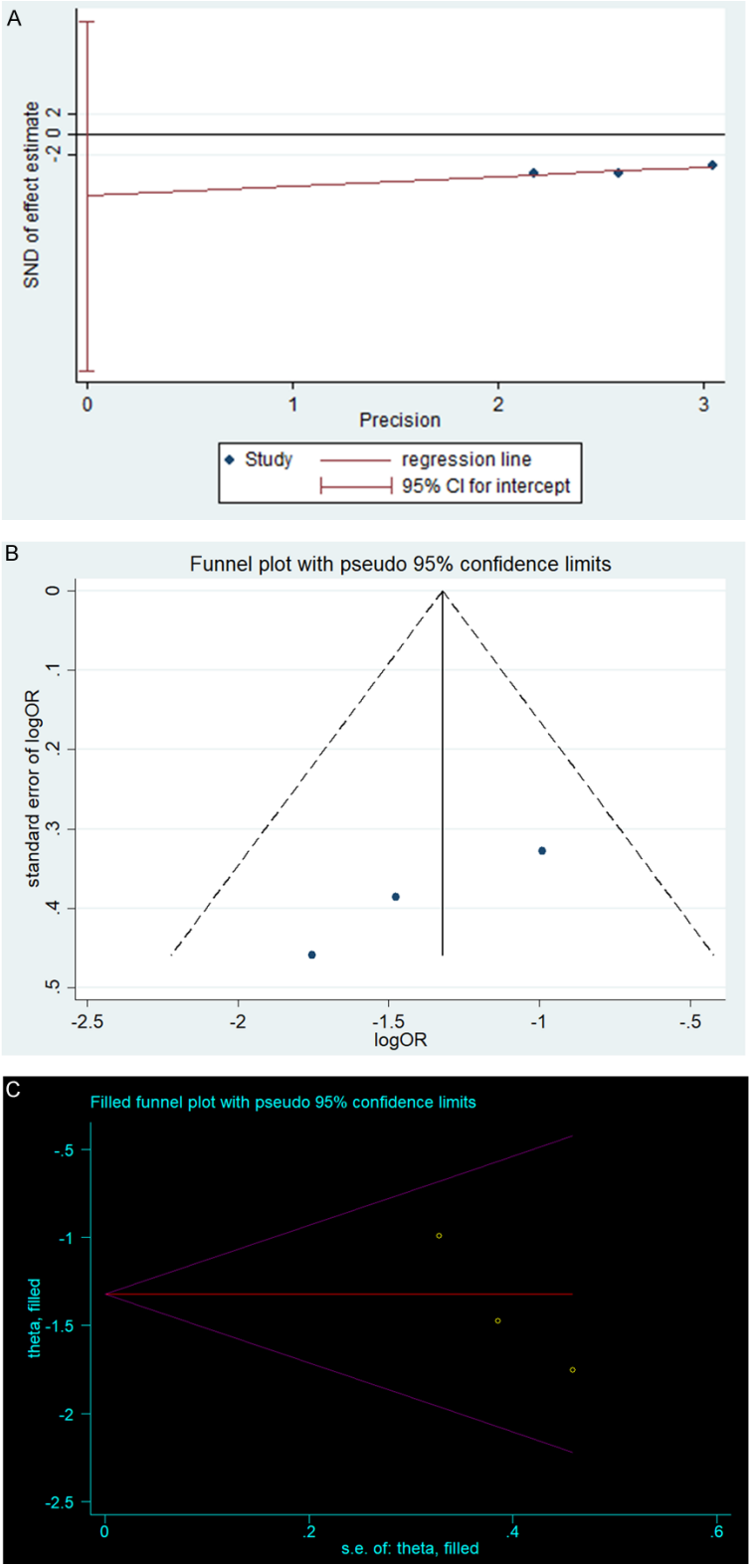



**Figure 4.** Begg's and Egger's tests were conducted to seek for publication bias. A. Egger's publication bias plot for claudin-1 expression with histological grade of GC patients. B. Funnel plot for claudin-1 expression with histological grade of GC patients. C. Filled funnel plot for claudin-1 expression with histological grade of GC patients.

533 GC patients. Fallouts failed to display any correlation of claudin-1 with lymphoid node metastasis of GC (OR: 1.01, 95% CI: 0.44-2.34, P= 0.979).

There were there studies [12, 14, 16] that mentioned vascular invasions. There were no significant differences between the two cohorts (OR: 0.78, 95% CI: 0.31-1.96, P=0.598).

Subgroup analysis was performed by variables that potentially contributed to heterogeneity. However, results did not indicate any inconsistent results (**Table 3**).

## Discussion

Occurrence and development of GC is a stepwise process involving numerous gene mutations and subsequent changes in molecular signalling networks [18]. It has been recognized that cell adhesion plays a key role in occurrence and progression of GC, since local invasion is critical for the stage and prognosis of GC [19, 20]. Claudin family has been narrowly correlated to the regulation of molecular networks during the formation of tight junctions, which are essential parts of cell adhesion [21, 22]. However, tissue-dependant expression patterns makes the function of claudin isoforms a mystery [23], especially the character of claudin-1 in progression of GC. Zhang et al. believed that the appearance of claduin-1 decreased progressively from intestinal metaplasia to GC tissue centre, indicating that expression of claudin-1 was negatively connected to tumor

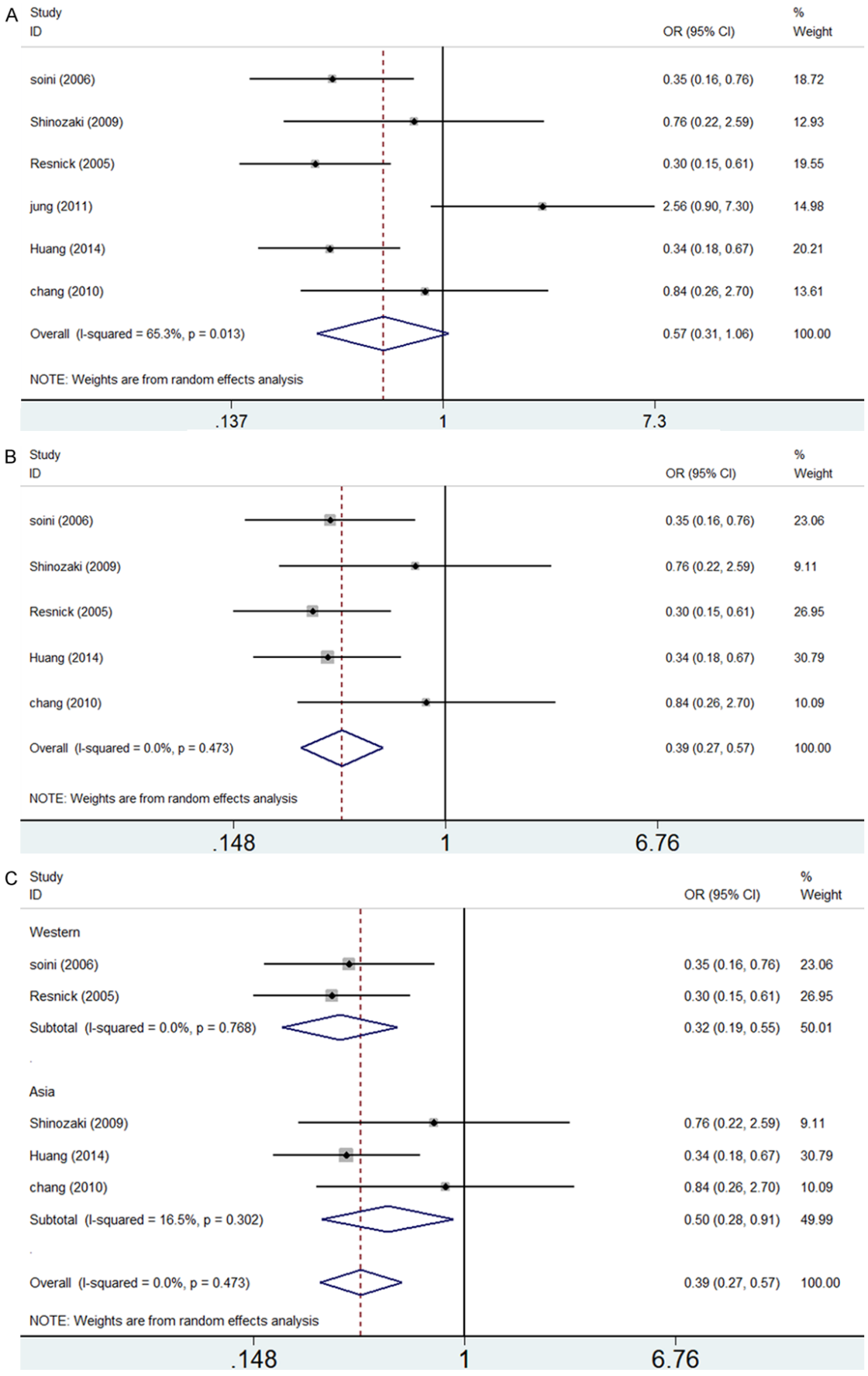
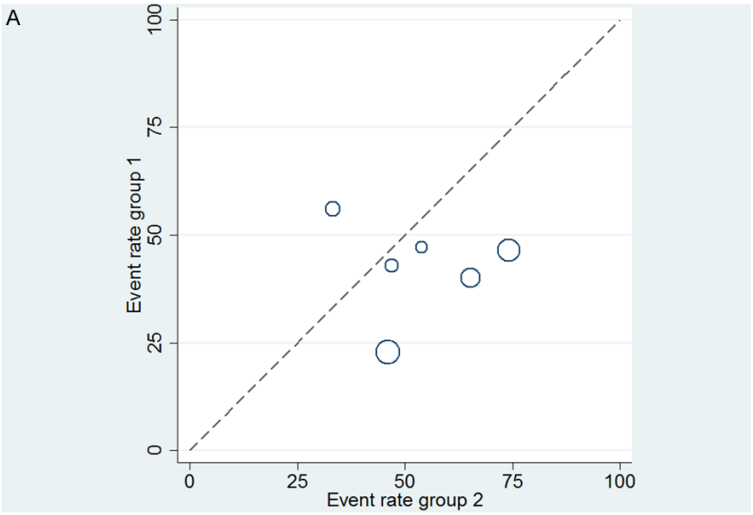
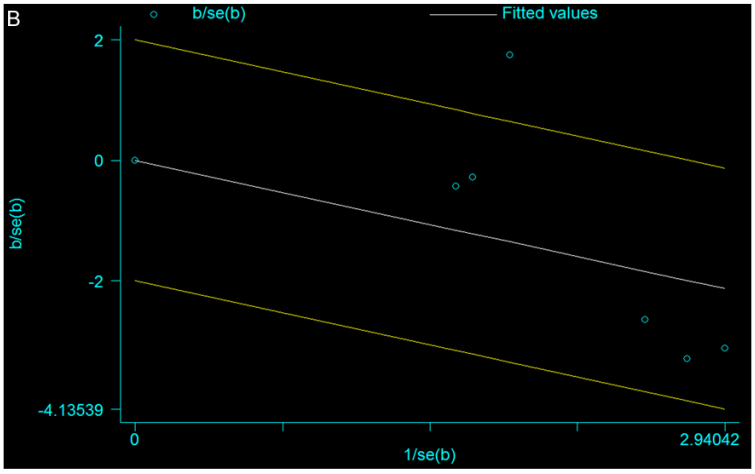

A
Study ID
OR (95% CI)
% Weight
soini (2006) 0.35 (0.16, 0.76) 18.72
Shinozaki (2009) 0.76 (0.22, 2.59) 12.93
Resnick (2005) 0.30 (0.15, 0.61) 19.55
jung (2011) 2.56 (0.90, 7.30) 14.98
Huang (2014) 0.34 (0.18, 0.67) 20.21
chang (2010) 0.84 (0.26, 2.70) 13.61
Overall (I-squared = 65.3%, p = 0.013) 0.57 (0.31, 1.06) 100.00
NOTE: Weights are from random effects analysis
.137
1
7.3
B
Study ID
OR (95% CI)
% Weight
soini (2006) 0.35 (0.16, 0.76) 23.06
Shinozaki (2009) 0.76 (0.22, 2.59) 9.11
Resnick (2005) 0.30 (0.15, 0.61) 26.95
Huang (2014) 0.34 (0.18, 0.67) 30.79
chang (2010) 0.84 (0.26, 2.70) 10.09
Overall (I-squared = 0.0%, p = 0.473) 0.39 (0.27, 0.57) 100.00
NOTE: Weights are from random effects analysis
.148
1
6.76
C
Study ID
OR (95% CI)
% Weight
Western
soini (2006) 0.35 (0.16, 0.76) 23.06
Resnick (2005) 0.30 (0.15, 0.61) 26.95
Subtotal (I-squared = 0.0%, p = 0.768) 0.32 (0.19, 0.55) 50.01
Asia
Shinozaki (2009) 0.76 (0.22, 2.59) 9.11
Huang (2014) 0.34 (0.18, 0.67) 30.79
chang (2010) 0.84 (0.26, 2.70) 10.09
Subtotal (I-squared = 16.5%, p = 0.302) 0.50 (0.28, 0.91) 49.99
Overall (I-squared = 0.0%, p = 0.473) 0.39 (0.27, 0.57) 100.00
NOTE: Weights are from random effects analysis
.148
1
6.76

**Figure 5.** Forest plot of claudin-1 expression with Lauren type of GC patients. A. Claudin-1 expression was significantly associated with intestinal type of GC patients. However, there was strong heterogeneity. B. Meta-analysis was re-conducted after excluding low quality research (Jung 2011). C. Subgroup analysis were consistent in Western areas and in Asia.



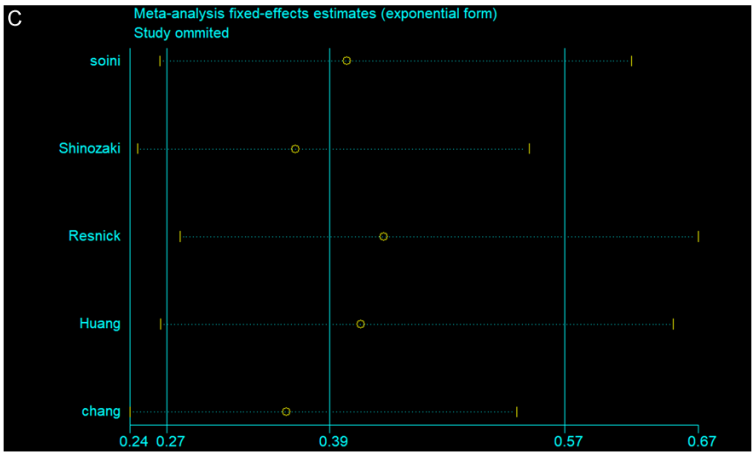




**Figure 6.** heterogeneity and sensitivity analysis was conducted to check the reliability. A. The L'Abbe plot for claudin-1 expression with Lauren type of GC patients. B. The Galbraith plot for claudin-1 expression with Lauren type of GC patients. C. The influence of each record for the outcome of the meta-analysis after excluding low quality research (Jung 2011).

stage and prognosis of GC [24]. Although claudin-1 is likely to promote the establishment of the epidermal barrier [25], it does not mean that its expression is able to inhibit progression of GC. In Eftang's paper, complete genomic cDNA microarray analysis revealed a high expression of claduin-1 in GC tissues in 20 patients cases, predicting worse prognosis and survival [26]. However, the specific regulatory mechanisms have remained principally mysterious between claudin-1 dysregulation and downstream signalling molecules.

In this meta-analysis, nine studies with 920 GC patients were enrolled. It was discovered that claudin-1 expression was significantly associated with intestinal type in Lauren classification and better histological grades of GC. A relationship was widely recognized between the biological and clinical behaviour of Lauren's cancer types and better histological grades. Based on this theory, it was reasonable to believe that claudin-1 is a well predictor or biomarker for GC patients. Furthermore, expression of claudin-1 was involved in the formation of the epidermal barrier. Predominantly, the absence of claudin-1 lead to epithelial-mesenchymal transition, the initial step in GC progression.

However, this study was unable to display a significant relationship between claudin-1 and gender, tumor stage, lymphoid node metastasis, or

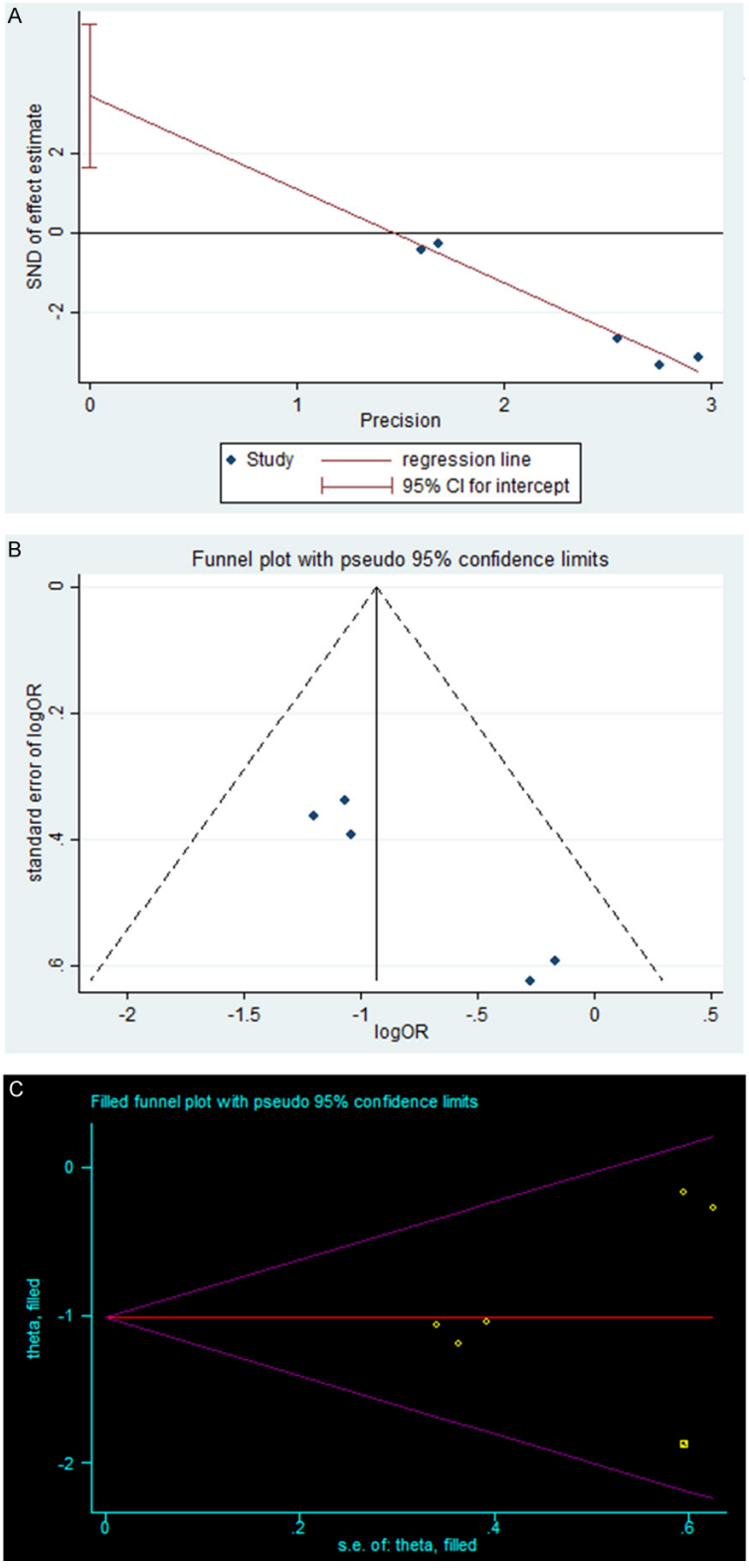



**Figure 7.** Begg's and Egger's tests were conducted to seek for publication bias. A. Egger's publication bias plot for claudin-1 expression with Lauren type of GC patients. B. Funnel plot for claudin-1 expression with Lauren type of GC patients. C. Filled funnel plot for claudin-1 expression with Lauren type of GC patients.

vascular invasion of GC. First, there was moderate heterogeneity among these studies. This was a consequence from variances in staining sites, diagnostic criteria, cut-off values, and antibody sources. This study was unable to eliminate the interference of heterogeneity, completely. Second, this study was unlikely to draw a perfect comprehensive conclusion because of limited records, caused by small sample sizes or lack of unified IHC diagnostic criteria. Thus, publication bias may have interfered with the conclusions. Third, cell adhesion is not an exclusive factor determining prognosis of GC. Lymphoid node metastasis, vascular invasion, and distant metastasis contribute to GC stage and lead to poor outcomes. Moreover, there was not enough data to elucidate whether claudin-1 was associated with progression free survival or overall survival of GC. Thus, further research is necessary to justify this association.

## Conclusion

In summary, the present meta-analysis expatiated that claudin-1 expression is correlated with intestinal type and well-to moderately-differentiated GC. In other words, claudin-1 is a well predictor or biomarker for differentiation of GC.

## Disclosure of conflict of interest

None.

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**Table 3.** Subgroup analysis of gender, TNM staging, lymph node metastasis, and venous invasion

| Variable | Subgroup | Gender | TNM staging | Lymph node metastasis | Venous invasion |
|---|---|---|---|---|---|
| Country | Western | NA | OR: 1.10, 95% CI: 0.50-2.46, P=0.810, n=1 | NA | NA |
| | Asia | OR: 1.04, 95% CI: 0.64-1.72, P=0.865, n=6 | OR: 1.10, 95% CI: 0.33-3.67, P=0.879, n=3 | OR: 1.01, 95% CI: 0.44-2.34, P=0.979, n=5 | OR: 0.78, 95% CI: 0.31-1.96, P=0.598, n=3 |
| Year of publication | ≤2010 | OR: 1.81, 95% CI: 0.84-3.89, P=0.128, n=2 | OR: 1.22, 95% CI: 0.59-2.50, P=0.595, n=2 | OR: 1.22, 95% CI: 0.59-2.50, P=0.595, n=2 | OR: 0.60, 95% CI: 0.17-2.08, P=0.416, n=1 |
| | >2010 | OR: 0.86, 95% CI: 0.48-1.51, P=0.589, n=4 | OR: 0.90, 95% CI: 0.17-4.90, P=0.907, n=2 | OR: 0.90, 95% CI: 0.17-4.90, P=0.907, n=2 | OR: 0.93, 95% CI: 0.20-4.27, P=0.928, n=2 |
| Sample size | ≤100 | OR: 1.15, 95% CI: 0.68-1.97, P=0.597, n=4 | OR: 0.72, 95% CI: 0.15-3.45, P=0.678, n=2 | OR: 0.50, 95% CI: 0.27-0.93, P=0.029, n=3 | OR: 0.78, 95% CI: 0.31-1.96, P=0.598, n=3 |
| | >100 | OR: 0.95, 95% CI: 0.25-3.64, P=0.945, n=2 | OR: 1.57, 95% CI: 0.87-2.85, P=0.136, n=2 | OR: 2.43, 95% CI: 1.45-4.07, P=0.001, n=2 | NA |

NA not available.

University School of Medicine, No. 1665 Kongjiang Road, Shanghai 200092, China. E-mail: Dongping1050@163.com

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