Review Article

MUC1 Immunohistochemical Expression as a Prognostic Factor in Gastric Cancer: Meta-Analysis

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MUC1, a member of the mucin family, is expressed in tumors of various human organs and may function as an antiadhesion molecule that inhibits cell-to-cell adhesion, inducing tumor metastasis, and served as a potential biomarker of tumor progression in early gastric cancer. However, its prognostic significance in gastric cancer is still in dispute. We performed a meta-analysis to evaluate the relationship between MUC1 expression and prognosis of gastric cancer. A total of ten eligible studies with 834 cases and 548 controls were included. MUC1 positive cases were highly positive in intestinal-type carcinomas (OR = 1.76, 95% CI: 1.27–2.44, $P = 0.0008$ fixed-effect), higher rate of vascular invasion (OR = 1.64, 95% CI: 1.13–2.39, $P = 0.009$ fixed-effect), and lymph node metastasis (OR = 2.10, 95% CI: 1.20–3.67, $P = 0.01$ random-effect), as well as lower 5-year survival rate (HR = 0.27, 95% CI: 0.11–0.66, $P = 0.004$ random-effect). However, the presence of MUC1 was not associated with gender, tumor size, histologic differentiation, and clinical stage. In summary, MUC1 is a prognostic factor in gastric cancer, which acts as a marker of poor outcome in patients with gastric cancer. Further clinical studies are needed to confirm the role of MUC1 in clinical practice.

1. Introduction

Despite overall decline in gastric carcinoma (GC) prevalence, it is still the second most frequently malignant tumor in Eastern Asia, particularly in China [1, 2]. Patients with gastric cancer have excellent survival if there is no regional lymph node involvement [3]. Unfortunately, gastric cancer is difficult to be diagnosed at an early stage. As a result, there is great interest in finding a prognostic marker for this potentially curable group of patients.

Mucins are a group of high molecular weight glycoproteins, and nine apomucins (MUC1-8 and MUC5B) have been identified to date. MUC1 is a membrane-bound mucin, which plays an important role in the impairment of cell-cell adhesion, the immune response, and/or altered intracellular signaling, and is involved in the development and progression of gastric cancer [4]. A number of reports have demonstrated that MUCl antigen is expressed in human gastric cancer, and it has been shown to be an indicator of clinicopathological significance of gastric carcinomas [5–8]. However, the relation between MUC1 expression and clinicopathological features remains controversial. So far several studies have demonstrated that MUC1 positive expression in gastric cancer was determined to be statistically significant, with worse differentiation and higher rate of lymph node metastasis [9–11]. However, Kocer and colleagues showed that there was no association between MUC1 expression and lymph node metastasis of gastric carcinoma [12]. Therefore, because of the limits of the single study and insufficient samples, we conducted a meta-analysis to investigate the correlation between MUC1 and prognosis of GC and to consider MUC1 expression as a novel prognostic biomarker for survival in GC patients.

2. Methods

2.1. Literature Search Strategy. PRISMA statement is performed in this meta-analysis [19]. We carefully searched the relevant studies (published before 10 November 2015) that investigated the prognostic value of MUC1 expression in gastric cancer from Web of Science, Embase, PubMed, MEDLINE, and Cochrane Library. The language of articles was limited to English. Studies were selected using following key terms: (MUC OR MUC-1 OR MUC1) AND (Gastric carcinoma OR GC OR Gastric cancer) AND (prognosis OR prognostic OR outcome OR mortality OR survival). The references of manuscript were also examined to confirm potential studies. XTW and FBK conducted the search and assessed the eligibility of studies independently.

2.2. Study Selection. Inclusion criteria were as follows. (1) The study must explore the association between MUC1 and human gastric cancer. (2) The species must be human. (3) Tumors were pathologically verified. (4) Articles provided sufficient data to evaluate odds ratio (OR), hazard ratio (HR), and their 95% confidence interval (CI). (5) Articles focused on relationship between MUC1 and GC clinicopathological character. (6) MUC1 expression was assessed by immunohistochemistry (IHC). (7) MUC1 expression was estimated in GC samples. (8) Not any form of preoperative neoadjuvant therapy was received.

Exclusion criteria were as follows: (1) publication that was of nonresearch articles; (2) data duplication or missing important information for this meta-analysis; and (3) studies that were based on animal or human cell lines. If we needed additional information and data which cannot be found in article, we will email the authors for further information.

2.3. Data Acquisition and Quality Assessment. Relevant characteristics and outcome data were collected by two independent reviewers. The main characteristics of articles were listed as follows: (1) first author; (2) year of publication; (3) country; and (4) median follow-up. The relevant clinical data of studies included (1) patients' number; (2) gender (male/female); (3) age (years); (4) pathological pattern; (5) histologic origin; (6) antibody source; (7) dilution; (8) evaluation method of MUC1 expression level; and (9) low versus high MUC1. HR of 5-year survival rate was first calculated from multivariable analysis or Kaplan-Meier survival curves in article. Any disagreement was resolved by discussion. The quality of each of the available studies in our analysis was assessed by Newcastle-Ottawa Scale (NOS).

2.4. Statistical Analysis. OR with 95% CI was performed to combine the pooled data. Heterogeneity was tested by the Q test which was considered statistically significant when P values < 0.01 and inconsistency index I^2 statistic which takes values between 0% and 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%–50\%$, medium heterogeneity; $I^2 = 50\%–75\%$, high heterogeneity; $I^2 = 75\%–100\%$, resp., heterogeneity). According to the heterogeneity of studies, it is considered to be significant when $P < 0.01$ or $I^2 > 50\%$; the random-effects model (based on DerSimonian and Laird method) or fixed-effects model (based on Mantel-Haenszel method) was used for meta-analysis [20]. The data on the predictive ability of MUC1 overexpression for 5-year survival rate were combined across studies using fixed- and random-effect models for the synthesis of hazard ratio (HR). The HR of 5-year survival rate was calculated from the reported data directly by number of events within 5 years after surgery was used or data reading from Kaplan-Meier survival curve. The funnel plot was examined to explore the possibility of publication bias [21].

Kaplan-Meier curves were read by Engauge Digitizer version 2.11. $P < 0.05$ was considered as statistically significant publication bias. All of the calculations were performed by Review Manager 5.2 (RevMan version 5.2 (Copenhagen); the Nordic Cochrane Centre, the Cochrane Collaboration).

3. Results

3.1. Eligible Studies. As shown in Figure 1, our initial search yielded 238 studies. According to the inclusion and exclusion criteria, 10 papers [9–18] were recruited into our meta-analysis. Studies were carried out in China, Turkey, Korea, Japan, and Taiwan. Table 1 presents the study characteristics for the included trials.

3.2. High MUC1 Expression and Prognosis of GC. The putative MUC1 was not associated with gender (pooled OR = 0.59, 95% CI: 0.96–1.75, $P = 0.09$ fixed-effect), tumor size (pooled OR = 1.29, 95% CI: 0.21–1.65, $P = 0.32$ random-effect), tumor differentiation (OR = 1.58, 95% CI: 1.13–2.21, $P = 0.007$ fixed-effect), and clinical stage (OR = 0.80, 95% CI: 0.39–1.67, $P = 0.59$ random-effect) (Figures 2(a), 2(c), 2(d), and 2(e)). However, MUC1 expression in gastric cancer was associated with biologically aggressive phenotypes such as vascular invasion (OR = 1.64, 95% CI: 1.13–2.39, $P = 0.009$ fixed-effect) and lymph node metastasis (OR = 2.10, 95% CI: 1.20–3.67, $P = 0.01$ random-effect) (Figures 2(f) and 2(g)). In accordance with the Lauren classification, the expression rate of MUC1 in intestinal-type carcinomas was significantly higher than that in diffuse-type carcinomas (pooled OR = 1.76, 95% CI: 1.27–2.44, $P = 0.0008$ fixed-effect) (Figure 2(b)). Analysis of these data showed that MUC1 was highly correlated with lower 5-year survival rate (pooled OR = 0.27, 95% CI: 0.11–0.66, $P = 0.004$ random-effect) (Figure 2(h)).

3.3. Publication Bias. The interpretability of publication bias was assessed by using the inverted funnel plot approach recommended for meta-analyses [22]. As shown in Figure 3, no publication bias was detected in all comparisons.

4. Discussion

Although the risk of GC has dropped off in recent years, it remains the fifth most common malignant neoplasm around the world [23]. Some clinical studies revealed that the prognosis of GC patients depends on the tumor histological
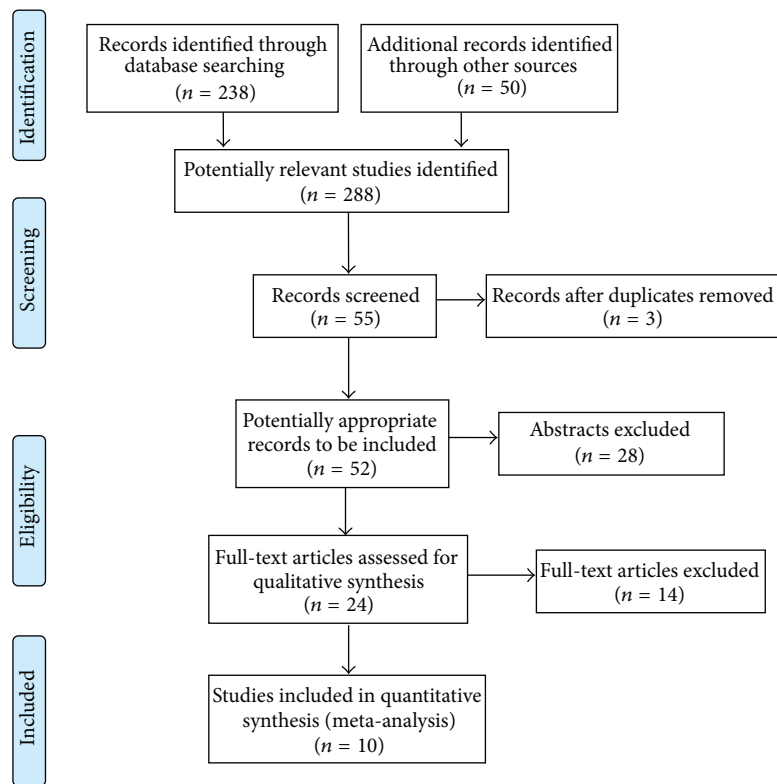
Figure 1: Flowchart of the search process.

Table 1: Study characteristics for the included studies.

Author (year, country)	Samples	Median age (range)	M/F	Adequacy of evaluating MUC1 expression	Study period	Median follow-up (months)	NOS score
Akyürek et al. [13] (2002, Germany)	143	NS	94/49	Yes	NS	30 (2–80)	9
Barresi et al. [14] (2006, Italy)	40	69.4 (54–77)	23/17	Yes	NS	NS	9
Ilhan et al. [9] (2010, Turkey)	257	NS	201/56	Yes	2000–2007	NS	8
Kocer et al. [12] (2004, Turkey)	44	59.7 (27–77)	31/13	Yes	1996–2001	25 (1–79)	7
Lee et al. [11] (2001, Korea)	59	NS	56/17	Yes	1995-1995	42 (1–60)	9
Ohno et al. [15] (2006, Japan)	202	63	142/60	Yes	1993–2000	NS	9
Reis et al. [16] (1998, UK)	180	NS	105/75	Yes	NS	NS	8
Wang et al. [17] (2003, China)	76	65 (32–84)	52/24	Yes	1996–1998	30 (1–58)	7
Wang and Fang [18] (2003, China)	46	54.6 (30–70)	34/12	Yes	NS	NS	8
Zhang et al. [10] (2004, China)	94	52.1 (25–75)	64/30	Yes	1989–2000	NS	8

NA: not available, M/F: male/female, and NOS: Newcastle-Ottawa Scale.

Study or subgroup	MUC1 positive		MUC1 negative		Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total			
Akyürek 2002	59	82	35	61	14.9%	1.91 [0.95, 3.84]	
Barresi et al. 2006	17	28	6	12	4.4%	1.55 [0.40, 6.03]	
Kocer et al. 2004	19	28	12	16	6.5%	0.70 [0.18, 2.80]	
Lee et al. 2001	56	73	147	227	22.0%	1.79 [0.98, 3.29]	
Ohno et al. 2006	65	90	77	112	25.2%	1.18 [0.64, 2.18]	
Wang et al. 2003	29	49	20	27	13.9%	0.51 [0.18, 1.42]	
Wang and Fang 2003	23	29	11	17	3.8%	2.09 [0.55, 7.99]	
Zhang et al. 2004	51	77	13	17	9.5%	0.60 [0.18, 2.04]	
Total (95% CI)		456		489	100.0%	1.29 [0.96, 1.75]	
Total events	319		321				

Heterogeneity: $\chi^2 = 8.34$, df = 7 ($P = 0.30$); $I^2 = 16\%$
Test for overall effect: $Z = 1.69$ ($P = 0.09$)

(a)

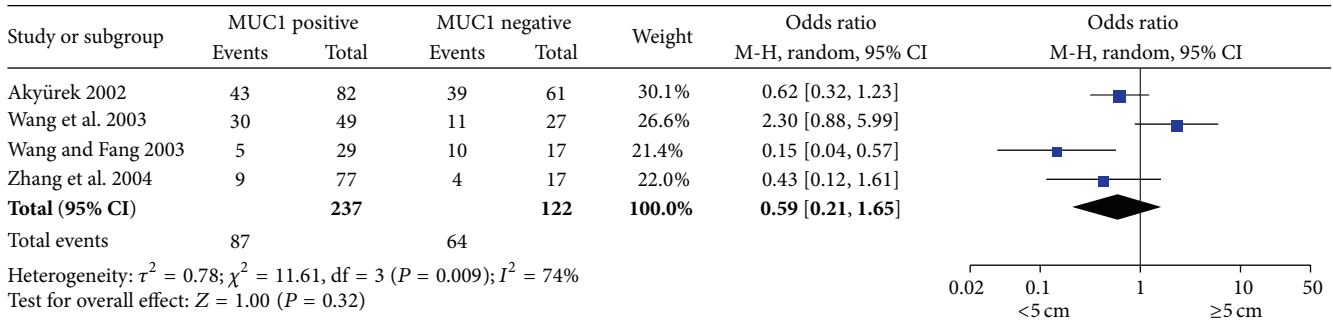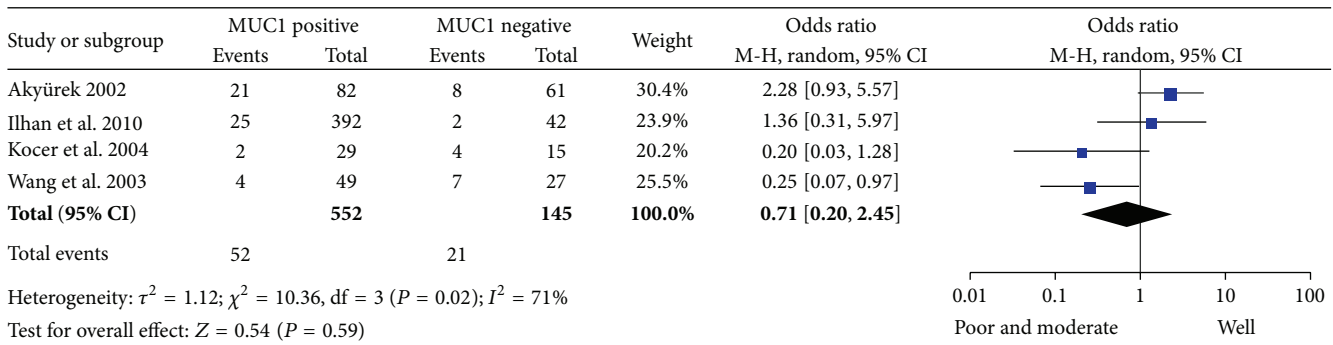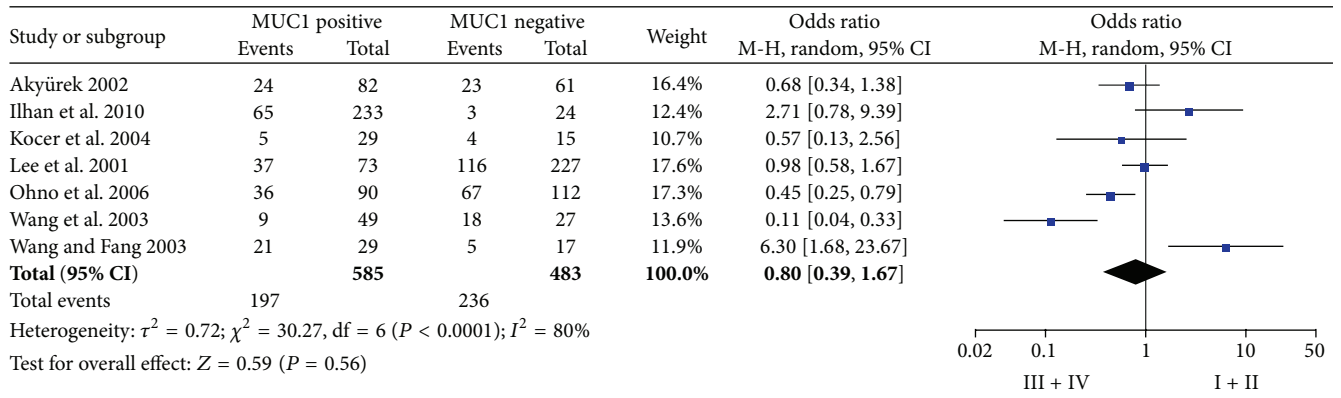| Study or subgroup	MUC1 positive		MUC1 negative		Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total			
Akyürek 2002	62	82	35	61	18.4%	2.30 [1.13, 4.71]	
Barresi et al. 2006	23	28	4	12	1.9%	9.20 [1.97, 42.97]	
Kocer et al. 2004	10	29	6	15	9.7%	0.79 [0.22, 2.861]	
Lee et al. 2001	37	73	76	227	34.3%	2.04 [1.20, 3.49]	
Reis et al. 1998	73	144	17	36	25.2%	1.15 [0.55, 2.39]	
Wang and Fang 2003	13	29	8	17	10.5%	0.91 [0.28, 3.04]	
Total (95% CI)		385		368	100.0%	**1.76 [1.27, 2.44]**	
Total events	218		146				

Heterogeneity: $\chi^2 = 9.20$, df = 5 ($P = 0.10$); $I^2 = 46\%$
Test for overall effect: $Z = 3.37$ ($P = 0.0008$)

(b)

Study or subgroup	MUC1 positive		MUC1 negative		Weight	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
	Events	Total	Events	Total			
Akyürek 2002	43	82	39	61	30.1%	0.62 [0.32, 1.23]	
Wang et al. 2003	30	49	11	27	26.6%	2.30 [0.88, 5.99]	
Wang and Fang 2003	5	29	10	17	21.4%	0.15 [0.04, 0.57]	
Zhang et al. 2004	9	77	4	17	22.0%	0.43 [0.12, 1.61]	
Total (95% CI)		237		122	100.0%	**0.59 [0.21, 1.65]**	
Total events	87		64				

Heterogeneity: $\tau^2 = 0.78$; $\chi^2 = 11.61$, df = 3 ($P = 0.009$); $I^2 = 74\%$
Test for overall effect: $Z = 1.00$ ($P = 0.32$)

(c)

Study or subgroup	MUC1 positive		MUC1 negative		Weight	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
	Events	Total	Events	Total			
Akyürek 2002	21	82	8	61	30.4%	2.28 [0.93, 5.57]	
Ilhan et al. 2010	25	392	2	42	23.9%	1.36 [0.31, 5.97]	
Kocer et al. 2004	2	29	4	15	20.2%	0.20 [0.03, 1.28]	
Wang et al. 2003	4	49	7	27	25.5%	0.25 [0.07, 0.97]	
Total (95% CI)		552		145	100.0%	**0.71 [0.20, 2.45]**	
Total events	52		21				

Heterogeneity: $\tau^2 = 1.12$; $\chi^2 = 10.36$, df = 3 ($P = 0.02$); $I^2 = 71\%$
Test for overall effect: $Z = 0.54$ ($P = 0.59$)

(d)

FIGURE 2: Continued.

Study or subgroup	MUC1 positive Events	MUC1 positive Total	MUC1 negative Events	MUC1 negative Total	Weight	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
Akyürek 2002	24	82	23	61	16.4%	0.68 [0.34, 1.38]	
Ilhan et al. 2010	65	233	3	24	12.4%	2.71 [0.78, 9.39]	
Kocer et al. 2004	5	29	4	15	10.7%	0.57 [0.13, 2.56]	
Lee et al. 2001	37	73	116	227	17.6%	0.98 [0.58, 1.67]	
Ohno et al. 2006	36	90	67	112	17.3%	0.45 [0.25, 0.79]	
Wang et al. 2003	9	49	18	27	13.6%	0.11 [0.04, 0.33]	
Wang and Fang 2003	21	29	5	17	11.9%	6.30 [1.68, 23.67]	
Total (95% CI)		**585**		**483**	**100.0%**	**0.80 [0.39, 1.67]**	
Total events	197		236				

Heterogeneity: $\tau^2 = 0.72$; $\chi^2 = 30.27$, df = 6 ($P < 0.0001$); $I^2 = 80\%$
Test for overall effect: $Z = 0.59$ ($P = 0.56$)

0.02 0.1 1 10 50
III + IV   I + II

(e)

Study or subgroup	MUC1 positive Events	MUC1 positive Total	MUC1 negative Events	MUC1 negative Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Akyürek 2002	61	82	45	61	30.6%	1.03 [0.49, 2.20]	
Kocer et al. 2004	9	28	2	15	4.1%	3.08 [0.57, 16.63]	
Ohno et al. 2006	55	90	54	112	43.3%	1.69 [0.96, 2.96]	
Reis et al. 1998	83	144	14	36	22.0%	2.14 [1.01, 4.51]	
Total (95% CI)		**344**		**224**	**100.0%**	**1.64 [1.13, 2.39]**	
Total events	208		115				

Heterogeneity: $\chi^2 = 2.47$, df = 3 ($P = 0.48$); $I^2 = 0\%$
Test for overall effect: $Z = 2.61$ ($P = 0.009$)

0.02 0.1 1 10 50
Absent   Present

(f)

Study or subgroup	MUC1 positive Events	MUC1 positive Total	MUC1 negative Events	MUC1 negative Total	Weight	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
Akyürek 2002	62	82	40	61	14.2%	1.63 [0.78, 3.38]	
Barresi et al. 2006	20	28	7	12	8.6%	1.79 [0.44, 7.32]	
Ilhan et al. 2010	171	233	23	24	5.4%	0.12 [0.02, 0.91]	
Kocer et al. 2004	23	29	12	15	7.7%	0.96 [0.20, 4.52]	
Lee et al. 2001	30	73	54	227	15.8%	2.24 [1.28, 3.90]	
Ohno et al. 2006	69	90	72	112	15.2%	1.83 [0.98, 3.40]	
Reis et al. 1998	131	144	25	36	12.5%	4.43 [1.79, 11.01]	
Wang et al. 2003	45	49	10	27	9.4%	19.13 [5.28, 69.25]	
Zhang et al. 2004	46	77	8	17	11.2%	1.67 [0.58, 4.80]	
Total (95% CI)		**805**		**531**	**100.0%**	**2.10 [1.20, 3.67]**	
Total events	597		251				

Heterogeneity: $\tau^2 = 0.44$; $\chi^2 = 23.91$, df = 8 ($P = 0.002$); $I^2 = 67\%$
Test for overall effect: $Z = 2.59$ ($P = 0.010$)

0.01 0.1 1 10 100
Absent   Present

(g)

Study or subgroup	MUC1 positive Events	MUC1 positive Total	MUC1 negative Events	MUC1 negative Total	Weight	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
Lee et al. 2001	43	73	169	227	28.0%	0.49 [0.28, 0.86]	
Ohno et al. 2006	33	90	79	112	27.6%	0.24 [0.13, 0.44]	
Reis et al. 1998	51	144	16	36	25.7%	0.69 [0.33, 1.44]	
Wang et al. 2003	9	49	23	27	18.8%	0.04 [0.01, 0.14]	
Total (95% CI)		**356**		**402**	**100.0%**	**0.27 [0.11, 0.66]**	
Total events	136		287				

Heterogeneity: $\tau^2 = 0.63$; $\chi^2 = 17.36$, df = 3 ($P = 0.0006$); $I^2 = 83\%$
Test for overall effect: $Z = 2.90$ ($P = 0.004$)
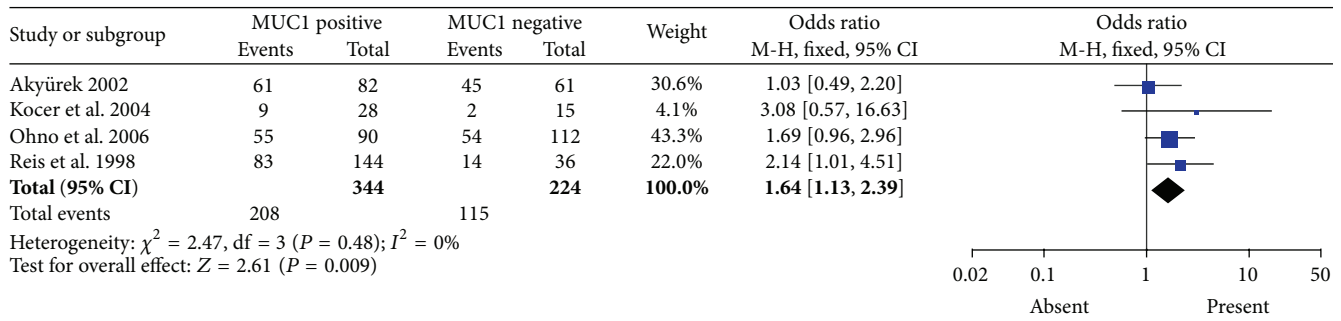
0.01 0.1 1 10 100
Lower 5-year   Higher 5-year
survival   survival
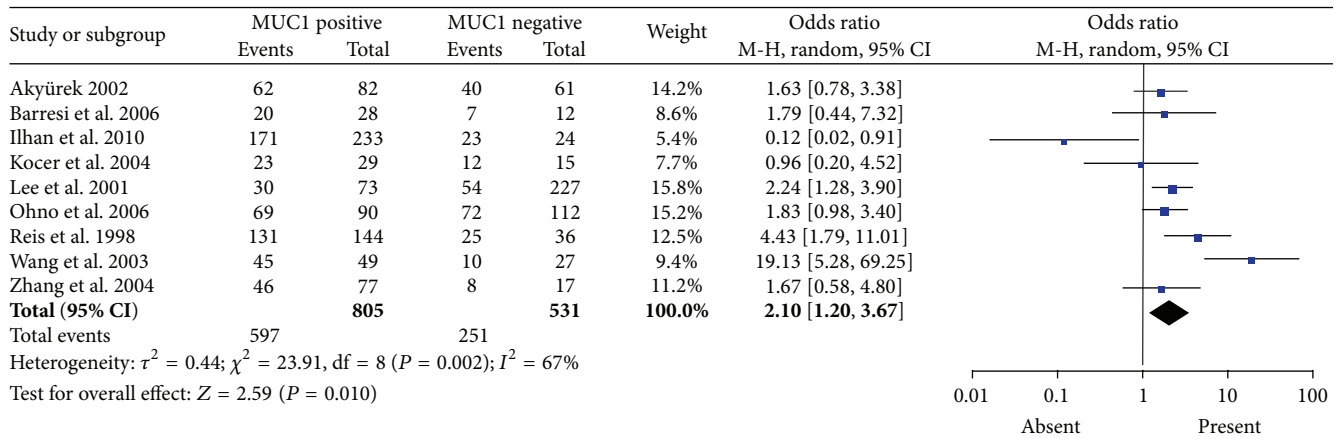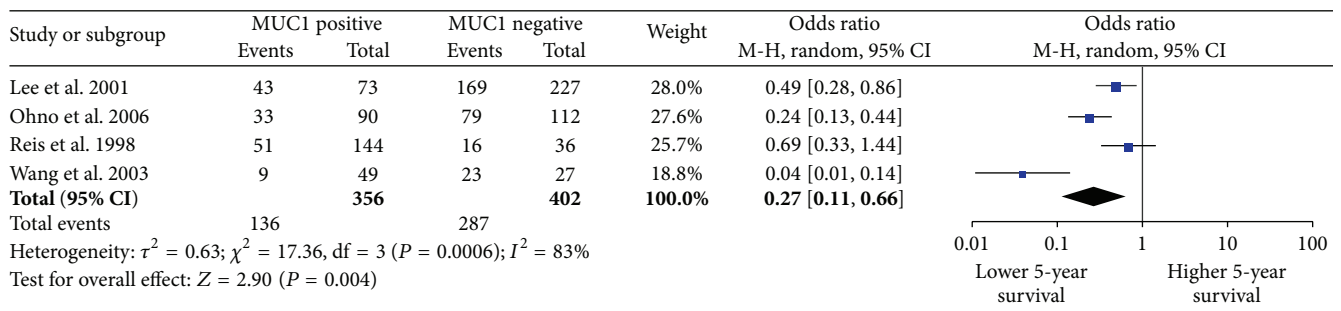
(h)

FIGURE 2: Forest plot of OR was assessed for association between MUC1 and clinical pathologic features, such as gender (a), Lauren classification (b), tumor size (c), tumor differentiation (d), clinical stage (e), vascular invasion (f), lymph node metastasis (g), and 5-year survival rate (h).
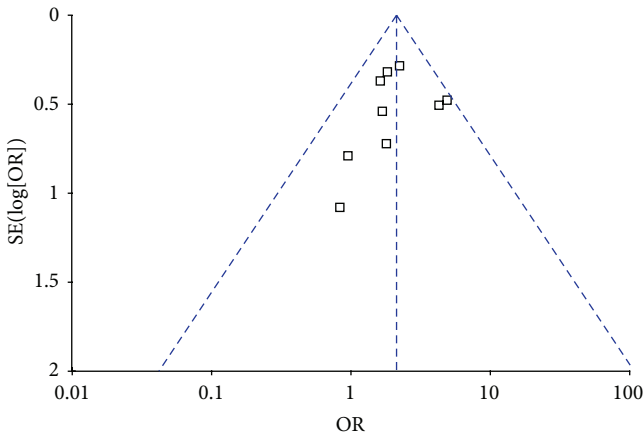
FIGURE 3: Funnel plot of studies to detect publication bias.

morphology and tumor-node-metastasis (TNM) classification [24–26]. However, there are not any GC-specific markers to predict the gastric cancer metastasis and survival [27]. Therefore, it is essential to detect an established biomarker to investigate the progression of gastric carcinomas and improve treatment of GC patients.

There is some indication that MUC1 expression is involved in tumor progression as well. MUC1, an epithelial mucin glycoprotein, is highly expressed in lactating mammary glands [28]. Some researches have shown that alterations of mucin expression take place in gastric carcinomas [29]. Under pathological conditions, such as colon adenocarcinoma and pancreas adenocarcinoma or stomach adenocarcinoma, MUC1 would change its expression fashion and rate [8]. In previous reports, gastric carcinomas were found to contain a higher level of MUC1 mucin expression than normal gastric mucosa [18, 30, 31]. Lee et al. [11] found that MUC1 positive Korean patients suffering from gastric carcinoma showed significantly poorer survival than those negative for MUC1. Utsunomiya et al. and Baldus and colleagues also found that MUC1 expression was associated with a poor outcome, irrespective of its glycosylation status, as assessed by the use of monoclonal antibodies recognizing only core peptides [32, 33]. They indicated that MUC1 was an independent prognostic indicator for gastric carcinoma. It can be concluded that MUC1 expression was a precursor of gastric carcinoma and served as a reliable tumor marker in gastric cancer.

However, other studies showed that no significant correlation could be determined between MUC1 and clinicopathological parameters [12, 17]. These researches suggested that MUC1 did not affect the progression of human gastric cancer. These conflicting results were likely due to small sample size of the study.

Meta-analysis was originally developed to combine the results of randomized controlled trails, and recently this approach has been applied successfully for identification of prognostic indicators in patients with malignant diseases [34, 35]. This meta-analysis is the first study to systematically estimate MUC1 expression and its relationship with the

patients' clinicopathological characteristics. Statistical significance was reached that MUC1 overexpression, as detected by immunohistochemistry, was significantly associated with vascular invasion, lymph node metastasis, and 5-year survival. We observed a correlation of MUC1 positivity with higher rate of vascular invasion and lymph node metastasis. These findings indicated that MUC1 positive might be related to invasiveness of gastric carcinoma cells, which is in accordance with the experimental results that MUC1 positive tumors were associated with synchronous liver metastasis and overexpression of MUC1 in carcinoma cells decreases cell-cell interaction and increases the metastatic capacity of carcinoma cells, favoring invasion of tumor cells into the underlying stroma, lymph, and blood vessels [36]. Moreover, although there was not a significant correlation of MUC1 positive with tumor size, tumor differentiation, and clinical stage, it still had the tendency toward higher expression in advanced stage of cancer. The reason for this result may be too small sample size included in the meta-analysis. In addition, MUC1 positive gastric cancer patients also displayed lower 5-year survival rate than MUC1 negative ones. Therefore, high levels of MUC1 expression were found to be related to poor prognosis, as was the case in the present study.

There were several limitations in our meta-analysis. First of all, only published studies were included in the meta-analysis. Therefore, publication bias may have occurred, even though the use of a statistical test did not show it [37]. We tried to retrieve all relevant data that was not available from the published reports, but it is unavoidable that some data could still be missing. Missing information may reflect "negative" or more conservative association of MUC1 with clinicopathological parameters that could reduce the significance of MUC1 expression as a predictor of outcome in gastric cancer. Second, non-English literature was included in our meta-analysis which leads to losing some potential important survival data; meanwhile there might be selection bias. Moreover, heterogeneity between studies was low for most of the dichotomous variables examined in this analysis but was marked for all the continuous variables. There was significant variability in terms of definitions, inclusion criteria, exclusion criteria, operating technique, and measurement of outcomes. It was not possible to match all patient groups for age, BMI, preoperative therapy, and previous abdominal history. All these factors may have contributed to the high heterogeneity between studies. Although RE model was used to decrease heterogeneity between studies, it is not totally ruled out. Finally, the available data do not evaluate whether MUC1 may influence the response to specific therapeutic regimens. Therefore, we minimized the bias by confirming a detailed protocol before initiating the study, by performing a careful search for published studies, and by using explicit methods for study selection, data extraction, and data analysis.

5. Conclusion

In conclusion, our meta-analysis suggests that MUC1 expression might be a marker of poor prognosis for survival in patients with gastric cancer, if detected by immunochemistry. However, because of the heterogeneities of included studies

and bias of meta-analysis, our conclusions need to be interpreted with caution.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Xiao-Tong Wang and Fan-Biao Kong contributed equally to this work.

Acknowledgments

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