

Prognostic role of MUC-2 expression in patients with gastric carcinoma: a systematic review and meta-analysis

L.-N. HU, W. SU, X.-Z. GUO, T. XU, H. WANG, M.-H. YU

Department of Oncology, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, Pudong, Shanghai, China

Abstract. – OBJECTIVE: This meta-analysis aimed to assess the association of MUC-2 expression with clinicopathological parameters in gastric carcinoma (GC) patients.

MATERIALS AND METHODS: Clinical databases based on the study aim were searched in detail. The relative risk ratios (RRs) and associated 95% confidence intervals (95% CIs) were computed after eligible trials were included in the study.

RESULTS: Nineteen trials involving 2,363 GC patients were included in this meta-analysis. The expression of MUC-2 showed correlation with clinical stage (I/II vs. III/IV) (RR = 1.09, 95% CI: 1.00-1.18, $I^2 = 24\%$, $p = 0.194$), and lymphatic invasion (present vs. absent) (RR = 0.83, 95% CI: 0.72-0.95, $I^2 = 22.3\%$, $p = 0.252$). However, no significant association was identified between the MUC-2 expression and other clinicopathological parameters, including gender (male vs. female), tumor size (>5 vs. ≤ 5 cm), Lauren's classification (intestinal vs. diffuse), tumor differentiation (poorly vs. well and moderately), lymph node metastasis (present vs. absent), vascular invasion (present vs. absent), and 5-year survival (yes vs. no) of GC patients.

CONCLUSIONS: Our meta-analysis findings suggested that MUC-2 positive cases were correlated with lower tumor stage and lower rate of lymphatic invasion. Further clinical studies are warranted to confirm the role of MUC-2 in clinical practice.

Key Words:

Gastric carcinoma, MUC-2, Clinicopathological parameters, Systematic review, Meta-analysis.

Abbreviations

GC: gastric carcinoma; RRs: risk ratios; IM: intestinal metaplasia; CNKI: China National Knowledge Infrastructure; IHC: immunohistochemistry; ISH: in situ hybridization; RR: relative risk; TA-MUC: tumor associated MUC.

Introduction

Gastric carcinoma (GC) is a common tumor malignancy that accounted for the fifth highest incidence in the world and secondary to lung cancer in death rate¹. There are more than 300,000 newly diagnosed cases and 260,000 deaths recorded every year in China². The reasons for the poor prognosis of GC include high incidence of late-stage disease, high recurrence rate, high metastatic rate and abnormal gene expression. Although surgery and chemotherapy have made great progress, the mortality rate still remained very high². Therefore, new treatment strategies are urgently needed to improve the diagnosis and prognosis of GC.

Mucin is a high molecular weight glycoprotein that consists of a mucin core protein (apomucin) and O-linked oligosaccharides are synthesized by various epithelial tissues and encoded by MUC gene³. It forms a mucus gel on the surface of the epithelial tissue that assists in lubrication and protection of epithelial tissue⁴⁻⁶. MUC-2 is the main type of mucin present in intestinal mucosa and respiratory system and show no staining in the normal gastric epithelium. However, *de novo* expression occurs in intestinal metaplasia (IM) areas and malignant tumors⁷⁻⁹. MUC-2 expression is very commonly seen in the mucinous carcinoma of breast, colon and prostate¹⁰⁻¹². Many studies^{13,14} have reported that MUC-2 antigen is expressed in human GC and proved as an indicator for the clinicopathological significance of GC. However, the relationship between the expression of MUC-2 and the clinicopathological characteristics of GC still remained controversial. Due to small sample size, some studies might lead to inconsistency in the results. Therefore, a systematic review

and meta-analysis was conducted to resolve the relationship between MUC-2 expression and prognostic value and common clinicopathological parameters of GC.

Materials and Methods

This meta-analysis was conducted according to the guidelines established by the preferred reporting items for systematic reviews and meta-analyses ([Supplementary Material-PRISMA](#))¹⁵.

Search Strategy

Public databases such as PubMed, EMBASE, Cochrane Library, Wanfang and China National Knowledge Infrastructure (CNKI) were searched for relevant studies without any restriction to language from inception to July 2020. The main search terms included “mucin/MUC/MUC-2”, “gastric carcinoma/gastric cancer”, and “prognosis/prognostic”. The reference lists of the previously published review articles were manually searched to identify relevant articles if any.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) studies that detected MUC-2 expression by immunohistochemistry (IHC) or *in situ* hybridization (ISH) analysis in human GC tissues; (2) studies that evaluated the relationship between MUC-2 expression and clinicopathological parameters and/or GC prognosis; and (3) studies that provided sufficient data to evaluate the relative risk (RR), and their 95% confidence interval (CI). The exclusion criteria were as follows: (1) duplicate or irrelevant articles; (2) reviews, letters, and case reports; and (3) non-human studies.

Data Extraction and Quality Assessment

The data was independently extracted by 2 reviewers by using a predefined data extraction form, and any disagreements between them were resolved by discussion. The extracted data included first author name, publication year, country, mean age, gender, detection method, antibody used, the number of MUC-2 positive GC patients, the number of MUC-2 negative GC patients, and the time to follow-up. The Newcastle-Ottawa Scale (NOS)¹⁶ was used to evaluate the quality of included studies, and those studies with scores ≥ 6 were regarded as high quality.

Statistical Analysis

All data analyses were performed using Stata14.0 software (STATA Corporation, College Station, TX, USA). The RR and 95% CI of the included studies were considered as the combined effect size. After that, heterogeneity test was conducted. When $p \geq 0.05$ or $I^2 < 50\%$, then no apparent heterogeneity was present, and so fixed-effects model should be applied for a merger. When $p < 0.05$ or $I^2 \geq 50\%$, then high heterogeneity was observed, and so a random-effects model was applied. The robustness of the results was assessed by sensitivity analysis by removing each study at a time. Begg funnel plot and Egger test linear regression tests were used to detect publication bias of the literature included. $p < 0.05$ indicates obvious publication bias.

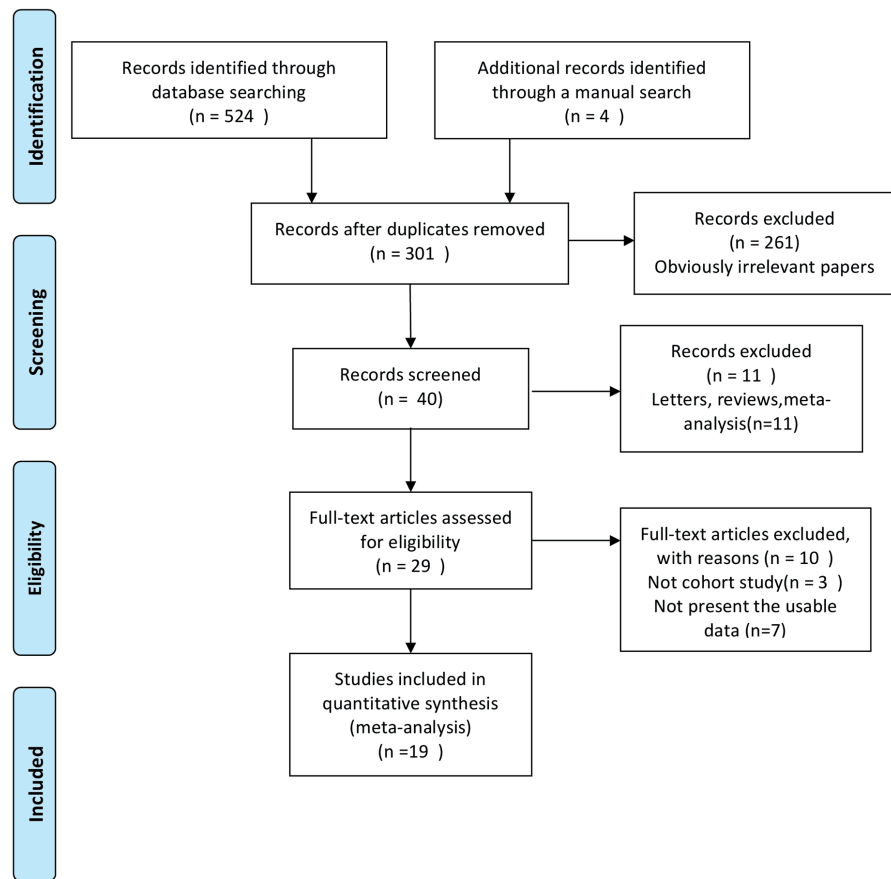
Results

Study Properties

After screening and assessment of potentially relevant studies, 301 were found as non-duplicated records and 19 articles entered into the meta-analysis^{4-6,13,14,17-30}. The study flowchart was shown in Figure 1. The characteristics of included articles were summarized in Table I. The included studies were published between 1998 and 2017. Of the 19 studies, 9 studies were conducted in China, 3 in Korea, 2 in Japan, 2 in Turkey, 1 in Germany, 1 in Italy, and 1 in Egypt. Thirteen studies were published in English, and 6 studies were published in Chinese. The expression of MUC-2 in GC patients was determined by IHC in all the included studies. The NOS score for each included study in this meta-analysis was ≥ 6 , indicating high quality of studies (Table II).

Meta-Analysis Outcome

The expression of MUC-2 showed correlation with clinical stage (I/II vs. III/IV) (RR = 1.09, 95% CI: 1.00-1.18, $I^2 = 24\%$, $p = 0.194$) (Figure 2A), and lymphatic invasion (present vs. absent) (RR = 0.83, 95% CI: 0.72-0.95, $I^2 = 22.3\%$, $p = 0.252$) (Figure 2B). However, no significant association was identified between the expression of MUC-2 and other clinicopathological parameters, including gender (male vs. female) (RR = 0.94, 95% CI: 0.87-1.02, $I^2 = 23.8\%$, $p = 0.185$) (Figure 3A), tumor size (>5 vs. ≤ 5 cm) (RR = 1.01, 95% CI: 0.81-1.27, $I^2 = 0\%$, $p = 0.551$) (Figure 3B), Lauren's classification (intestinal vs. diffuse) (RR = 0.98, 95% CI: 0.80-1.19, $I^2 = 71.5\%$, $p < 0.001$)

Figure 1. Flow diagram of study inclusion.**Table I.** Characteristics of studies included in this meta-analysis.

Authors/ year of publication	Country	Mean age (Y)	Male (%)	Detection method	Antibody used	GC patients		Follow- up
						MUC-2(+)	MUC-2(-)	
Baldus/1998 ¹³	Germany	61.7	53.5	IHC	4F1	49	79	120M
Wang/1999 ¹⁷	China	54.6	73.9	IHC	CCP58	31	15	NA
Lee/2001 ¹⁴	Korea	NA	67.7	IHC	NCL-MUC-2	82	218	60M
Akyurek/2002 ⁵	Turkey	NA	65.7	IHC	CCP58	57	86	80M
Tanaka/2003 ¹⁸	Japan	63.1	66.9	IHC	CCP58	83	126	60M
Wang/2003 ¹⁹	China	54.6	73.9	IHC	CCP58	31	15	NA
Zhang/2004 ⁶	China	52.1	68.1	IHC	NA	78	16	NA
Barresi/2006 ⁴	Italy	69.4	57.5	IHC	CCP58	20	20	NA
Lee/2007 ²⁰	Korea	NA	67.3	IHC	MS-1037-P1	53	45	NA
Wang/2007 ²¹	China	55.6	75	IHC	PMH1	20	48	NA
Zhao/2009 ²²	China	51.5	55	IHC	M53	32	27	100M
Ilhan/2010 ²³	Turkey	NA	78.2	IHC	MS-1037-P	233	24	NA
Khattab/2010 ²⁴	Egypt	54.7	70.6	IHC	NCL-MUC2	22	6	NA
Xiao/2012 ²⁵	China	66.7	30.6	IHC	NA	131	300	140M
Chen/2014 ²⁶	China	62	75	IHC	M53	5	31	NA
Shiratsu/2014 ²⁷	Japan	69.9	77.2	IHC	CCP58	22	79	60M
Yang/2014 ²⁸	China	60.1	67.3	IHC	NA	34	21	60M
Pyo/2015 ²⁹	Korea	NA	68.3	IHC	NA	58	109	NA
Zhang/2017 ³⁰	China	61.2	59.6	IHC	NA	21	36	NA

GC: gastric carcinoma; MUC: mucin; IHC: immunohistochemistry; Y: years; M: months; NA: Not available.

Table II. Quality assessment of included studies by NOS.

Author	Year	Selection	Comparability	Outcome
Baldus	1998	★★★	★★	★★★
Wang	1999	★★★	★★	★★
Lee	2001	★★★	★★	★★★
Akyurek	2002	★★★	★★	★★★
Tanaka	2003	★★★	★★	★★★
Wang	2003	★★★	★★	★★
Zhang	2004	★★★	★★	★★
Barresi	2006	★★★	★★	★★
Lee	2007	★★★	★★	★★
Wang	2007	★★★	★★	★★
Zhao	2009	★★★	★★	★★★
Ilhan	2010	★★★	★★	★★
Khattab	2010	★★★	★★	★★
Xiao	2012	★★★	★★	★★★
Chen	2014	★★★	★★	★★
Shiratsu	2014	★★★	★★	★★★
Yang	2014	★★★	★★	★★★
Pyo	2015	★★★	★★	★★
Zhang	2017	★★★	★★	★★

(Figure 3C), tumor differentiation (poorly vs. well and moderately) (RR = 0.81, 95% CI: 0.57-1.14, $I^2 = 85.9\%$, $p < 0.001$) (Figure 3D), lymph node metastasis (present vs. absent) (RR = 0.94, 95% CI: 0.78-1.13, $I^2 = 66.9\%$, $p < 0.001$) (Figure 3E), vascular invasion (present vs. absent) (RR = 0.82, 95% CI: 0.46-1.47, $I^2 = 66.7\%$, $p = 0.029$) (Figure 3F), and 5-year survival (yes vs. no) (RR = 1.07, 95% CI: 0.83-1.36, $I^2 = 75.3\%$, $p = 0.007$) of GC (Figure 3G).

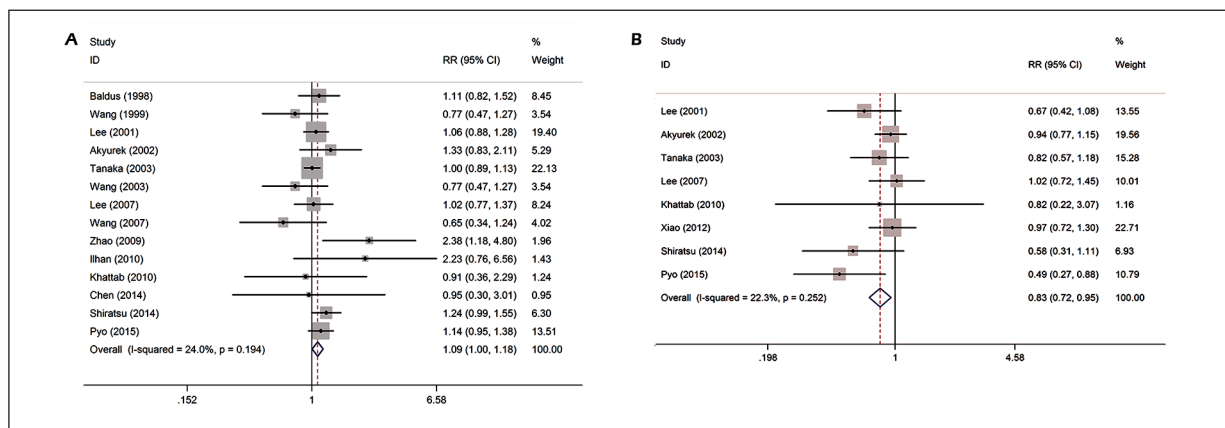
Sensitivity Analysis

A sensitivity analysis of pooled RRs was performed by removing each study at a time to check

the influence of individual study on the results. The corresponding pooled RRs are consistent, indicating stable and robust results in this meta-analysis (Figure 4).

Publication Bias

Begg's funnel plot and Egger's linear regression test was performed to assess publication bias. No significant bias was found across the studies with regard to gender (Begg test, $p = 0.685$; Egger test, $p = 0.972$) (Figure 5A), clinical stage (Begg test, $p = 1.000$; Egger test, $p = 0.691$) (Figure 5B), and lymph node metastasis (Begg test, $p = 0.913$; Egger test, $p = 0.571$) (Figure 5C).

**Figure 2.** Forest plots of clinical stage and lymphatic invasion in GC patients. **A**, Clinical stage; and **B**, Lymphatic invasion.

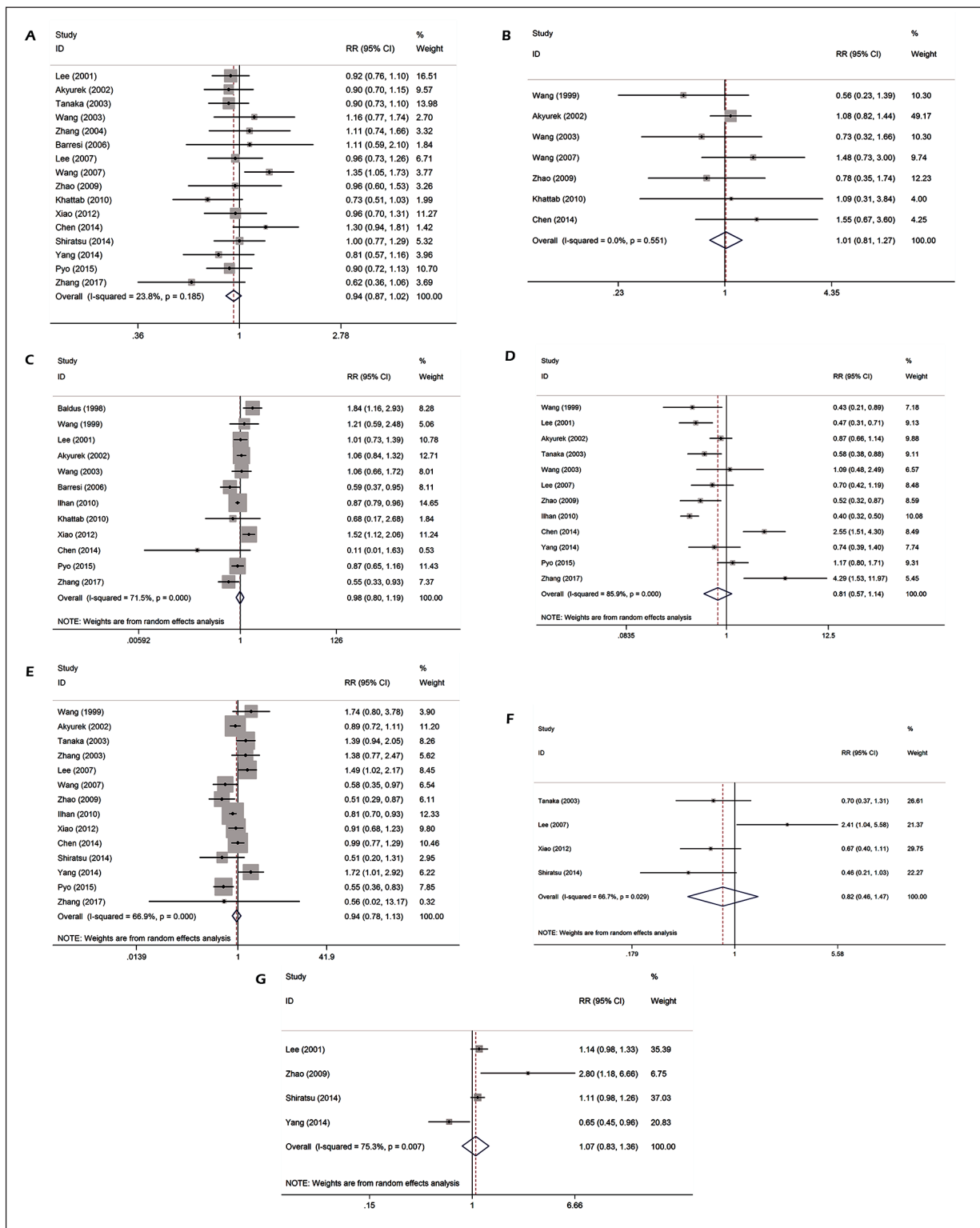


Figure 3. Forest plots of other clinicopathological parameters in GC patients. **A**, Gender; **B**, Tumor size; **C**, Lauren's classification; **D**, Tumor differentiation; **E**, Lymph node metastasis; **F**, Vascular invasion; and **G**, 5-year survival rate.

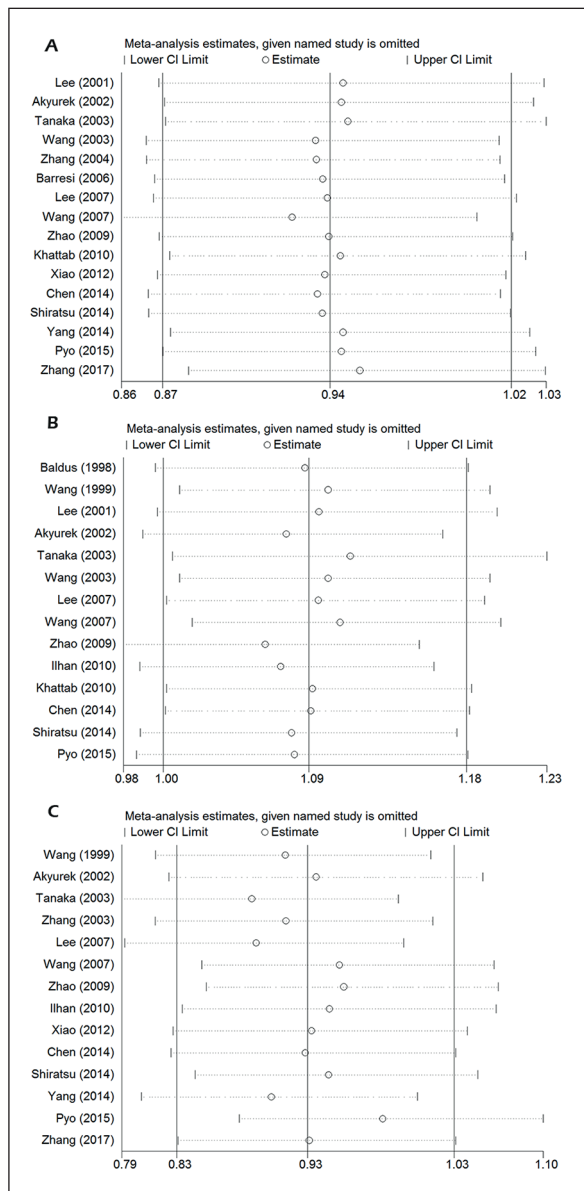


Figure 4. Sensitivity analysis examining the influence of individual studies on pooled results. **A**, Gender; **B**, Clinical stage; and **C**, Lymph node metastasis.

Discussion

According to laboratory results, abnormal over-expression, mislocalization and glycan truncation of tumor-associated MUC (TA-MUC) are regarded as common changes in various types of epithelial cancers¹⁰. The complexity of TA-MUC structure and function emphasizes its key role in cancer pathogenesis and development^{31,32}. MUC-2 is a gel-forming mucin and is shown to be highly expressed in normal intestinal tissues but not in

normal gastric mucosa. However, when metastasis of gastric mucosa occurs, then it is re-expressed in the stomach⁷. In the present study, the correlation between MUC-2 expression and clinicopathological parameters of GC patients was investigated using meta-analysis. A total of 19 eligible studies with 2,363 cases were included to conduct this meta-analysis, wherein the results showed that MUC-2 positive cases were correlated with lower tumor stage and lower rate of lymphatic invasion. However, no significant association was identified

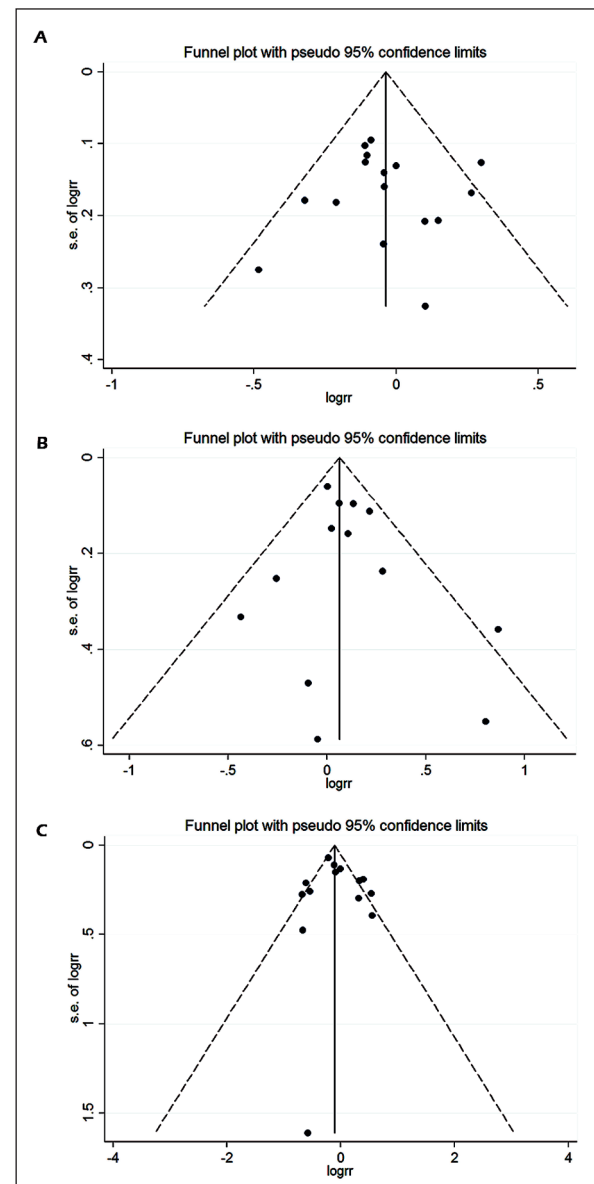


Figure 5. Funnel plots for assessing publication bias. Each point represents a separate study for the indicated association. **A**, Gender; **B**, Clinical stage; and **C**, Lymph node metastasis.

between the expression of MUC-2 and gender, tumor size, Lauren's classification, tumor differentiation, lymph node metastasis, vascular invasion, and 5-year survival rate.

The prognostic role of MUC-2 expression in GC patients has been investigated by several meta-analyses studies previously²⁹. To the best of our knowledge, this is the largest meta-analysis study to investigate the association of expression of MUC-2 with clinicopathological parameters of GC patients, wherein 2,363 GC patients from 19 studies were included. Recently, Pyo et al²⁹ have conducted a comprehensive meta-analysis on the association of MUC-2 expression and GC. In the present study, more eligible studies with more GC patients than the study conducted by Pyo et al²⁹ were included and performed a detailed analysis with respect to gender, tumor size, lymphatic invasion, vascular invasion, and 5-year survival rate. The results revealed that patients positive to MUC-2 showed correlation with lower tumor stage and higher rate of lymphatic invasion.

MUC-2 is an intestinal mucin that is not expressed in normal gastric mucosa. However, *de novo* expression has been observed in the tumors. Barresi et al⁴ have found that the expression rate of MUC-2 was significantly higher in diffuse carcinoma, especially in mucinous carcinoma, and this was consistent with the study conducted by Zhang et al⁶. However, Baldus et al¹³ have reported that MUC-2 was expressed more frequently in intestinal adenocarcinoma (tubular and papillary) than diffuse (signet ring cell) type of cancers. In the present study, no significant difference was observed in MUC-2 expression between intestinal and diffuse type carcinomas, and this was in agreement with Akyurek et al⁵. This might be due to multiple factors such as the composition of tumor types, differences in countries, differences in the number of cases analyzed, etc., as well as the heterogeneity associated with MUC-2 positive.

However, there are some limitations in this meta-analysis that need to be addressed. Firstly, the 5-year survival rate was extracted from Kaplan Meier survival curve due to lack of raw data from some studies. Secondly, the threshold for MUC-2 expression was different in the studies included, which might in turn lead to heterogeneity. Thirdly, there are obvious heterogeneities in Lauren classification, tumor differentiation, lymph node metastasis, vascular invasion and 5-year survival rate analysis, reducing the reliability of the results. Fourthly, some studies did not specify

the duration of follow-up period. Finally, most of the studies in this meta-analysis are retrospective in nature, leading to selection bias.

Conclusions

Despite the above-mentioned limitations, our meta-analysis results indicated that MUC-2 positive patients showed correlation with lower tumor stage and lower rate of lymphatic invasion. However, prospective and well-designed clinical trials using standardized methods, with long-term follow up, are warranted to confirm our results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval and Consent to Participate

Institutional Review Board approval was not required because this article is a meta-analysis. The data comes from published articles and does not require ethical approval.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

LN. H., W. S. carried out the studies, participated in collecting data, and drafted the manuscript. XZ. G., T. X. performed the statistical analysis and participated in its design. H. W., MH. Y. participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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